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Novel Techniques for Rapid Cardiac Perfusion Magnetic Resonance Imaging with Whole Heart Coverage

Haonan Wang
Brigham Young University

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Novel Techniques for Rapid Cardiac Perfusion Magnetic Resonance Imaging

with Whole Heart Coverage

Haonan Wang

A dissertation submitted to the faculty of
Brigham Young University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Neal K. Bangerter, Chair
David G. Long
Karl F. Warnick
Brain A. Mazzeo
Scott R. Burt

Department of Electrical and Computer Engineering
Brigham Young University
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ABSTRACT

Novel Techniques for Rapid Cardiac Perfusion Magnetic Resonance Imaging with Whole Heart Coverage

Haonan Wang
Department of Electrical and Computer Engineering, BYU
Doctor of Philosophy

Magnetic Resonance Imaging (MRI) is a non-invasive medical imaging method that is used in the diagnosis of many common diseases. Compared to other medical imaging modalities, MRI has the ability to provide high-resolution 2D and 3D images in arbitrary orientations, without the use of potentially damaging ionizing radiation. Myocardial perfusion MRI is a promising non-invasive clinical way to detect cardiac disease. It can also provide quantitative analysis for blood flow within the heart. However, MRI requires longer scan times to acquire images at comparable resolutions to some other imaging modalities. Increasing image resolution, both spatially and temporally, is very important to myocardial perfusion MRI.

The work presented in this dissertation focuses on the development of novel dynamic contrast-enhanced (DCE) MRI that is able to achieve both high spatial and temporal resolutions, as well as suitable spatial coverage of the heart. Three novel acquisition and reconstruction frameworks are proposed and analyzed in this dissertation.

The first framework we propose uses a highly undersampled 3D Cartesian acquisition and total variation (TV) constrained reconstruction to accelerate the acquisition of myocardial perfusion images. This technique increases temporal resolution for contrast tracking without sacrificing spatial resolution. An analysis of the effect of different k-space trajectories using this technique is performed.

The purpose of the second framework is to simplify cardiac perfusion studies. An ECG-gated saturation recovery sequence is regularly used for cardiac perfusion imaging. However, using an ungated acquisition has the potential benefit of reducing the acquisition time by eliminating the need for the ECG trigger signal. We present a novel non-Cartesian 2D multi-slice ungated acquisition, and demonstrate that it is a promising alternative to ECG-gated cardiac perfusion studies. An optimization analysis of our ungated acquisition is also presented.

The third method in this dissertation combines the 2D ungated acquisition with multi-band excitation, which enables the excitation of multiple slices simultaneously. This method is able to reduce scan time not only through the ungated acquisition, but also from obtaining multiple slices at once. This allows us to achieve whole heart coverage without sacrificing temporal resolution.

The contributions presented in this dissertation demonstrate the basic feasibility of cardiac perfusion MRI achieving whole-heart coverage in a clinical setting by overcoming the major existing limitations: speed of acquisition and spatial coverage.

Keywords: Magnetic Resonance Imaging (MRI), Cardiac Perfusion, Compressed sensing, Multi-band Excitation, Constrained Reconstruction
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CHAPTER 1. INTRODUCTION

Magnetic Resonance Imaging (MRI) is a widely used non-invasive medical imaging modality due to several advantages it provides over other commonly used modalities. The first benefit is the safety of the MRI scan. Compared with other traditional imaging methodologies, such as computed tomography (CT) and positron emission tomography (PET), MRI utilizes a strong magnetic field rather than ionizing radiation to produce an image [1]. Ionizing radiation can cause severe damage to cells in the body, and there are thus limits on the amount of time a person can be imaged using these modalities. Another benefit of MRI is its ability to provide high-resolution 2D and 3D structural images in arbitrary orientations. With different parameter settings, MRI also has the ability to provide near-limitless contrasts between tissues. Other imaging techniques often require injections of contrast agents to achieve even a single different contrast. MRI, on the other hand, has the ability to achieve drastically different contrasts between tissues by manipulating the spin physics that yield the MRI signal. In addition to visualizing anatomy, MRI is a powerful tool for measuring physiological function, such as blood flow, temperature, and tissue connections in a non-invasive way, making it compelling for a broad range of clinical applications.

1.1 Motivation

The American Heart Association defines coronary artery disease (CAD) as an ischemic heart disease [2, 3]. Ischemic heart disease encompasses a group of diseases that include myocardial infarction (heart attack), sudden heart death, and stable and unstable angina (lack of blood flow in the heart). CAD is the leading cause of death globally. In 2013, 8.14 million people died due to CAD related diseases [3, 4]. During the onset of CAD, cholesterol plaque deposits in the main coronary blood vessels, chronically narrowing the coronary arteries. The narrowed vessels then limit blood flow to the heart, and the myocardial cells (heart muscle cells) suffer from lack of oxygen, resulting in what is called myocardial ischemia. Myocardial ischemia can then lead
to dysfunction in the myocardium. In the worst cases, the plaque can block the artery, forming a thrombus (clot) that causes myocardial infarction. If the myocardial infarction lasts long enough (10-15 minutes) the myocardial cells will die due to the lack of oxygen. These cells are very specialized and will not grow back once they have died, unlike most other cells in the body. If the damage is extensive enough the heart will no long be able to pump enough blood to the brain and body and the person will die. If clinicians can catch these narrowed blood vessels before the heart tissue dies they can usually save the tissue and the patients life. [3, 5]

Cardiac perfusion imaging is an important non-invasive assessment used to diagnose patients with known or suspected CAD. Although perfusion imaging does not directly image the arteries themselves, it can be used to tell when the arteries providing blood to certain areas of the myocardium are blocked. It can also provide information about the extent of damage to the myocardium after a myocardial infarction. The most common clinical examination used to perform perfusion studies is Single Photon Emission Computed Tomography (SPECT). Although SPECT is widely available, it has limitations. It uses ionizing radiation that can damage tissues, and also suffers from attenuation artifacts. Furthermore, SPECT is sensitive to motion and cannot achieve high spatial resolution. [6].

MRI is beginning to be explored as an alternative method for assessing myocardial perfusion. Cardiac perfusion MRI monitors the enhancement (increase in MRI signal) of the myocardial wall continuously by acquiring a series of MRI images after injecting an MRI contrast agent [7, 8]. In addition to MRI being much safer than SPECT, it also provides the advantage of high spatial resolution and relatively short scan times [9]. Furthermore, MRI cardiac perfusion studies provide data that can be used for true quantification analysis of cardiac perfusion [10].

Despite these potential advantages, MR imaging of myocardial perfusion has not yet been widely used clinically due to several challenges. Most of the limitations arise from the innate character of MRI. Unlike CT, PET, or SPECT, MRI collects data in the frequency domain (commonly referred to as k-space); only one k-space or pixel line can be acquired per MRI excitation/readout cycle [11]. To achieve images at a reasonable resolution and field of view, this excitation/readout process needs be repeated until all the necessary k-space has been covered. An ideal myocardial perfusion image needs to be high in spatial resolution (less than 2 mm x 2 mm in plane resolution) and temporal resolution (2-3 frames per second). It is also desirable to have coverage of the whole
heart; acquiring more than 6 slices across the heart makes it less likely to miss an ischemic area. Normally, after the contrast agent is injected, only about 40 seconds is available during which images must be acquired. This is an extremely short acquisition time to achieve good image quality.

In the meantime, the workflow of myocardial perfusion MRI is complicated due to cardiac motion. Typically myocardial perfusion data acquisition has to be synchronized with the heart beat to freeze the cardiac motion. It is also usually performed during breath-holds in order to minimize image artifacts from respiratory-motion [12, 13]. Sometimes different types of heart arrhythmias can break the synchronization and lead to images that are not usable for diagnosis. Breath-hold capabilities can also vary considerably across subjects, and requiring the breath hold increases patient discomfort, making myocardial perfusion MRI much more challenging.

1.2 Previous Work

Many researchers have devoted significant effort to increase MR image acquisition speed, and MRI acquisition speed has increased dramatically over the past 30 years. These increases are due to developments in hardware, new image acquisition techniques, and novel reconstruction methods.

Relevant hardware improvements include: multiple channel phased-array receiver coils, which allow for the acquisition of high SNR images in a short time; and high performance gradient coils, which allow for faster traversal through k-space.

Many new image acquisition techniques have been recently developed and are now beginning to be used clinically. For example, Echo-Planar Imaging (EPI) [14] allows the acquisition of multiple k-space lines in a single excitation/readout cycle. Other examples include Fast Spin-Echo (FSE) imaging [15] and Fast Low Angle SHot (FLASH) imaging, both of which employ clever manipulations of the underlying MR physics to save scan time [16].

Several very clever ideas have been proposed to accelerate image acquisition speed using novel reconstruction methods. The first of these successful ideas was to skip a certain amount of the (formerly) necessary k-space measurements and then synthesize (or fill in) that missing data based on known properties of the MR data to avoid losing much of the images quality. Examples include partial Fourier imaging, which utilizes the conjugate symmetry character of the frequency domain data of real images to skip acquisition of part of the k-space data [17]. When acquiring
time series (multiple frames) of data, a data sharing scheme can be used that allows high spatial frequency k-space data to be undersampled in each time frame and then shared across temporal frames to fill in the missing k-space data in each frame [18–20].

In the late 1990s, a variety of what are called “parallel imaging” techniques were proposed to further accelerate acquisition speed. Parallel imaging accelerates data acquisition by exploiting the additional information you get from using multiple receive coils to “unfold” the aliasing that occurs from undersampling k-space. Imaging is accelerated by undersampling k-space, and images from each individual receive coil then exhibit aliasing. However, clever combination of the information from the aliased images from all of the receive coils allows the aliasing to be unfolded, and a single un-aliased image to be reconstructed. There are multiple ways to use the coil information to remove aliasing from undersampled images. Three commonly used techniques are Simultaneous Acquisition of Spatial Harmonics (SMASH) [21], Sensitivity Encoding (SENSE) [22], and Generalized Auto calibrating Partially Parallel Acquisition (GRAPPA) [23].

The spatial and temporal correlations in dynamic MRI (where a time-series of MR images are acquired) can also be utilized to accelerate data acquisition. In the early 2000s, series “k-t” acceleration methods were invented, which exploit these spatial and temporal correlations to accelerate image acquisition. Examples include k-t BLAST, k-t SENSE, and k-t PCA [24, 25]. These methods use the correlation of dynamic images in the temporal direction and thus enable higher accelerations.

In 2006 and 2007, a pair of landmark papers proposed the MR theory of “compressed sensing”, which overcame the Nyquist sampling limitation and created a powerful approach to accelerate the acquisition speed of MRI [26,27]. As we know from the Nyquist sampling theorem, if we want to recover a band-limited signal without aliasing we need the sampling frequency to be greater than twice the maximum frequency present in the band-limited signal (when using a uniform sampling scheme). To meet the Nyquist criterion in MRI, a large amount of k-space data must often be sampled, resulting in long acquisition times for MRIs. However, if a signal (such as an MRI image) is “sparse” in some transform domain (Fourier, Wavelet, etc.), the theory of compressed sensing indicates that we can often use a sample rate far below the Nyquist rate to acquire data and still successfully recover an unaliased signal. Compressed sensing typically
employs a pseudo-random sampling pattern that produces incoherent “noise-like” aliasing, which can then be removed by enforcing reconstructed signal sparsity in the transform domain.

1.3 Dissertation Contribution and Outline

Chapter 1 has provided an introduction of the motivation for my research and a summary of previous work.

Chapter 2 briefly explains some necessary background principles of MRI, image reconstruction algorithms, and specific clinical applications of MRI.

Chapter 3 presents my analysis comparing centric and reverse centric k-space trajectories for highly accelerated 3D saturation recovery cardiac perfusion MRI. The major contribution of the work presented in this chapter is the demonstration of how sensitive highly undersampled 3D saturation-recovery sequences are to the order in which k-space data is acquired, since much of the data acquisition in these sequences is performed before the MR signal reaches steady state. I further demonstrate that the contrast can change significantly from slice to slice across the imaging volume, since non-ideal RF excitation profiles lead to flip angle variations across the volume that significantly affect the transient and steady-state signals. This effect has not been previously well studied, and many people are applying various k-space trajectories for cardiac perfusion imaging without understanding the implications on image contrast. I performed a back-to-back comparison between the different trajectories, and demonstrated the differences in contrast following a single contrast injection.

Chapter 4 presents a novel myocardial perfusion acquisition scheme that removes the need for an ECG trigger, and then outlines a framework for the analysis of the new ungated 2D technique. The framework is then used to conduct an analysis of the effect of the RF slice excitation profile on ungated 2D steady state cardiac perfusion imaging. I developed and tested simulations to investigate and model this effect, and then verified my models experimentally. I further used the framework to develop a technique to estimate the flip angle that maximizes enhanced/unenhanced myocardial contrast in both single-slice and multi-slice ungated acquisitions, which I simulated and tested as well. Previous work by others has typically ignored the effects of non-idealities in the RF excitation, resulting in the use of flip angles that do not actually optimize the contrast of
interest in these kinds of studies. My work provides a way of estimating the flip angle that will yield much more optimal contrast.

Chapter 5 establishes the framework for an ungated 2D multi-slice cardiac perfusion study using multi-band excitations. The multi-band excitation is a slice acceleration technique that acquires multiple slices at the same time. It is just beginning to be applied to myocardial perfusion MRI. In this work, we developed a radial multi-band excitation with data undersampling and constrained reconstruction to improve the utility of the ungated cardiac perfusion acquisition. We tested the proposed framework with a traditional saturation recovery turboFLASH sequence, as well as without saturation recovery using a steady-state spoiled gradient echo (SPGR) sequence in animal and human studies. I adapted and tested the SPGR pulse sequence for this project as well as its reconstruction. This is one of the first demonstrations of the feasibility and potential of accelerated radial simultaneous multi-slice MRI for assessing myocardial perfusion.

Chapter 6 provides a summary and conclusion of the work presented in this thesis, as well as a discussion of potential future research building on my work.
CHAPTER 2. MAGNETIC RESONANCE IMAGING BACKGROUND

This chapter presents a brief review of basic MRI principles, including MR signal formation, signal acquisition, reconstruction, and several related advanced topics. The content in this chapter is focused on providing information relevant to the subsequent chapters of the dissertation. My development of MRI background and the associated equations and derivations was informed from a variety of sources, including these two excellent books: [28, 29], two theses: [30, 31] and several handouts [32, 33]. The reader is referred to these and other cited sources for a more thorough treatment of the topics introduced.

2.1 MR Signal

2.1.1 The Nuclear Magnetic Resonance Effect

Nuclear magnetic resonance was first measured in molecular beams by Isidor Rabi in 1939 [34], and was then further expanded for use in liquids and solids by Felix Bloch and Edward Purcell in 1946 [35, 36]. Rabi, Bloch, and Purcell knew that any spinning charged particle could create an electromagnetic field that would interact with a static magnetic field. Actually, atoms with an odd number of protons and/or neutrons possess spin angular momentum since the unpaired nucleon will possess a tiny magnetic dipole moment. Macroscopically, those dipoles are randomly aligned, and so the net magnetic moment, which is the vector sum of all the individual dipole moments, equals zero, as shown in Figure 2.1a.

When a strong external magnetic field $B_0$ is applied, the nuclei tend to align with the $B_0$ field as shown in Figure 2.1b. From a quantum mechanical perspective, there are two energy states available to the nuclei in the external field: one state with lower energy where the nucleus is aligned parallel to the main magnetic field, labeled as (n+), and the other state with higher energy where the nucleus aligns in the anti-parallel direction (n-). Since the lower energy state is relatively
more stable, the population of n+ is slightly higher than the n- population (the ratio being about 1:0.999993 for H\textsuperscript{1} nuclei at 1.5 Tesla) giving a net magnetization in a direction parallel to the magnetic field. The nuclear magnetization for a spin-1/2 system such as H\textsuperscript{1} is calculated using

\[
M_0 = \frac{B_0 \gamma^2 \hbar^2 N}{3kT},
\]

where \(B_0\) is the external magnetic field strength, \(N\) is the number of spins, \(k\) is Boltzmann's constant (1.38x10\(^{-23}\) J/K), \(T\) is the temperature in Kelvin, \(\gamma\) is the gyromagnetic ratio (42.58x10\(^6\) Hz/T for H\textsuperscript{1}), and \(\hbar\) is Planck's constant (6.626x10\(^{-34}\) J-s).

2.1.2 Excitation

If a spin is tipped out of alignment with the applied magnetic field, it begins to precess at a certain frequency called the Larmor frequency. The Larmor frequency is nucleus dependent, and
is defined as
\[ \omega_0 = \gamma B_0. \] (2.2)

$B_0$ is the external applied magnetic field, and $\gamma$ is gyromagnetic ratio, a fundamental property of the nucleus. This precessing magnetic moment results in a circularly-polarized radio-frequency (RF) wave at the Larmor frequency. This is magnetic resonance signal.

