March 2018

Multi-Channel MR Phase Image Processing for Non-Contrast Tissue Characterization

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A thesis submitted in partial fulfillment of the requirements for the degree in Doctor of Philosophy

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Abstract

Magnetic resonance imaging (MRI) enables tissue characterization using the intrinsic tissue properties. By manipulating a number of imaging parameters different image contrasts can be achieved. Multi-echo gradient recalled echo (ME-GRE) enables acquisition of two distinct images, magnitude and phase, in a relatively short time. Phase image, specifically, contains a wealth of information for generation of quantitative maps, with the local tissue susceptibility differences as a source of contrast. GRE imaging is sensitive to field-inhomogeneities. This challenge presents more strongly in multi-channel acquisition, where the coil sensitivity variations impose complications in extracting information from the underlying anatomy. This calls for a phase-sensitive coil-combination approach. While many approaches have been presented to-date, ME-GRE remains an unpopular clinical tool due to the commonly observed susceptibility artifacts in phase and magnitude images.

This thesis presents ME-GRE acquisition considerations and post-processing tools for tissue characterization using readily available clinical acquisition protocols. The main contribution of the work presented here is in the proposed post-processing techniques that enable extraction of quantitative maps from these image data. These post-processing techniques are designed, optimized and validated for the first time through the work done in the present dissertation. The proposed approaches demonstrate the benefits of extracting information from each channel in the array of coils prior to combining the images.

The proposed techniques were applied in neurological and cardiac imaging. The former allowed for development of a robust approach, which enabled the extraction of tissue susceptibility information. The latter allowed for translation of these techniques to account for region-specific phase biases as well as different chemical environments. Quantitative maps of the brain and multi-parametric quantitative cardiac maps were generated for healthy participants as well as for cohorts of patients with multiple sclerosis and heart failure. The work of this thesis can easily be translated into clinic as it does not change the routine image acquisitions and has a focus on the post-processing workflow. With the techniques developed, non-contrast tissue mapping is made possible, especially benefiting patients with poor renal function.

Keywords: tissue characterization, multi-channel imaging, MR phase image, magnetic susceptibility, quantitative maps, heart failure, multiple sclerosis
Co-Authorship Statement

This thesis is presented in an integrated article format and Chapters 2 through 4 are based on the following publications that are either published or under review.


My contribution to this work included defining the research question, formulating the experimental steps to answer the question, acquiring and processing the data. Additionally, I wrote the manuscript. Dr. Junmin Liu provided the code for part of the technical methods, which had been previously published (MRM, 2015; 73(4):1654-61); additionally he oversaw the initiation of this project and provided valuable insights for the improvement of the methods. I.S. assisted in implementing the processing algorithms developed through the course of this project in C to significantly reduce the processing time. Dr. Ravi Menon provided access to the data used in this manuscript and shared his expertise of the high-field imaging system. Dr. Maria Drangova provided technical reviews throughout the evolution of the project, shared valuable suggestions on improving the approaches, and immensely helped in the process of manuscript preparation. I worked on a single round of revision comments that were received from the editorial team at JMRI prior to the acceptance of the manuscript.


My contribution to this work included defining and refining the research question through the course of the early stages of the project. I supervised Dr. Jacob Matusinec to implement an earlier version of the experimental setup, which was presented at the International Society of Magnetic Resonance in Medicine. I subsequently refined the procedures, completed the processing of the previously acquired data and designed the study as it stands at submission. Dr. David Rudko recruited the patients as part of a previous study (Radiology, 2014; 272(3): 851-864), but additionally provided valuable insights on the methods of the manuscript. Dr. Benjamin YinMing Kwan, Dr. Fateme Salehi and Dr. Manas Sharma were the clinical collab-
orators from neuroradiology, who completed the image assessments as experts. Dr. Marcelo
Kremenchutzky was the neurologist who recruited the patients with Dr. David Rudko and
provided valuable clinical guidance and insights during the course of the project. Dr. Maria
Drangova initiated the collaborations with the clinical contacts. Dr. Ravi Menon and Dr. Maria
Drangova provided valuable insights through the course of the project as well as for the formul-
lation of the manuscript.

Chapter 4: Z. Hosseini, J. Liu, N. Tzemos, R. Yee, M. Drangova, ”Multiparametric my-
ocardial mapping from a single acquisition by non-iterative correction of individual channel
phase errors”, submitted to Magnetic Resonance in Medicine.

My contribution to this work included defining the research question, assisting in preparing
the ethics application and image acquisition for the recruited patients and the control volun-
teers. In addition, I implemented and performed the signal processing and data analysis. Dr.
Junmin Liu provided guidance throughout the course of this project for integrating his previ-
ously published work (MRM, 2015; 74(4):1177-88). Dr. Nikolaos Tzemos was the clinical
expert in interpreting the clinical significance of the imaging results. Dr. Raymond Yee was
the clinical collaborator who diagnosed and recruited the patients for this study. Dr. Maria
Drangova oversaw the progress of the project and provided valuable constructive feedback
throughout the course of the work. In addition, Dr. Maria Drangova initiated the collaboration
with the clinical contacts. I wrote the first revision of the manuscript and implemented the
valuable feedback received from the co-authors and the MRM reviewers.
Acknowledgements

I deservedly would like to start by acknowledging the support of my supervisor, Dr. Maria Drangova, throughout my PhD studies and her earnest and critical reviews of my work at each stage of my progress. Without Dr. Drangova’s support and guidance, the completion of this research would not be possible. I sincerely thank her for enabling me to develop and test new ideas. Her valuable insights helped me become a better scientist and develop a critical view of my research field.

I thank my advisory committee (Dr. Junmin Liu, Dr. Charles McKenzie, Dr. Raymond Yee and Dr. Robert Bartha) for their time and incredibly valuable guidance and insights over the course of my PhD.

I acknowledge the unconditional support of my family who helped me balance my stressful life in the last few years and to find happiness and harmony in their presence. This dissertation is dedicated to my father, who taught me to rise above my stereotypes. It is dedicated to my mother who taught me to have principles and stand up for what I believe. It is dedicated to my sisters, Boshra and Shera, who taught me to have a big heart and to always pay attention to my mental and physical health. It is dedicated to my brother, Mateos, who taught me to respect myself and never regret the time and money I invest in myself.

I acknowledge generous and true friends, Charmaine Cruje, Olivier Nguyen, and Sagar Buch, who offered me their genuine friendship, support and advice.

I acknowledge the numerous hours Dr. Aaron Ward spent with me, in the classroom and otherwise in meetings, teaching me to be strategic. I acknowledge the magnanimous help of Dr. Karla Miller, who was a long distance mentor, but did not hesitate to remotely meet with me; she helped me find ways to give back to my research society (the International Society of Magnetic Resonance in Medicine - ISMRM), which has given me and many other trainees so much - I additionally acknowledge the generous help of Dr. Mark Griswold for his support to enable me to get involved with ISMRM. I acknowledge the generous time and help of Dr. Darren Meister, who enabled me to unravel my inner leader. I have been fortunate to have met and worked with these individuals during my PhD training.

I thank the Biomedical Engineering Graduate Program, Christine Ellwood, Dr. Terry Peters, Dr. Jim Johnson and Dr. Jim Lacefield, who gave me and many others their support.
Life is difficult. This is a great truth, one of the greatest truths. It is a great truth because once we truly see this truth, we transcend it. Once we know that life is difficult - then life is no longer difficult. Because once it is accepted, the fact that life is difficult no longer matters.

