DESIGN-DIRECTED MEASUREMENTS OF B1 HETEROGENEITY AND SPIN-LATTICE RELAXATION FOR 8 TESLA MRI

A Thesis

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By

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* * * * *

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ABSTRACT

The current trend toward magnetic resonance imaging (MRI) above 4 Tesla requires design-directed research before the benefits of increased signal to noise ratio (SNR) associated with high field MRI can be realized clinically. In this work the well-known radiofrequency (RF) heterogeneity is explored with respect to imaging the human brain and performing $T_1$ measurements. $T_1$ data are presented in a number of applications including in-situ measurements and relaxivity measurements of gadolinium diethelene pentaacetic acid (Gd-DTPA) in protein solutions.

Many authors have noted increased heterogeneity of the RF pulses used to excite hydrogen nuclei in MRI experiments. While theoretical approaches differ, it is generally agreed that this heterogeneity is a result of the interaction between the magnetic field ($B_1$) associated with the RF excitation and the electromagnetic properties of the sample, namely the dielectric constant and conductivity. After reviewing theoretical approaches to model this interaction and experimental methods to quantify the $B_1$ field, experimental data are presented for the field distribution in a uniform, spherical phantom. The fields are shown over a range of six operating modes for the transverse electromagnetic (TEM) coil which produces the $B_1$ field. Based on these phantom results, human brain images and field distributions are shown for a normal volunteer for three of the operating modes.
These images suggest that coils may be tuned to a particular mode to target a specific anatomical structure.

MRI techniques can provide quantitative measurements in addition to anatomic images. The robustness of one such measurement, spin-lattice relaxation rate, is explored in light of the $B_1$ field heterogeneity noted above. Phantom and in-situ data are presented for common methods of determining the exponential time constant, $T_1$, associated with spin-lattice relaxation. Numerical simulations and experimental data show that the Inversion Recovery (IR) method, while time consuming, provides the most stable $T_1$ measurements in light of $B_1$ heterogeneity.

Based on the robustness of the IR method, relaxivity data are presented for the contrast agent Gd-DTPA. The 8 Tesla data in this work support the argument that the presence of biomacromolecules increases the relaxivity of contrast agents. These data contribute to researchers who model the underlying mechanisms which cause paramagnetic agents to cause increased relaxation when compared to studies of pure contrast agents in saline.

The results of this work provide valuable experimental data to theoretical debates over electromagnetic field modeling in the imaging volume, the reliability of $T_1$ measurements under conditions of $B_1$ heterogeneity and contrast enhancement mechanisms. Furthermore, lessons learned with respect to RF coil modes and ranges of $T_1$ values can be directly applied to patient studies at 8 Tesla.
DEDICATION

For Jacob Thomas, Benjamin Patrick and Samuel Paul -

Most people will think that this book is about experiments and stuff.

But to me, it's the story of a daddy who loved God and loved his family with all his heart.
ACKNOWLEDGEMENTS

While I could thank each member of the 8 Tesla group at OSU for helpful explanations, technical assistance and friendship; I would rather use this space to recognize a few of the most significant contributors.

This work would not have been possible without the guidance of Frau Professor Doktor Petra Schmalbrock. She has been very patient when my other roles in life distracted me from being a typical graduate student. Even if this document never gets signed, I could still say that I learned a great deal working for Petra. I don't know where to begin in thanking Ryan Gilbert. I admire Ryan's ability to turn complex problems into simple solutions, and I respect his convictions on issues of faith and politics. My big brothers in Biomedical Engineering were Jim Ibinson and Antonio Algaze. They guided me through paperwork and procedures at times when I thought that I might never write the dissertation that you are now reading. Also, when it comes to making complex statistical concepts seem simple, you can't find better tutors than these guys. Klaus Baudendistel was very often my go-to guy for questions about computers or general MRI physics. When I thought that a question might sound dumb, I knew that Klaus would give a thorough and patient answer. Drs. Michael Knopp and Johannes Heverhagen provided computer resources to handle the large amount of data in Chapter 3. I would like to thank my equally favorite officemates, Chastity Diane Shaffer Whitaker and
Trong-Kha Truong. It's funny that three totally different people will soon be missing each other so much. Also, Dr. Ming Yang was translated an article written in Chinese which proved to be very central to Chapter 5.

Finally, I would like to thank my wife Gretchen. In terms of my career, these years have been very difficult, but I feel that our marriage has never been stronger. She points me in the right direction when things are unclear, and reminds me that there's more to life than work. Thanks.
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PUBLICATIONS


FIELDS OF STUDY

Major Field: Biomedical Engineering
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CHAPTER 1

INTRODUCTION

1.1 Background

In recent years, considerable interest in magnetic resonance imaging (MRI) research has focused on the development of systems with increased magnetic field strength (vau02, nor03). Images acquired on systems with magnetic fields ranging from 3 to 8 Tesla have demonstrated increased signal-to-noise ratio (SNR) and better resolution than those from clinical systems utilizing magnetic fields at 1.5 Tesla and below (fra03, kim03, abd99).

The advantages of high field MRI are not without drawbacks. Images acquired using increased magnetic field strengths are often associated with heterogeneous signal intensity. In addition, differentiation between brain tissues can be difficult due to changes inherent to the relaxation properties of the object being imaged. Other drawbacks include safety concerns over the use of high frequency radio frequency (RF) pulses (cha03) and image artifacts introduced at interfaces between anatomic structures of differing magnetic susceptibility properties (nor03).
The purpose of this work is to develop methods to quantify factors affecting the first two drawbacks mentioned above: image heterogeneity caused by non-uniform excitation and spin-lattice relaxation. A better understanding of these factors will serve as a guide in developing hardware and pulse sequences for the clinical implementation of high field imaging.

While these two factors may appear quite distinct, it is important to note their interrelationship. The MRI signal is acquired by establishing an equilibrium distribution of protons in a strong magnetic field \( B_0 \) then perturbing that equilibrium with a second magnetic field \( B_1 \). The subsequent return of the protons to equilibrium is characterized by the time constant \( T_1 \). It follows that the timescale of the return to equilibrium cannot be determined without first perturbing that equilibrium. Furthermore, it will also be shown that common methods for measuring \( T_1 \) are predicated on specific perturbations caused by a predetermined \( B_1 \) field strength.

1.2 Outline

The goals of this work are to quantify the signal heterogeneity associated with 8 Tesla MRI, to test experimental techniques for \( T_1 \) measurement at 8 Tesla and to apply these methods to determining \( T_1 \) values \textit{in situ} and in contrast agent solutions. After a brief introduction to the physics of MRI in Chapter 2, the connections between image heterogeneity and flip angle heterogeneity will be shown in Chapter 3. In that chapter, methods for \( B_1 \) field mapping are compared, field mapping is employed in a uniform phantom using the resonant modes of a transverse electromagnetic (TEM) coil, and \( B_1 \) field maps for these modes are applied to \textit{in-vivo} brain and ocular imaging. In Chapter 4, numerical simulations and experimental data are used to test methods of \( T_1 \) measurement.
for robustness with respect to $B_1$ field heterogeneity, and *in-situ* values are provided for human brain anatomy. In Chapter 5, $T_1$ measurements are performed in contrast agent samples in varying biomacromolecule admixtures, and results are presented which demonstrate increased spin-lattice relaxation rates at 8 Tesla for samples containing bovine serum albumin (BSA). Finally, conclusions are presented in Chapter 6 with respect to $B_1$ field mapping and the reliability of $T_1$ mapping in the presence of $B_1$ field heterogeneities.
CHAPTER 2

THE PHYSICS OF MRI

2.1 Definitions

The origin of the study of nuclear magnetic resonance (NMR) can be traced to two groups who submitted their results for publication nearly simultaneously in December 1945 and January 1946 (bec96). While Purcell and Bloch both received the 1952 Nobel prize for leading these groups, the theoretical approach of Bloch is used herein to explain the underlying physics relevant to this work. The following section relates RF excitation and relaxation to signal strength in MRI.

2.1.1 NMR Precession

To explain the resonant nature of NMR, one must consider the properties of subatomic particles placed in a magnetic field. The laws of quantum mechanics place strict rules on the interactions of particles with intrinsic spin equal to an odd multiple of \( \hbar/2 \) (hua87) where \( \hbar \) is Planck’s constant, \( \hbar \), divided by \( 2\pi \). These rules dictate that the magnetic moment, \( \mathbf{\mu} \), of a particle with an intrinsic spin of \( \hbar/2 \) does not align with the magnetic field. Further, when such a particle is placed in a magnetic field, the vector
component of its spin along the direction of the field can assume only two values: $+\hbar/2$
(hereafter called parallel or spin-up) and $-\hbar/2$ (antiparallel or spin-down).

At this point, some authors treat the proton as a magnetic moment and use classical electromagnetism to determine the equations of motion for its precession about the applied magnetic field (jin99). However, in this work, it suffices simply to use quantum mechanics to determine the energy difference between the parallel and antiparallel states.

Following the theoretical treatment used by Shankar (sha80), the intrinsic angular momentum, $\mathbf{J}$, of the particle is related to the magnetic moment, $\mu$, by the so-called gyromagnetic ratio, $\gamma$, using equation (2.16) from Haacke, et. al. (haa99)

$$\mu = \gamma \mathbf{J}.$$  \hspace{1cm} 2.1

Second, the energy associated with the alignment of the magnetic moment with the magnetic field, $B_0$, is given by

$$E = \mu \cdot B_0.$$  \hspace{1cm} 2.2

Because the components of the angular momentum along the magnetic field are restricted to the values $\pm \hbar/2$, equations (2.1) and (2.2) imply that the energy difference between the parallel and antiparallel state is given by

$$\Delta E = \frac{\gamma \hbar}{2} B_0 - \left(\frac{-\gamma \hbar}{2}\right) B_0 = \gamma \hbar B_0.$$  \hspace{1cm} 2.3

Therefore, a photon which excites the proton from the parallel to the anti-parallel state must have an energy $\hbar \omega = \Delta E$ where

$$\omega = \gamma B_0.$$  \hspace{1cm} 2.4
This is the so-called Larmor equation, and $\omega$ is often called the Larmor frequency of the system (haa99). The Larmor frequency for protons at 8 Tesla is 340.56 MHz.

2.1.2 Flip Angle

Having defined a resonance frequency, $\omega$, for the system of a proton in a magnetic field, one can excite this system from the parallel state to the antiparallel state by subjecting the system to electromagnetic (EM) pulses with a frequency equal to $\omega$. In the case of proton NMR, the Larmor frequency generally falls in the radiofrequency (RF) range, and such pulses are called RF pulses. RF pulses must be clearly defined because one of the sources of the previously mentioned image heterogeneity in high field MRI is the spatial non-uniformity in the excitation caused by these RF pulses.

For completeness, it should be noted at this point that only a continuous wave can truly consist of a single frequency. In MRI, the RF pulses have a finite duration and therefore are comprised of a range of frequencies centered around $\omega$. This range of frequencies is hereafter called the bandwidth of the pulse.

To understand the interaction between an RF pulse and the protons in a sample, it is helpful to consider a collection of a large number of protons. This is a reasonable assumption for modeling experimental data because a cubic millimeter of water contains a number of protons on the order of $10^{19}$. Figure (2.1) represents the distribution of a large number of magnetic moments in both the parallel and antiparallel states. It is generally assumed for a large collection of protons that their magnetic moment vectors would be equally distributed at all angles on the surface of a cone because only the $z$ component and magnitude of the vector is fixed. This equal distribution is justified by
the fact that the $x$- and $y$-components of the magnetization uncertain under the rules of quantum mechanics (sha80).

If the $x$ and $y$ components of the magnetic moment vectors in this large sample are equally distributed, the vector sum of all these vectors will be directed along the $z$ axis. In thermodynamic equilibrium at a finite temperature, an overabundance of protons is expected in the parallel energy state because it is lower in energy than the antiparallel state by $\hbar \omega$. This gives a net magnetization, $\mathbf{M}$, along the $z$-axis such that

$$\mathbf{M} = N\mu_0 \hat{z}$$  \hspace{1cm} (2.5)

where $N$ is the difference between the number of parallel and antiparallel spins per unit volume, and $\hat{z}$ is a unit vector directed along the $z$ axis. The interaction between the electromagnetic pulse and the large collection of protons can then be reduced to the interaction between the pulse and the net magnetization $\mathbf{M}$.

A continuous, circularly polarized EM wave of frequency $\omega$ is comprised of crossed electric and magnetic fields oscillating at that frequency (lor88). In a reference frame rotating with frequency $\omega$, the magnetic field associated with this wave, $B_1$, must then appear constant (e.g. along the $x'$ direction). Thus in this reference frame, the application of an EM wave will cause a precession about $B_1$ by the same reasoning as the preceding discussion. The direction of this rotation is seen in figure (2.2) where the axes are labeled $x'$, $y'$ and $z'$ to indicate a reference frame rotating about $\mathbf{B}_0$ at frequency $\omega$.

In the rotating reference frame, the frequency of the precession about $B_1$ is given by the Larmor equation as $\omega_1 = \gamma B_1$. The extent of this rotation can be controlled by the duration of the RF pulse and the strength of the $B_1$ field. In figure (2.3) an arbitrary rotation is obtained such that
where $\theta$ is called the flip angle and $\tau$ is the duration of the applied RF pulse.

If the rotated magnetization vector in figure (2.3) is viewed in the laboratory reference frame, the $z$-component is the same as the $z'$-component in the rotating frame. However, the transverse components in the $x$-$y$ plane will be observed to oscillate with frequency $\omega = \gamma B_0$. These oscillating components produce the signal in NMR and MRI experiments by inducing currents in specialized RF coils described in this work. Because these transverse components depend upon the flip angle $\theta$, signal strength in NMR and MRI experiments depends strongly on the excitation produced by the $B_1$ field.

Numerous studies (kan99, nor03, tro04) have shown significant variation in the $B_1$ field in high field MRI experiments. In this work, methods for quantifying $B_1$ field heterogeneity are presented and implications of this heterogeneity on in-vivo imaging are explored.

2.1.3 Relaxation

After an RF pulse has rotated the magnetization vector away from alignment with $B_0$, it follows that the magnetization will decay (i.e. relax) back to its equilibrium value. As the magnetization vector in figure (2.3) rotates back toward the $z'$-axis, its $z'$-component, $M_z(t)$ will grow back to its equilibrium value, $M_0$. The timescale of this relaxation is called $T_1$, and the evolution of $M_z(t)$ is given by

$$M_z(t) = M_z(0)e^{-t/T_1} + M_0\left(1-e^{-t/T_1}\right)$$

The time constant of spin-lattice relaxation, $T_1$, is affected by temperature, sample composition, viscosity and $B_0$ strength (car99). $T_1$ is often called the spin-lattice relaxation time.
relaxation time because it represents the exchange of energy from the relaxing protons to the surrounding medium.

The second relaxation process is related to the loss of synchronicity in the precession of the protons. Figure (2.4) shows that a group of magnetic moments which have precessed asynchronously (i.e. dephased) will produce a smaller vector sum than four collinear vectors. The differences in precessional frequency which create this dephasing are attributed to thermodynamic effects and external field induced effects (hao99).

Thermodynamic effects contributing to dephasing include intrinsic properties of the sample which make perturbations in the magnetic field on a microscopic level. The relative positions of nuclei in a molecular structure as well as the mobility of protons in solution can cause these perturbations. This apparent loss in the transverse components of the magnetization vector is called spin-spin relaxation and it is governed by an exponential decay constant $T_2$ such that the transverse components decrease in time as

$$M_{xy}(t) = M_{xy}(0)e^{-t/T_2}, \quad 2.8$$

where $M_{xy}(t)$ is the magnitude of the $x$ and $y$ components of the magnetization vector $M$ such that

$$M_{xy}(t) = \sqrt{M_x^2(t) + M_y^2(t)}. \quad 2.9$$

On the other hand, the external field induced dephasing effects are a result of the design of the magnet producing the static field $B_0$ and from susceptibility variations in the imaging volume. The decay of transverse components of magnetization due to these
external effects occurs with a timescale called $T_2'$. The combination of $T_2$ effects and external effects create a combined transverse dephasing characterized by $T_2^*$ where

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'}.$$  \hspace{1cm} 2.10

Haacke, et. al. (haa99) state that the difference between $T_2$ and $T_2'$ effects is that $T_2'$ dephasing can be recovered in spin echo experiments while $T_2$ dephasing is inherent and unavoidable.

The relaxation timescales $T_1$, $T_2$ and $T_2^*$ are important determinants of the signals generated from the transverse components of magnetization. While $T_2$ and $T_2^*$ are not measured specifically in this work, they will appear in theoretical discussions that follow. On the other hand, $T_1$ values have been studied herein with respect to the evaluation of experimental techniques for accurate measurement and the collection of data relevant to the development of subsequent studies. $T_1$ values often set the duration for the entire imaging sequence (kra87). Knowledge of $T_1$ is crucial for designing experiment test devices and for the development of contrast agents (tót01).

2.2 Image Formation in MRI

There are three types of signals in MRI appear throughout this work: the gradient recalled echo, the spin echo and the stimulated echo. The sequences used to create these signals and mathematical expressions are derived below for subsequent use the following chapters.

2.2.1 The Gradient Recalled Echo (GRE) signal

The data values comprising a single-slice MR image can be contained stored in a two-dimensional matrix with $N_x$ elements in the x-direction and $N_y$ elements in the y-
direction. The spatial dimensions MR images are generally characterized by volume elements (voxels). The dimensions of a voxel in an image are given by

\[
\begin{align*}
\Delta x &= \frac{FOV_x}{N_x} \\
\Delta y &= \frac{FOV_y}{N_y} \\
\Delta z &= d
\end{align*}
\]

where \(FOV_i\) denotes the length of the field of view (FOV) in the \(i\)-direction, and \(d\) is the slice thickness. In Section 2.1.2 it was shown that an applied \(B_1\) field rotates the magnetization vector in a sample as indicated in figure (2.3).

In order to encode the spatial characteristics of a sample, a controlled variation in the effective magnetic field can be created between the location of a voxel and the field strength experienced at its location. To do this, gradient magnetic fields are applied such that \(B_0\) is perturbed by an amount \(\Delta B\) given by

\[
\Delta B = G_x
\]

where \(x\) is the spatial coordinate in the resting reference frame. It is important to note that the gradient field is directed along \(B_0\), but its variation is in the direction to be encoded. This means that the local field experienced in a voxel at a given location is equal to the sum of \(G \cdot x + B_0\). For example, a gradient field along the \(x\) direction is given by

\[
G_x(x) = \hat{z} \frac{2\pi \cdot BW}{\gamma \cdot FOV_x} \cdot x
\]

where \(BW\) is the bandwidth of frequencies used for sampling the signal induced in the RF coil, and \(x\) is the distance along the \(x\)-axis. This means that spins with a negative \(x\)-
coordinate will experience a lower effective field and precess more slowly than those with a positive $x$-coordinate.

With a variation in Larmor frequencies along the $x$-axis, the precessing spins will lose coherence and rotate out of phase in a manner similar to those in figure (2.4). In order to reverse this trend and return the spins to coherence, it is possible to reverse the direction of $G_x$. This will have the effect of creating a faster precession for the spins which formerly were precessing slowly and vice versa.

After the application of an RF pulse, the signal induced in the RF coil will initially be strong due to the coherence of magnetization vectors. As the vectors diphase, this signal will decay. This signal immediately after the RF pulse is called the free induction decay (FID). When magnetization vectors rephase and rebuild their coherence, the signal is called an echo. The time from the center of the RF pulse to the formation of the echo is called TE, and the time between RF pulses is called the repetition time, TR.

Figure (2.5) is a graphical representation of the timing of a basic GRE imaging sequence (haa99). In the figure, the time course of the $z$-component of a gradient magnetic field applied as mentioned above is labeled readout gradient. After the negative lobe of this gradient rephases the spins, the positive lobe of the gradient serves to spatially encode frequency with position. The signal induced in the RF coil by the rephasing of spins will be centered around the time indicated by the dotted line on the readout gradient trace. By Fourier transforming this time domain signal, the frequencies can be extracted. The position follows then from these frequencies due to the linearity of the gradient field.
Also indicated in figure (2.5) is a slice selective pulse labeled RF and its associated slice select gradient. The RF pulse as shown is a truncated version of the sinc function where

\[ \text{sinc}(\omega t) = \frac{\sin(\omega t)}{t}. \]  \hspace{1cm} 2.14

Because the function \( \text{sinc}(\omega_0 t) \) is the sum of sine waves over a continuum of frequencies centered around \( \omega_0 \) ranging from \( (\omega_0 - \Delta \omega) \) to \( (\omega_0 + \Delta \omega) \), the truncated version of a sinc pulse in figure (2.5) will produce a nearly uniform excitation of spins precessing in that range of frequencies. The slice select gradient is applied during the pulse in order to create a one-to-one correspondence between frequency and location along the \( z \) direction. The bandwidth of frequencies comprising the sinc pulse will determine the spatial locations of spins which are excited by this pulse such that

\[ \mathbf{G}_z(z,t) = \hat{z} \frac{2\pi \cdot BW_{RF}}{\gamma \cdot d} \]  \hspace{1cm} 2.15

where \( d \) is the thickness of the slice.

The remaining gradient trace seen in figure (2.5) is the phase encoding gradient. The phase encoding gradient is also directed along \( \mathbf{B}_0 \), but it varies in a direction perpendicular to the readout gradient. The timecourse indicated in the figure is repeated \( N_{ph} \) times, where \( N_{ph} \) is the number of phase encoding steps selected for the experiment. This gradient is applied over a range of strengths as indicated in order to create a phase shift between subsequent repetitions. The phase shifts vary from \(-\pi\) to \(\pi\) radians in \( N_{ph} \) increments.
During a GRE sequence as seen in figure (2.5), the number of echoes created is equal to $N_{ph}$. If a long time elapses between RF pulses, it can be seen from equation (2.7) that the exponential terms are negligible, and the magnetization will relax back to its equilibrium value. Thus at the beginning of each of the $N_{ph}$ phase encoding steps, the $z$-component of the magnetization always starts from the same value. However, if the time between pulses is short enough that the $z$-component of the magnetization does not reach equilibrium, then the magnetization for the $i$th phase encoding step will depend on its predecessors. If the $z$-component of the magnetization varies then the transverse components of magnetization producing the signal from the $i$th echo will also depend on its predecessors.

For a GRE sequence with short TR, Haacke, et. al. (haa99) have determined the resulting equilibrium signal resulting which will build up after repeated pulses. The behavior of this signal through the pulse sequence can be determined by considering the vector components of magnetization. In a spoiled GRE sequence, any transverse components of magnetization which linger after the acquisition of the echo are forced to zero either by varying the phase of the RF pulses or by additional gradients (vla99). If the RF pulses are repeated until the magnetization from one repetition is essentially equal to the previous repetition, equilibrium is then achieved, with the transverse components during the $n$th echo for a spoiled GRE sequence given by

$$M_{xy}(\theta, t_n) = \frac{M_0 \sin \theta (1 - e^{-TR/T_1}) e^{-TE/T_1}}{1 - \cos \theta e^{-TR/T_1}}$$

where $\theta$ is the flip angle of each pulse, and $M_0$ is the equilibrium value for the magnetization.
In the sections that follow, the usefulness of GRE sequences in experimental $B_1$ field mapping will be discussed. Equation (2.16) can be used in the limit of long TR to determine the effective flip angle during imaging. Because the flip angle $\theta$ can be related to the effective $B_1$ field through equation (2.6), a map of the $B_1$ field can then be created at each point in the imaging volume.

2.2.2 The Spin Echo (SE) signal

In the previous section, a rephasing lobe in the readout gradient was used to return dephasing spins to coherence and create an echo. An additional method for rephasing spins comes from applying an additional RF pulse to create a so-called spin-echo (hah52). The effect of this additional pulse will be explained below.

In figure (2.6), the initial RF pulse resembles that of the GRE sequence in figure (2.5). Similarly, the phase encoding gradient is varied through its $N_{\text{ph}}$ steps as in the GRE sequence. However, the initial RF pulse is calibrated to produce a flip angle of 90º, and rephasing is accomplished by a slice selective RF pulse which is chosen to create a flip angle of 180º.

2.2.2.1 Differences Between SE and GRE Signals

The net effect of this combination of pulses is to tip the magnetization vectors into the transverse plane. As the spins dephase at different rates as discussed above, the 180º pulse reverses the direction of their precession, but the precession frequency of each individual magnetization vectors remains the same after the pulse. This has important implications for the internal and external sources which cause the loss of coherence mentioned in Section 2.1.3. For the external sources of dephasing, a the magnetization
voxel which experiences a net magnetic field $B_0+\delta B$ will precess in the rotating reference frame through an angle given by

$$\varphi = \gamma \delta B \frac{TE}{2}$$

before the refocussing pulse applied at time $TE/2$. After the pulse, the same magnetization will precess in the opposite direction through the same angle, $\varphi$. This is not the case for the GRE sequence above. During the rephasing lobe of the readout gradient, the magnetization vector will precess in the rotating frame through an angle

$$\varphi_1 = \gamma (\delta B - G_x) \Delta t$$

where $G_x$ is the magnitude of the gradient lobe, and $\Delta t$ is the duration of the rephasing lobe. Between the end of the rephasing lobe and time $TE$, the magnetization will precess through an angle of

$$\varphi_2 = \gamma (\delta B + G_x) \Delta t$$

Because $\varphi_1$ is not equal to $\varphi_2$, the magnetization vectors in the GRE experiment have not precessed back to phase coherence. Thus the GRE sequence cannot rephase the external sources characterized by $T_2'$. It should be noted that the internal sources of dephasing (diffusion, molecular structures) cannot be controlled and affect both sequences.

2.2.2.2 Phase Coherence Graphs

To predict the signal behavior for sequences employing multiple RF pulses, phase coherence graphs are a useful tool. Using phase coherence graphs, the transverse and longitudinal components of magnetization can be tracked by following different pathways caused by the application of multiple RF pulses. While more thorough
treatments may be found elsewhere (haa99, hen86,hen86a), a brief description is
presented here.

For the case of the application of an RF pulse of arbitrary flip angle $\theta$ about the $x$-
axis on a magnetization vector at equilibrium, the resulting magnetization vector is given
by

$$
\begin{bmatrix}
M_x^+
M_y^+
M_z^+
\end{bmatrix} =
\begin{bmatrix}
1 & 0 & 0 \\
0 & \cos \theta & \sin \theta \\
0 & -\sin \theta & \cos \theta
\end{bmatrix}
\begin{bmatrix}
M_x^-
M_y^-
M_z^-
\end{bmatrix}
$$

where the superscripts - and + reflect the magnetization before and after the RF pulse,
respectively. The matrix algebra can then be simplified (haa99, hen86) by substituting
$M_+ = M_0 + jM_s$ to represent the dephasing magnetization and substituting its complex
conjugate $M_+^* = M_0 - jM_s$ to represent the rephasing magnetization. This results in the
following:

$$
M_+^+ = M_+^- \cos^2 \left(\frac{\theta}{2}\right) + M_-^- \sin^2 \left(\frac{\theta}{2}\right) + \frac{j}{2} M_-^- \sin \theta
$$

and

$$
M_-^+ = M_-^- \cos \theta - \frac{j}{2}(M_-^- - M_-^+) \sin \theta.
$$

To represent equations (2.21) and (2.22) graphically, a plot can be constructed in
which the $z$ components of magnetization are represented as horizontal lines. Transverse
components are represented as sloping lines with dephasing magnetization, $M_+$, shown
above the horizontal and dephasing magnetization, $M_-$, below.

From equation (2.22) the $z$-component, $M_-^+$, before an RF pulse of flip angle $\theta$
will contribute a fraction equal to $\cos \theta$ to the $z$-component after the pulse, $M_+^+$. Equation
(2.21) shows that \( M_z^- \) will contribute a fraction equal to \( \sin \theta \) to the dephasing transverse component after the pulse, \( M_z^+ \). This is represented in figure (2.7a) as a horizontal line which is split at point A by an RF pulse into a diverging transverse component and a component which remains along the \( z \)-axis. The fractions are indicated on each branch.

Figure (2.7b) shows that the splitting of a dephasing path is more complicated. The application of an RF pulse at point B creates a \( z \)-component and a dephasing component which continue to evolve from point B. From equation (2.21), the fraction \( \cos^2(\theta/2) \) of \( M_z^- \) remains as \( M_z^+ \). From equation (2.22), the fraction \( \frac{1}{2} \sin \theta \) from \( M_z^- \) remains as \( M_z^+ \). Taking the complex conjugate of both equations (2.21) and (2.22) reveals that the fraction \( \sin^2(\theta/2) \) of \( M_z^- \) is inverted to the rephrasing transverse component \( M_z^+ \) shown at point C, and \( \frac{1}{2} \sin \theta \) of \( M_z^+ \) is stored in the component \( M_z^+ \). This component will be useful in the following discussion on stimulated echoes.

2.2.2.3 The SE Signal

Figure (2.7c) shows the phase coherence pathways for the formation of a spin echo by the application of two pulses with flip angles \( \theta_1 \) and \( \theta_2 \) separated by time interval \( \tau \). The pathways are split by the two rules shown in figures (2.7a) and (2.7b). An echo is formed when the rephrasing magnetization component formed at point G returns to coherence at the point indicated by the circle in figure (2.7c). This graph, therefore, determines the time occurrence of the spin echo at time \( 2\tau \). Also, the magnitude of its echo is given by applying the fraction created at point G to the fraction created at point D. Thus the amplitude of the transverse magnetization components during the echo is given by
\[ M_{xy}(\theta, \tau) = M_0 \sin \theta_1 \sin^2 \left( \frac{\theta_2}{2} \right) e^{-2\tau/T_2} \] 

where a fraction of \( \exp(-\tau/T_2) \) is applied for the intervals from point D to point E and from point G to the echo to account for spin-spin relaxation. In equation (2.23), \( T_2 \) is used instead of \( T_2^* \) because the echo is refocused by an RF pulse rather than gradient switching as discussed in Section 2.2.2.a.

The result in equation (2.23) will be used below to give the echo amplitude as a function of the flip angles and the timing of pulses in a SE sequence. It can then be applied to \( B_1 \) field mapping experiments in Chapter 2. Also, the dependence of the transverse magnetization components in equation (2.23) on \( T_1 \) will be used in \( T_1 \) mapping experiments in Chapter 4.

2.2.3 The Stimulated Echo (STE) signal

A stimulated echo imaging sequence is shown in figure (2.8). It includes three RF pulses. The gradient behavior is similar to the SE sequence except that in this particular implementation the first two pulses are non-selective. The repetitive pulses produce multiple echoes which can be explained using phase coherence pathways as seen in figure (2.9).