On the other hand, when the net magnetization is in the direction of the applied field $B_0$, we say that the magnetic moment is at “thermal equilibrium”, and it cannot create an MR signal. It is only when the magnetization has a component in the plane orthogonal to the main field that precession results and an MR signal can be generated. The process to knock the magnetic moment out of alignment from the direction of the main magnetic field is called excitation. This process can be achieved by introducing external energy generated from a radio-frequency field at the Larmor frequency. We denote this applied RF field used for excitation of the MR signal as $B_1$. It is ideally circularly polarized in a plane orthogonal to the main magnetic field $B_0$. How far the magnetization is tipped into the transverse plane is called the flip angle $\alpha$. The relationship between $B_1(t)$ and flip angle can expressed as
\[ \alpha = \int_0^T \gamma B_1(t) dt, \] (2.3)
where $T$ is the duration of the excitation. The strength of the signal that can be detected is proportional to the component of magnetization in the transverse plane, so a 90-degree flip angle gives the maximum transverse component and typically the greatest signal.

### 2.1.3 Relaxation and the Bloch Equation

After each excitation, we typically turn off the radio frequency excitation field for a certain amount of time while we acquire the signal and before the next excitation. During this period, the spins gradually return to their lowest energy state aligned with the main polarizing field (thermal equilibrium position). This causes the MR signal to decay in a phenomenon called relaxation. There are two important relaxation mechanisms in MRI. The first type of relaxation is called longitudinal relaxation or spin-lattice relaxation. It describes how quickly the magnetization returns to the equilibrium position along the longitudinal axis (the direction of the main polarizing field).
The return to thermal equilibrium along the longitudinal axis is exponential in nature, with a time constant referred to as $T_1$. The longitudinal relaxation is described in Equation (2.4).

$$\frac{\partial M_z}{\partial t} = -(M_z - M_0)\frac{\hat{k}}{T_1},$$

(2.4)

where $M_z$ is the longitudinal magnetization and $M_0$ is the magnitude of the longitudinal magnetization vector in thermal equilibrium. This equation has a solution given by

$$M_z(t) = M_0 + (M_{z}^{\text{initial}} - M_0)e^{-t/T_1},$$

(2.5)

where $M_{z}^{\text{initial}}$ is the initial status of the longitudinal magnetization and $t$ is the time elapsed from the initial state.

The second relaxation mechanism is transverse relaxation or spin-spin relaxation. This relaxation describes the rate at which the transverse component of the magnetization vector (the component perpendicular to the main polarizing field) decays. This decay is also exponential in nature, and is characterized by a time constant called $T_2$. The transverse relaxation is described by the following equation:

$$\frac{\partial M_{xy}}{\partial t} = -\frac{M_{xy}}{T_2},$$

(2.6)

where the $M_{xy}$ is transverse magnetization. The equation has a solution:

$$M_{xy}(t) = M_{xy}^{\text{initial}}e^{-t/T_2},$$

(2.7)

where $M_{xy}^{\text{initial}}$ is the initial status of the transverse magnetization.

Finally, combining these two relaxation mechanisms with the behavior of the net magnetization vector when exposed to a strong external magnetic field, we arrive at the Bloch equation introduced by Felix Bloch:

$$\frac{\partial \mathbf{M}}{\partial t} = \mathbf{M} \times \gamma \mathbf{B} - \frac{M_z \mathbf{i} + M_y \mathbf{j}}{T_2} - \frac{(M_z - M_0)\mathbf{k}}{T_1}.$$ 

(2.8)
The Bloch equation can be rewritten in matrix form as

\[
\frac{\partial \vec{M}}{\partial t} = \begin{bmatrix}
-1/T_2 & \gamma B_0 & 0 \\
-\gamma B_0 & -1/T_2 & 0 \\
0 & 0 & -1/T_1
\end{bmatrix}\vec{M} + \begin{bmatrix} 0 \\ 0 \\ M_0/T_i \end{bmatrix}.
\] (2.9)

The MR signal arises from the projection of the magnetization vector in the transverse plane (by convention the x-y plane), and is denoted by \( M_{xy} \). \( M_{xy} \) can be expressed as a complex number

\[ M_{xy} = M_x + iM_y. \] (2.10)

The Bloch equation in transverse plane can be rewritten as:

\[
\frac{\partial M_{xy}}{\partial t} = \frac{\partial M_x}{\partial t} + \frac{\partial M_y}{\partial t} = -\left(\frac{1}{T_2} + i\omega_0\right)M_{xy},
\] (2.11)

which has a solution of the form:

\[ M_{xy}(t) = M_{xy}^{\text{initial}} e^{-t/T_2} e^{-i\omega_0 t}. \] (2.12)

### 2.2 MR Signal with Spatial Information

Although we can produce an MR signal via RF excitation, the signal we have produced comes from all the transverse magnetization within a volume and does not include any spatial information. In order to get spatial information, additional electromagnets are employed that create spatial linear gradients in the polarizing magnetic field. These are called gradient coils. Modern scanners are equipped with an x-gradient magnet (which produces a gradient in the polarizing field as a function of position in the x direction), as well as y- and z-gradients. When a gradient is applied to the imaged area, it generates a difference in the resonance frequency determined by the strength of the gradient and the relative spatial position. The general form of the gradient can be expressed as the time varying function:

\[ \vec{G}(t) = G_x(t)\hat{i} + G_y(t)\hat{j} + G_z(t)\hat{k}, \] (2.13)
where $G_x$, $G_y$ and $G_z$ are the corresponding gradient field magnitudes in each of the three directions. When the gradient is added to the main static polarizing field, the total magnetic field is:

$$B(r,t) = B_0 + G(t) \cdot r,$$

where $r$ is the spatial position of the subject. Since the extra gradient field is added, the equation for $M_{xy}$ changes to

$$\frac{\partial M_{xy}}{\partial t} = \frac{\partial M_x}{\partial t} + \frac{\partial M_y}{\partial t} = -\left(\frac{1}{T_2} + i\left(\omega_0 + \gamma G(t) \cdot r\right)\right)M_{xy}.$$

(2.15)

The solution of the signal from the transverse plane can then be expressed as:

$$M_{xy}(t) = M_{xy}^{initial} e^{-t/T_2} e^{-i\omega_0 t} \exp \left(-i\gamma \int_0^t G(\tau) \cdot r d\tau\right).$$

(2.16)

This equation illustrates the pivotal role the gradients play in affecting the MR signal. It is these gradient fields that allow us to achieve spatial localization of the signal in MRI.

### 2.2.1 Selective Excitation

In an MRI acquisition, most of the time we only want to image a specific region of the subject. In 2D imaging, that means we want to excite only those magnetic moments within a given slice. For 3D imaging, a larger slab covering the volume of interest is excited. This process is called selective excitation. To achieve selective excitation, typically a constant gradient is applied orthogonal to the slice or slab plane. From equations 2.2 and 2.14 we could find the additional gradient needed to enable a variation of Larmor frequency in the slice or slab direction. A pre-tuned RF pulse with a bandwidth that matches this Larmor frequency range is then applied simultaneously with this gradient, and we can achieve selective excitation as shown in Figure 2.2.

### 2.2.2 Spatial Encoding

After the desired area has been excited, we must now derive some additional spatial information from the excited area. Two additional gradients are applied to enable this task, known as
Figure 2.2: Excitation of a single slice or slab of spins across a volume is achieved through a process called selective excitation. Selective excitation combines a pre-tuned RF pulse with a spatial gradient, causing only spins within a given slice or slab to resonate at frequencies within the spectral band of the RF pulse.

“We phase-encoding gradient” and “readout gradients”. Normally for 2D imaging, the phase-encoding gradient is applied first. As previously mentioned, if a gradient is turned on, the Larmor frequency will vary. At this point, we assume the phase-encoding gradient is in the y direction and is represented as $G_y$, the Larmor frequency therefore depends on position in the y direction and is given by

$$\omega(y) = \gamma (B_0 + G_y(t) \cdot y)$$

and the solution form of equation 2.16 changes to

$$M_{xy}(t) = M_{xy}^{\text{initial}} e^{-t/T_2} e^{-i\omega_0 t} \exp\left( -i\gamma y \int_0^t G_y(\tau) d\tau \right).$$

Here, notice the y gradient gives the previous solution a phase shift term. After time $t$ the gradient is turned off, and spins at different y locations have accumulated different relative phases. Therefore in the y direction, the location of each spin can be distinguished by the phase. Similarly, if a gradient in the x direction is turned on, the spins in the x direction will experience different Larmor frequencies. By analyzing the frequency content of the signal, we can determine which portion of the signal arises from which x location. Combining the x and y gradients, the solution to the Bloch
equation becomes:

\[ M_{xy}(t) = M_{xy}^{\text{initial}} e^{-t/T_2} e^{-i\omega_0 t} \exp \left( -i\gamma \int_0^t G_y(\tau) d\tau \right) \exp \left( -i\gamma \int_0^t G_x(\tau) d\tau \right). \]  

(2.19)

This combination of phase encoding and frequency encoding, allows the spins within the excited plane to be distinguished as demonstrated in Figure 2.3.

Figure 2.3: Illustration of “phase encoding” and “frequency encoding”, the techniques used to achieve spatial localization in MRI. (a). After excitation all the spin precess at the same frequency (the Larmor frequency), regardless of their spatial location. (b). A “phase encoding” gradient is applied for a certain period of time before the signal is sampled, resulting in different phase accumulation at different spatial locations. (c). the frequency encoding gradient is applied while the signal is sampled, causing spins at different spatial positions to precess at different frequencies during signal sampling. Repeated application of these two types of encoding, with repeated sampling of the signal, allows us to ultimately completely localize spins across the imaged volume.

2.2.3 Signal Equation and k-Space

From the previous section, we arrived at an equation for the magnetization after phase and frequency encoding. The MR signal is then the accumulation of the magnetization:

\[ s(t) = \int_x \int_y M_{xy}^{\text{initial}} e^{-i2\pi[k_x(t)x + k_y(t)y]} dx dy, \]  

(2.20)
where the $e^{-i\omega t}$ factor has been dropped and the relaxation effects ignored. We define

$$k_x(t) = \frac{\gamma}{2\pi} \int_0^t G_x(\tau)d\tau \quad \text{and} \quad k_y(t) = \frac{\gamma}{2\pi} \int_0^t G_y(\tau)d\tau. \tag{2.21}$$

This equation for the signal at time $t$ can be understood as the 2D Fourier transform of $M(x,y)$ at a certain spatial frequency where the spatial frequency has been determined by the time integrals of the applied gradient waveform. This 2D Fourier transform space is called k-space.

2.3 MR Image Formation

In the previous section, we described the gradient encoding scheme used in MRI and the signal equation of MR. By applying an additional gradient, we can collect the signal with spatial information. In this section, we will discuss how an MR image is formed from the MR signal.

2.3.1 k-Space Trajectory and Pulse Sequence

From equation 2.20 we can find that the method we use to traverse k-space can be manipulated by altering the gradient waveforms in equation 2.21. In other words, turning our gradients on allows us to “drive” through k-space. If we turn on the x-gradient, we begin moving through k-space in the $k_x$ direction. The larger the gradient amplitude, the faster we move through k-space. We use the y- and z-gradients to move through k-space in the $k_y$ and $k_z$ directions. As we navigate through k-space, we sample data until we have critically sampled the full section of k-space that we need to fill. The path we follow to cover k-space is called the “k-space trajectory”. A common trajectory to cover k-space is a line-by-line scan on a Cartesian grid. This k-space trajectory yields data that is easy to reconstruct directly via an FFT algorithm. However, we can also use more complicated k-space trajectories, such as a radial trajectory, where we acquire data in k-space along spokes leading out from the center of k-space. This is a so-called “non-Cartesian” trajectory, since the k-space data that is acquired does not fall neatly onto a Cartesian grid. The reconstruction for non-Cartesian acquisitions is not as straightforward, and requires a process called “gridding”. Some of the work presented in this dissertation makes use of radial k-space trajectories. There are several benefits from using radial trajectories to acquire MR data, including short acquisition time,
less sensitivity to motion, and incoherent aliasing in the event that the Nyquist criterion is not met when acquiring the k-space data. This is demonstrated later in the image reconstruction section.

A pulse sequence diagram in MRI is the standard tool to represent the steps used to acquire data. By analyzing a pulse sequence diagram, we can determine the timing of several events, such as RF excitation and acquisition, as well as the k-space trajectory. A two-dimensional gradient echo (GRE) sequence will be described here as an example of using both Cartesian and radial trajectories (Figure 2.4). This sequence is then used in the subsequent sections.

In this figure, we can further understand the k-space trajectory by looking at the gradients. First, we can observe the slice excitation in section 1 from both Cartesian and radial acquisitions. In section 2 we move out in k-space to where we want to begin sampling. In a Cartesian acquisition, a positive phase encode gradient $G_y$ and negative frequency encode gradient $G_x$ are turned on to allow the corresponding section 2 movement in k-space. In the radial acquisition, both negative $G_y$ and $G_x$ gradients were employed to achieve the corresponding movement in k-space. Section 3 is where the signal is acquired; sample points are indicated as red dots.

### 2.3.2 MR Image Parameters

In MRI acquisitions, several common parameters are often reported and are briefly explained here. The repetition time (TR) is a parameter defined as the time between adjacent RF excitations. A short TR clearly allows shorter scan times for the acquisition of a fixed set of points in k-space, but does not allow the magnetization to return to thermal equilibrium before subsequent excitations. A second useful parameter is the “echo time”, or TE. The echo time is defined as the time between the excitation and the time during signal sampling when the k-space trajectory is closest to the center of k-space.

In practice, we use discrete sample points instead of continuous time signals. The matrix of sample points defines our base resolution. The sampling periods in k-space are $\Delta k_x$ and $\Delta k_y$, which is the distance between two red dots in Figure 2.4 (b). After the Fourier transform, the discrete sampling will lead to the periodic replication of data in the transformed domain, which is the image domain. The replication will be at intervals of $1/\Delta k_x$ and $1/\Delta k_y$, which is referred to as the field of view (FOV) for the image acquisition. The closer together the samples are in k-space, the greater
the FOV. The farther out in k-space we sample in a given direction, the higher the resolution in that direction.

Figure 2.4: Example of pulse sequence diagrams and their corresponding k-space trajectories.
2.4 MR Image Reconstruction

As mentioned in Sec. 2.2.3, MRI data is acquired in k-space. The reconstruction of the image is transforming the k-space data into the image domain. For traditional Cartesian sampling, all the sampled points are perfectly located on a Cartesian grid, and the image can be reconstructed directly by applying an inverse Fourier transform. In this dissertation, besides the traditional Cartesian acquisition, we also use non-Cartesian acquisition schemes such as the radial trajectory implemented for 2D myocardial perfusion studies.

2.4.1 Non-Cartesian Image Reconstruction

Unlike the traditional Cartesian sampling trajectory, k-space can also be traversed with a non-Cartesian trajectory. Although there are benefits to acquiring data with a non-Cartesian trajectory, the reconstruction process is not as straightforward as the Cartesian trajectory. The sampling points are generally not located on a Cartesian grid, so a direct inverse Fourier transform is no longer possible. One common method to reconstruct such images is to resample the non-Cartesian data to a Cartesian grid, and then apply the inverse Fourier transform. This process is called gridding reconstruction. Gridding reconstruction has been extensively studied. Currently, the most common method for gridding reconstruction is a convolution-based method because it is computationally efficient and has adequate image quality [37]. The ideal case for the convolution-based gridding reconstruction can be understood in the following way. If we meet the Nyquist sampling criterion in k-space, then the object imaged will have finite extent in the image domain and any aliasing will be outside the object that was imaged. To reconstruct the image, we need to multiply the object in the image domain by a rectangular function, which is the same as a convolution of the k-space data with a sinc function. Following convolution in k-space, the resampled data is then onto a Cartesian grid. These steps can be represented in k-space and image space respectively using the following equations:

\[
\hat{M}(k_x, k_y) = \left[ M(k_x, k_y)S(k_x, k_y) \right] * C(k_x, k_y) \times \text{III}\left( \frac{k_x}{\Delta k_x}, \frac{k_y}{\Delta k_y} \right)
\] (2.22)
and:

\[
\hat{m}(x, y) = \left[ (m(x, y) * s(x, y)) * c(x, y) \right] * \text{III}\left( \frac{x}{\text{FOV}_x}, \frac{y}{\text{FOV}_y} \right),
\]

(2.23)

where \( M(k_x, k_y)S(k_x, k_y) \) is the data sampled on a non-Cartesian grid, \( C(k_x, k_y) \) is the gridding kernel and \( \text{III}\left( \frac{k_x}{\Delta k_x}, \frac{k_y}{\Delta k_y} \right) \) is the Cartesian sampling function. Ideally, the convolution kernel should be a sinc function, but due to the infinite length of the sinc function, the computational time is too long making a true sinc as the convolutional kernel impractical. A variety of substitute gridding kernels can be used, but the Kaiser-Bessel function provides nearly optimal results and thus is one of the most common gridding kernels [37].

