Design of Practical T_2 -Selective RF Excitation (TELEX) Pulses

by

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A thesis submitted in conformity with the requirements
for the degree of Masters of Science
Graduate department of Medical Biophysics
University of Toronto

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Traditional T_2 -based imaging techniques are geared towards imaging long- T_2 species. Traditional techniques are therefore not optimal in clinical situations where the information of interest lies in the short- T_2 species. T_2 -selective RF excitation (TELEX) is a technique for obtaining a T_2 -based contrast which highlights short- T_2 's while suppressing long- T_2 's — opposite to traditional T_2 contrast. Potentially, TELEX offers several advantages over other short- T_2 imaging techniques. Previously, TELEX has been demonstrated qualitatively to highlight only very short- T_2 's ($T_2 \approx 0.001$ s). When applied to longer- T_2 's ($T_2 \geq 0.01$ s), TELEX becomes sensitive to B_0 non-uniformities. This restricts its application to problems in which the T_2 of interest is very short. In this thesis, TELEX is characterized quantitatively. Furthermore, a bandwidth broadening scheme is developed which reduces the B_0 sensitivity of TELEX. This permits the technique to be applied to longer- T_2 's. The capabilities and limitations of a practical implementation of TELEX are discussed.

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Glossary

transverse relaxation rate	$1/T_2$	xii
longitudinal relaxation rate	$1/T_1$	xii
Contrast	signal difference between objects	1
MRI	magnetic resonance imaging	1
T_2	transverse relaxation time constant	1
MS	multiple sclerosis	1
CNS	central nervous system	1
CNR	contrast-to-noise ratio	2
SNR	signal-to-noise ratio	2
TELEX	T_2 -selective RF excitation	2
short- T_2	the shortest- T_2 within a set of T_2 species	3
long- T_2	the longest- T_2 within a set of T_2 species	3
B_0	static magnetic field	4
$\hat{i}, \hat{j}$ and $\hat{k}$	unit x,y and z vectors	4
$\vec{M}_{eq}$	equilibrium magnetization	5
$\vec{M} = [M_x, M_y, M_z]$	magnetization	5
γ	gyromagnetic ratio	5
$\mathbf{f}$	mapping matrix describing the displacement of the magnetization from its initial equilibrium value	5
magnetization behaviour	behaviour described by $\mathbf{f}$	5
f_{xy}	transverse mapping function	5

f_z	longitudinal mapping function	5
ω_0	Larmor frequency	6
$\Delta\omega$	off-resonance frequency	6
T_1	longitudinal relaxation time constant	6
RF	radiofrequency	7
ω	frequency of RF pulse	7
B_1	amplitude of RF pulse	7
$\vec{\omega}_{eff}/\gamma$	effective RF field	7
τ	RF pulse length	7
transverse relaxation rate	$1/T_2$	8
longitudinal relaxation rate	$1/T_1$	8
lineshape	inhomogeneously broadened lineshape	10
M_0	inhomogeneously broadened lineshape	10
BW	bandwidth	10
S_{xy}	signal from the transverse magnetization	12
linewidth	width of lineshape	12
$M_{0_{tot}}$	total magnetization in the sample	12
on-resonance TELEX	magnetization behaviour of TELEX analyzed on-resonance	12
$\mathcal{F}\{\}$	Fourier transform	13
$\mathcal{H}$	Heavyside step function	13
$\mathcal{L}_{hom}$	homogeneously broadened lineshape	13
S_z	signal from the longitudinal magnetization	16
short- T_2 contrast	contrast which highlights the short- T_2 species and sup- presses the long- T_2 species	21
$\mathcal{B}_1$	$\mathcal{F}\{B_1\}$	37
*	complex conjugate	37
$f_{xy_{ss}}$	steady state value of the transverse mapping function .	43
$f_{z_{ss}}$	steady state value of the longitudinal mapping function	43

$w_{T_2\text{short}}$	short- T_2 magnetization content	59
$w_{T_2\text{long}}$	long- T_2 magnetization content	59

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Chapter 1

Introduction

1.1 Motivation

1.1.1 Clinical Problems

Contrast between objects in an image is equal to the difference between the signals of the objects [1]. Contrast in magnetic resonance imaging (MRI) is achieved through differences in tissue-specific MR parameters. One common parameter is the MR signal decay rate as characterized by a tissue specific decay time constant, T_2 . Different tissues and tissue structures are discriminated based on their relative T_2 values. Traditional “ T_2 -weighted contrast” images tend to highlight tissue components with long- T_2 values while suppressing those with short- T_2 values. Traditional T_2 -weighted contrast is therefore better suited towards visualizing components with long- T_2 values. There are clinical problems however, including atherosclerosis [2], knee imaging [3] and multiple sclerosis [4], in which there is information of interest in the short- T_2 components of the tissue. The particular clinical condition guiding the work in this thesis is multiple sclerosis (MS), a demyelinating disease afflicting white matter in the central nervous system (CNS). There is evidence to suggest that the white matter myelin component of interest in MS is a short- T_2 species [4, 5, 6, 7].

1.1.2 Limitations of Current Short- T_2 Imaging Techniques

Currently, two different techniques exist which are capable of highlighting short- T_2 species. These techniques, image subtraction and multiexponential decay analysis [8, 5, 6], both suffer from various restrictions that limit the amount of information available. Image subtraction, in general, has a poor contrast-to-noise ratio (CNR) performance ($\text{CNR} \equiv \text{contrast}/\text{noise} \equiv \text{signal difference}/\text{noise}$). Multiexponential decay analysis tends to have very high signal-to-noise ratio (SNR) demands [9] resulting in excessively long scan times and/or low spatial resolution ($\text{SNR} \equiv \text{signal}/\text{noise}$). To date, neither of these techniques has gained widespread acceptance in short- T_2 imaging for the aforementioned clinical problems. This highlights the need for an imaging technique which is capable of obtaining the required short- T_2 information, but without the limitations of the other techniques. In particular, a technique is required which provides adequate contrast without excessive SNR requirements.

1.1.3 Alternative Short- T_2 Imaging Technique: TELEX

Pauly *et al.* [10] have proposed a novel T_2 -based contrast generation method, “ T_2 -Selective RF Excitation Contrast” hereafter called “TELEX” contrast, which would suppress the signal from long- T_2 components while sparing the signal from short- T_2 components — opposite to the contrast achieved with traditional T_2 -weighting. TELEX consists of an MR pulse sequence which selectively affects different T_2 species. In particular, TELEX can be designed to preferentially affect short- T_2 species. This can be observed in Fig. 1.1 which is a plot that compares the traditional T_2 -weighted signal with an example of the signal theoretically achievable with TELEX. The image contrast will be the difference between the signal from the short- T_2 ’s and the signal from the long- T_2 ’s. Fig. 1.1 illustrates that traditional T_2 -weighted imaging highlights long- T_2 ’s and suppresses the short- T_2 ’s while TELEX does the opposite.

As will be shown later in this thesis, TELEX has the potential of significantly better CNR performance than image subtraction. As well, TELEX does not have overly demanding SNR requirements like those for multiexponential decay analysis. In light of the imaging requirements

Figure 1.1: Normalized plots of MR signal versus $1/T_2$. In the figure, a traditional T_2 -weighted signal following an echo time of $TE=0.01$ s and an equivalent TELEX signal are plotted. Note that TELEX highlights the short- T_2 's and suppresses the long- T_2 's while traditional T_2 -weighting does the opposite.

mentioned in Sec. 1.1.2, the initial proposal by Pauly *et al.* suggests that the TELEX technique may provide a useful means of generating a contrast which highlights short- T_2 species.

1.1.4 Current Limitations of TELEX

The TELEX technique, as originally proposed [10], is restricted in the range of T_2 values to which it is applicable. Given a set of T_2 species, the TELEX technique will generate a contrast which highlights the shortest- T_2 components in the set while suppressing the longest. This does not imply, however, that the shortest- T_2 components in the set are necessarily short in absolute terms. (Hereafter, references made to “short- T_2 ” and “long- T_2 ” species will be taken to mean, respectively, the shortest- T_2 and longest- T_2 species within a set of T_2 species). Experimentally, TELEX contrast has been demonstrated qualitatively [2, 3] in highlighting only very short (in absolute terms) short- T_2 species ($T_2 \approx 0.001$ s). When applied to highlighting longer short- T_2 species ($T_2 \geq 0.01$ s), TELEX becomes very sensitive to non-uniformities in the static magnetic field. In fact, sensitivity to field non-uniformities results in a significant loss of contrast for TELEX [11]. As a consequence, TELEX is readily applicable to highlighting only relatively short short- T_2 species ($T_2 \leq 0.01$ s).

This restriction limits the range of clinical short- T_2 species for which TELEX may be useful. In this thesis, a modification to TELEX is presented which allows the technique to be applied to a broader range of short- T_2 species.

1.2 Statement of Thesis

The purpose of this thesis is to characterize the capabilities and limitations of TELEX. To date, the TELEX technique as proposed theoretically by Pauly *et al.* has only been demonstrated qualitatively. To accurately predict (and in the future optimize) the effects of the TELEX technique, *it is hypothesized that TELEX can be characterized quantitatively.* As discussed in the previous section, TELEX, as currently proposed, is restricted in the range of T_2 values for which useful contrast can be generated. To be more generally applicable *in vivo*, the range of TELEX must be extended to include the ability to highlight longer short- T_2 species ($T_2 \geq 0.01$ s). *It is further hypothesized that modifications to the technique can be made which would permit TELEX contrast to be generated for a broad range of T_2 values.*

1.3 Physics of MR

A brief description of some of the relevant physics concepts used in this thesis will be given in this section. For a more detailed discussion see, for example, Refs. [12, 13].

1.3.1 Bloch Equations and MR Signal

In this section, the equations of motion describing the magnetization behaviour (the “Bloch equations”) will be presented. Various definitions and notations that will be used throughout the thesis will also be introduced.

When placed in a static magnetic field $\vec{B}_0 = B_0 \hat{k}$, where $\hat{k}$ is the unit z-vector (and for future reference $\hat{i}$ and $\hat{j}$ are the unit x and y vectors respectively), the equilibrium (steady state) magnetization will be given by:

$$\vec{M}_{eq} = M_0 \hat{k} \tag{1.1}$$

where M_0 is a constant. Bloch [14] showed that the classic behaviour of the magnetization ($\vec{M} = [M_x, M_y, M_z]$) will then be governed by:

$$d\vec{M}/dt = \vec{M} \times \gamma \vec{B} - M_x/T_2 \hat{i} - M_y/T_2 \hat{j} - (M_z - M_0)/T_1 \hat{k} \quad (1.2)$$

where T_1 and T_2 are system specific parameters, $\vec{B} = B_x \hat{i} + B_y \hat{j} + B_z \hat{k}$ is the total magnetic field experienced by the magnetization and γ is a constant ($= 2\pi \times 42.58$ MHz/T for protons) known as the gyromagnetic ratio. For the purposes of this thesis, it will be assumed that B_0 is constant and B_x and B_y are piecewise constant. In this case, the solution to Eq. 1.2 will take the form [15]:

$$\vec{M} = \mathbf{f} \vec{M}_{eq} \quad (1.3)$$

where $\mathbf{f} = \mathbf{f}(\vec{B}, T_1, T_2)$ is a mapping matrix describing the displacement of the magnetization from its initial equilibrium value. Eq. 1.3 is useful because $\mathbf{f}$ is experiment-independent whereas $\vec{M}_{eq}$ is an experiment-specific parameter. Throughout this thesis, the term “magnetization behaviour” will be understood to refer to the behaviour as described by $\mathbf{f}$. For future reference, the quantity known as the transverse magnetization will be defined as:

$$M_{xy} \equiv M_x + i M_y \quad (1.4)$$

M_z is referred to as the longitudinal magnetization. The transverse (f_{xy}) and longitudinal (f_z) mapping functions, derived from Eq. 1.3, will be defined as the functions taking the equilibrium magnetization to the transverse and longitudinal magnetization respectively:

$$\begin{aligned} M_{xy} &\equiv f_{xy} M_0 \\ M_z &\equiv f_z M_0 \end{aligned} \quad (1.5)$$

The MR signal (S_{xy}) is proportional to the transverse component of the magnetization [16]:

$$\begin{aligned} S_{xy} &\propto M_{xy} \\ &= f_{xy} M_0 \end{aligned} \quad (1.6)$$

1.3.2 Rotating Frame and Relaxation

Relaxation is a process which describes the decay of magnetization. If magnetization lies initially at some non-equilibrium value, then it will not remain static. Instead, it will decay via the process of relaxation. To illustrate the effects of relaxation, assume that only the B_0 field is present and that the magnetization initially lies at some non-equilibrium value. In this case, Eq. 1.2 can be solved as:

$$\begin{aligned} M_{xy} &= M_{xy}(t=0)e^{i\omega_0 t}e^{-t/T_2} \\ M_z &= M_0 + (M_z(t=0) - M_0)e^{-t/T_1}. \end{aligned} \quad (1.7)$$

where

$$\omega_0 \equiv \gamma B_0 \quad (1.8)$$

is called the Larmor frequency .

Rotating Frame

Eq. 1.7 implies that the magnetization rotates in the transverse plane at the Larmor frequency. For the rest of this thesis, however, a rotating reference frame will be assumed. In particular, in a reference frame rotating at the Larmor frequency, the ω_0 dependence in Eq. 1.7 will disappear. More generally, for a frame rotating at ω , the magnetization will rotate in the frame at frequency:

$$\Delta\omega = \omega_0 - \omega \quad (1.9)$$

Relaxation

In a frame with $\Delta\omega = 0$, the transverse magnetization behaviour is pure monoexponential decay. T_2 is the time constant which governs the transverse decay. Typical T_2 values observed in medical imaging are $T_2 \approx 0.005 - 2$ s. T_1 , on the other hand, is a time constant governing the recovery of M_z back to its equilibrium (steady state) value. Typical T_1 values observed in medical imaging are

$T_1 \approx 0.1 - 2$ s. Image contrast can be achieved through differences in relaxation rates of different tissues. The bulk of this thesis will deal with T_2 -based contrast.