M. Scott Peck.
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List of Abbreviations

2D - two dimensional
3D - three dimensional
ACC - adaptive channel combination
ACS - auto-calibration signal
AUTO-SMASH - automatic SMASH
B0 - main magnetic field of MRI
B0-NICE - B0 mapping with non-iterative correction of phase errors
BOLD - blood oxygen level dependent
CPMG - Carr, Purcell, Meiboom, and Gill
CVS - central vein sign
ECG - electrocardiogram
ECM - extracellular matrix
EDSS - extended disability status scale
FF - fat fraction
FLAIR - fluid attenuated inversion recovery
FOV - field of view
FSL - Functional MRI of the brain Software Library
GRE - gradient recalled echo
HF - heart failure
HPH - homodyne high-pass filter
IC-NICE - individual coil processing with non-iterative correction of phase errors
IEV - inter echo variance
IR - inversion recovery
LA - left atria
LFS - local frequency shift
LPS - local phase shift
LGE - late gadolinium enhancement
LV - left ventricle
ME-GRE - multi-echo gradient recalled echo
mIP - minimum intensity projection
MRI - magnetic resonance imaging
MS - multiple sclerosis
NAIMS - nother american imaging in multiple sclerosis
PDF - projection onto dipole fields
PPI - partially parallel imaging
ppm - parts per million
PUROR - phase unwrapping using recursive orthogonal referring
PVWML - perivenous white matter lesion
QSM - quantitative susceptibility mapping
R2 - transverse relaxation rate
rads - radians
RDF - relative difference field
RF - radio frequency
ROI - region of interest
RRMS - relapsing-remitting multiple sclerosis
SHARP - sophisticated harmonic artifact reduction of phase data
SMASH - simultaneous acquisition of spatial harmonics
SNR - signal to noise ratio
SR - saturation recovery
SVD - singular value decomposition
SVD-CC - SVD channel combination
SWI - susceptibility weighted imaging
T - Tesla
T1 - longitudinal recovery time
T2 - transverse decay time
TE - echo time
TI - inversion time
TR - repetition time
VD-AUTO-SMASH - variable density AUTO-SMASH

WML - white matter lesion
Chapter 1

Introduction

1.1 Overview

Magnetic resonance imaging (MRI) is an established part of many clinical diagnostic and interventional protocols. With the ability to utilize intrinsic tissue properties to generate contrast between different tissues, MRI enables the non-invasive characterization of tissue and the differentiation of healthy and diseased tissue components.

MR imaging signal is complex valued and as a result gives rise to two separate images, magnitude and phase, each of which provide different means of assessing the health of the underlying tissues. It is not surprising that, whereas magnitude images can relatively easily be interpreted or otherwise processed to generate quantitative maps of the underlying tissue, the phase image, due to its inherent cyclic property, introduces unique challenges in post-processing. The cyclic nature of phase leads to wrapping, while other factors such as the external (background) sources of field as well as the field gradients between different tissue types and field shift due to the chemical environments, add a bias to the phase image.

A growing body of evidence over the last two decades lends support to the significance of the role MR phase images play in quantitative assessment of pathologies. As a result, focused research attention has been dedicated to developing more robust phase processing techniques. The current MR image acquisition practice, in clinical and research applications, involves multiple receiver coils, which calls for phase-sensitive channel combination. This has received attention from several research groups but a robust processing pipeline is yet to be proposed.
This thesis presents the results of new approaches for processing complex MRI data acquired using multiple receiver coils; these methods are further compared to the conventional processing practices to validate the resulting images and assess the potential advantages resulting from the proposed approaches.

1.2 Background

Magnetic resonance imaging is an established and often preferred non-invasive imaging modality in many different clinical applications [1, 2, 3]. This is due, in part, to the outstanding soft tissue contrast and the lack of ionizing radiation. Nevertheless, MR imaging is faced with several difficulties in acquisition and post-processing. MRI is an inherently time-consuming imaging modality, and the novel fast acquisition techniques are not readily available in the clinic. Therefore the patient motion, as well as the natural tissue motion (e.g. peristalsis, cardiac and respiratory motion) often result in suboptimal image quality.

The amount of signal acquired by conventional MRI systems is heavily influenced by the hydrogen content in the underlying tissue. The placement of a hydrogen-rich object inside the magnetic field of a MRI system, results in alignment of the spin isochromats along the field (i.e. with or against the field) and the application of an excitation radio frequency (RF) pulse with specifically designed parameters results in a known pattern of motion for these spin isochromats [4]. This gives rise to two phenomena, which dictate the contrast in the resulting image: the longitudinal relaxation and the transverse decay time constants. By considering the physical properties of the tissue, it is possible to design special pulse sequences that result in images with known contrast between various tissues and tissue compartments. These approaches are referred to as image weighting in MR imaging, which conventionally utilize the magnitude component of the MRI data.

In addition to intrinsic tissue properties, which are used as conventional means of generating contrast between the different tissues and even their sub-components, exogenous contrast agents have also been used. These exogenous contrast agents have been developed for MRI applications in order to shorten the acquisition time and to enhance the contrast between different tissues [5]. An area of major interest for contrast enhanced MRI is in time-sensitive
applications such as cardiac imaging.

Gradient-recalled echo (GRE) imaging sequence allows for extraction of meaningful phase information in addition to magnitude data. The phase component of multi-echo GRE image data contains a wealth of information but its processing is non-trivial. The immediate challenge in utilizing phase, which was the reason for its elimination in early years of MRI, is its inherent cyclic topology. This property of phase leads to its values being restricted to the range of \([-\pi : \pi]\), which means at the upper boundary of this range the phase value will wrap to the lower boundary. In addition, phase is directly affected by additional field contribution due to large gradients at the air/tissue and bone/tissue interfaces. Other factors such as hardware imperfections can cause additional inhomogeneity in the main field, the contribution of which to phase component of the image is unavoidable.

In addition to being a standalone source of information, the phase images in tandem with magnitude data provide the means of image correction and restoring the full dynamic range of the signal. One such instance of image correction using the phase information is in inversion recovery sequences such as late gadolinium enhancement (LGE) MRI [6]. When solely using the magnitude image to compute such images, it is impossible to know the information about the direction of the magnetization and as a result only half of the dynamic range of the signal is used. In phase-sensitive inversion recovery [7] the phase information is used to compute the full dynamic range of values thereby achieving a higher SNR and a more accurate contrast between different tissues. In addition to correction applications, complex MRI data can be used to extract multiple quantitative maps of the tissue, including field map, fat fraction, relaxation map and more.

As mentioned above, raw phase data as retrieved from the MRI scanner is not an appealing image to work with as it often contains wraps, through which the underlying tissue is hardly differentiable. But an additional challenge arises in the common clinical and research image acquisition practice, which utilize specialized array of receiver coils to enhance the image quality and specifically signal-to-noise ratio (SNR). An immediate implication of this practice is the requirement for robust coil combination techniques. With the advent of phase imaging application in many clinical fields, more research and development focus has been dedicated to phase-sensitive coil combination techniques [8, 9, 10]. A recent approach by our group
explored the reverse approach by firstly processing the individual channel phase data prior to application of channel combination [11]. The result of this channel combination approach is high-pass filtered phase data, and therefore its application is limited to imaging scenarios that do not require low frequency contents of the tissue (e.g. susceptibility weighted imaging (SWI)). This phase-sensitive channel combination approach inspired the overall motivation of this dissertation, which was to develop robust post-acquisition processing pipeline for MR images that, regardless of anatomical region, enables the extraction of high quality quantitative maps of the tissue based on information in the phase and magnitude data by processing the individual channel images prior to application of channel combination. This approach is the reverse of the conventional clinical and research practice where channel combination is preceded by other post-processing steps. By design, this approach requires long processing time and therefore, for practicality, non-iterative methods are desired to enable parallel computation.