In addition to the gridding considerations, a non-Cartesian acquisition, such as a radial trajectory, generally has non-uniform data sampling; the center of k-space is sampled more densely than other areas. Density compensation is needed before gridding can be properly performed and is normally calculated by weighting each position in k-space. Equation 2.22 is therefore changed to:

\[
\hat{M}(k_x, k_y) = \left[ (M(k_x, k_y)S(k_x, k_y)) * C(k_x, k_y) \right] * \text{III}\left( \frac{k_x}{\Delta k_x}, \frac{k_y}{\Delta k_y} \right),
\]

(2.24)

with \( d(k_x, k_y) \) being the density compensation function. In particular, for a radial trajectory, we often use the Ram-Lak filter to compensate.

### 2.4.2 Parallel Imaging

Parallel imaging, a reliable MR acceleration method introduced in the late 1990s, uses the spatially sensitive information inherent in an array of RF receive coils to provide spatial information that normally requires spatial encoding performed by gradients. Using the sensitivity information from RF coils allows us to skip some of the phase encoding lines and recover that information later. This allows for accelerated MR acquisition. A variety of techniques for parallel imaging were developed over the past 20 years, and can be separated into two categories: image domain techniques and k-space domain techniques. Two popular examples of parallel imaging techniques are sensitivity encoding (SENSE) [22] in the image domain and generalized autocalibrating partially parallel acquisitions (GRAPPA) [23] in the k-space domain. The concept of a SENSE reconstruction can be understood as follows. First the MR images from multiple receive
coils can be expressed as:

\[ I_n(x,y) = C_n(x,y)S(x,y), \]  

where \( n \) is the number of receive coil index, \( C \) is the coil sensitivity, \( S \) is the real signal, and \( I \) is the image from each individual location of the image object. For simplicity, we use acceleration factor = 2 in this example, which means k-space will be acquired with one line gap, reducing the acquisition time by a factor of two. This undersampling pattern is shown in Figure 2.5 (c). From the Nyquist sampling theorem, aliasing will be observed when the sample rate does not meet \( 1/\text{FOV} \). The result can be expressed as:

\[ I_n(x,y) = C_n(x,y + \frac{\text{FOV}}{2})S(x,y + \frac{\text{FOV}}{2}). \]

Putting this into matrix formation, we have:

\[
\begin{bmatrix}
  I_1(x,y) \\
  I_2(x,y)
\end{bmatrix}
= \begin{bmatrix}
  C_1(x,y) & C_1(x,y + \frac{\text{FOV}}{2}) \\
  C_2(x,y) & C_2(x,y + \frac{\text{FOV}}{2})
\end{bmatrix}
\begin{bmatrix}
  S_1(x,y) \\
  S_2(x,y + \frac{\text{FOV}}{2})
\end{bmatrix}
\]

and rewriting the equation in a simple form:

\[ I = CS. \]

If the number of coils is equal to or larger than the acceleration factor, the solution of the equation can be achieved by computing the Moore-Penrose pseudoinverse:

\[
\hat{S} = [(C^H \psi^{-1} C)^{-1} C^H \psi^{-1}] I,
\]

where \( \psi \) is the \( n \times n \) size coil noise correlation matrix used to describe the correlation of noise between different receive coils. Normally, we assume the noise correlation matrix is identity and the equation simplifies to:

\[
\hat{S} = [(C^H C)^{-1} C^H] I.
\]
In practice, parallel MRI reconstruction methods can be combined with non-Cartesian sampling. Since there is a unique aliasing pattern from Cartesian acquisitions, an iterative reconstruction method is often employed which will be covered in a later section. Other parallel imaging algorithms, such as GRAPPA, are not utilized in this dissertation. Details can be found in other papers [21,23].

Figure 2.5: Illustration of the SENSE reconstruction. (a) is the ideal image, and (b) is the corresponding k-space. (c) is the undersample pattern, the white line is the position collected, and the black line is the area which is missing and the acceleration is R = 2. The direct inverse Fourier transform result from undersampled k-space is demonstrated in (d). Notice that half of the FOV is aliased. The overlapped signal is indicated with the green dot in (d). It is the combination resulting from two different coils, demonstrated in images (e-h). Images (e-h) are the signal intensity and corresponding coil sensitivity.

2.4.3 Simultaneous Multi-Band Excitation

In the previous section, parallel imaging was described. The main idea of parallel imaging is to utilize coil sensitivity information to compensate for missing spatial information. Based on this idea, another acquisition technique (named Controlled Aliasing in Parallel Imaging Results
in Higher Acceleration or CAIPIRINHA) [38] was proposed to accelerate the acquisition speed in the slice direction by exciting multiple slices simultaneously and reconstructed via parallel imaging methods.

Referring back to Figure 2.2, we use the selective gradient with a pre-tuned RF pulse to enable a slice selective excitation. If we employ an RF pulse with two or more different frequency bands with the same gradient, we can excite two or more slices at the same time. However, with this technique, multiple slices are excited and acquired simultaneously, which means each k-space line contains the information coming from more than one slice. The resulting image is a combination of images from different slices that are overlapped and are difficult to separate. If two slices are excited simultaneously, for example, as seen in Figure 2.5, and the resulting images overlap each other which can be understood via Eq. 2.26. In a multi-slice case, that equation could be rewritten as:

\[
\begin{bmatrix}
I_1(x,y) \\
I_2(x,y)
\end{bmatrix}
= \begin{bmatrix}
C_1 - S_1(x,y) & C_1 - S_2(x,y) \\
C_2 - S_1(x,y) & C_2 - S_2(x,y)
\end{bmatrix}
\begin{bmatrix}
S_1(x,y) \\
S_2(x,y)
\end{bmatrix}.
\] (2.31)

In this new equation, \(S_1\) and \(S_2\) are the signals from two different slices. The \(C_1 - S_1\) means the coil sensitivity of coil number 1 at the first slice. The problem with attempting to solve this equation is the coil sensitivity exhibits a small amount of variation along the slice direction, which means \(C_1 - S_1\) and \(C_1 - S_2\) are almost the same. Then the equation turns into an underdetermined problem that has an infinite number of solutions. To overcome the similar sensitivities for each slice in Eq. 2.31, CAIPIRINHA alters the phase of the second RF pulse, which generates a phase shift in the k-space domain. Based on a property of the Fourier transform, this phase shift in the k-space domain leads to a spatial shift in the image domain. If there is a 90-degree phase shift in k-space, this shifts the corresponding image half a FOV in the image domain, as shown in the top column of Figure 2.6. This shift in the image domain enables a SENSE type reconstruction to be much more effective. This result can be expressed by combining Eq. 2.27 and Eq. 2.31 as:

\[
\begin{bmatrix}
I_1(x,y) \\
I_2(x,y)
\end{bmatrix}
= \begin{bmatrix}
C_1 - S_1(x,y) & C_1 - S_2(x,y + \frac{\text{FOV}}{2}) \\
C_2 - S_1(x,y) & C_2 - S_2(x,y + \frac{\text{FOV}}{2})
\end{bmatrix}
\begin{bmatrix}
S_1(x,y + \frac{\text{FOV}}{2}) \\
S_2(x,y + \frac{\text{FOV}}{2})
\end{bmatrix}.
\] (2.32)
In practice, CAIPIRINHA is a very important technique for dynamic contrast enhanced imaging, since CAIPIRINHA allows more slice coverage without losing temporal resolution. Similar to parallel imaging, CAIPIRINHA can also be combined with non-Cartesian sampling schemes.

A radial CAIPIRINHA acquisition pattern is shown at the bottom row of Figure 2.6. Unlike Cartesian sampling, the slice with phase alternative RF pulse looks like noise since the center of k-space has been canceled by the phase alternation [39]. The recovery of the second slice can be achieved by multiplying by the conjugate phase modulations. Then an iterative reconstruction method can be employed to recover the images, which will be covered in Chapter 5.

![CAIPIRINHA Acquisition Pattern](image)

Figure 2.6: An illustration of CAIPIRINHA acquisition where two slices were acquired simultaneously, one without phase alternation, and another with phase modulation, which causes a FOV shift in Cartesian case. The radial acquisition with phase modulation generates noise-like images.

### 2.4.4 Compressed Sensing in MRI

Although tremendous effort has been devoted to the acceleration of MRI acquisition over the past two decades, most of the work proposed was still based on satisfying the Nyquist sampling
criteria until the arrival of Compressed Sensing (CS). The basis of Compressed Sensing is that a sparse or compressible signal can be successfully reconstructed with fewer measurements than the Nyquist sampling rate. In order to successfully implement the framework of CS, three requirements need to be met. First, the signal that needs to be reconstructed must be sparse in a certain domain. Second, there must be incoherent aliasing artifacts (like noise) in the sparse domain due to undersampling. Third, a nonlinear reconstruction must be used [26, 27].

The first requirement for implementing CS is the sparsity of the signal, meaning that the signal can be represented with only a few significant or non-zero values within a certain transformed domain. In other words, the signal that needs to be reconstructed can be compressed in a certain domain. The Fourier transform, wavelet transform, and curvelet transform are all examples of sparsifying transforms. All of these transforms can represent certain images with only a few large coefficients. Sparsity is not only achievable in the spatial domain, but also in the temporal domain since there is a high correlation from frame to frame that makes a series of images also compressible. In time series of MR images, the total variation (TV) domain is often used as the sparse domain.

The second requirement of CS is incoherent aliasing in the sparse domain, which is normally a result of the sampling pattern. As we mentioned in the section on parallel imaging, uniform undersampling makes the aliasing coherent in certain domains as shown in Figure 2.7(a). Some examples of how to generate incoherent aliasing include, but are not limited to, random undersampling on a Cartesian grid as demonstrated in Figure 2.7 (b), and non-Cartesian sampling such as a radial trajectory as shown in Figure 2.7 (c). Incoherent aliasing can also be achieved in the temporal direction for dynamic imaging by varying the sample pattern from frame to frame. Finally, we need a non-linear reconstruction method to recover the highly undersampled signal. A common method is to optimize an objective function with a constraint that the reconstructed signal be sparse in a certain domain as well as maintain consistency with the collected data. This process can be represented by the following equation:

\[
\text{minimize} \| \psi x \|_0 \quad \text{subject to} \quad \| \Phi x - d \|_2.
\] (2.33)
In this equation, the $\psi$ is the sparse transform, $\Phi$ is the undersampling pattern, and $d$ is the under-sampled data. The $L_0$ norm is defined as the number of non-zero values, which is hard to achieve in the optimization process. The $L_1$ norm was employed instead, which is the summation of the absolute values of all numbers and the equation becomes

$$\argmin_x \| \Phi x - d \|_2^2 + \lambda \| \psi x \|_1,$$

(2.34)

where $\lambda$ is the weight of the sparsity term that can be tuned to achieve the best perceptual image quality.

Although there are a variety of sparsifying transforms available under the compressed sensing framework, we use the finite differences or total variation as the sparsifying transform throughout most of this dissertation [32]. Total variation was used to measure how much the signal magnitude changes between adjacent signal locations, which could be adjacent pixels in an image, for example. Total variation can be applied in the spatial domain and, perhaps more importantly, in the temporal direction. In our application we focus on dynamic imaging which acquires a series of

Figure 2.7: Illustration of the aliasing pattern from different undersample pattern.
images of an object at different time points. High correlation exists in the temporal direction, so the gradient in the temporal direction is sparse. For an $N$ point signal $x(n)$, total variation can be represented as

$$TV(x) = \sum_{2}^{N} |x(n) - x(n - 1)|.$$  \hfill (2.35)

In order make the TV term differentiable for every $x$, a small positive value $a$ is added to make Equation 2.35 turn into

$$TV(x) = \sum_{2}^{N} \sqrt{x(n)^2 - x(n - 1)^2 + a^2}.$$  \hfill (2.36)

In addition, an advantage of total variation is computational simplicity, which is important for large size data sets. It also has the capability to preserve edges. Further details of how TV are used during image reconstruction is discussed in the subsequent chapters of this dissertation, since its application differs depending on how the data was acquired.
CHAPTER 3. COMPARISON OF CENTRIC AND REVERSE-CENTRIC TRAJECTORIES FOR HIGHLY ACCELERATED 3D SATURATION RECOVERY CARDIAC PERFUSION IMAGING

3.1 Introduction

First-pass myocardial perfusion imaging provides a powerful and noninvasive method for characterizing ischemic heart disease [40,41]. Much of the work in first-pass myocardial perfusion imaging has been conducted with 2D perfusion techniques [41–47]. However, a 3D myocardial perfusion acquisition may be desirable for clinical perfusion studies in order to get more complete coverage of the heart. The 3D perfusion acquisition can potentially provide a more accurate estimation of the size of ischemic zones [40] since it is intrinsically better registered between slices, and trades inter-frame out-of-plane motion problems that can impact 2D imaging for potentially easier out-of-slab motion problems. However, 3D perfusion imaging requires more phase encodes and hence a much longer readout than the 2D case. Because of this longer acquisition time, intra-frame cardiac and respiratory motion will affect image quality more than the 2D case. A highly accelerated acquisition scheme is thus essential for 3D cardiac perfusion to achieve sufficient spatial and temporal resolution. Recent advances in compressed sensing, parallel imaging, and related reconstruction techniques are beginning to enable such rapid acquisitions in 3D cardiac perfusion studies [40,48,49], although spatial and temporal resolutions are not as high as 2D.

A saturation-recovery sequence is often used in first-pass myocardial perfusion imaging to enhance T1 contrast [50]. However, with a saturation recovery sequence, the magnetization is often not in steady state when the central portion of k-space is acquired [51–53]. Variations in the transient signal level over the course of image acquisition can have a large impact on image contrast.

Kim analyzed this effect in the 2D case [54]. He demonstrated that, in a fully-sampled 2D Cartesian acquisition, the T1-weighting due to the saturation recovery pulse is affected sig-
nificantly by the choice of phase encode ordering in k-space. The dynamic T1-weighted signal can be modified by simply varying the k-space trajectory, without changing other parameters like saturation recovery time (SRT) and contrast dosage.

Furthermore, cardiac perfusion imaging often employs a very short TR, necessitating very short RF pulses [50,55]. This can result in a less than ideal slab selective excitation profile, causing significant deviations from the nominal prescribed flip angle from slice to slice. These variations in flip angle have a significant impact on the signal evolution during the transient, potentially causing considerable cross-slice variations in contrast when a centric phase encode ordering scheme is used [56].

In this work, we explore the effects of k-space trajectory and phase encode ordering using a highly-accelerated 3D acquisition scheme (acceleration factor R = 11). In this case, the magnetization may be far from steady state during many of the signal measurements [51–53]. As a consequence, the k-space trajectory and phase encode ordering employed can be critical factors in determining image contrast for 3D myocardial perfusion imaging [56]. We analyze and compare the contrast resulting from a centric phase encode ordering versus a reverse-centric phase encode ordering in highly accelerated 3D saturation recovery myocardial perfusion imaging. The effect of deviations from the nominal flip angle on signal levels and contrast for each trajectory (centric versus reverse-centric) is also analyzed. We demonstrate that the contrast achievable with the centric trajectory can be preferable if variations in the flip angle from slice to slice are small. However, the reverse-centric trajectory yields more consistent contrast when significant variations in flip angle are present across the slab profile. It is also possible to choose a flip angle to make the magnetization be in or near steady-state even with a centric trajectory [57]. This flip angle is relatively weakly dependent on T1 [58].

3.2 Methods

3.2.1 Pulse Sequence

We modified a 3D saturation-recovery TurboFLASH pulse sequence to acquire data at an acceleration factor of R = 11 using the polynomial variable density phase encode mask shown in Figure 3.1 [26, 59]. The sampling pattern has more density in the center and less so towards the
outside. The probability density function (PDF) for the variable density mask is given by:

\[
PDF(m,n) = \left(1 - \frac{1}{2^p} (m \times \Delta k_y)^2 + (m \times \Delta k_y)^2\right)^p
\]

and

\[
m = \frac{-M}{2} : \frac{M}{2} - 1 \quad \text{and} \quad n = \frac{-N}{2} : \frac{N}{2} - 1,
\]

where \(M\) and \(N\) are the number of samples in the phase encode directions, \(\Delta k_y = 2/\text{sample points}\) in the \(y\)-direction, \(\Delta k_z = 2/\text{samples points}\) in the \(z\)-direction, and \(p\) is the polynomial number to control the sampling density in the center (in this case, \(p\) was set to 6). A different variable density mask for each time frame was generated based on random sampling of the PDF.

Figure 3.1: Variable-density random sampling scheme employed for dynamic 3D acquisitions. (Left) PDF of the variable sampling density in \(k_y-k_z\) space. High sampling densities are used in the center of \(k\)-space, and the sampling density then drops off with increased distance from the center. (Middle) Example of a sampling mask for a single time frame. In this plot, the white points are the phase encodes actually acquired in the \(k_y-k_z\) plane, and the black areas are the points, which were not collected. The mask has a higher sampling density in the center of \(k\)-space and lower sampling density far from the center. (Right) Dynamic 3D sampling in the \(k_y-k_z\) plane and the temporal direction. 55 temporal frames are shown here, since the centric and reverse-centric trajectories share the same undersampling pattern (but with a reversed phase encode order).