Starting with figure (2.7c), the addition of a third RF pulse of flip angle \( \theta_3 \) after a time interval \( \tau_2 \) will cause splitting which follows the rules shown in figures (2.7a) and (2.7b). From the rigorous treatment and diagram found in reference (haa99), five echoes will result when \( \tau_2 > \tau_1 \). The timing and amplitudes of these echoes are given in Table (2.1).
The transverse component of magnetization during the echo labeled E2 in Table (2.1) is the so-called stimulated echo with echo amplitude

\[ M_{xy}(\theta_1, \theta_2, \theta_3, \tau_1, \tau_2) = \frac{M_0}{2} \sin \theta_1 \sin \theta_2 \sin \theta_3 e^{-\tau_2/T_1} e^{-2\tau_1/T_1}. \] 2.24

This signal results from the storage of magnetization along the z-direction during the interval between the second and third pulses. This is the horizontal pathway in figure (2.7c) which originates at point F and then is partially turned into refocusing magnetization by the third pulse. The spin-lattice relaxation term \( \exp(-\tau_2/T_1) \) results from the decay of the z-component between the second and third pulses in accordance with equation (2.7). STE sequences have been applied to both \( B_1 \) and \( T_1 \) mapping as will be seen below. It will also be utilized below for determining the RF power requirement to produce a 90° flip angle.
Figure 2.1 A collection of a large number of magnetic moments (red) precessing about a z-directed magnetic field in both the parallel and antiparallel states. The net magnetization vector is shown in green (not to scale).
Figure 2.2 A weak magnetic field along the $x'$ axis (green) is sufficient to cause the magnetization (red) to precess about the x direction in the $y'$-$z'$ plane.
Figure 2.3 By controlling the strength of the $B_1$ field (green) and the duration of the RF pulse, the magnetization vector (red) is rotated through a specific flip angle $\theta$ in the rotating reference frame.
Figure 2.4 Five vectors of equal length \( a \) will produce a smaller vector sum than five collinear vectors due to the cancellation of the \( x' \)-components.
Figure 2.5 Simplified GRE pulse sequence (haa99). The readout gradient causes the refocussing of spins to form the gradient echo.
Figure 2.6 SE pulse sequence (haa99). It is the second RF pulse which causes the dephasing spins to return to coherence and create the spin echo.
Figure 2.7 (a) The splitting of purely longitudinal magnetization into transverse and longitudinal components. (b) The splitting of a transverse component (diagonal) into four components. (c) A two-pulse sequence causes six pathways due to the splitting rules shown in (a) and (b).
Figure 2.8 STE pulse sequence (hao99). The signal is acquired during the second lobe of the readout pulse. It is created by magnetization that is stored along the z-direction during the interval between the second and third RF pulses.
Figure 2.9 Pathway diagram for an STE pulse sequence (haa99). The five echoes (see Table 2.1) which occur when $\tau_2 > \tau_1$ are shown in red. The pathway leading to the stimulated echo is shown in purple. The magnetization stored along the z-direction between the second and third pulses is indicated by the purple horizontal line.
<table>
<thead>
<tr>
<th>Echo number</th>
<th>Time of echo</th>
<th>Echo amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>E1</td>
<td>$2\tau_1$</td>
<td>$\sin \theta_1 \sin^2(\theta_2/2) \exp(-2\tau_1/T_2)$</td>
</tr>
<tr>
<td>E2</td>
<td>$2\tau_2$</td>
<td>$\sin \theta_1 \sin^4(\theta_2/2) \sin^2(\theta_3/2) \exp(-2\tau_2/T_2)$</td>
</tr>
<tr>
<td>E3</td>
<td>$2\tau_1+\tau_2$</td>
<td>$\frac{1}{2} \sin \theta_1 \sin \theta_2 \sin \theta_3 \exp[-2\tau_1/T_2-\tau_2/T_1]$</td>
</tr>
<tr>
<td>E4</td>
<td>$\tau_1+2\tau_2$</td>
<td>$[1-(1-\cos \theta_1)\exp(-\tau_1/T_1)] \sin \theta_2 \sin^2(\theta_3/2) \exp(-2\tau_2/T_2)$</td>
</tr>
<tr>
<td>E5</td>
<td>$2\tau_1, 2\tau_2$</td>
<td>$\sin \theta_1 \cos^2(\theta_2/2) \sin^4(\theta_3/2) \exp[-2(\tau_1+\tau_2)/T_2]$</td>
</tr>
</tbody>
</table>

**Table 2.1** Amplitudes and timing of the 5 echoes created for a three pulse sequence. The three pulses produce flip angles of $\theta_1$, $\theta_2$, and $\theta_3$. The first two pulses are separated in time by $\tau_1$, and the second two pulses are separated by $\tau_2$. 


CHAPTER 3

B₁ FIELD MAPPING

3.1 Introduction

Previous theoretical predictions suggested that MRI would be limited to static field strengths below 5 Tesla due to limited penetration of the B₁ field (rös86). Despite the many successes in human MRI using fields up to 7 and 8 Tesla (ugu03, nor03, rob98), B₁ field heterogeneity remains a concern in theoretical studies (tro04, col02) and clinical applications (kim03a, cha02). This chapter explores the sources of B₁ field heterogeneity, the tuning of the operating modes of RF coils and the methods for quantifying B₁ field heterogeneity. Applications of B₁ field mapping and RF coil tuning are then utilized for in-vivo brain imaging.

3.1.1 Modeling the B₁ Field

Theoretical approaches to modeling the B₁ field used for MR imaging experiments have evolved along with the transition toward stronger magnets. For example, Hoult and Lauterbur (hou79) assumed a constant B₁ field when modeling the signal to noise ratio (SNR) in a 1 milliliter sample of water at 1 MHz (0.0235 Tesla). While this assumption is justifiable in such a small volume, the B₁ field was described in Chapter 2 as a component of an electromagnetic wave of angular frequency ω₀=γB₀. When such a wave
is propagating through a medium, its wavelength $\lambda$ is shortened relative to its free space wavelength. The wavelength in the medium is a function of its frequency as well as the permeability $\mu$ and permittivity $\varepsilon$ of the medium itself (lor88) such that

$$\lambda = \frac{2\pi}{\omega_0 \sqrt{\varepsilon \mu}}. \quad 3.1$$

When this wavelength is much larger than the dimensions of the imaging volume, the assumption of a constant $B_1$ field is justified. This is the case in imaging experiments up to 0.5 Tesla (jin99), but in 8 Tesla in-vivo imaging this wavelength averages 12 centimeters (ibr01a). Thus the wavelength is smaller than the object to be imaged (e.g. structures in the human head). This will be shown below to lead to variations in the strength of the $B_1$ field in the imaging volume.

$B_1$ field models are not only complicated by wavelength. At higher frequencies the interaction between the electric field component of the electromagnetic wave and the medium become significant (jin99). This electric field component is responsible for localized heating (zyp96). It will be shown below that the interactions between the electric and magnetic fields within the imaging volume are intimately connected through the conductivity of the sample as well as its permittivity and permeability. Thus, it is important to model the coil and the patient as a single system in order to include the interaction of the electric and magnetic fields (ibr01b).

Theoretical models can be broken down into two major approaches. Some authors (tro04, hou00) have pursued analytic solutions of simple cylindrical or spherical phantoms while others have utilized numerical methods. Numerical methods include finite difference time domain (FDTD) (ibr00a, col02), finite element modeling in the
frequency domain (FEM) (vau94, yan02) and the method of lines (bod03, jin99). While numerical methods can be applied to the complex geometry and heterogeneity of in-vivo imaging (yan02), analytic methods can be used to examine underlying mechanisms and provide conceptual understanding.

3.1.1.1 Dielectric Resonance

A term that is often used in $B_1$ field modeling is *dielectric resonance*. This term comes from the field of microwave engineering to describe the reflections imposed on electromagnetic waves at the interface between different media.

To understand such reflections, it is helpful to consider an infinite medium containing an evacuated cavity. To simplify the discussion, it can be assumed that the waves are restricted to travel along the $x$-direction.

Starting with Maxwell’s equations, it can be shown (lor88) that the electric and magnetic fields are governed by the following coupled, differential equations

$$\nabla^2 \mathbf{E} - \varepsilon \mu \frac{\partial^2 \mathbf{E}}{\partial t^2} - \mu \sigma \frac{\partial \mathbf{E}}{\partial t} = 0$$

$$\nabla^2 \mathbf{B} - \varepsilon \mu \frac{\partial^2 \mathbf{B}}{\partial t^2} - \mu \sigma \frac{\partial \mathbf{B}}{\partial t} = 0$$

where $\sigma$ is the conductivity of the medium, and $t$ is time. Solutions to these equations are of the form

$$\mathbf{E}(\mathbf{x}, t) = E_+ e^{j(kx - \omega t)} + E_- e^{-j(kx - \omega t)}$$

$$\mathbf{B}(\mathbf{x}, t) = B_+ e^{j(kx - \omega t)} + B_- e^{-j(kx - \omega t)}$$

where $E_\pm$ and $B_\pm$ are chosen to satisfy boundary conditions, $\mathbf{x}$ is a position vector, and $j$ is the imaginary number $\sqrt{-1}$. The vector $\mathbf{k}$ is the so-called wave vector which points in the direction of propagation and is related to the wavelength by
\[ |\mathbf{k}| = \frac{2\pi}{\lambda}. \]  

3.4

The substitution of equation (3.3) into equation (3.2) sets the following restriction on the wave vector

\[ |\mathbf{k}|^2 = \epsilon \mu \omega^2 \left[ 1 + \frac{j \sigma}{\omega \epsilon} \right]. \]  

3.5

Due to differences in wave propagation in the cavity and in the material surrounding it, the result in equation (3.5) produces three different cases. First, in a non conductor when \( \sigma \) is zero, the magnitude of the wave vector is \( \omega (\epsilon \mu)^{1/2} \). This gives the free-space result in the evacuated cavity such that

\[ |\mathbf{k}| = \omega (\epsilon_0 \mu_0)^{1/2} = \omega c \]  

3.6

where \( \epsilon_0 \) and \( \mu_0 \) are the permittivity and permeability of free space, and \( c \) is the speed of light in a vacuum. The dependence on \( \epsilon \) and \( \mu \) also gives the aforementioned shortening of wavelength in various media.

In the second case, when \( \sigma \) is very large compared to the product of \( \omega \) and \( \epsilon \), the imaginary term on the right hand side of equation (3.5) dominates. This leads to the approximation

\[ |\mathbf{k}| \approx \sqrt{\mu \sigma \omega} \sqrt{j} = \sqrt{\frac{\mu \sigma \omega}{2}} [1 + j] = \beta + j \alpha. \]  

3.7

Substituting this complex value for the wave vector into equation (3.3), the imaginary component of the wave vector will behave as an exponential decay term. The characteristic length of this decay is called the skin depth, \( \delta = 1/\alpha \). As the conductivity \( \sigma \) approaches infinity, the skin depth would become so short that no energy would
propagate in the material surrounding the cavity, and all the energy of the electromagnetic wave would be confined to resonate in the cavity. If one considers only waves propagating along the $x$-axis, the exponential terms in equation (3.3) will reduce to rightward directed waves (where $+k \cdot x = +kx$) and leftward travelling waves (where $-k \cdot x = -kx$). Enforcing the boundary condition that the fields vanish at the edge of the cavity will create perfect reflections which create the resonant condition that

$$|k|a = n\pi$$

where $n$ is a positive integer.

In the third case, when the imaginary term in equation (3.5) is too large to be negligible and too small to dominate the real term, the magnitude of the wave vector will be a complex number. While more rigorous treatments of this boundary value problem can be found in references (jac75) or (lor88), it will suffice in this discussion to point out that a resonant condition similar to the second case will develop. The principal difference is that the reflections at the edges of the cavity are no longer perfect reflections (i.e. the skin depth would no longer approach zero). This implies that a fraction of the energy of the EM wave leaks from the evacuated cavity into the surrounding material while the remainder of the energy is reflected back into the cavity. The interference of the leftward- and rightward-directed waves will establish a resonant wavelength in the cavity. These resonant wavelengths will not necessarily satisfy the condition seen in equation (2.8) for the case of a perfectly conducting medium due to the energy lost into the surrounding material.
In microwave engineering, materials of mismatched dielectric constants are sometimes used to create such a resonant condition. These so-called dielectric resonantors are used to replace bulky waveguides and metallic, resonant cavities with lightweight, inexpensive materials which are easy to fabricate (poz90). Because the ratio of the amplitudes of the reflected and transmitted waves is controlled by the dielectric constants, the amount of energy confined within the dielectric material is greater for a large mismatch of dielectric constants.

Several authors have applied dielectric resonance theory to high field MRI to explain $B_1$ heterogeneity. Because of the relationship between $B_1$ and MRI signal intensity described in Chapter 1, models of the $B_1$ field have been used to explore the dependence of image heterogeneity on sample geometry and permittivity. For example, Kangarlu, et. al. (kan99) used a simple analytic model for a spherical phantom imaged at 8 Tesla. This model related dark and bright rings observed in images of a spherical phantom to constructive and destructive interference of the EM waves.

The effect of varying the dielectric constant has also been investigated in imaging experiments. Pure water phantoms were observed by Tofts, et. al. to exhibit dielectric resonance even at 1.5 Tesla (tof97). The authors point out that this is because pure water has low conductivity (the effect of conductivity is further discussed below) and a high dielectric constant ($\varepsilon_r=80$) as a result of the electric dipole moment of water molecules. Experiments on phantoms containing oils of low dielectric constant (kan99, tof97) showed less evidence of dielectric resonance. This can be attributed to the prediction from dielectric resonance theory that a material with low $\varepsilon_r$ would allow more transmission and less reflection at the interface between the phantom and air.
Among models of dielectric resonance, it is widely agreed that the conductivity of the sample dampens the resonant effect (hou00). This is because the attenuation of reflected waves avoids patterns of constructive and destructive interference (yan02). In theoretical models (hou00) and experimental studies (tof97, kan99) phantoms of increased conductivity exhibited less contrast between bright and dark regions in MR images.

3.1.1.2 Field Focussing

Some theoretical models (tro04, hou00) have pointed out another contribution to $B_1$ heterogeneity in addition to dielectric resonance. Hoult defines field focusing as an increase in the $B_1$ field in the central region of the imaging volume. Field focusing differs from dielectric resonance because dielectric resonance occurs when the dimensions of the sample to be imaged is an integer multiple of the half-wavelength of the EM wave. On the other hand, field focusing occurs consistently in the central region regardless of the size of the sample.

Unlike dielectric resonance, this second form of inhomogeneity increases the usefulness of ultra high field MRI. Because field focusing occurs consistently in the central region of the imaging volume, it opposes the previously mentioned limitations in RF penetration predicted by Röschmann (rös86).

The nature of field focusing is seen in the competition between the displacement current and the free charge current as seen in Ampère’s law (vau94)

$$\nabla \times \frac{B}{\mu} = \mu_0 \left( J_f + \frac{\partial D}{\partial t} \right)$$

3.9
where $\mathbf{B}$ is the magnetic flux density, $\mu_0$ is the permeability of free space, $\mathbf{J}_f$ is the free current density, and $\mathbf{D}$ is the electric flux density. The effective $\mathbf{B}_1$ field in the sample is clearly affected by two terms on the right side which function as current densities: the free current density, $\mathbf{J}_f$, and the displacement current density, $\partial \mathbf{D}/\partial t$ (yan02). The free current density, $\mathbf{J}_f$, is related to the electric field inside the sample as

$$\mathbf{J}_f = \sigma \mathbf{E}. \quad 3.10$$

As previously mentioned, the electric field inside the imaging volume creates localized heating. This lost energy is written off by Vaughan and co-workers (vau94) as induced eddy currents which do not contribute to the $\mathbf{B}_1$ field. The second current density term in equation (3.9) becomes increasingly significant at high frequencies because of its definition as a time derivative.

Because the displacement current density is dependent on the rate of change of the electric polarization of the sample (lor88), it follows that the displacement current term should not be significant below 100 MHz (jin99). In both the analytic model of Tropp (tro04) and numerical simulations of Yang and co-workers (yan02) the displacement current enhancement compensates for eddy current losses in the central region. Vaughan and co-workers (vau94) go on to state that brain imaging with high field MRI is possible due only to the “fortuitous coincidence of tissue $\sigma/\varepsilon$.”

From the preceding discussion, it can be concluded that models of $\mathbf{B}_1$ field distribution in ultra high field MRI experiments must include a great deal of information concerning the geometry and electrical properties of the sample to be imaged. Furthermore, numerical modeling (ibr00a) has shown that the design of the RF coil must also be included. In Ibrahim’s study, simulated phantom images created with a numerically
modeled coil and with a simulated $B_1$ field in the absence of a coil showed subtle
differences related to the geometry of the coil and its circuitry. Thus a discussion of $B_1$
field heterogeneity is not complete without a review of coil designs.

3.1.2 RF Coils

Because the interactions between coil and sample have been shown by numerical
models to be a significant factor in MRI, coils must be carefully chosen, particularly in
ultra high field MRI. There are several types of coils for use in MRI, and each has
advantages and disadvantages.

3.1.2.1 RF Coil Designs

The RF coil is an antenna which can transmit the RF pulse and/or receive and
subsequent signal emitted from the sample. The simplest design is a surface coil in the
form of a loop of wire (vla99). The magnetic field produced by a current-carrying loop
such as this can be predicted using the Biot-Savart law to produce a field which drops off
sharply with distance from the coil (vau02). Multiple loops are often used in phased
array coils to (roe90, wri97). This combines increased volume coverage with the SNR
advantages associated with small coils (vla99).

Birdcage coils are cylindrical coils designed to create more homogeneous $B_1$
fields. As stated by Liu and co-workers (liu04), a cylindrical arrangement of infinitely
long rods like that of figure (3.1) will create a uniform magnetic field in its interior if the
current in the $i$th rod, $I_i$, is given by

$$I_i = I_0 \cos \left(2\pi \frac{i}{N} \right)$$

3.11
where $N$, the total number of rods, is very large, and $i$ ranges from 0 to $(N-1)$. Birdcage coils serve as a practical approximation of this cylinder by placing a sufficient number of current carrying rods (or struts) in a cylindrical configuration. Birdcage coils are used clinically in the high-pass configuration shown in figure (3.2). Liu and co-workers (liu04) showed in a recent paper using FDTD simulations that the standard birdcage coil design produced the most uniform $B_1$ field at 64 and 125 MHz in the absence of a patient when compared to shielded variations of birdcage coils. However, when the coil was loaded with a simulated patient, the best SNR, most homogeneous $B_1$ field, and least energy loss was observed in a variation of the birdcage coil surrounded by a conducting shield electrically connected to each end ring.

Transverse electromagnetic (TEM) coils have been widely used in ultra high field MRI (vau01, ibr01b). Figure (3.3) shows that this design borrows the shielding mentioned above for birdcage coils. The placement of the shield is intended to limit electric field losses and therefore lessen the required power (vau94). However, the struts in the TEM coil in figure (3.3) differ from those in the birdcage coil in that the TEM struts have copper rods at their ends which are electrically connected to the shield. A free-floating copper cylinder is held electrically isolated from these rods. Thus, the struts themselves serve as tunable capacitors (ibr03) unlike the high-pass birdcage coil. This allows the coil to be tuned for the specific dielectric and conductive properties of the patient or phantom to be imaged.

3.1.2.2 Coil Excitation Modes

Many oscillating systems from musical instruments to the resonant cavity described in this chapter are capable of resonating at multiple frequencies; TEM coils
used in MRI also exhibit multiple operating frequencies. In the example of the struts which produced a uniform magnetic field in the previous section, the phase difference in the current of adjacent struts was $2\pi/N$. If the currents, $I_i$, were replaced with sinusoidal functions of time with phase shifts similar to equation (3.11), then

$$I_i(t) = I_{\text{max}} \cos(\omega t + 2\pi i / N)$$ \hspace{1cm} 3.12

for $i$ ranging from 0 to $N-1$. It follows from equation (3.12) that the phase difference between $I_{N-1}$ and $I_0$ would be $2\pi/N$ which is the same as the phase shift between each pair of adjacent struts.

Because of this phase difference, each strut will experience its maximum current at a different time. This maximum current occurs when the argument of the cosine function in equation (3.12) is equal to zero. For a phase shift of $2\pi/N$, this gives a unique result for each strut such that the time of maximum current occurs when

$$t_{\text{max},i} = 2\kappa \pi - \frac{2\pi i}{N \omega}$$ \hspace{1cm} 3.13

where $\kappa$ is a positive integer reflecting the periodicity of the current in time. Since this maximum current is experienced by the $i$th strut followed immediately by strut $(i-1)$, the current distribution has an effective component rotating azimuthally around the cylinder.

This azimuthal component of the current creates a restriction which allows only discrete values for the phase shifts between adjacent struts. For example, if each adjacent pair of struts had a phase shift of $\pi/N$, then strut $N-1$ and rod 0 would be nearly $\pi$ radians out of phase. This would create destructive interference which would dampen an azimuthal component with that particular phase shift between adjacent struts.
In practical implementation for MRI, the struts of the TEM coil will likely have small differences in capacitance, these differences will lead to phase shifts in the currents that resonate in the struts (vau94). As above, these phase differences will give rise to azimuthal components in the current distribution which Vaughan and co-workers modeled as a Fourier series of clockwise and counterclockwise traveling waves such that
\[
I = \sum_{M=0}^{\infty} \left[ A_M \cos(\omega t - M\phi + \iota) + B_M \cos(\omega t + M\phi + \zeta) \right]
\] 3.14
where \(I\) is the current, \(t\) is time, \(\phi\) is the azimuthal position, and \(A_M, B_M, \iota\) and \(\zeta\) are arbitrary amplitude and phase constants. Continuity conditions require that resonant modes exist when the phase difference between adjacent struts is \(2M\pi/N\) where \(M\) varies from 0 to \(N/2\). For \(M\) greater than \(N/2\), degenerate modes occur (e.g. a phase difference of \(9\pi/8\) produces the same current distribution as a phase difference of \(\pi/8\)).

To clarify the effect of these strut-to-strut phase differences on the \(B_1\) distribution a simple program was created, *TEMcoil_B1.pro* (see Appendix A). Using Ampere’s law, the magnetic field created at a point a distance \(r\) from an infinite wire carrying current \(I\) in the \(+z\) direction is given by
\[
\mathbf{B} = \frac{\mu_0 I}{2\pi r} \mathbf{\phi}
\] 3.15
where the unit vector \(\mathbf{\phi}\) is given by the right hand rule (lor88). The vector components of \(\mathbf{B}\) in the \(x-y\) plane must be combined to simulate the \(B_1\) field in the interior of an unloaded 16-strut TEM coil. Clearly, this simple model does not include eddy currents, displacement currents nor mutual inductance (ibr01b) between struts. Two-dimensional maps of the \(B_1\) field were created for figure (3.4) for modes 0 through 8 by introducing
phase differences between struts. Rather than model the current as it changes in time, the program relies on a snapshot of the $B_1$ field to demonstrate its distribution. In figure (3.4), the field distribution for mode 1 closely resembles the uniform field predicted above for an infinite, hollow cylinder of section 3.1.2.1. The other modes generally display a weak $B_1$ field in the interior with varying patterns of constructive and destructive interference in the periphery.

This simple model explains some features of the effect of coil mode on the $B_1$ field distribution. More sophisticated models are needed to predict coil performance. For example, Vaughan and co-workers (vau94) included dispersion, the difference in wave propagation velocity as a function of frequency in the copper end rings, to predict the resonant frequencies of the azimuthal current distribution of a TEM coil. The transmit/return plot as a function of frequency for a 16-strut TEM coil loaded with a sphere containing Gd-DTPA and NaCl (see below) is shown in figure (3.5). The 9 resonances correspond to the modes 0 through 8 as predicted above. Since equation (3.14) models the current distribution as a Fourier series, it follows that the amplitudes of the resonances in figure (3.5) represent weights which vary as a function of the phase shifts between struts (vau94).

3.1.3 Experimental Field Mapping

From the previous discussion, it is clear that a great deal of effort has been placed in theoretical modeling and predicting the behavior of the $B_1$ field in ultra high field MRI experiments. Next, it is necessary to determine a method to provide experimental evidence of the behavior of the $B_1$ field.

3.1.3.1 Effective and Nominal Flip Angle
Based on the theoretical arguments above, it is entirely reasonable to approach $B_1$ field mapping with the assumption that significant variations in $B_1$ will occur in the imaging volume. From the equations derived in the previous section, it will be shown below that mathematical relationships can determine the effective flip angles which produce an observed signal behavior. However, fitting a signal curve as a function of effective flip angles requires a mathematical link between flip angles and the experimental variable which controls in flip angles. The $B_1$ field strength is determined by the power delivered to the RF coil.

In order to establish the desired transmit amplifier setting, a sequence should be selected which will produce a maximal signal when the equilibrium magnetization is rotated 90° into the transverse plane. The transmitted power required to produce the RF pulse which maximizes signal can serve as a reference for a 90° pulse. However, the heterogeneity of flip angles requires that this sequence must be capable of localizing the signal from a selected volume with dimensions which are small compared to the length scales of the heterogeneities.

The pulse sequence STEAM (stimulated echo acquisition mode) can be used to determine the RF power setting needed to determine a 90° pulse within a desired volume (per89). The STEAM sequence is similar to the STE sequence seen in figure (2.8) except that slice selective gradients are applied during each pulse, and each slice select gradient is directed along a different axis. This excites three orthogonal slices, and a stimulated echo is observed only in the volume that is formed by the intersection of the three slices (i.e. the target volume in which excitation is produced by all three pulses). If the three pulses in a STEAM sequence are all identical, then equation (2.24) predicts that the STE
signal will be proportional to \(\sin^3 \theta\). Clearly, the transmission power setting which produces the maximum STE signal will correspond to 90°. This transmission power will be called the reference power setting.

Throughout this work, the term *nominal flip angle* is used to refer to the flip angle occurring in the location of the STEAM sequence volume based on the reference power setting. For example, if \(P_0\) is the power required to maximize the STEAM sequence, it must therefore produce a field \(B_{1,0}\) sufficient to rotate the magnetization in the test location through 90°. If a 45° angle is desired, then the required field is \(\frac{1}{2} B_{1,0}\) which corresponds to \(\frac{1}{4} P_0\) because the intensity of the wave is proportional to the square of its magnetic field (lor88). Henceforth, instead of stating the reference power employed to produce a desired rotation in the target location of a STEAM sequence, it will be sufficient to refer to the desired flip angle in the target volume as the nominal flip angle and to state the location of the target volume in the STEAM sequence.

A distinction is drawn between the *nominal flip angle* and the *effective flip angle* at locations throughout the imaging volume. By its definition, the nominal flip angle refers to the flip angle in the target volume of the STEAM sequence. The effective flip angle in a given voxel is the flip angle inferred for that voxel based on its signal behavior. It will be convenient to use the flip angle ratio, \(a_1\), where

\[
a_1(x, y) = \frac{\theta_{\text{eff}}(x, y)}{\theta_{\text{nom}}}
\]

and \(\theta_{\text{eff}}\) and \(\theta_{\text{nom}}\) are the effective and nominal flip angles, respectively. After determining the transmit amplifier setting \(T_{90}\) associated with a 90° flip angle, the nominal flip angle for a given transmission setting (in decibels) can be determined by
\[ \theta_{\text{nom}} = 90^\circ \cdot 10^{(T_x - T_{\text{ref}})/20} \]  
\[ \text{3.17} \]

where \( T_x \) is the user defined transmit amplifier setting on the control console. The factor of 20 is the product of the factor of 10 associated with the definition of the decibel and a factor of 2 for the quadratic relationship between power and \( B_1 \) field strength.

### 3.1.3.2 Relating the MR Signal to Magnetization

The previous discussions on pulse sequences have dealt with the dynamics of magnetization vectors under the influence of RF pulses and fluctuating magnetic field gradients. In order to transition from theoretical discussions to experimental results, the relationship between the MR signal from a voxel and its magnetization vector must be specified. The signal strength of the echo as measured in the RF coil is also dependent on the reception characteristics which must also be discussed.

Haacke, et. al. (haa99) reason that the measured signal \( S(x,y) \) from a voxel located at position \((x,y)\) is proportional to the transverse magnetization \( M_{xy} \) as well as the receive field of the coil \( B_{1\text{rec}}(x,y) \) such that

\[ S(x,y) \propto M_{xy}(x,y)B_{1\text{rec}}(x,y). \]  
\[ \text{3.18} \]

The term \( B_{1\text{rec}}(x,y) \) accounts for the possibility that there are regions of an image where the signal intensity may be weak or regardless of the size of the flip angle in that voxel.

The \( B_{1\text{rec}} \) term has been equated (hou00) to the component of the \( B_1 \) field rotating in the opposite sense of the component that appears at rest in the rotating reference frame. Hereafter, \( B_1^+ \) will be used to indicate the component of \( B_1 \) that is at rest in the rotating frame and thus causes rotation of the magnetization as was seen in Chapter 2. \( B_1^- \) will be used to indicate the component rotating in the opposite sense. The argument which
equates $B_{1r}^{\text{rec}}$ and $B_{1r}$ borrows heavily from the Reciprocity Theorem used in antenna theory. The Reciprocity Theorem states that the transmission pattern and the reception pattern for an antenna are identical (stu98). Antenna engineers frequently use this result to avoid the difficult process of determining the reception pattern of an antenna simply by measuring its transmission pattern.

Applying the Reciprocity Theorem to RF coils in MRI, $B_{1r}^{\text{rec}}$ is simply $B_{1r}$ as viewed propagating toward the source rather than away from it. This is significant in MRI because Friis’ equation (stu98) requires that the polarization of the incoming wave and the polarization of the receive pattern of the antenna match. Matching the polarization of the receive pattern and the echo signal requires a change of vantage point which the direction of its polarization and therefore its direction of rotation. This is taken to imply that $B_{1r}^{\text{rec}}$ is $B_{1r}$.

While the Reciprocity Theorem is believed to hold true for low field MRI, results at 3 Tesla (sei04), 7 Tesla (col02), and 8 Tesla (ibr04) suggest that reciprocity is not valid at increased field strength. It is the intent of this work to avoid the assumption of reciprocity and to refer to $B_{1r}^{\text{rec}}$ as defined in equation (3.17) simply as the receive sensitivity of the coil.

3.1.4 Pulse Sequences and Data Analysis

In the following sections, specific approaches to $B_{1}$ field mapping are discussed using pulse sequences and image analysis methods. These methods will be grouped by the relevant pulse sequences discussed in section 2.2.

3.1.4.1 GRE $B_{1}$ Field Mapping
In GRE sequences employing long TR intervals ($TR \gg T_1$), the exponential term in equation (2.16) becomes negligible, and the expression for the magnitude of the transverse components of magnetization can be greatly simplified to

$$M_{xy} = M_0 \sin \theta e^{-TE/T_1^*} \quad 3.19$$

for $TR \gg T_1$. Substitution of this result into equation (3.18) suggests the following signal dependence:

$$S = M_0 B_1^{rec} \sin \theta e^{-TE/T_1^*}. \quad 3.20$$

The terms in equation (3.19) can be grouped together by their spatial dependence into a parameterized form for the signal such that

$$S_i(x, y) = a_0(x, y) \cdot \sin(a_1(x, y) \cdot \theta_{i, nom}) \quad 3.21$$

where $a_0$ and $a_1$ are constants of proportionality, $S_i(x, y)$ refers to the signal produced in a voxel located at point $(x, y)$ in the $i$th image, and $\theta_{i, nom}$ is the nominal flip angle associated with the transmitted power selected for the $i$th image. This simple result creates a connection between the $B_1$ field and signal intensity in long TR, GRE images.