1.3 Clinical Motivation

The work of this dissertation spans neurological and cardiac applications, the clinical motivation behind each of which is presented here. While the specific clinical patient groups are presented in each of the following two sub-sections, the application of the techniques developed through the work of this dissertation may be expanded to several other clinical cases. As such, each section starts with a generic introduction of the MRI techniques used for the specific neurological and cardiac applications prior to introducing the specific clinical cohorts.

**Neurological Application: Phase-Driven Contrast**

Susceptibility weighted imaging (presented in detail in section 1.5.3) is an established clinical tool for many neurological applications, including but not limited to visualization of cerebral veins and microbleeds [3], haemorrhage [12, 13], and differentiation of tumors [14]. SWI utilizes the information from the phase component of MR images to generate contrast in the magnitude images. In order to effectively extract the susceptibility-based information from the phase data, careful processing steps must be designed. It has been demonstrated that poor quality phase images result in artifactual signal mimicking the appearance of microbleeds [15].
Alternatively these artifacts may take the appearance of vessels.

One of the clinical applications where SWI provides potentially useful information is in multiple sclerosis (MS). MS is a neurodegenerative autoimmune disorder, which is characterized by premature demyelination of white matter neurons. MS is clinically diagnosed, after the presentation of neurological symptoms, using magnetic resonance imaging and specifically the McDonald criteria, which require the observation of changes in white matter demyelinations in space and time [16]. In doing so, patients are monitored over a followup period and the changes in white matter lesions are documented. White matter lesions appear as abnormal hyperintensities on the T2-weighted fluid attenuated inversion recovery (FLAIR) images and, therefore, MRI plays a key role in diagnosis and monitoring of MS. However, there are other neurological disorders that mimic MS in the appearance of white matter lesions on T2-weighted FLAIR images (e.g. neuromyelitis optica spectrum disorders) [17]. Therefore, the knowledge of MS-specific white matter lesion morphology may benefit the diagnosis and staging of this disorder. More recent studies have demonstrated the ability of magnetic resonance imaging for earlier diagnosis of MS [18, 19, 20]; earlier diagnosis of MS enables the earlier start of therapeutic treatment, which may result in improved outcomes [21].

Perhaps a more specific imaging biomarker is the central vein seen in the core of the MS plaques. The histological observations of central vein goes as far back as 1860’s [22], a finding which is now termed the central vein sign (CVS). The perivascular space is known to be an ideal location for immune cells and, during an inflammatory response, these regions are primarily affected [23, 24]. The histological observation of CVS was demonstrated in vivo using MRI studies [25]. The early imaging studies, performed at lower field strength (1.5T), demonstrated high percentage of MS lesions with central vessel in their core. Later studies, translated into high field strengths, reported similar findings.

The methods employed for visualizing cerebral venous vasculature has not been consistent in the study of CVS and this has impeded the translation of this imaging biomarker into a clinically used diagnostic test. Due to the small size of the veins, non-contrast venography techniques, such as SWI provide great advantage over contrast-based imaging (Fig. 1.1). The quality of the phase data that is used to generate the SWI determines the extent to which CVS can be accurately quantified and assessed in MS patients, which in turn determines the success
of utilizing CVS as an imaging biomarker to differentiate MS from its mimics.

Figure 1.1: High resolution FLAIR (a) and SWI (b) images (acquired at 7T) and the superimposed FLAIR/SWI (c) enable the simultaneous visualization of MS white matter lesions and the spatial relation of the venous vasculature with respect to these lesions enabling the *in vivo* assessment of CVS. Several magnified regions are shown in panel (d), with the magnified FLAIR regions shown on the left panel and the corresponding magnified SWIs shown on the right.

The variations in the approaches taken by scientific and clinical research groups to identify CVS has led to a new consensus statement published by the North American Imaging in Multiple Sclerosis (NAIMS) [26]. This statement presented a set of guidelines that must be considered in studying MS using CVS as an imaging biomarker. The consensus statement provided an overview of possible morphological appearance of the MS lesions with respect to cerebral venous vessels and proposed future studies to focus on deriving a radiological definition for CVS.

The derivation of an accurate radiological definition of CVS would benefit from initial imaging at high field [27, 28, 29]. Imaging at high field has been shown to result in enhanced diagnostic ability, specifically for multiple sclerosis [30]. However, phase image acquisition and processing is more challenging at higher field strength, which is a result of large gradients often observed at air/tissue interfaces. One way that this challenge has been overcome is to employ the magnitude image for *in vivo* visualization of cerebral venous vasculature. However, there is no doubt about the superior ability of SWI to delineate small vessels compared to solely the magnitude image.

Recently, several reports of incidental findings of white matter lesions in otherwise healthy individuals have emerged [31, 32]. The first motivating clinical application of this dissertation is the implementation of the guidelines of the NAIMS consensus and derivation of an accurate
1.3. **Clinical Motivation**

Radiological definition for CVS. In doing so, the image data of a cohort of relapsing-remitting MS patients and a cohort of healthy participants with benign white matter lesions are used.

**Cardiac Application: Myocardial Tissue Characterization**

Magnetic resonance imaging is used in many clinical cardiac applications to evaluate the structure and function of the heart. MRI offers an effective and reproducible means of assessing myocardial tissue and cardiac function using the intrinsic tissue contrast; for instance standard cinematic images (*i.e.* cine) can be acquired of patients to enable the non-invasive visualization of cardiac function.

Cardiac MRI applications (*e.g.* coronary angiography, myocardial tissue characterization and scar imaging, etc.) often make use of exogenous contrast agents to enable faster imaging as well as enhanced contrast between different structures. One of the cardiac MR imaging applications that vastly benefits from the use of contrast agents is LGE, which is the gold standard of imaging myocardial scar. Myocardial scar has been classified as either diffuse or replacement. Diffuse scar has only been shown using the contrast-based measurements of extracellular volume [33, 34]. The main cause of replacement fibrosis in the myocardium is the excessive presence of extracellular matrix (ECM). The expansion of ECM results in an increased amount of collagen I in the myocardial wall [35]. As collagen I has a higher stiffness than myocyte, this results in stiffening of the myocardium. In addition, electrical impulse in the cardiac circuit cannot propagate properly in such an environment. Additionally, using contrast-based imaging, fatty infiltration has previously been identified within chronic myocardial scar [36, 37].

A major downside of contrast-based imaging is the nephrotoxic effects caused by MRI contrast agents (*e.g.* nephrogenic systemic fibrosis [38]). As a result of early catastrophic outcomes of injecting patients with poor renal function, more strict guidelines are employed in the clinic to exclude such patients from contrast-based studies [39, 40, 41]. Availability of a robust non-contrast imaging approach would benefit these patients.

Non-contrast means of imaging the heart have also been proposed using parametric tissue mapping (*i.e.* $T_1$, $T_2$, and $T_2^*$-mapping). Expectedly, these approaches require specialized cardiac pulse sequences to account for cardiac and respiratory motion [42, 43]. These imaging sequences are not always available on clinical scanners. Additionally, these imaging approaches...
utilize multiple cardiac cycles to acquire image data at multiple time-points to enable accurate fitting. As such, identification and removal of motion-related artifacts are essential in correct calculation of relaxation times for a given pixel.