The sequence was implemented on a 3T Siemens whole-body scanner (Siemens Medical Systems, Erlangen, Germany). The raw acquisition matrix was 144 (readout) x 108 (phase en-
code) x 10 (phase encode slice direction, including 25% oversampling). An asymmetric echo was employed in the readout direction (83%), and no partial Fourier acquisition was used in the phase encode and slice directions. A 600 µs duration slab-selective RF pulse was used for excitation and a non-selective saturation recovery pulse was employed triggered by the ECG pulse. One oversampled slice at each edge was discarded resulting in an acquisition matrix of 144 x 108 x 8 across a region with readout FOV 300-350 mm, phase FOV 225-263 mm, and slab thickness of 40-60 mm. This yields a voxel size of 2-2.4 mm in the readout and phase directions, and 4-6 mm in the slice direction. No start-up pulses were used to drive the magnetization closer to steady state prior to signal acquisition. The acceleration factor \( R = 11 \) resulted in 98 phase encodes per temporal frame. The fast RF pulse allowed a TR/TE of 2.6/1.1 ms. Other parameters employed were: saturation recovery time SRT = 150 ms, bandwidth = 1389 Hz/pixel, and nominal flip angle = 12 degrees. A total of 110 temporal frames (more than necessary to track the contrast uptake) were acquired in all of the studies.

A basic diagram illustrating the pulse sequence is shown in Figure 3.2. The sequence was programmed to interleave centric and reverse-centric phase encode orderings every other temporal frame, with both centric and reverse-centric orderings using the same phase encode mask for each temporal frame (as illustrated in Figure 3.3). This approach was adopted in order to most directly compare contrast and signal between the two trajectories [54]. The total of 110 temporal frames acquired in the studies yielded 55 temporal frames for each trajectory.

### 3.2.2 Image Reconstruction

The same image reconstruction algorithm was used for both simulated and actual data. The interleaved data set (with 110 time frames) was separated into centric and reverse-centric datasets, each consisting of 55 time frames. Each under-sampled dataset was then reconstructed by minimization of the cost function in equation (2.2) below. The procedure employed spatiotemporal constraints [60] with 4 dimensional TV (3 spatial dimensions and the temporal dimension) as the constraints:

\[
C(m) = \| F_d m - y \|_2^2 + \lambda_1 \| \nabla_t m \|_1 + \lambda_2 \| \nabla_s m \|_1,
\]

(3.2)
**Figure 3.2:** Illustration of the acquisition scheme for the comparison between the centric and reverse-centric trajectories. The trajectories were hard coded to alternate at each heartbeat. The lower part of the figure illustrates a small section near the center of k-space to clarify the ordering of the k-space trajectories. The number in each sample (circle) shows the order of the phase encodes, and is based on the distance from the k-space center. Note the figure is approximately to scale ($\Delta k_y = 0.003 \text{ mm}^{-1} - 0.0035 \text{ mm}^{-1}$, $\Delta k_z = 0.017 \text{ mm}^{-1} - 0.025 \text{ mm}^{-1}$, with small variations due to the size of subjects). The slice direction k-space sampling is much larger than the phase direction.

where $\|F_um - y\|_2^2$ is the data consistency term, $F_um$ is the undersampled Fourier operator, $y$ is the acquired undersampled k-space data, and $m$ is the reconstruction image. The second term $\lambda_1\|\nabla_t m\|_1$ is the temporal TV constraint term, where $\nabla_t$ is the TV operator in the temporal direction and $\lambda_1$ is the weight factor for the temporal TV term which equals 0.003 multiplied by the maximum value of the image set. The third term $\lambda_2\|\nabla_s m\|_1$ is the spatial TV constraint term. The $\nabla_s$ is the TV operator contains 3 spatial dimensions. $\lambda_2$ is the weight factor for the spatial TV term set to 0.0003 multiplied by the maximum value of the image set. $\lambda_1$ and $\lambda_2$ were determined by a simulation which employed the reconstruction offline on the undersampled data and compared it with the fully sampled data, collected from a resolution phantom, to achieve the minimum error. These weightings were increased for in vivo data sets to achieve better perceptual results due to
motion. The temporal weight factor was chosen to be 10 times higher than the spatial TV weight factor.

All images were reconstructed off-line using MATLAB (Mathworks, Natick, MA) on a 16-core Linux workstation with 64 GB of RAM. Reconstruction time for a dataset consisting of 55 time frames from one coil was approximately one hour. These reconstruction times could be vastly accelerated by an optimized implementation on dedicated hardware.

### 3.2.3 Numerical Phantom Simulations

We performed a numerical phantom simulation of the sequence to estimate the signal levels across a range of T1 values, with SRT and T2* fixed. The effect of flip angle variations across the slab profile on signal level and contrast was also estimated. Image artifact and blurring for each trajectory from transient variations in the signal were assessed. The simulation calculated the expected signal levels for the region of interest (ROI) at each excitation/readout during the approach to steady state based on equation (3.3) below [53, 61]. These signal levels were then applied as weightings to the k-space data that would be sampled during the corresponding readouts [60].

\[
M_{xy}(n) = M \left(1 - e^{TD/T1}\right) \alpha^n + M \frac{1 - e^{-TR/T1}}{(1 - \alpha^n)}, \tag{3.3}
\]
where

\[ M = M_0 \sin(FA) e^{-TE/T_2^*}, \quad \text{and} \quad \alpha = \cos(FA) e^{-TR/T_1} \]

and \( n \) is the \( n \)th excitation/phase encode.

Figure 3.4: Illustration of the simulation scheme for a single time frame. We first generate a vial-shaped numerical phantom and assume that each slice receives a different flip angle based on its position. We then weight the signal intensity of each slice to account for both flip angle and calculated signal level. Then, following the undersampled k-space trajectory, we acquire one 3D readout line for each RF pulse. We repeat this process 98 times to simulate the acquisition for one time frame. The figure shown here portrays the centric ordering; we also simulated the reverse-centric ordering in the same way, but with reversed acquisition order.

The simulation process is illustrated in Figure 3.4. The k-space data was derived from a simple 3D numerical phantom with fixed T1 times. The numerical phantom simulation mirrored the \( R = 11 \) acceleration of our actual sequence, and uses the same undersampling mask and phase encode order. To validate the accuracy of our numerical phantom simulation, we performed experiments on phantoms (as described in Phantom Experiments below) and compared them to the results predicted from our numerical simulation. We also applied the simulation to a range of flip
angles from 0 to 20 degrees to study how the two different trajectories affect the signal intensity and contrast at each flip angle.

### 3.2.4 Phantom Experiments

To validate the accuracy of our numerical phantom simulation described above, we acquired phantom data and compared the results to those predicted by the numerical simulation. We imaged two uniform phantoms with measured T1 values of \( \sim 300 \) ms and \( \sim 1000 \) ms. The phantom with T1 of \( \sim 300 \) ms mimics the expected peak signal intensity in myocardial tissue during a perfusion study [54, 62, 63], and that with T1 of \( \sim 1000 \) ms mimics the expected signal intensity in unenhanced myocardium.

We measured the flip angle variations across the slab profile by first measuring the flip angle of the center slice using the dual-angle B1 mapping method [64]. A birdcage coil with excellent field uniformity was employed. The flip angle in the center slice was measured to be 12 degrees by the dual angle method. The flip angles at the other (non-center) slices were then determined using the signal equation and the signal intensities of each slice. We expect this technique to yield a more accurate estimate of flip angle than applying the dual angle method to slices where the flip angle is small (the edge slices). Both phantoms were oriented such that the slice direction was along the long axis of each phantom, which coincided with the main field direction. In cardiac perfusion studies, the relatively homogeneous body RF coil is used for excitation, and thus we expect the flip angle variation to mainly be affected by the frequency characteristics of the RF pulse. For a homogeneous transmit coil, we also expect the slab profile to rotate with variations in the acquisition axis, and expect the variations within a slice to be small, since the slab excitation profile induces variations in flip angle predominantly in the slice direction. We then applied the flip angles measured across the slab profile and the measured T1 values of each vial to the numerical phantom simulation, allowing us to compare the measured contrast versus the contrast predicted by the numerical simulation in both the centric and reverse centric cases. Specifically, the signal levels from this phantom experiment were compared to the signal levels predicted by the numerical simulation at the flip angle measured for each slice, as a verification of the accuracy of our simulation.
3.2.5 In Vivo Experiments

The sequence was tested in 4 male volunteers (age = 52, 56, 64 and 66) with approval from the University of Utah institutional review board (IRB) and informed consent from each subject. Imaging was also performed in two canines under an approved IACUC protocol. The highly-accelerated 3D pulse sequence previously described was employed, and 110 temporal frames (55 centric, 55 reverse centric, interleaved as previously described) were acquired after gadolinium injection. Orientation was chosen to yield a short-axis stack of slices. Subjects were instructed to hold their breath as long as possible during the acquisition. Image reconstruction was performed using the spatiotemporal constrained reconstruction (Equation.3.2). Enhancement curves were generated for manually drawn ROIs in the myocardium in each slice.

3.3 Results

3.3.1 Validation of Numerical Simulation Using Phantom Experiments

The normalized signal-to-noise ratio (SNR) versus slice number for both vial phantoms (T1 = ~300 ms and T1 = ~1000 ms) is shown in Figure 3.5. Also shown in the same figure are the normalized SNR values predicted in each slice by the numerical phantom simulation. System noise was measured separately with the same phantom loading and the measured noise level was then applied in our simulations.

The simulation results agree with the measured results. A flatter profile across the slab is predicted by simulation and observed in the phantom experiments when using the reverse-centric trajectory. The centric trajectory, on the other hand, yields better contrast towards the center of the slab where the nominal flip angle is actually achieved, but suffers from large variations in normalized SNR and contrast towards the edges of the slab where the flip angle decreases.

Recall that the simulation SNR were calculated based on the flip angles actually measured at each slice across the slab profile. These measured flip angle values for each slice were (2.5, 4.6, 7.7, 10.4, 11.8, 12, 10.8, 8.4, 5.2, and 2.7 degrees) (Figure 3.5). The 2.5 and 2.7 degree edge slices correspond to the two oversampled slices.
3.3.2 Simulation Results

Figure 3.6 shows the simulated signal levels across this range of flip angles for tissues with $T_1 = 1000 \text{ ms}$ and $T_1 = 300 \text{ ms}$. In this simulation, we assume that an ideal RF pulse was applied so that there is no flip angle variation across the slices. From Figure 3.6, we observe that the signal intensity and CNR for the centric ordering appears to give increasing contrast as the flip angle is increased, which could also be explained from equation (3.3). However, when we increase the flip angle over 25 degrees it is also important to note that the image artifact from the centric trajectory is expected to become more severe due to larger transient signal variations. This is illustrated in
Figure 3.7, where the variations in image quality are shown across a range of flip angles from 0 to 60 degrees for both the centric and reverse centric trajectories for an object with T1 of 300 ms. It is evident from Figures 3.6 and 3.7 that the centric trajectory results in larger variations in contrast as the flip angle is varied, whereas the reverse-centric trajectory yields more consistent contrast across, for example, a flip angle range from 5-20 degrees.

Figure 3.6: Signal variations with each trajectory as a function of flip angle. Signal intensities for tissue with T1 = 300 ms and T1 = 1000 ms are shown on the left for both trajectories. On the right, CNR between the two tissues is shown as a function of flip angle for each trajectory.

3.3.3 In Vivo Experiments

Figure 3.8 shows representative 3D perfusion images from one of the human subjects. The average signal intensities for each time frame are shown from manually segmented ROIs in the myocardial wall region for each slice. As expected from the simulation and phantom results, the reverse-centric trajectory yields higher signal intensity than the centric acquisition at the edge slices where the flip angle is attenuated, while the centric trajectory shows higher signal intensity in the
Figure 3.7: Simulation of the transient artifacts of the centric and reverse-centric trajectories for a tissue with T1 = 300 ms across a range of flip angles. As can be seen, the centric trajectory shows severe transient artifacts as the flip angle is increased, even though it yields much higher signal intensity at higher flip angles than the reverse-centric trajectory.

center slices. It is also evident that the reverse-centric trajectory exhibits less variation across slices than the centric trajectory. These results agree with the simulation and phantom experiments.

Figure 3.9 shows 3D perfusion results from another subject; in this figure, RV enhancement, LV enhancement, and myocardial enhancement are shown for both centric and reverse-centric trajectories.
Figure 3.8: Comparison of in vivo results for centric and reverse-centric trajectories. The images shown are the peak contrast enhanced frame. The time curves shown beneath each image show the signal level change over time from an ROI in the myocardial wall region.

3.4 Discussion

The initial finding that motivated this work was that the signal profiles across slices for centric and reverse-centric 3D cardiac perfusion were quite different, even though the same RF excitation was employed in each case (presumably leading to the same slab excitation profile). While not immediately intuitive, this is consistent with the slab profile from the centric case being proportional to the sine of the flip angle, and the reverse-centric case being closer to the steady-state spoiled gradient-recalled echo (SPGR) signal that is less affected by flip angle, which follows from
Right Ventricular (RV) Enhancement
Centric (Top Row) Reverse-Centric (Bottom Row)

Left Ventricular (LV) Enhancement
Centric (Top Row) Reverse-Centric (Bottom Row)

Myocardial Wall Enhancement
Centric (Top Row) Reverse-Centric (Bottom Row)

Figure 3.9: Representative 3D perfusion images from one volunteer. The first two rows show the right ventricle enhancement for centric and reverse-centric trajectories. The third and fourth rows show the left ventricle enhancement for each trajectory, and the fifth and sixth rows show the myocardial wall enhancement status for each trajectory. The signal level drop-off from the center slices to the edge slices is also very apparent in these figures for both centric and reverse-centric trajectories.

equation (3.3) in the manuscript. These findings illustrate the different nature of the 3D perfusion acquisition compared to 2D multi-slice methods. Kim compared centric and other trajectories for 2D [54], and the trajectory mostly alters contrast due to the variation in effective SRT and is essentially a 1D weighting or point spread function in the phase encode direction. Recent works have shown that for a given T1 and SRT, a flip angle can be calculated such that the magnetization
is immediately at steady-state, as shown and discussed in [58, 65]. These in-plane effects are similar for 2D and 3D acquisitions. In contrast, 3D acquisitions also have slab profile effects that interact with the k-space trajectory to determine the contrast of the images. The results here indicate that for relatively standard flip angles and fast RF slab select pulses, the edge slices exhibit much reduced signal relative to the center slices when a centric trajectory is employed.

Reverse-centric gives a flatter slab profile, reflecting more of an SPGR-type of contrast, which also depends less on the SRT. The centric trajectory shows higher CNR than the reverse-centric as the flip angle increases, which is also noticeable in the in vivo experiment. However, it is evident that the increased artifact at higher flip angles limits the flip angle that can be used with a centric trajectory in practice.

The results are also a function of the oversampling factor and the RF pulse design. A 25% oversampling was used here with 8 slices; 10 slices were acquired but only the central 8 used. This and the RF pulse design will clearly affect the flip angle attenuation of the outer slices.

Although the normalized SNR was reported using a separate noise scan, the reconstruction method gives spatially variant SNR that can also depend on the object being reconstructed [66]. Standard SNR measures are often still useful as an approximation. In addition, while this study used TV constraint terms, other constrain terms are expected to show somewhat different results compared to TV. The weighting of the constraints can also affect the results. In this study, variation of the TV weight parameters by 20% gave nearly identical results.

For quantitative results, the scale will directly affect the perfusion estimates in different slices, particularly since a single arterial input function (AIF) from a basal slice is likely to be used. Even if the scaling can be modeled and compensated, the reduced signal and contrast in the edge slices would be expected to decrease the precision of perfusion measurements in the off-center slices. This effect will be greater with a centric acquisition. However, the scaling is unlikely to alter the detection of disease when images are read qualitatively by physicians, where variations in noise levels and contrast across slices have a smaller impact on qualitative assessment.

3D perfusion acquisitions are beginning to be evaluated; Table 1 surveys results to date for 3D studies [40, 49, 58, 65, 67–74]. Quantitative 3D has not yet been validated. The findings reported here relative to trajectory choice should be considered carefully in such cases. Other types of 3D acquisitions have recently been reported in which the order does not matter since
no saturation preparation is employed and the imaging is done at steady state [70, 73]. We also briefly explored the effect of a linear trajectory, and as expected the results were between those obtained for the centric and reverse-centric trajectories. Transient artifacts were reduced compared to centric ordering, but the signal level was also reduced, negating some of the positive contrast effects achieved with the centric ordering. Compared with reverse-centric, a linear ordering also preserved more of the flip angle variation. Further work is needed to determine the best set of tradeoffs for myocardial perfusion imaging.