3.1.4.1.1 Multiple angle method

The term multiple angle method will be used to describe the process of collecting multiple GRE images over a range of transmit amplifier settings to give several values for $\theta_{i, nom}$ in equation (3.21). If $n$ single-slice images are acquired such that they are identical in every way except for the setting of the transmitted power, then the $n$ signals produced in a voxel located at point $(x, y)$ can be fitted as a function of $\theta_{i, nom}$. These data can then be fit with the parameterized form of equation (3.21). By equation (3.16), the matrix of
values \( a_1(x,y) \) can then be displayed as a map of the flip angle ratio. Using equation (2.6) in Chapter 2, where

\[
\theta_{\text{eff}}(x,y) = a_1(x,y) \cdot \theta_{\text{nom}} = \gamma B_1^+(x,y)t \quad 3.22
\]

where the matrix of \( a_1(x,y) \) values serves as a map of the effective \( B_1^+ \) field strength relative to the nominal \( B_1^+ \) determined in the target volume of the STEAM sequence.

By inspection of equation (3.20), the parameter \( a_0(x,y) \) in equation (3.21) includes the effect of the \( B_1^\text{rec} \) term. In homogeneous media, this provides a useful map of the RF coil receive sensitivity. However, the other terms on the right hand side of equation (3.20) make \( a_0 \) also dependent on proton density and \( T_2^* \). Thus in heterogeneous media such as the human brain, the individual contributions of proton density and receive field strength on \( a_0 \) values can not be separated.

3.1.4.1.2 Double Angle Method

The double angle method (ins93, sto96) also uses the signal from a gradient echo sequence with \( TR \gg T_1 \). However, in order to reduce the time required to acquire multiple data points, one can perform two GRE scans in which all parameters are kept constant except that the nominal flip angles of \( \theta_1 \), and \( \theta_2 \) are selected such that \( \theta_2=2\theta_1 \).

Using the trigonometric identity

\[
\sin(2\varphi) = 2 \cos \varphi \sin \varphi , \quad 3.23
\]

the ratio of the second signal, \( S_2(x,y) \), to the first, \( S_1(x,y) \), is

\[
\frac{S_2}{S_1} = \frac{\sin \theta_2}{\sin \theta_1} = \frac{2 \cos(\theta_1) \sin(\theta_1)}{\sin(\theta_1)} = 2 \cos \theta_1 . \quad 3.24
\]

By using the result of equation (3.24), the double angle method involves taking the voxel-wise ratio of two gradient echo scans where the nominal flip angle of the second is twice
that of the first. The effective flip angle at a given location is a function of the ratio of
the signal intensities of the two images such that
\[
\theta_{\text{eff}} = \cos^{-1} \left[ \frac{S_2}{2S_1} \right].
\]

While this method has the advantage of requiring only two images, it is also more
susceptible to the image noise. Furthermore, for computational implementation, it is
important to avoid situations where noise fluctuations might drive the ratio of \(S_2/S_1\) to a
value greater than unity and thereby cause an error in calculating the inverse cosine. A
comparison of the multiple angle and double angle methods is presented below.

3.1.4.2 Spin Echo Method

A variation on fitting a curve to multiple points was used by Barker, et. al. (bar98)
for a spin echo sequence as seen in figure (2.6). From Table (2.1), the flip angle
dependence of the signal from a spin echo sequence would be given by
\[
S = \sin^3 \theta_i e^{-TE/T_2}
\]
when the first and second RF pulses in figure (2.6) are \(\theta_i\) and 2 \(\theta_i\) respectively. Images
were acquired for a range of values for \(\theta_i\) and fit with a parameterized form of equation
(3.26). Figure (3.6) shows a comparison of the sharp peak of the graphs of \(\sin^3 \theta\) and \(\sin \theta\). The \(\sin^3 \theta\) curve is flatter in the region of \(\theta=0,\) and \(180^\circ\). This leads to uncertainties in
curve fitting those areas, particularly when noise is present in the echo signal are few data
points are available (bar98). On the other hand the sharp peak of the \(\sin^3 \theta\) curve is
advantageous when setting the transmission power required for a nominal flip angle of
90° (per89) as was employed in the STEAM sequence which also demonstrates a \(\sin^3 \theta\)
dependence.
3.1.4.3 Multiple echo method

The multiple echo method was employed by Akoka and co-workers (ako93) to reduce the number of required scans to just one. Using a stimulated echo sequence of the form of figure (2.8) with flip angles $\theta$, $2\theta$ and $\theta$; they collected echoes E1 and E3 in Table (2.1). After reconstructing separate images for the SE signal (E1) and the STE signal (E3), two images were generated. Substituting equation (3.23) into the ratio of the signal intensities of gave

$$\frac{S_{STE}(x,y)}{S_{SE}(x,y)} = \frac{\frac{1}{2} \sin \theta \sin 2\theta \sin \theta \exp(-2\tau_1/T_2 - \tau_2/T_1)}{\sin \theta \sin^2 \theta \exp(-2\tau_1/T_2)} \approx \cos \theta$$

when the interval $\tau_2$ was short compared to the $T_1$ of the sample. While the authors showed successful field maps in phantoms and in-vivo, the method involves taking the ratio of signals which can produce spurious results in the presence of image noise.

3.1.5 Experimental Objectives

In the experimental section of this chapter, results from mapping the $B_{1}^{+}$ and $B_{1}^{rec}$ fields for a simple system of a spherical phantom are compared with numerical simulations. Data were gathered for the spherical phantom in a 16-strut TEM coil using six of its nine modes to characterize these modes. Lessons learned from phantom studies were applied to in-vivo field mapping and imaging.

3.2 Methods

3.2.1 MRI system

All the images were acquired on the 8 Tesla Magnex superconducting whole body magnet at Ohio State University (rob99) with acquisition done by a Bruker Avance
console. Gradient echo images were used for all field-mapping experiments using the Bruker module *gefi_tomo*.

### 3.2.2 Coils

To compare the double angle and multiple angle methods for gradient echo $B_1$ field mapping, phantom and *in-vivo* images were acquired. A single TEM coil was used in field mapping studies. For imaging a spherical phantom, a closed-end configuration of coil was needed with additional copper foil enclosing its ends. The foil was kept in the electrical contact with the copper foil of the outer shield, and a cylindrical styrofoam insert was used to hold the sphere in place. For *in-vivo* imaging, the copper foil and styrofoam were removed, and the coil was used in an open-ended configuration. A coaxial acrylic cylinder was placed between the patient and the struts as described below.

The coil was made from a 34 cm diameter acrylic cylinder cut to a length of 21 centimeters. *For in-vivo* imaging, the coaxial acrylic cylinder was 24 cm in diameter and was fixed in place by an acrylic ring which spanned the gap between the cylinders. The interior of the outer cylinder was covered in copper foil to function as a shield as described by Liu, *et al.* (liu04). An exploded view of the TEM coils can be seen in figure (3.3).

Sixteen struts were uniformly spaced azimuthally at a distance of 4 cm from the outer cylinder. Previous investigations by Ibrahim, *et al.* (ibr01b) revealed that a significant increase in $B_1$ field homogeneity was obtained when using a 16 strut coil instead of an 8 strut coil. The struts consisted of 3/8” copper rods placed as seen in figure (3.7). Along the axis of the copper rods was placed copper foil wrapped around a teflon cylinder which maintained electrical isolation between the rods and the foil thereby
functioning as a tunable capacitor. One of the interior copper cylinders was connected to
the excitation source through a 50 Ω BNC connector which was grounded to the copper
foil on the outer cylinder. In series with the excitation port was a matching capacitor for
tuning the coil.

The calibration and linearity of the transmit amplifier with the console setting was
verified using a calibrated load. Figure (B.1) in Appendix B shows a plot of measured
power absorbed by the calibrated load and the transmit amplifier setting $T_x$ in equation
(3.17). The figure demonstrates close agreement with the exponential dependence
indicated in equation (3.17).

3.2.2.1 Coil Tuning

Tuning the coils and selecting the mode of operation was accomplished with a
Hewlett-Packard 4195A Network Analyzer. In T/R mode, the network analyzer
transmits over a range of frequencies and measures the reflection coefficient for the coil.
Resonant modes are seen in figure (3.5) as a decrease in the return loss (poz90). This
mode is useful for determining the mode to which the coil is tuned.

To decrease signal loss, impedance matching is important between the 50 Ω
cabling and the coil. Impedance matching was ensured by examining a Smith plot of a
coil once its desired mode was selected. A Smith plot is a polar diagram of the complex
reflection characteristics of a component (e.g. an RF coil). A matched 50 Ω load would
appear as a point in the center of the chart while any mismatched reactance would cause
the point to be rotated away from the horizontal such that a negative reactance (a
capacitative mismatch) would be rotated below the horizontal line.
In Smith chart mode, the HP 4195A also sweeps the frequency of the transmitted signal over a user-specified bandwidth. Because of the frequency dependence of the load’s impedance characteristics, the frequency sweep creates a curve on the Smith chart. A perfectly balanced 50 Ω load would intersect the horizontal axis at the desired frequency of 340.56 MHz. During tuning, the lowest possible reactance (preferably below 1 Ω) was attempted while maintaining a 50 Ω resistance. For higher order modes, this was not always possible as is seen in comparing the Smith chart for modes 0 and 3 in figure (3.8). While the impedance for mode 0 was 49.0 + j0.25, the impedance in mode 3 was 39.1 -j0.26. While this impedance mismatch decreased both the power transmitted and the power received, it should be noted that the multiple angle method is able to fit weak signals and show relative receive sensitivity and flip angles over a wide range of signal strength.

The transmit/return plot as a function of frequency for a 16-strut TEM coil loaded with a sphere containing Gd-DTPA and NaCl (see below) is shown in figure (3.5). The 9 resonances correspond to the modes 0 through 8 as predicted above. Since equation (3.14) models the current distribution as a Fourier series, it follows that the amplitudes of the resonances in figure (3.5) represent weights which vary as a function of the phase shifts between struts (vau94).

3.2.3 Phantom Imaging

The 18.5 cm sphere within the closed-end coil contained water, a gadolinium-based MRI contrast agent and sodium chloride. The contrast agent was added to decrease the $T_1$ of the solution in the ball to decrease the scan time required for each experiment. A sufficient amount of gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) was
added to make its concentration 0.5 mM. The sodium chloride concentration was 0.125 M to bring the conductivity to physiologic levels (ibr03).

The phantom images had a field of view of 20 cm x 20 cm with a matrix of 256 x 256. They were acquired in 10 parallel slices 5 mm thick and spaced 15 mm in between in axial, sagittal and coronal planes as specified below. To allow longitudinal relaxation of the solution in the sphere to satisfy the approximation in equation (3.20), a long TR of 2000 msec was chosen because the $T_1$ of 0.5 mM a Gd-DTPA was determined to be 350 msec at 8 Tesla in previous work (sch02). A constant TE of 6.3 msec was used for all scans to provide maximum signal. The RF pulse used in each image was a tri-lobed sinc function shape with a bandwidth of 750 Hz and a duration of 8.000 msec.

3.2.4 In-vivo Imaging

A normal 34 year-old volunteer was selected for field mapping and imaging in accordance with a protocol approved by the Internal Review Board of the Ohio State University Medical Center. The same TEM coil used for the phantom studied was utilized after the copper end caps and sphere were removed.

Only modes 0 through 2 were tested after the phantom data showed that the higher modes produced large regions of signal loss. For modes 0 and 1, the scanning was performed with the excitation port of the coil placed both in front of the patient’s head and in back along the midline. Mode 2 was utilized only with the excitation port in the back. For each combination of mode and placement of the excitation port, a series of low resolution GRE images were acquired for the multiple angle method, and high resolution images were acquired for anatomic images.

3.2.5 Curve Fitting
The IDL program *double_flip.pro* (see Appendix A) was created to calculate flip angle maps for the double angle method using equation (3.25). The program simply parses through the image pixel by pixel and calculates the arcosine. When the ratio in the argument of the arcosine function is greater than unity, logical statements are used to place a value of zero in the flip angle map.

To create field maps for the multiple angle method images as a function of nominal flip angle, the IDL program *fit_sin_neg.pro* (see Appendix A) was created to fit equation (3.21) to the image data. In fitting a sine function to each voxel in magnitude images which have strictly positive values, a method must be implemented to handle the negative values of the sine function for nominal flip angles greater than 180º. Specifying a fitting function with an absolute value would not work because the IDL routine *curvefit* requires the continuity of the fitting function and its partial derivatives. The program *fit_sin_neg.pro* resolves the confusion over negative values by a two-pass fitting method. First the signals from a single voxel are sorted as a function of their nominal flip angles. A first-pass fitting is the performed using equation (3.21) on the data points up to the first peak. From the fitted value for $a_1$, the fitted sine function should cross the horizontal axis when the product $a_1 \theta = 180^\circ$. Therefore the sign of any subsequent signals is negated when the nominal flip angle satisfies $180^\circ / a_1 < \theta_{nom} < 360^\circ / a_1$. Furthermore, the assignment of negative signs can be generalized for arbitrary values of the effective flip angle by multiplying the signal by a factor, $f_p$, such that

$$f_p = (-1)^n \theta / 180$$

(3.28)
for $\theta_i$ in degrees. This will subsequently allow the sine function to be fit to all the data points without confusion between the negative values in the fitting equation and positive data points.

To compare the performance of the double angle and the multiple angle methods, images were tested by both methods. For both the phantom studies, the program $double\_flip.pro$ was run on two images selected from the multiple angle method for which the criterion $\theta_2=2\theta_1$ was satisfied. This minimized set up errors and ensured that all scanning parameters were the same for both methods.

### 3.3 Results

#### 3.3.1 Phantom Data

**3.3.1.1 Phantom Data Fitting Parameters**

Figure (3.9) shows the typical behavior of data points and the fitted parameters $a_0$ and $a_1$ from equation (3.21). The spatial location indicated by the letter A shows a signal behavior typical for points with a large value for $a_0$ and a small value for $a_1$. The signal intensity at point A reaches its maximum signal intensity at a larger nominal flip angle than the other curves. This is because it has a smaller effective flip angle for a given nominal flip angle than points B and C. The lower flip angle manifests itself as a small value for $a_1$ at point on the parameter map on the right side of figure (3.9). The peak value of the curve is determined by its $a_0$ value which appears to be relatively high compared to point B. The opposite case (low $a_0$ and high $a_1$) is seen in the data associated with point B. The maximum and minimum signal intensities fall at smaller nominal flip angles because the $a_1$ value for curve B is higher. On the other hand, a low $a_0$ value places the maximum signal intensities in the curve considerably below the other.
curves. This is consistent with the inverse relationship between $B_1^+$ and $B_1^{\text{rec}}$ noted by Seifert, et. al. (sei04). Finally, point C is characterized by relatively high values on both the $a_0$ and $a_1$ maps. This implies a high maximum signal occurring at a lower nominal flip angle.

3.3.1.2 Comparison of Fitting Methods

A comparison of the double angle method and the multiple angle method for RF field mapping can be seen in figure (3.10). The unprocessed image and the thresholded image are also included to show the regions of extremely weak signal as well as ghosting along the phase encoding direction. At first glance, the multiple angle method gives a field map which appears smoother. The curvature of the dark lines in the field map from the double angle method suggests that the ghosts exert considerable influence on the resulting field map. On the other hand the multiple angle method displays scattered points which give incongruous values for $a_1$. These points tend to coincide to regions of low signal in which the increased influence of noise pulled the fitting routine toward erroneous high values for $a_1$. It should be noted that similarly elevated values in the field map do not appear in the double angle method because many points in regions of low signal and high noise are excluded (i.e. set to zero) by the program double_flip.pro because the argument of the arccosine function is greater than one.

3.3.1.3 Comparison of Coil Tuning Modes

Figures (3.11a), (3.11b) and (3.11c) show image data along with parameter maps for $a_0$ and $a_1$ in axial, coronal and sagittal planes for modes 0 through 5. In this figure, only the central slice of a ten-slice acquisition is shown in order to convey the general effect of tuning modes.
Before discussing general attributes of the modes, it should be noted that regions of low signal in the image data significantly affect the fitted parameter maps. In such regions, small fluctuations due to noise can be significant in proportion to the signal. For example, the sum of a signal plus noise can be interpreted by the fitting algorithm as a high-frequency, low-amplitude oscillation which will produce a very large value for $a_1$ and a small value for $a_0$. On the other hand, the fitting algorithm may produce large values for $a_0$ and small values for $a_1$ if the sum of the signal and noise are fitted with a very low frequency sine wave as an approximation to a straight line.

Generally, the location of the strut connected to the excitation port produces increased signal. This increase is believed to be a result of the emission of RF energy from the fine tuning capacitor connected to the excitation port. This capacitor allows flexibility in tuning and impedance matching. It is a necessary component of the coil, and the image brightening associated with it cannot be avoided. Conversely, the effect of the capacitor cannot be easily included in the numerical model (ibr03).

In figure (3.11a), mode 0 is seen to produce a fairly uniform image intensity throughout the phantom with the clear exception of the central region. Comparison of all three planes reveals that this region is cylindrical along the z axis. This implies that it may be useful for imaging cortical regions of the brain rather than central structures such as the brain stem or limbic system.

The images from mode 1 do not demonstrate the uniform $B_1$ excitation predicted in figure (3.4). While the central region is better visualized in mode 1 images than in mode 0 images, the $a_1$ parameter map shows that the central region is surrounded by a region of low signal. This trend has been observed in 8 Tesla human images (cha04) in
which central structures are often visualized at the expense of cortical regions. Curiously, the images are brighter on the side distal to the excitation port.

The star-shaped pattern of signal loss in mode 2 axial images appears to be a result of an $a_0$ parameter map with low central values and an $a_1$ map with low values found in a small central region and in spokes radiating outward. This pattern is somewhat similar to that seen in the simplified model in figure (3.4). In that figure, modes 2 and above showed a weak center and alternating patterns of constructive and destructive interference in $B_1$ vectors peripherally. This pattern continues in modes 3, 4 and 5. In the parameter maps for these modes, many low-signal regions produce the incongruous values for $a_0$ and $a_1$ mentioned in this section. For the sake of completeness, all 10 slices are presented for each mode in three planes in Appendix C, figures (C.1) through (C.18).

3.3.2 In-vivo Data

3.3.2.1 In-vivo Data Fitting Parameters

In section 3.1.4.1, it was explained that the $a_0$ term in equation (3.21) contains not only the receive field, $B_1^{\text{rec}}(x,y)$, but also the proton density and $T_2^*$ exponential decay factor. These two terms may vary significantly between voxels due to anatomic structure. While the homogeneity of the phantom made $a_0$ purely dependent on $B_1^{\text{rec}}$, this is not the case in in-vivo field mapping as seen in figure (3.12). In this figure, the $a_1$ parameter map shows a smooth variation in $B_1^+$ in the posterior region of the brain. However, in the $a_0$ parameter map gray matter and white matter patterns can be visualized. These millimeter-sized variations are in stark contrast to the $a_0$ parameter.
map from figure (3.11a) which verifies that the proton density and $T_2^*$ decay term in equation (3.20) contribute to $a_0$.

Because anatomical variations on $a_0$ maps occur on short length scales, a simple low-pass filter was applied to mediate their appearance. A boxcar smoothing filter was applied only to $a_0$ maps using the IDL routine called smooth which replaces the value of an element of an array (or image) with the average of its nearest neighbors in a box seven pixels wide by seven pixels long. The 7x7 boxcar filter was applied after the images had been resized from 256 x 64 to 256 x 256 using the IDL routine rebin which uses linear interpolation to create the additional array elements. Therefore, the 7x7 boxcar filter was smoothing over a square with sides of 5.5 millimeters. This lengthscale appeared to be sufficient to remove most of the anatomic detail except for the ventricles and other large CSF-containing spaces.

3.3.2.2 In-vivo Field Mapping

The influence of the tuning and positioning of the coil on in-vivo field maps is summarized in figure (3.13). Using “cut-away” views with the left superior quadrant of the brain removed, $a_0$ and $a_1$ parameter maps show in three dimensions the results of field mapping. Because the in-vivo data exhibit less symmetry than the phantom data shown above, this three-dimensional summary was chosen rather than the multiple planes which summarized the phantom data in figure (3.11). The complete set of in-vivo field maps and anatomic images are found in Appendix D figures (D.1) through (D.21).

In figure (3.13) parameter maps of mode 0 show the greatest $a_0$ and $a_1$ values near the location of the excitation port. Generally, in mode 0, much less signal is received in regions of the brain distal to the excitation port. This differs significantly from the
phantom image results in figure (3.11a) which demonstrated an axial cylinder of low signal surrounded by a ring of strong signal.

Mode 0 images demonstrate weak signals in lateral slices. This is seen in the mode 0 in-vivo images in figure (D.1) which were used to generate the mode 0 parameter maps with posterior placement of the excitation port. This is a result of an asymmetry in the $a_0$ and $a_1$ parameter maps. Moving from left to right through the $a_0$ and $a_1$ maps in figures (D.2) and (D.3) shows the asymmetry between $B_1^+$ and $B_1^{rec}$ noted by Seifert, et al. (sei04). This is more easily visualized in figure (3.14) in which the 20 sagital slices of a0 and a1 parameter maps from figures (D.2) and (D.3) are rendered in coronal planes. Because of the low resolution in the left to right direction, the 20 slices were interpolated into 260 pixels using the IDL linear interpolation command rebin. Clearly, the $a_0$ parameter suggests greater receive sensitivity on the patient’s right side while the $a_1$ parameter map indicates greater flip angles on the opposite side.

When the coil is tuned to mode 0, but the excitation port is placed anteriorly in front of the patient’s face, the pattern is similar to that of mode 0 with the excitation port placed posteriorly, as above. Figure (D.4) also shows the brightest signal intensity in the medial slices. Again, this is a result of the disparity in the distributions of the receive sensitivity in figure (D.5) and figure (D.6). However, in this case, the $a_0$ distribution is stronger on the patient’s left side as seen in figure (3.15). Although the asymmetry of the $a_0$ and $a_1$ parameter maps is not as pronounced as in figure (3.14), this implies that the mode 0 field distributions are similar with respect to the rotation of the coil by 180°. The small differences in the overall pattern were attributed to slight differences in coil tuning.
For images acquired in mode 1 with the port placed posteriorly, figure (D.7) shows increased signal intensity centrally surrounded by regions of signal loss. A similar pattern as was seen in the phantom data from figures (3.11a) through (3.11c). It is significant to clinical imaging in mode 1 that the asymmetry of $a_0$ and $a_1$ displayed in mode 0 does not appear in the medial slice of figure (3.16) for parameter maps acquired in mode 1 with the excitation port placed posteriorly. Generally, mode 1 will produce strong signals in the central region because both $B_1^+$ and $B_1^{rec}$ are relatively uniform in that region. This trend continues in the images of mode 1 with the excitation port placed anteriorly in figure (3.17). When the coil is tuned to mode 1, there is greater signal intensity in the central region of images despite the change in the location of the excitation port. It is interesting to note in comparing mode 1 images in figures (D.7) and (D.10) that the signal loss observed posterior to the central sulcus is reversed to signal loss anterior to the central sulcus when the excitation port is switched from posterior to anterior.

Finally, images were acquired for more 2 in the posterior excitation port configuration. All three slices of both $a_0$ and $a_1$ parameter maps in figure (3.18) show generally increased signal intensity in lateral slices. The increased signal intensity in lateral slices is also seen in the images in figure (D.13). Images for mode 2 with the port placed anteriorly were not acquired because the data from the first mode 2 configuration were too complicated to be useful for any realistic, imaging application.

It should be noted that the curve fitting process in the in-vivo images was hindered by the use of a small number (either 3 or 4) flip angles mandated by the length of time the patient was placed in the magnet. This can lead to difficulties in fitting data.
points in regions of high flip angles as seen in figure (3.19). A suspicious region of low flip angles surrounded by high flip angles is indicated with a black cross in the inset image. The data points from that voxel are plotted in the figure as a function of nominal flip angle along with the fitted curve (solid line) determined by the program fit_sin_neg.pro. While the solid curve fits the points closely, another reasonable fit can be obtained with a higher flip angle as shown with the dashed line. While both curves appear to be proper fits, the location of the suspicious region suggests that the higher flip angle curve (dashed line) is the correct fit. In this case, a greater number of data points would allow the program to determine more reliably which fitting function was more accurate.

3.3.3 Potential Utility of In-vivo Imaging in Modes 0, 1 and 2

In the previous section, it was observed that mode 0 produced images which demonstrated increased signal close to the excitation port and near the midline of the brain. Mode 1 was characterized by strong signals both near the excitation port and distal to it. Strong signals were also observed centrally with nearby regions of signal loss. Finally, mode 2 produced strong signals in lateral slices and distal to the excitation port. This section describes our initial exploration into the use of complex $B_1^+$ and $B_1^{rec}$ patterns for high-performance localized imaging at 8 Tesla. Additional images can be found in Appendix D, figures (D.16) through (D.21).

Figures (3.20) and (3.21) show two coronal slices through the brain stem and cerebellum which were acquired in mode 0 with the excitation port placed posteriorly. Because the slice in figure (3.20) was located more anteriorly than that in figure (3.21),
the characteristic loss of lateral signal in mode 0 is seen as well as an increase in image noise.

Based on these posterior slices acquired in mode 0, the orientation of the coil was reversed, and images of the frontal lobe and eyes were acquired in coronal slices in mode 0 with the excitation port placed anteriorly. Figure (3.22) shows that these images display the same loss of lateral signal with increased distance from the excitation port. Unfortunately, the locations of the eyes are too lateral to produce strong signals in most slices. Furthermore, the images are strongly degraded by motion artifacts as well as significant signal loss and image distortion as a result of susceptibility differences in the anterior slices. The entire set of images can be found in figure (D.17).

Images acquired with the coil tuned to mode 1 are shown in figures (3.23) and (3.24) for posterior placement of the excitation port. In a slice located posterior to the central sulcus in figure (3.23), significant signal loss is observed centrally. However, overall signal is higher in medial slices near the central sulcus with good SNR in lateral regions of the temporal lobes, as in figure (3.24). This pattern of signal loss comparable to that noted in field mapping in the spherical phantom seen in figure (3.11) when mode 1 exhibited a slight increase in the central region adjacent to regions of signal loss.

When the excitation port is rotated an anterior placement relative to the head, the region of signal void also rotates to the front while strong signals are observed posteriorly. This trend was noted in figure (3.17). Thus the images acquired in mode 1 with the excitation port anterior to the head generally show more uniform images in the posterior regions of the brain as noted in figure (3.25).
Finally, the images acquired for mode 2 in figures (3.26) and (3.27) show significant signal losses medially. However, it should be noted that increased signal is observed in the lateral regions of the temporal lobes of both images. This suggests that this mode may be useful to supplement the signal loss observed for the other modes in these anatomical regions.

It is interesting to note that the images acquired in different modes display complementary signal intensities. Figure (3.28) shows three slices in the anatomical region posterior to the central sulcus which was imaged in three different modes: mode 0 with the port placed posteriorly, mode 1 with the port placed anteriorly and mode 2 with the port placed posteriorly. Because patient motion could not be avoided while removing the patient from the bore of the magnet and re-tuning the mode with the network analyzer, it is impossible to image precisely the same slice in each. However, slices were selected to be as similar as possible for the different modes, and the apex of the tentorium was selected as a reference to translate the images in two dimensions for alignment of the signal intensity profiles. Simple addition of the signals from these magnitude images (after alignment) shows a more uniform profile in figure (3.29). This suggests a complementarity between the modes which may be used to supplement regions of weak signals by changing the operating mode of the coil.

Unfortunately, the complementarity of the operating modes was not predicted based from the phantom data in figure (3.11). As such, patient immobilization and reproducibility in the in-vivo experiments were not sufficient to make a clear statement about the complementarity of the modes. However, these data appear promising, and future work will be directed to explore this complementarity of modes.
3.4 Conclusions

In comparing the multiple angle method and the double angle method for $B_1^+$ mapping, it was determined that the multiple angle method is more stable against image noise provided that a sufficient number of images are acquired and fit with equation (3.21). This method was applied to the spherical phantom to map the effective fields for modes 0 to 6 of a TEM coil. These data showed that mode 3 through 5 showed significant signal loss in the interior of the phantom. The weak interior signals seen in modes 0 and 2 were contrasted by strong central signals in mode 1.

A similar complementarity was observed in modes 0 through 2 when applied to human brain imaging. While mode 1 was useful in visualizing a large portion of coronal slices distal to the location of the excitation port, it was noted that the mode 0 and mode 2 images produced stronger signals in medial and lateral areas, respectively. This suggests that coil tuning may prove useful in imaging specific anatomic targets using ultra high field MRI.
Figure 3.1 An array of rods placed in a cylindrical orientation. For sinusoidal currents oscillating in the rods, a uniform, circularly-polarized magnetic field can be created in the interior if each rods is phase shifted by $\pm \frac{2\pi}{N}$ relative to its neighboring rods.
Figure 3.2 Basic design of a high-pass birdcage coil. The gray boxes represent capacitors which give the coil its high-pass operating characteristics.
Figure 3.3 Exploded view of the TEM coil. Copper rods (a) are inserted through teflon rods wrapped in copper foil (b) and placed inside a grounded cylinder (c) wrapped in copper foil.
Figure 3.4 Simulated magnitudes and directions for a snapshot map of the $B_1$ field in the interior of an unloaded 16-strut TEM coil. The program TEMcoil_B1.pro places the vector in the lower right-hand corner as a unit length to maintain constant scaling between the 9 calculated modes.
Figure 3.5 Transmit/return loss plot as a function of frequency for a 16-strut coil loaded with a sphere containing water, Gd-DTPA and NaCl. Nine modes are clearly visible.
Figure 3.6 Comparison of the graphs of \( \sin \theta \) (solid) versus \( \sin^3 \theta \) (dashed).
Figure 3.7 Oblique view of the TEM coil used for head imaging. The interior copper cylinders insulated from the adjustable copper rods by Teflon functioned as variable capacitors.
**Figure 3.8** Screen dumps from the Hewlett-Packard 4195A Network Analyzer show Smith charts for mode 0 (left) and mode 3 (right). These demonstrate the resonant frequency of the particular mode by the position of the cursor (diamond) which should be on or near the horizontal axis to indicate a small reactance. The resistance and reactance are indicated on the left by the letters R and X, respectively. The deviation of the impedance of mode 3 was typical for tuning higher order modes.
Figure 3.9 Signal intensity as a function of nominal flip angle for three points indicated by A, B and C in a uniform phantom. From the appearance of the images and parameter maps above, the coil is clearly tuned to mode 0. The curves are overlayed with their fitted form of equation (3.21).
Figure 3.10 Comparison of the double angle method of flip angle mapping versus the multiple angle method in the spherical phantom. (A) Axial gradient echo image from a TEM coil tuned to mode 1. (B) The same gradient echo image thresholded to highlight ghosting along the phase encoding direction. (C) Flip angle map from the multiple angle method. (D) Flip angle map from the double angle method.
**Figure (3.11a,b,c)** A summary of modes 0 through 5 for a central slice in 3 planes. The location of the excitation port is shown with a red dot only in the mode 0 image for each plane. The location was kept the same for each all modes within a given plane.
Figure 3.12 A central axis sagittal image is shown with its \( a_0 \) parameter map (center) and \( a_1 \) parameter map (right). The smooth variation in flip angles is contrasted with the anatomical details which are carried into the \( a_0 \) map as a result of its dependence on proton density and \( T_2^* \) decay.