1.3.3 Radiofrequency (RF) Excitation

The previous section noted that relaxation effects are observed as magnetization decays away from some non-equilibrium state. Radiofrequency (RF) pulses provide the means of initially displacing the magnetization from its equilibrium value. When a radiofrequency (RF) pulse of frequency ω and amplitude B_1 is applied to the system, in a reference frame rotating at frequency ω , Eq. 1.2 can be written as:

$$d\vec{M}/dt = \vec{M} \times \omega_{eff} - M_x/T_2\hat{i} - M_y/T_2\hat{j} - (M_z - M_0)/T_1\hat{k} \quad (1.10)$$

where

$$\vec{\omega}_{eff} = \gamma\vec{B}_1 + \Delta\omega\hat{k} \quad (1.11)$$

(and $\vec{B}_1$ and $\vec{M}$ are understood to be defined in the rotating frame). Typical RF amplitudes ($= |\gamma/2\pi\vec{B}_1|$) used in magnetic resonance imaging are on the order of 1 kHz. This is significantly larger than the inverse of the typical relaxation time constant values mentioned in Sec. 1.3.2. As a result, for the short duration over which an RF pulse is typically played out, Eq. 1.10 can be accurately approximated by:

$$d\vec{M}/dt = \vec{M} \times \vec{\omega}_{eff}. \quad (1.12)$$

If one assumes that $\omega = \omega_0$ (i.e. $\Delta\omega = 0$) and $\vec{B}_1$ is polarized along the x-axis in the rotating frame, Eq. 1.12 can be solved at time τ as:

$$\begin{aligned} M_{xy}(\tau) &= M_0 \sin(\gamma B_1 \tau) \\ M_z(\tau) &= M_0 \cos(\gamma B_1 \tau). \end{aligned} \quad (1.13)$$

Eq. 1.13 implies that the magnetization is rotated about the applied RF field. The rotation or “flip angle” of the magnetization is given by the area of the RF pulse:

$$\text{Area of RF pulse} = \gamma B_1 \tau. \quad (1.14)$$

More generally, for an arbitrary RF pulse, magnetization is rotated about the “effective” magnetic field $\vec{\omega}_{eff}/\gamma$.

Fig. 1.2 illustrates the magnetization together with the RF and relaxation processes mentioned above. The relative size of the arrows is a representation of the relative magnitude of each of these effects.

Figure 1.2: Driving RF pulse and relaxation decay effects on the magnetization ($\vec{M}$). In a typical MR experiment, the RF amplitude ($\gamma/2\pi B_1$) is much greater than the transverse relaxation rate ($1/T_2$) which is in turn much greater than the longitudinal relaxation rate ($1/T_1$).

1.3.4 Traditional T_2 Contrast Experiment

As noted in Secs. 1.1.1 and 1.3.2, differences in T_2 values of tissue can be exploited to generate T_2 -based contrast in an image. Fig. 1.3 is a schematic of the sequence of events in a traditional T_2 contrast experiment. The first step in the experiment is the application of an RF pulse. This will rotate the magnetization away from its equilibrium value and into the transverse plane. (The reason for doing this is because, as mentioned in Sec. 1.3.1, the MR signal is proportional to the transverse component of the magnetization). During the time TE, the transverse magnetization from the various different tissues will have undergone T_2 decay. In this case, the short- T_2 magnetization will have decayed away relative to the long- T_2 magnetization. When the signal is acquired, this will

Figure 1.3: Traditional T_2 contrast experiment. Signal from the short- T_2 dies away more quickly than signal from the long- T_2 thus giving rise to T_2 contrast in the image.

give rise to a T_2 -based *contrast* in the image (see Fig. 1.1). Note, however, that this contrast is achieved as a result of signal loss from the short- T_2 species.

1.3.5 B_0 Non-Uniformities

The TELEX technique, as originally proposed by Pauly et al. [10], was derived based on the assumption of a perfectly uniform B_0 field. This section will illustrate how B_0 non-uniformities can have a significant impact on magnetization behaviour and the resulting MR signal. Sensitivity to B_0 non-uniformities will be shown to ultimately limit the applicability of the TELEX technique.

Inhomogeneously Broadened Lineshape

Throughout any finite sample volume, the B_0 field, and therefore the Larmor frequency via Eq. 1.8, will not be perfectly uniform. Non-uniformities will arise primarily due to inhomogeneities in the static magnetic field as well as differences in magnetic susceptibility between adjacent structures [17]. The total magnetization in the sample will therefore be distributed over a range of Larmor frequencies (via Eq. 1.8).

$$M_0 = M_0(\Delta\omega) \quad (1.15)$$

The distribution characterized by Eq. 1.15 is known as the “inhomogeneously broadened lineshape” hereafter referred to simply as lineshape . An example of a typical experimentally determined lineshape can be seen in Fig. 1.4.

Mapping Function in a Non-Uniform Field

The distribution of Larmor frequencies in a sample is significant because, according to Eq. 1.11, magnetization behaviour will depend on $\Delta\omega$:

$$f = f(B_1, T_2, T_1, \Delta\omega) \quad (1.16)$$

This can be seen in Fig. 1.4 where, overlaid against the lineshape, the simulated transverse and longitudinal mapping functions in response to $\tau=0.005$ s and $\tau=0.05$ s $\gamma B_1 \tau = \pi/2$ rectangular RF pulses are plotted as a function of $\Delta\omega$. Because there is a range of $\Delta\omega$ in the sample, the magnetization behaviour will not be uniform throughout the sample.

Mapping Function Bandwidth

For the transverse mapping function, the width between the first zero crossings is called the *bandwidth* (BW) of f_{xy} . For the longitudinal mapping function, the bandwidth is defined as the width between the points at which f_z equals one. (Note that this differs from the more traditional full width at half maximum (FWHM) definition of bandwidth. The reason for this particular definition will become apparent in later sections). From Fig. 1.4 it can be inferred that, as the length of the RF pulse increases, the bandwidth decreases.

$$BW \sim 1/\tau \quad (1.17)$$

Effects of B_0 Non-Uniformities on the MR Signal

The presence of a range of Larmor frequencies within the sample will influence the resulting MR signal. The total MR signal, immediately following an RF excitation, is generalized from Eq. 1.6 by integrating the transverse magnetization over all Larmor frequencies in the sample:

$$S_{xy}(B_1, T_2, T_1) = \int_{-\infty}^{\infty} M_{xy}(\Delta\omega) d\Delta\omega$$

Figure 1.4: Simulated (a) longitudinal and (b) transverse mapping functions for $\tau=0.005$ s and 0.05 s 90° rectangular RF pulses together with an example of a normalized inhomogeneously broadened lineshape (from one of our experiments) plotted as a function of $\Delta\omega/2\pi$. In the $\tau=0.05$ s case, the mapping function shows significant variation over the lineshape.

$$= \int_{-\infty}^{\infty} f_{xy}(B_1, T_2, T_1, \Delta\omega) M_0(\Delta\omega) d\Delta\omega \quad (1.18)$$

If the bandwidth of the mapping function is much greater than the width of the lineshape ($\equiv$ linewidth), then Eq. 1.18 reduces to:

$$\begin{aligned} S_{xy} &\approx f_{xy}(B_1, T_2, T_1, \Delta\omega = 0) \int_{-\infty}^{\infty} M_0(\Delta\omega) d\Delta\omega \\ &\equiv f_{xy}(\Delta\omega = 0) M_{0_{tot}} \end{aligned} \quad (1.19)$$

where $M_{0_{tot}}$ is the magnitude of the total magnetization in the sample. In this case, the MR signal is proportional to the value of the mapping function on-resonance (i.e. $\Delta\omega = 0$). Eq. 1.19 would be true in the case of a perfectly uniform field. Alternatively, in the presence of a finite linewidth, Eq. 1.19 is valid if the bandwidth is large enough. For example, in Fig. 1.4, Eq. 1.19 would be valid for the mapping function associated with the $\tau=0.005$ s RF pulse but *not* for the $\tau=0.05$ s pulse.

Effects of B_0 Non-Uniformities on Original TELEX Theory

The original theoretical formulation of TELEX [10] was based on an on-resonance analysis of the mapping function. Hereafter, this will be referred to as on-resonance TELEX. The actual MR signal, however, is determined by S_{xy} . Therefore, on-resonance TELEX is accurate only if Eq. 1.19 is valid. As will be shown later, TELEX requires the use of relatively long RF pulses. According to Eq. 1.17, this could result in a narrow bandwidth. In this case, the actual signal will be described by Eq. 1.18 but *not* the approximation of Eq. 1.19. As a result, the signal will be sensitive to B_0 non-uniformities and on-resonance TELEX theory will *not* accurately describe the actual MR signal. The consequences of this deviation will be explored in this thesis.

Homogeneously Broadened Lineshapes

In most cases, the analytic expression of the mapping function f is extremely complicated [15, 18]. In certain restricted cases, however, a simple analytic expression can be derived. In these cases, magnetization behaviour will be determined, in part, by a quantity known as the homogeneously broadened lineshape. It was mentioned in Sec. 1.3.5 that the *inhomogeneously* broadened lineshape arises due to inhomogeneities in the B_0 field or due to susceptibility effects. The existence of the

homogeneous lineshape, on the other hand, is due to small local magnetic fields associated with dipolar interactions among protons [19]. In terms of its effect on the magnetization behaviour, the homogeneous lineshape is associated with T_2 decay. Ordinarily, the effects of the homogeneous lineshape are implicitly included in $\mathbf{f}$ as T_2 dependence. Under certain restricted conditions, however, the effects of the homogeneous lineshape can be seen explicitly. If one assumes that the tip angle of the magnetization is small [20] and that $t \gg T_2$, then the transverse mapping function can be written [13, 21, 22, 23] as:

$$\begin{aligned} f_{xy}(\Delta\omega) &= \mathcal{F}\{e^{-\tau'/T_2}\mathcal{H}(\tau')\} \\ &= (i + \Delta\omega T_2)/[1 + (\Delta\omega T_2)^2] \\ &= \mathcal{L}_{hom}(\Delta\omega) \end{aligned} \tag{1.20}$$

where $\mathcal{F}$ is the Fourier transform operation, $\mathcal{H}(\tau')$ is the Heavyside step function ($=1$ for $\tau' > 0$, $=0$ for $\tau' < 0$), τ' is the RF pulse length and $\mathcal{L}_{hom}$ is identified as the homogeneously broadened lineshape. The signal immediately following the RF pulse will then be given by:

$$S_{xy} = \int_{-\infty}^{\infty} \mathcal{L}_{hom}(\Delta\omega) M_0(\Delta\omega) d\Delta\omega \tag{1.21}$$

The explicit dependence of magnetization behaviour on the homogeneous lineshape will prove insightful when off-resonance behaviour is analyzed (Sec. 2.4). An important point to bear in mind, however, is that Eq. 1.21 is valid *only* if the small tip approximation as well as the condition $t \gg T_2$ is valid. For most of this thesis, therefore, the magnetization behaviour will be analyzed from the point of view of the full solutions to Eq. 1.10.

1.4 Overview of TELEX

TELEX depends on the interaction of the RF pulse and T_2 decay on the magnetization behaviour. From Sec. 1.3.3, one can effectively ignore the effects of relaxation which occur during the application of the pulse (Eq. 1.12) for typical short, large amplitude RF pulses used in MR. Under these circumstances, the mapping function will depend on the RF amplitude and duration only:

$$\mathbf{f} = \mathbf{f}(\gamma B_1 \tau) \tag{1.22}$$

On the other hand, if one intentionally lowers the amplitude of the pulse and increases its duration, the effects of relaxation *during* the pulse must be considered (Eq. 1.10). In this case, the mapping function will be given by:

$$f = f(\gamma B_1 \tau, \tau/T_2) \quad (1.23)$$

It is this T_2 dependence which allows for the selective excitation of T_2 species and the subsequent generation of the short- T_2 contrast of TELEX. To illustrate this, consider Fig. 1.5 which is a plot of f as a function of τ/T_2 for an RF pulse with $\gamma B_1 \tau = \pi/2$. For a fixed RF pulse length, the long- T_2

Figure 1.5: Mapping function f versus τ/T_2 in response to a rectangular $\gamma B_1 \tau = \pi/2$ RF pulse. The long- T_2 components are flipped into the transverse plane while the short- T_2 components are stored along the longitudinal axis. Short- T_2 contrast results from the preferential weighting of short- T_2 's along the z-axis.

components have been rotated into the transverse plane while the short- T_2 components have been stored along the longitudinal axis. The selective excitation of the long- T_2 species has therefore preferentially stored the short- T_2 species along the z-axis. This preferential short- T_2 weighting results in a short- T_2 contrast “stored” along the z-axis. The short- T_2 contrast stored along the z-axis forms the basis of the TELEX technique.

1.4.1 Comment on Notation

When discussing magnetization behaviour, one typically describes the magnetization behaviour relative to three input variables — RF amplitude (B_1), RF pulse length (τ) and T_2 . On the other hand, unless otherwise stated, the description given here will utilize the minimally required normalized variables $\gamma B_1 \tau$ and τ/T_2 . In later sections, variables describing off-resonance and T_1 effects will be added. The plots in Fig. 1.5, for example, are plotted with this two-variable dependence.

1.4.2 TELEX Pulse Sequence

Fig. 1.6 is a schematic of the TELEX pulse sequence. A T_2 -selective pulse is played out which,

Figure 1.6: TELEX pulse sequence

as shown in the previous section, generates a short- T_2 contrast along the z-axis. Recall, however, that the MR signal is proportional to the transverse component of the magnetization. To observe the contrast “stored” along the z-axis, the long, low amplitude T_2 -selective pulse is followed by a large amplitude 90° pulse of short duration (hereafter referred to as a hard pulse). This pulse will rotate all of the magnetization by 90° , flipping the z-components into the transverse plane where they can be measured as signal. For the remainder of this thesis, M_z (and by extension

f_z) will be understood to mean, depending on the situation, either the magnetization stored along the z-axis after a T_2 -selective pulse or the transverse magnetization after the subsequent hard 90° pulse. Therefore, the signal (S_z) due to magnetization “stored” along the z axis after a T_2 -selective pulse will be given by:

$$S_z(\gamma B_1 \tau, \tau/T_2) = \int_{-\infty}^{\infty} f_z(\gamma B_1 \tau, \tau/T_2, \Delta\omega) M_0(\Delta\omega) d\Delta\omega. \quad (1.24)$$

1.4.3 Bandwidth Broadening Scheme

A limitation with TELEX is the necessity for long RF pulses. The narrow mapping function bandwidth associated with long RF pulses will make TELEX very sensitive to B_0 non-uniformities. As will be shown in Sec. 2.2, this can result in a significant decrease in contrast performance of the technique. To allow the use of longer RF pulses, and therefore extend the applicability of TELEX to highlight longer short- T_2 species, a technique has been developed which will increase the bandwidth of the mapping function. The bandwidth broadening technique [11, 24] is an extension of the approach used by Williams *et al.* [25] to reduce the chemical shift sensitivity of RF pulses. The sequence is illustrated in Fig. 1.7. The idea is similar to that of the ordinary spin echo [26]. Like spin echoes, this technique attempts to minimize the phase dispersion associated with off-resonance magnetization. The key to the technique is the presence of the 180° refocussing pulses interspersed at regular intervals τ_{180} . Consider first the effects of the refocussing pulses on the transverse magnetization in the absence of the RF pulse: during the interval between the refocussing pulses, off-resonance magnetization in the transverse plane rotates about the z-axis (see Fig. 1.8). After a refocussing pulse, the phase of the magnetization is conjugated. Magnetization then rotates again about the z-axis so that it is completely rephased at the end of the refocussing interval.