110 time frames were acquired during our in vivo experiments. We use all of the time frames for the reconstruction. Since the study subjects only could hold their breath for part of the acquisition, respiratory artifacts were expected. For the time curve plot, we only used the first portion of each acquisition where a good breath hold was obtained. The images suffer from significant artifacts if respiratory motion is present. Even with good breath-holds, dark rim artifacts can be present; more rapid, higher resolution 3D readouts would be useful to reduce such artifacts. An improved 3D RF excitation would also be desirable. In this study, the default fast 3D RF slab selective pulse was used, which has a pronounced slab profile. However, achieving a flatter profile will likely require a longer RF excitation, which will decrease temporal resolution and potentially make it difficult to capture the heart when nearly static. Flatter profiles would still show differences for centric and reverse-centric trajectories, but the differences would be expected to be less pronounced.

3.5 Conclusion

Both centric and reverse centric k-space trajectories can be used to successfully perform highly undersampled 3D cardiac perfusion imaging. However, the different trajectory orderings offer different trade-offs. The centric k-space trajectory can provide higher CNR for the acquisition as compared to the reverse-centric trajectory, but is more sensitive to flip angle variation between slices. On the other hand, the reverse-centric trajectory is more robust to flip angle variations, which is important for 3D quantitative analysis. Further work is needed to evaluate the impact of these differences for specific task.
Table 3.1: Summary of the 3D cardiac perfusion papers.

<table>
<thead>
<tr>
<th></th>
<th>Year, first author and reference number of paper</th>
<th>Field Strength</th>
<th>Acceleration Method</th>
<th>TR/TE/SRT Acquisition window (msec)</th>
<th>Acquisition pattern/Trajectory</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2008 Shin, T</td>
<td>3T</td>
<td>6x SENSE</td>
<td>2.3/0.9/130/304</td>
<td>Cartesian/not given</td>
</tr>
<tr>
<td>2</td>
<td>2011 Vitanis, V</td>
<td>3T</td>
<td>10x k-t PCA</td>
<td>1.8/0.7/150/225</td>
<td>Cartesian/not given</td>
</tr>
<tr>
<td>3</td>
<td>2011 Manka, R</td>
<td>3T</td>
<td>6.3x k-t SENSE</td>
<td>1.8/0.7/150/200</td>
<td>Cartesian/not given</td>
</tr>
<tr>
<td>4</td>
<td>2012 Shin, T</td>
<td>1.5T</td>
<td>stack of spatial k-t SENSE</td>
<td>9.8/7.1/140/230</td>
<td>stack of spiral/not given</td>
</tr>
<tr>
<td>5</td>
<td>2012 Jogiya, R</td>
<td>3T</td>
<td>10x k-t PCA</td>
<td>1.8/0.7/150/not reported</td>
<td>Cartesian/not given</td>
</tr>
<tr>
<td>6</td>
<td>2012 Manka, R</td>
<td>1.5T</td>
<td>10x k-t PCA</td>
<td>1.9/0.8/150/not reported</td>
<td>Cartesian/not given</td>
</tr>
<tr>
<td>7</td>
<td>2012 Chen, L</td>
<td>3T</td>
<td>stack of radial TV regularization</td>
<td>2.1<del>2.9/1.1</del>1.4 /140~160/300</td>
<td>stack of radial/centric in kz</td>
</tr>
<tr>
<td>8</td>
<td>2013 DiBella, E</td>
<td>3T</td>
<td>stack of radial TV regularization</td>
<td>2.4/1.3/without sat/250</td>
<td>stack of radial not relevant</td>
</tr>
<tr>
<td>9</td>
<td>2013 Akcakaya, M</td>
<td>1.5T</td>
<td>10x TV regularization</td>
<td>2.1/1.2/100/250</td>
<td>Cartesian/centric</td>
</tr>
<tr>
<td>10</td>
<td>2013 Giri, S</td>
<td>1.5T</td>
<td>3x GRAPPA</td>
<td>2.7/1.04/without sat/300~380</td>
<td>Cartesian/not relevant</td>
</tr>
<tr>
<td>11</td>
<td>2013 Schmidt, J</td>
<td>3T</td>
<td>10x k-t PCA</td>
<td>2<del>2.2/0.9</del>1/140 /205~225</td>
<td>Cartesian/linear</td>
</tr>
<tr>
<td>12</td>
<td>2014 Motwani, M</td>
<td>3T</td>
<td>10x k-t PCA</td>
<td>1.8/0.7/150/192</td>
<td>Cartesian/linear</td>
</tr>
</tbody>
</table>

Note: SPGR with saturation recovery was applied in study 1-7 and 9,11,12. SPGR without saturation recovery was applied in study 8. b-SSFP without saturation recovery was applied in study 10. No start up pulses mentioned in study 1-9 and 11,12. Dummy pulses were applied in study 10 to maintain steady state. No specific trajectory order mentioned in studies 1-8 and 10,11. Study 9 reports the use of the centric order and 11,12 use linear order.
CHAPTER 4. EFFECT OF SLICE EXCITATION PROFILE ON UNGATED STEADY STATE CARDIAC PERFUSION IMAGING

4.1 Introduction

First-pass myocardial perfusion MRI with ECG-gated saturation recovery acquisition is useful for the detection of ischemic heart disease [7, 9, 75–77]. However, some patients do not provide an ECG signal of sufficient quality for accurate gating. Geriatric patients, for example, often have reduced amplitude ECG signals, making consistent triggering challenging. The varied R-R intervals in the ECG signals of patients suffering from cardiac arrhythmias pose another challenge to effective ECG gating. These poor or inconsistent ECG signals can have adverse effects on image quality and cause loss of important diagnostic information.

A new acquisition technique with no need for an ECG trigger was recently proposed for cardiac perfusion [70, 78–80]. The sequence eliminates the saturation preparation and has sufficiently rapid acquisition speed to eliminate the need for cardiac gating. A spoiled gradient echo (SPGR) sequence is used to drive the acquisition into steady state. It has been implemented in both 3D [70] and 2D. The 2D versions have been implemented in both a single slice and a three interleaved slice mode [78–80]. (The interleaving of more than three slices currently leads to an unacceptable temporal resolution.) In these ungated cardiac perfusion techniques, it is crucial to reduce the acquisition time below approximately 100-200 ms per temporal frame to effectively freeze the cardiac motion because we do not have the advantage of ECG trigger information. Therefore a very short TR is often employed, which in turn necessitates a very short RF pulse duration. Very short RF pulses exhibit significant variation in the achieved flip angle across a slice, which in turn can lead to significant variations in the achieved steady-state signal across the slice. This complicates the choice of nominal prescribed flip angle for the sequence, as described below.

Before continuing, it is useful to carefully define several terms. We will use slice excitation profile or slice flip angle profile to describe the spatial variations in flip angle in the slice direction.
across a slice. These variations in flip angle across a slice lead to variations in both the initial and steady-state signals emanating from various positions across the slice. We describe the spatial variations in the steady-state signal (as opposed to the flip angle) across a slice as the slice steady-state signal profile, and the spatial variations in initial signal (defined as the signal after a single RF excitation pulse) across a slice as the slice initial signal profile.

The nominal prescribed flip angle for an ungated first-pass myocardial perfusion sequence (with no saturation pulse) is typically determined by calculating the single flip angle that maximizes contrast between enhanced and unenhanced myocardium. This calculation typically assumes an ideal slice excitation profile (i.e., that the flip angle is constant across the entire slice), which implies an ideal slice steady-state signal profile. While this assumption can be reasonably accurate for longer RF pulses with close to ideal slice excitation profiles, it breaks down for short RF pulses where the slice excitation profile can deviate significantly from the ideal. Hänicke et al. [81] demonstrated in 1988 that the prescribed flip angle that achieves maximum signal from a slice could be significantly higher than the computed Ernst angle when the RF slice excitation profile is poor. They demonstrated that at high nominal flip angles or low TR/T1 ratios, a severely distorted slice steady-state signal profile can be observed due to the non-uniform distribution of the flip angle across the slice [81]. More recently, Sharif et al. used phantom studies to determine empirically an optimal flip angle for single slice and multi-slice interleaved ungated perfusion sequences [78, 82]. The work here extends this effort by explicitly modeling RF excitation pulses like those used in myocardial perfusion sequences, and then demonstrating how the slice excitation profiles of these short RF pulses can lead to a significant underestimation of the nominal prescribed flip angle.

We present a framework for analyzing and understanding how the slice excitation profile affects contrast in ungated 2D steady-state SPGR cardiac perfusion studies, and how interactions across slices (due to non-ideal slice excitation profiles) affects steady-state contrast in both multi-slice and simultaneous multi-slice acquisitions. We then demonstrate how the framework can be used to estimate the nominal prescribed flip angle that will maximize contrast between enhanced and unenhanced myocardium in both the single slice and multi-slice cases.
4.2 Methods

4.2.1 Pulse Sequence

We modified a cardiac pulse sequence to enable a golden ratio radial k-space trajectory for continuous (no saturation pulse) ungated myocardial perfusion data acquisition (SPGR). The sequence was implemented on a 3T Siemens whole-body scanner (Siemens Medical Systems, Erlangen, Germany). 144 readout samples on each of 24 radial lines were acquired for each slice. The sequence employed both RF and gradient spoiling. Both a single slice and three interleaved slice mode were implemented. Note that operating the sequence in three interleaved slice mode gives three times the TR than when the sequence is operated in single slice mode. In both modes, a FOV of 280-300 mm\(^2\) was used, yielding an in-plane resolution of 1.9-2.1 mm. Readout bandwidth was 1389 Hz/pixel. The TR, TE, RF pulse characteristics, slice thickness, and slice distance were varied for the different study cases discussed below.

4.2.2 Numerical Simulation

We performed a numerical Bloch simulation of the sequence accounting for the RF slice excitation profile to estimate the actual steady state signal level from the slice. The RF slice excitation was applied to a region 15 times thicker than the nominal (prescribed) slice width divided into 300 sub-slices, each sub-slice receiving a different effective flip angle based on its location. The signal contributions were summed across all of the sub-slices, and the overall signal from the actually excited slice volume was then used for signal and contrast optimization. Alternately, the signal at each sub-slice was plotted to show the signal profile. The simulation was applied in both single-slice mode and multi-slice mode, and takes the RF pulse profile exported from the Siemens sequence simulator (IDEA VB17) as an input in order to mirror the actual RF pulse used during acquisition. The simulated thickness (15 times the nominal width of a single slice) allowed for excitation outside the nominal slice width to be included in our calculations for the cases considered below, and was kept constant for both our single slice and multi-slice experiments. The simulation models all of the RF excitations, to account for the effect of cross-talk between slices. For a given parameter set, the simulation performed 2000 excitations to reach steady state. We found that this number of excitations ensured that steady state was reached for all of the TR/T1
values studied. The simulation takes as inputs the T1 and T2 of the tissue being studied, the TR and TE of the SPGR sequence, the nominal prescribed flip angle, the RF excitation pulse characteristics, the nominal prescribed slice width, the slice selection gradient characteristics, the RF center frequency, and the inter-slice gap (in the multi-slice case only). To help elucidate the differences between the slice excitation profile, the steady-state signal profile, and the initial signal profile, the simulation was used to generate plots of each for the single slice case (Case 1 described below) and the three interleaved slice case with large and zero inter-slice distance (Case 2 and Case 3 described below). The simulation was performed for a low flip angle close to the ideal slice-profile maximum-contrast angle (8 degrees and 15 degrees respectively for the single slice and three interleaved slice cases) and at a larger flip angle (20 degrees and 36 degrees respectively for the single slice and three interleaved slice cases) closer to the true maximum-contrast angle.

4.2.3 Phantom Experiments with Comparison to Numerical Simulation

To validate the accuracy of the numerical simulation, we imaged two uniform phantoms with measured T1 values of $\sim 300$ ms and $\sim 1000$ ms. For all of the phantom studies, 150 time frames were acquired with 3600 radial lines for each slice. The body coil was used for both RF transmit and signal reception in all phantom experiments, because it provides both excellent transmit and receive RF homogeneity (removing coil inhomogeneity effects from the evaluation). Four different phantom imaging cases were investigated to validate simulation accuracy and to illustrate the significant effect RF slice excitation profile can have on nominal flip angle estimation for optimal contrast.

Case 1: Determination of nominal flip angle for optimal enhanced/unenhanced contrast, single slice case

The simulation was first run in single slice mode across a range of nominal flip angles (8 degrees to 50 degrees in 2 degree increments) assuming an ideal (perfect rectangular) RF slice excitation profile. Steady-state signal levels at each flip angle were determined for tissues with T1 of $\sim 300$ ms (enhanced myocardium) and T1 of $\sim 1000$ ms (unenhanced myocardium). Contrast between enhanced and unenhanced myocardium was then determined at each flip angle (using the simulated steady-state signal difference), allowing the nominal flip angle that yields maximum contrast to be determined. Imaging parameters assumed for the simulation were TR/TE = 3.2/1.5.
ms and a nominal slice thickness of 5 mm. The above simulation was then repeated, but using the actual RF slice excitation profile for a truncated sinc pulse excitation with 1000 μs duration and time bandwidth product of 2. Finally, the two phantoms mimicking enhanced and unenhanced myocardium were imaged using the same imaging parameters as the simulation, and the actual RF excitation pulse described above. The phantom experiments were also repeated at nominal flip angles of 8 to 50 degrees in 2 degree increments. (Flip angles higher than 50 degrees were not considered due to expected SAR limitations in vivo at flip angles greater than 50 degrees.) Average signal intensities were measured across each vial, and the contrast calculated as the difference in the average signal intensities. Overall signal scaling from the phantom scans was normalized to the simulation signal levels. A single normalization constant was determined for each tissue and applied across all flip angles. The normalized contrast versus flip angle curve from the phantom experiment was then compared to the two simulated cases (ideal RF slice excitation profile and actual RF slice excitation profile).

**Case 2: Determination of nominal flip angle for optimal enhanced/unenhanced contrast, three interleaved slice, large inter-slice distance case**

The above study was repeated for a three interleaved slice acquisition case with a large inter-slice gap. The nominal slice thickness was 5 mm and the inter-slice gap was 15 mm (yielding a center-of-slice separation of 20 mm). The same scan parameters and non-ideal RF pulse were used as in Case 1. However, note that the effective TR for a single slice was tripled by the three interleaved slice acquisition, yielding an effective slice TR/TE of 9.6/1.5 ms. Normalized contrast versus flip angle curves from the phantom experiment were then compared to the two simulated cases for each of the three imaged slices.

**Case 3: Determination of nominal flip angle for optimal enhanced/unenhanced contrast, three interleaved slice, zero inter-slice distance case**

Case 3 was identical to Case 2, but with the inter-slice distance set to 0 mm (no inter-slice gap) to illustrate the most extreme case of cross-talk between slices. All parameters except inter-slice distance were as previously described, and normalized contrast versus flip angle curves from the phantom experiment were generated and compared to the two simulated cases for each of the three imaged slices.
In addition, the phantom experiment outlined in Case 1 was repeated using three additional RF pulses, one with a short duration that duplicated the RF pulse for the in vivo studies, and the other two with longer duration than the pulse studied in Case 1 but with the same spectral bandwidth. The RF pulse studied in Case 1 was a truncated sinc with duration of 1000 µs and time bandwidth product of 2. The three additional RF pulses studied were truncated sincs with duration 600 µs, 4000 µs and 8000 µs and time bandwidth products of 1.6, 8 and 16 respectively. In order to accommodate the longer RF pulse durations, we use TR/TE = 16/9 ms for each of the four different RF pulses studied. The same phantom was imaged with flip angles ranging from 12 to 60 degrees in 4 degree increments. Normalized contrast versus flip angle curves were generated from each of these two phantom experiments.

**Simultaneous Multi-Slice Acquisitions:** Also of interest is the effect of slice excitation profile and cross-talk between slices in simultaneous multi-slice acquisitions. We simulated a simple simultaneous multi-slice acquisition where two slices (1st, 3rd and 2nd, 4th) were simultaneously excited with a total of 4-slice coverage and an interleaved readout. The nominal slice thickness assumed for the simulation was 5 mm and the inter-slice gap was 2.5 mm. The multi-band RF pulse used was 1 ms in duration with a time-bandwidth product of 2. Other parameters were: TR/TE = 6.4/1.3 ms and T1 = 300 ms.

### 4.2.4 In Vivo Experiments

The three interleaved slice sequence was tested in vivo on five human subjects using a 32-channel surface coil just after gadolinium injection. All tests involving human subjects were approved by the University of Utah Institutional Review Board (IRB), and informed consent was obtained from each subject. The in vivo tests employed a truncated sinc RF pulse of 600 µs duration and time/bandwidth product = 1.6, TR/TE = 8.34/1.3 ms, 8 mm slice thickness and a 2.4 mm inter-slice gap.

A comparison experiment was first performed; the subject was imaged using the sequence mentioned above with three different flip angles (22, 30, and 36 degrees) at both pre-contrast and approximately 2 minutes post-contrast. A set of 50 temporal frames (10 seconds) was acquired at each flip angle at both time points. For the actual dynamic contrast enhanced acquisition, subjects were scanned using a flip angle of 36 degrees, which is closer to the expected true optimal flip
angle given slice profile and cross-talk effects. A total of 300 time frames were acquired over 61 seconds.