Multi-echo GRE imaging allows for fast imaging and the acquired data enables the extraction of multiple quantitative maps of the heart. For instance, water/fat separation techniques have been employed to visualize fatty infiltration in chronic scar [36] using multi-echo GRE imaging. This was accomplished at 1.5T, in order to avoid unwanted field inhomogeneity-related dephasing and signal loss at the lung/myocardium interface. While the superior image SNR of > 3T systems is well established, imaging, and especially MR phase imaging is less appealing at higher field strength of 3T; this is because the large phase gradients at the interface of the heart with the lungs are more pronounced at higher fields and result in images with sub-optimal clinical utility.

The specific patient group that were recruited and studied for the work of this dissertation were heart failure (HF) patients; HF is a condition in which the patient’s heart is unable to pump enough blood to the systemic circulation. The role of contrast-based MRI, and specifically LGE, in predicting HF patient response to interventional procedures is well established [44, 45, 46]. Using LGE together with other typical cardiac imaging protocols (e.g. cine) it is possible to differentiate the regions of scar from healthy myocardium (Fig. 1.2). Utilizing such imaging methods, the implantation location for device leads (e.g. cardiac resynchronization therapy device), can be carefully determined, thereby improving patient response to therapy.

The previously mentioned nephrotoxic effect can particularly affect heart failure patients, as a large HF patient population also suffer from poor renal function. Therefore these patients are often unable to benefit from pre-procedural planning using LGE.

The second motivating clinical application of this dissertation is to develop and validate a robust post-processing pipeline for multi-echo GRE images that enables the extraction of quantitative phase- and magnitude-based maps of the heart without the need for administration of exogenous contrast agents.

The following sections present a background on the current state of a number of key topics related to the work of this dissertation. For the interested reader, Appendix A includes a more in-depth theory on these topics.
1.4 MRI Phase Image

The physics of MR imaging revolves around the phenomenon of the precessing magnetization vector around the main static field. The information about the orientation of the magnetization vector is in the phase component of MR images, which is the cornerstone of many effective imaging techniques.

Whereas the magnitude component of MR data is readily comprehensible, the phase component was traditionally discarded due to the presence of phase wraps and therefore the difficulty of recognizing the underlying tissue. The field of MRI research and clinical applications has come a long way since, demonstrating the extent of information that can be extracted from an unwrapped phase image.

Information in MRI Phase

Several quantitative measures can be extracted from MRI phase. In order to calculate any of these quantitative maps from multi-echo GRE data a phase map must be extracted from the complex raw data. Once the initial phase map is available, the local field variations can be extracted and used to enhance the contrast between different tissues using their susceptibility differences [47]. The local phase information at the tissue boundaries are high frequency variations and are often extracted through high-pass filtering of the unwrapped phase or otherwise.
by application of Homodyne filter to the original (wrapped) complex data \[48\].

Additionally, information about the chemical shift effect, which reflects the chemical environment in which the different hydrogen atoms are located, can also be extracted from the phase. This enables the distinction of clinically significant tissues such as fat. The hydrogen atoms on the fat macromolecule have a shorter $T_1$ than other tissues and often appear bright on MR images. This interferes with many contrast-based techniques, which are timed specifically to illustrate pathologic tissue as bright. Phase-based techniques that enable water/fat separation can, therefore, enable the accurate distinction of pathologic tissue.

**Requirements for Phase Image Processing**

It was mentioned earlier in this chapter that the current practice of MR image acquisition is to utilize specialized receiver coils for each anatomical region. Phase images are specifically sensitive to the channel combination approach used. The phase wraps present in the imaging field of view (FOV) of a given coil may have an interfering pattern with respect to one or more of the other coils in the array. This results in destructive interference, which in turn results in a singularity or increased phase noise. Singularities in the final image cannot be unwrapped and therefore appear as artifacts in any derived quantitative data. Increased phase noise will complicate phase unwrapping; this is because definite evaluation of phase in low signal regions, or equivalently high noise regions, is not possible.

The advances made in fast acquisition and sophisticated post-processing techniques, including phase-sensitive channel combination approaches that have been proposed (e.g. \[8\]), have facilitated the extraction of the above-mentioned information from the phase data. The following sections provide an overview of the current state-of-the-art processing steps for extraction of quantitative maps from acquired phase data.

### 1.5 Quantitative Phase Processing

The robust extraction of tissue information from MR phase data relies heavily on the quality of the phase unwrapping technique employed to calculate the initial phase map. Inaccuracies such as remnant phase wraps, open-ended fringelines, and singularities reduce the diagnostic
efficacy of the resulting images. Once the initial phase map is calculated, further processing can be employed, as discussed in Sections 1.5.2 to 1.5.5, for calculating images of clinical utility.

### 1.5.1 Phase Unwrapping

Figure 1.3 demonstrates the behavior of phase in three imaging planes (axial, sagittal, and coronal, from top to bottom) when a 3D acquisition protocol is employed. The pattern of the phase wraps demonstrate the spatial location at which the limits of the allowed range of phase values are reached. It is clearly demonstrated in this figure that the wraps increase in number and shift in space with increasing echo time. Several approaches to phase unwrapping have been proposed, which can be divided into three paradigms.

![Figure 1.3](image)

Figure 1.3: The evolution of phase over time is shown for a 3D dataset on each of the axial (top), sagittal (middle) and coronal (bottom) planes, at four consecutive echo times - images acquired at 7T; TEs: [12.15,16.64,21.33,26.22] (ms).

The most commonly used phase unwrapping paradigm is the approach where phase is treated as a quantity evolving linearly over time [49, 50, 51, 52, 53]. It is assumed that the gradient of the phase between any two neighbouring voxels is less than $2\pi$. Therefore, the
change in phase can be calculated using the following equation:

$$\phi_{\text{lin}}(r) = \phi_{\text{wrapped}}(r) + 2\pi n$$  \hspace{1cm} (1.1)

In the equation above, $\phi_{\text{wrapped}}(r)$ is the measured phase, and $n$ represents the number of times the transverse magnetization vector has rotated around the unit circle. The unwrapped phase, $\phi_{\text{lin}}(r)$ can then be processed using a filter with appropriate kernel design in order to extract information about the tissue of interest.

The second paradigm involves the direct application of Homodyne filtering [48] to the original wrapped complex data and has a popular application in the susceptibility weighted imaging (SWI) literature [47]. This filter does not exclusively perform phase unwrapping, but rather utilizes the complex data to estimate a background field, which is then subtracted from the original phase to give a high-pass filtered phase that contains local anatomical information (with almost no phase wraps, depending on the imaging echo time).

The first and second phase processing paradigms assume a linear phase evolution over time. Nevertheless, as was mentioned earlier, phase is inherently cyclic. The third phase processing paradigm aims to model the cyclic property of phase in an objective function in order to enable the calculation of a background and anatomical phase map [54]. The background and the anatomical phase are then separated in a similar way to the Homodyne approach in the second paradigm.

Each phase processing paradigm has its own benefits and drawbacks; the first paradigm is slow, but performs a more thorough processing and results in a more accurate phase map. The second paradigm is fast, but often suffers from remnant phase wraps, particularly at longer echo times, which are necessary for susceptibility weighting. The third paradigm aims to combine the best of the first two paradigms by faster processing of phase, compared to the first paradigm, and more accurate modelling of the phase, compared to the second paradigm. It is noteworthy that the third paradigm was proposed in the very recent past and the investigation of the advantages of its application in different regions of the body remains to be done.