<table>
<thead>
<tr>
<th>Mode 0</th>
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<tr>
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<td>Anterior</td>
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Figure 3.13 A summary of \textit{in-vivo} field mapping for modes 0, 1 and 2 with the excitation port placed anteriorly and posteriorly. Data for mode 2 were acquired only for the port in the posterior side. Generally, mode 0 produces the greatest signal intensity near the location of the excitation port. Mode 1 produces central excitation, at the expense of surrounding regions of signal loss. Mode 2 has significant signal loss centrally, but increased signal laterally. Detailed images and parameter maps can be found in figures (D.1) through (D.15).
Figure 3.14 Mode 0 / Port Posterior Three slices for $a_0$ (top) and $a_1$ (bottom) in-vivo parameter maps rendered into coronal planes for field mapping in mode 0 with the excitation port placed posteriorly. In the posterior portion of the head, near the excitation port, the $a_0$ and $a_1$ maps show an asymmetric distribution.
Figure 3.15 Mode 0 / Port Anterior Three slices for $a_0$ (top) and $a_1$ (bottom) *in-vivo* parameter maps rendered into coronal planes for field mapping in mode 0 with the excitation port placed anteriorly. While $a_0$ and $a_1$ parameter maps show the same asymmetric distribution as mode 0 with a posterior port (figure (3.14)), the pattern is reversed due to moving the excitation port 180° with respect to the patient’s head.
Figure 3.16 Mode 1 / Port Posterior Three slices for $a_0$ (top) and $a_1$ (bottom) in-vivo parameter maps rendered into coronal planes for field mapping in mode 1 with the excitation port placed posteriorly. Generally, the $a_0$ and $a_1$ parameter maps are more uniform in the medial slice. This allows mode 1 to image the central volume of the head.
Figure 3.17 Mode 1 / Port Anterior Three slices for $a_0$ (top) and $a_1$ (bottom) in-vivo parameter maps rendered into coronal planes for field mapping in mode 1 with the excitation port placed anteriorly. Greater receive sensitivity ($a_0$) and excitation ($a_1$) are seen in the posterior slice, distal to the excitation port.
Figure 3.18 *Mode 2 / Port Posterior* Three slices for $a_0$ (top) and $a_1$ (bottom) *in-vivo* parameter maps rendered into coronal planes for field mapping in mode 1 with the excitation port placed anteriorly. Greater receive sensitivity ($a_0$) and excitation ($a_1$) are seen in the posterior slice, distal to the excitation port.
Figure 3.19 The difficulty of fitting equation (3.21) to only three data points is shown for the $a_1$ (flip angle) parameter map for mode 0 with the excitation port placed anteriorly. The plot shows data from the voxel indicated by a cross in the inset $a_1$ map. Even though the fitted curve (solid) appears appropriate for these data, this curve gives the suspicious low flip angle region (yellow) in the inset parameter map. A second fitted curve (dashed) also gives good agreement with these data as well as a higher $a_1$ value which demonstrates better agreement with the surrounding region in the inset parameter map. This ambiguity in curve fitting is avoided by using more data points, particularly for high flip angle regions.
Figure 3.20 GRE Image of the cerebellum and occipital lobe of a normal volunteer acquired in mode 0 with the excitation port located posteriorly. The image was masked to remove flow artifacts in the inferior region. The frequency encode direction was superior to inferior, a flip angle of 30° was used and the acquisition matrix was 512 x 384 yielding a resolution of .5 mm (left-to-right) and .4 mm (superior-to-inferior) in the raw image. For the purpose of display, the image was expanded to a 512 x 512 matrix through linear interpolation using the IDL function congrid.
Figure 3.21 Coronal image from the same set of slices as figure (3.20). Because this slice was more distal from the excitation port (more anterior), significant signal loss and increased noise are seen in the lateral regions.
Figure 3.22 Coronal image acquired in mode 0 with the excitation port placed anteriorly while using the same imaging parameters as figures (3.20) and (3.21). The eyes are poorly visualized due to lateral signal loss, and susceptibility differences are manifested as signal loss (S) and image distortion (I).
Figure 3.23 Coronal image acquired in mode 1 with the excitation port placed posteriorly while using the same imaging parameters as figures (3.20) through (3.22). Significant signal loss is seen in medial structures for slices posterior to the central sulcus. Also, signal intensity is generally weak superiorly.
Figure 3.24 Coronal image acquired in mode 1 with the excitation port placed posteriorly while using the same imaging parameters as figure (3.23) except that the image is 1.5 cm anterior. In this medial region, the images are more uniform and do not exhibit the signal loss noted in figure (3.23). As in figure (3.23), the superior region of the image demonstrates weaker signal intensity.
Figure 3.25 Coronal image acquired in mode 1 with the excitation port placed anteriorly while using the same imaging parameters and in the same anatomic region as figure (3.23). In the region posterior to the central sulcus, the images are more uniform and do not exhibit the signal loss noted in figure (3.23). Again the signal loss in the superior region is noted.
Figure 3.26 Coronal image acquired in mode 2 with the excitation port placed posteriorly. While signal losses are noted medially and superiorly, image intensity in the lateral regions is significantly greater than that observed in mode 0.
Figure 3.27 Coronal image acquired in mode 2 with the excitation port placed posteriorly. Unlike the other high-resolution, anatomic images in figures (3.20) through 3.26, the frequency encode direction was changed to left to right to mediate flow artifacts. The frontal lobe is shown to demonstrate the strong lateral signals associated with mode 2. Again, weak signals are noted superiorly.
**Figure 3.28** Slices near the same location in the region posterior to the central sulcus were selected are shown for three different modes. The pink lines loosely show the location of the signal intensity profiles which are shown below each image. The profiles were selected to intersect the apex of the tentorium. The strong lateral signals of mode 2 complement the weak signals in the other modes.
Figure 3.29 When the images in figure (3.28) are coregistered about the apex of the tentorum a more uniform profile results.
CHAPTER 4

$T_1$ MAPPING

To realize the clinical use of magnetic resonance imaging at 8 Tesla, $T_1$ relaxation times must be known to optimize pulse sequences for $T_1$-weighted images, for in-vivo evaluation of contrast agents and for assessment of contrast mechanisms. While preliminary $T_1$ values at 7T (kwa01) and 8T (sch02) were described in prior works, the accuracy of common $T_1$ measurement techniques with whole-body ultra high field systems must be evaluated for their robustness against $B_1$ field inhomogeneity throughout the imaging volume. In this chapter, the theory of commonly used $T_1$ measurement techniques will be described. Experimental data and results of computer simulations will demonstrate that the inversion recovery method, while time-consuming, is the most reliable method for mapping $T_1$ values in light of $B_1$ field inhomogeneity.

4.1 Theory

As was seen in Chapter 2, $T_1$ is, by definition, the time constant of the exponential re-growth of the longitudinal magnetization following rotation by a radio-frequency (RF) pulse. To measure this re-growth experimentally requires one to alter the magnetization in a manner which can be mathematically modeled and then to observe the return of the magnetization to equilibrium. In MRI, independent treatment of the signal from each
voxel can create a map of $T_1$ values to describe their spatial distribution. The most common methods for doing this are based on spin-echo methods, gradient-echo methods and steady-state methods. Each will be considered below.

4.1.1 Spin-Echo Methods

4.1.1.1 Saturation Recovery Spin Echo (SR-SE)

The simple spin-echo sequence pictured in figure (2.6) can be used as a method to measure $T_1$. In Chapter 2, the time-dependent behavior of a SE sequence was discussed only for a single pair of pulses $\theta_1$ and $\theta_2$ in equation (2.23). This description of the magnetization is complete only when subsequent RF pulses are given after a long repetition time, $TR >> T_1$. When this condition is satisfied, the $z$-component of magnetization has sufficient time to relax back to its equilibrium value, $M_0$. On the other hand, if a shorter TR is chosen, complete relaxation will not occur and the $z$-component, $M'$, will be less than $M_0$. The subsequent pulse which rotates $M'$ into the transverse plane will produce an echo of smaller amplitude than the previous echo by a factor of $M'/M_0$.

When a SE sequence is used with flip angles $\theta_1=90^\circ$ and $\theta_2=180^\circ$, the echo amplitude follows an exponential curve of the form (haa99)

$$S(t) = S_0 \left[ 1 - e^{-TR/T_1} \right] e^{-TE/T_2} \quad 4.1$$

where $S_0$ is the maximum signal. Equation (4.1) is plotted in figure (4.1) as a function of $TR$ with $T_1$ chosen arbitrarily to be 0.4 seconds. The shape of the curve confirms the previous argument that strong signal intensity is obtained for long $TR$ because the magnetization vector is allowed to relax to its full equilibrium value.
To determine $T_1$ in an imaging experiment, the SE sequence is used to acquire multiple SE images for different values of $TR$. The choice of $TR$ values must cover the range of signal intensities in figure (4.1). When plotted versus TR, the signal from a given voxel is expected to follow an exponential growth. However, with high-field MRI equation (4.1) can not be applied to the signal of each voxel in an imaging experiment because a perfect 90° and 180° flip angle is not present throughout the imaging volume. The signal behavior as a function of TR for arbitrary values of $\theta_1$ and $\theta_2$ is best fit with a parameterized equation of the form (kin99a)

$$S(x, y, TR) = a_0(x, y)\left[\frac{1 + a_2(x, y)e^{-a_1(x, y)TR}}{1 + a_3(x, y)e^{-a_1(x, y)TR}}\right]$$

4.2

where $a_0$, $a_1$, $a_2$ and $a_3$ are fitting parameters. A map of $T_1$ values can subsequently given by $T_1(x, y) = 1/a_1(x, y)$.

A practical problem arises from using equation (4.2) to fit a curve to data points from an SE sequence. Because this fitting equation has four parameters to be optimized, computer algorithms for curve fitting can sometimes diverge toward parameter values which appear to fit the data, but produce unrealistic results for $T_1$. Furthermore, the SR-SE is method is often used for $T_1$ measurements (tra96) without testing flip angle variation while using a simplified version of equation (4.1) such that

$$S(x, y, TR) = a_0(x, y)[1 - a_2(x, y)e^{-a_1(x, y)TR}].$$

4.3

Thus, it is useful to determine, from experimental data, the range of flip angles over which equation (4.3) can be used in SR-SE experiments.

Ultra high-field MRI provides a useful experimental setting for testing methods of $T_1$ measurement against the flip angle variations shown in Chapter 3. In a uniform
phantom of known $T_1$, a range of flip angles can be experimentally determined over
which equation (4.3) can produce the known $T_1$ value. Numerical simulations and
experimental data will be presented in this chapter to determine this range of flip angles.

The measurement of $T_1$ using a series of SE sequences with variable TR values is
often called saturation recovery (SR). The term saturation comes from spectroscopy
where multiple RF pulses are used to ensure complete rotation of the magnetization into
the transverse plane (mar80). In imaging, a single 90° pulse is used in place of this train
of pulses in order to minimize RF transmission into the patient (kin99b). However, the
term saturation recovery is still applied to the method. In this work, the abbreviation SR-
SE is borrowed from reference (kin99a) to refer to $T_1$ mapping using a series spin echo
images of varying TR.

4.1.1.2 Inversion Recovery Spin Echo (IR-SE)

In order to extend the range of values over which the z-component of
magnetization relaxes, an additional 180° pulse is employed at the beginning of a spin-
echo sequence (mar80) followed by a delay period called the inversion time (TI).
Because the initial 180° pulse inverts the magnetization, this sequence is often called
inversion recovery (IR). A pulse sequence diagram can be found in figure (4.2).

For the idealized case of an IR sequence with a series of perfect 180°-90°-180°
pulses, the signal intensity will evolve (haa99) as

$$ S(t) = S_0 \left[ 1 - 2 e^{-TI/T_1} \right] e^{-TE/T_2}. $$

Clearly, this curve has the same exponential decay constant as in equation (4.1) with the
exception that the magnetization starts at $S(0) = -S_0$. This increases the so-called dynamic
range over which the magnetization is sampled as seen in figure (4.3). By distributing
the data points over a greater range, the curve fitting process is more stable against signal noise variations (kay91). Because of this extended range, this method is often regarded as the “gold standard” (kin99a) to which other $T_1$ measurement methods are compared (blü93, cra88).

For mapping $T_1$ with MRI, a series of $N$ images must be acquired with an IR sequence covering a range of $TI$ values. For each phase of the $N_{ph}$ encoding steps in each of the $N$ images, $TR$ is chosen to be at least five times as long as the longest $T_1$ in the imaging volume. This requirement ensures sufficient relaxation to ensure that each inversion pulse is acting upon the equilibrium magnetization. Because of the increased dynamic range and the return to equilibrium before each inversion pulse, the use of IR is considered the gold standard for $T_1$ measurements. However, very long scan times result when complete relaxation is required for each phase encoding step in each image. The duration of the entire experiment is at least $N_{ph} \cdot N \cdot TR$ assuming negligible set up time between the acquisitions.

In this work the abbreviation (IR-SE) is borrowed from reference (kin99a) to refer to the creation of $T_1$ maps using an IR sequence as in figure (4.2). To determine the echo amplitude for a three pulse sequence, a phase coherence diagram can be constructed with flip angles $2\alpha$, $\alpha$ and $2\alpha$ occurring at time $t=0$, $TI$ and $TI + TE/2$ as in figure (4.4). The pathway producing the IR echo at time $TI + TE$ is indicated by the bold line in that figure. From table (2.1) in Chapter 2 with $TR \gg T_1$, the echo amplitude can be determined to be

$$S(TI + TE) = \left[1 - (1 - \cos 2\alpha) e^{-T_1/T_1} \right] \left[\sin^3 \alpha e^{-T_2/T_1}\right].$$

Because the magnetization is allowed to return to equilibrium before each inversion pulse, this formula can be applied to each phase encoding step in each image. In
parameterized form, the signal from a given voxel at location (x,y) can be given as a function of TR by

\[ S(x, y, TI) = a_0(x, y)\left[1 - a_2(x, y)e^{-a_1TI}\right]. \]

It should be noted that equation (4.6) has the same form as equation (4.3) with the substitution of \( TI \) in place of \( TR \).

Using numerically simulated data, Kingsley (kin99a) modeled an IR-SE pulse sequence of the form \( 2\alpha - \alpha - 2\alpha \). These simulations showed that that the IR-SE method produced reliable values for \( T_1 \) when \( \alpha \) deviated from 90° by up to 50%. In this chapter additional numerical simulations as well as experimental data will be used to determine the range of flip angles over which reliable \( T_1 \) values can be obtained from the IR-SE method.

4.1.1.3 Inversion Recovery using multiple echo Spin Echo (IR-RARE)

Because of the long duration of IR sequences, many authors have attempted to capitalize on the dynamic range of IR-SE data while minimizing scan times. One such method uses multiple echoes from a rapid acquisition with relaxation enhancement (RARE) sequence (hen86) to accelerate the rate of data acquisition.

The IR-RARE sequence has additional refocusing pulses which create these echoes. The extra echoes can then be used to fill additional lines of k-space. If \( N_{\text{echo}} \) refocusing pulses are added, the number of \( TR \) intervals needed to fill k-space and create an image is decreased by a factor of \( 1/N_{\text{echo}} \).

Before multiple refocusing pulses can be employed in \( T_1 \) mapping, the additional \( T_2 \) weighting of the additional echoes must be taken into account. Because the dephasing and rephrasing pathways (i.e. sloping lines) in figure (4.5) carry a factor of \( e^{-\tau/T_2} \), each
subsequent echo is more significantly affected by spin-spin relaxation. To downplay the influence of T2 weighting, echoes can be placed selectively in k-space to control their effect on the reconstructed image. Because the central region of k-space controls the contrast of the reconstructed images, the earlier echoes with less T2 weighting are placed there. Then the echoes which are more heavily T2 weighted can be placed in the more distal regions of k-space.

In this work, the abbreviation IR-RARE will be used to refer to T1 mapping through the acquisition of IR images with a multiecho readout as seen in figure (4.5). When using the IR-RARE method, the effect of T2 relaxation is minimized by placing the later echoes in the more distal regions of k-space. Also, TR is chosen to sufficiently long to allow relaxation between TR intervals. Because of these two factors, equation (4.6) can be used to fit the signal intensity of each voxel in the reconstructed image as a function of the TI associated with that image. Phantom and in-situ data will be presented in this chapter to determine the reliability of the IR-RARE method.

4.1.2 Gradient Echo Method

Spoiled GRE sequences can also be used to create T1 maps. Starting with the steady-state magnetization in a GRE sequence in equation (2.16), the echo signal from a particular voxel can be expressed (haa99) as

$$S(\theta) = \frac{S_0 \sin \theta (1 - e^{-TR/T_1})e^{-TE/T_2}}{1 - \cos \theta e^{-TR/T_1}},$$

where $S_0$ is an empirical constant and $\theta$ is the effective flip angle in that voxel. Following the method of Venkatesan, et. al. (ven98), equation (4.7) can be rearranged by multiplying both sides by $(1 - \exp(-TR/T_1))/\sin \theta$ such that
Equation (4.8) represents the GRE signal strength in the form of a linear equation of an independent variable \( w = \frac{S(\theta)}{\tan \theta} \) and a dependent variable, \( h = \frac{S(\theta)}{\sin \theta} \). The slope of this linear equation is the exponential factor, \( e^{-TR/T_1} \). After acquiring multiple data points over a range of flip angles and fixed \( TR \), linear regression can be used to determine \( T_1 \) uniquely.

This method has also been implemented in a two-point method requiring only two scans to be performed (imr99). However, it should be noted that this study was performed at 0.5 Tesla, and flip angle heterogeneity was not significant. In cases where flip angle heterogeneity is significant, this method requires a flip angle map (ven98) to determine the flip angle terms in equation (4.7) for each voxel.

The principal problem with this method is the sensitivity of equation (4.8) in the range of small flip angles. The two significant terms in that equation contain trigonometric functions in their denominators. Small fluctuations in small flip angles can lead to large errors in the linearized variables \( w \) and \( h \) (sch02). Furthermore, the flip angle can vary significantly across slice profiles for large flip angles (sch02, par01). Therefore, this method is hindered by its strong dependence on flip angles.

4.1.3 Steady State Methods

Clearly, the spin echo and gradient echo methods above do not cover all the possible imaging sequences in MRI. Many methods have been proposed for \( T_1 \) measurements which utilize steady-state imaging sequences. The magnetization vector
achieves a steady-state value when subjected to multiple RF pulses closely spaced by a short interval $TR$ between subsequent pulses. Because the steady state is dependent on the flip angle of each pulse and the spin-lattice relaxation in the longitudinal direction, it follows that the establishment of the steady state is a function of $T_1$.

4.1.3.1 Single Shot $T_1$ Mapping

This is the theory behind the Look-Locker (loo70) method which is commonly used in NMR spectroscopy to measure $T_1$. In this method, a series of RF pulses of constant flip angle are used to prepare the steady state for which the transverse magnetization is measured. The approach to steady state and the known flip angle are used to calculate $T_1$.

To model the behavior of the magnetization when subjected to a train of pulses with flip angle $\alpha$, Deichmann and Haase (dei92) argued that the magnetization will follow the exponential approach to an equilibrium magnetization, $M_{SS}$, such that the magnetization immediately before the $i$th pulse, $M_{i-1}$ follows

$$M_{i-1} = M_{SS} - (1 + M_{SS})\left[\cos \alpha \cdot e^{-TR/T_1}\right]^{-1}.$$  \hfill (4.9)

By inspection, equation (4.9) is the form of an exponential decay where

$$S(t) = b_0 + b_1 e^{-t/T_1^*}$$  \hfill (4.10)

where $t=(i-1)TR$. The effective timescale of the decay curve, $T_1^*$ is related to $T_1$ by

$$\frac{1}{T_1^*} = \frac{1}{T_1} - \frac{1}{T_R} \ln|\cos \alpha|.$$  \hfill (4.11)

It should be noted that the logarithmic term is never positive which implies that the $T_1^*$ rate on the left hand side is always less than or equal to the spin-lattice relaxation rate,
1/\(T_1\). Also, the logarithmic term in equation (4.11) varies significantly over the range of likely flip angles as is shown in figure (4.6).

Because of advances in fast imaging sequences, the Look-Locker method has been applied to so-called single shot techniques or TOMROP (T One by Multiple Read Out Pulses). Nekolla and co-workers (nek92) acquired 16 images over a three second interval to create \(T_1\) maps of rodents. The rapidly acquired images were created with a FLASH sequence (Fast Low Angle Shot) which is a short-\(TR\) gradient echo sequence with a small flip angle. In the case of Nekolla, et. al. a \(TR\) of 2.6 milliseconds was employed.

Single shot techniques have demonstrated a considerable reduction in the time required for acquiring a \(T_1\) map. In addition, Crawley and Hankelman (cra88) showed that a single shot FLASH technique demonstrated acceptable accuracy and precision as well as a brief acquisition.

Single shot methods have been implemented using other fast imaging techniques to generate the images which follow the initial inversion pulse. Echo planar imaging (ste90) and TrueFISP (sch01) have been used with success. However these sequences are not available on the 8 Tesla Whole Body Scanner at Ohio State University. Furthermore, the \(TR\) intervals used in references (cra88) and (nek92) are shorter than the length of RF pulses feasible with the 8 Tesla system. Therefore, single shot methods are not practicable in this work.

4.1.3.2 Multi-shot \(T_1\) Mapping

Several authors have pointed out that the single shot techniques for \(T_1\) mapping can not always be implemented. The short \(TR\) intervals may not be possible due to
hardware limitations (hin88) or gradient rise times for whole body imaging (blü93, dei99). To accommodate longer $TR$ intervals, it is possible to acquire only one image after a delay, $TI$, following the inversion pulse. This creates a single image associated with the delay $TI$. Thus the data can be fit in a pixel-wise fashion in a manner analogous to the IR-SE method.

$$S(x, y, TI) = a_0(x, y)\left[1 - a_2(x, y)e^{-\frac{a_1(x, y)}{T_1}(x, y)TI}\right]$$

where the parameter $a_1^*$ is $1/T_1^*$ as shown in equation (4.11).

While the multi-shot method cannot generate a $T_1$ map as quickly as the single-shot method, the multi-shot method is more rapid than conventional spin echo-based methods. Unfortunately, the $T_1$ values obtained from these methods are sensitive to flip angle variation (blü93, sch01). Blüml and co-workers (blü93) showed at 1.5 Tesla that $T_1$ values from a series of FLASH images could be over 30% above reference values obtained with IR-SE when the flip angle $a$ varied by only $6\degree$.

In the following sections, $T_1$ data from multi-shot FLASH images obtained at 8 Tesla will be shown for a uniform phantom. These results will be compared with the IR-SE method which serves as the reference measurement in this work.

4.2 Numerical Simulations

To predict the results produced by the SR-SE and IR-SE methods, numerical simulations were carried out. These two methods were used because they are the two most commonly used (kin99b) and because an earlier study (kin99a) was available for comparison. Using the formalism introduced above, mathematical models will be developed in this section and computer algorithms will be described.
4.2.1 IR-SE Simulation

A simulation of the IR-SE method is easier to implement than the SR-SE simulation in the following section because of the design of the IR sequence. Since full relaxation can be assumed for \( TR \geq 5 \cdot T_1 \), the inversion pulse for each TR interval is assumed to act upon the equilibrium magnetization (kin99a). This implies that the result from equation (4.5) can be used for the echo amplitude for each TR interval.

To model the IR-SE signal, the simulation assumed a single voxel which is subjected to a pulse sequence of flip angles \( 2 \alpha, \alpha \) and \( 2 \alpha \) occurring at time \( t=0 \), \( TI \) and \( TI+TE/2 \). It should be noted that the inversion and refocusing pulses are assigned a fixed relationship at \( \alpha \) and \( 2 \alpha \). Even though the amplitude of the \( B_1 \) field can vary across the thickness of a slice when using slice selective pulses (par01), the assumption of a fixed relationship between \( \alpha \) and \( 2 \alpha \) is reasonable given the wide spatial variation of flip angles at 8 Tesla, and given that the relationship between flip angle and transmission power produced the reliable field mapping results seen in figure (3.9) of Chapter 3.

The program \textit{ir_sim_5perc350deg.pro} was created in IDL (Research Systems, Inc, Boulder, CO, USA). In the simulation, the flip angle \( \alpha \) was stepped through 10° steps from 10° to 170°. For each of these flip angles, the signal expected from equation (4.5) was calculated for nine different \( TI \) intervals from 25 to 6400 msec. This process was repeated 1000 times for each flip angle. A nominal \( T_1 \) of 227 msec was assumed along with a \( T_2 \) of 250 msec. Random noise of 5% was added to the signal expected from equation (4.5) in order to simulate imaging conditions. The data were then fit with the \( T_1 \) fitting algorithm described in Section 4.3.3 of this chapter.
From the 1000 iterations for each flip angle, a distribution of $T_1$ values is created. The mean and standard deviation of the distribution associated with a given flip angle are then estimates of the robustness of the IR-SE method in the range of that flip angle. For example, in the range of $\alpha = 10^\circ$, all three of the pulses produce very little rotation of the magnetization from equilibrium regardless of the delay $T_I$. As a result, weak signals are expected for that value of $\alpha$, and these weak signals will be strongly influenced by the noise fluctuations. Therefore, in the range of very low flip angles, the distribution of fitted $T_1$ values is expected to cover an extremely divergent range.

Results of the IR-SE simulation will be shown below. By correlating experimental $T_1$ data with flip angle maps created using the multiple angle method in Chapter 3, experimental $T_1$ distributions as a function of flip angle will be compared with the IR-SE simulation in Section 4.4.1 of this chapter.

4.2.2 SR-SE Simulation

In Section I.1.1.a the behavior of the SE sequence was discussed for short $TR$ intervals. Because a short TR interval does not allow the magnetization sufficient time to relax to its equilibrium value, one can not assume that each subsequent RF pulse rotates the magnetization in the same manner as its predecessor. In other words, the use of the formula derived from phase coherence pathways can not be used as it was for simulating IR-SE.

To include the effect of partial relaxation between $TR$ intervals, the rotation of the magnetization vector was calculated using the iterative Bloch equations. In the rotating reference frame (see Chapter 1), the effect of an RF pulse is to rotate the magnetization about the direction of $B_1^+$. Representing the magnetization in a the $x'y'z'$ coordinate
system, a pulse with $B_1^+$ along the $x'$-axis can be represented by a rotation matrix (hva99) given by

$$
R_x(\alpha) = \begin{bmatrix}
1 & 0 & 0 \\
0 & \cos \alpha & \sin \alpha \\
0 & -\sin \alpha & \cos \alpha
\end{bmatrix}
$$

where $\alpha$ is the flip angle. The relaxation of the magnetization vector between pulses can be expressed by

$$
S(t) = \begin{bmatrix}
e^{-t/T_1} & 0 & 0 \\
0 & e^{-t/T_2} & 0 \\
0 & 0 & e^{-t/T_1}
\end{bmatrix}
$$

where $t$ is the time following the most recent pulse. The simulation also takes into account the differing rates of precession about $B_0$ by using a rotation matrix about $z'$ such that

$$
R_z(\theta) = \begin{bmatrix}
\cos \theta & \sin \theta & 0 \\
-\sin \theta & \cos \theta & 0 \\
0 & 0 & 1
\end{bmatrix}.
$$

In the SR-SE simulation, the magnetization after the first pulse $M_1^+$ is given by rotating the magnetization before the pulse $M_1^-$ such that

$$
M_1^+ = R_x(\alpha)M_1^-.
$$

During the interval between the pulses, the magnetization evolves according to the precession matrix $R_{x'}$ in equation (4.15), the relaxation matrix $S(t)$ in equation (4.14), as well as the longitudinal relaxation given by equation (2.7) in Chapter 2. In terms of matrices, this implies that the magnetization before the second pulse is $M_2^-$ given by

$$
M_2^- = R_z(\theta)S(\tau)M_1^+ + (1 - e^{-\tau/T_1})M_0
$$
where $M_0$ is the equilibrium magnetization and the time between pulses $t=TE/2$. The second pulse produces another rotation of the form of equation (4.16) where

$$M^+_2 = R_x(2\alpha)M^-_2. \quad 4.18$$

The echo is produced following another interval of length $\tau$ characterized by relaxation and precession as was given in equation (4.17) where

$$M_e = R_z(\theta)S(\tau)M^+_2 + (1 - e^{-\tau/T_1})M_0. \quad 4.19$$

After the echo, the magnetization will experience precession and relaxation given by

$$M_{TR} = R_z(\theta_{TR})S(\theta_{TR})M_e + (1 - e^{-(TR-TE)/T_1})M_0 \quad 4.20$$

where $\theta_{TR}=(TR-TE)\theta/\tau$ is the precession angle which evolves after the echo assuming that the rate of precession is the same as that before the echo.

The SR-SE simulation program called *th1_th2.pro* was written in the IDL programming language. In this program, this process outlined above was averaged over a uniform distribution of 60 equally spaced values for $\theta$ from 0 to $2\pi$ and repeated over 50 TR intervals to allow the magnetization to establish a steady state. Values for $T_1$ and $T_2$ were both chosen to be 227 and 250 milliseconds to be consistent with the IR-SE simulation mentioned in the previous section. The points were then fitted with equation (4.3) in the same manner used for a single voxel in the SR-SE method. By varying the value of the flip angle $\alpha$ in equation (4.13), a range of flip angle was determined for which the fitted value of $T_1$ is equal to 227 milliseconds.

The motivation for the SR-SE simulation differs slightly than that for the IR-SE simulation. Because of the assumption of complete relaxation between TR intervals, the IR-SE simulation uses the standard formula in equation (4.5) to test the effect of noise
with respect to the accuracy and precision of fitting the data with equation (4.6). Numerical simulations and experimental data will be introduced below to define an effective flip angle range wherein the signal behavior as a function of $TI$ can produce reliable $T_1$ measurements despite typical levels of image noise.

On the other hand, the SR-SE simulation calculates the complex behavior of the magnetization during the build up of a steady state during multiple short-$TR$ intervals. It has been shown by Kingsley (kin99b), that a fitting equation of the form of equation (4.2) should be used. However, the number of parameters in this fitting equation will be shown below cause the fitting algorithm to produce spurious results. The simulated data and experimental measurements presented below will be used to determine an effective range of flip angles over which the simplified form of equation (4.3) can be used to fit SR-SE data within acceptable tolerances.

4.3 Materials and Methods

With the exception of the single-shot steady-state method, all the methods presented in this chapter were utilized for $T_1$ measurements using the 8 Tesla whole-body MRI scanner at the Ohio State University. In addition, numerical simulations were used to predict the behavior of the IR-SE and SR-SE methods.

