3D Fast Spin Echo $T_2$–weighted Contrast for Imaging the Female Cervix

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science

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Analysis of 3D Fast Spin Echo $T_2$ Contrast for Imaging the Female Cervix

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Master of Science  
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University of Toronto  
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Abstract

Magnetic Resonance Imaging (MRI) with $T_2$-weighted contrast is the preferred modality for treatment planning and monitoring of cervical cancer. Current clinical protocols image the volume of interest multiple times with two dimensional (2D) $T_2$-weighted MRI techniques. It is of interest to replace these multiple 2D acquisitions with a single three dimensional (3D) MRI acquisition to save time. However, at present the image contrast of standard 3D MRI does not distinguish cervical healthy tissue from cancerous tissue. The purpose of this thesis is to better understand the underlying factors that govern the contrast of 3D MRI and exploit this understanding via sequence modifications to improve the contrast. Numerical simulations are developed to predict observed contrast alterations and to propose an improvement. Improvements of image contrast are shown in simulation and with healthy volunteers. Reported results are only preliminary but a promising start to establish definitively 3D MRI for cervical cancer applications.
To my parents and sister with love
Acknowledgments

This thesis is the product of a supportive team; I was very fortunate to have been introduced to every one of you.

I owe special thanks to my co-supervisors. Dr. Philip Beatty, for challenging me to think critically about everything MRI and non-MRI related and Dr. Simon Graham for welcoming me to his lab and helping me navigate through the little hurdles of grad school. It has been a great learning experience to have you both as co-supervisors, thank you both for your patience, valuable guidance and mentorship.

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<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>EPG</td>
<td>Echo Phase Graph</td>
</tr>
<tr>
<td>ESP</td>
<td>Echo Spacing</td>
</tr>
<tr>
<td>ETL</td>
<td>Echo Train Length</td>
</tr>
<tr>
<td>FA</td>
<td>Flip Angle</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of View</td>
</tr>
<tr>
<td>FSE</td>
<td>Fast Spin Echo</td>
</tr>
<tr>
<td>Gd-DTPA</td>
<td>Gadolinium-diethylenetriaminepentaacetic Acid</td>
</tr>
<tr>
<td>HPV</td>
<td>Human Papilloma Virus</td>
</tr>
<tr>
<td>IR</td>
<td>Inversion Recovery</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic Resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NEX</td>
<td>Number of Excitations</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>PI</td>
<td>Parallel Imaging</td>
</tr>
<tr>
<td>PSD</td>
<td>Pulse Sequence Diagram</td>
</tr>
<tr>
<td>RF</td>
<td>Radio Frequency</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SAR</td>
<td>Specific Absorption Rates</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Spin Echo</td>
</tr>
<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
</tr>
<tr>
<td>SNR Eff</td>
<td>Signal-to-Noise Efficiency</td>
</tr>
<tr>
<td>$T_1$</td>
<td>Longitudinal Relaxation Time</td>
</tr>
<tr>
<td>$T_{1,\text{REP}}$</td>
<td>Representative Longitudinal Relaxation Time</td>
</tr>
<tr>
<td>$T_1W$</td>
<td>$T_1$-weighted</td>
</tr>
<tr>
<td>$T_2$</td>
<td>Transverse Relaxation Time</td>
</tr>
<tr>
<td>$T_{2,\text{REP}}$</td>
<td>Representative Transverse Relaxation Time</td>
</tr>
<tr>
<td>$T_2W$</td>
<td>$T_2$-weighted</td>
</tr>
<tr>
<td>TE</td>
<td>Echo Time</td>
</tr>
<tr>
<td>TE $\text{Eff}$</td>
<td>Effective Echo Time</td>
</tr>
<tr>
<td>TE $\text{Eqv}$</td>
<td>Equivalent Echo Time</td>
</tr>
<tr>
<td>TI</td>
<td>Inversion Time</td>
</tr>
<tr>
<td>TR</td>
<td>Repetition Time</td>
</tr>
<tr>
<td>VFA</td>
<td>Variable Flip Angle</td>
</tr>
<tr>
<td>xETL</td>
<td>Extended Echo Train Length</td>
</tr>
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</table>
1 Introduction

1.1 Clinical Motivation

1.1.1 Current Status of Cervical Cancer

Each year in Canada, approximately 1500 women will be diagnosed with cervical cancer and 380 women will die of the disease [1]. The most important risk factor for cervical cancer is exposure to the human papillomavirus (HPV) and co-factors include smoking, multiple births, sexual activity and oral contraceptives. Measures that can decrease the mortality rate of cervical cancer include vaccination against HPV and a healthy life style, which includes exercise, not smoking, a diet with fruits and vegetables and a healthy weight. However, regular screening tests are most important [2]. The mortality rates of cervical cancer have decreased by 55% since 1970 [3] due to the implementation of routine screening procedures such as the Pap test [4], which in Canada are performed every 1-3 years (depending on the province or territory) [2]. These screening tests detect abnormal changes to tissue at an early stage, and increase the chances of successful treatment. The most advanced stages of cancers have been found in women who do not participate in regular screening. [1]

Following diagnosis of cervical cancer, the process of tumour staging is used to determine the appropriate treatment plan, which could involve surgery, radiotherapy, chemotherapy or a combination of these options. Tumour staging assesses the depth of tumour infiltration, as well as the volume and compromise of adjacent organs/tissues, according to the system established by FIGO (the International Federation of Gynecology and Obstetrics). Imaging technologies including Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) play a major role in staging of cervical cancers, and also in treatment monitoring [1].
1.1.2 Cervical Cancer Imaging Techniques

Both CT and MRI have solidly established roles in the management of cervical cancer. The pelvic CT exam lasts 5-15 minutes although a waiting period of approximately 2 hours is required prior to the exam for the appropriate uptake of an iodinated contrast agent which improves lesion conspicuity and also can be used to exclude pulmonary metastases. Computed tomography is quite widely available in Canada but necessitates delivering a dose of ionizing radiation to the patient. In comparison, pelvic MRI exams require 30-45 minutes without the use of ionizing radiation, although the lengthier acquisition time requires administration of an agent to reduce motion of the bowel. MRI systems are also less widely available, but the ability to perform MRI in an oblique plane is an important advantage due to the variability of uterus position and flexions among patients. Furthermore, MRI has excellent soft-tissue contrast in comparison to CT and the capability to image in multiple different orientations enables the extent of lesions to be determined. Only axial imaging is possible with CT, which can result in degraded image quality after reformatting the viewing plane. [1] MRI is recognized as the first-line imaging modality for treatment planning of radiotherapy and chemotherapy. MRI also provides useful monitoring of treatment effects by distinguishing post-treatment scar tissue from recurrent malignant tissue after six months of treatment [5, 6].

1.1.3 MRI of Cervical Cancer

Due to the advantages summarized above, MRI is the preferred modality for assessing cervical cancer. Tumor size is best visualized at FIGO stage IB or greater, with a diameter of 1 - 2 cm or a volume of 2 - 4 cm³, with stacks of multi-slice images acquired in multiple orientations. The tumor staging protocol for MRI consists of image acquisitions referred to as multiple “$T_2$-weighted” sequences and a “$T_1$-weighted” sequence. Details of $T_1$-weighted and $T_2$-weighted sequences and their relevance to MRI signal contrast are discussed further below. Sequences
shown in Table 1.1 are standard at Sunnybrook Department of Medical Imaging. (The terms Fast Spin Echo, TE and TR are defined in Section 1.2.3.3). These sequences are similar to suggested sequences reported in literature [1]. These are the minimum number of recommended sequences, and additional orientations and resolutions are up to the discretion of the attending radiologist. Additional acquisitions may be necessary due to the variations of the positioning of the uterus across patients. Other options for other types of contrast are available that are beyond the scope of this thesis. [1]

Presently, $T_2$ contrast is the most useful contrast for distinguishing cervical cancer from cervical stroma. Cervical cancer appears as a region of higher signal against a region of low signal corresponding to cervical stroma, as shown in Figure 1.1 Multiple $T_2$-weighted images are suitable for determining the location of the tumor, the growth pattern including the depth of invasion in cervical stroma and the extension and invasion into adjacent organs (vagina, bladder, and rectum). [1]

![Sample $T_2$-weighted images of the female pelvis](image)

**Figure 1.1** Sample $T_2$-weighted images of the female pelvis in a) axial oblique and b) sagittal planes. The cervix, tumor (star) and areas of fat, muscle and bladder are shown.
On a $T_1$-weighted image, cervical cancer and stroma are indistinguishable, so it is common to perform contrast-enhanced imaging using rapid intravenous administration of a contrast agent (typically gadolinium chelated to a macromolecule). Enhanced contrast uptake within the tumour leads to increased signal relative to that of cervical stroma. Contrast-enhanced $T_1$-weighted images also help distinguish between tumor (bright signal) and edema (dark signal); and to distinguish tumor in regions of high fat content because tumors typically have lower signal intensity relative to fat [1]. Although useful, contrast enhancement does involve some risk to the patient, as well as adding time and cost to the examination [7]. The use of $T_1$-weighted MRI is not considered further in this thesis.

In addition, MRI distinguishes post-operative changes in tissue from recurrent tumour as early as six months after treatment. Fresh scars have high signal intensity on $T_2$-weighted images due to inflammation and neovascularization. After approximately six months, scars typically exhibit

Table 1.1: Suggested standard protocol for MRI of cervical cancer at 1.5 T.

<table>
<thead>
<tr>
<th>MRI Sequence</th>
<th>Orientation</th>
<th>TE (ms)</th>
<th>TR (ms)</th>
<th>Slice Thickness (mm)</th>
<th>Acquisition time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2-weighted Fast Spin Echo</td>
<td>Sagittal</td>
<td>95.4</td>
<td>4000</td>
<td>4.0</td>
<td>6 - 7</td>
</tr>
<tr>
<td>T2-weighted Fast Spin Echo</td>
<td>Axial</td>
<td>95.4</td>
<td>3000</td>
<td>4.0</td>
<td>6 - 7</td>
</tr>
<tr>
<td>T2-weighted Fast Spin Echo</td>
<td>Oblique</td>
<td>95.4</td>
<td>3000</td>
<td>3.0</td>
<td>6-7</td>
</tr>
<tr>
<td>T2-weighted Fast Spin Echo</td>
<td>Coronal</td>
<td>75.0</td>
<td>3000</td>
<td>8.0</td>
<td>6-7</td>
</tr>
<tr>
<td>T1-weighted Fast Spin Echo</td>
<td>Axial</td>
<td>10</td>
<td>500</td>
<td>6</td>
<td>6-7</td>
</tr>
</tbody>
</table>
lower signal intensity similar to that of muscle. Recurrent tumors typically show high signal intensity similar to the original tumors. [5, 6]

1.1.4 2D vs. 3D MRI: Simple Comparison

Although a common MRI approach is to image a volume of interest (VOI) using multi-slice “stacks” of two-dimensional (2D) images, each with a slice thickness of several millimeters, it is also common to acquire truly three-dimensional (3D) images (i.e. a single data matrix representing MRI signals from tissue anatomy in x, y, and z, dimensions). This thesis focuses on adapting and improving existing 3D MRI acquisitions to examine the female pelvis, toward the specific application of treatment monitoring and planning in the setting of cervical cancer. A simple comparison between 2D and 3D MRI is presented in the following two sections to motivate the 3D method from a clinical point of view.

1.1.4.1 Exam time and Image resolution

Two-dimensional (2D) MRI is the standard imaging sequence for multiple pelvic examinations, including cervical cancer. It is typified by high in-plane resolution of approximately 0.5 - 1 mm and lower through-plane resolution (slice thickness) of 3 - 5 mm. Thus, a reformatted view of the stack of images results in a loss of image quality, as shown in Figure 1.2.
Figure 1.2 a) Example axial oblique 2D $T_2$ weighted image of the female pelvis, taken from a 2D multi-slice dataset. b) Multi slice dataset reformatted to generate a sagittal image, showing degraded spatial resolution due to slice thickness effects in the $z$ direction. c) Zoomed-in image of data set reformatted to the sagittal plane.

Given imaging parameters for pelvic exams, a single 2D image stack is typically acquired in 4 - 6 minutes. Evaluation of anatomical features requires three different viewing plane orientations, (typically, axial sagittal and coronal or oblique) requiring approximately 12 - 18 minutes. In comparison, 3D MRI is typically conducted with voxel dimensions close to isotropic (0.5 - 1 mm) in the $x$, $y$ and $z$ directions. This allows the viewing plane to be reformatted without a major loss of quality, as shown in Figure 1.3.
Figure 1.3 **a)** Example axial image of the female pelvis taken from a 3D $T_2$-weighted dataset. **b)** Dataset reformatted to generate a sagittal image. Spatial resolution is maintained in the reformatted image due to 3D acquisition with isotropic voxels. The white lines indicate where the two images intersect.

A single 3D dataset is acquired in approximately 10 minutes, which is shorter than the time required to image stacks of 2D MRI data in three viewing planes. Higher resolutions and increased time efficiency motivate the use of 3D MRI over 2D MRI where possible. There is also an additional benefit to 3D MRI when considering the signal-to-noise (SNR) efficiency, as described below.

### 1.1.4.2 SNR and SNR Efficiency

A common measure to analyze image quality with respect to the pulse sequence is to compare the signal of interest relative to the noise of the image, namely the Signal-to-Noise ratio (SNR) [8]:

$$ SNR \triangleq \frac{signal}{Noise} \propto \delta_x \delta_y \delta_z \sqrt{t_{read}}, $$  \hspace{1cm} (Eq. 1.1)
where the noise is defined as the standard deviation of image noise, $\delta_x\delta_y\delta_z$ describe the spatial resolution of the image in each voxel dimension and $t_{\text{read}}$ is the cumulative time that signal is being ‘read’ to perform spatial encoding. It is common to describe SNR as the proportionality to voxel size and time of reading signal to compare the effects of changing acquisition parameters where the signal intensity of the samples of interest remains unchanged, for example to compare two 2D MRI acquisitions. In the subsequent comparisons of 2D MRI and 3D MRI that follow, it is assumed that the signal amplitudes of samples are equivalent.