The work of this dissertation employs a non-iterative phase unwrapping approach [53] based on the first paradigm. The use of a non-iterative phase unwrapping approach enables
the parallel implementation of post-processing pipelines, thereby making a channel-by-channel processing approach feasible. Additionally, the second and the third paradigms result in high-pass filtered phase images, which limits their application to an extent; for example, the extraction of quantitative tissue susceptibility information, benefits from retention of both high and low frequency contents of the underlying tissue.

1.5.2 Local Frequency Shift Mapping

During imaging, signal is mainly detected from the regions of high receiver coil sensitivity. However, the magnetic field perturbation is caused by the magnetic susceptibility distribution throughout all the space detectable by the MRI hardware. These additional contributions are collectively referred to as background field. This background field manifests in the phase map as low frequency content [55].

The background phase is often assumed to be smoothly varying and therefore by applying a high-pass filter one can separate the background and tissue phase components in the complex MR data [47]. Once the background field is removed the local frequency shift (LFS) map can be utilized to study the local field shifts between tissue compartments. Notice that in this dissertation, the term local phase shift (LPS) may be used interchangeably with LFS; when doing so, it is made sure that an appropriate frequency to phase conversion is performed. This simple approach works well for SWI. Nevertheless, mere high-pass filtering also removes the low-frequency contents of the tissue signal, which may be of interest. For quantitative mapping of susceptibility, the relative difference field (RDF) is of interest, which includes both high- and low-frequency contents of the underlying tissue [56]. Extraction of RDF requires more sophisticated filters, which account for the differences in the physical properties of the background and foreground fields.

For general high-pass filtering, the size of structures that can be visualized in the LFS maps depend on the filter design and parameters; some filters are more sensitive to size (e.g. Homodyne filter) while other filters may cause blurring (i.e. Gaussian filter). This is not the case for RDF calculation, where the filter designs used are based on the physical properties of the field experienced by the tissue and the background field. As a result, the filter parameters
should not affect the size of structures that can be resolved in the RDF map. However, as Section 1.5.4 demonstrates, many other factors play a role in the quality and the accuracy of RDF and the resultant susceptibility maps.

Figure 1.4: Local frequency shift maps are shown, for three slices of brain of a healthy volunteer, as obtained from application of high-pass filter to unwrapped phase data. The examples clearly demonstrate the tradeoff between tissue contrast and the removal of background field contributions to the LFS maps; yellow arrows point to the regions near the interface of bone and brain tissue, where the large phase gradients are difficult to remove; meanwhile outstanding contrast is achieved between the vessels and surrounding white matter/gray matter (small white arrows) and between the white matter and gray matter (larger white arrows). Source images are acquired at 3T.

Figure 1.4 illustrates three example LFS maps generated from GRE images of a healthy volunteer acquired at 3T. The figure clearly demonstrates that if the processing pipeline is well optimized, LFS maps with outstanding contrast between various tissues can be generated. The contrast in Fig. 1.4 is adjusted to highlight some of the challenges faced when processing phase information, particularly at higher fields. While the LFS maps offer exquisite contrast for veins, white/gray matter, as well as the deep nuclei of the brain (white arrows), large phase gradients at the bone/tissue interface cause the noisy signal in the anterior section of all these image slices (yellow arrows).

The LFS maps (obtained through high-pass filtering) may be used as a standalone source of information, or in combination with the magnitude image in SWI applications, discussed in Section 1.5.3.
1.5.3 Susceptibility Weighted Imaging

Susceptibility is a material or tissue property that enables the prediction of its behavior when placed in a magnetic field. In other words, susceptibility is the constant that relates the main magnetic field to the frequency shift detected in the MR images and can be represented by the following equation:

\[ \Delta f_k = \frac{\gamma}{2\pi} B_0 \Delta \chi \]  

(1.2)

where \( \gamma \) is the gyromagnetic ratio, in units of \( \text{rad/s} \), and \( \Delta \chi \) is the susceptibility difference, in units of parts per million (ppm), between the tissues being investigated.

Susceptibility weighted imaging was proposed by Haacke et al. [47] after the initial observation of blood oxygen level dependent (BOLD) signal by Ogawa et al. [57]. The initial BOLD observation was made in the magnitude component of GRE images. Haacke et al. demonstrated that a phase mask can be generated from the high-frequency contents of the GRE phase images, which when applied to the magnitude component of GRE data enhances the image contrast based on the underlying tissue susceptibility differences. The imaging parameters, \( e.g. \) the acquisition time and the imaging voxel aspect ratio) can be selected to enable an optimum contrast [58, 59]. It may be challenging to simultaneously generate images with optimal contrast between more than two tissues, as the echo time at which the contrast is maximum between two given tissue might not result in optimal contrast between other tissues.

Owing to its efficiency, clinical SWI applications utilize a Homodyne filter [48] to extract the high-frequency information of the underlying tissue. A filter size of 64 × 64 was proposed initially [47], and later studies investigated the effect of filter size more rigorously [59]. As was mentioned previously, Homodyne filtering suffers from residual phase wraps, especially at longer echo times, which may interfere with tissue assessment in the clinic. Alternatively, the phase image can be processed through the first phase unwrapping paradigm \( i.e. \) firstly unwrapped and subsequently filtered in two separate stages). Regardless of the paradigm employed to calculate the LFS map, these high frequency data are then used to extract a SWI mask.

The conventional SWI mask is a linear model, but other alternative models have also been proposed to enhance the visibility of different structures. For a conventional negative linear
phase mask (Fig. 1.5), the phase value in the range of $[-\pi, 0]$ are linearly mapped to the range of $[0, 1]$, the values above 0 are mapped to 1, and those below $-\pi$ are mapped to 0 [60]. In this way, the negative shift in the phase, which is expected at the interface of diamagnetic tissue with paramagnetic tissue, is enhanced in the phase mask with values less than 1 and greater than 0.

![Linear negative phase mask model](image)

Figure 1.5: Linear negative phase mask model is used for extracting the paramagnetic tissue information to enhance contrast in magnitude images.

Assuming the imaging parameters are appropriately selected to enhance the contrast between the structures of interest, the level of contrast generated through SWI processing is still somewhat sensitive to the filter kernel parameters applied to the phase [59]. Figure 1.6 demonstrates the effect of filtering; a small filter size results in the propagation of background field into the resulting LFS (first column of Fig. 1.6), which will appear in the resulting phase mask and subsequently in the SW image. On the other hand, with more rigorous filtering, the LFS map becomes overly smoothed (third column of Fig. 1.6), which in turn will result in a phase mask with minimal to no information about the underlying tissue; in this case the final SWI resembles the original magnitude image.

When the linear phase mask is used, the contrast enhancement can be controlled to affect either the paramagnetic tissue or the diamagnetic tissue. Alternatively a triangular mask can enable simultaneous enhancement of contrast between diamagnetic and paramagnetic tissue, however their differentiation is not possible in the resulting SWI. Quantitative mapping of susceptibility allows for the differentiation of diamagnetic and paramagnetic tissues. Quantitative susceptibility mapping (QSM) is the means through which the tissue susceptibility values can be mapped on a pixel-by-pixel basis.
1.5.4 Susceptibility Mapping

The high-pass filters used for SWI cannot be used to extract quantitative maps of the susceptibility because, as was mentioned earlier, these filter designs eliminate the background field as well as the low frequency content of tissue signal. Instead, special filters must be employed to extract RDF from the unwrapped phase. The filters that have been proposed for quantitative mapping of susceptibility model the background and local fields using their respective physical properties. A key difference between the background and local fields is that the former is an order of magnitude stronger than the latter [61]. The second important property is that Laplace’s equation holds for the background field. This equation can be solved by assuming a boundary
value [62]. Examples of commonly used background field removals include the sophisticated harmonic artifact reduction for phase data (SHARP) [63, 64] and projection onto dipole fields (PDF) [65].