4.3.1. Phantom Measurements

A uniform, cylindrical phantom filled with a solution of 0.5 mM Gd-DTPA and 0.125 M NaCl was imaged using the SR-SE, IR-SE, IR-RARE and three versions of the multi-shot FLASH method. Because this experiment was aimed at creating a wide range of flip angles, a single excitation port, 16 strut transverse electromagnetic (TEM) head coil was chosen to maximize the variation in flip angle across the cylinder. The coil was
tuned to mode 1 using the HP 4195A Network Analyzer as outlined in Chapter 3. The sodium chloride was added to dampen the dielectric resonance pattern noted in Chapter 3. The contrast agent gadolinium diethylenetriamine pentaacetic acid (Gd-DPTA) was added to increase the relaxation rate of the phantom and allow shorter repetition times.

Testing of the gradient echo $T_1$ mapping method in Section 4.4.2.2 was performed on a cylindrical bottle of diameter 11.5 centimeters. The bottle was filled with a mixture of gelatin, sodium chloride and copper sulfate (CuSO$_4$). Again, the sodium chloride was added to damp the dielectric resonance pattern. Copper sulfate is a commonly used compound for increasing the relaxation rate in phantoms. The same 16-strut, single excitation port coil was used in mode 1.

4.3.1.1 Spin Echo $T_1$ Measurements

The three SE methods (IR-SE, SR-SE and IR-RARE) used the same geometry: 20cm field of view, 256 x 192 matrix, and 5 mm axial. The IR-SE and IR-RARE methods used a $TE$ of 19.2 milliseconds, $TR$ of 3000 milliseconds, and $TI$ ranging from 80 to 2950 milliseconds. The same $TE$ was chosen for the SR-SE method, but $TR$ was allowed to vary from 80 to 3000 milliseconds.

The nominal transmission power setting required for a 90° RF pulse (8 millisecond, sinc3 pulse) was determined from the maximum signal from a STEAM sequence (see Chapter 3). This power setting was used for the 90° RF pulse in the IR-SE, SR-SE and IR-RARE sequences with a nominal flip angle of $\theta_{\text{nom,1}}=90^\circ$. To ensure that a larger range of flip angle was obtained in the experiment, this power setting was increased by 4 dB such that $\theta_{\text{nom,2}}=142^\circ$. This increase pushed the power required for a
$180^\circ$ RF pulse to the limit feasible for the chosen pulse length and RF power amplifier. When the nominal flip angle was increased to $\theta_{\text{nom},1}=142^\circ$, each of the three SE sequences was repeated. The scatter plots of fitted $T_1$ as a function of flip angle in Section 4.4.2.1 are obtained by combining the $T_1$ maps associated with nominal flip angles $\theta_{\text{nom},1}$ and $\theta_{\text{nom},2}$ for each of the three methods.

A flip angle map was acquired using the multiple angle method in Chapter 3. The slice thickness, field of view and matrix were chosen to match the geometry of the $T_1$ mapping methods above. A total of 22 GRE images were acquired for nominal flip angles ranging from $6^\circ$ to $285^\circ$. The $a_0$ and $a_1$ parameter maps were acquired as specified in Chapter 3. Because the local effective flip angle is given by equation (3.16), only a single parameter map for $a_1(x,y)$ was acquired. That is, the flip angle map associated with a given $T_1$ method using $\theta_{\text{nom},1}$ is simply given by

$$\theta_1(x, y) = \theta_{\text{nom},1} \cdot a_1(x, y).$$  \hspace{1cm} (4.21)

The flip angle map, $\theta_2(x,y)$, for the same $T_1$ method using nominal flip angle $\theta_{\text{nom},2}$ follows from equation (4.21) by replacing the nominal flip angle.

4.3.1.2 Gradient Echo $T_1$ Measurements

For the gradient echo images, a single 5 millimeter axial slice was localized through the plastic bottle filled with CuSO$_4$. A flip angle map was acquired using the double angle method from Chapter 3 for nominal flip angles of $45^\circ$ and $90^\circ$. These local flip angles were saved for substitution into equation (4.20).
To calculate the $T_1$ map, the image signals from each were substituted into equation (4.20) along with the associated flip angle for that voxel. The linear regression function `regress` in IDL was used to calculate the slope of $h$ as a function of $w$.

### 4.3.1.3 Multi-shot Inversion Recovery Prepared FLASH $T_1$ Measurements

FLASH images were acquired on the 8 Tesla scanner using the pulse sequence `snap_tomo` on the Bruker console. It has been noted (blü93) that the order within the echoes are written into $k$-space strongly affects the $T_1$ weighting of the final image. Therefore three different $k$-space encoding schemes available on the 8 Tesla system were tested for image acquisition. These schemes are designated linear encoding, centric encoding and user-defined encoding. The linear $k$-space encoding scheme writes each echo in even steps from the most negative line in the phase encoding direction to the most positive. The centric $k$-space encoding scheme writes the central line of $k$-space first and then moves outward in both directions as pictured in figure (4.7). The user-defined scheme uses a randomized placement of each line in $k$-space as is seen in figure (4.7).

For each of these three phase encoding schemes, a single axial slice was acquired using the `snap_tomo` sequence with a variable delay, $TI$, following a nominal $180^\circ$ inversion pulse. The images had a 16 centimeter by 16 centimeter field of view and a 128 x 128 matrix. The RF amplifier could not allow $TR$ intervals shorter than 50.63 milliseconds without faulting, and $TE$ was chosen to be 5.8 milliseconds which was also the minimum allowed. A nominal flip angle of $12^\circ$ was chosen for the low flip angle pulses based on the results of Blüml and co-workers (blü93).

### 4.3.2 In-situ Measurements
Due to the extremely long scan times (e.g. approximately 6 seconds per phase encoding step with IR-SE) *in-vivo* studies were not feasible. Therefore, studies were conducted on four cadavers within 24 hours post-mortem. Each cadaver was scanned using a four-port, 16 strut TEM coil, and relevant imaging parameters and a brief history are indicated in Table 4.1.

The four-port coil was tuned with the head of the cadaver inside using the HP 4195A Network Analyzer. Each excitation port was separately tuned to mode 1, and the Smith chart was used to verify that the resistance of the coil was 50 $\Omega$ and that the reactance was acceptably near zero.

### 4.3.3 Data Reduction

The image data were reconstructed into magnitude images and stored with their associated $T_1$ value. Before a voxel-wise fit of the image data can be performed using equation (4.6), it is useful to limit the fitting algorithm to a specified region of interest in the image space. Because running a curve-fitting program through the empty spaces outside the phantom would waste a considerable amount of computing time, a mask matrix is created using the program *tracemagroi.pro* also written in IDL. This program allows the user to trace a magnified view of the image data and create a matrix containing the value 0 for points which do not require $T_1$ fitting. A value of unity is assigned to points for which a $T_1$ fit will be performed.

One of the difficulties associated with curve fitting of sequences involving inversion pulses is that the signals in magnitude images are non-negative (gow03, kim94). Figure (4.8) shows each image acquired using the IR-SE method on the cylinder
containing Gd-DTPA and NaCl. In figure (4.9), the signal intensity is taken from a single voxel in each image in figure (4.8) and plotted as a function of $T_1$. The absolute value of the fitted form of equation (4.6) is plotted over these data.

Before a curve in the form of equation (4.6) is to be fitted, a method must be employed to determine the point at which the slope transitions from negative to positive in a graph of the signal intensity magnitude. This is the so-called zero crossing. Using the zero crossing, negative signs are assigned to data points in the region of negative slope in order to allow fitting equation (4.6) over its full dynamic range without the discontinuity seen in figure (4.9). The program $fit_{t1 \_twice.pro}$ (see Appendix A) was written in IDL to perform this task. The program performs two separate fitting operations to determine the most likely value for $T_1$. First, the zero crossing is estimated by considering the weakest signal intensity point on the curve in figure (4.9). It is possible that this point is slightly above or slightly below the axis. If the weakest point is slightly negative, the point before it and the point after it as a function of $T_1$ must be negative and positive respectively. Similarly, if the weakest point is slightly positive, the point before it and the point after it must still be negative and positive respectively. Therefore, the points occurring at shorter $T_1$ than the weakest point are declared negative, and the points for longer $T_1$ are allowed to remain positive. Because only the weakest point remains uncertain, it is removed, and a first-pass fit is performed on all the data points with their assigned positive and negative signs. From this fitted curve, the sign of the weakest point can be determined by $T_1$ value for which the curve crosses the axis. A second-pass fit is then performed so that a realistic value for the error in the fitted parameters can be obtained.
The removal of the minimum signal point during the two-pass fitting is an attempt to minimize the influence of noise on small signals near the zero crossing. However, it is possible that the other weak signals in that range might affect the fitting process adversely. Simulated data are shown in Section 4.4.1.1 to test the reliability of the fitting algorithm \textit{fit\_t1\_twice.pro} against noise fluctuations in the weak signal range.

**4.4 Results**

*4.4.1 Numerical Simulations*

**4.4.1.1 Effect of Noise on the Fitting Algorithm**

To test the stability of the fitting algorithm \textit{fit\_t1\_twice.pro} against noise near the zero crossing, a series of six sample data sets was created to simulate an IR-SE relaxation curve with \(TI\) values matching the phantom data in this chapter. In the first data set, the values from equation (4.4) were not altered before curve fitting. In the five remaining data sets five points in the zero crossing range were forced to have the same value to simulate the situation in which image noise might render these points indistinguishable. In turn, each of these five points was forced to serve as the point of minimum signal, and the fitted value of \(T_1\) was determined for that data set using the program \textit{fit\_t1\_twice.pro}.

Each of the six sets began with the typical signal from a single voxel for which the parameters in equation (4.6) were fixed at \(a_1=1\), \(a_2=2\) and \(a_3=0.00333\). This produced a curve of the simplified form of equation (4.4) with \(T_1\) equal to 300 milliseconds. This simple curve is shown in figure (4.10a). The points labeled 1 through 5 in that figure were then altered in the remaining five data sets figures (4.10b) through (4.10f). To
simulate the case in which noise renders these five points indistinguishable, four of them were set equal to 0.2, and the remaining point was forced to the value of 0.1.

Regardless of which of the five points is forced to be the minimum, the plateau of values with a signal of 0.2 has a tendency to flatten the exponential curve and return values larger than 300 milliseconds. This flattening is worse in figure (4.10f) in which four of the plateau values are negated than the case in figure (4.10d) in which only two are negated while two remain positive.

These simulated data represent an extreme case in which noisy data create several indistinguishable data points in the IR-SE curve. It should be noted that these elevated values are not very sensitive to the choice of the minimum data point in figures (4.10b) through (4.10f) for which the fitted $T_1$ values ranged from 378 to 426 milliseconds. This implies that the elevated values are a result of the data plateau of constant signal intensities rather than the choice of the zero crossing point. Regardless, these data underline the importance of verification of the goodness of fit between the data points and fitted curve. In this chapter and in Chapter 5, “spot checks” of $T_1$ maps were performed by hand simply by plotting raw data and parameterized curves in regions of low signal.

4.4.1.2 SR-SE Simulation

The simulation described in section II.2 of this Chapter was implemented to determine an effective range of flip angles over which equation (4.3) can produce reliable results for $T_1$. The fitted $T_1$ value as a function of flip angle $\alpha$ can be found in figure
While the true $T_1$ value was programmed to be 250 milliseconds, flip angles between 60° and 120° result in $T_1$ values between 210 and 270 milliseconds.

The range of fitted $T_1$ values shown in figure (4.11) are a result of the behavior of the individual signal points in the limits of small and large flip angles. The short $T_1$ values which result from small flip angles can be explained by considering figure (4.12). For low flip angles, the plot of signal versus $TR$ shows elevated values for short $TR$. By fitting equation (4.3) to these data, the abrupt curvature results in a short $T_1$ value. In contrast, the slow re-growth of signal exhibited for the case of high flip angles produces a longer $T_1$ value.

4.4.1.3 IR-SE Simulation

The simulation described in section 4.2.1 of this chapter produced simulated IR-SE data which were fit with the fitting algorithm in fit_t1_twice.pro. The fitted $T_1$ values for the simulated data at a given flip angle are taken as a single distribution. The mean and standard deviation of the distribution for each flip angle are plotted in figure (4.13). The figure shows that a broad plateau covering the range between 30° and 150° which resulted in standard deviations less than 8% for 5% input noise. It should also be noted that flip angles between 20° and 160° produced standard deviations less than 13%.

4.4.2 Phantom Data

4.4.2.1 Results for Spin Echo Methods

Because the single strut coil was chosen and axial slices were acquired, the $B_1$ within the cylindrical phantom showed considerable heterogeneity. This can be seen in figure (4.14) which shows the an IR image along with the $B_1^+$ and $B_1^{rec}$ maps. As
mentioned above, the wide range of flip angles inferred from the map of $B_1^+$ provides a unique opportunity to test methods of $T_1$ measurement against flip angle fluctuations.

Figure (4.15) shows three $T_1$ maps generated using the IR-SE, SR-SE and IR-RARE methods as described in Section 4.3.1 using a nominal flip angle of 90º. The flip angle contours (from the $B_1^+$ map) overlaid on the $T_1$ maps correlate well with the border between $T_1$ measurements in the range of 227 milliseconds and the very large values obtained by failed curve fitting in the periphery. On the other hand, comparison of figures (4.14) and (4.15) shows less correlation between the receiver sensitivity map and the $T_1$ maps except for regions in which elevated $T_1$ values are noted in regions of low receiver sensitivity. Regions with a combination of intermediate flip angles and low receive sensitivity are indicated by the yellow boxes in both figures.

Below each of the $T_1$ maps in figure (4.15) is a histogram of the $T_1$ values within the region bounded by the 30 and 140º contour lines. The narrow distribution of $T_1$ values in the histogram below the IR-SE image implies that the IR-SE method, while time consuming, is the most reliable of the spin echo methods.

4.4.2.2 Results for the Gradient Echo $T_1$ Mapping Method

The Gradient Echo Method was employed on the CuSO₄ phantom described in section 4.3.1.2 of this chapter. The mean $T_1$ value across the phantom was determined to be 445 milliseconds by the Gradient Echo Method. However, the $T_1$ reference value was determined using the SR-SE method in a region of interest in which the flip angle map determined an effective flip angle of 90º. The fitted value for $T_1$ in this region of interest
was 665 milliseconds which implies that the Gradient Echo Method deviated significantly.

4.4.2.3 Results for the Multi-shot FLASH Method

The FLASH snap_tomo images are shown in figures (4.16), (4.17) and (4.18) for the centric, linear and user defined encoding schemes. The images for centric and linear encoding schemes are almost indistinguishable. The artifacts in these images clearly carry through into the $T_1$ maps shown in figure (4.19).

The $T_1$ maps in figure (4.19) clearly show that the FLASH methods, regardless of phase encoding scheme, produce unreliable results in the central region in which IR-SE provides consistent $T_1$ values. In the central region of the phantom, the $T_1$ was $217\pm37$ which is consistent with previous IR-SE measurement of this phantom. It is interesting to note that the user-defined phase encoding scheme produced images with less pronounced artifacts in figure (4.18). However, closer inspection of the image data reveals high-frequency fluctuations which produce relatively flat relaxation curves and exaggerated $T_1$ values from the fitting algorithm.

4.4.3 In-situ Results

A comparison of in-situ $T_1$ maps with flip angle contours is shown in figure (4.20). These data were acquired using the cadaver listed under 2 Dec 2002 in table (4.1) which demonstrated a wide range of flip angles in the imaging volume. Again the locations of noise and extraneous $T_1$ values correlate well with the overlaid flip angle contours.

Unfortunately, these $T_1$ maps give the impression that the SR-SE method gives reliable $T_1$ values over the entire brain including the ventricles (center). However, the
scaling of the images to enhance the gray/white matter contrast hides the fact that the fitted \( T_1 \) values in the center of the SR-SE \( T_1 \) map are not consistent with values for cerebrospinal fluid (CSF) given below. Figure (4.21) displays a histogram of the fitted \( T_1 \) values obtained from the SR-SE map within the 140° contour line.

The accumulated data in figure (4.22) demonstrate that the range of \( T_1 \) values for CSF in figure (4.21) are not realistic and are the result of fitting errors. The similarity of values for white matter (WM) and gray matter (GM) are consistent with the loss of contrast noted in ultra high field imaging (nor03).

4.5 Conclusions

In summary, the IR-SE method produced the most reliable results for \( T_1 \) mapping. In homogeneous phantoms it showed a wide range of flip angles over which a reliable \( T_1 \) value could be determined. While the time required for the IR-SE method is a major drawback for \textit{in-vivo} studies in which patient motion and comfort need to be considered, these factors are less significant in \textit{in-situ}, phantom or relaxivity studies. In the following chapter, \( T_1 \) measurements are performed on samples of varying concentrations of Gd-DTPA and bovine serum albumin (BSA). The accuracy and precision of the IR-SE are worth the addition time requirement for scanning.
Figure 4.1 Plot of equation (4.1) for a series of 20 SE measurements spaced equally over a range of TR values from 0.05 to 1.95 sec. An arbitrary value of .4 sec was chosen for T₁.
Figure 4.2 An IR-SE sequence adapted from Haacke (haa99). The initial pulse inverts the magnetization and the remaining two pulses serve to sample the longitudinal magnetization.
Figure 4.3 Plot of equation (4.1) as a function of $TR$ (solid) compared to equation (4.4) as a function of $TI$. An arbitrary value of .4 sec was chosen for $T_1$. 
Figure 4.4 Coherence pathway diagram for a three-pulse IR sequence with pulses $2\alpha$, $\alpha$ and $2\alpha$ occurring at time $t=0$, $TI$ and $TE/2$. Dashed lines are used to indicate pathways which do not contribute during the acquisition of the echo.
Figure 4.5 Coherence pathway diagram for an IR-RARE sequence with an initial inversion pulse and a saturation pulse of flip angles $2\alpha$ and $\alpha$ along with multiple refocusing pulses. Extraneous pathways have been removed for simplicity.
Figure 4.6 Flip angle dependence of the \( \ln |\cos \alpha| \) term in equation (4.11). A slight error in the flip angle, \( \alpha \), can cause a significant change in the function.

Figure 4.7 The order that echoes are written into k-space is shown as a function of order in the FLASH pulse sequence for centric encoding (left) and user define encoding (right).
Figure 4.8 Image data from the IR-SE method on the cylinder containing Gd-DTPA and NaCl for 11 different $TI$ values. $TI$ values range from 80 milliseconds in the lower left and increase to 2950 millisecond in the upper right. Although the cylinder is circular in cross section, the choice of a single strut coil exaggerates the field inhomogeneity in the axial plane. Significant high frequency artifacts can be seen for short $TI$. The values for $TI$ were 80, 100, 150, 200, 300, 400, 500, 750, 1000, 1500 and 2950 milliseconds.
Figure 4.9 Signal intensity is plotted as a function of $TI$. The data points (triangles) are taken from the 11 images in figure (4.8) from the voxel located at the plus sign in the figure (insert). The contrast of the figure is decreased to indicate the edge of the phantom.
Figure 4.10 Simulated IR data (crosses) created using equation (4.4) for $T_1=300$ msec overlaid with the fitted curve from the program `fit_t1_twice.pro` (solid). The five unaltered points in (a) are sequentially altered in (b) through (f) such that four points were made indistinguishable and one was set to a minimum value. This simulation shows the vulnerability of the fitting algorithm to cases of extreme noise in which the low signal intensity points near the zero crossing are indistinguishable.
Figure 4.11 Values of $T_1$ determined from fitting equation (4.3) to the output of the SR-SE simulation are plotted as a function of flip angle. While the true $T_1$ value was programmed to be 250 milliseconds, flip angles between 60° and 130° result in $T_1$ values between 210 and 270 milliseconds.

Figure 4.12 Simulated SR-SE data points are shown with the least squares fit of the form of equation (4.3). For low flip $\alpha=30°$ (left), the signal strength of the short $TR$ signals cause the fitting algorithm to return a short $T_1$ in comparison to the expected value returned for $\alpha=90°$ (center). For large flip angle $\alpha=160°$ (right), the data show slower relaxation, and a longer fitted value for $T_1$. 
Figure 4.13 Values of $T_1$ determined from fitting equation (4.6) to the output of the IR-SE simulation are plotted as a function of flip angle. While the true $T_1$ value was programmed to be 227 milliseconds, flip angles between 30° and 150° resulted in standard deviations less than 8%.

Figure 4.14 Magnitude image of the cylinder filled with Gd-DTPA (left) along with its flip angle map (center) and receiver sensitivity map (right). The scale of the flip angle map is predicated on a nominal flip angle of 90°. The yellow squares indicate regions of low receive sensitivity but intermediate flip angles.
Figure 4.15 $T_1$ maps created by SR-SE (left), IR-SE (center) and IR-RARE (right). The red curve represents a 30° countour line from the flip angle map in figure (4.14). The blue and green curves represent 90° and 140° contours, respectively. Below each $T_1$ map is a histogram of the $T_1$ values returned in the region bounded by the 30° and 140° contours. The yellow regions from figure (4.14) are included on the IR-SE map to indicate that regions of low receive sensitivity can create elevated $T_1$ values due to the influence of noise.
Figure 4.16 FLASH images acquired with centric encoding and varying inversion times $TI$ from 50 milliseconds (lower left) to the 1500 milliseconds (upper middle).
Figure 4.17 FLASH images acquired with linear encoding and varying inversion times $TI$ from 50 milliseconds (lower left) to the 1500 milliseconds (upper middle).
Figure 4.18 FLASH images acquired with user-defined encoding as seen in figure (4.7) and varying inversion times $TI$ from 50 milliseconds (lower left) to the 1500 milliseconds (upper middle).
Figure 4.19 $T_1$ maps acquired with FLASH images are shown in comparison to an IR-SE map (left). Note that the IR-SE $T_1$ map differs from that shown in figure (4.15) because the data were acquired 6 months apart.

Figure 4.20 In-situ $T_1$ maps from SR-SE(left), IR-SE(center) and IR-RARE(right) methods. The contour overlays indicate flip angles of 30° (red), 90° (blue) and 140° (green). The left/right asymmetry of the $T_1$ maps is a result of a previous stroke which was unrelated to the cause of death.
Figure 4.21 A histogram of $T_1$ values from the central region of the *in-situ* SR-SE $T_1$ map in figure (4.20) shows that a wide range of values is hidden in the grayscale of the figure. The $T_1$ values shown were taken from a region of interest bounded by the 140° contour line.
Figure 4.22 Accumulated *in-situ* $T_1$ values from the four cadavers listed in table (4.1) using the IR-SE method. The similarity of the gray matter and white matter values explains the previously mentioned loss of contrast associated with ultra high field images (nor03).
<table>
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<th>Scan Date</th>
<th>TI(msec)</th>
<th>TR(msec)</th>
<th>TE(msec)</th>
<th>Matrix</th>
<th>History</th>
</tr>
</thead>
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<td>4500, 3000, 1500, 1000, 500, 250</td>
<td>5000</td>
<td>20.6</td>
<td>512x256</td>
<td>73 year old male with Alzheimer’s disease</td>
</tr>
<tr>
<td>16 June 2003</td>
<td>5000, 3500, 2000, 1000, 500, 250</td>
<td>5500</td>
<td>21.1</td>
<td>512x384</td>
<td>85 year old male, normal brain, cause of death colon cancer</td>
</tr>
<tr>
<td>2 Dec 2002</td>
<td>5000, 3000, 1500, 1000, 500, 250</td>
<td>5500</td>
<td>20.4</td>
<td>512x255</td>
<td>68 year old male with previous right hemispheric stroke, cause of death colon cancer</td>
</tr>
<tr>
<td>16 Sept 2002</td>
<td>5000, 2000, 1000, 500, 250</td>
<td>5500</td>
<td>21.5</td>
<td>512x384</td>
<td>69 year old male with frontotemporal dementia</td>
</tr>
</tbody>
</table>

Table 4.1 Cadaver histories and scanning parameters used for IR-SE $T_1$ mapping *in-situ.*
5.1. Introduction

Since signal strength in MRI is a function not only of the density of water protons but also the rates at which spins relax, it is important to quantify relaxation rates. Furthermore, current interest in ultra high field MRI has created the need to extend the range of measurements seen in previous studies, and explore the impact of increased field strength on the underlying mechanisms.

First, the important parameters of MRI must be known to design phantom materials in order to devise experiments to test new pulse sequences and for experiments on the basic physics of MRI. Kraft, et. al. (kra87) pointed out that the creation of stable phantoms for the comparison of different MR scanners and/or different pulse sequences requires precise knowledge of relaxation rates in order to insure that such comparisons are relevant to the range of relaxation rates found in-vivo.

Second, the influence of increased field strength on the relaxation effects of contrast agents impacts the clinical use of contrast agents. The high field behavior of contrast agents must be explored in order to specify the dosage of contrast agent required
to enhance a targeted anatomic structure (ful92) and to choose a suitable pulse sequence and its parameters (run01).

Third, some studies in dynamic contrast enhanced MRI (DCE-MRI) use the signal intensity in a $T_1$-weighted image to infer the amount of contrast agent absorbed in a physiologic process. Examples include the measurement of hepatic perfusion (mat02), assessment of spinal cord injury (bil01), and studies of articular cartilage (nie02, reg03). In order to make this inference, the relationship between contrast agent concentration and relaxation enhancement must be quantified. However, this relationship is not clear as evidenced by the fact that both increases (mør03) and decreases (sch01a, xie01) in relaxation rates have been reported in tissue and cells due to the decreased mobility of water protons across anatomical barriers (don94).

To isolate the influence of molecular effects from anatomic effects, Stanisz and Henkelman (sta00) published a communication on an experiment in which varying amounts of protein solutions were added to varying concentrations of the contrast agent Gd-DTPA (gadolinium dimethylamine pentaacetic acid). They were able to show very simply that the effect of the contrast agent is amplified at higher macromolecular concentrations even without anatomical barriers. This complicates the determination of contrast agent content from signal intensity in DCE-MRI.

The findings of Stanisz and Henkelman (sta00) suggest that relaxivity is significantly influenced even by small amounts of protein in solution. However, their data were gathered using a combination of proteins obtained from eggs, milk, and agar. To explore the findings of Stanisz and Henkelman, an experiment was devised to
determine the effects of bovine serum albumin (BSA) concentration, temperature, and field strength on the relaxivity of Gd-DTPA.

5.1.1 Contrast Agents

Contrast agents are “…pharmaceuticals that increase the information content of diagnostic images...” (wat92). Examples of contrast agents in other radiological imaging modalities include barium compounds which attenuate the transmission of x-rays or microbubbles which increase the ultrasonic reflections. In MRI, all contrast agents are used to reduce the relaxation times of water protons in a target anatomical region (mån01).

The ability of paramagnetic ions to increase NMR relaxation rates was observed (blo57) soon after Bloch’s initial paper on NMR (blo46). As seen below, the Solomon-Bloembergen equation predicts that the rate of $T_1$ relaxation for a proton in the presence of a paramagnetic ion is proportional to $S(S+1)$ where $S$ is the total spin of the paramagnetic ion. Since the magnetic moment of an electron is 658 times that of a proton, interest in contrast agents has traditionally focused on transition metals and lanthanide series metals which hold many unpaired electrons in their valence shell (mån01). Unfortunately, the direct administration of such metal ions would be toxic (hen93).

For completeness, it should be noted that contrast agents have been developed using iron oxide crystals in the form of particles typically 5 to 200 micron in diameter. These particles can be coated with a biocompatible layer and administered $in$-$vivo$. Such contrast agents are called superparamagnetic agents because of the influence of their large magnetic moment on $T_2$ and $T_2^*$ relaxation (mån01). Iron oxide particles larger than
50 nm in diameter are classified called supermagnetic iron oxide (SPIO) particles, and smaller iron oxide particles are called ultra-small SPIO particles (USPIO). These agents are not the focus of this work. However, a complete review can be found in reference (mul01).

One means to safely administer lanthanide series and transition metal ions involves chelating, or binding the ion tightly to a macromolecular ligand. Such paramagnetic chelates must satisfy five important criteria if they are to be used clinically (nel95). First, the agent must efficiently increase relaxation rates so as to minimize the dose administered. Second, the agent should demonstrate great specificity in identifying an anatomic target or physiological process in order to minimize false positive results. Third, the contrast agent must be cleared from the body in a reasonable amount of time. Fourth, the contrast agent must have a low toxicity and no long-term risks. Fifth, the contrast agent must be chemically stable to prevent breakdown in vivo and to allow convenient storage in a clinical setting. Each of these criteria is satisfied by the four contrast agents currently approved for use in the central nervous system in the United States. They are gadopentetate dimeglumine (also called gadolinium dimethylamine pentaacetic acid, Gd-DTPA), gadoteriol (Gd HP-DO3A), gadodiamide (Gd DTPA-BMA), and gadoversetamide (Gd DTPA-BMEA). The focus of this work is on Gd-DTPA and its relaxation enhancement in protein solutions.

5.1.2 Definitions

The influence of paramagnetic contrast agents on water protons can be described through the basic interactions of magnetic dipoles. Since the proton possesses no quadrupole moment, the dominant mechanism for inducing relaxation is dipole-dipole
coupling between the water proton and another dipole such as another nucleus or an unpaired electron in a contrast agent (ful92). As noted above, the greater magnetic moment of an electron makes the use of unpaired electrons in paramagnetic ions more feasible.

Starting on a macroscopic level, the influence of the contrast agent on the relaxation of protons in a solution can be described by

\[
\frac{1}{T_1} = \frac{1}{T_{1,0}} + R_1 \cdot [M] \tag{5.1}
\]

where \(1/T_1\) is the rate of spin-lattice relaxation after the addition of the contrast agent, \(1/T_{1,0}\) is the intrinsic spin-lattice relaxation rate without any contrast agent, \(R_1\) is the relaxivity of the contrast agent and \([M]\) is the concentration of the paramagnetic ion. The contribution of the paramagnetic agent can be further broken down (lau87) such that

\[
R_1 \cdot [M] = \frac{1}{T_{1,IS}} + \frac{1}{T_{1,OS}} \tag{5.2}
\]

where the two labels IS and OS represent the contributions of the so-called inner sphere and outer sphere mechanisms.