It is also useful to compare 3D MRI and 2D MRI in terms of SNR Efficiency ($SNR_{\text{Efficiency}}$) which is defined as the square root of the ratio of time spent acquiring signal from a given slice, $t_{\text{read}}$, to that spent acquiring the entire stack of images, $t_{\text{total}}$ [9]:

$$SNR_{\text{Efficiency}} \triangleq \sqrt{\frac{\text{Time of Signal Aquisition per Voxel}}{\text{Total Acquisition Time}}} = \sqrt{\frac{t_{\text{read}}}{t_{\text{total}}}}.$$  (Eq.1.2)

Instead of summarizing the principles of MRI physics that lead to Eq 1.1 and Eq 1.2, at present it suffices to state that signals from a voxel within the volume of interest are acquired within successive time intervals of a duration parameterized by the Repetition Time (TR). During each TR, a fraction of time is spent ‘reading’ the signal. For purposes of illustration, consider a VOI of size $256 \text{ mm} \times 256 \text{ mm} \times 128 \text{ mm}$, imaged with both with 2D MRI and 3D MRI at a low voxel resolution and high through-plane voxel resolutions.

A low though-plane voxel resolution of $4 \text{ mm}$ and high in-plane resolution $1 \text{ mm} \times 1 \text{ mm}$, this results 32 slices ($N_{\text{slices}} = 32$), each with $256 \times 256$ voxels and a $TR = 3,000 \text{ ms}$ (this TR is assumed in sequence calculations). In 2D MRI, signal is acquired independently for each slice and in our example, it is reasonable to posit that each slice requires 16 TRs and $8\%$ of each TR is spent ‘reading’ the signal from the voxel, then $t_{\text{read}} = 3s \times 8\% \times 16 = 3.84 \text{ s}$. Slice
interleaving, where multiple slices are acquired simultaneously by interleaving the slice excitation and data acquisition with signal recovery can shorten the acquisition time and improve SNR efficiency for 2D stacks of slices, but there is a limit to the number of slices that can be packed into a TR. For the example given, it is estimated that a maximum of 9 slices could be interleaved and collected simultaneously. Thus to collect the full 32 slices, this process must be repeated four times (4 passes) in order to collect the entire number of slices for a total exam of \( t_{\text{total}} = 64 \, TRs = 192 \, s \). From Eq. 1.2, \( SNR_{\text{Efficiency}} \) is 16.3%.

In a 3D MRI acquisition signal, the ‘reading’ of signal comes from the entire volume, as opposed to only a slice in the 2D method. The analogous values are \( t_{\text{read}} = 18.43 \, s \), \( t_{\text{total}} = 64 \, TR = 192 \, s \), corresponding to an \( SNR_{\text{Efficiency}} \) of 30%, these are shown in Table 1.2 for comparison. At this resolution, the scanning time is equivalent, however is it possible in 3D MRI to read signal from the slices for a longer time, increasing the SNR efficiency (Section 1.2.7 describes the pulse sequence requirements that achieve this).

Now consider imaging the same volume of interest with isotropic resolution of \( 1 \, mm \times 1 \, mm \times 1 \, mm \) (ie. \( N_{\text{slices}} = 128 \)). In this case, with the 2D MRI acquisition the total exam increases because of the increased number of slices demanding more passes (15 passes). As a result, the \( t_{\text{total}} \) is 720s while each slice is still imaged with equivalent \( t_{\text{read}} \) of 3.84 s, yielding \( SNR_{\text{Efficiency}} \) = 7%. Compared to the low resolution voxel prescription discussed above, this 2D MRI implementation decreases the \( SNR_{\text{Efficiency}} \).

Using a 3D MRI acquisition for these high-resolution voxels, \( t_{\text{total}} \) increases to 768 s and \( t_{\text{read}} \) increases to 73.7 s, yielding \( SNR_{\text{Efficiency}} \) of 30%. Thus, in the present context, the efficiency
of 3D MRI is independent of voxel size. The values discussed immediately above are shown for comparison in Table 1.2.

**Table 1.2** SNR and $SNR_{Efficiency}$ of 2D and 3D MRI at low and high through-plane resolution

<table>
<thead>
<tr>
<th></th>
<th>2D</th>
<th>3D</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Through-plane</td>
<td>4</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Resolution (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$t_{read}$ (s)</td>
<td>3.64</td>
<td>18.4</td>
<td>3.84</td>
<td>73.7</td>
</tr>
<tr>
<td>$t_{total}$ (s)</td>
<td>192</td>
<td>192</td>
<td>720</td>
<td>768</td>
</tr>
<tr>
<td>$SNR_{Efficiency}$</td>
<td>14.1</td>
<td>30</td>
<td>7</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 1.2 shows one of the limitations of 2D MRI acquisitions, even though the low-resolution 2D MRI takes the shorter scanning time as the target isotropic voxel resolution is approached the relative SNR of both 2D MRI acquisition decreases, the efficiency is decreased because the time of reading signal from a given slice is the same. This example also assumes that the achieved SNR is appropriate for clinical imaging, but it is common to repeat this acquisition to reach the SNR resulting in a longer scan time.

Comparing the 2D MRI and 3D MRI at low resolution, the 3D MRI has higher $SNR_{Efficiency}$ and SNR (ignoring differences in signal intensities in 2D MRI and 3D MRI). In this case, multiple acquisitions are still required and the precision of placing the volumes of interest properly is subjective to the expertise of the MRI technician. A single stack acquisition (high resolution 3D MRI) that can be retrospectively reformatting improves the imaging workflow and overall removes the need for patients to have to return for additional orientations that may have not been properly previously.

Although 3D MRI is advantageous to 2D MRI in terms of spatial resolution as well as time and $SNR_{Efficiency}$, 3D MRI has an important limitation. In clinical applications involving the
female pelvis, the efficiency of 3D MRI is confounded by difficulties in achieving the desired signal contrast.

1.1.5 Image Contrast in Cervical Cancer

Image contrast is described by the relative signal intensities between tissues of interest. In applications where there are multiple tissues of interest, as in cervical cancer monitoring, contrast is characterized as the ratio of the signal intensity of the tissue of interest to the signal intensity of a reference tissue,

\[
Contrast \ Ratio = \frac{Signal_{Tissue}}{Signal_{Reference}}. 
\]  
(Eq.1.3)

In this case, the tissues of interest are tumour/recurrence, cervical stroma, muscle and radiation fibrosis, each with associated \(T_1\) and \(T_2\) values, the parameters primarily responsible for determining MRI signal contrast. It is standard to set muscle as the reference tissue, a previous study showed that for \(T_2\)-weighted imaging of a group of patients, radiation fibrosis exhibited low signal similar to muscle, with a mean ratio of 0.9 +/- 0.33, whereas recurrent or untreated tumors appeared brighter relative to muscle with a mean ratio of 3.78 +/- 1.26. These values are used later in the analysis of 2D and 3D MRI contrast in Chapter 2 [5].

1.1.6 Contrast Alterations in 3D MRI

As mentioned in Section 1.1.5 2D \(T_2\)-weighted MRI is the preferred imaging method to distinguish between normal tissue, recurrent cervical cancer and scar tissue (fibrosis) arising from surgery or radiotherapy. This is because muscle and fibrosis have similar \(T_2\)-weighted signal intensities, whereas recurrence has a higher signal intensity. However, 3D \(T_2\)-weighted MRI alters the signal intensities of muscle and fibrosis, such that they appear brighter whereas tumour and recurrence remain relatively unaltered, as shown in Figure 1.4. Consequently, a misdiagnosis of
tumor recurrence becomes more likely because important tissues cannot be distinguished [10]. This effect has been a major factor blocking 3D MRI from gaining acceptance among clinicians for applications in cervical cancer. The main objective of this thesis, therefore, is to identify underlying physical mechanisms that affect the $T_2$-weighted image contrast of 3D MRI of the female pelvis. To provide background for the proposed research, the next section describes basic physics of MRI methods leading to the technical details of contrast alterations and current correction methods.

![Figure 1.4 Schematic representation of contrast alterations among tissues of interest in cervical cancer for a) 2D T2-weighted MRI, and b) 3D T2-weighted MRI. “Stroma” refers to the normal appearance of the cervix on MRI.](image)

### 1.2 Physics of MRI

Magnetic Resonance Imaging (MRI) is a powerful non-invasive imaging modality based on the Nuclear Magnetic Resonance (NMR) effect. This effect refers to the ability of certain nuclei to absorb and emit electromagnetic energy when they are subjected to specific radiofrequency (RF) irradiation in the presence of an external static magnetic field. The NMR effect is exhibited by
the protons in water molecules. Due to the abundance of water in the human body, and its favorable NMR properties, protons in water are the species of preference for MRI [11]. A variety of imaging measurements can be made of the tissue microenvironment, by studying the NMR properties of the associated water molecules. Examples include quantifying the proton density (the number of protons per unit volume of tissue), water dynamics by measuring “relaxation parameters” or diffusion, as well as measuring local magnetic properties [12].

1.2.1 Magnetization, Larmor Frequency and Bloch Equation

For simplicity the proton can be thought of as a positively charged particle spinning around an axis. The spinning charge generates a magnetic field, much like a very small bar magnet, which is represented mathematically by the magnetic moment vector $\mu$. Figure 1.5 shows a simplified version of the configuration of magnetic moment vectors in the absence and presence of an external magnetic field ($B_o$).

\[ \mu \]

\[ B_o \]

\[ M_O \]

**Figure 1.5** a) In tissue, magnetic moments $\mu$ of protons in water are randomly oriented in the absence of an external static magnetic field. b) In the presence of a static magnetic field ($B_o$) pointing in the z direction, the orientations of the moments in the transverse (x-y) plane are random, and the magnetic moments experience a torque that causes precession about the $B_o$ direction, as indicated by the grey curved arrow. In addition, the magnetic moments $\mu$ are quantized into two energy states aligning in the direction parallel and antiparallel with the static
magnetic field. c) Slightly more magnetic moments align parallel to $\mathbf{B}_o$ than antiparallel, creating the bulk magnetization $\mathbf{M}_o$.

In the absence of a magnetic field, the spin axes of all the protons are oriented randomly. In the presence of an external static magnetic field, $\mathbf{B}_o$, conventionally set to point along the $z$-axis, a magnetic torque is applied to each proton. The external field has two consequences on the magnetic moments. First, the magnetic moments precess clockwise about the axis of the external magnetic field, similar to the wobble of a spinning top under the influence of gravity. The precession frequency, $f_o$, is known as the Larmor frequency and has a magnitude given by

$$f_o = \frac{\gamma}{2\pi} B_o,$$  

(Eq. 1.4)

where $\gamma$ is the gyromagnetic ratio, a nuclear constant. For protons, $\frac{\gamma}{2\pi} = 42.58 \frac{MHz}{T}$. Therefore, $f_o = 63.87 MHz$ at $B_o = 1.5 T$ [12], the most common magnetic field strength for clinical MRI. Second, the magnetic field orients magnetic moments to occupy one of two possible energy states. These are “spin-up” or “spin-down” states, involving two possible projections onto the $z$-axis ($\pm \mu_z$) while the projections onto the transverse plane ($\mu_{xy}$) remain random. The net macroscopic effect in this case, namely that the magnetization, $\mathbf{M}_o$ is described by the sum of vector magnetic moments

$$\mathbf{M}_o = \sum_{i}^{N_{TOTAL}} \mathbf{\mu}_i,$$  

(Eq.1.5)

where $N_{TOTAL}$ is the overall number of protons and $i$ is an incremental variable. Figure 1.5 c) shows the magnetization with a zero transverse component, due to the random orientation of the magnetic moments, and a non-zero magnetization pointing in the direction of the external field,
known as the equilibrium magnetization, $\mathbf{M}_o$. The equilibrium magnetization occurs because the spin-up state is very slightly more populated than the spin-down state [12]. Very large static magnetic fields are used in MRI to create more of an imbalance in populating these energy states, increasing the strength of the very small MRI signals as much as possible.

1.2.2 Radiofrequency Pulses, Excitation and Signal Detection

Once $\mathbf{M}_o$ has been created, it can be manipulated with the use of radiofrequency (RF) pulses to generate an MRI signal [8, 12, 13]. In the macroscopic picture, magnetization is described by the Bloch equation [14]:

$$\frac{d\mathbf{M}}{dt} = \gamma \mathbf{M} \times \mathbf{B} - \frac{(M_x \hat{x} + M_y \hat{y})}{T_2} - \frac{(M_z - M^o) \hat{z}}{T_1},$$

(Eq. 1.6)

where $\mathbf{M}$ is the time-dependent magnetization vector, $t$ is the time, $\mathbf{B}$ is the magnetic field, $T_1$ and $T_2$ represent characteristic relaxation time constants of decay in the longitudinal and transverse plane, $M_x$, $M_y$ and $M_z$ are the components of the magnetization in the x, y and z directions, and $\hat{x}$, $\hat{y}$ and $\hat{z}$ are the respective unit vectors. The physical processes that underlie the relaxation time values are described in Section 1.2.3.

The RF pulses are represented in the $\mathbf{B}$ term of Eq. 1.6 and are typically represented as a time-varying oscillating magnetic fields $\mathbf{B}_1(t)$ of duration $\tau_{\text{pulse}}$. To simplify subsequent discussions and calculations, it is common to describe the effect of RF pulses on the magnetization in a reference frame that is rotating at the Larmor frequency, with axes $x'$,$y'$ and $z'$ (rather than the fixed “laboratory” frame with axes x,y, and z). In this frame, the net effect of resonant excitation by an RF pulse (ie. the RF pulse oscillates at the Larmor frequency) is that the equilibrium magnetization ($\mathbf{M}_o$) is rotated about the $x'$ (or $y'$) axis by a “flip angle” $\alpha$ from the direction of the main static field, as shown in Figure 1.6. An RF pulse that tips magnetization completely into
the transverse plane \((x', y')\) is said to have a flip angle of 90° pulse. The amplitude of the flip angle from the \(z\)-axis is defined by the shape and duration of pulse, according to

\[
\alpha = \gamma \int_0^{\tau_{\text{pulse}}} B_1(t') dt'.
\]  

(Eq. 1.7)

Throughout the thesis and according to convention, the flip angle of the RF pulse is also referred to as “FA”.