Image orientation in all cases was chosen to yield a short-axis stack of slices. Subjects were instructed to hold their breath as long as possible during the acquisition. Image reconstruction was performed using the spatiotemporal constrained reconstruction described below.

### 4.2.5 Image Reconstruction

Since the golden ratio radial trajectory was used and no motion is expected, a sliding window reconstruction algorithm was expected to perform well and was adopted for the experiments outlined above [83]. A total of 2400 radial lines (from the last 100 frames when the signal is expected to be in steady state) was regrouped to form one single frame, and a nonuniform FFT routine was used to generate the images [84].

For the in vivo data sets, the reconstruction was performed independently for each slice by using SENSE-based spatiotemporal constraints with 3 dimensional TV (2 spatial dimensions and the temporal dimension) as the constraints [60, 85].

Before reconstruction, the in vivo data from the 32-channel multi-coil was combined to 8 virtual coils via coil PCA to speed up the computation process [86, 87]. An eigenvector estimation method was employed for coil sensitivity maps [88]. In order to keep the TV weight factor consistent, the maximum value of each data set was normalized to 1. The temporal weight factor was chosen as 3e-4, which is 10 times higher than the spatial TV weight factor, set at 3e-5. A total of 250 iterations of the reconstruction were performed for each slice. All images were reconstructed off-line using MATLAB (Mathworks, Natick, MA) on a 16-core Linux workstation with 64 GB of RAM.

### 4.3 Results

#### 4.3.1 Numerical Simulation

The results of the numerical simulation illustrating differences between the shape of the slice excitation profile, the steady-state signal profile, and the initial signal profile (the signal level
after a single RF excitation) are shown in Figure 1. The top row of the figure illustrates the single slice case, at a low flip angle (8 degrees, close to the maximum contrast flip angle if an ideal slice excitation profile is assumed) and a larger flip angle (20 degrees, close to the maximum contrast flip angle if the actual excitation profile is taken into account). As illustrated, the signal evolves over time at larger flip angles to yield a steady-state signal profile that is very different in shape from both the slice excitation profile and the initial signal profile. A concave shape signal profile is observed in steady state at the higher flip angle. The non-ideal slice profile leads to flip angle variation across the slice. This causes the edge area to experience a lower flip angle that is closer to the Ernst angle, and therefore produces higher signal intensity than the center area. Since the total signal from a given slice is an integral of the signal across the slice, it is important to take into account these actual slice signal profiles when determining the flip angle that will yield the highest contrast between enhanced and unenhanced myocardium.

The middle and bottom rows of Figure 4.1 illustrate the three interleaved slice case with a large inter-slice gap (middle row) and no inter-slice gap (bottom row). Note that a TR three times as long as the TR of the single slice case is used due to the multi-slice interleaving. As would be expected, when a large inter-slice gap is used there is very little cross-talk between the slices, and the signal profile evolves in much the same way as the single slice signal profile for each slice. However, when the inter-slice gap is eliminated, cross-talk becomes significant. Mutual influences between the slices cause the slice profiles to differ from the none cross-talk case by spreading the concave shape of the profile across the three slices. Consequently the outer slices have peaks, while the center slice is more flat. In this case, contrast may vary for the middle slice versus the edge slices, and it may not be possible to maximize enhanced/unenhanced myocardium contrast simultaneously for both the middle and edge slices.

### 4.3.2 Phantom Experiments with Comparison to Numerical Simulation

Figure 4.2 illustrates the signal levels as a function of flip angle of enhanced (T1 = 300 ms, left column) and unenhanced (T1 = 1000 ms, middle column) myocardium, as well as the contrast-to-noise ratio (CNR, calculated in this case as the signal differences) between the two (right column). The blue trace on each graph denotes the simulated signal levels assuming an ideal slice excitation profile. The green trace illustrates the simulated signal levels when the actual slice
Figure 4.1: Simulation of the slice initial signal profile and steady state signal profile for the RF pulse with slice excitation profile shown. Three different cases are demonstrated: the single slice acquisition case, a three slice multi-slice acquisition with large interslice gap (no slice cross-talk), and a three slice mutli-slice acquisition with zero interslice gap (showing slice cross-talk). The top row of each case uses a low flip angle that is close to the ideal maximum contrast flip angle (when an ideal slice excitation profile is assumed). The bottom row of each case utilizes a higher flip angle that is close to the actual maximum contrast flip angle.

excitation profile is taken into consideration. Finally, the red trace shows the result of the phantom experiment, where vials with known T1 values of \(~300\) ms and \(~1000\) ms were scanned across a range of flip angles.
Figure 4.2: Variations in signal intensity and CNR as a function of flip angle for both single slice and three slice multi-slice acquisitions. Phantom results are shown in red, and are compared to simulation results assuming an ideal slice excitation profile (blue) and those incorporating the actual slice excitation profile (green). (a) Single slice case: the theoretical optimized flip angle for CNR is $\sim 12$ degrees, while the phantom study and simulation using the actual slice profile shows an optimal flip angle of $\sim 22$ degrees. (b) 3 slices with large inter-slice gap: the CNR was maximized at $\sim 20$ degrees with an assumed ideal slice profile, but at $\sim 36$ degrees when the actual slice excitation profile was considered. (c) Edge slice results for the 3 slice multi-slice case with no inter-slice gap. (d) Center slice results for the 3 slice multi-slice case with no inter-slice gap. In all cases, the actual phantom experiment results are in much better agreement with the simulation results that take into consideration the actual slice excitation profile.

The top row (Figure 4.2a) illustrates the single slice case (Case 1), and the second row (Figure 4.2b) illustrates the three interleaved slice case with an inter-slice gap equal to the nominal slice thickness of 5 mm (Case 2). The third and fourth rows illustrate the three interleaved slice case with no inter-slice gap for the edge slices (Figure 4.2c) and the middle slice (Figure 4.2d). It is interesting to note that the differences between the middle and edge slices in the three interleaved
slice case are clearly evident in the phantom experiments, validating our model of excitation cross-talk between the slices.

In all cases, the phantom experiments are in excellent agreement with the numerical simulation when the actual slice excitation profile is taken into consideration. It is also evident in all cases that the flip angle that maximizes contrast between enhanced and unenhanced myocardium is significantly different than would be expected given an ideal slice excitation profile. Assumption of an ideal slice excitation profile results in all cases in a significant underestimation of the flip angle that will actually yield maximized contrast. For the RF excitation profile and parameters used in these experiments, the maximum-contrast flip angle increased from 12 degrees (assuming an ideal slice excitation profile) to 20 degrees when the actual profile was taken into consideration. Similar results are seen in Cases 2 and 3 illustrated.

Figure 4.3 illustrates how the contrast versus flip angle results vary (in numerical simulation) when RF pulses with short duration and RF pulses with longer duration (and the same spectral bandwidth as the pulse studied in Case 1) are used. The RF envelope with a short duration (with time-bandwidth product of 1.6) that was used for the in vivo studies is shown in Figure 4.3a. The RF pulse of the original pulse used in Case 1 (with time-bandwidth product of 2) is shown in Figure 4.3b, and those of the two additional pulses that were simulated are shown in Figures 4.3c and 4.3d (with time-bandwidth products of 8 and 16 respectively). These longer RF pulses progressively get closer to an ideal slice excitation profile. Enhanced/unenhanced myocardial contrast versus flip angle is shown in Figure 4.3e for each of the three RF pulses. The curve assuming an ideal excitation profile is also shown for comparison. As expected, the longer RF pulses provide a more ideal slice excitation profile, pushing the expected maximum-contrast flip angle closer to that of the ideal case.

Finally, the results from the simultaneous multi-slice acquisition simulation are shown in Figure 4.4 at two different flip angles, 12 and 30 degrees. While the slice cross-talk effects are relatively small at a 12 degree flip angle, they become significant at a 30 degree flip angle, especially for the center two slices.
Figure 4.3: Four different RF pulses were tested with fixed TR/TE=16/9 ms in a single slice. The RF excitation envelopes for each pulse are shown in (a)-(d). In (e), phantom results for each RF pulse (denoted with the symbol o on the graph) are compared with the simulation result assuming an ideal slice excitation profile (denoted with the symbol x on the graph). As can be seen, the phantom results approach the simulated (ideal slice excitation) results as a longer duration (larger TBW) RF pulse is used.

4.3.3 In Vivo Experiments

Figure 4.5 shows a human imaging result demonstrating the CNR achieved at different flip angles. The highest CNR between enhanced and unenhanced myocardial tissue was observed at a flip angle of 36 degrees rather than the 22 degree flip angle that was close to the flip angle predicted by a theoretical optimization that assumed an ideal slice profile. Figure 4.6 shows the 2D multi-slice perfusion results from another subject with a 36 degree flip angle; in this figure, RV enhancement, LV enhancement, and myocardial enhancement are shown.

4.4 Discussion

While numerous studies have addressed the effect of slice profiles on SPGR imaging, this study investigates in depth this effect on a new method for acquiring cardiac perfusion data. This extends work by Sharif et al. that used the same acquisition method to acquire ungated no saturation pulse cardiac perfusion data. In their work, for an RF pulse with 600 µs duration and 10 mm
slice thickness, they reported that a flip angle of \( \sim 30 \) degrees yields maximal CNR. Our analysis gives a similar result and also reports optimal flip angles for other pulses.

When acquiring adjacent or nearby slices, the cross-talk between slices is important to consider. Examples were shown for adjacent slices in this work, and also results from a basic simulation of a simultaneous multi-slice excitation. Both of these multi-slice acquisitions, when performed at TBW = 2 and 1000 \( \mu \)s duration RF pulse, still exhibit cross-talk effects at slice separations of 50\% with a nominal slice thickness of 5 mm. In the multi-slice acquisition case with 3 slices, a large slice gap (100\%) is typically appropriate. However, with the simultaneous multi-slice methods (SMS) that are becoming useful in cardiac studies [89–91], four, six, or even more slices are reasonable. The gap between slices could then be quite small, and the slice cross-talk effects will be more pronounced.

In general, the cross-talk effects generated by non-ideal slice excitation profiles cannot be avoided. However, if the slice profile can be estimated, the effects of cross-talk can be minimized. For example, the cross-talk effects lead to different optimal flip angles for different slices. Future studies could estimate the different flip angles needed at each slice to optimize slice CNR, and flip angle could be varied for each slice individually based on the results.
Figure 4.5: In vivo results showing signal intensity variations at different flip angles both pre-contrast and post-contrast. The highest CNR between enhanced and unenhanced myocardial tissue was observed at a flip angle of 36 degrees, significantly higher than the 22 degree flip angle predicted by a theoretical optimization that assumed an ideal slice profile.

Our work did not take into consideration additional variations in the spatial excitation profile resulting from RF transmit coil characteristics and tissue properties. While many excitation systems do a very good job at delivering homogenous flip angles over the field of view, this assumption of B1 transmit homogeneity is not strictly valid. Others have studied these effects in different contexts (e.g., for DCE MRI of the breast [92]). Other issues, such as the efficacy of the RF and gradient spoiling, were not considered here. Our analyses also used relatively simple sinc pulses; the RF pulse design could be tailored to improve slice profiles even for relatively fast excitations.

The slice profile issues described here are also important for other sequences commonly used in cardiac imaging, such as balanced SSFP and saturation recovery with turboFLASH or
Figure 4.6: In vivo 2D three slice multi-slice perfusion results in a human subject using a flip angle of 36 degrees. The images show excellent dynamic contrast enhancement at this high flip angle in the RV and LV, as well as myocardial wall uptake stages.

SSFP readouts. Balanced SSFP has a similar slice profile issue as SPGR [93, 94]. The ECG-gated saturation recovery sequence, which is much more widely used in cardiac perfusion imaging than ungated SPGR, employs a non-selective saturation pulse, typically with a rapid gradient echo (SPGR) readout [95]. Depending on T1 and sequence parameters, the readouts may reach steady state rapidly. Regardless, the repeated application of short RF pulses with poor slice profiles leads to the same type of effects that were quantified here, although further work is needed to better quantify the effects and the improvements possible with new RF pulses.
CHAPTER 5. RADIAL SIMULTANEOUS MULTI-SLICE CAIPI FOR UNGATED MYOCARDIAL PERFUSION

5.1 Introduction

First-pass myocardial perfusion imaging with MRI is a valuable method for characterizing blood flow in myocardial tissue and is a powerful tool for assessment of coronary artery disease [7,9,41,96,97]. Despite numerous advances, clinical application of first-pass myocardial perfusion MRI is still hampered by several factors, including the limited slice coverage achieved by current methods, and by ECG-gating issues [98]. Obtaining high spatial and temporal resolution often limits the number of slices to three per heartbeat at high heart rates. Greater or complete heart coverage without losing resolution is desired as this may allow better and more confident detection of disease due to visualizing more of the myocardium. This can also enable more accurate identification and sizing of ischemic zones.

To address this problem of limited coverage, undersampled acquisitions combined with advanced reconstruction methods like compressed sensing have been proposed [26, 27]. Non-Cartesian k-space acquisition trajectories like radial and spiral have also been used to achieve increased slice coverage without sacrificing spatial and temporal resolutions [40, 58, 60, 99, 100]. 3D acquisitions offer more coverage but thus far are slow (~200 ms readout) and have relatively poor spatial resolution [101]. Alternatively, parallel imaging can be performed not only in-plane but in the slice direction with 2D acquisitions to obtain multiple slices at the same time. This method is termed SMS imaging or, when the phase of each slice is adjusted separately to improve the separability of the slices, controlled aliasing in parallel imaging results in higher acceleration (CAIPIRINHA or CAIPI). Cartesian CAIPI achieves increased imaging coverage without losing temporal resolution and image quality [38, 90, 102]. The CAIPI method uses alternating multi-band RF pulses to excite multiple slices simultaneously. The phase modulation of the individual slices, along with reconstructions that exploit coil sensitivity, provides good image quality. Benefits
from applying CAIPI to Cartesian myocardial perfusion imaging have been shown [90]. Radial CAIPI phase modulates sequential rays instead of sequential phase encodes [39], and may offer advantages compared to Cartesian CAIPI. Instead of shifting the FOV in the modulated slices as in Cartesian CAIPI, the adjacent rays in the modulated slices of radial CAIPI cancel to an extent so only a residual of each slice interferes with the non-modulated slice.

Standard perfusion imaging requires ECG gating to minimize cardiac motion effects. Gating depends on a reliable electrocardiographic (ECG) signal to image a given slice at the same phase of the cardiac cycle over multiple heartbeats [12,50]. In many patients an accurate ECG signal cannot be obtained, particularly when the patient has a cardiovascular disorder like arrhythmias. Low amplitude ECG signals or the varied R-R interval width of the ECG can make accurate gating challenging. The amount of information obtained from the scans can be significantly affected if the ECG signal is poor and misses beats, or if the heart rate increases such that an acquisition is only acquired every other beat. Eliminating the need for the ECG signal also makes the protocol simpler to prepare, since the number of slices acquired is not dependent on the heart rate.

To address the limitations of the ECG problem, ungated (non-ECG-gated) perfusion acquisitions have been proposed [70, 78, 80, 82, 103, 104]. These methods typically shorten the acquisition time of each time frame to obtain sufficient temporal frames of each slice to self-gate the images retrospectively. The ungated methods have been employed with saturation recovery turboFLASH sequences, and with steady state spoiled gradient echo (SPGR) sequences to acquire first pass cardiac perfusion imaging.

An ungated saturation recovery turboFLASH method was implemented on three to five slices in [103,104], and SPGR sequences were performed in 3D, 2D single slice and 2D with three slices interleaved in [70, 78, 80, 82]. Although the ungated approach provides a new method for cardiac perfusion studies, the acquisition is still restricted by the limited spatial coverage due to the requirement of high temporal resolution. In this study we propose a multi-slice acquisition pattern that combines the simultaneous multi-slice excitation imaging technique and the ungated acquisition method. Both the saturation recovery turboFLASH sequence and the steady-state-based SPGR sequences are demonstrated using CAIPI for the application of myocardial perfusion imaging.
5.2 Methods

Two different ungated acquisition methods with radial CAIPI were implemented in this study: a 2D saturation recovery turboFLASH sequence [89, 105], and a steady-state SPGR sequence without saturation pulses [91]. Both the ungated saturation recovery turboFLASH and steady-state SPGR sequences employed a golden ratio radial k-space trajectory with 2, 3, or 5 simultaneous multiple slices acquired. The acquisition scheme is demonstrated in Figure 5.1. A more conventional single slice sequence with golden ratio radial trajectory for both types of acquisitions was also performed for comparison. The term multi-band factor or MB indicates the number of slices that were acquired simultaneously.

Figure 5.1: Illustration of the acquisition scheme for the ungated saturation recovery sequence and ungated SPGR sequence. For each excitation, two slices were excited simultaneously as a pair. In the saturation recovery sequence, the phase was alternated between $(0, 0)$ and $(0, \pi)$ for subsequent RF pulses. In the ungated SPGR sequence, interleaving makes the phase ordering $(0, 0), (0, 0)$ and $(0, \pi), (0, \pi)$. A multi-band factor of 2 is shown here for brevity. A multi-band factor of 3 will have three slices excited simultaneously, and the phase will follow $(0, 0, 0)$ and $(0, 2\pi/3, 4\pi/3)$.