5.1.2.1 Inner Sphere Effects

The inner sphere mechanism refers to the relaxation of protons in water molecules which temporarily bind to the inner coordination sphere of the paramagnetic ion. Because the dipole-dipole interaction Hamiltonian is proportional to \(r^{-3}\), where \(r\) is the distance between the two dipoles, the dipole-dipole contribution to the rate of inner sphere relaxation is proportional to \(r^{-6}\).
The inner sphere relaxation rate is simply a function of the mole fraction of the bound water nuclei $P_m$, the number of bound water molecules per metal ion $q$, the lifetime of the bond between the water molecule and the complex $\tau_m$, and the spin lattice relaxation time of a proton in a bound water molecule $T_{1m}$ such that

$$\frac{1}{T_{1m}} = \frac{P_m q}{T_{1m} + \tau_m}.$$ \hspace{1cm} (5.3)

In the slow exchange regime, $\tau_m$ is long, and the denominator is controlled by $\tau_m$. If the exchange of water molecules is not slow, $T_{1m}$ must be calculated using the Solomon-Bloembergen equations (Tót01) in which two terms contribute

$$\frac{1}{T_{1m}} = \frac{1}{T_{1m}^{DD}} + \frac{1}{T_{1m}^{SC}}.$$ \hspace{1cm} (5.4)

In equation (5.4) $[1/T_1]^{DD}$ is the dipole-dipole term such that

$$\frac{1}{T_1^{DD}} = \frac{2}{15} \left( \frac{\gamma_I^2 g^2 \mu_B^2}{r_{GdH}^6} \right) S(S+1) \left( \frac{\mu_0}{4\pi} \right)^2 \left( \frac{7}{1 + \omega_S^2 \tau_c^2} + \frac{3}{1 + \omega_I^2 \tau_c^2} \right)$$ \hspace{1cm} (5.5)

where $\gamma_I$ is the proton gyromagnetic ratio, $g$ is the electron g-factor, $\mu_B$ is the Bohr magneton, $r_{GdH}$ is the distance between the proton and the paramagnetic ion, $S$ is the spin state of the paramagnetic ion, $\mu_0$ is the permeability of free space, and $\omega_I$ and $\omega_S$ are the nuclear and electron Larmor frequencies. The variables $\tau_{ci}$ where $i=1,2$ represent the correlation times for factors associated with $T_1$ and $T_2$ relaxation specified by

$$\frac{1}{\tau_{ci}} = \frac{1}{\tau_R} + \frac{1}{T_{1e}} + \frac{1}{\tau_m}.$$ \hspace{1cm} (5.6)

In equation (5.6), $\tau_R$ is the rotational or so-called re-orientational correlation time of the metal-proton vector, and $T_{1e}$ and $T_{2e}$ are the electronic spin-lattice and spin-spin
relaxation times respectively. From equation (5.5), one sees the expected $r^{-6}$ dependence and the strong dependence on the spin of the paramagnetic ion, $S$.

The scalar term $[1/T_1]_{SC}$ in equation (5.4) is expressed as

$$\left[ \frac{1}{T_1} \right]_{SC} = \frac{2S(S+1)}{3} \left( \frac{A}{\hbar} \right)^2 \frac{\tau_{e_2}}{1 + \omega_S^2 \tau_{e_2}^2}$$  \hspace{1cm} 5.7

where

$$\frac{1}{\tau_{e_2}} = \frac{1}{T_{2e}} + \frac{1}{\tau_m}. \hspace{1cm} 5.8$$

The scalar term represents the quantum mechanical probability that there will be a contact interaction between the paramagnetic ion and the proton (wat92). This term is negligible above 10 MHz (tot01) and is therefore not relevant for the field strengths used in this work (64 MHz and 340 MHz).

The effects of the correlation times on the inner sphere mechanism are less clear, but can be seen using a Nuclear Magnetic Relaxivity Dispersion (NMRD) curve as seen in figure (5.1). NMRD curves are measured using fast field cycling (FFC) relaxometers which measure relaxivity or relaxation rate (1/$T_1$) covering a range of Larmor frequencies. A detailed description of their operation can be found in (tot01). Because each of the two terms in equation (5.5) is a Lorentzian shape of the form $x/(1+x^2)$, a significant increase in $[1/T_1]_{DD}$ is seen when $\omega_I \approx 1/\tau_{e_1}$ (car99). Such an increase is seen in figure (5.1) where experimental data points are overlaid with two calculated curves. One curve shows relaxivity calculated using a realistic value of $\tau_R = 58$ picoseconds while the second curve shows the effect of setting $\tau_R$ equal to 58 ns. The peak of the NMRD
curve occurs near $(58 \text{ ns})^{-1} \approx 17 \text{ MHz}$. This value for the rotational correlation time, $\tau_R$, is of the order expected for Gd-DTPA bound to serum albumin (tót01).

5.1.2.2 Outer Sphere Effects

The relaxation enhancement due to water molecules bound in the outer sphere was represented by the term $[1/T_1]_{OS}$ in equation (5.2). Generally, this term is also used to include the contributions of outer sphere water molecules diffusing past the paramagnetic complex as well as the second sphere water molecules (lau87, tót01) which bind to pairs of oxygen atoms in the carboxylate group (car99). Although the theoretical treatment of these second sphere water molecules should be similar to that of the inner sphere (with corrections for $r$ and $\tau_m$), the second sphere is generally included in theoretical models in modifications to the outer sphere mechanism (car99).

While the outer sphere mechanism is also a dipole-dipole interaction, the diffusion of solvent molecules must be taken into account. Keeping the convention that subscripts on the rotational frequencies, $I$ and $S$, refer to the water proton and electron spins, respectively, the outer sphere contribution to the $T_1$ relaxation rate has the form

$$
\left[ \frac{1}{T_1} \right]_{OS} = \frac{32\pi}{405} \left( \frac{\mu_0}{4\pi} \right)^2 \frac{N_A[Gd]}{dD} \gamma_I^2 \gamma_S^2 \hbar^2 S(S+1) \left[ j_2(\omega_I - \omega_S) + 3j_1(\omega_I) + 6j_2(\omega_I + \omega_S) \right]
$$

where $N_A$ is Avagadro’s number, $[Gd]$ is the molar concentration of gadolinium, $d$ is the distance of closest approach, $D$ is the relative diffusion coefficient, and $j_1$ and $j_2$ are spectral density functions for the diffusion of dipoles past one another such that

$$
j_k(\omega) = \text{Re} \left( \frac{1 + z/4}{1 + z + 4z^2/9 + z^3/9} \right)
$$
for \( k = 1, 2 \) and

\[
z = d \sqrt{\frac{i\omega}{D} + \frac{1}{DT_{ke}}}.
\]

Clearly, the equations for the inner sphere and outer sphere components of \( T_1 \) relaxivity shown above contain a great many parameters. Several studies (cla01, che94, pow96) have been able to specify the important physical parameters by combining information from O-17 NMR and electron paramagnetic resonance (EPR) experiments.

5.1.3 Protein-bound Gd chelates

The large increase in relaxivity seen in figure (5.1) led to interest in studying Gd chelates bound to proteins in order to slow their rotational correlation time, \( \tau_R \) (aim01, pow96). The most widely studied system of a protein bound to a Gd chelate is albumin labeled with Gd-DTPA (aim01). However, many of these studies have been targeted at slowing the rotation rate in order to increase the relaxivity of the protein-chelate system into the range of 10-100 MHz. From figure (5.2), a sharp increase in relaxivity is seen between 10 and 100 MHz for the complex of 43 molecules of Gd-DTPA bound to human serum albumin (HSA).

While this frequency range is below the 340.56 MHz proton larmor frequency at 8 Tesla, it should be noted that the complex was prepared specifically to bind 43 Gd-DTPA molecules to each HSA protein. Other studies of Gd-DTPA molecules bound to proteins have used large ratios of up to 43 molecules of Gd-DTPA to each protein molecule (spa92, car99). However, these studies used advanced synthesis techniques such as the use of nitriloacetic acid as a complexant to increase the binding of Gd-DTPA to HSA in the case of spa92. The study reported in aim01 and seen figure (5.2) used a technique in
which synthesis was carried out in a solution containing acetonitrile at low temperature.

While these experiments explore the relaxivity of very specific Gd-DTPA and protein complexes, they differ from the approach of Stanisz and Henkelman to explore the change in relaxivity when macromolecules are introduced without catalysts or special synthesis techniques.

To this end Li and co-workers studied the relaxivity of solutions of Gd-DTPA with 0.725 mmol/liter BSA (li00) at 9.4 Tesla. The solutions were prepared at room temperature without catalysts. Their approach to modeling the data was to add additional terms to equation (5.1) for the complexes of Gd-DTPA bound to BSA such that

\[
\left[ \frac{1}{T_1} \right]_{\text{total}} = \frac{1}{T_{1,0}} + R_1 \cdot [\text{Gd} - \text{DTPA}] + \sum_{n=1}^{N} R_{1,n} \cdot [(\text{Gd} - \text{DTPA})_n \cdot \text{BSA}]
\]  

5.12

where \( R_{1,n} \) is an additional relaxivity constant, and \( N \) is chosen to cover all likely binding ratios. For chemical reactions of the form \( \text{BSA} + n(\text{Gd-DTPA}) \leftrightarrow (\text{Gd-DTPA})_n \cdot \text{BSA} \), the chemical equilibrium constant is of the form

\[
K_n = \frac{[(\text{Gd} - \text{DTPA})_n \cdot \text{BSA}]}{[\text{Gd} - \text{DTPA}]^n \cdot [\text{BSA}]}
\]  

5.13

Substituting this result into equation (5.12) simplifies the sum

\[
\left[ \frac{1}{T_1} \right]_{\text{total}} = \frac{1}{T_{1,0}} + R_1 [\text{Gd} - \text{DTPA}] + \sum_{n=1}^{N} R_{1,n} K_n [\text{BSA}][\text{Gd} - \text{DTPA}]^n .
\]  

5.14

Using \( A_n = R_{1,n} K_n \cdot [\text{BSA}] \), equation (5.14) becomes a power series in [Gd-DTPA]

\[
\left[ \frac{1}{T_1} \right]_{\text{total}} = \frac{1}{T_{1,0}} + R_1 [\text{Gd} - \text{DTPA}] + \sum_{n=1}^{N} A_n [\text{Gd} - \text{DTPA}]^n
\]  

5.15
where $A_n$ can be calculated from published values for $K_n$ and $[\text{BSA}]$ was determined experimentally.

The authors reasoned that a rarely occurring complex of the form $(\text{Gd-DTPA})_i\cdot\text{BSA}$ would not contribute to the relaxivity sum in equation (5.15). This implies that the coefficient of the $i$th term would have negligible statistical significance. Therefore, the statistical significance of terms in equation (5.15) can be used to infer which complexes occur too rarely in solution to contribute to the relaxivity.

They then fit equation (5.15) to $T_1$ relaxation rates in the various solutions. Based on the statistical significance of the resulting coefficients, they found that the majority of complexes were of the form $(\text{Gd-DTPA})\cdot\text{BSA}$ or $(\text{Gd-DTPA})_2\cdot\text{BSA}$ and that complexes with higher binding ratios were formed by less than 0.13% of Gd-DTPA molecules. Thus, the sums in equations (5.14) and (5.15) need not go beyond $n=2$.

Based on the findings of Li and co-workers to analyze the relaxation rate data in this study, equation (5.15) was modified. First, the series in $[\text{Gd-DTPA}]$ was terminated at $N=2$. Second, the constant terms in equation (5.15) were assumed to be quadratic functions of $[\text{BSA}]$ because Stanisz and Henkelman (sta00) reasoned that Gd-DTPA relaxivity appeared to be a quadratic function of macromolecular content measured in percentage weight-to-weight. Thus a multivariate version of equation (5.15) was employed which included quadratic terms in both $[\text{BSA}]$ and $x=[\text{Gd-DTPA}]$ as follows:

$$
\left[ \frac{1}{T_1} \right]_{\text{total}} = \alpha_0 + \alpha_1[\text{BSA}] + \alpha_2[\text{BSA}]^2 + \alpha_3 + \alpha_4[\text{BSA}] + \alpha_5[\text{BSA}]^2 \cdot x + \alpha_8[\text{BSA}] + \alpha_6[\text{BSA}]^2 \cdot x^2
$$

where the coefficients $\alpha_i$ are parameters determined by multivariate regression.

5.1.4 Temperature dependence

152
Reichenbach, *et. al.* studied the temperature dependence of Gd-DTPA solutions in saline (rei97). They showed that $T_1$ increases linearly with temperature in the range of 20-50 °C despite the fact that the temperature dependence of $T_1$ is carried in the correlation times $\tau_{ci}$ in equation (5.5). Therefore, if $T_1$ becomes longer with increasing temperature, $1/T_1$ will shorten, and relaxivity is expected to decrease.

### 5.2 Methods

The findings of Stanisz and Henkelman (sta00) suggest that relaxivity is significantly influenced even by small amounts of protein in solution. However, their communication was written using a combination of proteins obtained from eggs, milk, and agar. To explore the findings of Stanisz and Henkelman, an experiment was devised to determine the effects of bovine serum albumin (BSA) concentration, temperature, and field strength on the relaxivity of Gd-DTPA.

#### 5.2.1 Sample Preparation

Precise control of the chemical composition of the samples is imperative in an experiment aimed at determining the effects of protein concentration on Gd-DTPA relaxivity. Dilutions of commercially available Gd-DTPA and BSA (see below) were placed in 0.5 mm Eppendorf microcentrifuge tubes (T-5149, Sigma-Aldrich, St. Louis, MO, USA) using 1000 microliter and 200 microliter micropipettes (Fisher Scientific, Hampton, NH, USA) whose accuracies were quoted by Fisher Scientific to be ± (1.0 to 0.6)% and ± (1.8 to 0.6)%, respectively. It was decided that only BSA would be used as a source of protein in order to avoid introducing a potential source of variability in the binding properties among different proteins. Furthermore, BSA has been widely studied in the literature as mentioned in the previous section.
Solutions of varying Gd-DTPA concentration were prepared from a clinically available source (Magnevist®, Berlex, Wayne, NJ). These concentrations were chosen to be 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75 and 2.00 millimoles per liter of total solution (mM). Even spacing of Gd-DTPA concentration was chosen to avoid data points having excess influence or leverage in the subsequent linear regression mentioned below. Four sets of eight Gd-DTPA samples were prepared in this way. To each sample in these four sets, an amount of BSA solution (ImmucorGamma Houston, Houston, TX, USA) was added such that the final volume-to-volume BSA concentration of the sample would be 0%, 3%, 12% or 18% relative to the total volume of the solution. The maximum BSA concentration was limited by the 30% concentration BSA volume to volume of water received from the supplier. Thus, the maximum BSA concentration possible in a solution of 2.0 mM Gd-DTPA was 18% volume-to-volume.

5.2.2 Temperature Control

As mentioned above, temperature affects the longitudinal relaxivity of protons through changes in the mobility of water molecules in the solution. To control this variable, an MR-safe, temperature-controlled sample holder was created specifically for use in the 8 Tesla system.

Temperature control can be effectively maintained using commercial, off-the-shelf devices. However, safety concerns prevent current-carrying devices such as electric heaters and water pumps from being used in or near the 8 Tesla system. Thus a system was needed which could transfer hot or cold water into a sample holder placed within the imaging volume of the 8 Tesla scanner. Control of the remote water heater also required feedback from the actual temperature measured in the sample holder.
The temperature control system in figure (5.3) (affectionately called “Das Wasserspiel”) consisted of a reservoir of 20 liters of water which held a heating element and water pump. The pump flowed water through approximately 30 feet of tubing to the sample holder and back to the reservoir. The reservoir was a simple 40 liter kitchen garbage can (Sterlite, Lake Havasu City, AZ, USA). Heating and temperature regulation within it were both accomplished using a Model 72 temperature controller (Yellow Springs Instruments - YSI, Yellow Springs, OH, USA). A steel, heater coil was connected to the temperature controller, and a YSI Model 400 thermistor ran from the controller to the reservoir. A user-specified temperature and tolerance were set using dials on the controller.

An induction-motor, fishtank pump (Danner Manufacturing, Inc., Central Islip, NY, USA) supplied the flow of water through ¼ inch x 3/32 inch Class VI Tygon tubing (Saint Gobain Performance Plastics, Charny, France) from the reservoir to the sample holder. The sample holder was a 710 ml plastic food dish (Servin’ Saver, Rubbermaid, USA). As seen in figure (5.4), two holes were drilled through the side of the sample holder, and plastic fittings were inserted and sealed with silicone rubber (732 Multipurpose Sealant, Dow Corning, Midland, MI) to serve as feed-throughs for the water flow. Although the sample holder was filled with water to surround the Eppendorf tubes, the flow of heated water was restricted to thin-walled latex hose (3/8 inch outer diameter x ¼ inch inner diameter, Lowe’s, USA) in order to minimize flow artifacts while maintaining heat exchange between the flowing water and the water inside the sample holder. The returning water passed through the feed-through in the wall of the sample container and returned to the reservoir via similar Tygon tubing.
Fluoroptic temperature monitoring was used for real-time temperature measurement of the samples as they were imaged. A fiberoptic probe from the Model 790 (Luxtron Corporation, Santa Clara, CA, USA) was placed through a small hole in the top of the sample holder. Before placement of the coil and sample holder in the magnet, the fiberoptic lead could be inserted into the water adjacent to the Eppendorf tubes. The fluoroptic temperature measurements were interfaced with a personal computer using the TrueTemp program (Version 1.1.0, Luxtron Corporation, Santa Clara, CA, USA).

Admittedly, there was no direct feedback loop between the Luxtron measurements and the temperature of the reservoir. Thus, a predetermined temperature for the samples could not be achieved without trial-and-error adjustments of the YSI temperature controller setting at the reservoir. However, within two hours of setting the desired temperature on the YSI temperature controller, the entire Wasserspiel system came to an equilibrium and maintained the steady temperature control indicated in Table 5.1

5.2.3 Imaging Methods

First, the Eppendorf tubes had to be placed in the sample holder. The tubes were held in small racks (Fisher Scientific, Hampton, NH, USA) such that a coronal slice through the sample holder would cut a circular cross-section through the tubes. Before closing the sample holder, it was filled with enough water to ensure that a coronal slice would not include any air and introduce susceptibility artifacts. The sample holder was placed in a 16 strut, single excitation port coil as was used in Chapter 2. The coil was tuned to place mode 1 at 340.56 MHz using a Hewlett-Packard 4195A Network Analyzer.
(Chicago, IL, USA). The sample holder and samples were fixed with masking tape inside the coil before tuning.

The coil was placed into the imaging volume of the 8 Tesla scanner using the removable patient table. The center frequency was tuned using the routine *Auto-SF* which is resident on the Bruker console which controls the scanner. The 3D gradient echo sequence 3Profile was used to verify and adjust the positioning of the table to place the samples at the isocenter of the magnet. Because of the variability of flip angle throughout the imaging volume, the STE sequence *vsel_ste_spec* was to determine a nominal flip angle of $90^\circ$ in a $1 \text{ cm}^3$ voxel in the phantom as described in Chapter 3. This voxel was selected to be in the sample holder amid the Eppendorf microcentrifuge tubes. As previously mentioned, the sequence *vsel_ste_spec* produces a narrow peak as a function of the transmission power and allows for easy determination of the power requirements for a nominal saturation (*i.e.* $90^\circ$) pulse.

A flip angle map was acquired on the 8 Tesla scanner using the multiple angle method from Chapter 3 to ensure acceptable variation of flip angles for the use of the IR-SE method. Gradient Echo (GRE) images with a short $TE$ of 7 milliseconds and a long $TR$ of 6 seconds were acquired with four different transmission power settings corresponding to four different nominal flip angles ($45^\circ$, $60^\circ$, $90^\circ$, and $120^\circ$). The same excitation pulse as was used in the stimulated echo sequence above was employed (8000 microsecond, sinc3 pulse of bandwidth 750 Hz) to allow that the nominal flip angles could be determined. For flip angle maps, the images were acquired for a field of view of $20 \text{ cm} \times 15 \text{ cm}$ and a matrix of $128 \times 64$. Low spatial resolution was used to shorten scan times and because variations in $B_1^+$ and $B_1^{\text{rec}}$ demonstrated slow spatial variations in
Chapter 3. The low resolution allowed these long TR scans to be performed in less than 7 minutes each. The temperature of the samples during this period averaged 17.3° C. The multiple angle method of flip angle determination showed no obvious temperature variation, and, therefore, there was no reason to perform flip angle mapping at each temperature for which $T_1$ maps were created. The gradient echo images were fit with the parameterized equation (5.21) in Chapter 3. The relative flip angle map showed acceptable flip angle variation.

Having verified acceptable flip angle variation in the sample holder, $T_1$ mapping of the samples was done using the IR-SE method at temperatures of 14°, 21°, 29° and 36°. A long TR of 6 seconds was used to ensure complete, longitudinal relaxation in the samples between inversion pulses. After allowing the fluoroptic temperature readings to equilibrate at one of the desired temperatures, eight scans were performed for value of TI=5000, 1200, 500, 350, 250, 100, 75, 50, and 25 milliseconds. The same 20 cm x 15 cm field of view was used as in the flip angle maps, but the matrix size was increased to 256 x 128. The same pulse duration and bandwidth for the sinc3 pulse was used for all three pulses in the inversion recovery sequence.

The 1.5 Tesla data were acquired using a mobile Signa 1.5 Tesla scanner from General Electric Medical Systems (Milwaukee, WI, USA). The sample holder was placed in an extremity coil (USA Instruments, Cleveland, Ohio, USA). The computer interface for the Luxtron fluoroptic temperature monitor could not be moved to the trailer housing the mobile scanner. Thus temperature readings were simply read from the LED display on the Luxtron controller and recorded at the beginning of each scan. The IR-SE method was used with 12 fast spin echo inversion recovery (FSE-IR) scans with variable...
$TI$=4000, 2000, 1200, 800, 500, 300, 200, 150, 100, 80, 65, and 50 milliseconds. The $TR$ and $TE$ were chosen to be 8 seconds and 12 milliseconds, respectively. A 20 cm x 15 cm field of view was acquired with a 256 x 192 matrix and a slice thickness of 5 millimeters. An echo train length (ETL) of 4 was employed to allow 4 lines of k-space to be acquired for each TR. This shortened the scan time to 4 minutes and 56 seconds for each FSE-IR scan.

A flip angle map was not acquired on the 1.5 Tesla system because no evidence of significant flip angle variation had been observed in previous experience. The determination of central frequency, the power requirements for a saturation pulse, and the appropriate amplifier settings were determined automatically using the resident prescan algorithm on the scanner.

5.2.4 Data Analysis

The IDL program $fit_t1_twice.pro$ based up to the IDL routine $curvefit$ was used as described in Chapter 4 and Appendix A. To avoid fitting extraneous data points on the periphery of the sample holder, a binary mask was created using the program $tracemagroi.pro$ (also found in Appendix A). The completed $T_1$ maps were then analyzed using the program $regressT1.pro$ (see Appendix A). This program allowed the user to create a regions of interest (ROI) in each vial, and to check a histogram of the $T_1$ values in each vial. $T_1$ values which deviated significantly from the histogram of values within the vial could be removed if an artifact in the image data suggested that erroneous $T_1$ values might result.

After a region of interest was specified for each vial, the fitting parameters $a_1(x,y)$ from equation (4.6) and associated fitting error for each individual voxel located at the
point \((x,y)\) in the ROI were written to a text file. The fitted \(a_1\) values were used because equation (5.1) relates contrast agent concentration to relaxation rates.

Rather than calculate a single mean value for \(a_1\) in a given ROI, it was necessary to regress each individual \(a_1\) value in the ROI as a separate data point because each \(a_1\) value had an associated error, \(\sigma_{a_1}(x,y)\) given by the IDL fitting routine \textit{curvefit} in the program \textit{fit\_tl\_twice.pro}. Thus the entire set of \(a_1\) values in the ROI had two sources of variance: the variance associated with the distribution \(a_1\) values in that vial, and a variance associated with the goodness of fit of each individual \(a_1\) value. To ensure that both types of variance were accounted, it was necessary to regress the large set of individual values rather than a single mean for each vial (net06).

The actual regression of the relaxation rate, \(a_1=1/T_1\) data was performed in the statistical analysis program MINITAB (MINITAB, Inc., State College, Pennsylvania, USA). After importing the text file containing the \(T_1\) data, the regression of \(1/T_1\) could be performed through a spreadsheet user interface. The imported rates were assigned weights in MINITAB using the errors returned by the program \textit{fit\_tl\_twice.pro}. The weight associated with error \(\sigma_{a_1}(x,y)\) was defined in the software help utility as

\[
w(x,y) = \left[ \frac{1}{\sigma_{a_1}(x,y)} \right]^2.
\]

The inverse nature of the definition of \(w\) allows stronger leverage in the regression for points with reliable fitting parameters.

In the first method of regression, henceforth called \textit{subset regression}, only vials of the same BSA concentration, temperature and field strength were grouped for linear regression. Thus the regressions were performed on a subset of all the vials. This
method was used by Stanisz and Henkelman (sta00) for calculating the relaxivity as a function of BSA concentration. A second method of regression, hereforth called multivariate regression, used based on the form of equation (5.16). Using multivariate regression, the data needed to be grouped only by temperature and field strength.

5.3 Results

Although the reasoning behind regressing the individual data points in a region of interest was covered in Section 5.2.3, a summary of $T_1$ values as a function of temperature and BSA concentration is given to show the general trends in the data. Tables (5.2) through (5.5) show mean $T_1$ values in BSA admixtures for temperatures of 14, 21, 29 and 36 °C, respectively. From these data, figure (5.5) was plotted to demonstrate the linear temperature dependence predicted by Reichenbach, et. al., (rei97).

5.3.1 Signal to Noise Ratio

To gauge the reliability of the IR-SE method, flip angle maps and signal to noise ratio (SNR) were calculated. A histogram of the flip angle map in the sample holder region which contained vials is shown in figure (5.6). The effective flip angles for a nominal 90° pulse generally fall within 50° to 120°, indicating that the use of the IR-SE method is reliable in the sample holder. The calculated SNR was generally adequate for fitting $T_1$ from IR-SE data. SNR was calculated using the ratio of average signal intensity in a region of interest divided by the standard deviation among pixels in the upper left corner of the magnitude images. Using a region of interest in the corner prevented any ghosting from skewing the noise measurement.

Because of the variation in flip angle from the left side to the right side of figure (5.7), the SNR was expected to be greater in the right hand side region of greater signal
intensity. To gauge the dependence of SNR on flip angle, average signal intensities were calculated for 5x5 pixel blocks around the “plus” sign in the low flip angle region of the left hand side and around the “x” in the high flip angle region. The SNR was obtained by dividing these average values by the standard deviation of the noise as defined above. Figure (5.8) shows typical SNR values in the region of the “x” in figure (5.7) as a function of the time to inversion ($TI$). Similarly, figure (5.9) shows SNR in the region of the “plus” sign in figure (5.7). If one assumes constant noise for each image regardless of TI, then either of the SNR curves should simply follow the signal intensity expected in any inversion recovery experiment. However, both curves show a decrease in SNR for the longest $TI$ while signal intensities are at a maximum. Clearly, constant noise for all $TI$ can not be assumed. It is believed that the 90°-180° pulses after a long $TI$ interval leave residual transverse magnetization which is not spoiled before the end of the TR interval. Unfortunately, each point was assigned equal weight in the curve fitting program fit_t1_twice.pro because this decrease in SNR for long $TI$ went unnoticed until after the statistical analysis of this chapter was completed. Possible consequences of this omission will be discussed below.

5.3.2 Subset Regression Results

By applying the subset regression method used by Stanisz and Henkelman, $(1/T_1)$ was linearly regressed with respect to Gd-DTPA concentration in the form of equation (5.1) in subsets for each combination of BSA concentration, temperature and field strength. Relaxivity values were obtained from the slope of the best-fit line as seen in figure (5.10).
To verify the experimental method and statistical analysis, data from 1.5 Tesla were compared with the data from Stanisz and Henkelman (sta00). Table (5.6) lists the spin-lattice relaxivity, \( R_1 \), in equation (5.1) measured at 1.5 Tesla and 22 °C for comparison with the data from sta00 seen in figure (5.11). Except for an anomalous point at 12 % v/v BSA, the 1.5 Tesla data follow those of Stanisz and Henkelman over the more narrow range of macromolecular concentrations used in this work.

5.3.3 Multivariate Regression Results

The method of multivariate regression expressed in equation (5.16) was also fitted to relaxation rate data as a function of Gd-DTPA and BSA concentrations for each combination of field strength and temperature. Because the relaxivity is defined as the coefficient of \([Gd]\) in equation (5.1), the terms \( \alpha_3, \alpha_4 \) and \( \alpha_5 \) in equation (5.16) can be combined into an effective relaxivity

\[
R_{1,\text{eff}} = \alpha_3 + \alpha_4 [BSA] + \alpha_5 [BSA]^2
\]

for comparison with the relaxivities obtained through the subset regression. While this ignores higher order terms in equation (5.16), it will be shown below that the p-values associated with these terms suggest that they are insignificant to the regression. Figure (5.12) allows relaxivities from subset regression to be compared with effective relaxivities from multivariate regression for all four temperatures tested at 8 Tesla.

With the exception of the 29 °C curve in figure (5.12), the 8 Tesla relaxivities at all temperatures show more curvature between 0 and 20 % w/w BSA concentration than the data of sta00. To quantify this curvature, the relaxivities for each temperature were separated. For a given temperature, the four relaxivities from subset regression were
combined with the effective four relaxivities from multivariate regression. Then this combined set of eight relaxivities was regressed with a second order polynomial of the form

\[ R_{1,\text{comb}} = \beta_0 + \beta_1 \cdot [BSA] + \beta_2 \cdot [BSA]^2. \]  

These quadratic fits for \( R_{1,\text{comb}} \) are indicated in figure (5.12) for the 8 Tesla data, and in figure (5.13) for the 1.5 Tesla data. Because the range of BSA concentrations in this work is smaller than the range used by Stanisz and Henkelman, the second order regression term in the 1.5 Tesla data returned a p-value of 0.12, indicating that it did not contribute significantly to the goodness of fit. Thus, the line determined by linear regression shown in figure (5.13) demonstrates good agreement with both the effective relaxivities and the relaxivities determined by subset regression. The statistical significance of the terms in equation (5.19) to the 8 Tesla data is shown in table (5.7). Except for the case of 29 °C, the three other polynomial fits at 8 Tesla showed a lower p-value for the quadratic term (i.e., greater statistical significance). However, when \( \beta_1 \) in equation (5.19) was subsequently forced to be zero, two of these three fits showed only a slight increase in \( r^2 \) as seen in table (5.8).

Finally, table (5.9) shows the statistical significance of the coefficients obtained from regressing the \( 1/T_1 \) data with equation (5.16). The data were regressed in two ways, expressing the concentration of Gd-DTPA in molarity and in terms of molality which is defined as the number of moles of Gd-DTPA per unit mass of water. The reasoning for this comparison was to determine if the change in relaxivity was more closely correlated to the increase in Gd-DTPA molecules per unit volume or with the effective decrease in
water molecules per unit volume caused by the addition of BSA and Gd-DTPA molecules. More p-values were increased than decreased when regressing with respect to molarity indicating fewer parameters were needed to model the data. This suggests that the addition of Gd-DTPA is the dominant effect in the increased relaxivity in the presence of macromolecules.

5.4 Conclusions

The relaxivity of Gd-DTPA in solutions of BSA was explored as a function of temperature and BSA concentration. Measurements at 1.5 Tesla and 22 °C were consistent with previous work by Stanisz and Henkelman (sta00). Maintenance of steady temperature control allowed measurements of $T_1$ as a function of temperature as well as the variation of relaxivity versus BSA concentration. As predicted by Reichenbach, et. al. (rei97), $T_1$ appeared linear over the range of 14-36 °C with a decreasing slope with increasing Gd-DTPA concentration. Furthermore, while relaxivity generally decreased with increased temperature, the strong dependence of relaxivity on BSA concentration remained.