**Figure 1.6** In the rotating frame, an RF pulse applied on resonance tips the bulk magnetization by a flip angle \(\alpha\).

In the context of this thesis, RF pulses have two purposes: excitation and refocusing. Excitation pulses are used to flip longitudinal \((z)\) magnetization into the transverse plane, where the magnetization can be recorded. A 90° pulse maximizes the transverse magnetization, and this flip angle will be assumed throughout unless specifically indicated. Refocusing RF pulses are applied after an excitation pulse to manipulate magnetization that has already been placed in the transverse plane. The ideal \(\alpha\) value for a refocusing pulse is 180°, which moves a magnetization vector oriented at an arbitrary phase in the transverse plane into its complex
conjugate position. As explained below, refocusing pulses are essential for measuring MRI signals with \( T_2 \)-weighted contrast.

1.2.3 Relaxation Processes

As discussed in the previous section, signal detection is possible when magnetization is excited into the transverse plane. However, once magnetization is excited it will “relax” over time back to the equilibrium state. Relaxation processes are tissue-dependent, and also dependent on specific details of the MRI experiment (e.g. the \( B_0 \) value). Relaxation processes are grouped into two broad categories known as longitudinal relaxation and transverse relaxation described by the characteristic times \( T_1 \) and \( T_2 \). It is primarily the differences in \( T_1 \) and \( T_2 \) properties of biological tissues that are responsible for the image contrast available in MRI.

1.2.3.1 Longitudinal Relaxation

After an RF pulse excites protons by tipping magnetization away from its equilibrium state into the transverse plane, absorbed energy must be released as equilibrium magnetization is restored. This process is called longitudinal relaxation, which involves the “recovery” of magnetization in the z-direction, \( M_z \), according to the following component of the Bloch equation:

\[
\frac{dM_z}{dt} = - \frac{(M_z - M_o)\hat{z}}{T_1}.
\]  
(Eq. 1.8)

The solution to this equation is

\[
M_z(t) = M_o \left( 1 - e^{-t/T_1} \right) + M_z(0),
\]  
(Eq. 1.9)

Where \( M_z(0) \) describes the value of the longitudinal magnetization at time \( t = 0 \), immediately after RF excitation. Thus, for a 90° RF excitation pulse, \( M_z(0) = 0 \) and \( M_z(t) \) follows an exponential recovery to the \( M_o \) value. The time constant \( T_1 \) describes the time at which 63% of
the longitudinal magnetization is recovered. Figure 1.7 shows the longitudinal recovery of two tissues with typical $T_1$ values of 800 ms and 1200 ms, respectively. Typically, MR images that are generated to sample a specific time point on such $T_1$-recovery curves are described as “$T_1$-weighted”. In a $T_1$-weighted image, tissues with lower $T_1$ values appear brighter (recover faster and have larger MRI signals) relative to tissues with higher $T_1$ values.

![Figure 1.7](image)

**Figure 1.7** Normalized $T_1$-recovery curves for tissues with $T_1$ values of 1200 ms (solid line) and 800 ms (dashed line), respectively.

1.2.3.2 Transverse Relaxation

The largest achievable MRI signal occurs immediately after the application of an RF excitation pulse because the precessing magnetic moments of protons are “coherent” and point in the same direction in the transverse plane at this time. This coherence does not persist, however, and the transverse magnetization signal immediately begins to decay in the transverse plane due to “de-
phasing”. This effect can be thought of as the magnetization from sub-groups of “similar” protons fanning outwards in the transverse plane, in the rotating frame. As dephasing becomes more pronounced, the net magnetization in the transverse plane has a vector sum that becomes smaller, and eventually the transverse magnetization relaxes to zero.

Multiple processes influence the time required for magnetization to decay in the transverse plane. For example, individual protons experience a local magnetic field that may vary slightly from the average $B_o$ value. This can arise because of experimental difficulties in making the external magnetic field perfectly uniform in space, and because the magnetic susceptibility (a property describing how magnetic fields are supported within a material) varies on a microscopic scale in tissues. Irrespective of the source, $B_o$ inhomogeneity causes protons to exhibit a distribution of Larmor frequencies with some either precessing at a higher or lower frequency relative to the bulk Larmor frequency value. Typically, the effect of these inhomogeneities is approximated as a rapid, mono-exponential decay of transverse magnetization as characterized by the time constant $T_2^*$. Fortunately, this type of de-phasing is reversed by the “spin echo” method described below.

1.2.3.3 The Spin Echo

The Spin Echo, first observed by Hahn in 1950 [15], provides a very useful method to suppress the dephasing effects from $B_o$ inhomogeneity. A sequence of two RF pulses, consisting of a 90° excitation pulse followed by a 180° refocusing pulse, affects the magnetization as shown in Figure 1.8. First, the excitation pulse tips the longitudinal magnetization into the transverse plane. Due to $B_o$ inhomogeneity, de-phasing occurs and some components of the magnetization precess faster (components #1, 2 and 3) and some precess slower (components #4, 5 and 6) relative the average Larmor frequency. After a time $TE/2$, the refocusing RF pulse flips all transverse components to the
respective conjugate positions, after which each component continues to precess with the original rate and direction. The refocusing pulse affects the components such that a coherence is created at a the “spin echo” time $TE$.

![Diagram of spin echo formation](image)

**Figure 1.8** Spin echo formation. a) At time zero, magnetization at equilibrium is excited by a 90° RF pulse into the transverse plane b). c) Dephasing of magnetization components (thin black arrows) occurs due to static magnetic field inhomogeneity. d) A 180° refocusing RF pulse is applied at time $t = \frac{TE}{2}$ to flip spins to their conjugate phase position in the transverse plane. e) Magnetization components refocus, creating a spin echo at time $t = TE$.

The spin echo method does not suppress all dephasing processes in the transverse plane, however. Phase coherence is also lost as the protons interact magnetically during the motion of water molecules in tissue. The loss of phase coherence characterized by the parameter $T_2$. As might be
expected, $T_2$ is larger than $T_2^*$. In the case of the spin echo sequence, the transverse magnetization is described by the following component of the Bloch equation:

$$\frac{dM_{xy}}{dt} = - \frac{M_{xy}}{T_2},$$

(Eq. 1.10)

where $M_{xy}$ is the amplitude of the net magnetization in the transverse plane. The solution to this equation is

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

(Eq. 1.11)

where the exponential time constant $T_2$ describes the time at which the initial transverse magnetization, $M_{xy}(0)$, decays to 37% of its initial value.

Thus, the amplitude of a spin echo is given by

$$M_{xy}(TE) = M_{xy}(0) e^{-\frac{TE}{T_2}},$$

(Eq. 1.12)

providing the simplest method of obtaining a $T_2-$weighted MRI signal. Figure 1.9 shows the $T_2-$decay curve for tissues with $T_2$ values of 60 ms and 120 ms, respectively. Thus, a $T_2-$weighted image acquired at a particular $TE$ value will depict tissues with higher $T_2$ values as brighter (i.e. with larger MR signals) than those with low $T_2$ values.
Figure 1.9 Normalized T2-decay curve for tissues with T2 relaxation times of 60 ms (solid line) and 100 ms (dashed line), respectively.

1.2.4 Spatial Encoding

According to (Eq. 1.4), protons precess at the Larmor frequency according to a linear relationship involving the static magnetic field, $B_o$. However, to generate an image it is necessary to spatially encode MR signals from protons. This is achieved by varying the longitudinal magnetic field strength linearly in space using gradients. Spatial encoding gradients can be applied along any physical direction [13]. The two axes are usually labelled as: 1) the “phase encoding” direction (y-axis); and 2) the “frequency encoding” direction (x-axis) to describe the encoding along these orthogonal directions. Thus, the distribution of precession frequencies over space is the following:

$$f(x, y) = \frac{Y}{2\pi} \left( B_o + G_x(t)x + G_y(t)y \right),$$

(Eq.1.13)
where the gradients $G_x$ and $G_y$ are represented as a function of time. Let $M(x, y)$ be the distribution of magnetization in space. Then the acquired signal, $S(t)$ is represented by the volume integral, as well as the time integral that accounts for the phase of all magnetization components in space as they evolve:

$$S(t) = \int\int_{x,y} M(x, y)e^{-iy\int_0^t (B_0 + G_x(t')x + G_y(t')y)dt'}
\ dx
dy$$  \hspace{1cm} (Eq. 1.14)

Defining two new variables,

$$k_x(t) = \frac{\gamma}{2\pi} \int_0^t G_x(t')dt',
\ \ \ \ \ \ \ \ \ \ \ (Eq. 1.15)
$$

$$k_y(t) = \frac{\gamma}{2\pi} \int_0^t G_y(t')dt'.$$

then (Eq.1.14) simplifies to [8]

$$S(t) = e^{-i\omega_0 t}
\int\int_{x,y} M(x, y)e^{-i2\pi(k(t)_x x + k(t)_y y)}
\ dx
dy.$$  \hspace{1cm} (Eq.1.16)

Demodulation techniques allow for the term $e^{-i\omega_0 t}$ to be ignored. By inspection, the right hand side of the (Eq.1.16) then becomes to the Fourier Transform of the magnetization in space. Thus, the challenge involves measuring signals $S(t)$ to sample Fourier space sufficiently that inverse Fourier transformation will reconstruct the data into an image of the object. Typically, multiple acquisitions of $S(t)$ are performed, each sampling a particular trajectory in Fourier space. For obvious reasons, relating to (Eq.1.16), the Fourier space is commonly referred to as “k-space” where the spatial- frequencies $k_{(x,y)}$ are in units of cycles per unit length. Notable, the information corresponding to the image contrast resides near the center of k-space ($k_x = k_y = 0$), whereas the edge detail is located at higher k-space values in all dimensions.
(Eq.1.16) describes the spatial encoding process in a manner where the imaging gradients are considered in a common framework, in this example two encoding gradients describe a 2D acquisition sequence, a 3D acquisition sequence would include a second phase-encoding gradient ($G_x(t)$), in an orthogonal direction to the other two. In reality, however, there are slight distinctions with the spatial encoding process involving each gradient axis. The fundamental 2D spin echo sequence is shown in Figure 1.10 to frame the discussion. First, the slice selection gradient is applied perpendicular to the imaging plane, during the application of a “slice-selective” RF pulse. Such RF pulses cause resonant excitation of magnetization only in the narrow band of Larmor frequencies corresponding to the slice of interest. This procedure simplifies (Eq.1.16) such that k-space encoding is only necessary in the plane of the slice, involving the $G_x$ and $G_y$ gradients. For historical reasons, the $G_x$ gradient is also referred to as the “frequency-encoding
gradient” or the “readout gradient”, whereas the $G_y$ gradient is referred to as the “phase-encoding gradient”.

**Figure 1.10** Pulse Sequence Diagram (PSD) of a Spin Echo MRI sequence. See text for details.
Figure 1.11 The k-space trajectory associated with the spin echo pulse sequence of Figure 1.10. The labels A, B, C and D correspond to specific time points in the pulse sequence. See text for details.

From (Eq.1.15), the traversal through k-space is dictated by the time integral under one or more gradient waveforms. In addition, it is also necessary to recall that the effect of a refocusing pulse is to flip magnetization to its conjugate location (phase) in the transverse plane. With this information, it is possible to determine the k-space trajectory for the pulse sequence of Figure 1.10, which is shown in Figure 1.11 with maximum extents of $k_{x\,\text{max}}$ and $k_{y\,\text{max}}$ in the $k_x$ and $k_y$ directions, respectively. Key points in time are labelled consistently with the same letters in
both Figures. In this specific example, k-space is travelled in a Cartesian trajectory, but other trajectories are possible including spirals, and radial spokes, depending on the temporal characteristics of the gradient waveforms that are applied.

After the 90° excitation pulse (time point A) magnetization is coherent within the transverse plane at the center of k-space (0,0). Both $G_x$ and $G_y$ are then turned on, causing the magnetization to traverse diagonally across k-space down to time point B, located at $(k_{x\text{ max}}, -k_{y\text{ max}})$. The 180° refocusing pulse is subsequently applied at time $\frac{TE}{2}$ (time point C), locating the magnetization at the complex conjugate location $(-k_{x\text{ max}}, k_{y\text{ max}})$. The readout gradient is then applied for the final horizontal traversal of k-space, reaching $(k_{x\text{ max}}, k_{y\text{ max}})$ once more at time point D. Note that data acquisition occurs during application of the readout gradient, and halfway through the readout a spin echo is created at time $TE$. Figure 1.11 shows acquisition of the MRI signal for the k-space line with the largest phase encoding value, $k_{y\text{ max}}$. The pulse sequence is then repeated after a repetition time, TR, for $N_y$ different incremental amplitudes of the phase encoding gradient and all other pulse sequence parameters held constant. In this manner, successive lines with different $k_y$ values are acquired and the complete k-space matrix is filled, so that an image with the appropriate spatial resolution and field of view is generated after the inverse Fourier transformation.

For 3D MRI sequences, k-space is three-dimensional with two phase encoding directions ($k_y$ and $k_z$) and one frequency encode direction $k_x$. There are $N_y$ phase encoding steps required of the $G_y$ gradient for each of the $N_z$ steps required of the $G_z$ gradient, or $N_y \cdot N_z$ phase encoding steps in total. The 2D FSE example in Section 1.1.4.2, required 8192 phase encodes (32 slices × 256 phase encodes per slice), increasing the slice resolution from 4 mm to 1 mm effectively increases the
number of slices and the total number of phase encodes by a factor of 4, which in turn increases the scanning time, acceleration techniques are then needed to bring 3D FSE scanning time to an acceptable time and are discussed later in Section 1.2.7.2.