Once an accurate RDF is calculated for the tissue of interest, the bulk magnetic susceptibility can be resolved by inverting the dipole equation. However, the dipole expression is not defined along the surface of a double cone in 3D K-space, which complicates the dipole inversion as it implies a division by zero at each location along the double cone. As a result of this, several approaches have been proposed to enable the inversion of the dipole expression for QS mapping. The most basic approach is thresholded K-space division [66]. Expectedly, the quality and accuracy of the results of this approach depend heavily on the selected threshold [67]. More sophisticated techniques attempt to regularize this inverse problem by using iterative methods such as conjugate gradient to minimize the difference between the measured field and the calculated field [68]. The necessary prior knowledge about the underlying tissue is extracted from the magnitude data.

It is clear from this description that QS mapping is very sensitive to noise. At any of the above-mentioned stages (phase unwrapping, background removal, or dipole inversion), the presence of residual errors due to noise will interfere with the ability to calculate an accurate QS map.

While the application of QSM is not investigated as part of the work of this dissertation, as the Conclusion chapter highlights, the work completed here has potentially significant implications on the ability to generate high quality QS maps, particularly in the heart.

### 1.5.5 Chemical Shift Imaging

MRI phase images also contain information about the specific chemical environment in which the hydrogen atoms reside. In the same way that the susceptibility difference between the neighboring tissues manifests as frequency shift (Eq. 1.2), the hydrogen atoms in different chemical environments can be detected using the information about their frequency shift with respect to the center frequency (hydrogen frequency at a specific field strength).

The cause of chemical shift effect observed in MRI is the different levels of shielding of the
hydrogen atoms, depending on the (macro)molecule it is attached to. The possibility to separate fat and water signals is an immediate application of the chemical shift effect, where the shift in the frequency of the hydrogen atoms attached to the fat macromolecule can be rather easily distinguished from the frequency of free water. The carbon atoms of the fat macromolecule provide more shielding than the mere oxygen atom to which the hydrogen atoms in free water are attached. The result is a predictable frequency shift, since the NMR spectrum of fat macromolecule is well known [69, 70, 71]. From this spectrum the frequency of each of the hydrogen atoms of fat can be calculated using Eq. 1.3.

\[ \Delta f_{cs,i} = \frac{\gamma}{2\pi} B_0 \Delta \delta_i \]  

where \( \Delta \delta_i \) is the chemical shift frequency, in units of parts per million, of the \( i^{th} \) fat peak with respect to the center frequency of water.

A usual means of employing this frequency shift information is in quantitative mapping of the tissue fat component, commonly referred to as fat fraction (FF) mapping. A FF map is obtained through calculation of water and fat content on a pixel-by-pixel basis and conversion of this information into a fraction between 0 and 1, each value reflecting the percentage of fat in that voxel.

The simplest way to separate water and fat in the imaging field of view is to select two imaging echo times where water and fat are in- and out-of-phase, respectively. This is known as the two-point Dixon technique [72], and allows for addition and subtraction of the two images, thereby leaving a water-only and a fat-only images, respectively. This method has been extended to three point Dixon [73], to allow for compensation of the field inhomogeneity related effects that disrupt the actual in- and out-of-phase time point for water and fat. Water/fat imaging has also been implemented with an iterative approach using images acquired at a multiple asymmetric echo time points [74, 75]. This approach calculates a fat fraction map by minimizing the errors in the field map through an iterative least squares approach. Recently, a method for calculating an accurate \( B_0 \) map was presented by Liu and Drangova [76], which utilizes a non-iterative approach for correction of phase errors (B0-NICE) based on the information in both magnitude and phase images. This approach utilizes a magnitude-driven and
a phase-driven fat mask to compute the phase errors and as a consequence of this, a phase error-corrected FF map is also generated. The B0-NICE field mapping approach does not require exact in- and out-of-phase echo times for an effective fat/water separation. Moreover, the non-iterative nature of this approach enables its parallel implementation, which is expected to save computational time.

1.6 Current State of Multi-Channel Phase Image Processing

The common aspect of all currently employed phase processing techniques is that the signal as acquired by the receiver channels is firstly combined. This is then followed by application of other processing that may be required to extract the relevant information from the MR data (such as those discussed in Section 1.5). In following this processing approach, care must be taken to utilize channel combination approaches that are especially designed to spare the information in the phase image. In other words, phase combination approaches are needed to avoid destructive or otherwise noise amplifying combination of phase information from different channels.

In the early days of multi-channel image acquisition practice, it was demonstrated that the optimal magnitude image can be obtained through channel combination using the sum-of-squares approach [77]. A complex sum could be used to calculate the channel combined complex data, from which the phase information can be extracted. This approach is most prone to resulting in loss of phase information due to destructive phase combination.

Channel images contain significant amount of information in their high sensitivity regions, but there is significant SNR loss in the low sensitivity regions of each channel. Additionally, the spatial extent of the signal received from the subject/object by the different channels is unique to that channel. Figure 1.7 illustrates this fact through an example of signal acquired by two channels in an array of 30 receiver coils. As a result of channel-specific coil sensitivity, signal may be compromised through a poor channel combination process, which does not appropriately allocate weighting to each channel and their respective high-SNR regions. One such approach is magnitude weighting, in which the channel magnitude image is used to differentiate between the high- and low-SNR regions of the field of view. This information is
normalized across all the channels and is used as a weighting factor for channel combination [10].

The accurate definition of high SNR regions in an array of receiver coils is more crucial in cardiac applications, where the presence of the lungs results in low signal in the majority of the FOV. The equal weighting of all the coils in a cardiac array will result in an increased likelihood of meaningful signal being lost or corrupted by noise. Even in neurological applications, where all the receiver coils are positioned in close proximity of the tissue, simply adding the signals from the different coils results in signal cancellation due to destructive interference.

![Figure 1.7](image)

Figure 1.7: Magnitude (a) and phase (b) images of two channels demonstrate the implication of coil sensitivity in a patient’s brain image slice. Line profiles demonstrate the signal behavior in the FOV for magnitude (c); the line profiles demonstrate the increase in noise in areas of the FOV away from the coil. The line profiles in the phase (d) clearly demonstrate the cyclic topology of phase providing evidence of phase wrapping. (The black and maroon lines as shown on magnitude images correspond to the top and the bottom rows of (c) and (d), respectively).

The individual channels in an array of coils are phased in order to enable generation of a smoothly varying combined phase image after the application of channel combination process. This is the basis of the techniques that simultaneously reconstruct and channel combine the images acquired through partially parallel acquisition [78]. This channel-specific bias phase must be calculated and removed in the process of channel combination. The accurate estimation of this term, which is a spatially varying and temporally constant term, is made easy with
the advent of multi-echo imaging.

Commonly used phase sensitive channel-combination approaches use the Eigen-analysis of the sample correlation matrices. This is the mathematical basis behind Adaptive channel combination [8] and singular value decomposition [9, 79]; two phase-sensitive channel combination techniques that are widely used. A new approach was proposed by Liu et al. that reversed the processing steps [11] by requiring the individual channel images to be unwrapped and subsequently filtered prior to application of channel combination. The technique computes a weighting from the high-pass filtered channel frequency maps based on the variations between the different channels. It is expected that the local frequency shift maps have no variations in temporal dimension. Therefore, by allocating low weighting for channels with high temporal variations and, inversely, by allocating high weighting to channels with low temporal variations, a high quality channel-combined local frequency shift map can be achieved.