At 8 Tesla (340 MHz), relaxivity was observed to increase sharply as a quadratic function of BSA concentration compared to a more gradual increase noted by Stanisz and Henkelman (sta00) at 64 MHz. Because a significant increase in relaxivity was noted in the range of 50 MHz due to increased rotational correlation time for complexes of 43 Gd-DTPA molecules per molecule of HSA (aim01), the data in this chapter suggest the existence of a similar increase in relaxivity for low binding ratio complexes of Gd-DTPA and BSA in the region of 340 MHz. This suggestion is corroborated by the work of Li
and co-workers (li00) who noted binding ratios of two or fewer Gd-DTPA molecules per BSA molecule using similar chemical preparation techniques as were used herein.
Figure 5.1 NMRD profile with spin-lattice relaxivity with data points for [Gd(DTPA)(H_2O)]^2 (figure 2.12 from tót01). Two calculated NMRD curves are plotted for the indicated values of \( \tau_R \).
Figure 5.2 Figure 5.1 from aim01 shows NMRD curves for (Gd-DTPA)$_{43}$-HSA complexes measured at 25 °C (■) and 39 °C (●).
**Figure 5.3** The temperature control system consisted of a reservoir of water (A) which contained a water pump and a heating coil. Water was pumped through Tygon® tubing to a sample holder (B) which held the samples during imaging. A temperature control device (C) selectively supplied current to the heating coil based on input from a thermistor placed in the reservoir.
Figure 5.4 A plastic food container was used to hold the Eppendorf microcentrifuge tubes containing the samples. After the samples were in place, the entire container was filled with water to prevent susceptibility artifacts at air interfaces. The latex tubing inside the container provided adequate heat exchange while limiting flow artifacts.
Figure 5.5 The linear dependence of $T_1$ as a function of temperature is seen as predicted in ref97. As the BSA concentration is increased, $T_1$ becomes shorter.
Figure 5.6 Histogram of flip angle values in the region of the sample holder containing the Gd-DTPA/BSA vials.
**Figure 5.7** Inversion recovery image acquired for 14°C, TI=3800 msec. The “plus” sign in the low flip angle region on the left hand side indicates the 5 x 5 block of pixels which were used to calculate the minimum SNR plotted in figure (minSNR). The “x” on the high flip angle of the right hand side indicates the 5 x 5 block of pixels used to calculate the maximum SNR plotted in figure (5.7).
Figure 5.8 Maximum SNR ratio for each inversion recovery image acquired for 14°C. For TI less than 2000 msec, a pattern similar to the signal intensity of inversion recovery images is seen. The low SNR at 3800 msec suggests an increase in noise lowers the overall SNR.
Figure 5.9 Minimum SNR for each inversion recovery image acquired at 14°C. A decrease in SNR at maximum TI similar to figure (5.7) is seen.
Figure 5.10 Data subsets for regression of $R_1=(1/T_1)$ with respect to [Gd-DTPA] for four fixed values of BSA concentration at 36 °C (top L-R: 0% v/v BSA, 3% v/v BSA; bottom L-R 12% v/v BSA, 18% v/v BSA).

Figure 5.11 Relaxivity as a function of macromolecular concentration at 1.5 Tesla and 20°C from sta00.
Figure 5.12 Gd-DTPA relaxivity at 8 Tesla as a function of BSA concentration for the four temperatures as indicated. The triangles represent relaxivities obtained by subsetting the data for fixed BSA concentration and temperature. The squares represent effective relaxivities obtained from equation (5.19) using the regression coefficients from equation (5.16). The curves are least square polynomial fits to second order in $[BSA]$. 
Figure 5.13
Table 5.1 Temperatures desired for Gd-DTPA relaxivity data and temperature ranges from fluorotopic measurements.

<table>
<thead>
<tr>
<th>Desired Temperature (°C)</th>
<th>Mean Temperature (°C)</th>
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</thead>
<tbody>
<tr>
<td>14</td>
<td>14.1 ± 0.3</td>
</tr>
<tr>
<td>21</td>
<td>20.9 ± 0.2</td>
</tr>
<tr>
<td>29</td>
<td>29.6 ± 0.1</td>
</tr>
<tr>
<td>36</td>
<td>36.2 ± 0.1</td>
</tr>
</tbody>
</table>

Table 5.2 $T_1$ values in milliseconds for solutions of Gd-DTPA and BSA at 14 °C.

<table>
<thead>
<tr>
<th>[Gd-DTPA] (mM)</th>
<th>0% BSA</th>
<th>3% BSA</th>
<th>12% BSA</th>
<th>18%BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>604 ± 51</td>
<td>716 ± 73</td>
<td>490 ± 35</td>
<td>423 ± 59</td>
</tr>
<tr>
<td>0.50</td>
<td>367 ± 77</td>
<td>409 ± 43</td>
<td>289 ± 30</td>
<td>258 ± 43</td>
</tr>
<tr>
<td>0.75</td>
<td>230 ± 23</td>
<td>301 ± 30</td>
<td>209 ± 53</td>
<td>177 ± 52</td>
</tr>
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<td>1.00</td>
<td>190 ± 14</td>
<td>224 ± 24</td>
<td>168 ± 149</td>
<td>131 ± 210</td>
</tr>
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<td>172 ± 20</td>
<td>129 ± 39</td>
<td>115 ± 31</td>
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<td>1.50</td>
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<td>121 ± 16</td>
<td>104 ± 24</td>
<td>118 ± 36</td>
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<tr>
<td>1.75</td>
<td>114 ± 15</td>
<td>131 ± 15</td>
<td>89 ± 29</td>
<td>72 ± 47</td>
</tr>
<tr>
<td>2.00</td>
<td>102 ± 17</td>
<td>116 ± 14</td>
<td>86 ± 80</td>
<td>50 ± 41</td>
</tr>
</tbody>
</table>

Table 5.3 $T_1$ values in milliseconds for solutions of Gd-DTPA and BSA at 21 °C. Indicated values in the vials containing 18% BSA were obscured by artifacts.
<table>
<thead>
<tr>
<th>[Gd-DTPA] (mM)</th>
<th>0% BSA</th>
<th>3% BSA</th>
<th>12% BSA</th>
<th>18% BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>806 ± 57</td>
<td>899 ± 91</td>
<td>662 ± 58</td>
<td>614 ± 74</td>
</tr>
<tr>
<td>0.50</td>
<td>498 ± 40</td>
<td>531 ± 53</td>
<td>417 ± 54</td>
<td>338 ± 52</td>
</tr>
<tr>
<td>0.75</td>
<td>356 ± 31</td>
<td>353 ± 28</td>
<td>316 ± 63</td>
<td>274 ± 79</td>
</tr>
<tr>
<td>1.00</td>
<td>259 ± 13</td>
<td>294 ± 30</td>
<td>259 ± 197</td>
<td>230 ± 252</td>
</tr>
<tr>
<td>1.25</td>
<td>211 ± 14</td>
<td>242 ± 19</td>
<td>181 ± 15</td>
<td>160 ± 25</td>
</tr>
<tr>
<td>1.50</td>
<td>158 ± 17</td>
<td>174 ± 19</td>
<td>148 ± 17</td>
<td>130 ± 43</td>
</tr>
<tr>
<td>1.75</td>
<td>144 ± 13</td>
<td>152 ± 18</td>
<td>140 ± 42</td>
<td>111 ± 63</td>
</tr>
<tr>
<td>2.00</td>
<td>139 ± 12</td>
<td>146 ± 17</td>
<td>112 ± 96</td>
<td>41 ± 49</td>
</tr>
</tbody>
</table>

**Table 5.4** $T_1$ values in milliseconds for solutions of Gd-DTPA and BSA at 29 °C.

<table>
<thead>
<tr>
<th>[Gd-DTPA] (mM)</th>
<th>0% BSA</th>
<th>3% BSA</th>
<th>12% BSA</th>
<th>18% BSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>981 ± 108</td>
<td>994 ± 194</td>
<td>858 ± 79</td>
<td>670 ± 91</td>
</tr>
<tr>
<td>0.50</td>
<td>604 ± 55</td>
<td>605 ± 62</td>
<td>453 ± 55</td>
<td>391 ± 63</td>
</tr>
<tr>
<td>0.75</td>
<td>413 ± 30</td>
<td>402 ± 32</td>
<td>322 ± 64</td>
<td>276 ± 97</td>
</tr>
<tr>
<td>1.00</td>
<td>319 ± 22</td>
<td>321 ± 42</td>
<td>266 ± 187</td>
<td>218 ± 188</td>
</tr>
<tr>
<td>1.25</td>
<td>237 ± 21</td>
<td>255 ± 20</td>
<td>226 ± 17</td>
<td>179 ± 31</td>
</tr>
<tr>
<td>1.50</td>
<td>192 ± 19</td>
<td>192 ± 18</td>
<td>179 ± 24</td>
<td>162 ± 39</td>
</tr>
<tr>
<td>1.75</td>
<td>168 ± 12</td>
<td>183 ± 16</td>
<td>159 ± 37</td>
<td>127 ± 60</td>
</tr>
<tr>
<td>2.00</td>
<td>160 ± 12</td>
<td>147 ± 15</td>
<td>125 ± 70</td>
<td>101 ± 57</td>
</tr>
</tbody>
</table>

**Table 5.5** $T_1$ values in milliseconds for solutions of Gd-DTPA and BSA at 36 °C.

<table>
<thead>
<tr>
<th>BSA (% v/v)</th>
<th>BSA (%w/w)</th>
<th>$R_1$ (mM·sec)$^{-1}$</th>
<th>$r^2$ (%)</th>
<th>$R_1$ (mM·sec)$^{-1}$ (sta00)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>4.59 ± 0.01</td>
<td>100.0</td>
<td>4.5</td>
</tr>
<tr>
<td>3</td>
<td>3.41</td>
<td>4.60 ± 0.01</td>
<td>99.9</td>
<td>4.8</td>
</tr>
<tr>
<td>12</td>
<td>13.45</td>
<td>6.81 ± 0.01</td>
<td>100.0</td>
<td>5.6</td>
</tr>
<tr>
<td>18</td>
<td>20.02</td>
<td>6.62 ± 0.01</td>
<td>99.9</td>
<td>6.3</td>
</tr>
</tbody>
</table>

**Table 5.6** Relaxivity as a function of macromolecular concentration at 1.5 Tesla and 22°C. Comparison values from Stanisz and Henkelman (sta00) are presented.
Table 5.7 Statistical significance of the parameters in equation (5.19) when regressed to the combined set of relaxivities from subset and multivariate regressions at 8 Tesla. Except for the relaxivity at 29 °C, the other temperatures show greater significance for the quadratic term than the linear term.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>p-value($\beta_1$)</th>
<th>p-value($\beta_2$)</th>
<th>$r^2$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.227</td>
<td>0.053</td>
<td>78.6</td>
</tr>
<tr>
<td>21</td>
<td>0.964</td>
<td>0.403</td>
<td>62.8</td>
</tr>
<tr>
<td>29</td>
<td>0.005</td>
<td>0.546</td>
<td>97.9</td>
</tr>
<tr>
<td>36</td>
<td>0.733</td>
<td>0.305</td>
<td>84.8</td>
</tr>
</tbody>
</table>

Table 5.8 Statistical significance of the parameters in equation (5.18) when $\beta_1$ is set to zero. Comparison with table (5.7) shows an increase in $r^2$ for three of the four temperatures.

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>p-value($\beta_1$)</th>
<th>$r^2$(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>0.003</td>
<td>75.4</td>
</tr>
<tr>
<td>21</td>
<td>0.007</td>
<td>69.0</td>
</tr>
<tr>
<td>29</td>
<td>0.000</td>
<td>90.0</td>
</tr>
<tr>
<td>36</td>
<td>0.000</td>
<td>87.0</td>
</tr>
<tr>
<td>Coefficient</td>
<td>14°C mM</td>
<td>14°C mmolal</td>
</tr>
<tr>
<td>-------------</td>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>(\alpha_0)</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>(A_1)</td>
<td>0.048</td>
<td>0.055</td>
</tr>
<tr>
<td>(\alpha_2)</td>
<td>0.203</td>
<td>0.203</td>
</tr>
<tr>
<td>(A_3)</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>(A_4)</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>(A_5)</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>(A_6)</td>
<td>0.632</td>
<td>0.299</td>
</tr>
<tr>
<td>(A_7)</td>
<td>0.236</td>
<td>0.123</td>
</tr>
<tr>
<td>(A_8)</td>
<td>0.157</td>
<td>0.070</td>
</tr>
<tr>
<td>(r^2) (%)</td>
<td>97.8</td>
<td>97.7</td>
</tr>
</tbody>
</table>

**Table 5.9** Tabulated p-values for the parameters in equation (5.16) fitted to 8 Tesla \(T_1\) relaxation rate data. The header row indicates whether the regression was performed with respect to the molarity or molality of Gd-DTPA. The arrows indicate changes in p-value greater than 0.05. Arrows are omitted when the p-value of a parameter was greater than 0.40 regardless of whether molarity or molality was considered.
CHAPTER 6

CONCLUSIONS

The installation of ultra high field MRI scanners is becoming more widespread (vau02, nor03), and researchers have reaped benefits of increased signal to noise ratio, high resolution and enhanced susceptibility effects (nor03). These benefits have come at a cost of image heterogeneity caused in part by large variations in the $B_1$ field used to excite spins in the imaging volume. Furthermore, decreased longitudinal relaxation rates and decreased contrast between tissues have been noted (ugu03).

This work began by quantifying $B_1$ field heterogeneity and exploring the impact on the $B_1$ field when a TEM coil is tuned to different modes. Based on the results of $B_1$ field mapping, methods of performing $T_1$ measurements were assessed for their efficacy under the conditions of extreme $B_1$ heterogeneity. After arriving at a suitable $T_1$ mapping method, relaxivity measurements were performed on solutions of Gd-DTPA and BSA. These data provide an important, high-field contribution to the ongoing debate (sta00) over the influence of biomacromolecules on the relaxivity of contrast agents.
With respect to field mapping, the spherical phantom data presented in this work have already provided a experimental data used to verify the accuracy of an FDTD model (ibr04). Such numerical methods have been used to test coil designs (liu04) and verify the underlying $B_1$ field physics (jin99).

By systematically mapping the fields produced as the coil was tuned, it was determined that modes 0, 1 and 2 had the best applicability for *in-vivo* images. *In-vivo* images of a healthy volunteer loosely followed the field distribution expected from the spherical phantom data. Based on these field maps, areas of the brain were targeted for image heterogeneity. It is interesting to note, that coronal slices slightly posterior to the central sulcus demonstrated a complimentarity between the three modes. That is to say that mode 1 provided the most homogeneous image, but that its low signal areas medially and laterally were complemented by strong signals in the images from mode 0 and mode 2 respectively.

In comparing methods of $T_1$ mapping, the gold standard, IR-SE, method was determined to be the least influenced by field inhomogeneity over the range of $40^\circ$ to $150^\circ$. The SR-SE method produced unreliable $T_1$ values, and $T_1$ maps created using the IR-RARE method were characterized by artifacts which carried through from the original images. The Gradient Echo Method (ven98) could not reproduce the $T_1$ in homogeneous phantom. And $T_1$ maps created from FLASH images were dominated by artifacts in the images attributed to long $TR$ times.

Based on the reliability of the IR-SE method, $T_1$ measurements were performed on samples of Gd-DTPA with varying admixtures of BSA. Previous studies at 1.5 Tesla (sta00) demonstrated that the relaxivity of the sample increases quadratically with BSA...
concentration. In this work, this quadratic dependence was shown to be more pronounced at 8 Tesla than at 1.5 Tesla. Based on a previous study of the binding of BSA and Gd-DTPA complexes, it was inferred that the 8 Tesla measurements were near a resonance in the NMRD curve of this complex. These data will provide useful insight into theoretical models of the molecular mechanisms of contrast agents.
BIBLIOGRAPHY


A.1 TEMcoil_B1.pro

This IDL program uses Ampere’s law to calculate the $B_1$ field in the interior of a 16-strut TEM coil for each of the 9 operating modes. The results are plotted as a snapshot in time with two-dimensional vectors in an axial plane.

;parameters
nstrut=16       ;number of struts
radius=4.       ;coil size
NN=200.        ;computed matrix size
skip=10.      ;size of gaps in displayed images
FOV=10.    ;field of view outside the coil
I=1.        ;maximum current
;variable declarations
Bx=fltarr(NN,NN) ;x components of $B_1$ field
By=fltarr(NN,NN) ;y components of $B_1$ field
bxtot=fltarr(nstrut,NN,NN) ;x component of vector sum
bytot=fltarr(nstrut,NN,NN) ;y component of vector sum
mask=fltarr(NN,NN) ;mask to avoid calculating the $B_1$ field outside the coil
xstrut=fltarr(nstrut) ;x components for locations for struts
ystrut=xstrut     ;y components for locations for struts
xpos=FOV/NN*findgen(NN) - FOV/2. ; convert strut locations to cm
ypos=xpos

;position struts on a circle
for i=0,nstrut-1 do begin
   xstrut(i)=radius*cos(2.*!Pi/nstrut*i)
   ystrut(i)=radius*sin(2.*!Pi/nstrut*i)
endfor

iphi=0
bxmin=fltarr(NN/skip,NN/skip) ; define a decimated matrix for display
bymin=bxmin & bymin(NN/skip-1,0)=82.
; display empty vector plot
velovect,bxmin,bymin,length=2 ,dots=1,title='Mode'+string(iphi)

; define boundaries of mask
A=(NN*radius/FOV)^2.
for ix=0,NN-1 do begin
  for iy=0,NN-1 do begin
    if (((ix-NN/2.)^2+(iy-NN/2)^2.) lt A) then mask(ix,iy)=1.
  endfor
endfor

; loop through all modes of the coil, making a field map for each
; Ampere’s law for an infinite wire \( B=\mu I/r \) is calculated in relative unit such that \( \mu \) and the conversion for length \( r \) are dropped
Also, trigonometric functions are replaced by \( (y/r) \) and \( (x/r) \)
for iphi=0,fix(nstrut/2) do begin
  bx=fltarr(NN,NN)
  by=fltarr(NN,NN)
  deltaphi=iphi*2.*!Pi/nstrut
  phistrut=deltaphi*findgen(nstrut)
  for ix=0,NN-1 do begin
    for iy=0,NN-1 do begin
      if (mask(ix,iy)) then begin
        for istrut=0,nstrut-1 do begin
          x=xpos(ix)-xstrut(istrut)
          y=ypos(iy)-ystrut(istrut)
          r=sqrt(x^2.+y^2.)
          ; ignore points too close to the strut
          if (r gt 0.2) then begin
            Bx(ix,iy)=Bx(ix,iy) +I*y/r^2. *cos(phistrut(istrut))
            By(ix,iy)=By(ix,iy)+I*x/r^2. *cos(phistrut(istrut))
          endif else begin
            Bx(ix,iy)=0.
            By(ix,iy)=0.
          endelse
        endfor
      endif
    endfor
  endfor
  bxtot(iphi,*,*)=bx(*,*)
  bytot(iphi,*,*)=by(*,*)
endfor

; display field map – expand the decimated matrix
for ii=0,fix(nstrut/2) do begin
  bxmin=fltarr(NN/skip,NN/skip) &
  bymin=bxmin
  bymin(NN/skip-1,0)=82. ; place a standard value in each matrix to standardize length scale
  velovect,bxmin,bymin,length=2 ,dots=1,title='Mode'+string(ii)
endfor
for iy=0,fix(NN/skip)-1 do begin
  bxmin(ix,iy)=bxtot(ii,skip*ix,skip*iy)
  bymin(ix,iy)=bytot(ii,skip*ix,skip*iy)
endfor
endfor

velovect,bxmin,bymin,length=2 ,dots=1,title='Mode'+string(ii)
; screen capture and save in JPEG format
cool=tvrd()
filename='Strut'+string(nstrut)+'Mode'+string(ii)+'skip'+string(skip)
write_jpeg,filename,not(cool),quality=100
endfor

end

A.2 fit_sin_neg.pro

This program fits equation (3.21) in a voxel-wise fashion to multiple GRE images acquired using the multiple angle method. For magnitude images, negative signs are assigned to signal data in order to allow fitting with a sine function which may include negative numbers. To this end, a first-pass fit is used on data points up to the first maximum. This fit is then used to determine the so-called “zero-crossing” points which specify the polarity of signal data. After assignment of positive and negative polarity, the entire set of signals is ready for fitting with equation (3.21).

; First, you must have ims(ix,iy,slice,flips), th=[flip angles]
;   mask(ix,iy,slice)
; Fitting function I: y = a(0)*sin(a(1)*th)
;
pro sin_fit,x,a,f,pder
  f=a(0)*sin(a(1)*x)
  if n_params() ge 3 then begin
    pder=fltarr(n_elements(x),2)
    pder(*,0)=sin(a(1)*x)
    pder(*,1)=a(0)*x*cos(a(1)*x)
  endif
end

starttime=systime()

;;;;;;;; main program ;;;;;;

outfile='ims_asigmachi_ballmodel_ax.dat'
index90=fix(0) ; index of ims(*,*,*,flip=90)
index45=fix(2) ; index of ims(*,*,*,flip=45)

v = 2  & nx=256  & ny=256 ; number of variables, and matrix size
nslice=10     ; number of slices

fit_func = 'sin_fit'
ims_a=fltarr(nx,ny,nslice,v)
ims_sigma=fltarr(nx,ny,nslice,v)
chisqr=fltarr(nx,ny,nslice)

;;;;; experimental flip angle th ;;;;;
thsrt=sort(th)
x = th(thsrt)
a = dblarr(v)             ; fitting parameters
w = fltarr(n_elements(th))+1       ; data point weighting = 1
tole=1.0e-12    ; fit function tolerance

for sl=0,(nslice-1) do begin
for ix=0,nx-1 do begin
for iy=0,ny-1 do begin
if (mask(ix,iy,sl) eq 0) then begin
ims_a(ix,iy,sl,*)=0.0
ims_sigma(ix,iy,sl,*)=0
endif else begin
;;;; assign the initial value to fit ;;;;
;;;; initial estimate of a(0) from max signal in voxel
a(0)=max(ims(ix,iy,sl,*))
;;;; initial estimate of a(1) from double angle method
if (ims(ix,iy,sl,index45) ne 0.) and (ims(ix,iy,sl,index90) lt $ 2.*ims(ix,iy,sl,index45)) then begin
a(1)=acos(0.5*ims(ix,iy,sl,index90)/ $
ims(ix,iy,sl,index45)) /(0.25*!Pi)
endif else begin ; if double angle is undefined, use max signal
a(1)=th(where(ims(ix,iy,sl,0:3) eq $
max(ims(ix,iy,sl,0:3))))/(0.5*!Pi)
endelse

;;;; extract signal intensity ;;;;;

y = reform(ims(ix,iy,sl,*))
y = y(thsrt)

;;;; first pass fit is through the first sine function peak
maxind=where(y(*) eq max(y(*)))
maxindex=maxind(0)
maxxi=maxindex-1

for ii=0,maxxi do begin
if (abs(y(ii+1)-y(ii)) ne (y(ii+1)-y(ii))) then begin
maxindex=ii-1
ii=fix(maxxi)
endif
endfor
if (maxindex lt 2) then maxindex=2

;;;;; non-linear least-squares fit ;;;;;
if (maxindex lt (n_elements(y)-2)) then begin
  xshort=x(0:maxindex+1) & yshort=y(0:maxindex+1)
  yfitsh=curvefit(xshort,yshort,w,a,sigma,function_name=fit_func,$
    chisq=chi, iter=it, itmax=1000, tol=tol)
  ; assign polarity based on first-pass
  y(*)=y(*)*(-1)^fix((a(1)*x(*)/!Pi))
endif else begin
  ; if first-pass fails, assign a(1) with max(signal) at 90 deg
  a(1)=0.5!*Pi/max(x)
  a(0)=max(y)
endelse

yfit=curvefit(x,y,w,a,sigma,function_name=fit_func,$
  chisq=chi, iter=it, itmax=1000, tol=tol)

chisqr(ix,iy,sl)=chi$
  ims_a(ix,iy,sl,*)=a$
  ims_sigma(ix,iy,sl,*)=sigma
endelse
endfor
endfor
save, filename=outfile,ims_a,ims_sigma,th,chisqr
print, 'Started ',starttime
print, 'Finished', systime()
end

A.3 double_flip.pro

This program uses equation (3.25) to create a two-dimensional map of the
effective flip angle using the double angle method for two GRE images acquired with
nominal flip angles of $\alpha$ and $2\alpha$. The user can input a value for the nominal flip angle so
that the effective flip angles can be normalized to dimensionless values like the $a_1$
parameter maps obtained with the multiple angle method.

; you must have a mask mask(nx,ny) already.
; parameters
count=0
nx=n_elements(ims(*,0,0,0))
ny=n_elements(ims(0,*,0,0))
nslice=10
read, 'Nominal flip angle (alpha) in degrees',nomflip
nomflip=float(nomflip)

indexal=1  ; subscript of alpha image
index2al=0  ; subscript of 2alpha image

; declaration
flip=fltarr(nx,ny,nslice)

for islice=0,(nslice-1) do begin
    im1=fltarr(nx,ny)
    im1(*,*)=ims(*,*,islice,indexal) ; the alpha flip image
    im2=fltarr(nx,ny)
    im2(*,*)=ims(*,*,islice,index2al) ; the 2alpha flip image
    
    for ix=0,nx-1 do begin
        for iy=0,ny-1 do begin
            if ((mask(ix,iy,islice)) and (im2(ix,iy) lt $ 2.*im1(ix,iy))) then begin
                flip(ix,iy,islice)=180./!Pi* $ acos(im2(ix,iy)/(2.*im1(ix,iy)))
            endif
        endfor
    endfor
endfor
flip=flip/nomflip
print,outfile, systime()
save, filename=outfile,flip
end

A.4 ir_sim_5perc350deg.pro

Over a range of flip angles, this program calculates the signal expected for an IR
sequence as a function of 9 different TI values and then adds 5% noise. These data are
then fit with the same fitting routine as is used in the program fit_t1_twice.pro found
below. The resulting distribution of fitted T1 values is plotted as a function of the flip
angle.

pro mono3t1fit,x,a,f,pder
; define the fitting function and partial derivatives
;    for the fitting routine

f=a(0)*(1.0-a(2)*exp(-a(1)*x))
if n_params() ge 4 then begin
    pder=fltarr(n_elements(x),3)
pder(*,0)=1.0-a(2)*exp(-a(1)*x)
  pder(*,1)=a(2)*a(0)*x*exp(-a(1)*x)
  pder(*,2)=-a(0)*exp(-a(1)*x)
endif
end

;CHAD CHANGES-------------
n_iter=3000 ; number of iterations
n_loop=35 ; number of flip angles
outfile='new_ir_sim_15perc350deg.dat'
noisemax=.05 ;
;--------------------------

starttime=systime()
a=dblarr(3)
t1=300.  ; predetermined T1 value
t2=20.  ; predetermined T2 value
taul=2^indgen(9)*25.  ;variable TI
x=taul  ; taul = inversion time (TI)
noise=fltarr(9)
s4=fltarr(9)

tau2=7.5  ; TE/2
thnom=fltarr(n_loop+1)
tlarr=fltarr(n_loop+1,n_iter)
stlarr=fltarr(n_loop+1,n_iter)
a0arr=fltarr(n_loop+1,n_iter)
a2arr=fltarr(n_loop+1,n_iter)
chiarr=fltarr(n_loop+1,n_iter)
tp=3
fit_func = 'mono3t1fit'

for tloop=1,n_loop do begin  ; flip angle loop
  if (tloop eq 2) then flip2time=systime()
  th1deg=10.*float(tloop) ; PREVIOUSLY 10.*float(tloop)
  print, 'flip = ',th1deg
  thnom(tloop)=th1deg
  th2=th1/2.
  th3=th2
  se4=1-(1-cos(th1))*exp(-tau1/t1)
  se4=se4*sin(th2)*(sin(th3/2.))^2*exp(-2*tau2/t2)

  for i=0,n_iter-1 do begin ; repeat fitting process 3000 times
    noise=noisemax*randomn(seed,9)
    s4(*)=se4(*)*(1.+noise)
    s4=abs(s4)
    ;-----t1 fit
    y = s4
    ;y = y(tisort)
  ;;;; assign the initial value to fit ;;;;
  a(0)=max(y)
  a(1)=0.001
a(2)=2.
tole=1.0e-12
;;; polarity restoration ;;;
minind=where(y eq min(y))
mini=fix(minind(0))
if ((mini gt 0) and (mini lt (n_elements(y)-1))) then begin
  y1=fltarr(n_elements(y) -1)
  x1=fltarr(n_elements(y) -1)
  y1(0:mini-1)=-1.*y(0:mini-1)
  y1(mini:*)=y(mini+1:*)
  x1(0:mini-1)=x(0:mini-1)
  x1(mini:*)=x(mini+1:*)
endif else begin
  x1=x(where(y(*) ne min(y)))
  y1=y(where(y(*) ne min(y)))
endelse

w=replicate(1.,n_elements(y1))
yfit=curvefit(x1,y1,w,a,sigma,function_name=fit_func,$
  chisq=chi,iter=it,itmax=1000,tol=tole)
tiinit=alog(a(2))/a(1)
negti=where(x lt tiinit)
if (negti(0) ne -1) then begin
  y(negti)=-1.*y(negti)
endif

;the first fit will give initial values for a and determine
zero crossing

;;; non-linear least-squares fit ;;;
  w=replicate(1.,n_elements(y))
yfit=curvefit(x,y,w,a,sigma,function_name=fit_func,$
  chisq=chi,iter=it,itmax=1000,tol=tole)
  tlarr(tloop,i) = 1/a(1)
  chiarr(tloop,i)=chi
  a0arr(tloop,i)=a(0)
  a2arr(tloop,i)=a(2)

endfor
endfor

save, filename=outfile,tlarr,chiarr ,a0arr,a2arr,thnom
print, 'start:  ',starttime
print, 'flip2time: ',flip2time
print, 'finish:  ',systime()
end

A.5 th1_th2.pro

To calculate the effect of applying equation (4.3) to SR-SE data, simulated spin
echo signals are created using a Bloch equation simulation over a range of flip angles.
The signal is allowed to evolve to a steady state before storing the magnetization. These stored values are fit as a function of $TR$. The fitted $T_1$ values are plotted as a function of flip angle.