The above description relied on the fact that magnetization behaviour consists only of a linear phase accrual between the refocussing pulses. When an RF pulse is present between the refocussing pulses, however, there will be an amplitude modulation in addition to the phase accrual of the magnetization. However, if the phase dispersion can be kept small, then the amplitude modulation can be minimized and magnetization can be refocussed. Phase accrual can be kept small by making the refocussing interval (τ_{180}) sufficiently short. Fig. 1.9a is a plot of f_{xy} for a

Figure 1.7: Refocussed RF pulse. The RF pulse is broken up by a series of 180° refocussing pulses at intervals τ_{180} . The effect is to broaden the bandwidth of the mapping function.

Figure 1.8: Spin echo formation. Different arrow types represent different off-resonance magnetization. Phase accrues linearly in the transverse plane from off-resonance spins so that the f_{xy} is dispersed at time $TE/2$. After the 180° refocussing pulse, the phase of f_{xy} is conjugated. Phase then again accrues linearly so that there is not net phase at time TE .

$\tau=0.05$ s $\gamma B_1 \tau = \pi/2$ pulse for various different refocussing intervals. Bandwidth increases as τ_{180} decreases:

$$BW \sim 1/\tau_{180} \quad (1.25)$$

Similarly, Fig. 1.9b indicates that f_z will be broadened in a similar manner.

Figure 1.9: Plot of (a) $|f_{xy}|$ and (b) f_z as a function of $\Delta\omega/2\pi$ for a $\tau=0.05$ s $\gamma B_1 \tau = \pi/2$ pulse at various different refocussing intervals τ_{180} . Note that the bandwidth increases as τ_{180} decreases.

1.5 Multiple Sclerosis (MS)

In this thesis, the capabilities and limitations of the TELEX technique itself are characterized. Ultimately, however, the applicability of the technique will be dictated by the contrast requirements of the specific clinical problem of interest. The clinical problem guiding the work in this thesis is multiple sclerosis (MS). Multiple sclerosis is an inflammatory disease afflicting white matter in the CNS [27]. Multiple sclerosis is an example of a clinical problem in which the information of interest (myelin) reportedly lies in the short- T_2 species [4, 5, 6, 7]. Based on the characterization performed in the thesis, TELEX will be analyzed in terms of its potential applicability to MS imaging.

1.5.1 Clinical Overview

White matter is formed from cells consisting of a central axon fiber surrounded by layered sheaths of myelin (see Fig. 1.10). In the brain, a barrier normally exists which prevents the blood from mixing

Figure 1.10: Typical white matter fiber consisting of a central axon surrounded by a myelin sheath.

directly with the brain. In MS, the blood brain barrier breaks down and results in the formation of focal lesions known as “acute plaques”. After the breakdown of the blood brain barrier, the immune system can attack the myelin sheath and cause the white matter fibers to become “demyelinated”. When the blood brain barrier is restored a residual lesion known as the “chronic plaque” usually

remains. MRI has been shown to be very sensitive and specific in identifying MS [28]. Thus far, however, MRI (or any other technique) is not a successful predictor of the clinical course or degree of disability of the disease [29, 30]. One reason for this may be due to the current inability of MRI to efficiently image myelin [9]. The inability to image myelin prevents one from monitoring a major component in the pathology of the disease – namely demyelination.

1.5.2 Short- T_2 Myelin Imaging

Table 1.1 lists the different components of the T_2 -spectrum of white matter obtained from multi-exponential decay analysis [31]. There are two major components of white matter: A $T_2 \approx 0.01$ s

<i>Component</i>	T_2 (s)	T_1 (s)	<i>Percent of Total Signal</i>
short- T_2	0.01	0.54	8.5%
long- T_2	0.11	0.75	90%

Table 1.1: T_1 , T_2 and relative signal contribution from the T_2 -spectrum of white matter obtained through multiexponential decay analysis (from Ref. [31])

component and a $T_2 \approx 0.1$ s component. The signal contribution from the long- T_2 component is about 10 times that from the short- T_2 component. There is evidence to suggest that the $T_2=0.1$ s component is due to axonal or extracellular water while the $T_2=0.01$ s component is due to water associated with myelin [4, 5, 6, 7]. The contrast available with TELEX may be useful to visualize the short- T_2 myelin component while suppressing the long- T_2 axonal component. The challenge in this case is to adapt the TELEX technique to highlight the relatively long (for TELEX) $T_2=0.01$ s short- T_2 species.

1.6 Thesis Outline

The purpose of this thesis is to characterize the capabilities and limitations of TELEX. TELEX itself is a T_2 -selective excitation technique which generates contrast as a consequence of the effects of the interaction of T_2 decay and the RF pulse on the magnetization. Section 1.3 noted that, for typical large amplitude, short duration RF pulses, one can effectively ignore T_2 effects which occur

during the pulse. However, if the RF amplitude is intentionally reduced and the pulse duration is increased, T_2 effects *will* have a significant impact on the magnetization throughout the pulse duration. In this case, the magnetization behaviour will be a function of its T_2 value. The T_2 effects give TELEX the ability to generate contrast which highlights the short- T_2 species and suppresses the long- T_2 species hereafter referred to as short- T_2 contrast. The means through which this occurs is discussed in Sec. 2.2 where TELEX is analyzed theoretically. In Sec. 2.3 measurements were made to quantify TELEX experimentally. As alluded to earlier, a limitation with TELEX is the necessity for long RF pulses. The narrow mapping function bandwidth associated with long RF pulses will make TELEX very sensitive to B_0 non-uniformities. As will be shown in Sec. 2.2, this can result in a significant decrease in contrast performance of the technique. To allow the use of longer RF pulses, and therefore extend the applicability of TELEX to highlight longer short- T_2 species, a technique has been developed in Sec. 2.4 which will increase the bandwidth of the mapping function. Secs. 2.5 and 2.6 quantify the experimental performance of the bandwidth broadening technique. Based on these techniques, it will be shown, quantitatively, that TELEX *can* generate short- T_2 contrast for a broad range of T_2 species.

This work has been published in abstract form at SMRM [11] and is currently in the process of submission to *Magnetic Resonance in Medicine*.

Chapter 2

T_2 -Selective RF Excitations

2.1 Introduction

In this chapter, the TELEX technique for generating short- T_2 contrast will be characterized. The technique will first be analyzed theoretically and then characterized experimentally. As mentioned in Sec. 1.1.4, the sensitivity to B_0 non-uniformities reduces the effectiveness of the technique in highlighting longer short- T_2 species. In an attempt to overcome this limitation, a modification of TELEX is presented which reduces the sensitivity to B_0 non-uniformities. The modification will be shown to extend the range of TELEX to highlight a broader range of short- T_2 species.

2.2 TELEX Theory

2.2.1 Introduction

TELEX generates short- T_2 contrast based on selective excitation of short- T_2 species. To analyze TELEX, one therefore must look closely at behaviour of the magnetization under the influence of both the RF pulse and T_2 decay. In Sec. 2.2.2, TELEX is first analyzed (as in its original formulation) by looking at the mapping function on-resonance. As noted in Sec. 1.3.5, however, this description assumes that the actual MR signal can be characterized by the value of the mapping function on-resonance alone. This assumption will be valid only if the mapping function bandwidth

is broad in comparison with the linewidth. If this condition is not satisfied, TELEX will be sensitive to B_0 non-uniformities. Sec. 2.2.3 will assess the impact of the B_0 -sensitivity of TELEX.

2.2.2 On-Resonance TELEX

In this section, on-resonance TELEX is analyzed. To do this, the interaction between the RF pulse and T_2 decay on the magnetization must be understood. To fully describe the effects of relaxation during an RF pulse, the mathematical solution to the Bloch equations (Eq. 1.10) is required. Before this is presented, a more intuitive description (hard pulse approximation) will be given.

Hard Pulse Approximation Description

According to the hard pulse approximation [32, 33], if one ignores T_2 effects, an RF pulse (generally time varying) can be accurately approximated by a series of constant amplitude steps over small time increments δt . This approach can be extended to include the effects of T_2 decay. Fig 2.1 illustrates this process.

In the first time increment a “hard” RF pulse is assumed to rotate all of the (different T_2 species) magnetization down by some small angle ϕ_1 from its equilibrium value. T_2 decay then follows the rotation in a separate step. The resulting mapping function for the short- and long- T_2 species is given by:

$$\begin{aligned} f_{xy_{short-T_2}} &= 0 \\ f_{z_{short-T_2}} &= \cos(\phi_1) \\ f_{xy_{long-T_2}} &= i \sin(\phi_1) \\ f_{z_{long-T_2}} &= \cos(\phi_1) \end{aligned} \tag{2.1}$$

At this point there is a difference in flip angle between the two T_2 species (ϕ_1 for the long- and zero for the short- T_2 species). In the next time increment, the hard RF pulse again rotates all of the magnetization by ϕ_1 .

$$f_{xy_{short-T_2}} = i \cos(\phi_1) \sin(\phi_1)$$

Figure 2.1: Hard pulse description of the development of short- T_2 TELEX contrast between long ($-$) and short ($-$) T_2 species. Long- T_2 species are preferentially rotated down into the transverse plane. As a result, short- T_2 magnetization is preferentially stored along the z-axis.

$$\begin{aligned}
f_{z_{short-T_2}} &= \cos(\phi_1)^2 \\
f_{xy_{long-T_2}} &= i \sin(2\phi_1) \\
f_{z_{long-T_2}} &= \cos(2\phi_1) \\
&= \cos(\phi_1)^2 - \sin(\phi_1)^2
\end{aligned} \tag{2.2}$$

Eq. 2.2 implies that after this last time increment, $f_{z_{long-T_2}} < f_{z_{short-T_2}}$. A “contrast” has therefore been generated along the z-axis which suppresses the long T_2 -component relative to the short T_2 -component. The hard pulse derivation therefore illustrates how magnetization can be selectively excited based on its T_2 value to generate short- T_2 contrast along the z-axis. Unfortunately this sort of treatment does not allow for an appreciation of some of the more subtle behaviour associated with T_2 -selective excitations. To investigate the RF- T_2 interaction more closely, an analytic solution is required.

Analytic Description

The mapping function in response to an on-resonance, constant-amplitude RF excitation about the x-axis (neglecting T_1) has been solved analytically in Refs. [18, 34] as:

$$\begin{aligned}
f_{xy} &= ie^{-\tau/2T_2} \gamma B_1 \tau \sin(\sqrt{(\gamma B_1 \tau)^2 - (\tau/2T_2)^2}) / \sqrt{(\gamma B_1 \tau)^2 - (\tau/2T_2)^2} \\
f_z &= e^{-\tau/2T_2} [\cos(\sqrt{(\gamma B_1 \tau)^2 - (\tau/2T_2)^2}) + \\
&\quad \tau/2T_2 \sin(\sqrt{(\gamma B_1 \tau)^2 - (\tau/2T_2)^2}) / \sqrt{(\gamma B_1 \tau)^2 - (\tau/2T_2)^2}]
\end{aligned} \tag{2.3}$$

There are three regimes of spin behaviour:

$$1. \quad \gamma B_1 \gg 1/2T_2 \quad \text{underdamped regime} \tag{2.4}$$

In this case, Eq. 2.3 reduces to:

$$\begin{aligned}
f_{xy} &= ie^{-\tau/2T_2} \sin(\gamma B_1 \tau) \\
f_z &= e^{-\tau/2T_2} \cos(\gamma B_1 \tau)
\end{aligned} \tag{2.5}$$

This “underdamped” regime is the traditional regime in which MR is performed. The effective RF “driving” term ($= \gamma B_1$) is much stronger than the decay rate constant ($= 1/T_2$). This results in

the magnetization being rotated about the x-axis in a decaying sinusoidal manner.

$$2. \quad \gamma B_1 = 1/2T_2 \quad \text{critically damped regime} \quad (2.6)$$

In this case, Eq. 2.3 reduces to:

$$\begin{aligned} f_{xy} &= ie^{-\tau/2T_2} \tau/2T_2 \\ f_z &= e^{-\tau/2T_2} (1 + \tau/2T_2) \end{aligned} \quad (2.7)$$

This “critically” damped regime occurs when the RF driving term and decay rate balance each other. In this regime, the RF force is sufficient to drive the magnetization off the z-axis. The large relative decay rate, however, ensures that transverse magnetization decays quickly.

$$3. \quad \gamma B_1 \ll 1/2T_2 \quad \text{overdamped regime} \quad (2.8)$$

In this case, Eq. 2.3 reduces to:

$$\begin{aligned} f_{xy} &\approx 0 \\ f_z &= e^{-(\gamma B_1 \tau)^2/(\tau/T_2)} \end{aligned} \quad (2.9)$$

This “overdamped” regime occurs when the driving RF term is much weaker than the decay rate. In this case, the T_2 decay occurs so rapidly that transverse magnetization is effectively zero throughout the pulse. Saturation occurs quite slowly, however, because significant magnetization is never driven into the transverse plane where it would decay. Magnetization is therefore “stored” along the z-axis where it decays away slowly.