No in-depth analysis of the benefits of reverse order post-processing (channel image data processing followed by the application of channel combination) has been presented prior to the work of this dissertation. This is in part due to an extended processing time required for channel-by-channel processing of MR data. Additionally, the extent to which the information in the MR complex data, and especially the phase images, may be compromised, even when employing a sophisticated and phase sensitive channel combination, may be counter-intuitive. Therefore, the aim of this thesis is to exploit the cost and benefits of channel-by-channel phase image processing; this is accomplished by developing and validating image processing pipelines for extracting quantitative maps from the individual channel data prior to the application of channel combination. To address the potential concerns about added processing time for channel-by-channel processing, where possible, non-iterative processing methods are exploited.

1.7 Thesis Scope

In this dissertation, several post-processing approaches are presented for the specific purpose of extracting tissue information from the complex MR data collected by individual receiver channels. The approaches presented through the dissertation enable the non-invasive extrac-
1.8. Thesis Outline

This thesis is divided into five chapters. This introductory chapter provided the necessary background for the current state-of-the-art post-processing techniques that are available for tissue assessment and characterization using magnetic resonance images acquired by multiple receiver coils. Additionally, by highlighting the shortcomings of the currently available techniques, the motivation behind the work of the presented dissertation was highlighted in this chapter.

Chapter 2 presents the technical development of a novel multi-channel MR phase image processing approach and its validation through an imaging study involving healthy human volunteers. The specific aim of the work presented in Chapter 2 is to quantify the effect of the order of the post-processing steps in multi-channel image acquisition. The work of this chapter
has been published in the Journal of Magnetic Resonance Imaging in 2017, with manuscript title: "Susceptibility-weighted imaging using inter-echo-variance channel combination for improved contrast at 7 tesla”.

Chapter 3 presents a neurological application study of the new processing technique presented in Chapter 2. Through the study presented in Chapter 3, images with clinically valuable information are presented to our collaborators in the clinical neurology and neuroradiology department to enable sensitive and specific differentiation of white matter lesions as belonging to MS cohort versus benign white matter lesions. The work of Chapter 3 has been submitted to the American Journal of Neuroradiology in February 2018, with manuscript title: "Morphology-specific discrimination between MS white matter lesions and benign white matter hyperintensities using ultra-high field MRI”.

Chapter 4 presents an in-depth overview of the considerations needed to translate the findings of Chapter 2 from neurological application to cardiac imaging. The clinical application of the work of Chapter 4 is in the heart to account for the range of complications and challenges expected in the MR imaging of the body (i.e. outside of the brain). This chapter, in addition to presenting the new technical methodology for extracting multi-parametric quantitative maps of the heart from a single acquisition, presents a validation study in a small cohort of six HF patients. The work of Chapter 4 has been submitted to Magnetic Resonance in Medicine in March 2018, with manuscript title: "Multi-Parametric Myocardial Mapping from a Single Acquisition by Non-Iterative Correction of Individual Channel Phase Errors”.

Chapter 5 summarizes the findings and contributions of the work that resulted from this dissertation. In addition, Chapter 5 presents the future direction and the limitations of the work presented in this dissertation. Several preliminary results are presented to demonstrate the feasibility of the proposed future directions.
References


Chapter 2

A New Approach to Multi-Channel MR Phase Processing

This first major development of this dissertation was to, for the first time, investigate the effect of the order in which the post-processing steps are applied to multi-channel MR image data. A version of this chapter has been published in the *Journal of Magnetic Resonance Imaging* in 2017. Permission to include the paper in this thesis has been obtained from the JMRI and is included in Appendix C.

2.1 Overview

It was mentioned in the Introduction Chapter that the benefits gained through MR imaging using multiple receiver channels is the added SNR and faster acquisition; note that this increase in SNR is gained through closer proximity of receiver coils to the tissue being imaged while the image SNR in partially parallel imaging practice is decreased relative to the corresponding image obtained from a fully acquired K-space. The diagnostic value of the images resulting from this practice depends heavily on the channel image combination used. This is particularly crucial in MR phase imaging where, broadly speaking, the destructive interference between the phase component of the different receivers may result in noise amplification, or otherwise singularities in the channel combined images.

The focus of this chapter is to investigate the benefits resulting from reverse-ordered post-
processing of multi-channel MRI data. Specifically, in the current standard of practice, the images acquired from the multiple receiver coils are combined immediately after acquisition. The proposed methods of this chapter considers the technical requirements for processing the individual channel data prior to application of channel combination. The work of this chapter further validates this approach against the common practices employed in multi-channel MR image processing. Susceptibility weighted imaging is utilized in this chapter as a means for quantifying the benefits of the proposed approach against the conventional approaches. This is because, using the same channel-combined magnitude image data, by processing the phase image using different processing pipelines, it is possible to effectively isolate the benefits and disadvantages of each approach.

The work of this chapter is completed in the brain to make use of the already in-place set of post-processing techniques reported by different scientific groups in order to enable a fair comparison between the conventional approaches and the proposed multi-channel image processing pipeline.

### 2.2 Introduction

Susceptibility weighted imaging (SWI) was introduced in the late 1990s for visualization of venous vasculature [1, 2] and has since been incorporated in many clinical neuroimaging protocols, including tumor [3, 4], stroke [5], trauma [6, 7], multiple sclerosis, and small vessel disease [8]. Briefly, SW images are generated by multiplying the magnitude image by phase-based mask, which takes advantage of the effect of deoxygenated blood on local phase shift (LPS) [1, 2]. To estimate the LPS, single-echo or multi-echo (≥ 2) gradient echo (GRE) pulse sequences are used to map the phase, followed by background removal through post-processing (high-pass filtering). Without increasing scan time, it has been shown that multi-echo GRE images can enhance signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) through signal averaging [9].

While achieving high resolution SWI (< 1 mm in-plane) is of clinical and research interest, it is not easily achieved at clinical field strengths (1.5T and 3T), due to low SNR and long echo times (TE) required to allow for the manifestation of tissue susceptibility dif-
2.2. Introduction

Imaging at higher field strengths, 7T and above, promises higher resolution and shorter TE. Unfortunately, high-field imaging brings its own obstacles, namely, more severe B0-inhomogeneities, difficulty in achieving uniform B1-shimming, and increased susceptibility effects at tissue/air/bone interfaces, such as near the sinuses and the base of the brain, resulting in phase maps that are challenging to process.

At 7T, data are typically acquired using multi-channel transmit/receive radio-frequency coils, therefore, requiring channel combination before image reconstruction. Most multi-channel SWI techniques use a two-step approach, where channel-combination is followed by high-pass filtering of the combined complex data [2] or of unwrapped phase maps [10]. While many channel-combination techniques have been developed, phase singularities, comprising fringelines, cutlines, and poles, caused by field inhomogeneities and/or noise [11] often remain in the channel-combined data. Because spatial phase unwrapping techniques are sensitive to such singularities, the LPS maps calculated from the unwrapped phase images may reduce the diagnostic value of the final SW images [12]. To address the concern of potential irreversible artifacts caused by phase singularities associated with imperfect channel combination, a single-step multi-channel LPS mapping technique, which uses the inter-echo variance (IEV) as a weighting factor for combining LPS over all channels, has been introduced [13]. The IEV weights reflect the stability of a given channel over time; the channels that demonstrate higher variations (and are therefore less stable) are given lower weighting factors, while the channels with lower variation over time are assigned higher weighting during channel combination.