5.2.1 Simulation

Simulation and phantom studies were performed initially to help better understand the image differences with and without saturation preparation at multi-band factor $= 2$. For the sim-
Table 5.1: Ungated SMS sequence parameters.

<table>
<thead>
<tr>
<th>Saturation recovery sequence</th>
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<tbody>
<tr>
<td>multi-band factor</td>
<td>MB factor = 2</td>
<td>MB factor = 3</td>
</tr>
<tr>
<td>matrix size (kx-ky-kz)</td>
<td>144 × 144 × 8</td>
<td>144 × 144 × 6</td>
</tr>
<tr>
<td>phase modulation</td>
<td>(0, π)</td>
<td>(0, 2π/3, 4π/3)</td>
</tr>
<tr>
<td>study subjects</td>
<td>2 volunteers</td>
<td>6 canines</td>
</tr>
<tr>
<td></td>
<td>2 canines</td>
<td></td>
</tr>
</tbody>
</table>

**Common parameters:**
- Field of View (FOV) = 250 mm\(^2\), slice-thickness = 8 mm with 4 mm slice gap, flip angle = 12°
- Saturation recovery time (SRT) = 30 ms, TR/TE = 2.8/1.5 ms, rays/frame = 24
- Each subsequent group of slices had ~67 ms extra SRT due to sequential acquisition after the saturation pulse
- Time frames = 50, bandwidth = 992 Hz/pixel, dose = 0.05 mmol/kg

<table>
<thead>
<tr>
<th>Steady-state SPGR sequence</th>
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</thead>
<tbody>
<tr>
<td>multi-band factor</td>
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<td>MB factor = 3</td>
</tr>
<tr>
<td>matrix size (kx-ky-kz)</td>
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<td>(0, 2π/3, 4π/3)</td>
</tr>
<tr>
<td>study subjects</td>
<td>2 volunteers</td>
<td>2 volunteers</td>
</tr>
</tbody>
</table>

**Common parameters:**
- Field of View (FOV) = 250 mm\(^2\), slice-thickness = 8 mm with 4 mm slice gap, flip angle = 25°
- TR/TE = 2.8/1.5 ms due to the interleaved acquisition
- RF spoiling and gradient spoiling, time frames = 200
- Ray/frame = 24, bandwidth = 1389 Hz/pixel, dose = 0.05 mmol/kg

Simulations, we assumed that the multi-band RF pulse was perfectly formed by the summation of single-band RF pulses. Single-band RF profiles used in the simulation were exported from the pulse sequence in order to have realistic slice profiles. The simulation split the RF pulse into 300 subsections. The signal level of each subsection was evaluated based on the effective flip angle at the position of the subsection. The summation of all subsections was taken to determine the signal level of the slice. For the saturation recovery sequence, we performed 24 selective excitations to
simulate acquiring 24 rays, and then averaged the signal level from each excitation to calculate the final signal level. For the SPGR sequence, 1500 excitations were used to ensure steady state. The signal contributions from each subsection were summed across all of the subsections after steady state was reached. A numerical simulation with an ideal slice profile was also performed using the same method. The simulation employed a multi-band factor of 2. The parameters are listed in table 5.1 under multi-band of 2. The T2 was set to 10 ms. In order to avoid cross-talk effects, a large slice gap was also used in the simulation. We assumed a T1 of 350 ms for pre-contrast and T1 of 1000 ms for post-contrast (the same as used for the phantom studies described below). The slice thickness was 8 mm and a 16 mm slice gap was also included. Flip angle was varied from 8 to 32 degree in 4 degree increments for both acquisition methods.

5.2.2 Phantom Studies

To validate the numerical simulations, a phantom scan was performed and compared to the simulation results. Two saline vials ~2 cm in diameter with different concentrations of gadolinium (Gd-BOPTA) were imaged. The concentration of the gadolinium was adjusted to mimic a pre-contrast T1 (~1000 ms) and a post-contrast T1 (~350 ms). The two vial phantoms were approximately 2 cm apart, and oriented such that the slice direction was along the long axis of each phantom, which coincided with the main field direction. The built-in body coil with excellent field uniformity was used. Different flip angles (8 to 32 degrees with 4 degree increment) were performed with both the ungated saturation recovery turboFLASH sequence and the interleaved SPGR sequence with multi-band factor of 2. An 8 mm slice thickness and 16 mm slice gap distance were used to reduced slice cross-talk effects, matching the simulation. For both the sequences, each pair of slices contains 24 radial lines for one time frame and 200 time frames were acquired (4800 rays). The signal level was evaluated as the mean signal intensity from large uniform regions.

5.2.3 In Vivo Experiments

First pass cardiac perfusion studies were performed with both of the ungated SMS methods, with the sequence parameters listed in Table 5.1. To compare the image quality acquired from different multi-band factors, a comparison experiment was also performed on two subjects at a
post-contrast stage, with both the ungated saturation recovery sequence and the SPGR sequences. The scans were performed for approximately 60 seconds each, starting approximately two minutes after the contrast injection.

Multi-band factors of 3 and 5 were employed as well as a single band acquisition with 2 slices. The acquisition of multi-band factor of 5 covered 10 slices with phase cycle \((0, 2\pi/5, 4\pi/5, 6\pi/5, 8\pi/5)\). For these multi-band factor comparisons, 20 rays were acquired every time frame for single band and a multi-band factor of 5, and 21 rays per time frame were acquired for a multi-band factor of 3.

All of the studies were approved by the University of Utah institutional review board (IRB) and informed consent was obtained from each subject. The animal studies were performed under an approved IACUC protocol and were being imaged for other purposes; the resting perfusion scans were added. Short-axis slices were acquired for all of the studies. All of the imaging was performed on 3T whole-body scanners (Siemens Medical Systems, Erlangen, Germany) with a 32 channel cardiac surface coil.

### 5.2.4 Image Reconstruction

For the phantom experiments, only single channel data was acquired. Phase demodulation and reconstruction with a non-uniform FFT (NUFFT) was used to generate the images for individual slices [99,106]. A total of 2400 rays acquired after obtaining steady state of the SPGR sequence were used for a single image. Figure 5.2 shows the reconstruction pipeline for the in vivo datasets collected by the two SMS acquisition methods. First, coil compression with principal component analysis (PCA) was performed to reduce the reconstruction time [87]; the original 32 coils were reduced to 8 virtual coil elements. The coil sensitivities of each slice were determined using the temporal average of all frames from each coil of the demodulated CAIPI radial acquisition.

The eigenvector method estimation was applied to obtain the coil sensitivity maps \(S\) [88]. The cost functional \(C\) in equation (5.1), below, was then minimized with a projection onto convex sets method [107].
Figure 5.2: Illustration of the general pipeline of the image reconstruction.

\[
C(I) = \sum_{i=1}^{nc} \left\| \sum_{j=1}^{nsl} \phi_j(GS_{ij}I_j) \right\|^2 + \alpha_t \sum_{j=1}^{nsl} TV_t(I_j) + \alpha_s \sum_{j=1}^{nsl} TV_s(I_j) + \alpha_l \sum_{j=1}^{nsl} \sum_{b=1}^{Nblock} \lVert BI_{bj} \rVert_2, \quad (5.1)
\]

where \(d\) is the acquired radial CAIPI data for coil index \(i\), and \(nc\) is the number of (compressed) coils, \(I_j\) is the reconstructed image corresponding to slice index \(j\), \(nsl\) is the number of simultaneously excited slices. \(S_{ij}\) is the coil-sensitivity for coil element index \(i\) and slice index \(j\); \(\phi_j\) phase
modulates k-space data for slice $j$ to match the CAIPI acquisition (alternating phase cycles starting with 0, $2\pi/3$, $4\pi/3$ for MB=3), and $G$ is the gridding operator using non-uniform FFT, to convert image data to radial k-space data. The first $L_2$-norm enforces data fidelity to the acquired CAIPI data. The second and third terms are temporal and spatial total variation constraints with weightings $\alpha_t$ and $\alpha_s$ [60, 85]. $B$ is a block-based low rank operator with nuclear norm that is applied on each slice separately and $\alpha_l$ is the low rank weight factor. $N_{\text{block}}$ is the number of blocks within slices.

For both of the SMS acquisition types, to keep the TV weight factors consistent, the peak value in each dataset was normalized to 16. The temporal weight factor was chosen as $3e^{-3}$ for SPGR data and $2e^{-4}$ for saturation recovery data, and the spatial TV weight factor was set to $3e^{-4}$ for SPGR data and $3e^{-5}$ for saturation recovery data. The block size was defined as 8x8, and the weight for the low rank term was 0.03. Each group of slices used 150 iterations for the reconstruction. Images were reconstructed off-line using MATLAB (Mathworks, Natick, MA) on a 16-core Linux workstation with 64 GB of RAM. Reconstruction time for a dataset consisting of 200 time frames from 8 virtual coils with multi-band factor of 2, 3, and 5 were approximately 30, 45 and 65 seconds per time frame individually. These reconstruction times could be greatly accelerated by an optimized implementation on dedicated hardware.

We also compared this reconstruction pipeline with a SENSE reconstruction similar to that used in the original radial CAIPI paper [39]. The comparison was performed on one ungated SPGR case with multi-band factor = 3.

5.3 Results

5.3.1 Simulation and Phantom Experiments

The normalized contrast-to-noise ratio (CNR) versus flip angle between the two vial phantoms ($T1 = \sim 350$ ms and $T1 = \sim 1000$ ms) is shown in Figure 5.3, along with the relevant simulation results. In the phantom studies, the normalized CNR was plotted for the saturation recovery acquisition and ungated SPGR sequence both using a multi-band factor of 2. Figure 5.3 shows that the SPGR sequence had better CNR than the first two pairs of slices in the saturation recovery
acquisition, which had effective saturation recovery times less than 95 ms. For longer SRTs, the saturation recovery images had higher CNR than obtained by the SPGR sequence.

Figure 5.3: Phantom result (left) compared with the simulation result. The simulation assumes either a realistic slice profile (middle) or a perfect slice profile (right). The circles represent the ungated saturation recovery sequence, with red, green, blue and cyan showing different slices that experience different saturation recovery times (30, 95, 160 and 225 ms respectively). The triangles show the ungated SPGR sequence results, which have an effective TR = 6 ms. The simulations performed with a realistic slice profile match the phantom study results well. The ungated method shows better CNR than the saturation recovery sequence for slices with less 100 ms saturation recovery time, but the situation is reversed for slices with longer saturation recovery time. It is interesting to note that the assumption of a perfect slice profile (right) leads to a biased estimate of the optimal CNR flip angle.

5.3.2 In Vivo Experiments

Figure 5.4 shows SMS saturation recovery ungated perfusion images from one of the human subjects and from a canine study. The “+” indicates the two slices were acquired at the same time. One time frame for eight slices at different cardiac phases from apex to base for a dog (left) and a human (right) is shown.

Figure 5.5 shows a result from the SPGR sequence, without saturation recovery. Two slices were acquired simultaneously, and rays were interleaved for two sets of slices so that the block of 4 slices was kept at steady-state. The average signal intensities for each time frame are shown from manually segmented region of interest (ROI) in the myocardial wall region. Due to cardiac motion, the curves are jagged but have clear enhancement.
Figure 5.6 shows another result from the saturation recovery ungated perfusion sequence with a multi-band factor = 3 from one canine study. (Again, the “+” symbols denote that the three slices were acquired at the same time.)

Figure 5.7 shows the comparison results that were acquired from different multi-band factors with the ungated SPGR sequence. With the multi-band factor 3, a group of three slices acquired simultaneous demonstrated more streaks but reasonable image quality compared to the single band result. The multi-band factor of 5, however, showed degradation of image quality.

Figure 5.8 demonstrates the comparison results with the ungated saturation recovery sequence. Similar to the SPGR cases, the single band and multi-band factor 3 had similar quality. With the multi-band factor increased to 5, clear degradation of image quality could also observed.

Figure 5.9 shows a comparison between the two different reconstruction methods used. The new joint reconstruction method provides significantly better results than the SENSE method.

Figure 5.4: One time frame for each of the eight slices from an ungated saturation recovery sequence with multi-band factor = 2. Corresponding top and bottom slices linked with plus sign are simultaneously acquired. The left set of eight images is from a dog study and the right set of images is from a human study.

5.4 Discussion

The SMS radial CAIPI results presented here with and without saturation recovery show the promise of the proposed framework for increasing slice coverage for cardiac perfusion imaging
Figure 5.5: Different enhancement stages (RV, LV and myocardial wall uptake) are shown acquired from an ungated SPGR sequence. Corresponding top and bottom slices linked with a plus sign are simultaneously acquired. The time curve of the myocardial wall was plotted based on a manual segmentation.

Figure 5.6: One time frame for 6 slices from an ungated saturation recovery turboFLASH sequence. The multi-band factor is 3 in this study; the 1st, 3rd and 5th slices (linked with a plus sign) were acquired simultaneously, as were the other three slices.

without increasing scan time. In contrast to the Cartesian CAIPI acquisition with a slice acceleration factor of 2 [90], the radial CAIPI method potentially allows for higher slice and in-plane acceleration due to its robustness to in-plane undersampling and also more benign inter-slice interference. Another potential advantage of the undersampled radial acquisition is its robustness to inter-time frame motion compared to a Cartesian acquisition [60].
Figure 5.7: Results of different CAIPI factors for the ungated SPGR sequence. The top row shows a single band acquisition single band, followed by a multi-band factor of 3. The bottom shows the results using a multi-band factor of 5. As the multi-band factor increases, there is a clear degradation in image quality.

Figure 5.8: Results of different multi-band factors from the SMS saturation recovery sequence. The top row is from multi-band factor 1 (upper left), and MB=3 (upper right). The bottom row is the result from multi-band factor of 5. The multi-band factor of 5 degrades the image quality.

Although some initial non-CAIPI reports have appeared using the ungated SPGR sequence with no saturation pulses [78, 80, 82, 103], there have been few direct comparisons with saturation pulse methods [70, 78]. Our simulations show that the SPGR method can yield good CNR compared to saturation pulse methods that use relatively short saturation recovery times, although these comparisons depend on flip angle, TR, and the range of T1 values in the areas of interest.
Figure 5.9: Comparison between different reconstruction methods on one study subject acquired by ungated SPGR sequence with a multi-band factor of 3. The first row is the direct NUFFT result with combined coil sensitivity. The second row is the result from an iterative SENSE reconstruction. The bottom row is the result from the proposed new reconstruction method.

The use of CAIPI does not change these results. Moreover, the ungated SPGR sequence uses both RF and gradient spoiling, and the ungated saturation recovery sequence only employs RF spoiling (in order to reduce TR). How the imaging contrast is affected by these different types of spoiling also needs further investigation. In addition, the ungated SPGR method with golden angle radial acquisition provides a way to manipulate the temporal resolution by combining any number of radial lines to regroup images. This can also be done with saturation recovery sequences though the signal variations make it less straightforward [103].

It should be noted that the CAIPI phase modulation, which varies from excitation to excitation, when combined with the golden angle radial trajectory ordering yields a somewhat random phase modulation between adjacent radial spokes in k-space. We implemented a simulation at a multi-band factor of 2 to explore what affect this has on the image, and found that it had little affect on image quality. However, further investigation is needed at higher multi-band factors. Another
consideration in the 2D multi-slice approach is cross-talk effects; the non-ideal slice profile will make the excitation cover more area than the nominal slice thickness. Overlapping slices influence the slice profile of each slice. Acquiring large numbers of slices with small slice gaps requires further study. Finally, our experiments using both acquisition methods with a multi-band factor of 5 showed unacceptable image quality. Use of a multi-band factor of 4 or obtaining ECG-gated or breath-hold studies with less motion might be feasible and requires further investigation.

5.5 Conclusion

Our results suggest that radial simultaneous multi-slice acquisition for imaging two or three slices at the same time in an SMS ungated radial perfusion sequence is feasible. Both standard saturation recovery prepared perfusion sequences and SPGR methods without any saturation preparation can take advantage of acquiring slices simultaneously with this method. A constrained iterative reconstruction with TV and blockwise low rank provided better results than using an SMS SENSE method. Thus we expect that SMS for myocardial perfusion imaging will become widespread for both gated and ungated studies since spatial coverage can be increased nearly for free.
CHAPTER 6. SUMMARY AND FUTURE WORK

6.1 Summary

Cardiac perfusion MRI is a promising technique for detecting myocardial ischemia. High spatial and temporal resolution with whole heart coverage is desired to track contrast uptake patterns to distinguish the dysfunctional areas of the myocardial wall. In this dissertation, we have presented three novel techniques to achieve this goal. Our 3D gated saturation recovery sequence utilizes the standard saturation recovery sequence, but combines it with compressed sensing to enable the acquisition of a whole 3D volume in a fraction of a second, eliminating the need for cardiac gating. However, in this kind of acquisition, the signal levels (and hence image contrast) depend not only on the general acquisition parameters like TR, TE, and flip angle, but also very much on the order in which the k-space data is acquired. I developed a framework that allows the back-to-back comparison of two common k-space acquisition orderings (centric and reverse-centric) during a single contrast injection. (This is important, since it is nearly impossible to accurately compare contrast from MRI scans at different times with different contrast injections.) My analysis and tests demonstrated that a centric k-space acquisition ordering captures the contrast between enhanced and un-enhanced myocardium better than the reverse-centric scheme. However, I also noticed that the short duration RF pulses that we need to image this rapidly lead to non-ideal slab profiles (varying flip angles across the imaging volume), and this causes the contrast to vary from slice to slice across the imaging volume. I demonstrate that the reserve-centric k-space ordering scheme, while achieving lower contrast than the centric scheme, is more robust to these flip angle variations across the volume.