1.2.5 The Fast Spin Echo Sequence

The length of the conventional Spin Echo scan to achieve $T_2$-weighted images (approximately 25 minutes and derived below) is problematic for several reasons. Patients are required to remain still during the entire data acquisition period to maintain spatial resolution and image quality. However, patients become increasingly uncomfortable while attempting to remain still as scan times lengthen. Spatial encoding errors are thus introduced in the form of motion artifacts. Some of these artifacts are also introduced by involuntary motion. Thus, there is a strong motivation to reduce scan time to maintain patient comfort and reduce motion artifacts. In addition, reducing scan times increases patient throughput on clinical MRI systems for improved healthcare delivery.

Assuming a volume of interest of $256 \text{ mm} \times 256 \text{ mm} \times 128 \text{ mm}$, for a 2D Spin Echo acquisition 256 TRs are required to achieve a voxel resolution of $1 \text{ mm} \times 1 \text{ mm} \times 4 \text{ mm}$ in a single slice, incorporating the multi-slice acquisition results in 2 passes for the 32 slices and a $t_{total}$ of 25.6 minutes for the acquisition of a single orientation. A breakthrough introduced by J. Hennig [16] considerably reduces the long scan time for spin echo-like $T_2$-weighted MRI. This method is commonly referred to by several different acronyms and in this thesis, “Fast Spin Echo (FSE)” will be adopted. Prior to the development of FSE, it was recognized that several images with different $T_2$-weighted characteristics could be generated in the same 2D MRI scan by following the initial RF excitation pulse with a “train” of refocusing pulses that created multiple spin echoes to sample the $T_2$-decay curve. By this approach, one to four different $T_2$-weighted images could be generated in one scan. The key insight of the FSE method was the recognition
that each of these echoes could be assigned a different phase encoding step, thus accelerating the number of horizontal lines that could be filled in k-space from one RF excitation. More specifically, the scan time reduction factor for 2D FSE MRI compared to 2D SE MRI is primarily influenced by a quantity known as the echo train length (ETL), equal to the number of refocusing pulses after each RF excitation; the refocusing pulses are applied at time intervals called ‘echo spacing’ (ESP). Typical ETL values range from 11-32. In the Spin Echo example (Section 1.2.3.3), 256 TRs were required to fill the k-space of one image. Increasing the ETL to 16, for example, decreased the number of TR intervals required to fill this 2D k-space matrix by a factor of 16, (reducing the number of TRs by a factor of 16). An important consequence of the FSE method is that data (echoes) acquired at different phase encoding positions in k-space have different $T_2$-weightings, as shown in Figure 1.12. Consequently, the phase encodes must be ordered strategically such that the echo with the weight corresponding to the desired $T_2$-weighting image contrast is placed at the center of k-space. The time at which this echo is collected is known as the Effective Echo Time ($T_{E_{eff}}$).
1.2.6 Image Contrast and View-Ordering in Spin Echo Sequences

In FSE MRI, k-space must be filled in a manner such that the $T_2$-weighted effect does not introduce discontinuities in the $k_y$ direction or alter MR signals to the point that k-space signals are lost. The latter effect places a practical limit on the ETL value and also how far apart the refocusing pulses are separated in time, as parametrized by the ESP value. Furthermore, the “view-order” of phase encoding steps must be optimized. As shown in the k-space trajectory diagram Figure 1.13 for the 2D FSE sequence shown in Figure 1.12, for example the early echoes in the train are placed in the higher frequencies of k-space, and the third echo is placed at the center of k-space to correspond with the desired image contrast ($T_{E_{eff}}$). For each successive TR interval, the phase encoding gradient is adjusted such that all echoes in the train traverse...
horizontal lines in k-space that are shifted incrementally by one phase encoding increment. Early in the development of FSE, detailed comparison studies were undertaken to establish that the image contrast obtained with FSE with optimized view-ordering is equivalent to the contrast obtained with standard SE sequences [17].

**Figure 1.13** Placement of echoes in a 2D k-space matrix from a 2D FSE sequence

1.2.7 2D to 3D FSE MRI: Pulse Sequence Considerations

At the beginning of the introduction, several benefits were mentioned concerning use of 3D MRI versus 2D MRI. Technical developments have been pursued in recent years so that 3D FSE can be undertaken to realize these benefits. The present section briefly reviews such work, leading to the objectives of the thesis.
The fundamental difference between multi-slice 2D FSE and 3D FSE MRI relates to how the datasets are organized in k-space. In the former case, k-space is filled with phase encoding in one dimension ($k_y$) for each separate slice. In the latter case, two dimensions of phase encoding ($k_y$ and $k_z$) are used as part of storing all data within a single 3D k-space matrix. Thus, if the ETL and TE parameter ranges are equivalent to those used in 2D FSE MRI, the total imaging time for 3D FSE becomes unacceptable for clinical applications. In Section 1.1.4.2, the ETL for 2D was assumed to be 16, if the ETL for 3D FSE is maintained at 16, then exam time increases to 51 minutes from 12.8 minutes.

1.2.7.1 Extended Echo Trains with Variable Flip Angles

The additional phase-encoding time required for 3D FSE MRI makes it essential to increase the number of refocusing pulses and echoes per TR interval. This requires both an extended echo train length (xETL) and a reduced ESP value because $T_2$ decay occurs over a fixed time duration, beyond which the MR signal becomes too attenuated for effective k-space sampling. Typical values of the xETL and ESP for 3D FSE MRI are 60-120 and 5 ms, respectively. In particular, the ESP value is achieved by the use of shorter duration rectangular RF pulses rather than the typical smoother pulse waveforms of extended duration. However, the substantially increased number of refocusing pulses (with increased amplitude to achieve the same level of refocusing with shorter pulse duration) creates a potential safety issue. Power may be deposited by such RF pulse trains at levels which may surpass the permissible Specific Absorption Rate (SAR) in patients, especially in higher field magnets, causing heating of tissues [18, 19].

To increase echo sampling during $T_2$ decay at acceptable levels of RF power deposition, an xETL strategy was introduced that involves refocusing pulses with variable flip angles (VFA). The amplitude of each RF pulse in the VFA refocusing train is adjusted to a specific FA value $< 180^\circ$. 
The FA reductions limit power deposition and also flip magnetization to a state with a component along the longitudinal plane and the transverse plane. This means that the recorded MRI signals will exhibit a combination of $T_1$ recovery and $T_2$ decay. Because typically $T_1 \gg T_2$ in tissues, a refocusing pulse that flips magnetization components into the longitudinal direction will cause the components to be “stored” over time. The stored components are subsequently recalled to the transverse plane by later RF pulses in the train. The xETL and VFA strategy suppresses the signal decay over the echo train, therefore, and prolongs the time duration over which k-space data can be acquired for 3D FSE MRI.

There have been several extensive investigations of how to best implement xETL with VFA to minimize image blurring, maintain acceptable imaging time, and optimize signal contrast for brain tissues [17]. The general shape of the resultant VFA schedule for any ETL and ESP (FA for each successive refocusing pulse) is shown in Figure 1.14. The schedule has four FA “control points” $(a_{\text{initial}}, a_{\text{min}}, a_{\text{center}}, a_{\text{max}})$ with $a_{\text{initial}}$ set at $120^\circ$. The initial accelerated ramp-down (from $a_{\text{initial}}$ to $a_{\text{min}}$) establishes a static “pseudo-steady state” magnetization. [20-22]. The small incremental step between each flip angle after $a_{\text{min}}$ is reached ($|a_i - a_{i-1}| < 2^\circ$) prevents oscillations in the subsequent evolution of the signal at each echo [23]. The progression to the second control point ($a_{\text{min}}$) slows the effect of $T_2$ decay, storing magnetization in the longitudinal direction as mentioned above. As flip angles gradually increase from ($a_{\text{min}}$) to ($a_{\text{center}}$) and ($a_{\text{max}}$), stored magnetization is recalled and the signal can be acquired for longer times compared to a conventional train of refocusing pulses with a constant FA of $180^\circ$. 
As will be outlined in more detail below, this thesis involves extending the technique of xETL and VFA for applications involving 3D FSE MRI of the female pelvis. In practice, scanning times of 3D FSE MRI are further reduced by parallel imaging (PI), partial k-space and corner cutting, these techniques reduce the number of phase encoding required for image reconstruction. Parallel imaging uses coil sensitivities to reduce the number of phase encoding by skipping phase encodes along any axis, which results in the omission of every other point in that axis. Skipping every other phase encode is referred to as decreasing the sampling density. A detailed explanation of PI is beyond the scope of this thesis, but it suffices to say that it can reduce the phase encoding by a factor of 2-4 [24]. Together with partial k-space and corner cutting techniques, the phase encodes can often be reduced by a factor close to 10.
1.2.7.2 Flexible View-Ordering

The xETL and VFA method provides flexibility to sample more k-space per TR interval as required for 3D FSE MRI. In addition, the view ordering requires further consideration because it is important to decrease the number of phase encoding steps as much as possible. Figure 1.15 shows the preferred k-space sampling pattern of current 3D FSE MRI as described by Busse et al. [25].

![Diagram of k-space sampling pattern](image)

**Figure 1.15** Sampling pattern of a cross section of the 3D k-space matrix of a 3D FSE MRI sequence.

In the example shown, in a fully sampled 3D k-space matrix there are 32 phase-encodes in the $k_z$ direction and 256 in the $k_y$ direction requiring 8192 phase-encoding steps. For $ETL = 64$, 128 echo trains are required to fill the 3D matrix. It is possible to reduce this number through ‘corner-cutting’ and a reduced sampling density in k-space. Corner-cutting samples an elliptical-shaped
pattern in $k_y$ and $k_z$, recognizing that the portions of k-space left unfilled in the corners contain with high spatial frequency makes little difference in the point spread function of the image. As mentioned in Section 1.2.7.2, the view-ordering scheme also requires that the $T_2$-weighted signal of each individual phase-encoded echo is considered to minimize image reconstruction artifacts and to obtain the desired image contrast.

The importance of both xETL and reduction of phase-encodes can be illustrated by revisiting the example from Section 1.1.4.2, a volume of interest with resolutions of $1 \text{ mm} \times 1 \text{ mm} \times 4 \text{ mm}$ is imaged in 3.2 minutes with a 2D FSE sequence (ETL = 16, $N_{\text{slices}}$ = 32, TR =3000 ms, Number of phase encodes per slice 256). It is common to use a NEX of 2 in clinical imaging which doubles the scanning time to 6.4 minutes. Increasing the resolutions to $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$, increasing the $N_{\text{slices}}$ to 128 and maintaining the same ETL and TR (ETL = 16, TR =3000 ms), would increase the acquisition time to 12 minutes (24 minutes if the NEX is 2), this is still too long for clinical scans. Acquiring the same volume at high resolutions with a 3D FSE would require 2048 TRs (for 32,768 total phase encodes) and would take 102 minutes with the same ETL = 16 and TR= 3000ms. Extending the ETL to 64 and using VFA reduces the number of TRs to 512 with a scanning time of 25.6 minutes, adding phase-encode reduction techniques (reduce the number of phase encodes by 50% to 16,384) further reduces scanning time to 12.8 minutes, this time is now comparable to the acquisition time of a clinical 2D MRI sequence with the advantage of higher resolutions. Because of the VFA method used in 3D FSE MRI, the altered signal decay of the echo train requires additional consideration to meet the image contrast requirement. This is discussed in the following section.
1.2.8 Contrast Correction in 3D FSE MRI

Figure 1.16 shows the signal evolution of two tissues with a common $T_1$ value of 1000 ms and $T_2 = 40 \text{ ms}$ and $T_2 = 100 \text{ ms}$, respectively, for two different VFA schedules: 2D FSE MRI (ETL = 15, ESP = 17 ms) and 3D FSE MRI (ETL = 120, ESP = 5 ms). At a time approximately $TE_{eff} = 100 \text{ ms}$, the tissue with $T_2 = 40 \text{ ms}$ has the lower signal intensity of the two tissues. It is observed that the relative signal intensity (tissue contrast between the two tissues) at $TE_{eff} = 100 \text{ ms}$ is different between both VFA schedules. This raises the important question of which echo should be placed at the center of k-space such that 3D FSE MRI achieves the equivalent T2-weighted signal as achieved with 2D FSE MRI.

![Figure 1.16](image)

**Figure 1.16** Signal evolution of two tissues with the same $T_1$ value of 1000 ms and with $T_2 = 100 \text{ ms}$ and $40 \text{ ms}$, respectively, for a) 2D FSE MRI and b) 3D FSE MRI with xETL and VFA. The relative signal intensity (contrast) between the two tissues is different for 2D FSE MRI and 3D FSE MRI at the chosen $TE_{eff}$ of 100 ms (black arrows).