The above discussion showed that magnetization behaviour is determined by the relationship of the RF amplitude (γB_1) to the decay rate ($1/T_2$). Magnetization lying in the overdamped regime ($\gamma B_1 \ll 1/2T_2$) will decay away slowly along the z-axis. As a result, overdamped magnetization will be “stored” along the z-axis. On the other hand, magnetization in the underdamped regime ($\gamma B_1 \gg 1/2T_2$) will oscillate sinusoidally. If $\gamma B_1 \tau = \pi/2 + n\pi$; $n = 0, 1, 2, \dots$ then underdamped magnetization will be flipped into the transverse plane. The z-component of the underdamped magnetization will therefore be suppressed. As a result, overdamped magnetization will be preferentially stored along the z-axis. There is therefore a contrast between over and underdamped

magnetization stored along the z-axis. For a given set of T_2 species, if the RF pulse is chosen appropriately so as to place the short- and long- T_2 magnetization in the over- and underdamped regimes respectively, then a short- T_2 contrast will be generated along the z-axis. For a specific example, consider the response to an RF pulse with $\gamma B_1 \tau = \pi/2$ (Fig. 1.5). Let us assume that the RF amplitude ($\gamma B_1 \tau$) is fixed at $\gamma B_1 = 31.4$ rad/s and the duration is $\tau = 0.05$ s. According to Eq. 2.6, the critically damped point will be given by $\tau/T_2 = 2\gamma B_1 \tau = \pi$. This will give rise to a critical T_2 value of $T_{2_{crit}} = 0.016$ s. T_2 's less than the critical T_2 value will lie in the overdamped regime and their z-components will therefore be largely spared. T_2 's greater than the critical T_2 value will lie in the underdamped regime and their z-components will be largely suppressed. Thus, for a $\gamma B_1 \tau = \pi/2$ RF pulse, a short- T_2 contrast is generated.

2.2.3 TELEX Sensitivity to B_0 Non-Uniformities

On-resonance TELEX theory assumes that the actual TELEX signal ($S_z(\gamma B_1 t, t/T_2)$) is directly proportional to the mapping function on-resonance. When the mapping function bandwidth is narrower than the linewidth, however, sensitivity to B_0 non-uniformities invalidates this assumption. Fig. 1.5 implies that, in order to observe T_2 effects, the RF pulse length must be roughly equal to or greater than the T_2 value ($\tau \approx T_2$). Therefore, the longer the short- T_2 value, the longer the RF pulse length required to generate TELEX contrast. However, the longer the RF pulse length, the narrower the bandwidth and therefore the greater the B_0 sensitivity (Sec. 1.3.5). Fig. 2.2a is a plot of S_z (Eq. 1.24) as a function of τ/T_2 in the presence of a simulated 25Hz FWHM Gaussian lineshape. The on-resonance TELEX curve is also plotted in the figure. Fig. 2.2b is a plot of f_z as a function of $\Delta\omega$ for $\tau/T_2 = 0.01$. In the case of the short $\tau = 0.01$ s RF pulse, the full simulation TELEX signal is very similar to on-resonance TELEX signal since the bandwidth of f_z is much broader than the linewidth (Fig. 2.2b). For the longer RF pulses, however, there is significant deviation from on-resonance TELEX due to the narrower bandwidth of the mapping function associated with long RF pulses (Eq. 1.17). B_0 sensitivity associated with long RF pulses therefore invalidates the on-resonance analysis. B_0 non-uniformities will, in general, degrade the actual contrast of TELEX relative to the contrast predicted by on-resonance theory. The B_0 sen-

Figure 2.2: (a) TELEX signal (Eq. 1.18) versus τ/T_2 for various different length RF pulses in the presence of a simulated 25Hz FWHM Gaussian lineshape. As pulse length increases, bandwidth narrows and signal becomes increasingly sensitive to B_0 non-uniformities. (b) f_z as a function of $\Delta\omega/2\pi$ for $\tau/T_2 = 0.01$.

sitivity will increase with the length of the RF pulse. B_0 -sensitivity therefore limits the available TELEX contrast when applied to highlighting longer short- T_2 species.

2.3 TELEX Experiment

2.3.1 Introduction

The validity of the analytical TELEX characterization (Eq. 1.10) must be demonstrated experimentally. According to Eq. 1.23, the magnetization response is a function of two parameters — $\gamma B_1 \tau$ and τ/T_2 . In the case of TELEX, signal is generated as a function of τ/T_2 . The goal was therefore to measure experimentally the curves illustrated in Fig. 1.5. Experiments consisted of a series of RF pulses with $\gamma B_1 \tau$ held fixed and τ/T_2 varied over some range. For these experiments $\gamma B_1 \tau$ was fixed at $\pi/2$ because, according to the Fig. 1.5, this is an example of a value that generates short- T_2 contrast. The measured signals (S_{xy} and S_z) were then compared to those predicted theoretically from the solution to Eqs. 1.10, 1.18 and 1.24. Although only S_z is responsible for TELEX contrast, S_{xy} is monitored for a full accounting of the magnetization. Since the purpose of the thesis is a

proof of principle, experiments were performed on water samples doped with various concentrations of MnCl_2 to alter their relaxation times. All experiments were performed on an SMIS spectrometer with a 1.5T superconducting magnet (Nalorac Cryogenics Corp., Martinez, California).

2.3.2 Method

Experiment

The experiment was similar to that outlined in Fig. 1.6. A series of RF pulses were applied to a doped water phantom. The pulses were designed so that $\gamma B_1 \tau = \pi/2$ and τ/T_2 was varied logarithmically. In this fashion, the curves in Fig. 1.5 could be sampled. The transverse component of the magnetization was observed by acquiring the signal directly. The z-component was observed via the application of a short, large amplitude 90° pulse (as described in Sec. 1.4.2). Typically, the hard 90° pulse amplitude was set to ~ 5 kHz. This ensured that all T_2 species lay in the underdamped regime; thus, all of the magnetization was rotated by 90° . Because experiments were performed on a spectrometer, where imaging is not possible, each set of measurements was made on a single T_2 species. The τ/T_2 value was therefore varied by adjusting the RF pulse length (as opposed to looking at several T_2 values simultaneously) while appropriately scaling the RF amplitude to maintain $\gamma B_1 \tau = \pi/2$. The method for calibrating the RF amplitude is outlined in Appendix A. The experiment was repeated on samples with different T_2 values ($T_2 \approx 0.001$ s, 0.01 s and 0.1 s). The magnitude of the first point of the signal was used as the magnitude of the data. Each experimental measurement was performed four times and the results averaged yielding a typical SNR of about 4000. To ensure magnetization recovered completely to within noise level of the equilibrium value, a long repetition time (TR) of about $10T_1$ was used. To eliminate systematic baseline offsets as well as receiver and/or RF channel imbalances, the T_2 -selective pulse was phase cycled according to the four-sequence CYCLOPS [35] scheme. To assess random error contributions to observed discrepancies, each experiment was repeated three times.

Simulation

According to Eqs. 1.18 and 1.24, to predict the MR signal, both the magnetization mapping function f as well as the sample lineshape must be known. f_{xy} and f_z were derived based on solutions to Eq. 1.10 given in Ref. [15] applied to the T_2 -selective pulse sequence in Fig. 1.6. The lineshape was calculated for each T_2 sample from the Fourier transform of the signal [13], corrected for T_2 decay, following a short 90° pulse. In the case of the $T_2=0.001$ s species, however, this was not possible. The comparatively narrow (inhomogeneous) lineshape was obscured by the much broader homogeneous lineshape associated with the short- T_2 species. The short- T_2 lineshape in this case was instead determined from the lineshape measured on an identically shaped and positioned long- T_2 sample. To reduce the possible effects of susceptibility-induced lineshape differences between the short- and long- T_2 species, spherically shaped samples were used [17]. The proton density was determined from the value of the first data point following data collection at the highest sampling rate possible on our system (400 KHz). The T_1 and T_2 values in each experimental run were measured independently by Inversion Recovery (IR) and Carr-Purcell-Meiboom-Gill (CPMG) [36, 37] sequences respectively.

2.3.3 Results

Fig. 2.3 is a plot of S_{xy} and S_z versus τ/T_2 in response to RF pulses of various durations (with $\gamma B_1 \tau = \pi/2$). Experimental data as well as a full simulation for $T_2=0.1$ s, 0.01 s and 0.001 s are plotted. For comparison, the on-resonance simulation is also plotted in the figure. While there is a significant deviation from the on-resonance simulation, the data closely follows the full simulation. However, as will be shown in Sec. 2.3.4, deviation from the on-resonance behaviour causes a significant alteration in the actual TELEX signal relative to the desired on-resonance TELEX signal.

On average, S_{xy} and S_z data typically deviate by less than 2% from the predicted simulation value. This, however, is more than an order of magnitude greater than the noise level in the experiment ($\sim 0.03\%$). Thus the discrepancy is likely *not* due to the noise. To assess whether the source of the observed discrepancy was due to a bias or due to random error, each experiment

Figure 2.3: TELEX experiment measuring (a) S_z and (b) S_{xy} versus τ/T_2 by varying RF pulse length (maintaining $\gamma B_1 \tau = \pi/2$) for different T_2 species. Solid lines join expected values based on full simulation and symbols are data. Note that data agrees with the full simulation but significant deviation from the on-resonance simulation results from B_0 non-uniformities. Note that the simulation was evaluated only at the experimental data points. The lines connecting the simulated points are for visual aid only.

was performed a total of three times. The repeatability of the experiment gives an estimate of the magnitude of the random error. Fig. 2.4 is a plot the mean and standard error of the discrepancy between the full simulation and the data for $T_2=0.001$ s case. Although only the $T_2=0.001$ s data is shown, the subsequent discussion holds equally well for the $T_2=0.01$ s and 0.1 s data. The

Figure 2.4: Mean and standard error of experimental discrepancy (theory-data) of (a) S_z and (b) S_{xy} for $T_2=0.001$ s over three experiments.

S_z discrepancy is generally larger and exhibits more variation than the S_{xy} discrepancy. To test whether the observed discrepancies were within the random error associated with the repeatability of the experiment, a χ^2 test was performed:

$$\chi^2 = \sum_{i=1}^7 (\overline{dis}_i / (\sigma_i / \sqrt{3}))^2 \quad (2.10)$$

where $\overline{dis}_i$ is the mean discrepancy between S_{xy} or S_z and σ_i is the standard deviation of the discrepancy over the three repeat measurements. Note, however, that the σ_i used in Eq. 2.10 is only the best estimate of the “true” standard deviation. Since only three repeat measurements were performed, there is significant uncertainty in the estimate σ_i . In fact, σ_i is expected to estimate

the true standard deviation according to a χ^2_σ distribution [38] (where the σ subscript has been added to distinguish the χ^2_σ distribution governing σ from the χ^2 value used to test goodness of fit in Eq. 2.10). To assess the impact of uncertainty in σ_i on the overall goodness-of-fit, the χ^2 test was recalculated at various different confidence levels (36% (best estimate), 50% and 90%) for the estimate σ_i . At the 90% confidence level, the χ^2 test is passed if $\chi^2 \leq 12$. For S_{xy} , the χ^2 test fails

σ_i	$\chi^2_{S_{xy}}$	$\chi^2_{S_z}$
Best Estimate (36% Confidence)	1392	80
50% Confidence	965	55
90% Confidence	147	8

Table 2.1: χ^2 values for the data using estimates σ_i of the “true” standard deviation at various confidence levels. At the 90% confidence level, the χ^2 test is passed only in the case of S_z with a 90% confidence level in σ_i .

in all cases. Therefore, repeatability does *not* completely account for the S_{xy} discrepancy. There is clearly a systematic bias in the discrepancy. For S_z , the χ^2 test passes only at the 90% confidence level in σ_i . Therefore, although there is likely also a systematic component, a significant part of the S_z discrepancy *is* accounted for by random error.

Simulation indicates that B_1 amplitude and phase errors as well as lineshape errors could all contribute significantly to the observed discrepancy. Furthermore, random variations in these parameters could also introduce bias (via the non-linear transformation of the Bloch equations) into the resulting discrepancy. Simulation also indicates the S_z is much more sensitive to variations in these parameters than S_{xy} . Therefore, it is speculated that the S_z discrepancy is dominated by random variations in various MR parameters while the source of the smaller S_{xy} discrepancy is due to an unknown systematic bias.

2.3.4 Discussion

Magnetization Behaviour

Sec. 1.3.5 showed that the MR signal will be a function of both the mapping function *and* the lineshape. For these experiments, the lineshapes typically had FWHM linewidths on the order of 20-

35 Hz (see Fig. 1.4 for an example of a typical lineshape). TELEX will yield the desired on-resonance behaviour when the bandwidth of the mapping function is broader than the linewidth (Secs. 1.3.5 and 2.2.3). In the case of the $T_2=0.1$ s data, the observed deviation from the on-resonance simulation is due to this effect. In the experiments performed here, the $T_2=0.1$ s magnetization lies in the underdamped regime over the entire range of pulse lengths used. As the RF pulse length increases, the bandwidth of the mapping function in the underdamped regime decreases (Sec. 1.3.5). (A more detailed discussion of the off-resonance characteristics of the mapping function will be deferred until Sec. 2.4) As a result, for the longer RF pulse lengths, the magnetization behaviour deviates significantly from the on-resonance simulation. On the other hand, the $T_2=0.01$ s and $T_2=0.001$ s data lie in (or close to) the overdamped regime ($t/T_{2_{crit}} = \pi$). The bandwidth of the mapping function tends to be broader in the overdamped regime than in the underdamped regime (Sec. 2.4). As a result, overdamped magnetization is much less sensitive to B_0 non-uniformities. This is the reason that the $T_2=0.01$ s and $T_2=0.001$ s data more closely follow the on-resonance response. In fact, in the case of the $T_2=0.001$ s pulse, most of the discrepancy with the on-resonance simulation is due to T_2 -selective effects acting on the hard 90° pulse ($\gamma B_1 2T_2 \approx 20$ for the hard 90° pulse in the $T_2=0.001$ s case) in addition to T_2 decay occurring during the delay before data acquisition begins.

Discrepancy

The results section noted that the observed S_z discrepancy may be due to variation in MR parameters such as B_1 amplitude. *In vivo*, the magnitude of these variations is likely to be larger than the *in vitro* study performed here [39]. The significance of these errors depends on the specific clinical situation. For example, in the case of white matter, uncertainty in the B_1 amplitude could lead to incomplete suppression of the long- T_2 axonal component. This would result in a reduction in contrast.