A second novel method I introduced in this dissertation (Chapter 4) is an ungated 2D acquisition technique for myocardial perfusion imaging using a radial (non-Cartesian) trajectory, which can eliminate the need for an ECG trigger or for the saturation recovery pulse. This results in a much simpler acquisition protocol. This novel method employs a rapid SPGR sequence to enable
the acquisition at steady state. Similar to the 3D acquisition case, I noticed that the short duration of RF pulse required again leads to a non-ideal slice profile, which actually significantly affects what flip angle should be used to achieve optimal contrast. The calculations that most groups use to determine the flip angle for optimal contrast completely ignore this non-ideal slice profile effect, and consequently they often arrive at a flip angle that will not give them optimal contrast. My work provides an analytical framework, based on Bloch equation simulation, for determining the flip angle that will actually achieve optimal contrast given a non-ideal slice profile. I then extended this work to consider multi-slice acquisitions (which suffer from cross-talk effects between slices as well), and did some preliminary work applying my framework to simultaneous multi-slice acquisitions.

Finally, in Chapter 5, I presented work demonstrating the combination of an ungated cardiac perfusion sequence with simultaneous multi-slice acquisition techniques. This novel method allows us to achieve higher slice coverage without losing spatial and temporal resolution. In this study, we also carefully analyzed the difference between SPGR acquisitions and saturation recovery sequences by utilizing the simulation framework I developed in Chapter 4. The results demonstrated that the ungated SPGR method has the potential to provide higher contrast-to-noise ratio than a saturation recovery sequence with less than 100ms saturation recovery time.

6.2 Future Work

Despite the remarkable progress in cardiac studies that has been achieved, there is still much work to do.

One of the large remaining problems in cardiac perfusion studies using MRI is the problem of physiological motion, such as breathing. In the studies outlined in this dissertation, we normally asked the study subjects to hold their breath during the actual MRI scans to avoid respiratory motion artifacts. In reality, the length of time that people can hold their breath varies considerably from person to person. This imposes severe limitations on MR acquisition time for subjects that can’t hold their breath very long. The development of techniques that allow subjects to freely breath during a cardiac perfusion MR scan is worth investigating. Such a technique could remove the breath hold constraint, and could keep image quality much more consistent across different individuals.
A second area that needs further study is the quantitative analysis of cardiac perfusion imaging. Quantitative analysis of cardiac perfusion data has been well studied for the traditional saturation recovery techniques, but very little work has been done for ungated acquisitions such as some of those presented here (especially for SPGR-based acquisitions).

Finally, the time required for image reconstruction for many of the techniques outlined in this dissertation is significant. While the images are acquired rapidly, the reconstructions must now happen offline and often take hours to days. GPU-based parallel computation techniques, or even novel cloud distribution computation platforms, could be explored to improve reconstruction speed.
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APPENDIX A. WHOLE BRAIN DYNAMIC CONTRAST ENHANCED IMAGING VIA COMPRESSED SENSING TECHNIQUES

A.1 Introduction

3D Dynamic Contrast-Enhanced (DCE) magnetic resonance imaging (MRI) is a well-established technique for noninvasive characterization of tissue physiology, and has found broad application in a wide range of diseases. Rapid T1-weighted acquisitions are used to record the uptake of an injected contrast agent. In the brain, recent developments in pharmacokinetic modeling methodology have enabled the separation of flow and permeability components in these T1-weighted acquisitions [108], providing a potential alternative to conventional T2*-weighted perfusion MRI and the limitations imposed by the use of EPI acquisitions [109]. Stringent sampling rate requirements are essential to acquire data rapidly enough to characterize the transit of the first pass of the bolus through the vasculature, resulting in corresponding limitations on spatial coverage and/or image resolution. In stroke, certain types of tumors, and other diseases of the brain in which lesions may be large or widely distributed, the ability to obtain rapid, high-resolution whole-brain coverage is highly desirable. In order to achieve this objective, acceleration factors of 3-4 relative to current state-of-the-art data acquisition are needed. Here, we demonstrate whole brain 3D DCE-MRI data, acquired at 2 mm isotropic voxel size and 4.3 sec temporal resolution using a weighted pseudo-random undersampling scheme.

A.2 Method

First a full dataset was acquired so that we could simulate different undersampling patterns and have a “truth” for comparison. A 3D spoiled gradient echo sequence was performed on a volunteer with a 1.5T whole-body MR scanner. A 0.1 mM/kg dose of Gd-BOPTA was injected. Scan parameters were TR = 2.84 ms and TE = 1.8 ms, flip angle = 12 degrees and the acquisition matrix for this protocol is $k_x, k_y, k_z, t = 128 \times 96 \times 20 \times 96$. A 7/8 partial Fourier acquisition was used
in the \( k_y \) and \( k_z \) directions, bandwidth = 490 Hz/pixel. In order to compare the difference between undersampled and fully sampled, the data from each coil was undersampled offline with a pseudo-random undersampling mask with an acceleration rate \( R \) of 6 and 12, as shown in Figure A.1 [26]. To reconstruct the undersampled images, we used the STCR algorithm with total variation (TV) as the constraint term in both the temporal direction and the spatial directions [60]. Then a 3D spoiled gradient echo pulse sequence was modified to \( R = 6 \) based on the variable density mask shown in figure A.1. Imaging parameters for this full volume coverage “real” scan include: TR = 2.81 ms and TE = 1.3 ms, flip angle 12 degrees, and bandwidth = 490 Hz/pixel, which are the same as the fully sample protocol. Changes from the fully sampled case include the acquisition matrix \( k_x, k_y, k_z, t = 128 \times 96 \times 96 \times 96 \). With acceleration rate \( R = 6 \), there are 1536 phase encodes per time frame. This data was reconstructed in the same way as the fully sampled dataset described above. Both datasets were processed to generate pharmacokinetic parameter maps by regression of measured concentration-time curves [110] using a linearized Extended Tofts-Kety algorithm with both tissue permeability and blood volume terms [111]. Arterial input functions were determined separately for each reconstructed data set using a semi-automated algorithm for identifying and classifying the earliest enhancing voxels.

Figure A.1: Three different sampling masks with acceleration rate \( R = 6 \) and \( R = 12 \) for simulation and \( R = 6 \) for real scan. The vertical direction is \( k_y \) and the horizontal direction is \( k_z \). \( k_y \) is 96 and \( k_z \) for simulation is 20 and for real scan is 96.

A.3 Result

From the first “simulated” dataset with full sampling, it appears that \( R = 6 \) undersampling can give kinetic parameters comparable to the full data (Figure A.2). For the real undersampled ac-
quisition, 96 slice coverage of the whole brain was obtained, keeping the same temporal resolution and isotropic 2 mm resolution. Figure A.3 shows one slice from the full coverage data.

<table>
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<tr>
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<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure A.2: Comparison of fully sampled results and the undersampled simulation. The first row shows fully sampled data and undersampled reconstruction result with acceleration rates equal to 6 and 12 respectively. The second row is the Ktrans map for each of the results, and the third row is the vb map.

<table>
<thead>
<tr>
<th>Transverse</th>
<th>Sagittal</th>
<th>Coronal</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure A.3: Full coverage of the brain.
A.4 Discussion

Accelerated DCE imaging of the brain can likely provide additional coverage, enabling isotropic resolution. Further studies are needed to assess the performance of the methods with respect to clinical tasks such as assessing the success of tumor treatment.
APPENDIX B. DARK RIM ARTIFACTS FROM MOTION IN HIGHLY ACCELERATED 3D CARDIAC PERFUSION IMAGING

B.1 Introduction

First-pass myocardial perfusion imaging is a promising method for characterizing ischemic heart disease. 3D acquisitions are also desirable since they can provide greater coverage of the heart than 2D imaging, with more accurate estimation of the size of ischemia [40]. However, 3D imaging requires a much longer readout than the 2D case, leading to more artifacts than 2D acquisitions even when acceleration schemes are used. Dark rim artifacts are one of the major factors that impede accurate quantification and diagnosis of ischemia even when the image quality is otherwise reasonable [112]. Dark rim artifacts are not yet completely understood even in 2D perfusion imaging, although Gibbs ringing and cardiac motion are thought to be the main contributing factors [112–114]. In this work, we demonstrate that motion can explain the dark rim artifacts we observe in a highly-accelerated 3D acquisition scheme for first-pass myocardial perfusion imaging. We also show that dark rim artifacts are sensitive to both k-space trajectory and the timing of motion relative to the readout.

B.2 Method

A numerical simulation was designed to estimate the motion artifacts using a numerical heart phantom that mimics the initial high contrast agent concentration in the left ventricular blood pool. The simulation applied the appropriate signal weightings in k-space based on the saturation recovery sequence. We used the same acquisition mask as we did in the real scan. In order to simulate the motion, we applied physical shifts to the numerical phantom in the phase encode direction at different times (after 5PEs, 10 PEs, 20 PEs 30PEs, 40PEs, 50PEs, 60PEs, 70PEs, 80PEs and 90PEs). Image reconstruction was performed using a compressed sensing algorithm
with total variation (TV) applied as the constraint term in both the temporal and spatial directions for both real and simulated data [60].

B.3 In Vivo Experiments

The sequence was tested in vivo on a canine and 3 human subjects with a 32-channel coil. Image reconstruction was performed offline using the TV reconstruction.

![In vivo result](image)

Figure B.1: In vivo result shows the dark rim artifacts (white arrows) in the centric order acquisition (top row) for two slices near the middle of the slab. The bottom row is the reverse-centric order, in a time frame adjacent to that in the top row. The reverse-centric doesn't show dark rim artifact in this study.

B.4 Result

We observed severe dark rim artifacts using centric ordering in one of the in vivo datasets, shown in Figure B.1. We were able to simulate a similar artifact by shifting the virtual phantom during the early phase encodes, shown in Figure B.2. We observed that dark rim artifacts are sensitive not only to motion, but also the time during readout at which the motion occurs. From the simulation, it can be seen that if the motion occurs close to the time when the center of k-space is sampled, the artifacts are more severe. This is seen when the shift happens after the 5th PEs and
10th PEs for a centric phase encode order, and at the 90th PEs for a reverse-centric order. Very little artifact is observed when the shift occurs near the middle phase encodes of the acquisition. For example, motion near the 50th PEs causes very little artifact in both centric and reverse-centric scans.

![Figure B.2: Center slice taken from the 3D simulation, the result shows the artifacts due to the motion along the phase encode direction at different points in one time frame. Strong artifacts appear with the centric order (row 1 first two with arrow) when the motion happens earlier. A similar artifact was observed in the reverse-centric order (row 2 last two with arrow), when the motion happens close to the end of the 98 phase encodes.]

B.5 Conclusion

These results extend work by others [112–114] that showed from GRE scans that motion in 2D acquisitions could in theory produce dark rim artifacts. The relatively long 3D acquisition here is likely more sensitive to motion, and simulations were used to show that simple translations such as from sudden respiratory or cardiac motion can generate dark rim artifacts in undersampled 3D acquisitions. Moreover, the PE ordering plays a role since effects are larger when the center of k-space is sampled during significant cardiac motion. Based on this result, one could devise phase encode ordering schemes to mitigate the dark rim artifact. For example, occasionally revisiting the center of k-space might allow for a method to reduce the severity of the dark rim artifact caused by motion.
APPENDIX C. COMPARISON OF HIGHLY ACCELERATED TV AND LOW RANK METHODS FOR BREAST DCE DATA

C.1 Introduction

Dynamic Contrast-Enhanced (DCE) magnetic resonance imaging (MRI) of breast tumors provides a promising method for the evaluation of vessel permeability in the tumor area. By analyzing the time curve of uptake and washout, DCE-MRI can also be used to help determine if the tumor is benign or malignant. High spatial resolution is desirable to identify tumor location, and high temporal resolution can improve the accuracy of quantitative analysis of the uptake and washout curves [115]. However, high spatial resolution typically comes at the expense of high temporal resolution, and vice versa. For this reason, a variety of highly accelerated image acquisition schemes are under exploration to enable the acquisition of images with both high spatial and temporal resolutions for DCE-MRI. Recently, a number of constrained reconstruction algorithms using Total Variation (TV) [60] and Low Rank (LR) [116] have been proposed to mitigate the trade-off between spatial and temporal resolution. In this work, we compare two of these acceleration methods on DCE breast MRI.

C.2 Method

Bilateral imaging with fully sampled k-space data was acquired on two subjects; both with confirmed breast lesions, using 3D spoiled gradient echo sequence. Imaging was performed on a Siemens 3 Tesla scanner equipped with a seven channel dedicated breast coil. A 0.1 mL/kg dose of Omniscan was injected at 4 mL/sec after a 20 mL saline flush at 2 mL/sec. Scan parameters for the first subject were TR = 2.35 ms and TE = 0.99 ms, while those for the second subject were TR = 3.16 ms and TE = 1.24 ms. Both scans employed a flip angle of 10 degrees and an acquisition matrix $k_x, k_y, k_z, t = 256 \times 83 \times 64 \times 43$. A 3/4 partial Fourier acquisition was used in both the $k_y$ and $k_z$ directions. Temporal resolution was 12 seconds for the first scan and 15 seconds for the
second [117]. To compare the two different reconstruction methods, the data from each coil was undersampled offline with a pseudo-random undersampling mask with an acceleration rate $R$ of 13. The undersampling pattern for each time frame was chosen differently to obtain the incoherent aliasing required by compressed sensing techniques [26]. The reconstructed images were then compared both qualitatively and quantitatively to the images reconstructed from the fully-sampled dataset. The total error energy and signal-to-error ratio (SER) were used as quantitative measures of reconstruction performance.

![Two time frame sampling masks using variable density with acceleration rate $R = 13$.](image)

Figure C.1: Two time frame sampling masks using variable density with acceleration rate $R = 13$.

<table>
<thead>
<tr>
<th></th>
<th>TV</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject 1 SER (dB)</td>
<td>18.44</td>
<td>21.51</td>
</tr>
<tr>
<td>Subject 1 Total Error</td>
<td>$2.47 \times 10^4$</td>
<td>$1.77 \times 10^4$</td>
</tr>
<tr>
<td>Subject 2 SER (dB)</td>
<td>16.27</td>
<td>17.24</td>
</tr>
<tr>
<td>Subject 2 Total Error</td>
<td>$4.48 \times 10^4$</td>
<td>$4.07 \times 10^4$</td>
</tr>
</tbody>
</table>

Table C.1: Comparison of the quantitative results from TV and LR.

C.3 Result

Both TV and Low rank show impressively good results even at the acceleration rate $R = 13$, although LR shows slightly better performance than TV (Table C.1). As can be seen in Figure C.2, the LR images appear slightly more blurred than the TV images. However, LR appears to
better match the ROI intensity curves in most cases (Figures C.2c(3) and C.2f(3)). TV also blurs the images slightly, while smoothing out some of the detail in the ROI intensity curves (Figures C.2c(2) and C.2f(2)).

<table>
<thead>
<tr>
<th></th>
<th>(a) Subject 1</th>
<th>(b) MI in tumor area</th>
<th>(c) MI in non tumor area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full data</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td>TV</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td>Low Rank</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>(d) Subject 2</th>
<th>(e) MI in tumor area</th>
<th>(f) MI in non tumor area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Full data</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td>TV</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td>3</td>
<td>Low Rank</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
</tbody>
</table>

Figure C.2: Comparison of fully-sampled reconstruction, TV (R = 13), and LR (R = 13). Column (a) shows reconstructed images from a single coil (first subject), while column (d) shows images reconstructed from all seven-coil channels (second subject). Row 1 shows the fully-sampled reconstruction, while rows 2 and 3 show the R = 13 reconstructions for TV (row 2) and LR (row 3). Columns (b), (c), (e), and (f) show time curves of the mean signal intensity (MI) as a function of frame number in the ROIs indicated by the red boxes.
C.4 Discussion

Discussion: This work demonstrates that high acceleration rates are potentially feasible in DCE-MRI using both the TV and LR constrained reconstruction algorithms. Future work will seek to validate these results in actual accelerated patient scans. We will also explore the combination of different constraints to further improve image reconstruction quality.