This question was initially addressed by J. Hennig [16] as shown in Figure 1.17, by selecting an echo at a later time, $TE_{equ}$, that provides the desired signal contrast.
The $T_{E_{Eqv}}$ value is derived by comparing the MR signal evolution of tissues subject to constant 180° refocusing pulses producing a train of “pure” spin echoes and to a VFA train. In the latter case, there is no analytic solution for the signal evolution. However, the resulting signal from VFA can be numerically simulated using the Echo-Phase-Graph (EPG) formalism, which provides an efficient way of describing the magnetization as a configuration of states in the Fourier domain [26, 27]. The procedure for determining $T_{E_{Eqv}}$ [17, 23, 28] is summarized by the relationship:

$$T_{E_{Eqv}}(T_{E_{Eff}}) = -T_{2REP} \ln \left\{ \frac{f_{EPG}[VFA(T_{E_{Eff}}, T_{1REP}, T_{2REP}, ESP)]}{f_{EPG}[VFA(T_{E_{Eff}}, T_{1REP}=\infty, T_{2REP}=\infty, ESP)]} \right\}, \quad (\text{Eq.} \, 1.17)$$

where $f_{EPG}[VFA(T_{E_{Eff}}, T_{1REP}, T_{2REP}, ESP)]$ represents the signal generated at $T_{E_{Eff}}$ by the EPG algorithm for a tissue with “representative” relaxation parameters $T_{1REP}$ and $T_{2REP}$; $f_{EPG}[VFA(T_{E_{Eff}}, T_{1REP}=\infty, T_{2REP}=\infty, ESP)]$ represents the signal generated at $T_{E_{Eff}}$ by the EPG algorithm by ignoring transverse and longitudinal relaxation effects (setting $T_{1REP} = \infty$ and $T_{2REP} = \infty$). The argument in the logarithmic function is a scaled function of the 3D MRI signal evolution for tissue with $T_{1REP}$ and $T_{2REP}$ and it is called the ‘relaxation’ function ($f_{Rel}$) in literature [23, 28].
Choosing specific $T_{1\text{REP}}$ and $T_{2\text{REP}}$ values is equivalent to optimizing the VFA sequence to approximate $T_2$ decay appropriately for a specific representative tissue. This method works well for tissues with $T_1$ and $T_2$ values similar to $(T_{1\text{REP}}, T_{2\text{REP}})$. However, tissues that have $T_1$ and $T_2$ values very different from $T_{1\text{REP}}$ and $T_{2\text{REP}}$ may exhibit incorrect contrast. This is of direct relevance to 3D FSE MRI applied to the female pelvis because a) current clinical implementations of 3D FSE MRI are provided with a fixed choice of $T_{1\text{REP}}$ and $T_{2\text{REP}}$ appropriate for imaging the brain; and b) these fixed $T_{1\text{REP}}$ and $T_{2\text{REP}}$ values are substantially different from the relaxation characteristics of the tissues of interest.
1.2.9 Summary

Magnetic Resonance Imaging plays an essential role in the treatment planning and monitoring of cervical cancer. In particular, $T_2$-weighted MRI is of primary interest for its ability to provide signal contrast to distinguish tumor/recurrence from stroma and fibrosis/muscle. To improve image quality and throughput, the use of 3D FSE MRI is desirable for this application. However, 3D FSE MRI methods have not achieved acceptance among radiologists because the resulting image contrast is presently unsatisfactory. Current clinical implementations of 3D FSE MRI are optimized for the brain but not the female pelvis. It is hypothesized, therefore, that improved $T_2$-weighted contrast can be obtained by adjusting current clinical implementations of 3D FSE MRI by adjusting $TE_{Eqv}$ based on the selection of appropriate $T_1\text{REP}$ and $T_2\text{REP}$ relaxation parameters for pelvic imaging.

Research to test this hypothesis is subsequently described in Chapter 2. The effects of VFA are first investigated by developing a numerical simulation framework. The simulation framework is validated to ensure that its predictions are representative of the data observed in imaging experiments. Contrast alterations are quantified to demonstrate the limitations of standard 3D FSE MRI protocols applied to the female pelvis. Furthermore, improved contrast by appropriate $TE_{Eqv}$ adjustment is described and demonstrated in-vivo in healthy volunteers.

Chapter 3 discusses the conclusions that can be drawn from this research and investigates potential directions for future work to continue developing 3D FSE MRI, for applications involving cervical cancer.
2 Improved T2-weighted Signal Contrast for 3D Fast Spin Echo MRI of the Female Pelvis with Application to Cervical Cancer

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Specific contributions to Chapter 2 include: 1) study design by Andrea Vargas, Dr. Philip Beatty, Dr. Simon Graham and Dr. Laurent Milot; 2) computer simulation and experimental work by Andrea Vargas and Dr. Philip Beatty; 3) imaging of female volunteers by Andrea Vargas and Dr. Laurent Milot; 4) thorough revision of the manuscript by Dr. Philip Beatty and Dr. Simon Graham; and 5) minor manuscript revisions by all authors.

2.1 Introduction

Magnetic Resonance Imaging (MRI) is the first line modality for treatment planning and monitoring of cancers in the female pelvis. In addition to providing the flexibility to image along any anatomical plane with high spatial resolution, MRI depicts the various tissues of interest with excellent tissue contrast. The use of T2-weighted image contrast is particularly important in assessing cancer of the cervix to help determine treatment options, and to discriminate treatment-induced changes (such as radiation fibrosis) from recurrent tumors. On T2-weighted MRI, radiation fibrosis has similar signal to that of muscle, whereas tumors of the cervix have elevated signal and thus appear brighter.

Current clinical protocols for MRI of the female pelvis define the tumor extent accurately using two-dimensional (2D) multi-slice T2-weighted acquisitions in multiple orientations. These 2D
acquisitions are typically characterized by high in-plane resolution (0.5 - 1 mm) with reduced through-plane resolution (3 - 4 mm). Such highly anisotropic voxels make it impractical to reformat a given multi-slice dataset to inspect a different viewing plane, as the resulting reformatted images have poor in-plane resolution. Alternatively, three-dimensional (3D) MRI acquisitions are characterized by high spatial resolution (0.7 - 1 mm) along all voxel dimensions, making voxels nearly isotropic and improving imaging methods by allowing retrospective reformatting. This motivates work toward replacing multiple 2D MRI acquisitions with a single 3D MRI acquisition. Whereas 2D pelvic MRI requires approximately 5 - 7 minutes per orientation (i.e. 15 - 21 minutes for multiple orientations), a single 3D MRI takes approximately 10 minutes, reducing imaging time and increasing signal-to-noise ratio (SNR) efficiency.

Development of an appropriate 3D $T_2$-weighted MRI protocol requires careful pulse sequence modifications from the standard 2D approach of Fast Spin Echo (FSE) MRI. The 2D MRI approach uses trains of refocusing pulses with echo train lengths (ETL) per repetition time (TR) interval, and lengthy TR intervals to enable slice interleaving. The 3D FSE MRI acquisition requires phase encoding in an additional dimension of k-space, however. This drastically increases the number of phase encoding steps that are required and ensures that if the RF pulse trains of standard 2D MRI are maintained, then the imaging time becomes unacceptably long. To address this problem, clinical protocols of 3D FSE now include use of specialized RF pulses with extended echo train length (xETL) and variable flip angles (VFAs), enabling approximately 60 - 140 different phase encoded readouts from a single RF excitation, below safety limits for RF power deposition. Together with parallel imaging reconstruction and k-space corner-cutting, it is now possible to perform 3D FSE acquisitions with sufficient k-space sampling and minimal reconstruction artifacts in reasonable scan times [25].
The utility of 3D FSE MRI to provide multiple reformatted viewing planes from the same data set has been demonstrated for brain applications, as a promising alternative to acquiring multi-slice 2D FSE images in multiple independent orientations. In particular, the 3D FSE image contrast of brain tissues has been shown to agree well with 2D FSE results, although an additional manipulation of the 3D FSE acquisition parameters is required [17].

The use of a VFA schedule ensures that a component of magnetization is stored in the longitudinal direction at each refocusing interval. This magnetization is subject to $T_1$ recovery until subsequent refocusing pulses restore a component of the magnetization to the transverse plane. Thus, the overall effect of VFAs is to reduce the rate of signal decay during the echo train with a departure from true $T_2$-weighting. Using the echo phase graph (EPG) formalism [27], a procedure has been developed to characterize the modified signal decay in 3D FSE introduced by specific xETL, VFA schedules and echo spacing (ESP), yielding a prescription for the echo time $T_{Equiv}$ that achieves $T_2$-weighted signal contrast equivalent to that generated by a standard 2D FSE sequence for a given effective echo time, $T_{Eff}$. This procedure depends on knowledge of the $T_1$ and $T_2$ properties of a chosen representative tissue, $T_{1REP}$ and $T_{2REP}$, with values set at $T_{1REP} = 1000$ ms and $T_{2REP} = 100$ ms for brain [25, 26].

However, attempts to expand use of 3D FSE beyond brain applications have been of limited success. For example, 3D FSE MRI has not been adopted for cervical cancer exams. One of the main reasons for this exclusion has been the observation that 3D FSE MRI can alter image contrast in ways that are not clinically acceptable. In routine 2D FSE, cancerous tissues appear bright relative to the normal cervical stroma, whereas signals from fibrosis and muscle are very similar and have a dark appearance. In current 3D FSE implementations, the signal contrast
between cancerous and healthy cervical tissues, and between recurrence and fibrosis is much more difficult to observe.

The present work tests two hypotheses in an attempt to address this specific problem. First, it remains unclear at present how the contrast differences observed between 2D and 3D FSE MRI are generated by the two pulse sequences. Parsimoniously, it is hypothesized that the image contrast observed in 2D and signal intensity resulting from 3D FSE MRI can be replicated by applying the Bloch equations with pertinent tissues of interest represented solely by their $T_1$ and $T_2$ values. If this is proven, then the corollary statement must also hold that other tissue MR parameters and physical factors such as magnetization transfer, diffusion and perfusion do not have a strong influence on the observed contrast differences. To test hypothesis one, a simulation framework based on the EPG formalism is developed to predict 3D FSE MRI signal intensities of any tissue with $T_1$ and $T_2$ and any VFA and pulse train timing schedule. The simulation framework is validated by comparison to experimental results obtained by 3D FSE MRI at 1.5 T of phantoms with known relaxation properties.

As current 3D FSE implementations have been deployed with fixed $T_{1\text{REP}}$ and $T_{2\text{REP}}$ values for brain, it is a logical starting point to consider whether acceptable 3D FSE contrast is achievable by selecting $T_{1\text{REP}}$ and $T_{2\text{REP}}$ values that are more representative of tissues in the female pelvis. In particular, muscle and fibrosis are used as reference tissues in the assessment of recurrent cervical cancer, and exhibit $T_2$ values that are considerably less than those of brain tissues. Thus, the present work also tests the second hypothesis that signal contrast observed in 3D FSE MRI of the female pelvis can be substantially improved over the current “default” protocol, and made to approximate closely that of 2D FSE MRI by modifying the default values of $T_{1\text{REP}} = 1000$ ms and $T_{2\text{REP}} = 100$ ms to those representative of muscle and fibrosis, i.e. $T_{1\text{REP}} = 1000$ ms and
\( T_{2\text{REP}} = 40 \text{ ms} \). On successfully verifying hypothesis one, hypothesis two is tested at 1.5 T through a series of EPG simulations and initial 2D and 3D FSE MRI of healthy female volunteers.

2.2 Methods

2.2.1 Phantom Experiments: Evaluation of EPG Framework

First, a simulation framework based on the EPG formalism was developed in Python (www.python.org) and Matlab (Mathworks, Natick, MA) to predict the signal intensity of any tissue, using inputs of the tissue \( T_1 \) and \( T_2 \) values, as well as the VFA schedule and timing parameters of the desired pulse sequence. Python was used to generate the EPG simulations and Matlab was used for image analysis of in-vivo experiments, analysis of contrast ratios, and to generate plots.

In support of hypothesis 1, aqueous mixtures of agar gel and gadolinium diethylenetriaminepentacetate (Gd-DTPA) were formed at specific concentrations to yield relaxation values over a range of interest with \( T_1 \approx 1,000 \text{ ms} \) and \( T_2 \approx 40 – 120 \text{ ms} \). A complete description of the construction of the phantoms is found in Appendix A.

The phantoms were subsequently imaged using a 1.5T MRI system (MR450W, GE Healthcare, Waukesha, WI) with a 32-channel body phased array receiver coil. Data were collected with three pulse sequences: 2D SE MRI (six images acquired with \( TE = 20,40, 60, 120,150,200 \text{ ms} \), \( TR = 3000 \text{ ms} \), \( NEX = 2 \), \( FOV = 28 \text{ cm} \), through-plane resolution = 2 mm, \( 256 \times 128 \) acquisition matrix, 244 Hz/pixel readout bandwidth); 2D inversion recovery (IR) MRI (five images acquired with inversion time \( T1 = 100, 500, 800, 1600, 2600 \text{ ms} \), \( TR = 7000 \text{ ms} \), \( NEX = 2 \), \( FOV = 28 \text{ cm} \), through-plane resolution = 2 mm, \( 256 \times 128 \) acquisition matrix, 244 Hz/pixel readout bandwidth); and 3D FSE MRI with various \( TE_{eqv}, TE_{eff}, T_{2\text{REP}} \) and ETL parameters as listed Table 2.1 and Table 2.2. Control point parameters are identical to those defined in Section 1.2.7.1
and, the ESP was kept constant in simulations and experiments at $ESP = 4.8 \text{ ms}$. Other parameters were kept constant during 3D FSE MRI such as $T_{1\text{REP}} = 1000 \text{ ms}$, $TR = 3000 \text{ ms}$, $NEX = 1$, $FOV = 28 \text{ cm}$, and Through-plane Resolution $= 2 \text{ mm}$, Acquisition Matrix size $256$ by $256$ and Pixel Bandwidth $= 244 \text{ Hz}$. The SE and IR data were used to estimate the $T_2$ and $T_1$ values for each phantom. These values were then input to the EPG framework to simulate the signal intensities of each phantom for the 3D FSE MRI sequence parameters listed above, enabling comparison with the associated experimental results.

**Table 2.1** Select pulse sequence parameters for 3D FSE MRI of phantoms

<table>
<thead>
<tr>
<th>Image #</th>
<th>$TE_{\text{Eqv}}$ (ms)</th>
<th>$TE_{\text{Eff}}$ (ms)</th>
<th>$T_{2\text{REP}}$ (ms)</th>
<th>ETL</th>
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Table 2.2 VFA control point values used for each ETL value in 3D FSE MRI of phantoms. Control point parameters are identical to those defined in Section 1.2.7.1.

<table>
<thead>
<tr>
<th>ETL</th>
<th>$\alpha_{\text{initial}}$</th>
<th>$\alpha_{\text{min}}$</th>
<th>$i\text{-min}$</th>
<th>$\alpha_{\text{center}}$</th>
<th>$i\text{-center}$</th>
<th>$\alpha_{\text{max}}$</th>
<th>$i\text{-max}$</th>
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</table>

Figure 2.1 Representative axial 2D SE image of phantoms ($TE = 95\ ms$).