TELEX Contrast

The experiments were performed on individual T_2 species. It is therefore difficult from Fig. 2.3 to ascertain the actual T_2 contrast that would be achieved in response to any one particular RF pulse. Table 2.2 lists the normalized contrast (signal differences calculated from Fig. 2.3) that would be achieved between the shorter $T_2=0.01$ s and 0.001 s species and the longer $T_2=0.1$ s species in response to a given RF pulse. In response to the $\tau = 0.001$ s pulse, the $T_2=0.001$ s species is

<i>Pulse Length</i>	$S_{T_2=0.001\text{ s}}$	$S_{T_2=0.01\text{ s}}$	$S_{T_2=0.1\text{ s}}$	$Contrast_{T_2=0.001\text{ s}-0.1\text{ s}}$	$Contrast_{T_2=0.01\text{ s}-0.1\text{ s}}$
$\tau \approx 0.001\text{ s}$	0.33	0.09	0.02	0.31	0.07
$\tau \approx 0.01\text{ s}$	0.79	0.47	0.22	0.57	0.25
$\tau \approx 0.07\text{ s}$	0.9	0.9	0.75	0.15	0.15

Table 2.2: Normalized signal (S) and contrast (= signal difference) between the $T_2=0.01$ s and $T_2=0.1$ s species as calculated from the data in Fig. 2.3.

spared more substantially than the $T_2=0.01$ s component due to the fact that it lies further into the overdamped regime. There is therefore greater contrast between the $T_2=0.001$ s and 0.1 s species than the $T_2=0.01$ s and 0.1 s species. As the pulse length is increased to $\tau = 0.01$ s, the shorter $T_2=0.01$ s and 0.001 s species are moved further into the overdamped regime and are therefore spared more substantially. The result is greater contrast relative to the $\tau = 0.001$ s case. Note once again that there is significantly greater contrast associated with the very short $T_2=0.001$ s species than with the $T_2=0.01$ s species. Finally, in response to the long $\tau = 0.07$ s pulse, the shorter T_2 's are spared even more substantially as they are moved further into the overdamped regime. Since the long $T_2=0.1$ s magnetization still lies in the underdamped regime, on-resonance theory predicts that it can be largely suppressed. If on-resonance theory were to hold, then use of the longer pulse should result in a further increase in contrast. However, the B_0 sensitivity of the long- T_2 magnetization causes a substantial increase in its signal. As a result of the increased long- T_2 signal, there is actually a significant decrease in the contrast.

The data has shown that TELEX *can* generate a short- T_2 contrast. When applied to high-light short- T_2 's on the order of 0.001 s, short enough pulse lengths can be used such that significant

contrast can be generated. When applied to highlight a broader range of short- T_2 's (≥ 0.01 s), however, the longer pulse lengths required cause a sensitivity to B_0 non-uniformities. The B_0 sensitivity causes a significant reduction in the resulting contrast. As a result, TELEX is not readily applicable to highlighting longer short- T_2 's.

2.4 Bandwidth Broadening Scheme Theory

2.4.1 Introduction

The previous section illustrated the limitation of TELEX in highlighting longer short- T_2 species. Sensitivity to B_0 non-uniformities caused a significant degradation of the contrast relative to that predicted by on-resonance TELEX. The B_0 sensitivity was caused by the narrow bandwidth of the mapping function associated with the long pulses required with TELEX. In this section, a technique will be presented which broadens the bandwidth of the mapping function. With this technique, it will be shown that the sensitivity of TELEX to B_0 non-uniformities can be reduced. As a result, TELEX can be more readily applied to highlighting longer short- T_2 species.

To fully analyze the refocussing scheme, one must look to the solutions for the Bloch Equations (Eq. 1.12). Unfortunately, the full solution very quickly becomes unwieldy. Instead, to gain insight into the problem, the small tip angle approximation [20], mentioned in Sec. 1.3.5, will be used. This approach is only strictly accurate for the transverse magnetization and for small flip angles that are $\approx \pi/6$ or less. However, as will be shown later, the qualitative behaviour of the bandwidth of both f_{xy} and f_z for large tip angles will mimic the results derived using the small tip approach.

2.4.2 Small Tip Approximation Magnetization Behaviour

In this section, the bandwidth broadening scheme will be analyzed by the small tip approximation [20]. According to Eq. 1.3, magnetization after the N^{th} refocussing interval will be given by:

$$M^n = f_{xy}^N M_0 \quad (2.11)$$

where f_{xy}^N can be calculated recursively. For the analysis below, two separate cases will be considered:

1. In the first case, it will be assumed that $\tau_{180} \ll T_2$. This implies that the bandwidth of each piece of the RF pulse ($=1/\tau_{180}$) is much broader than the homogeneous linewidth ($=1/\pi T_2$). In this case, the small tip approximation of the Bloch equations can be solved to yield:

$$f_{xy}^N \approx e^{-i\Delta\omega\tau} [\mathcal{B}_1 + (f_{xy}^{N-1})^*] \quad (2.12)$$

where $\mathcal{B}_1 \equiv \mathcal{F}\{B_1\}$ and $*$ means that the complex conjugate is taken.

2. In the second case, it will be assumed that $\tau_{180} \gg T_2$. This implies that the bandwidth of the mapping function associated with each piece of the RF pulse is much broader than the homogeneous linewidth. Here, the small tip approximation of the Bloch equations reduces to:

$$\begin{aligned} f_{xy}^N &\approx \gamma B_1 \mathcal{L}_{hom} + e^{-(i\Delta\omega\tau + \tau/T_2)} (f_{xy}^{N-1})^* \\ &\approx \gamma B_1 \mathcal{L}_{hom} \end{aligned} \quad (2.13)$$

Mapping Function with $\tau_{180} \ll T_2$

For a constant amplitude RF pulse of duration τ , the mapping function can be calculated from Eq. 2.12 as:

$$f_{xy} = i\gamma B_1 \tau \sin(\Delta\omega\tau)/\Delta\omega\tau + \gamma B_1 \tau \sin^2(\Delta\omega\tau/2)/(\Delta\omega\tau/2) \quad (2.14)$$

For a pulse of total duration τ broken up by $N \geq 1$ equally spaced refocussing pulses (and with N even), f_{xy}^N can be calculated recursively from Eq. 2.12 as:

$$f_{xy}^N = i\gamma B_1 \tau \sin[\Delta\omega\tau/(2N)]/[\Delta\omega\tau/(2N)] \quad (2.15)$$

If N is odd, then Eq. 2.15 contains an additional, small, real component. Hereafter, it will be assumed that N is even so that this can be ignored. For the purposes of this thesis, bandwidth will be defined as the width of the of the mapping functions between the first zero crossings for f_{xy} and the point at which the value one is reached for f_z . Identifying $\tau_{180} = \tau/N$, the bandwidth (in Hz)

can be calculated from Eqs. 2.14 and 2.15 as:

$$\begin{aligned} BW &= 1/\tau & N &= 0 \\ BW &= 2/\tau_{180} & N &\geq 1 \end{aligned} \quad (2.16)$$

The bandwidth is therefore inversely proportional to the refocussing interval (thus verifying the qualitative observation of Eq. 1.25). By reducing the refocussing interval, the bandwidth can be made arbitrarily large.

The small tip description above is only strictly valid for the transverse component of the magnetization and for relatively small tip angles ($\approx \pi/6$ or less). On the other hand, even for pulses with large tip angles, the flip angle at the zero crossings will (by definition) be small. Thus Eq. 2.16 will hold even for large flip angles. With respect to f_z , the small tip approximation cannot be used. However, because it is assumed that $\tau_{180} \ll T_2$, magnetization will not undergo significant T_2 decay over the refocussing interval. This implies that the magnitude of the magnetization will remain roughly constant. As a result, the zero crossings of f_{xy} correspond to the ones of f_z . Therefore, the bandwidth of f_z equals the bandwidth of f_{xy} for both small and large tip angles.

Mapping Function with $\tau_{180} \gg T_2$

According to Eq. 2.13, magnetization with $\tau_{180} \gg T_2$ will not be affected by the refocussing scheme:

$$\begin{aligned} f_{xy} &\approx \gamma B_1 \mathcal{L}_{hom} \\ &= \gamma B_1 T_2 [i + \Delta\omega T_2] / [1 + (\Delta\omega T_2)^2] \end{aligned} \quad (2.17)$$

In this case, the bandwidth will be determined not by the refocussing scheme, but rather by the inherent bandwidth of $\mathcal{L}_{hom}$. Fig. 2.5 is a plot of f_{xy} and f_z for a $T_2=0.001$ s species in response to a $\gamma B_1 \tau = \pi/2$ pulse with various refocussing intervals. The mapping function (both f_{xy} and f_z) is virtually identical whether or not refocussing is used. Thus, when $\tau_{180} \gg T_2$, the refocussing scheme will have virtually no effect on the bandwidth of the mapping function.

Figure 2.5: Plot of (a) $|f_{xy}|$ and (b) f_z as a function of $\Delta\omega/2\pi$ for a $\tau=0.05$ s $\gamma B_1\tau = \pi/2$ pulse for $T_2 = 0.001$ s at various different refocussing intervals τ_{180} . The mapping function is virtually unaffected by the refocussing scheme.

2.4.3 Refocussed TELEX

On-resonance TELEX theory assumes that the MR signal can be characterized by its on-resonance value (Eq. 1.19):

$$S_{z_{unref}} \propto f_{z_{unref}}(\gamma B_1 \tau, \tau/T_2, \Delta\omega = 0) \quad (2.18)$$

Sec. 2.3 showed that this characterization will be invalid when the bandwidth is less than the linewidth. Using the refocussing scheme, the mapping function bandwidth can be broadened so that an on-resonance characterization is again possible:

$$S_{z_{ref}} \propto f_{z_{ref}}(\gamma B_1 \tau, \tau/T_2, \Delta\omega = 0) \quad (2.19)$$

Ideally, the refocussing scheme would reduce B_0 sensitivity without affecting the T_2 -selectivity of TELEX (i.e. $f_{z_{unref}}(\gamma B_1 \tau, \tau/T_2, \Delta\omega = 0) = f_{z_{ref}}(\gamma B_1 \tau, \tau/T_2, \Delta\omega = 0)$). However, this section will show that steady state effects can alter the T_2 -selectivity of refocussed TELEX.

The previous section discussed the mapping function behaviour in terms of the value of the refocussing interval in relation to the T_2 value. However, of greater relevance to TELEX, the behaviour of the mapping functions can also be related to the regime in which the magnetization lies (i.e under- or overdamped).

Refocussed Underdamped Magnetization Behaviour

In a typical TELEX sequence:

$$\gamma B_1 \tau_{180} < 1. \quad (2.20)$$

This is due to the fact that the RF amplitude (γB_1) is usually relatively small and, since a broad bandwidth is desired, the refocussing interval (τ_{180}) is kept small as well. For magnetization lying in the underdamped regime ($\gamma B_1 \gg 1/2T_2$), Eq. 2.20 implies that $\tau_{180} \ll T_2$. Therefore, in a typical refocussed TELEX sequence, the underdamped mapping function bandwidth will vary inversely as the refocussing interval (Eq. 2.16).

Refocussed Overdamped Magnetization Behaviour

In the case of overdamped magnetization, it is possible that $\tau_{180} \gg T_2$ or $\tau_{180} \ll T_2$. If $\tau_{180} \gg T_2$, then the bandwidth will be equal to the homogeneous linewidth ($= 1/\pi T_2$). If $\tau_{180} \ll T_2$, then the bandwidth will be equal to $2/\tau_{180}$. Therefore, for overdamped magnetization, the homogeneous linewidth represents a lower bound for the bandwidth of the mapping function. This implies that the overdamped bandwidth will always be greater than or equal to the underdamped bandwidth. As a result, overdamped magnetization will always be less sensitive to B_0 non-uniformities than underdamped magnetization.

Steady State Effects

In response to a constant amplitude RF pulse of duration τ , the steady state of the magnetization will be approached when $\tau > T_1$. However, the simulations in the previous sections ignored T_1 . Magnetization behaviour will more generally be given by:

$$\mathbf{f} = \mathbf{f}(\gamma B_1 \tau, \tau/T_2, \Delta\omega\tau, T_1/T_2) \quad (2.21)$$

To illustrate the effects of the steady state on the mapping functions, Fig. 2.6 is a plot of f_z both with and without refocussing as a function of τ/T_2 for various T_1/T_2 values and $\gamma B_1 \tau = \pi/2$. Unrefocussed TELEX is largely insensitive to variations in T_1 . This implies that steady state effects do not significantly alter unrefocussed TELEX signal. By comparison, Fig. 2.6b shows that refocussed TELEX is quite sensitive to variations in T_1 . When T_1 is infinite, in which case steady state effects will not be observed, the refocussed f_z is identical to the unrefocussed f_z . This implies that the refocussing scheme itself does not affect the T_2 -selectivity of TELEX. However, when T_1 is finite and the steady state is approached, the refocussed f_z becomes saturated (i.e. $|f| \rightarrow 0$). Fig. 2.6 implies that the steady state is approached when $\tau \geq 0.4T_1$. By comparison, the $T_1 = \infty$ plot implies that T_2 -selective effects are observed when $\tau \approx 10T_{2,short}$. Therefore, if $T_1/T_2 \leq 25$, steady state effects will reduce the refocussed TELEX signal relative to the unrefocussed on-resonance TELEX signal.

Figure 2.6: (a) Unrefocussed and (b) refocussed f_z plotted as a function of τ/T_2 for different T_1/T_2 ratios and $\gamma B_1 \tau = \pi/2$. Note that since T_1/T_2 is fixed for each curve, as τ/T_2 decreases, so too does τ/T_1 . Unrefocussed TELEX does not display significant steady state effects. Steady state saturation of refocussed TELEX can be observed when $\tau \approx 0.4T_1$.