; this program tries to calculate the approach to steady state by using the rotation matrices, etc. for only the ungated sequence. ; the amount of rotation due to inhomogeneity or rf phase cycling

```fortran
pro mono3t1fit,x,a,fder
    f=a(0)*(1.0-a(2)*exp(-a(1)*x))
    if n_params() ge 4 then begin
        fder=fltarr(n_elements(x),3)
        fder(*,0)=1.0-a(2)*exp(-a(1)*x)
        fder(*,1)=a(2)*a(0)*x*exp(-a(1)*x)
        fder(*,2)=-a(0)*exp(-a(1)*x)
    endif
    end
```

```fortran
v = 3
fit_func = 'mono3t1fit'

; size of ims
param = fltarr(v*2) ; array stores fitting result
a = dblarr(v) ; fitting parameters

pi=!Pi
tau=9.6
T1=227.0
t2=15.
print, tau,t1,t2
adeg1=indgen(19)*10.
adeg2=2.*adeg1
nadeg=n_elements(adeg1)
;print, adeg1, adeg2, 'degrees'
a1=adeg1*pi/180. & a2=adeg2*pi/180.
M0=[[0], [0], [1.]]

n=50 ; number of TR intervals
ntr=11 ; & ftr= 5000/ntr ; number of calcs for different TR ; tr=indgen(ntr)*ftr
tr=[3000., 80., 100., 150., 200., 300., 400., 500., 750., 1000., 1500.]; CHAD CHANGE
tr=tr(sort(tr))
nth=60. & fth=360/nth ; number of phase angles
thdeg=indgen(nth)*fth
th=thdeg*pi/180.
signal=complexarr(ntr,nadeg)
lll=fltarr(ntr,nadeg)
w = fltarr(n_elements(tr))+1 ; weighting = 1
t1fit=fltarr(nadeg)
```

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for ia=0,nadeg-1 do begin
  Rxa1=[[1.,0,0],[0 ,cos(a1(ia)), sin(a1(ia))],[0, -sin(a1(ia)),
cos(a1(ia))]]
  Rxa2=[[1.,0,0],[0 ,cos(a2(ia)), sin(a2(ia))],[0, -sin(a2(ia)),
cos(a2(ia))]]
  E1=exp(-tau/T1) & E2=exp(-tau/T2)
  S=[[E2,0,0],[0,E2,0],[0,0,E1]]

for j=1,ntr-1 do begin
  t=tr(j)-tau
  Elt=exp(-t/T1) & E2t=exp(-t/T2)
  St=[[E2t,0,0],[0,E2t,0],[0,0,Elt]]

  m1neg=fltarr(3,1)
  m2pos=fltarr(3,1)
  m2neg=fltarr(3,1)
  m2pos=fltarr(3,1)
  me=fltarr(3,n,nth) ; x, y, z coord, nth RF pulse, nth-th theta
  mtr=fltarr(3,n,nth)
  m1neg=M0

  for ii=0,nth-1 do begin
    Rz=[[cos(th(ii)), sin(th(ii)) ,0],[-sin(th(ii)) ,cos(th(ii)), 0],[0,
    0, 1]]
    tht=th*t/tau
    Rzt=[[cos(tht(ii)), sin(tht(ii)) ,0],[-sin(tht(ii)) ,
cos(tht(ii)), 0],[0, 0, 1]]

    m1pos=Rxa1##m1neg
    m2neg=Rz##S##m1pos+(1-E1)*M0
    m2pos=Rxa2##m2neg

    me(*,i,ii)=Rz##S##m2pos+(1-E1)*M0
    mtr(*,i,ii)=Rzt##St##m2pos+(1-E1t)*M0
    m1neg=mtr(*,i,ii)
  endfor ; nth RF pulse loop
endfor; theta loop

signal(j,ia)=total(complex(me(0,n-1,*),me(1,n-1,*)))/nth
  ll=|sin(a1(ia))*(sin(a2(ia)/2.))^2*E2*E2
  lll(j,ia)=ll*(1-e1t)
endfor

plot,tr,abs(signal(*,ia)),xtitle='TR',ytitle='signal',psym=1,title='fli
p angle alpha ='+string(fix(a1(ia)*180./!Pi));,yrange=[0,1]
print,adeg1(ia),'ready (integer)'
a(0)=max(abs(signal)) ; S(0)
a(1)=0.004                ; T1 rate
a(2)=1.0        ; DR
tole=1.0e-12

;;;; extract signal intensity ;;;;
y = abs(signal(*,ia))
x=tr
yfit=curvefit(x,y,w,a,sigma,function_name=fit_func,$
      chisq=chi,iter=it,itermax=1000,tol=tole)

param(0:v-1) = a
param(v:2*v-1) = sigma
tlfit(ia) = 1/a(1)

chaddy=findgen(max(tr))
print, tlfit(ia)
oplot, chaddy,a(0)*(1.-a(2)*exp(-chaddy*a(1))),linestyle=2

cool=not(tvrd())
write_jpeg, 'SRsim_flashe4
'+strcompress(string(fix(a1(ia)*180./!Pi)),/remove_all)+'deg.jpg',cool,
      quality=100

endfor ; end adeg loop
end

A.6 tracemagroi.pro

This program is an ROI tool which allows the user to specify an image or
parameter map in the array called picture. The user specifies a magnification factor and
draws a ROI using the IDL routine defroi. The function creates a binary mask in the array
called mask. The program then plots a histogram in the area of picture bounded by the
ROI. The user can specify upper and lower bounds for the ROI is some of the values are
believed to be the result of image artifacts. The thresholded mask is then used to
generate the mean and standard deviation of array elements in the region of interest.

; tracemagroi.pro
; start with your image in the array picture(*,*)
; left click on points along the border of the roi
; right click to close the roi
; outputpicture= is a float array of 0's and 1's
; the interior of the roi is filled

elem=size(picture)
print, 'Mag factor '
read, magf
magflt=float(magf)
window,0,xpos=0,ypos=fix(0.1*lngth),xsize=magflt*wdth,ysize=magflt*lngth
erase
tvsc1, rebin(picture,fix(magflt*wdth), fix(magflt*lngth))
pnts0=defroi(magflt*wdth,magflt*lngth)
pnts0=float(pnts0)
mask=fltarr(wdth,lngth)
xpnts=pnts0-magflt*wdth*float(fix(pnts0(*)/(magflt*wdth)))
ypnts=float(fix(pnts0(*)/(magflt*wdth)))
mask(fix(xpnts/magflt), fix(ypnts/magflt))=1.0
window,1,xpos=0,ypos=(magflt+0.1)*lngth,xsize=wdth,ysize=lngth
wset,0
erase
tvsc1, rebin(mask*picture,magflt*wdth,magflt*lngth)
print, 'pixels in roi: ',total(mask)
roiave=total(mask*picture)/total(mask)
print, 'average: ',roiave
stdv=sqrt(total((mask*picture-roiave*mask)^2)/(total(mask)-1))
print, 'standard dev: ',stdv
end

A.7 fit_t1_twice.pro

For an input array called \textit{ims(nx,ny,nslice,nti)}, a voxel-wise fit is performed on the data using the parameterized equation (4.6). The program also assumes a mask to specify the region of voxels to be fit, and a list of \textit{TI} intervals. After the parameters are defined, the magnitude data have their positive and negative signs assigned by the first-pass fit described in Section (4.3.3). The fitted \textit{T}_1 values are stored in an array called \textit{t1map}. The fitting parameters are also stored along with the associated error terms and the chi squared value for that voxel.

; fit_t1_twice.pro
;
; remove the minimum, perform a first-pass fit,
; use the first pass fit to determine the crossing point,
; then refit, with the first-pass parameters as a starting point
T1 computation using magnitude images

Required input parameters:
- ims (3D array with all subtracted images)
- mask (2D binary array for excluding unwanted region)
- ti (1D array contains TI times in s)

Fitting function I: \( y = a[0](1-a[2]\times\exp(-a[1]\times T1)) \)

where \( a[0] \) represents \( S_0 \), \( a[1] \) is \( 1/T1 \) and \( a[2] \) is dynamic range (DR)

```plaintext
pro mono3t1fit,x,a,f,pder
    f=a(0)*(1.0-a(2)*exp(-a(1)*x))
    if n_params() ge 4 then begin
        pder=fltarr(n_elements(x),3)
        pder(*,0)=1.0-a(2)*exp(-a(1)*x)
        pder(*,1)=a(2)*a(0)*x*exp(-a(1)*x)
        pder(*,2)=-a(0)*exp(-a(1)*x)
    endif
end
```

Main program:

```plaintext
v = 3
fit_func = 'mono3t1fit'

dim = size(ims)                      ; size of ims
param = fltarr(dim(1),dim(2),v*2)    ; array stores fitting result
chisqr=t1map

for loop begins
    for i = 0,dim(1)-1 do begin
        for j = 0, dim(2)-1 do begin
            if (mask(i,j) eq 0 ) then begin
                param(i,j,*) = 0.0            ;;var from mask31014.pro
            endif else begin
                y = reform(ims(i,j,0,*))
                y = y(tisort)

assign the initial value to fit
    a(0)=max(y)
```

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a(1)=0.001
a(2)=2.
tole=1.0e-12
;;;;; polarity restoration ;;;;;
minind=where(y eq min(y))
mini=fix(minind(0))
if ((mini gt 0) and (mini lt (n_elements(y)-1))) then begin
  y1=fltarr(n_elements(y) -1)
x1=fltarr(n_elements(y) -1)
y1(0:mini-1)=-1.*y(0:mini-1)
y1(mini:*)=y(mini+1:*)
x1(0:mini-1)=x(0:mini-1)
x1(mini:*)=x(mini+1:*)
endif else begin
  x1=x(where(y(*) ne min(y)))
y1=y(where(y(*) ne min(y)))
endelse
w=replicate(1.,n_elements(y1))
yfit=curvefit(x1,y1,w,a,sigma,function_name=fit_func,$
  chisq=chi,iter=it,itmax=1000,tol=tole)
tiinit=alog(a(2))/a(1)
negti=where(x lt tiinit)
if (negti(0) ne -1) then begin
  y(negti)=-1.*y(negti)
endif

;the first fit will give initial values for a and determine zero
crossing
;;;;; non-linear least-squares fit ;;;;;
w=replicate(1.,n_elements(y))
yfit=curvefit(x,y,w,a,sigma,function_name=fit_func,$
  chisq=chi,iter=it,itmax=1000,tol=tole)
param(i,j,0:v-1) = a
param(i,j,v:2*v-1) = sigma
t1map(i,j) = 1/a(1)
chisqr(i,j)=chi

endfor
endfor

save, filename=outfile,t1map,param,chisqr
print, 'starttime:  ',starttime
print, 'finished:  ',systime()
end

A.8 regressT1.pro
This program allows the user to specify multiple regions of interest in a $T_1$ map containing multiple contrast agent samples. The user assigns a parameter (i.e., contrast agent concentration) to the ROI, and the program calculates the mean and standard deviation within the ROI. The user is able to select thresholds for maximum and minimum values in case outlying points are apparent.

The program can regress a line through the mean $1/T_1$ values as a function of the assigned concentration parameter. Also, the program dumps all of the $1/T_1$ values along with their fitting error into a text file. These were the text files which were imported into MINITAB for subsequent regression.

; Chad changes ======== important parameters ========
regresstitle='allpoints regress 8 T 36 deg gdsatemp 4 points 18% BSA'
xt='Gd-DTPA (mM)'
yt='R1 (1/sec)'
nsamp=8.
magfx=6. & magfy=6.
realpic=t1map ; rebin(t1map,magfx*nx,magfy*ny)
nx=n_elements(realpic(*,0)) & ny=n_elements(realpic(0,*))
thresh=5.
maxv0=1300. & maxv=maxv0
;================================= 

crpnum=0
window, 0
tvscl, rebin(bytscl(realpic,min=0,max=maxv),2.*nx,2.*ny)
print, 'Number of samples' & read, nsamp ; number of sample vials

print, 'Select the upper left corner'
cursor,x,y,/dev
x=x/2. & y=y/2.
print, 'Hit an integer' & read, crpnum
print, 'Select the lower right corner'
cursor,xl,yl,/dev
xl=xl/2. & yl=yl/2.
realpic=realpic(x:xl,y1:yl)

; coarse zoom which doesn't interpolate like IDL function rebin
prettypic=fltarr(magfx*nx,magfy*ny)
for i=0,nx-1 do begin
  for j=0,ny-1 do begin

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prettypic(magfx*i:(magfx*(i+1)-1),magfy*j:(magfy*(j+1)-1))=bytscl(realpic(i,j),min=0,max=maxv0)
endfor
endfor

mask=fltarr(nx,ny,nsamp)
histi=fltarr(2.*nx,4.*ny,nsamp)
tax=sindgen(nsamp)
temp=fltarr(magfx*nx,magfy*ny)
parm=fltarr(nsamp)
means=fltarr(nsamp)
stdvs=fltarr(nsamp)
nn=fltarr(nsamp)
conc=fltarr(nsamp)
rlmap=param(x:x1,y:y,1) & rlerrmap=param(x:x1,y:y,4)
;flips=fltarr(nsamp)

window, 0,xsize=magfx*nx,ysize=magfy*ny
window, 1,xsize=2.*nx,ysize=4.*ny
cont='nope'
crp='a'
fnchad='a'
crpnum=0.
wset, 0 & tvscl, prettypic
;stop

for i=0,nsamp-1 do begin
  if strcmp(cont,'do',2,/FOLD_CASE) then i=i-1
  mask(*,*,i)=0.
temp=fltarr(magfx*nx,magfy*ny) & tempmask=fltarr(nx,ny)
  print, i,' Text label ' & read, crp
txt(i)=crp
  print, 'Parameter (e.g. concentration)'
  read, crpnum
  print, '  create ROI in window 0'
wset, 0 & cursor,xcntr,ycntr,/dev
  roi=defroi(magfx*nx,magfy*ny)
temp(roi)=1.
  for j=0,nx-1 do begin
    for k=0,ny-1 do begin
      tempmask(j,k)=total(temp(magfx*j:(magfx*(j+1)-1),magfy*k:(magfy*(k+1)-1)))
    endfor
  endfor
  tempmask=float(tempmask(*,* gt 0.)
  cont='nope'
  stop
  while ((not(strcmp(cont,'ok',2,/FOLD_CASE))) and
         (not(strcmp(cont,'do',2,/FOLD_CASE)))) do begin
    minv=1. & maxv=maxv0 & minverr=0. & maxverr=max(rlerrmap)
    maxie=max(realpic*temp)
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minnie = min(maxv, maxie)

wset, 1 & plot,
histogram(realpic * tempmask, min=1, max=minnie)

print, 'mean / number of ROI points'
meanie = total(tempmask * realpic) / total(tempmask)
print, meanie, total(tempmask)
print, 'T1 ', '1000*R1err'
roi = where(tempmask(*,*) ne 0.)
tempmask = tempmask * realpic

for k = 0, n_elements(roi) - 1 do begin
    print, tempmask(roi(k)), 1000.*r1errmap(roi(k)), '10^-3'
endfor

print, 'Continue (ok,h=histogram,do=do over) :' & read, cont
if (strcmp(cont, 'h', /fold_case)) then begin
    print, 'Min T1 value, min sigma value ' & read, minv, minverr
    print, 'Max T1 value, max sigma value ' & read, maxv, maxverr
endif

roi = where((tempmask(*,*) ge minv) and (tempmask(*,*) le maxv) and r1errmap(*,*) $
    and (r1errmap(*,*) lt maxverr) and (r1errmap(*,*) gt minverr))
tempmask = fltarr(nx, ny) & tempmask(roi) = 1.
wset, 1 & plot, histogram(realpic * tempmask, min=1)
endwhile
mask(*,*,i) = tempmask(*,*)
wset, 1 & histi(*,*,i) = tvrd()

tempr1 = tempmask * r1map(*,*) & temperr = tempmask * r1errmap(*,*) & wo = where(tempr1 gt 0.0000001)
if (i eq 0) then begin
    all_y = tempr1(wo) & all_yerr = temperr(wo) &
    parm = replicate(crpnum, n_elements(wo))
endif else begin
    all_y = [all_y, tempr1(wo)] & all_yerr = [all_yerr, temperr(wo)]
    & parm = [parm, replicate(crpnum, n_elements(wo))]
endelse

nn(i) = total(mask(*,*,i))
conc(i) = crpnum
endfor

all_y = 1000.*all_y & all_yerr = 1000.*all_yerr
result = regress(parm, all_y, SIGMA = sigma, CONST = const, MEASURE_ERRORS = all_yerr)
xchad = findgen(max([2, parm]) + 1.)
window, 0,xsize=500,ysize=350
plot, parm, all_y,
psym=5,title=regresstitle,ytitle=yt,xtitle=xt,xrange=[0,max(parm)+1.]
ophlet, xchad,const+result(0)*xchad,linestyle=2
errplot, parm, all_y-all_yerr, all_y+all_yerr
tvscl, not(tvrd())

window, 4,xsize=500,ysize=350
plot, parm, all_y,
psym=1,title=regresstitle,ytitle=yt,xtitle=xt,xrange=[0,max(parm)+1.]
ophlet, xchad,const+result(0)*xchad,linestyle=2
tvscl, not(tvrd())

print, const, result, sigma
print, '===================='
stamp=STRMID(SYSTIME(0), 0, 3)+STRMID(SYSTIME(0),
11,2)+STRMID(SYSTIME(0), 14,2)+STRMID(SYSTIME(0), 17,2)
fnchad='regression results '+stamp+regresstitle
save, filename=fnchad+'.dat',parm, conc, nn,all_y,all_yerr,const,
result, sigma,mask

window, 2,xsize=3.*nx,ysize=12.*ny
count=0
for i=0,nsamp-1 do begin
wset , 2
tvscl,
rebin(bytscl(realpic,min=0,max=maxv0)+100.*mask(*,*,i),nx,2.*ny),0,(4.*
(2.-count)+1.)*ny
tvscl, histi(*,*),nx,(4.*(2.-count))*ny
print, 'Sample: '+txt(i)
print, 'Parameter: ',conc(i)
print, ' pixels ',nn(i)
print, 'count=count+1
if ((count/3.) eq fix(count/3.)) then begin
print, 'Pausing =========='
read, crp
wset, 2 & erase
count=0
endif
endfor

print, 'Regression results'
print, 'const, slope, sigma'
print, const, result, sigma
print, 'R1= '+string(const)+' + '+string(result)+'*param'
print, 'slope = '+string(result)+'+/-'+string(sigma)
print, 'Not done YET'
print, 'Pausing =========='
print, 'dat and txt filenames =',fnchad
print, 'conc','r1s','r1serr'

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openw, 1, fnchad+'.txt'
for i=0, n_elements(parm)-1 do begin
    print, parm(i), all_y(i), all_yerr(i)
    printf, 1, parm(i), all_y(i), all_yerr(i)
endfor
close, 1

print, ' Basta cosi'
print, 'dat and txt filenames =', fnchad

delvar, histi
end
APPENDIX B

VERIFICATION OF TRANSMIT AMPLIFIER SETTING

The relationship between the console power setting, $T_x$ in equation (3.17), and the power produced by the transmit circuit was verified using a calibrated $50\Omega$ load. The $50\Omega$ attenuator (Tenuline Coaxial Attenuator, Model 8329-300, Bird Electronic Corp. Cleveland Ohio) was connected to the transmit line and pulsed for various settings of $T_x$ (in decibels) as used in typical scanning protocols. From equation (3.17) the expected relationship between transmitted power, $P$, and $T_x$ is

$$P = P_0 \cdot 10^{-(T_x - T_0)/10}.$$  \hspace{1cm} (B.1)

The loss of a factor of 2 in the exponent is a result of the quadratic dependence of power on magnetic field (see Section 3.1.3.1).

The data are shown in table (B.1) and plotted in figure (B.1) as a function of $T_x$. The IDL chi-squared minimization routine curvefit was used to create the best-fit function

$$P = (190.6) \cdot 10^{-0.0949 T_x}.$$  \hspace{1cm} (B.2)
for these data. In figure (B.1) the dashed line represents the plot of equation (B.2) and the solid line represents the plot of equation (B.1) with $P_0=190$ and $T_0=0$. Below $T_x$ settings of 20 dB, significant agreement is observed between equation (B.1) and the data points.
Figure B.1 Transmitted power in a 50Ω load as a function of $T_x$ setting (in decibels) on the control console.
<table>
<thead>
<tr>
<th>$T_x$ Setting (dB)</th>
<th>Power (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>0.002</td>
</tr>
<tr>
<td>40</td>
<td>0.016</td>
</tr>
<tr>
<td>30</td>
<td>0.158</td>
</tr>
<tr>
<td>20</td>
<td>1.452</td>
</tr>
<tr>
<td>15</td>
<td>5.076</td>
</tr>
<tr>
<td>14</td>
<td>6.402</td>
</tr>
<tr>
<td>13</td>
<td>8.223</td>
</tr>
<tr>
<td>12</td>
<td>10.583</td>
</tr>
<tr>
<td>11</td>
<td>13.416</td>
</tr>
<tr>
<td>10</td>
<td>17.987</td>
</tr>
<tr>
<td>9</td>
<td>21.855</td>
</tr>
<tr>
<td>8</td>
<td>28.105</td>
</tr>
<tr>
<td>7</td>
<td>34.572</td>
</tr>
<tr>
<td>6</td>
<td>44.2</td>
</tr>
<tr>
<td>5</td>
<td>55.1</td>
</tr>
<tr>
<td>4</td>
<td>67.9</td>
</tr>
<tr>
<td>3</td>
<td>89.2</td>
</tr>
<tr>
<td>2</td>
<td>114.5</td>
</tr>
<tr>
<td>1</td>
<td>148.1</td>
</tr>
<tr>
<td>0</td>
<td>188.7</td>
</tr>
<tr>
<td>-1</td>
<td>241.6</td>
</tr>
<tr>
<td>-2</td>
<td>305.2</td>
</tr>
<tr>
<td>-3</td>
<td>395.2</td>
</tr>
<tr>
<td>-4</td>
<td>470.4</td>
</tr>
<tr>
<td>-5</td>
<td>563.4</td>
</tr>
<tr>
<td>-6</td>
<td>689.9</td>
</tr>
</tbody>
</table>

**Table B.1** Transmitted power in a 50Ω load as a function of $T_x$ setting (in decibels) on the control console.
APPENDIX C

PHANTOM $B_1$ FIELD MAPPING
Figure C.1 Mode 0 /Axial Ten axial slices of phantom image data (top) along with parameter maps for \( a_0 \) (center) and \( a_1 \) (bottom) for a coil tuned to mode 0. The nominal flip angle of the image is 50º. The excitation port is located in the lower left hand corner as viewed by the reader between the 7 and 8 o’clock positions.
Figure C.2 Mode 0 / Coronal  Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 0. The nominal flip angle of the image is 45°. The excitation port is located nearest to the lowest slice (i.e. the most posterior for a prone patient) which occurs in this figure in the lower left corner in each of the three sets.
Figure C.3 Mode 0 / Sagittal Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 0. The nominal flip angle of the image is 45°. The excitation port is located near the bottom of each individual image (most posterior for a prone patient).
Figure C.4 Mode 1 / Axial Ten axial slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 1. The nominal flip angle of the image is $45^\circ$. The excitation port is located in the lower left hand corner as viewed by the reader between the 7 and 8 o’clock positions. The images appear bright on the side distal to the excitation port.
Figure C.5 Mode 1 / Coronal Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 1. The nominal flip angle of the image is 35°. The excitation port is located nearest to the lowest slice (i.e. the most posterior for a prone patient) which occurs in this figure in the lower left. Again, the brightest slices are distal to the excitation port as was seen in figure (C.4).
Figure C.6 Mode 1/Sagittal Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 1. The nominal flip angle of the image is 45°. The excitation port is located near the bottom of each individual image (most posterior for a prone patient). Regions of low signal demonstrate low values for $a_1$ and large values for $a_0$. 
Figure C.7 Mode 2 / Axial Ten axial slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 2. The nominal flip angle of the image is $57^\circ$. Patterns of radial spokes are seen in the both parameter maps. However, in a given slice, the patterns of spokes appear displaced on the $a_0$ and $a_1$ parameter maps.
**Figure C.8** *Mode 2 / Coronal* Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 2. The nominal flip angle of the image is $45^\circ$. 
Figure C.9 *Mode 2 / Sagittal* Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 2. The nominal flip angle of the image is 45°.
Figure C.10 Mode 3 / Axial Ten axial slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 3. The nominal flip angle of the image is $67^\circ$. Patterns of radial spokes are seen in the both parameter maps. However, in a given slice, the patterns of spokes appear displaced on the $a_0$ and $a_1$ parameter maps.
Figure C.11 Mode 3 / Coronal  Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 3. The nominal flip angle of the image is 45°.
Figure C.12 Mode 3 / Sagittal Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 3. The nominal flip angle of the image is 45°.
Figure C.13 Mode 4 / Axial  Ten axial slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 4. The nominal flip angle of the image is 45°. In the images and parameter maps, the most distal slices are contained within the central region of the TEM coil where very little excitation is observed.
Figure C.14 Mode 4 / Coronal Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 4. The nominal flip angle of the image is 45°.
Figure C.15 Mode 4 / Sagittal Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 4. The nominal flip angle of the image is $45^\circ$. 
Figure C.16 Mode 5 / Axial Ten axial slices of phantom image data (top) along with parameter maps for $a_0$(center) and $a_1$ (bottom) for a coil tuned to mode 5. The nominal flip angle in the image data is 45°. The weak signal intensity in the central region of axial slices was predicted by the heuristic model in figure (3.4). The weak signals are strongly influenced by noise which creates the erroneous values in the $a_0$ and $a_1$ parameter maps.
Figure C.17 Mode 5 / Coronal Ten coronal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 5. The nominal flip angle of the image is 45º. The fitted parameters are dominated by noise and artifacts.
Figure C.18 Mode 5 / Sagittal Ten sagittal slices of phantom image data (top) along with parameter maps for $a_0$ (center) and $a_1$ (bottom) for a coil tuned to mode 5. The nominal flip angle of the image is 45°.
**Figure D.1** Images used for generating field maps for brain imaging with a TEM coil tuned to mode 0. The excitation port of the coil is located near the occipital lobe. This accounts for the bright signal posteriorly.
Figure D.2 The parameter map for $a_0$ for a TEM coil tuned to mode 0 shows strong receive sensitivity near the location of the excitation port coil (posterior) and significant signal loss on the patient’s right side (top row).
Figure D.3 The parameter map for $a_1$ for a TEM coil tuned to mode 0 shows $B_1^+$ excitation near the location of the excitation port coil (posterior) and less excitation on patient’s left side (bottom row).
Figure D.4 Images used for generating field maps for a TEM coil tuned to mode 0. The excitation port of the coil is located near the frontal lobe. This accounts for the bright signal anteriorly.
Figure D.5 The parameter map for $a_0$ for a TEM coil tuned to mode 0 shows strong receive sensitivity near the location of the excitation port coil (anterior) and significant signal loss on the patient’s left side (bottom row).
Figure D.6  The parameter map for $a_1$ for a TEM coil tuned to mode 0 shows $B_1^+$ excitation near the location of the excitation port coil (posterior) and slightly less excitation on patient’s right side (top row).
Figure D.7 Images used for generating field maps for a TEM coil tuned to mode 1. The excitation port of the coil is located near the occipital lobe (posterior). While greater signal intensity is observed centrally, significant signal loss is observed posterior to the central gyrus.
Figure D.8  The parameter map for $a_0$ for a TEM coil tuned to mode 1 shows strong receive sensitivity near the excitation port coil (posterior) as well as distal to the excitation port (anterior) with signal loss between. Compared to the mode 0 results above, greater signal is observed in medial slices.
Figure D.9 The parameter map for $a_1$ for a TEM coil tuned to mode 1 shows the highest $B_1^+$ excitation near the location of the excitation port coil (posterior), very little excitation near the central gyrus and increased excitation in the frontal lobe in comparison to mode 0. Lateral slices demonstrate greater excitation than the mode 0 parameter maps above.
Figure D.10 Images used for generating field maps for a TEM coil tuned to mode 1. The excitation port of the coil is located near the frontal lobe (anterior). The increased signal intensity in lateral slices seen in figure (D.7) is more pronounced with the excitation port placed anteriorly.
Figure D.11  The parameter map for $a_0$ for a TEM coil tuned to mode 1 shows strong receive sensitivity near the location of the excitation port coil (anterior) as well as distal to the excitation port (anterior) with signal loss anterior to the central sulcus. Again, greater signal is observed in lateral slices compared to the mode 0 results above.
Figure D.12  The parameter map for \( a_1 \) for a TEM coil tuned to mode 1 shows more uniform \( B_1^+ \) excitation along the anterior/posterior direction than mode 0. Signal loss is seen anterior to the central sulcus, and lateral slices demonstrate greater excitation than the mode 0 parameter maps above.
Figure D.13 Images used for generating field maps for a TEM coil tuned to mode 2. While the excitation port is located near the occipital lobe (posterior), increased signal intensity is seen mostly in the frontal lobe. Instead of increased signal intensity in medial slices, lateral slices are better visualized.
Figure D.14  The parameter map for $a_0$ in a TEM coil tuned to mode 2 with the excitation port placed posteriorly shows strong receive sensitivity distal to the excitation port coil. Again, greater signal is observed in lateral slices compared than in the medial slices.
Figure D.15 The parameter map for $a_1$ for a TEM coil tuned to mode 2 shows more uniform $B_1^+$ in the frontal lobe and in lateral slices. However, very low flip angles are observed centrally.
Figure D.16 Mode 0 / Port Posterior Coronal slices acquired with a TEM coil tuned to mode 0 with the excitation port located posteriorly. The signal intensity in the lateral portions of these slices drops off quickly for the anterior slices. This is attributed to their distance from the excitation port. The images were truncated on the inferior aspect because of flow artifacts near the brainstem.
Figure D.17 Mode 0 / Port Anterior Coronal slices acquired with a TEM coil tuned to mode 0 with the excitation port located anteriorly. The loss signal intensity in the lateral portions of these slices prevents clear visualization of the eyes. This is attributed to their distance from the excitation port. Motion artifacts due to eye movements appear as horizontal bands in these images (blue). Also, image distortions due to B0 perturbations caused by susceptibility differences at air/tissue interfaces can be seen anteriorly (yellow).
Figure D.18 Mode 1 / Port Posterior Coronal slices acquired with a TEM coil tuned to mode 1 with the excitation port located posteriorly. While the more anterior slices (top) appear uniform from left to right, the posterior slices show signal loss as predicted by field mapping. Signal intensity also drops off in the superior direction.
Figure D.19 Mode 1 / Port Anterior Coronal slices acquired with a TEM coil tuned to mode 1 with the excitation port located anteriorly. The signal loss observed in figure (D.7) is not observed because field mapping predicted greater signal intensity in this region when the excitation port was placed anteriorly than when placed posteriorly.
Figure D.20 Mode 2 / Port Posterior / Posterior Slices Posterior slices through brainstem and cerebellum acquired with a TEM coil tuned to mode 2 with the excitation port placed posteriorly. Clearly, there is significant signal loss along the midline, but the lateral region. Specifically the patient’s left side is well visualized.
Figure D.21  Mode 2 / Port Posterior/ Anterior Slices Coronal slices through eyes acquired with a TEM coil tuned to mode 2 with the excitation port placed anteriorly. Because field mapping demonstrated strong signals in the periphery of the brain, images were acquired to visualize the eyes. The eyes are more visible in these images than in figure (D.4), but signal loss is observed in the frontal lobe.