Figure 2.1 shows the cross section of each phantom on a representative axial SE image. Substantial shading is evident across each phantom due to the non-uniform spatial sensitivity of the phased-array receiver coil. To quantify the relaxation properties of each phantom while avoiding biased results from coil shading, first the signal intensity at each voxel, denoted by the subscript $p$, in the SE image, $SE_p(TE)$, was modelled as
\[ SE_p(TE) = a_p e^{-\frac{TE}{T_{2,p}}} \]  
(Eq. 2.1)

where the coefficient \( a_p \) corresponded to the coil shading coefficient and \( T_{2,p} \) the transverse relaxation time at voxel location \( p \). Least-squares fitting was performed with Matlab to estimate \( a_p \) and \( T_{2,p} \) values for each phantom using the SE images over the range of TE values investigated. The \( T_2 \) value of each phantom was subsequently taken as the average of the \( T_{2,p} \) estimates from a square region of interest (ROI) located at the centre of each phantom (21.8 by 21.8 mm). The \( T_1 \) value of each phantom was obtained using the analogous procedure involving the IR signal equation

\[ IR_p(TR) = a_p \left( 1 - 2e^{-\frac{-TR}{T_1_p}} + e^{-\frac{T_2}{T_1_p}} \right), \]  
(Eq. 2.2)

Once the relaxation parameters for each phantom were estimated, the estimates were input into the EPG simulations to investigate the agreement between predictions and experimental results. The signal produced in each phantom by 3D FSE MRI at a given \( TE \) value, \( 3DFSE(TE_{eff}) \), was predicted as

\[ 3DFSE = f_{EPG}(TE_{eff}, T_1, T_2, VFA, ESP ) . \]  
(Eq. 2.3)

Where \( T_1 \) and \( T_2 \) correspond to the measured relaxation values of phantoms, \( VFA \) is the schedule of refocusing angles, \( ESP \) is the echo spacing and \( TE_{eff} \) is the determined effective echo time as it is dictated by Eq. 1.17. For comparison, the experimental results for SE and 3DFSE at each \( TE_{eff} \) value were normalized voxel by voxel to suppress coil shading effects according to the \( a_p \) values estimated as described above, followed by averaging over the same ROIs that were used to estimate relaxation times. The predicted and experimental signals were then compared for 3D FSE MRI using a Bland-Altman plot (which compares the similarity of two signals by
representing the difference between the two signals as a function of the average of the two signals).

2.2.2 Evaluation of Cervical Cancer Contrast

The existing $T_2$-weighted signal contrast data reported for patients with cervical cancer was compared with signal contrast predicted by the EPG framework for 2D FSE. EPG simulations were then used to establish hypotheses two.

Previous observations of 22 cervical cancer patients, undertaken with muscle as the reference tissue, reported $T_2$-weighted contrast with $TE = 70$ or $80$ ms (group mean $\pm$ standard deviation [lower range, upper range]) as $3.78 \pm 1.26$ [2, 10] for recurrent or untreated cancer, and $0.99 \pm 0.33$ [0.3, 1.2] for fibrosis, respectively [5]. Considering appropriate relaxation parameters to input to EPG simulations, a previous study of nine patients [29] reported $T_2$ values at 1.5 T for cervical tumor ranging from 64-97 ms with a group mean and standard deviation of $79 \pm 5$ ms, and analogous values for cervical stroma of 30-59 ms and $49 \pm 4$ ms, respectively. These values agree well with other studies which reported only the group mean and standard deviations of $T_2$ values [30]. Thus, EPG simulations were run using the relaxation estimates for each patient as reported in [29]. For each patient, the $T_1$ value of cervical stroma was estimated as 1135 ms [30]. As the $T_1$ value of cervical tumours has not been reported previously, an approximate value of 1000 ms was used. This assumption follows from the similar appearance in signal intensity of tumors and healthy tissues in $T_1$W images and thus these tissues have similar values of $T_1$ [5]. Lastly, the $T_2$ value for muscle was assumed to lie within the lower and upper bounds [31] of 35 and 45 ms, respectively, accounting for biological variability, with a constant $T_1$ value of 1008 ms.
Signal contrast was quantified as the MRI signal for the tissue of interest divided by the signal for a reference tissue (Eq. 1.3); where muscle is set as the reference tissue. The EPG simulations were subsequently conducted to predict the signal contrast for four different MRI sequences: a) 2D FSE MRI with $T_{E_{eff}} = 75$ ms (the median value of the TE used in [5]) b) 2D FSE with $T_{E_{eff}} = 95$ ms (the standard TE value used in clinical protocols); c) default 3D FSE MRI with matched $T_{E_{Eqv}} = 95$ ms using $T_{1REP} = 1000$ ms and $T_{2REP} = 100$ ms; and c) modified 3D FSE MRI with matched $T_{E_{Eqv}} = 95$ ms using $T_{1REP} = 1000$ ms and $T_{2REP} = 40$ ms. For each MRI sequence, EPG simulations were run to generate the signal intensity for the cervical stroma and tumor of the nine patients and the upper and lower bound of muscle. The distributions of ratios were plotted separately for the lower bound and upper bound of muscle using box and whisker plots. First 2D FSE sequence ratios were then compared to the mean, minimum and maximum bounds reported in [5] in support of hypothesis 1. Then the three remaining sequences were compared to one another to support hypothesis 2 and show improvements of contrast as a result of adjusting the $T_{2REP}$ parameter.

### 2.2.3 MRI of Healthy Volunteers

To confirm and extend the simulation results while testing the hypotheses further, 2D FSE and 3D FSE MRI were performed involving four healthy female volunteers ranging from 25 to 34 years old. All human imaging was performed using the same MRI system as described above with free and informed consent of the volunteers, and with approval of the Research Ethics Board at Sunnybrook Health Sciences Centre. Although cervical cancer patients are normally administered an antispasmodic (Buscopan) intravenously as part of the MRI exam at this institution, this was not undertaken in the healthy volunteers. Instead, volunteers were instructed not to consume solids for 6 hours prior to imaging to mitigate motion artifacts. Exams consisted of 2D FSE MRI
with $TE_{Eff}$ providing close to optimal $T_2$-weighted contrast; default 3D FSE MRI with matched $TE_{Eqv}$ using $T_{1Rep} = 1000$ ms and $T_{2Rep} = 100$ ms, NEX = 1; and modified 3D FSE MRI with matched $TE_{Eqv}$ using $T_{1Rep} = 1000$ ms and $T_{2Rep} = 40$ ms. Other imaging parameters that were kept constant included $TR = 3000$ ms, $FOV = 22$ cm, $320 \times 224$ acquisition matrix, and a readout pixel bandwidth of 61.05 Hz. The VFA control point parameter values used with each specific ETL value are listed in Table 2.4, these specific controls point are those automatically generated by the pulse sequence algorithm as the ETL is chosen. The images were subsequently evaluated qualitatively to assess contrast characteristics of pelvic tissues.

Table 2.3 VFA control point parameter values for each ETL value used in 3D FSE MRI of healthy female volunteers

<table>
<thead>
<tr>
<th>Volunteer #</th>
<th>Type</th>
<th>$TE_{Eqv}$ (ms)</th>
<th>$TE_{Eff}$ (ms)</th>
<th>$T_{2Rep}$ (ms)</th>
<th>ETL</th>
<th>Slice Thickness (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2D FSE</td>
<td>91</td>
<td>91</td>
<td>--</td>
<td>11</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>101</td>
<td>206</td>
<td>100</td>
<td>120</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>100</td>
<td>267</td>
<td>40</td>
<td>120</td>
<td>1.6</td>
</tr>
<tr>
<td>2</td>
<td>2D FSE</td>
<td>93</td>
<td>93</td>
<td>--</td>
<td>11</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>95</td>
<td>181</td>
<td>100</td>
<td>60</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>97</td>
<td>238</td>
<td>40</td>
<td>60</td>
<td>3.0</td>
</tr>
<tr>
<td>3</td>
<td>2D FSE</td>
<td>93</td>
<td>93</td>
<td>--</td>
<td>11</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>95</td>
<td>181</td>
<td>100</td>
<td>60</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>92</td>
<td>230</td>
<td>40</td>
<td>60</td>
<td>1.6</td>
</tr>
<tr>
<td>4</td>
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<td>94</td>
<td>--</td>
<td>11</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>98</td>
<td>194</td>
<td>100</td>
<td>65</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>3D FSE</td>
<td>95</td>
<td>243</td>
<td>40</td>
<td>65</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Table 2.4 Control points of VFA used in imaging of healthy female volunteers

<table>
<thead>
<tr>
<th>ETL</th>
<th>$\alpha_{\text{initial}}$</th>
<th>$\alpha_{\text{min}}$</th>
<th>$i$-min</th>
<th>$\alpha_{\text{center}}$</th>
<th>$i$-center</th>
<th>$\alpha_{\text{max}}$</th>
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<td>45</td>
<td>8</td>
<td>70</td>
<td>31</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>65</td>
<td>120</td>
<td>45</td>
<td>8</td>
<td>70</td>
<td>38</td>
<td>120</td>
<td>65</td>
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<td>120</td>
<td>120</td>
<td>45</td>
<td>8</td>
<td>70</td>
<td>53</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

2.3 Results

2.3.1 Phantom Experiments: Evaluation of EPG Framework

Table 2.5 lists the mean and standard deviation (SD) of the $T_2$ and $T_1$ values estimated from ROIs in each phantom. Overall, the $T_2$ values span the intended range with $T_1$ values maintained approximately constant at the intended value of 1000 ms. The $T_2$ values were intended to increase incrementally with increasing phantom number, however phantom #2 resulted in a $T_2$ value of 80 ms, higher than the intended value of approximately 50 ms. This result likely occurred from an error in preparing the correct concentration of agar. This phantom nevertheless showed relaxation time values within the intended target range and was still included in the imaging experiments.
Table 2.5 Estimated mean $T_1$ and $T_2$ values of phantoms with different aqueous concentrations of agar and GD-DTPA ($SD = \text{standard deviation}$).

<table>
<thead>
<tr>
<th>Phantom #</th>
<th>$T_2$ (ms)</th>
<th>$SD(T_2)$ (ms)</th>
<th>$T_1$ (ms)</th>
<th>$SD(T_1)$ (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38</td>
<td>0.9</td>
<td>1082</td>
<td>31</td>
</tr>
<tr>
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<td>1.4</td>
<td>1051</td>
<td>17</td>
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<tr>
<td>3</td>
<td>63</td>
<td>1.0</td>
<td>1062</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>1.0</td>
<td>1092</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>85</td>
<td>0.8</td>
<td>1014</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>97</td>
<td>0.8</td>
<td>1084</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>112</td>
<td>1.0</td>
<td>1012</td>
<td>17</td>
</tr>
</tbody>
</table>

Figure 2.2 shows the Bland-Altman plot comparing the agreement between predicted 3D FSE MRI signals using the values from Table 2.2 as inputs to the EPG simulations, and analogous signals observed experimentally in the phantoms. The agreement is excellent overall, with a very slight positive bias in the difference signal (experimental minus predicted) indicating under-prediction by the EPG simulations. This bias is approximately constant over the range of signals investigated, with a noise envelope that slightly overlaps the zero difference signal. Although the bias is statistically significant (Student’s t-test, $p < 0.05$), the bias is only 2 % of the maximum signal and the noise envelope is approximately 1 % of the maximum signal. These very slight discrepancies are much smaller than the biological variability associated with MRI signals in tissue, supporting the first hypothesis and allowing the use of EPG simulation framework to evaluate the changes of signal intensity of tissue in 3D MRI and formulate the second hypothesis.
Figure 2.2 Bland-Altman plot comparing signals measured experimentally and predicted by EPG simulations for 3D FSE MRI of phantoms with known $T_2$ and $T_1$ relaxation values at 1.5 T. The signal difference (Measured minus Predicted) is plotted as a function of the average of the two signals. The dashed line represents the mean signal difference over the range of signal values (a.u. = arbitrary units).

2.3.2 Evaluation of Cervical Cancer Contrast

Figure 2.43 illustrates how previous observations of $T_2$-weighted signal contrast at TE = 75 ms (tissue:muscle signal ratio) for radiation fibrosis and for recurrent cancer of the cervix [5] agree with EPG predictions using estimated relaxation values taken from the literature (circles), (note that in the boxplot for literature results the circles indicate the average value of the ratios because only the minimum, maximum and average values were reported in [5]), including for healthy
cervical stroma, as indicated in the Methods section. The experimental observations of signal contrast are shown as the average as well as the minimum and maximum values observed over 22 patients [29].

**Figure 2.3** $T_2$-weighted signal contrast (tissue:muscle signal ratio) boxplot for fibrosis, healthy tissue, and cancer of the cervix. For fibrosis and recurrence, circles indicate average value and boxes indicate the minimum and maximum bounds of experimental results of Ebner et al. from 22 patients at $TE = 70$ or $80$ ms [29]. The EPG simulation results for 2D FSE at $TE = 75$ ms using muscle $T_2 = 35$ ms (stars, lower bound) and muscle $T_2 = 45$ ms (triangles, upper bound) indicate the average (median) value plotted over the respective box plots. Note that the circles corresponding to the box plots of experimental results indicate the average value and not the median.

The signal contrasts predicted by EPG simulations, for all the $T_2$ values previously reported for nine patients [29], are shown as box plots for 2D FSE MRI at the $TE_{eff} = 95$ ms with the average shown by circles; default 3D FSE MRI with matched $TE_{Eqv}$ using $T_{1REP} = 1000$ ms and $T_{2REP} = 100$ ms (average shown by stars); and “modified” 3D FSE with matched $TE_{Eqv}$ using $T_{1REP}$ =
1000 ms and $T_{2\,REP} = 40$ ms (average shown by triangles). In each of these three cases, the mean value is plotted as the average over [31]. Results for ratios calculated with upper and lower bounds of muscle are shown in Figure 2.4.