Mathematical Description of Steady State Saturation

The saturation observed in the previous section is due to the drive towards the steady state of the magnetization. The steady state magnetization can be calculated from Eq. 1.10 by setting $d\vec{M}/dt = 0$:

$$\begin{aligned} f_{xy_{ss}} &= 1/[(\gamma B_1 T_2) T_1/T_2 + 1/(\gamma B_1 T_2)] \\ f_{z_{ss}} &= 1/[(\gamma B_1 T_2)^2 T_1/T_2 + 1] \end{aligned} \quad (2.22)$$

In the overdamped regime (i.e. $\gamma B_1 2T_2 \ll 1$) and provided $T_1/T_2 \leq 1/(\gamma B_1 T_2)^2$ (i.e. T_1/T_2 not too large), the steady state magnetization will be given by:

$$\begin{aligned} f_{xy_{ss}} &\approx 0 \\ f_{z_{ss}} &\approx 1 \end{aligned} \quad (2.23)$$

In the case of unrefocussed TELEX, T_2 effects store overdamped magnetization along the z-axis (i.e. $f_{xy} \approx 0$ and $f_z \approx 1$). Therefore, T_2 -selective effects of TELEX drive magnetization towards the same endpoint as the steady state. This is the reason, in Fig. 2.6a, that steady state effects are not strongly observed in the unrefocussed case. The situation is distinctly different when refocussing is used. In this case, the drive towards the steady state is dominated by the 180° refocussing pulses. Provided $\tau_{180} \ll T_2, T_1$, the series of 180° refocussing pulses can be analyzed as if it were a single long pulse. In this case, because the hard refocussing pulses are assumed to lie in the underdamped regime for all T_2 's ($\gamma B_1 2T_2 \gg 1$), Eq. 2.22 reduces to:

$$\begin{aligned} f_{xy_{ss}} &\approx 0 \\ f_{z_{ss}} &\approx 0 \end{aligned} \quad (2.24)$$

Unlike the unrefocussed case (Eq. 2.23), the steady state of the magnetization in the presence of refocussing is zero — opposite to the behaviour due to the T_2 effects of TELEX. Thus, the drive towards the steady state accounts for the saturation observed in Fig. 2.6b. The refocussing scheme therefore reduces B_0 -sensitivity, but will also reduce the contrast when $\tau > 0.4T_1$.

2.5 Bandwidth Broadening Experiment

2.5.1 Introduction

Experiments were performed to characterize quantitatively the performance of the bandwidth broadening technique. To accomplish this, the off-resonance characteristics of the mapping function were investigated. Fig. 1.9 shows f_{xy} and f_z in response to an RF pulse at various frequency offsets. According to Eq. 1.18, most of the signal will be due to the value of the mapping function around ω_0 ($f(\Delta\omega = 0)$). If the RF transmit frequency is varied by some amount $\Delta\omega$, the mapping function will be correspondingly offset by that amount. In this case, most of the signal contribution will be due to the value of the mapping function around $\Delta\omega$ ($f(\Delta\omega)$). By repeating this for different offsets, different frequency ranges of the mapping function can be explored. By repeating this experiment both with and without refocussing pulses, the effects of the bandwidth broadening scheme can be analyzed. If the scheme is successful in broadening the bandwidth, then the mapping function is expected to be more uniform as a function of $\Delta\omega$.

2.5.2 Method

The experimental method is similar to the one discussed in Sec. 2.3.2. In this case, the T_2 -selective RF pulse was fixed with a duration of $\tau=0.015$ s. $\Delta\omega/2\pi$ was varied over the range ± 300 Hz in 50 Hz increments. Two averages were taken using a phase cycling scheme [31] to remove baseline offsets and residual transverse magnetization. To investigate both the over- and underdamped regimes, the experiment was performed on both a short- T_2 ($T_2 \approx 0.001$ s) and long- T_2 ($T_2 \approx 0.001$ s) species. Experiments were performed both with ($\tau_{180} \approx 0.00075$ s) and without refocussing. To assess the magnitude of random discrepancies, each experiment was repeated three times. The experimental data was then compared with simulation. The simulation was performed in the same way as outlined in Sec. 2.3.2.

2.5.3 Results

The experimental results for the $T_2 = 0.1$ s and $T_2 = 0.001$ s data are plotted in Figs. 2.7 and 2.8 respectively. In the figures, experimental and simulated S_{xy} and S_z are plotted as a function of $\Delta\omega/2\pi$. On average, S_{xy} and S_z deviate by less than 2% from the predicted simulation value. The results of the error analysis are similar to the error analysis for the unrefocussed TELEX experiment (Sec. 2.3.3): noise and repeatability do not account for all of the observed discrepancy. In the case of S_z , however, repeatability accounts for a more significant part of the discrepancy. It is again speculated that a large part of the S_z discrepancy is due to uncertainties in the MR parameters listed in Sec. 2.3.3.

Figure 2.7: Bandwidth Broadening Experiment for (a) S_z and (b) S_{xy} for $T_2=0.1$ s. S_{xy} and S_z are plotted versus transmit frequency ($\Delta\omega/2\pi$). RF pulse length is $\tau=0.015$ s, $\gamma B_1\tau = \pi/2$ for both refocussed ($\tau_{180} \approx 0.00075$ s) and unrefocussed pulses. The off-resonance insensitivity of the refocussed magnetization implies a broad bandwidth mapping function.

Figure 2.8: Bandwidth broadening experiment for (a) S_z and (b) S_{xy} for $T_2=0.001$ s. S_{xy} and S_z are plotted versus transmit frequency ($\Delta\omega/2\pi$). RF pulse length is $\tau=0.015$ s, $\gamma B_1\tau = \pi/2$ for both refocussed ($\tau_{180} \approx 0.00075$ s) and unfocussed pulses. In both cases, off-resonance insensitivity implies a broad bandwidth mapping function. The steady state effects can be seen as the refocussed magnetization is saturated.

2.5.4 Discussion

The results in Fig. 2.7 indicate that, for underdamped magnetization, the refocussing scheme *is* effective in broadening the bandwidth of the mapping function. In the unrefocussed case, S_{xy} and S_z change dramatically as $\Delta\omega$ is varied; thus, the mapping function bandwidth is relatively narrow in comparison with the linewidth. On the other hand, S_{xy} and S_z in the refocussed case are seen to be relatively insensitive to variations in $\Delta\omega$; thus, the refocussed bandwidth is significantly broader than the linewidth. As a result, the refocussing scheme does indeed broaden the bandwidth of the underdamped mapping function.

In the case of overdamped magnetization, Fig. 2.8 illustrates that S_{xy} and S_z are relatively insensitive to variations in $\Delta\omega$ for both the refocussed and unrefocussed cases. This implies that the mapping function bandwidth is broad in both cases. In the case of the unrefocussed data, the bandwidth is broad because the homogeneous linewidth is broad (~ 300 Hz). For the refocussed data, the bandwidth is even broader because of the short refocussing interval ($BW = 2/\tau_{180} = 2600$ Hz). Also, in the refocussed data, the effects of steady state saturation can be clearly seen. This is expected because, for the $T_2=0.001$ s species, $\tau/T_1 \approx 1.5$ (Sec. 2.4.3).

The previous sections have shown that the refocussing scheme *does* broaden the bandwidth of the mapping function. This implies that, by appropriate choice of τ_{180} , the bandwidth can be made as large as desired. As a consequence, refocussed magnetization *can* be characterized by its on-resonance behaviour (Eq. 2.19). However, when refocussing is used, the drive towards the steady state can affect the magnetization behaviour. The effects of steady state on the TELEX technique are explored experimentally in the next section.

2.6 TELEX-Bandwidth Broadening Experiment

2.6.1 Method

In this section, TELEX is characterized quantitatively in the presence of the bandwidth broadening scheme. The experimental method is exactly the same as the previous TELEX experiment (Sec. 2.3 and Fig. 1.6) with the exception that the single long T_2 -selective pulse is replaced by a refocussed

pulse as illustrated in Fig. 1.7. To ensure that the effects of the refocussing pulses were highlighted, a short refocussing interval of $\tau_{180} \approx 0.00075$ s was utilized.

2.6.2 Results

The experimental results for $T_2=0.1$ s, 0.01 s and 0.001 s are plotted in Fig. 2.9. In the figures, experimental and simulated S_{xy} and S_z are plotted as a function of τ/T_2 . On average, S_{xy} and S_z deviate by less than 2% from the predicted simulation value. The results of the error analysis are similar to the error analysis for the unrefocussed TELEX experiment (Sec. 2.3.3): noise and repeatability do not account for all of the observed discrepancy. In the case of S_z , however, repeatability accounts for a more significant part of the discrepancy. It is speculated that a large part of the S_z discrepancy is again due to uncertainties in the MR parameters mentioned in Sec. 2.3.3.

Figure 2.9: Refocussed TELEX experiment measuring (a) S_z and (b) S_{xy} versus τ/T_2 by varying RF pulse length (maintaining $\gamma B_1 \tau = \pi/2$) for different T_2 species. Solid lines join expected value based on full simulation. Symbols are data. Note that, for MnCl_2 , $T_1/T_2 \approx 10$.

2.6.3 Discussion

In this section, the contrast performance of refocussed TELEX will be analyzed. Table 2.3 lists the normalized contrast (signal differences calculated from Fig. 2.9) that would be achieved between the shorter $T_2=0.01$ s and 0.001 s species and the longer $T_2=0.1$ s species in response to a given RF pulse (like Table 2.2 in the unrefocussed case). In response to the $\tau=0.01$ s pulse, the underdamped

<i>Pulse Length</i>	$S_{T_2=0.001\text{ s}}$	$S_{T_2=0.01\text{ s}}$	$S_{T_2=0.1\text{ s}}$	$Contrast_{T_2=0.001\text{ s}-0.1\text{ s}}$	$Contrast_{T_2=0.01\text{ s}-0.1\text{ s}}$
$\tau \approx 0.01\text{ s}$	0.16	0.22	0.03	0.13	0.19
$\tau \approx 0.07\text{ s}$	0.04	0.13	0.13	-0.06	0

Table 2.3: Normalized signal (S) and contrast (= signal difference) between the $T_2=0.01$ s and $T_2=0.1$ s species as calculated from the data in Fig. 2.9.

$T_2=0.1$ s species is suppressed while the overdamped $T_2=0.01$ s and 0.001 s species are spared. However, because of the steady state saturation, the signal from the short T_2 's is reduced relative to the unrefocussed case (compare with Table 2.2). As a result, the contrast is decreased. In response to the $\tau=0.07$ s pulse, unlike the unrefocussed case, the long- T_2 species is largely suppressed. This implies that the refocussing scheme is effective in reducing the B_0 sensitivity. However, as with the $\tau=0.01$ s case, the steady state saturation causes a signal loss from the short- T_2 's. As a result, the contrast is reduced. Note that a comparison of Table 2.2 and Table 2.3 implies that, in this particular case, unrefocussed TELEX actually performs better than refocussed TELEX in highlighting the $T_2=0.01$ s species. However, the performance of unrefocussed TELEX is strongly related to the range of B_0 non-uniformities. *In vivo*, the B_0 non-uniformities are expected to be significantly worse than in the phantom experiments performed here (see Sec. 3.2). As a result, unrefocussed TELEX is not expected to be useful in highlighting longer short- T_2 's *in vivo*.

It has been shown that refocussed TELEX is successful in reducing B_0 sensitivity. As a result, refocussed TELEX can be applied to a broad range of T_2 's. The cost of the refocussing scheme, however, is a reduction in contrast due to the drive towards the steady state.

2.7 Conclusions

This chapter has shown that TELEX is capable of generating contrast which highlights short- T_2 species while suppressing long- T_2 species – opposite to traditional T_2 -weighted contrast. This was accomplished by playing out long, weak RF pulses of duration on the order of the short- T_2 species of interest. As originally proposed [10], TELEX was derived from an on-resonance analysis of the Bloch equations. In this chapter, it was shown that this approach is only strictly valid if one can ignore B_0 non-uniformities. When the short- T_2 species of interest has $T_2 \approx 0.001$ s, TELEX *does* achieve the desired behaviour. However, when the short- T_2 species of interest has $T_2 \geq 0.01$ s, the corresponding long RF pulses required for TELEX make the technique quite sensitive to B_0 non-uniformities. When B_0 non-uniformities are taken into account, TELEX agrees with simulation to within an average discrepancy of less than 2%. *In vivo*, the noise level is typically about the same order of magnitude as this discrepancy. The effects of B_0 non-uniformities caused a significant degradation in the actual TELEX contrast relative to the desired on-resonance contrast. The degradation in contrast limits the performance of the technique when applied to highlight a broader range of (potentially clinically relevant) T_2 values ($T_2 \geq 0.01$ s).

To reduce the sensitivity of TELEX to B_0 non-uniformities, a refocussing scheme was applied. With the refocussing scheme, data and simulation again agreed to within an average discrepancy of less than 2%. The refocussing scheme was shown to be effective in reducing the sensitivity to B_0 non-uniformities. When the refocussing scheme was used, however, contrast was degraded by the drive towards the steady state. In the presence of the refocussing scheme, the steady state of the magnetization is zero. The steady state is approached when $\tau \approx 0.4T_1$. If $T_1/T_2 \leq 25$ (as in MnCl_2 as well as many tissues [40]), then saturation will be observed when $\tau \geq 40T_2$. Unfortunately, this is also the range of RF pulse lengths required to generate the T_2 -selective effects of TELEX. As a result, the drive towards steady state will oppose, and therefore degrade, the TELEX contrast. Therefore, in the presence of refocussing, TELEX performs best when T_1/T_2 is large.

Chapter 3

Issues Associated with the *In Vivo* Application of TELEX

3.1 Introduction

The results of the previous chapter have shown that, for MnCl_2 samples, magnetization behaves as predicted by TELEX theory. Although performed on uniform, homogeneous MnCl_2 samples, this characterization highlighted the fundamental issues affecting the performance of the TELEX technique — namely B_0 sensitivity and steady state effects. In this chapter, based on simulation, the performance of TELEX under conditions likely to be encountered *in vivo* is explored. In Sec 3.2, simulations are performed to assess the contrast performance of TELEX in the presence of B_0 non-uniformities and T_1 values typically found *in vivo*. (Since concern here is with the performance of the TELEX technique itself, potential confounding factors such as tissue compartmentalization [41] or magnetization transfer [31] will not be dealt with). Finally, in Sec. 3.3.2, the applicability of TELEX specifically to the case of white matter will be analyzed.

3.2 Contrast in the Presence of B_0 Non-Uniformities

Results from previous sections have shown that the contrast performance of TELEX will be influenced by the presence of B_0 non-uniformities. The impact of typical *in vivo* B_0 non-uniformities on TELEX contrast is analyzed here. To provide an illustrative example, the performance of TELEX is assessed for an RF pulse with $\tau=0.1$ s and $\gamma B_1 \tau = \pi/2$. This particular example is chosen because this pulse could be used to highlight clinically relevant [2, 4] T_2 values in the $T_2=0.01$ s range (Fig. 1.5). Analysis will be performed both with and without the refocussing scheme.