**Figure 2.4** Box plots and mean values of contrast ratios for 2D FSE (circles), 3D FSE (stars) default and 3D FSE modified (triangles) using representative relaxation characteristics of tissues from a study of 9 patients [29] are shown for comparison at TE= 95ms. **a)** shows ratios calculated using the upper bound ($T_2 = 45$ ms) of muscle and **b)** shows ratios calculated using the lower bound of muscle ($T_2 = 35$ ms).
Several important features are observed in Figure 2.3. First, the predicted signal contrast increases progressively from fibrotic tissue, to healthy cervical tissue, to recurrent tumour. The signal contrast predicted for 2D FSE MRI shows agreement with the published experimental data, minimum and maximum values that overlap. The maximum value for tumor reported by the is 10, compared to a maximum value of 5 predicted by EPG simulations, this could be due to the different size of samples and the variability of relaxation values across patients. The average value reported was 3.78 which was close to the and the average value for ratios calculated with the upper bound of muscle of 3.27. The default 3D FSE imaging results produce good signal contrast for fibrosis, and for healthy cervical tissue where default 3D FSE MRI exhibits the same mean value and variability as observed for 2D FSE MRI of the healthy cervix. For the 3D FSE default sequence, a substantial portion of signal contrast values are lower than the minimal signal contrast for 2D FSE, especially for those ratios calculated with the upper bound of muscle. The signal contrast values for modified 3D FSE MRI are an improvement over those observed for default 3D FSE MRI, showing a better overlap to 2D FSE in the ratios calculated with the upper bound of muscle. Signal contrast is still systematically less for the former method, however, with some results for modified 3D FSE still lying below the minimum bound of signal contrast observed.

2.3.3 MRI of Healthy Volunteers

Figure 2.5 shows representative axial-oblique results from default 3D FSE, 2D FSE, and modified 3D FSE MRI of the female pelvis for the four healthy volunteers. The key features to note are the signal intensity of the healthy cervix relative to the surrounding tissue, which can be either muscle or fat, and the definition of the outline of the cervix. Despite the variability in image contrast observed for the 2D FSE images across the volunteers, in all cases the modified 3D FSE image shows much more similar contrast to the 2D FSE image counterpart than is observed for the default 3D FSE image. In the default 3D FSE images, the cervix exhibits elevated signal in
relation to that observed for the 2D FSE images. Because of this, it is difficult to discriminate the boundary of the cervix in relation to the surrounding tissue in volunteers 1 and 3. However, the modified 3D FSE images depict the cervix with lower signal amplitude compared to the default 3D FSE images, very similar to the signals observed with 2D FSE imaging. The boundary between the normal cervix and surrounding tissues is consequently discriminated almost as well with modified 3DFSE imaging as with 2D FSE imaging for all four volunteers.

**Figure 2.5** Healthy volunteer cases, comparison with 3D T2w FSE stock sequence ($T_{2,REP} Brain = 100\, ms$) of 2D T2w FSE and modified 3D T2w FSE ($T_{2,REP} Muscle = 40\, ms$)
2.4 Discussion

Although 3D FSE MRI of the female pelvis is potentially attractive for cervical cancer applications, providing SNR efficiency in relation to 2D FSE MRI and enabling images to be reformatted into different viewing planes, this protocol has not been adopted clinically at present because of unacceptable signal contrast. The present work has been conducted to gain greater insight about the physical mechanisms that underlie this issue and to investigate the potential of a modified 3D FSE MRI protocol with improved signal contrast. Two hypotheses were posed and investigated: first, that the signal changes of tissues subject to any 2D or 3D FSE MRI sequence can be predicted by inputting their $T_1$ and $T_2$ into an EPG framework and second, that improved 3D FSE signal contrast is achieved by changing the representative tissue relaxation properties (which are required to determine $T_{E_{eq}}$) from the default settings for brain, to those of fibrosis and muscle (ie. $T_{1REP} = 1000$ ms and $T_{2REP} = 40$ ms). Simulations and experiments were subsequently undertaken with the results generating support for both hypotheses. The outcomes of the study are discussed below in more detail, including potential limitations of the work and aspects where future research is needed.

Although technologists and clinicians can manipulate signal contrast by changing pulse sequence parameters at the MRI system console (e.g. via $T_{E_{eff}}$ when performing 2D FSE MRI of patients with specific pathology), in practice the parameter options are limited and the adjustment process can be very open-ended, especially if the processes physically responsible for image contrast are not well understood. Thus, testing the first hypothesis was important to identify the key parameters influencing contrast in 3D FSE MRI in the present context, with the related goal of creating a simulation framework for quick and accurate determination of signal contrast properties for different 3D FSE (and 2D FSE) pulse sequence and tissue parameter inputs.
Hypothesis 1 was supported by showing that a simulation framework based on EPG accurately predicted experimental signal intensities of 3D FSE, as a function of VFA schedule and timing, $T_{1,REP}$, $T_{2,REP}$ and the tissue $T_1$ and $T_2$ values, by comparing the simulated and experimental signals on a Bland-Altman plot of phantoms with relaxation values pertinent to those of tissues of interest. It was evident that the errors in EPG signal predictions were very small in the present context, compared to the expected tissue biological variability.

In support of hypothesis one, whereas the signal contrast predicted for 2D FSE MRI agreed well with the previously reported ROI measurements, unacceptable reduced image contrast was observed for default 3D FSE MRI that was consistent with anecdotal observations: values for recurrent tumour were highly similar to the contrast observed for healthy cervix using 2D FSE MRI, and were too low in relation to the $T_2$-weighted signal contrast for recurrent tumour observed in ROI measurements. Overall, these findings indicate that in the present context, knowledge of the $T_1$ and $T_2$ values of a specific tissues are sufficient to predict the signal contrast of default 3D FSE MRI and 2D FSE MRI with appropriately chosen $T_{Equiv}$ and $T_{Eff}$, respectively. By extension, this also suggests that other potential factors such as tissue differences in proton density, perfusion, or magnetization transfer have minimal influence on the unacceptable levels of signal contrast observed with default 3D FSE MRI of the female pelvis. Together with this claim, it must be acknowledged that the reported relaxation time characteristics of tissues are generally variable [32, 33].

Further experiments to demonstrate hypothesis one would be performing detailed relaxation measurements of tissues of interest, as the most limiting factor in predicting the resulting image contrast is not the EPG model but the selection of appropriate $T_1$ and $T_2$ values for pertinent tissues. Given the relaxation values, predictions can be compared to ROI measurements of signal
contrast for 2D FSE and 3D FSE MRI in one imaging exam, for a group of patients with cervical cancer and a group of healthy controls and follow up patients.

Once hypothesis one was trusted, the EPG simulations then allowed for a thorough analysis of contrast correction methods, and showed that signals of tissues with $T_2$ values close to 100 ms, in the case of brain were properly corrected when using the $T_{2,Rep} = 100$ ms. On the contrary, signal correction of tissues with smaller $T_2$, as those of interest in cervical cancer, were not properly corrected as demonstrated by the shift of contrast ratios in the default 3D FSE; this led to the formulation of the second hypothesis to improve the contrast *in-vivo*.

Using a modified 3D FSE MRI approach with $TE_{Eq}$ calculated based on use of muscle as the representative tissue, EPG simulations showed that signal contrast was increased for healthy cervical stroma and for recurrent cervical cancer in relation to the signal contrast observed for default 3D FSE MRI. Although promising, the modification was not completely successful in restoring signal contrast to the levels achieved with 2D FSE imaging. In addition, compared to the results from previous ROI measurements [5], the range of signal contrast predicted for the modified 3D FSE MRI method suggests that increased frequency of failing to detect recurrent cancer could still occur.

The EPG simulation results were consistent with the appearance of 2D FSE, default 3D FSE and modified 3D FSE imaging of the female pelvis in four healthy volunteers. The signal contrast of the 2D FSE images was quite variable from volunteer to volunteer, but this is expected due to age and hormonal cycle effects [34]. Irrespective of this variability, the signal contrast in default 3D FSE images was insufficient to discriminate cervical stroma from surrounding normal tissues in two of four volunteers, whereas the image contrast of modified 3D FSE images was consistently much more similar to the appearance of the 2D FSE images across all volunteers. Thus, the MRI
component of the present work provides additional support for both hypotheses. However, the image contrast obtained with the modified version of 3D FSE MRI was not identical to that observed for 2D FSE MRI. This again suggests the possibility of increased levels of false negatives if patients with cervical cancer were imaged with the modified 3D FSE approach suggested here.

Although the present work focuses on cervical cancer applications, it is reasonable to speculate that the concept of appropriately modifying $T_{2\text{REP}}$ may be beneficial in other application areas which require 3D FSE MRI with improved signal contrast. Undoubtedly, this claim must be substantiated by additional research. In thinking of how such investigations should be conducted, it is noteworthy that although $T_{2\text{REP}}$ was reduced in the present work from the value for brain to that of muscle, a search for the optimal $T_{2\text{REP}}$ value was not conducted. The EPG simulation framework provides a useful tool for efficiently performing such a search. In the present scenario, further reduction should be considered but as $T_{2\text{REP}}$ is reduced, $T_{E\text{ff}}$ increases. This effect causes the echo corresponding to the centre of k-space to occur later in the echo train, potentially constraining the ETL and affecting the k-space sampling pattern. Another factor that should be considered is that the procedure for setting $T_{E\text{q}}$ assumes that tissues exhibit mono-exponential relaxation times, whereas detailed measurements reveal multi-component characteristics [32]. Further investigations are required to determine the maximal 3D FSE MRI signal contrast that can be realized by adjusting $T_{2\text{REP}}$ in practice.

One important limitation of the present study is the absence of imaging data from patient volunteers with cervical cancer, or volunteers with radiation fibrosis from successful radiation treatment of the disease. The results reported here can only be considered preliminary as a consequence. Despite this, this specific demonstration of improved 3D FSE MRI signal contrast
in the pelvis of female healthy volunteers is promising. In the future, the utility of optimized 3D FSE MRI can only be established definitively for cervical cancer applications by conducting reader studies involving patients with comparison to standard-of-care imaging protocols. The present work will play a useful role in developing such study designs.
3 Conclusions and Future Directions

3.1 Summary and Conclusions

Magnetic Resonance Imaging (MRI) is the modality of choice for treatment planning and monitoring of cervical cancer due to the ability to distinguish cancerous tissue versus normal tissue in images with $T_2$-weighted contrast. Current clinical protocols image the same volume of interest in three orthogonal planes using two dimensional (2D) $T_2$-weighted MRI techniques. It is of interest to replace these multiple 2D acquisitions with a single three dimensional (3D) MRI acquisition, to save time and improve spatial resolution.

However, at present the image contrast of standard 3D $T_2$-weighted MRI technique obscures the distinction of normal and cancerous tissue of the cervix. The purpose of this thesis is to characterize and improve 3D $T_2$-weighted MRI contrast by modifying key MRI acquisition parameters such that the contrast closely approximates that of the standard 2D $T_2$-weighted MRI. Two hypotheses are explored to address this specific problem. It is hypothesized that the image contrast observed in 3D FSE MRI can be replicated by applying the Bloch equations with pertinent tissues of interest represented solely by their $T_1$ and $T_2$ values. To test this hypothesis, a simulation framework based on the EPG formalism is developed to predict 3D FSE MRI signal intensities of any tissue with $T_1$ and $T_2$ and any VFA and pulse train timing schedule. The simulation framework is compared to experimental results obtained by 3D FSE MRI at 1.5 T of phantoms with known relaxation properties.

Current 3D FSE implementations employ contrast correction methods that depend on fixed $T_{1REP}$ and $T_{2REP}$ values representative of brain. Thus, it is a logical starting point to select $T_{1REP}$ and $T_{2REP}$ values that are more representative of tissues in the female pelvis. In particular, muscle and fibrosis are used as reference tissues in the assessment of recurrent cervical cancer, and exhibit
$T_2$ values that are considerably less than those of brain tissues. Thus, the second hypothesis states that signal contrast observed in 3D FSE MRI of the female pelvis can be substantially improved over the current standard protocol, and made to approximate closely that of 2D FSE MRI by modifying the "default" values of $T_{1REP} = 1000 \text{ ms}$ and $T_{2REP} = 100 \text{ ms}$ to those representative of muscle and fibrosis, i.e. $T_{1REP} = 1000 \text{ ms}$ and $T_{2REP} = 40 \text{ ms}$. On successfully verifying hypothesis one, hypothesis two is tested at 1.5 T through a series of EPG simulations and 2D and 3D FSE MRI of healthy female volunteers.

In support of hypothesis 1, aqueous mixtures of agar gel and gadolinium diethylenetriaminepentacetate (Gd-DTPA) were formed at specific concentrations to yield relaxation values over a range of interest with $T_1 \approx 1,000 \text{ ms}$ and $T_2 \approx 40 - 120 \text{ ms}$. Comparison of phantom signal intensities to theoretical signal intensities (predicted by the EPG framework) were performed on four 2D $T_2$-weighted FSE images and six 3D $T_2$-weighted FSE sequences with various ETL, $T_{E_{eff}}$, $T_{2REP}$ and sequence parameters similar to a clinical protocol. The SE and IR data were used to estimate the $T_2$ and $T_1$ values for each phantom. These values were then input to the EPG framework to simulate the signal intensities of each phantom for the 3D FSE MRI appropriate sequence parameters, enabling comparison with the associated experimental results. Comparison was performed with a Bland-Altman analysis, which plots difference signals (experimental and predicted) as a function of the average of signal. The agreement is excellent overall, with a very slight positive bias in the difference signal indicating under-prediction by the EPG simulations.

Based on these findings, it is concluded that the evidence partially supports both hypotheses under consideration. Neither hypothesis can be fully accepted, however, because the existing evidence is incomplete. The prediction of 3D FSE MRI signal contrast solely on relaxation time
characteristics for tissue types involved in cervical cancer applications will require imaging data to be collected from patients, not just healthy adult females as in the present work. Similarly, 3D FSE MRI of patients is required to establish whether the modified acquisition parameters provide an improvement over the defaults – and there is also scope for further parameter adjustments to improve signal contrast in 3D FSE MRI even further, if necessary. The remainder of this thesis discusses the potential avenues for future research that would be worthwhile to pursue in this field.