3.2.1 Without Refocussing

Fig. 3.1 is a plot of S_{xy} and S_z in response to an unrefocussed RF pulse in the presence of simulated Gaussian lineshapes of various linewidths. Clearly, B_0 non-uniformities have a significant effect on

Figure 3.1: (a) S_z and (b) S_{xy} in response to a $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse in the presence of various Gaussian lineshapes of various linewidths. As the linewidth increases, the signal from the long- T_2 increases. As a result, the contrast (=difference in signal between short- and long- T_2 's) decreases.

the signal. B_0 non-uniformities will cause an increase in the signal of the long- T_2 's. This will result

in a decrease in the contrast (=difference in signal between short- and long- T_2 's) of the technique. In the presence of a linewidth of 1 Hz, Fig. 3.1 implies that the contrast is comparable to that predicted by on-resonance unrefocussed TELEX (compare with Fig. 1.5). At a linewidth of 5 Hz, a slight contrast loss is observed. By 20 Hz, the contrast loss is substantial. In the human brain, voxel linewidths are typically in the 5-30Hz range [42]. There is therefore likely to be significant variation in the performance of TELEX over the brain. In the worst case, B_0 inhomogeneities could cause a substantial loss of contrast for unrefocussed TELEX.

A more significant source of B_0 non-uniformity is the field *shift* associated with voxels located adjacent to (or inside of) structures of differing magnetic susceptibilities [17]. Due to susceptibility effects, frequency shifts of up to 150 Hz are typically observed in the human brain [42]. Fig. 3.2 is a plot of S_{xy} and S_z in response to an unrefocussed RF pulse at various frequency shifts in the presence of a 5 Hz FWHM Gaussian lineshape. Even for relatively small shifts of 5 Hz, there is

Figure 3.2: (a) S_z and (b) S_{xy} in response to a $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse for various B_0 -shifts. Lineshape is a simulated 5Hz FWHM Gaussian. As the B_0 -shift increases, B_0 -sensitivity increases.

a significant contrast loss in the z-component of the magnetization. For larger shifts, the contrast

loss becomes nearly total. Thus, when the B_0 -shift is on the order of the linewidth, significant contrast loss can result. Since typical *in vivo* linewidths are less than 30 Hz, contrast loss due to B_0 shift is expected to be a significant problem.

The specific example given above ($\tau=0.1$ s pulse) highlighted T_2 's less than about $T_2 \approx 0.01$ s. Even in this case, the above discussion has shown that B_0 non-uniformities are expected to be a significant problem for unrefocussed TELEX. To highlight T_2 's greater than this would require even longer pulses. Such pulses would be even more sensitive to B_0 non-uniformities than the example given above and thus would be less effective in generating the desired contrast.

3.2.2 With Refocussing

This section will analyze the contrast performance of the refocussed TELEX sequence in the presence of B_0 non-uniformities. It will be assumed, as is often observed *in vivo* [40], that $T_1/T_2 = 10$. The choice of a refocussing interval will be dictated by the range of B_0 non-uniformities present. For the large non-uniformities discussed in the previous section, it is desirable to make the refocussing interval as small as possible. Ultimately, SAR limits will put an upper bound on the number of refocussing pulses that can be used [43]. On our GE SIGNA system [44], an average SAR limit of 1W/kg with a patient weight of 70 Kg, a sequence repetition time of 1s and a 180° RF amplitude of 600 Hz would allow about 50 refocussing pulses to be used. For a $\tau=0.1$ s, $\gamma B_1 \tau = \pi/2$ T_2 -selective RF pulse, this would yield a refocussing interval of $\tau_{180} = 0.002$ s. (Limits on the RF amplifier duty cycle may also put some constraints on the refocussing interval). Fig. 3.3 is a plot of S_{xy} and S_z in response to a refocussed $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse ($\tau_{180} = 0.002$ s) for Gaussian lineshapes of various linewidths. The signal is virtually independent of the linewidth. Thus the refocussing scheme is expected to be effective in reducing B_0 sensitivity over the typical range of B_0 inhomogeneities found in the body. Fig. 3.4 is a plot of S_{xy} and S_z for various B_0 shifts. In the presence of the refocussing scheme, TELEX is much more insensitive to B_0 shifts in comparison with the unrefocussed case (Fig. 3.2). It is only at the outer limits of the B_0 shift range (~ 150 Hz) that some sensitivity is observed.

The above discussion dealt with the case of a $\tau=0.1$ s RF pulse. As can be seen from Figs. 3.3

Figure 3.3: (a) S_z and (b) S_{xy} in response to a $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse in the presence of various Gaussian lineshapes of various linewidths in response to a $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse. With refocussing, TELEX is insensitive to B_0 inhomogeneities.

Figure 3.4: (a) S_z and (b) S_{xy} in response to a refocussed ($\tau_{180} = 0.002s$) $\tau=0.1$ s $\gamma B_1 \tau = \pi/2$ pulse for various B_0 -shifts. Lineshape is a simulated 5Hz FWHM Gaussian. Refocussed TELEX is largely insensitive to B_0 shifts in the range typically encountered *in vivo*.

and 3.4, this pulse highlights T_2 species with $T_2 \approx 0.03$ s (i.e $\tau/T_2 \approx 3$). The simulations indicated that the refocussing scheme *is* expected to be effective in reducing the TELEX B_0 sensitivity over the range of B_0 non-uniformities typically found *in vivo*. To highlight longer short- T_2 's, longer RF pulses are required. To maintain a similar degree of B_0 insensitivity, the refocussing interval must remain constant. This implies that more refocussing pulses and therefore more SAR is required. Therefore, for long RF pulse lengths, SAR limits will ultimately constrain the amount of B_0 insensitivity that can be achieved by the bandwidth broadening scheme.

3.3 Application of TELEX to Multiple Sclerosis

3.3.1 TELEX Imaging of White Matter

In this section, the contrast performance of TELEX in the case of white matter will be analyzed. The purpose of this section is to analyze theoretically the performance of the TELEX technique itself. As such, phenomenon like magnetization transfer [31] or exchange [41] (for example), which may additionally influence the contrast performance of TELEX, will be ignored. In a standard MR image (voxel resolution $\approx 1 \times 1 \times 5mm$), the SNR is typically on the order of 100 in the brain. Therefore, for the analysis in this section, it will be assumed that the $T_2=0.1$ s component of white matter has an SNR of 90 and the $T_2=0.01$ s component of white matter has an SNR of 10 (see Table 1.1). To assess the performance of TELEX, contrast was optimized (for a fixed $\gamma B_1 \tau$) by choosing the RF pulse length which maximizes the contrast between the two components.

Without Refocussing

For this section, the optimization was performed assuming that on-resonance TELEX is valid. The optimized TELEX CNRs are listed in Table 3.1. It can be seen that, while suppressing the long- T_2 component, the optimal unrefocussed TELEX contrast with $\gamma B_1 \tau = \pi/2$ also significantly reduces the signal from the short- T_2 component. However, as will be discussed in Sec. 4.1.2, TELEX contrast can be modified (and therefore potentially improved) by changing the $\gamma B_1 \tau$ value. For example, as listed in Table 3.1, a $\gamma B_1 \tau = 3\pi/2$ pulse maintains suppression of the long- T_2 species while

<i>Technique</i>	$SNR_{T_2=0.01s}$	$SNR_{T_2=0.1s}$	CNR
On-Resonance Unrefocussed TELEX $\gamma B_1\tau = \pi/2$	0.74	0.70	0.04
On-Resonance Unrefocussed TELEX $\gamma B_1\tau = 3\pi/2$	8.51	0.20	8.31
Refocussed TELEX $\gamma B_1\tau = 3\pi/2$	1.00	0.02	0.98
Image Subtraction	0.73	0.13	0.6

Table 3.1: Comparison of white matter contrast performance between various techniques. It is assumed that the total SNRs of the $T_2=0.01$ s and $T_2=0.1$ s components of white matter are 10 and 90 respectively. CNR is defined as $SNR_{T_2=0.01s} - SNR_{T_2=0.1s}$.

largely sparing the short- T_2 . Other pulse types or shapes may further improve the performance (see Sec. 4.1.2). As mentioned earlier, this assumes that B_0 non-uniformities are small enough so that on-resonance TELEX is valid. In fact, typical B_0 non-uniformities (~ 20 Hz linewidth and/or >50 Hz field shift) will degrade the contrast sufficiently so that TELEX would no longer be useful for whole-brain white matter imaging (since the long- T_2 component is ten times larger than the short- T_2 component, and Fig. 3.1 and 3.2 imply that there is greater than 10% residual long- T_2 signal in the presence of B_0 non-uniformities).

With Refocussing

In this section it will be assumed that the use of refocussing is sufficient to eliminate B_0 sensitivity. However, when refocussing is used, the contrast will be reduced due to the steady state effects. In the case of white matter, where $T_1/T_2 \approx 40$ for the short- T_2 component [31], the steady state effects will not be as severe as observed with $MnCl_2$ (where $T_1/T_2 \approx 10$). However, table 3.1 illustrates that steady state effects will reduce the contrast by about a factor of 10 relative to the unrefocussed on-resonance contrast. At a 95% confidence level, detection occurs [45, 46] at a CNR greater than 1.64 (assuming zero mean Gaussian noise statistics). Therefore, the data in Table 3.1 suggests that, refocussed TELEX should be capable of producing contrast that is at least in a range which is feasible for the detection of the short- T_2 peak. Optimizing $\gamma B_1\tau$ or more generally, allowing time-varying RF amplitudes, may further improve the performance of the technique. Alternatively, the CNR could be improved by increasing the voxel size or by performing a number of averages. However, this approach may negate some of the advantages of TELEX by placing restrictions on

resolution and/or scan time of the technique.

3.3.2 Alternate White Matter Imaging Techniques

Image Subtraction

Image subtraction is an alternate technique for obtaining short- T_2 information. This technique, however, generally has a relatively poor CNR performance. In the image subtraction method, a composite image is formed via the subtraction of a late echo image (after a time delay of TE) from an early echo image (assumed to be acquired at TE=0). The long- T_2 signal, which is roughly the same in both images, will cancel out. The short- T_2 signal, which ideally is only present in the early echo image, will remain. It will be assumed that the noise in the images is given by σ and that the relative magnetization content of the short- and long- T_2 species is given by $w_{T_2_{short}}$ and $w_{T_2_{long}}$ respectively. In the subtracted image, the CNR between the short- and long- T_2 species will then be given by:

$$CNR = [Signal_{T_2_{short}} - Signal_{T_2_{long}}]/(\sqrt{2}\sigma) \quad (3.1)$$

$$= [w_{T_2_{short}}(1 - e^{TE/T_2_{short}}) - w_{T_2_{long}}(1 - e^{TE/T_2_{long}})]/(\sqrt{2}\sigma) \quad (3.2)$$

where the $\sqrt{2}$ factor comes from the fact that uncorrelated noise adds in quadrature [45]. In the ideal case:

$$Signal_{T_2_{long}} \approx 0 \quad (3.3)$$

$$Signal_{T_2_{short}} \approx w_{T_2_{short}} \quad (3.4)$$

$$\Rightarrow CNR = w_{T_2_{short}}/(\sqrt{2}\sigma) \quad (3.5)$$

At best, the maximum CNR value is given by $w_{T_2_{short}}/(\sqrt{2}\sigma)$. There is therefore a CNR penalty of at least $1/\sqrt{2}$ in the image subtraction technique. In practice, Eqs. 3.3 and 3.4 will not be satisfied and the resulting CNR can be *significantly* worse than Eq. 3.5. The CNR can be optimized by an appropriate choice of the second echo time (the first echo time is assumed to be at TE=0 to maximize signal from short- T_2 species). Further optimization can be achieved by varying the

weighting factor of the second image. Table 3.1 lists the performance of optimized image subtraction in the case of white matter. It can be seen that the contrast performance of image subtraction is *inferior* to that of TELEX. Additional CNR improvement is only possible by increased voxel size and/or scan time. This differs from the situation with TELEX where a number of parameters could potentially lead to an improved CNR. In the case of white matter, therefore, TELEX is expected to yield a better contrast than image subtraction.

Relaxometry

The T_2 spectrum of white matter can be resolved through a multiexponential relaxation analysis applied to the MR signal decay curves [31, 4, 5, 6, 7, 47]. Potentially, this technique could directly visualize the short- T_2 myelin component. The success of this technique, however, is highly dependent on the SNR available in the tissue [9]. As a result, most studies were performed on bulk excised white matter where high SNR (≥ 1000) is available [31, 7, 47, 48, 49]. Graham et al. [9] performed an analysis in which they determined that a successful *in vivo* multiexponential decay analysis would require an SNR of about 700. As noted previously, the available SNR *in vivo* is on the order of 100. To increase the SNR, repeat scans or larger voxel sizes would have to be used. Repeating the scan to build up the SNR would require a scan time on the order of 100 minutes – too long to be clinically feasible. Increasing the voxel size would result in a poorer spatial resolution. Therefore, an *in vivo* implementation of multiexponential decay analysis would place restrictions on the available resolution and/or scan time [5, 6].

3.4 Conclusions

In this chapter, issues associated with the theoretical performance of TELEX *in vivo* have been analyzed. It has been shown that, over the range of B_0 non-uniformity and B_0 shifts typically found *in vivo*, the contrast performance of unrefocussed TELEX would be significantly degraded. The actual utility of TELEX will depend strongly on the specific parameters (primarily relative T_2 and proton density) of the tissues involved. In the case of white matter, B_0 sensitivity would likely

prevent unrefocussed TELEX from generating short- T_2 contrast in whole-brain imaging. Use of the refocussing scheme was shown to significantly reduce (or eliminate) the B_0 sensitivity of TELEX over typical ranges of *in vivo* B_0 non-uniformities. The cost of the reduced B_0 sensitivity, however, was contrast loss due to steady state effects. In the case of white matter, use of the refocussing scheme reduced the contrast by a factor of ten relative to (the unachievable) unrefocussed on-resonance TELEX contrast. Simulation showed, however, that refocussed TELEX is expected to give a CNR in a range that is at least feasible for the detection of the short- T_2 peak. Additionally, further contrast optimization is possible with TELEX.

The other two imaging techniques capable of providing short- T_2 information are image subtraction and multiexponential decay analysis. In the case of image subtraction, TELEX provides better contrast performance. In the case of multiexponential decay analysis, stringent SNR requirements make an *in vivo* application difficult to achieve. Even if possible, there would likely be significant restrictions placed on resolution and/or scan time.

Chapter 4

Future Directions and Conclusions

4.1 Future Directions

4.1.1 TELEX Applied to Tissue

The purpose of this thesis was to characterize the performance of the TELEX technique. As such, experiments were performed on doped water phantoms. The phantoms provided a well-characterized, homogeneous, isotropic system. Ultimately, however, one would like to apply this technique to actual clinical problems. To do so, one must investigate the performance of TELEX in tissues.

Ex Vivo TELEX

Unlike water phantoms, tissue is often characterized by a range of T_2 values [31, 49, 50, 51] (i.e. a T_2 spectrum). To investigate the tissue response to TELEX, one must determine the effects of TELEX on the different components of the spectrum. The T_2 spectrum itself can be resolved via the application of a CPMG sequence and the use of multiexponential decay analysis [4, 5, 31, 49, 47, 7, 50, 51, 52, 48] (Sec. 3.3.2). To observe the effects of TELEX on the different T_2 's of the spectrum, a CPMG sequence could be added at the end of the TELEX sequence. A multiexponential decay analysis of the resulting data would then indicate the effect of TELEX on the different T_2 components of the spectrum. As mentioned in Sec. 3.3.2, however, multiexponential

decay analysis is quite demanding in terms of SNR typically achieved in a clinical scan. Therefore, as a first step, experiments could be performed on bulk tissue *ex vivo* on a spectrometer where high SNR is available and a larger number of echoes (facilitating the analysis) can be acquired. Using this approach, some preliminary data has been acquired. Fig. 4.1 is a plot of the response of the T_2 spectrum of rabbit white matter to a refocussed $\tau=0.05$ s $\gamma B_1 \tau = \pi/2$ RF pulse. In response to

Figure 4.1: Response of T_2 spectrum of rabbit white matter to a refocussed $\tau=0.05$ s $\gamma B_1 \tau = \pi/2$ RF pulse. A spoiler gradient was used to get rid of any transverse magnetization remaining after the T_2 -selective pulse. The relative amplitude of the T_2 spectral components are plotted as a function of T_2 value. The SNR of each peak is the sum of the spectral amplitudes. The $T_2=0.01$ s peak is assumed to be associated with myelin water and the $T_2=0.1$ s peak with axonal water. The measured total SNR of each peak is listed together with the theoretically predicted value. The ratio of the SNR of the $T_2=0.1$ s to the $T_2=0.01$ s peak decreases in response to the RF pulse.

the RF pulse, the ratio of the total SNR of the $T_2=0.1$ s peak to the $T_2=0.01$ s peak decreases from 13 to 6. Thus, TELEX is effective in preferentially reducing the signal from the long- T_2 species. It should be noted, however, that the total SNR from both peaks is slightly greater than predicted by theory with the long- T_2 component deviating more significantly. Possible reasons for this may include B_1 and phase errors. Both of these error sources could increase the signal from the short- and long- T_2 components. Additionally, based on simulation, the underdamped long- T_2 component is expected to be more sensitive to the errors than the overdamped short- T_2 components.

Sec. 3.3.1 showed via simulation that, ignoring B_0 non-uniformities, unrefocussed TELEX was capable of almost completely suppressing the long $T_2=0.1$ s component while largely sparing the $T_2=0.01$ s component of white matter. Unfortunately, Sec. 3.2.1 showed that there is a significant contrast degradation in the presence of B_0 non-uniformities typically found *in vivo*. Refocussing can be used if one can achieve a clinically acceptable image in the presence of the contrast loss associated with steady state effects. Alternatively, if one restricts the field of view to smaller regions of relative B_0 uniformity, it may be possible to apply unrefocussed TELEX within those regions. In the most extreme case, TELEX could be performed on a single voxel as is done in MR spectroscopy. For larger regions, the performance of TELEX would depend on the size of the region over which the field is sufficiently uniform. As noted in Sec. 3.2.1, highlighting a $T_2=0.01$ s short- T_2 would require a linewidth on the order of a few Hz. By comparison, in MR spectroscopy, linewidths are typically shimmed to within a few Hz (at 1.5T) over a 1 cubic centimeter voxel [53].

4.1.2 Optimized TELEX

Contrast for Various $\gamma B_1 \tau$ Scalings

Up to this point, the assumption has been made that the RF pulse had $\gamma B_1 \tau$ fixed at $\pi/2$. More generally, scaling $\gamma B_1 \tau$ to other values will alter the TELEX signal curves. Fig. 4.2 is a plot of S_z for $\gamma B_1 \tau = n\pi$; $n=2,4,6,20$. In these cases, a “notch filter” contrast results (compare with the case where $\gamma B_1 \tau = \pi/2$ in Fig. 1.5). Thus, it can be seen that varying $\gamma B_1 \tau$ can alter the TELEX signal.

Fig. 4.2 also yields insight into the behaviour of magnetization in the different regimes. Magnetization in the underdamped regime behaves in a sinusoidal manner (Eq. 2.5). Consequently, underdamped magnetization is flipped by an angle equal to $\gamma B_1 \tau$ ($= n\pi$ in this case). In the critically damped regime, a region of saturation will grow outward from the critically damped point as $\gamma B_1 \tau$ is increased. In the $\gamma B_1 \tau = \pi/2$ case, $\gamma B_1 \tau$ was not yet large enough to saturate the critically damped magnetization. In the overdamped regime, magnetization will decay away slowly

Figure 4.2: S_z resulting from various $\gamma B_1 t$ values. Note the “notch filter” contrast resulting from $\gamma B_1 \tau = n\pi$. Also note the region of saturation that spreads outwards from the critically damped point as $\gamma B_1 \tau$ is increased.

along the z-axis in a manner similar to the $\gamma B_1 \tau = \pi/2$ case.

Contrast Optimization

Altering the $\gamma B_1 \tau$ value adds an extra parameter (in addition to pulse length) for contrast optimization. For example, in the case of white matter, Sec. 3.3.1 illustrated the contrast improvement in going from $\pi/2$ pulse to a $3\pi/2$ pulse. More generally, a more complex time varying pulse could be employed. In particular, the pulse could be broken up into a number of pieces and a numerical optimization performed to find the RF pulse which maximizes the contrast between a given set of T_2 species.

4.2 Conclusions

In this thesis, TELEX was characterized to within an average discrepancy of less than 2%. Based on this characterization, TELEX is capable of generating short- T_2 contrast. In the case of unrefocussed TELEX, B_0 sensitivity reduced the contrast performance of the technique. In particular, TELEX does not perform particularly well when applied to highlight longer short- T_2 species ($T_2 \geq 0.01$ s). With the use of the refocussing scheme, the B_0 sensitivity of TELEX is reduced. Refocussed TELEX is then able to highlight longer short- T_2 species. The cost of reduced B_0 sensitivity, however, is contrast loss due to steady state effects. The smaller T_1/T_2 , the more severe the contrast loss.

The results of this thesis have demonstrated the principles of short- T_2 contrast generation by TELEX over a broad range of T_2 values. The principles of TELEX were demonstrated on relatively homogeneous, isotropic MnCl_2 phantoms. *In vivo*, the actual utility of TELEX will depend on the specific clinical situation. In particular, the relative T_2 values, T_1/T_2 values, relative proton densities and B_0 non-uniformities of the tissues involved will significantly affect the contrast. In the case of white matter, simulation as well as preliminary data demonstrate that it is worthwhile pursuing the application of TELEX to the problem of the detection of the short- T_2 component of white matter.

Appendix A

RF Amplitude Calibration

A.1 Introduction

On the SMIS spectrometer, the transmitted RF signal can be adjusted by attenuating the RF output of the SMIS console. Unfortunately, the actual RF amplitude output does not scale linearly with this attenuation over the broad range of attenuations used in the experiments [54]. In this appendix, the method by which the RF amplitude was determined is outlined. The calibration was performed differently for long- T_2 and short- T_2 species. In this section, unlike the rest of the thesis, long- T_2 and short- T_2 will be understood to mean long and short in absolute terms.

A.2 Calibration of RF Amplitude on Long- T_2 Species

To calibrate the actual RF amplitude with the attenuation setting on the SMIS console for long- T_2 species, two assumptions were made:

1. The T_2 value of the sample on which the calibration is performed is long enough so that, for any calibrated RF amplitude, the sample magnetization always lies in the underdamped regime. In this case, the magnetization will behave according to Eq. 2.5.
2. The mapping function bandwidth of any calibrating RF pulse is broad enough so that the approximation of Eq. 1.19 can be used.

If these two assumptions are valid, then the signal following a constant amplitude RF pulse of duration τ will be given by:

$$S_{xy} \propto \sin(\gamma B_1 \tau) \quad (\text{A.1})$$

For a given RF attenuation setting, RF_i , the resulting RF amplitude output ($B_{1,i}$) was determined by finding the RF pulse length τ_i for which the signal is a minimum. At this minimum, Eq. A.1 implies that the flip angle will be equal to π . The RF amplitude was then simply calculated as:

$$RF_i \longrightarrow B_{1,i} = \pi / (\gamma \tau_i) \quad (\text{A.2})$$

In this manner, the RF amplitude was related to the attenuation settings on the SMIS console. The requirement of a broad bandwidth mapping function was not true for very weak RF amplitudes which required long RF pulses. However, by applying refocussing to the calibration pulses ($\tau_{180} \approx 7.5 \times 10^{-4}$ s), a broad bandwidth was maintained over all RF amplitudes. Thus, the broad bandwidth assumption was always valid.

A.3 Calibration on Short- T_2 Species

For the method above, the requirement that the magnetization lie in the underdamped regime was only valid (over the range of RF amplitudes used in the experiment: 5Hz-5kHz) when the calibration was performed on the $T_2=0.1$ s species. For the shorter $T_2=0.01$ and $T_2=0.001$ s species, the magnetization did *not* lie in the underdamped regime over the entire range of RF amplitudes. (In fact, measuring the non-underdamped regime behaviour is the *purpose* of the experiment in Secs. 2.3 and 2.6). Thus the RF calibration could not be performed directly on the short- T_2 species. Instead, it was assumed that the RF amplitude calibrated on the long- T_2 species could be used to determine the RF amplitude that will be played out on the short- T_2 species. This section gives a justification for this assumption.

A.3.1 Method

This section outlines the method used for calibrating the RF amplitude to the console attenuation settings for short- T_2 species. RF amplitudes were first calibrated to the console attenuations settings

on a long- T_2 (0.1 s) reference sample. The reference sample was then taken out and replaced with the short- T_2 sample. It was assumed that the RF calibration performed on the long- T_2 species can be used to calculate the RF calibration of the short- T_2 species that has replaced it. However, there are two major possible sources of error with this technique:

1. Random errors associated with sample replacement
2. Systemic errors due to differences in sample conductivity.

It is hypothesized that the systemic coil loading errors can be made small enough so as to lie within the random uncertainty due to repositioning error.

Random Error Due to Repositioning

When the long- T_2 species was replaced inside the coil with the short- T_2 species, one expects some random error associated with the process of taking out and repositioning the sample within the coil. To investigate the magnitude of these errors, the RF amplitude calibration was performed five times on the same long- T_2 sample. The mean and standard deviation of the calibrated RF amplitudes were then calculated to assess the magnitude of this error.

Systemic Error Due to Differences in Coil Loading

When the long- T_2 species was replaced inside the coil with the short- T_2 species, there is a possible additional source of error. Since the sample conductivity varies with the $MnCl_2$ concentration [55] (used to alter the T_2 value of the sample), systemic error may arise due to differences in coil loading of the two different samples [56, 57]. To reduce this systemic error, a correction factor, ϵ_{corr} was applied.

The calibration was performed as usual on the long- T_2 sample. The long- T_2 sample was then replaced with the sample of interest. As discussed in Sec. A.2, RF amplitudes *can* be calibrated if that particular amplitude is high enough to place the magnetization in the underdamped regime. Bearing this in mind, the RF attenuation was set to its minimum value (corresponding to $B_1 \sim 25kHz$) and that particular RF amplitude was calibrated for the sample. The RF amplitudes

corresponding to the other attenuation values are then calculated as:

$$B_{1_{sample}} = B_{1_{reference}} \times \epsilon_{corr} \quad (\text{A.3})$$

where

$$\epsilon_{corr} = (B_{1_{sample:25kHz}} / B_{1_{reference:25kHz}}) \quad (\text{A.4})$$

To investigate the effects of conductivity on RF amplitude, one would like to look at the RF amplitude played out on the various doped $MnCl_2$ samples. However, as noted above, the short T_2 value of the sample will prevent this. Instead, to look at the effects of conductivity alone, water was doped with various concentrations of NaCl. Changing the concentration of NaCl will change the conductivity but will leave T_2 largely unaltered. In this manner, the RF amplitude was calibrated on samples of various conductivities. A range of NaCl concentrations were used corresponding to the range of conductivities of the $MnCl_2$ samples.

A.3.2 Results

Repositioning Error

Fig. A.1 is a plot of the standard deviation (normalized to the mean of the calibrated RF amplitude) of the calibrated RF pulse amplitude for $T_2=0.1$ s $MnCl_2$ over five repeated measurements at various different RF attenuation settings. Over the range of RF attenuations used, the calibrated RF amplitude varies by as much as $\pm 4\%$. The error may possibly be due to temporal RF instabilities and/or B_1 -inhomogeneities inside the RF coil [58]. Thus, uncertainty in RF amplitude associated with sample repositioning introduces one source of random error into the experiment.

Calibrated RF Amplitudes of Repositioned Samples

The measured RF amplitudes of the NaCl samples (data not shown) did *not* lie within the uncertainty associated with sample repositioning. This implies that there is a systemic difference in RF amplitudes between samples of different conductivities. However, Fig. A.1 shows that, when divided by the correction factor, the NaCl RF amplitudes *do* fall within the limits of the repositioning error. This implies that, using the correction factor, the long- T_2 calibration accurately predicts the

Figure A.1: Plot of calibrated RF amplitude versus RF attenuation setting. Error bars are the standard deviation of the calibrated RF values on the long- T_2 reference sample over five repeat measurements. Symbols are measured NaCl RF amplitudes divided by ϵ_{corr} . All RF amplitudes are normalized by the mean of the long- T_2 calibrated RF amplitude. Note that the corrected RF amplitudes of the NaCl all fall within the random uncertainty associated with the long- T_2 calibration. This implies that the reference RF amplitudes *can* (with use of the correction factor) be used to accurately predict the RF amplitudes experienced by samples of different conductivities.

RF amplitude played out inside samples of different conductivities. In the case of TELEX, long- T_2 samples therefore *can* be used to calculate the RF amplitude experienced by the short- T_2 samples.

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