3.2 Future Directions

Although the present work focuses on cervical cancer applications, it is reasonable to speculate that the concept of appropriately modifying $T_2 \text{REP}$ may be beneficial in other application areas which require 3D FSE MRI with improved signal contrast. There is ample room for future investigations both utilizing the EPG simulation toolset that has been developed, and in vivo imaging studies with the aim of definitively establishing the utility of 3D FSE MRI for cervical cancer and other clinical applications. For example, future investigations of $T_2$ contrast from 3D FSE sequences include: 1) examining whether $T_2$-weighted signal contrast can be further improved by modifying control points in the VFA schedule and the ETL; 2) investigating a different contrast-correction method that takes into consideration the target signal contrast ratio of two tissues of interest, rather than the signal intensity of a single tissue; 3) investigating use of multi-slab acquisitions with VFA to optimize SNR, SNR efficiency and scanning time; and 4) performing a large-scale study focused on contrast alterations with patients undergoing tumor staging and post-treatment imaging. Each of these possible future investigations is described briefly below.
**Investigation 1.** In addition to the key parameter $T_{2\text{REP}}$, the VFA schedule has an effect on the evolution of tissue MR signals, and specifically the signal intensities observed at different $TE_{\text{Eqv}}$ values. The EPG simulation framework allows for modification of control points and quick prediction of their impact on 3D FSE MRI signal contrast in the treatment planning and monitoring of cervical cancer. Several studies have established the general shape of the VFA trajectory collectively, with the objective of minimizing steady state instabilities and maximizing the allowable time for signal sampling, but mostly ignoring signal decay effects due to tissue $T_1$ and $T_2$ values [20] [35] [25]. Presently, there is a lack of literature describing the relationship between the VFA control points and image contrast. The ETL should also be investigated further as part of such an endeavor. Because there is no standard ETL, imaging technologists currently can choose any ETL value up to 140 and this may have an effect on the resulting $T_2$ contrast. A study of this type could be undertaken considering various tissues of interest corresponding to specific clinical applications, such as cervical cancer.

**Investigation 2.** The current contrast correcting method takes into consideration the signal intensity of a specific tissue, namely a tissue with values $T_{1\text{REP}}, T_{2\text{REP}}$, which has been shown to yield satisfactory signal contrast of 3D FSE MRI in brain applications where the relaxation properties of the tissues of interest do not deviate substantially from those of the representative tissue. However, this has not been investigated exhaustively, and in analyzing cervical cancer it is critical to distinguish fibrosis, healthy tissue and cancerous tissue based on 3D FSE MRI signal contrast. An alternative approach to determining $TE_{\text{Eqv}}$ according to signals from a representative tissue is to make the determination based on signal intensity ratios (i.e. contrast, the parameter of direct clinical importance). For example, the target ratio for this clinical application would be the ratio between muscle and recurrent (rec) cervical cancer with values $T_{1\text{Muscle}}, T_{2\text{Muscle}}$, and
Following the conventional notation to express the signal intensity of a tissue ($f_{EPG}$) with the EPG algorithm, the ratios can be equated as following,

$$\frac{f_{EPG}[VFA(TE_{Eff}), T_{1,Rec}, T_{2,Rec}]}{f_{EPG}[VFA(TE_{Eff}), T_{1,Muscle}, T_{2,Muscle}]} = \frac{e^{-TE_{Eqv}}}{e^{T_{2,Rec}}}$$  \hspace{1cm} (Eq. 3.1)

which can be re-arranged to:

$$TE_{Eqv}(TE_{Eff}) = -\left[\frac{T_{2,Rec}}{T_{2,Muscle}}\right]ln\left\{\frac{f_{EPG}[VFA(TE_{Eff}), T_{1,Rec}, T_{2,Rec}]}{f_{EPG}[VFA(TE_{Eff}), T_{1,Muscle}, T_{2,Muscle}]}\right\}$$  \hspace{1cm} (Eq. 3.2)

The values for these two ‘representative’ tissues are chosen to be $T_{1,Muscle} = 1,000 \ ms$, $T_{2,Muscle} = 40 \ ms$, and $T_{1,Rec} = 1,000 \ ms$, $T_{2,Rec} = 87 \ ms$. Using the same numerical simulation and reporting procedure described in Section 2.2, the new average ratios between tissues of interest are shown in Figure 3.1 for 2D FSE MRI, 3D FSE MRI with default parameters, and modified 3D FSE MRI according to representative tissue contrast.
Figure 3.1 Box plots and mean values of contrast ratios for 2D FSE (circles), 3D FSE (stars) default and 3D FSE alternate method (triangles) using representative relaxation characteristics of tissues from a study of 9 patients [29] are shown for comparison at TE= 95ms. a) shows ratios calculated using the upper bound of muscle $T_2 = 45$ ms (upper bound) and b) shows ratios calculated using muscle $T_2 = 35$ ms (lower bound).
Numerical simulations show that this new contrast correction method matches the 3D FSE contrast with the 2D FSE for the three tissues of interest. Investigating how these modified ratios translate qualitatively into in-vivo image contrast is worth pursuing.

**Investigation 3.** The technique of multi-slab imaging, similar to 2D MRI, consists of exciting and acquiring signal from independent thick ‘slices’ but with additional phase encoding in the through-plane direction that is characteristic of 3D MRI. Thus, ‘slices’ are converted into slabs of 3D data [36]. The use of VFA refocusing pulses can be implemented for trade-offs in the SNR, SNR efficiency and total scanning time, which ultimately may have workflow implications for imaging cervical cancer and other MRI applications. For example, taking the volume of interest described in Section 1.1.4.2 of size $256 \text{ mm} \times 256 \text{ mm} \times 128 \text{ mm}$ with target isotropic resolution of $1 \text{ mm} \times 1 \text{ mm} \times 1 \text{ mm}$ could be divided into 6 slabs of $22 \text{ mm}$ of coverage.

With a typical $TR = 3,000 \text{ ms}$, the resulting scanning time would be reduced to $t_{total} \approx 69 \text{ s}$ from a time of $t_{total} \approx 294 \text{ s}$ for a single slab acquisition. with a $t_{voxel} \approx 6.9 \text{ s}$ which maintains the $SNR_{Efficiency} \approx 31.7\%$ as the previous example. Choosing to divide the volume of interest differently, for example 7 slabs with through-plane coverage of $18 \text{ mm}$ would double the $t_{total} \approx 138 \text{ s}$, with the same $t_{voxel} \approx 6.9 \text{ s}$ then the $SNR_{Efficiency} \approx 22\%$. Parameters such as ETL, ESP, which also control the design of the variable flip angle schedule are important to optimize sequence.

**Investigation 4.** A detailed large-scale clinical study will be required in the long-term to assess the performance of modified 3D FSE MRI in the staging and treatment monitoring of cervical cancer. Using the EPG framework, reasonable ETL and contrast-correction methods can be determined, for example involving the new approach suggested in Investigation 2. The two sequences of interest (default 3D FSE MRI and modified 3D FSE MRI) can be added to the
clinical staging exam, which includes 2D FSE MRI as standard. This will enable evaluation of
the signal contrast of both 3D FSE sequences to be investigated in relation to 2D FSE, toward
strengthening hypothesis 1 by taking measurements of pertinent ROIs and comparing contrast
ratios to predicted values. The precise imaging protocol will require careful development and
attention to a number of practical considerations. To keep the additional imaging time to a
practical limit (15 minutes, for example) 3D FSE MRI may need to be implemented with a smaller
FOV relative to standard 2D FSE, and the consequences of this compromise considered.
Although lengthier scanning is possible, the probability of deleterious motion artifacts increases
over time. Conversely, MRI of patients may require larger FOV values and additional fat-
saturation steps in comparison to MRI of healthy adults, which may motivate lengthier
examinations.

Assuming that positive results are obtained from such work, a single modified 3D FSE MRI
protocol can then be added to the staging and monitoring exams of a larger group of patients. The
single 3D FSE MRI protocol would have the same volume of coverage as 2D FSE MRI conducted
in multiple slice orientations, but with higher resolution in the slice-direction enabling multi-
planar reformatting. The resulting exams from the modified 3D FSE and 2D FSE MRI protocols
would have to be validated by multiple radiologists specialized in imaging of the female pelvis to
distinguish the boundary between tumor and healthy tissue. Validation is commonly done by
blinded reviews assessing both protocols using rating scales to determine which provides the
better radiological interpretation. Such a project will be essential to establish the clinical
applicability of 3D FSE MRI to cervical cancer.
3.3 Final Remarks

Quantitative assessment of the fundamental sequence parameters, MR properties of tissues and image contrast provides increased understanding of tissue biophysics to facilitate clinical implementation of more efficient MRI methods, and may well be important from the standpoint of improving MRI applications that involve detection of cancer, treatment planning and monitoring for potential recurrence. It is evident that such analyses, in particular those in clinical applications with tissues different than brain, are far from complete. This thesis has provided a useful basis for continued investigations in this field of research.
Appendix A: Preparation of Agar-Gadolinium-DTPA phantoms

Test objects (phantoms) constructed with different mixtures of agar powder and Gadolinium diethylenetriamine (Gd-DTPA) were prepared with relaxation time values in the approximate range for the tissues of interest, namely $T_1 \approx 1,000 \text{ ms}$ and $T_2 \approx 35 - 100 \text{ ms}$. Three different sets of phantoms were constructed: the first two with separate incremental concentrations of agar powder and Gd-DTPA to estimate the relaxivities of each agent; and the third with combined agar and Gd-DTPA concentrations to generate the required relaxation times using the relaxivities that were estimated.

The relationship between the concentration of a contrast agent and the modified values of water relaxation times ($T'_1$ or $T'_2$) described in terms of relaxation rates ($R'_1 = \frac{1}{T'_1}$, $R'_2 = \frac{1}{T'_2}$) is given by:

\[
R'_1(C_i) = R'_{1\text{water}} + C_i r'_1, \\
R'_2(C_i) = R'_{2\text{water}} + C_i r'_2.
\]  
(Eq. A.1)

where $R'_{1\text{water}} = \frac{1}{r'_{1\text{water}}}$, $R'_{2\text{water}} = \frac{1}{r'_{2\text{water}}}$, are the relaxation rates corresponding to water, $C_i$ represents the concentration of the $i$-th doping agent, and $r'_1$ and $r'_2$ correspond to the relaxivities of $i$-th agent in units of $\text{ms}^{-1} \text{M}^{-1}$ or $\text{ms}^{-1} (\frac{g}{\text{ml}})^{-1}$ for Gadolinium and agar powder, respectively [37].

First, the relaxivities of agar and Gd-DTPA were estimated separately as the slope of a relaxation rate vs. concentration curve of water doped with the agent in question. Then, the required concentrations of both agents to achieve the target values of $R'_1$ and $R'_2$ ($T'_1 \approx 1,000 \text{ ms}$ and $T'_2 \approx 35 - 100 \text{ ms}$) were determined by the following equations:

\[
R'_1(C_{Agar}, C_{Gd}) = R'_{1\text{water}} + C_{Agar} r'_{1\text{Agar}} + C_{Gd} r'_{1\text{Gd}},
\]  
(Eq. A.2)
\[ R_2'(C_{Agar, Gd}) = R_2^{water} + C_{Agar} r_2^{Agar} + C_{Gd} r_2^{Gd}. \]

To estimate the relaxivity of Gd-DTPA, nine phantoms with concentrations \([Gd-DTPA] = 0.0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 \, mM\) and agar eight phantoms with concentrations of \([Agar] = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0 \, \frac{g}{mL}\) were prepared. The values of \(T'_1\) and \(T'_2\) were estimated from standard sequences: Inversion Recovery (IR) and Spin Echo (SE), respectively for Gd-DTPA, seven IR sequences were used with \(TI = 100, 500, 800, 1000, 1500, 2500, 3500, 3500 \, ms\) and \(TR = 7,000 \, ms\) ; as well as seven SE sequences with \(TE = 20, 80, 120, 140, 160, 200, 300 \, ms\) and \(TR = 4,000 \, ms\). For agar gel, eight IR sequences were used with \(TI = 100, 500, 800, 1000, 1500, 2500, 3500, 3500 \, ms\) and \(TR = 7,000 \, ms\) and five SE sequences with \(TE = 20, 50, 60, 80, 120 \, ms\) and \(TR = 4,000 \, ms\). Fitting the relaxation model with one agent at a time, using linear least squares fitting in Matlab (Eq. A.1) estimated the relaxivity as the slope of agent \(R'_1\) and \(R'_2\) vs. agent concentration [38].

After estimating the relaxivities of agar and Gd-DTPA separately, the concentrations of each were estimated to achieve the target \(T'_1\) and \(T'_2\) values (Eq. A.2). Seven phantoms with mixtures of agar and Gd-DTPA were prepared with concentrations of \([Agar] = 0.28, 2.41, 1.70, 1.54, 1.19, 1.03, 0.85 \, \frac{g}{mL}\) and \([Gd] = 0.082, 0.087, 0.092, 0.093, 0.096, 0.097, 0.098 \, mM\).

Figure A.1 and Figure A.2 show the relaxation rate versus the concentration of doping agent for agar and Gd-DTPA, with the estimated slopes providing relaxivities, namely, \(r_1^{Agar} = 6.5 \times 10^{-5} \, m^{-1} s^{-1} \frac{g}{mL}^{-1}, r_1^{Agar} = 6.5 \times 10^{-5} \, m^{-1} s^{-1} \frac{g}{mL}^{-1}, r_2^{Agar} = 5.58 \times 10^{-3} \, m^{-1} s^{-1} \frac{g}{mL}^{-1}, r_1^{Gd} = 2.17 \times 10^{-1} \, m^{-1} s^{-1} m^{-1} and r_2^{Gd} = 2.55 \times 10^{-1} \, m^{-1} s^{-1} m^{-1}.\)
The relaxivities of both agar and Gadolinium show that gadolinium has a greater effect on modifying the $T_1$ value of water. Agar and Gd-DPTA have similar effect on the $T_2$ value, using these values and a range of $T_2$ values encompassing tissues of interests and a $T_1$ target of 1,000 ms.

![Graphs showing Agar $R_1$ and $R_2$ relaxivities as a function of concentration.](Image)

**Figure A.1** Relativities ($R_1^{Agar}$ and $R_2^{Agar}$) of agar as a function of the concentration of agent
Figure A.2 Relativities ($R_{1}^{\text{Gd}}$ and $R_{2}^{\text{Gd}}$) of Gadolinium-DTPA as a function of the concentration of agent
References