The purpose of the work presented in this chapter is to implement and optimize the IEV approach for generating SW images (IEV-SWI) and to investigate the effect of the order in which the post-processing steps are applied for SWI generation by comparing IEV-SWI to results obtained from two optimized traditionally used SWI pipelines in which channel combination is applied before SWI processing. This work was aimed to build the groundwork for understanding the required considerations for processing phase images acquired using multiple coils. Brain images were selected for this work to avoid added complications due to natural biological motion, presence of different chemical species, and presence of large phase gradients at air/tissue interface in the chest. While the undesirable effects of large phase gradients of lungs are avoided, we assessed the effect of such phase gradients on the post-processing pipelines in
the sinus cavities.

2.3 Methods

2.3.1 Image Acquisition

All data acquisition was performed in accordance to the requirements of the research ethics board at the University of Western Ontario. Informed consent was obtained from all volunteers. Five healthy volunteers (four females and one male, age range 34-48 years, median age 44 years, with no known medical conditions) were scanned at 7T (Agilent Technologies, Santa Clara, CA) using a 16-channel transmit/receive head coil. A three-dimensional (3D) flow-compensated six-echo GRE sequence with an acceleration factor of 2 in the phase-encode direction was used. The imaging parameters were as follows: TR/TE1/echo spacing 40/3.7/4.1 ms, flip angle 13°, voxel size 0.5 × 0.5 × 1.25 mm², total imaging time 15 minutes 55 seconds. Complex channel data were reconstructed using GRAPPA and saved for post-processing and SWI generation as described below. All post-processing steps were performed using MATLAB (R2014a, The MathWorks Inc., Natick, MA) on Linux workstation (Intel R Xeon R 2.66 GHz 12-core processor, 96 GB RAM).

2.3.2 IEV-Channel Combination for SWI Generation

IEV channel-combination and SWI processing were implemented into an IEV-SWI pipeline as shown in the flow chart of Figure 2.1. The inter-echo variance channel combination technique [13] first removes phase errors and wraps in the individual channel phase image using a non-interactive phase unwrapping technique [14]. The unwrapped phase data are then filtered with a Gaussian filter (see Section 2.3.3 below) on a channel-by-channel basis, as previously described [15], generating a multi-echo local frequency shift (LFS) map for each channel. For each image pixel the variance of the LFS values over the six echo times is calculated and its inverse is used as the weighting factor during channel combination. In this way, channels with lower variance are given higher weighting while those with higher variance between echoes are given lower weighting. The result of IEV channel combination is a multi-echo LFS map,
which is converted into phase by multiplying it by $2\pi TE_i$ (where $TE_i$ is the echo time of the $i^{th}$ echo).

Figure 2.1: Flow chart demonstrates the IEV-based post-processing of the complex data for generation of IEV-SWI. Magnitude- and phase-specific channel combination specially aims to preserve details of structures in the phase image datasets.

For SW image generation, a negative linear phase mask [16] was calculated for each echo and the fourth power of the phase mask was used with the root-sum-of-squares (SoS) [17] combined magnitude image to generate IEV-SWI; the fourth power of the phase mask was calculated to further enhance the contrast between the venous vasculature and the surrounding tissue. The fourth power of the mask was used in line with the prior work showing that for optimal vessel visualization a phase mask power in the range of three to five should be used [2]. Because prior SWI pipelines (see below) result in the “loss” of data from the first echo, the first echo phase and magnitude data from the IEV pipeline was also discarded before calculating echo-combined IEV-SWI images. This SWI processing (mask and magnitude) was used for all pipelines evaluated in this study.
2.3.3 Filter Kernel Optimization

Filter parameter optimization was performed to allow for optimal visualization of vessels in terms of absolute contrast. Line profiles drawn across vessels in the magnitude image were used in the characterization of contrast. For optimization of the filter kernel size, a single slice was identified for analysis from each volunteer. For each volunteer, a stack of images was generated consisting of the magnitude of the selected slice, followed by all IEV-SWI processed with different kernel sizes ($\sigma$, ranging from 1 to 50 mm) and SWI processed using two commonly used pipelines (described below). Because SWI are often presented as minimum intensity projections (mIP) through several slices, we also included mIPs generated from three, five, and seven slices (i.e., 3.75, 6.25, and 8.75 mm, centered at the same selected single slice SWI) from each of the processes in the stack of images prepared for analysis.

The analysis of the effect of filter kernel size on SWI contrast was performed by an experienced MR imaging researcher with three years of experience. To ensure objectivity, five veins less than 3 mm in diameter were manually identified on the magnitude images in different anatomical areas. The statistical analyses for identifying the optimal filter kernel size for each of the pipelines were performed on a total of 25 veins (five veins from five volunteers for a total of 25 veins). For each vein, three line segments were drawn perpendicular to the vein, between 1 and 2 mm apart. Selection of the vessels on the magnitude image allowed for consideration of blooming that is typically seen on GRE magnitude images and, therefore, ensure that the line segments drawn were long enough to intersect the vessel as well as surrounding tissue. For each segment, the contrast between the vein and surrounding tissue was calculated, the minimum intensity was selected as the "vein signal"; surrounding tissue (white/gray matter) intensity was defined as the mean intensity of the tails of the line profile starting from two pixels on either side of the minimum to the end of the line segment (five to seven pixels on either side). Finally, contrast for each vein was calculated as the absolute signal difference between the surrounding tissue and the vessel signal, and then averaged over the three adjacent segments.

For this evaluation, normalization was performed against the contrast measured in the single-slice magnitude images, i.e., contrast of the SWI (single slice or mIP images) was di-
vided by the contrast calculated from the single-slice magnitude, with the intent to characterize contrast enhancement solely due to the SWI processing. Analysis of the cumulative data, five vein segments from five volunteers, involved further normalization by the maximum normalized contrast for each vein (as a function of filter size).

Note that for filter optimization, contrast was selected as the metric, rather than contrast-to-noise ratio, because the expected blurring effect of increasing $\sigma$ results in a predictable reduction in noise that dwarfs the changes observed in contrast.

### 2.3.4 Prior SWI Approaches

The commonly used Hermitian-product/Homodyne filter approach and an alternative singular-value-decomposition approach for generating SW images, HPH-SWI and SVD-SWI, respectively, were also implemented and optimized before comparison with IEV-SWI.

In the HPH-SWI pipeline, the time-independent phase is removed by calculating the Hermitian inner product between all later echoes and the first echo complex data [18]. This operation is followed by channel combination using complex summation and Homodyne filtering [19] of the channel-combined phase image to isolate high-frequency phase components. The phase-mask and SWI generation steps described in the IEV-SWI pipeline were then performed. To ensure the best possible HPH-SWI, filter optimization (based on the normalized contrast as described above) was also performed for this pipeline, with the filter kernel varying between 10 and 90% of the field of view.

For the SVD-SWI pipeline, singular value decomposition was used to performed channel combination, using a method similar to that described by Bydder et al [20] for spectroscopy and Khabipova et al [21] for quantitative susceptibility mapping. Briefly, a matrix constructed with N coils and n echoes was factorized using singular value decomposition. The right eigenvector corresponding to the first singular value provided the channel-combined image (left eigenvector corresponding to coil sensitivity estimate was not used). Using the complex SVD for channel combination has the effect of normalizing the phase with respect to the first echo. The combined phase images were unwrapped using spatiotemporal phase unwrapping, with the temporal dimension along the echoes and 3D spatial unwrapping performed within each image.
The background field effects were removed from the unwrapped phase image using the Gaussian filter used in the IEV-SWI pipeline. SVD-SWI images were generated using the same phase mask process as above. Filter kernel optimization was again performed, based on normalized vessel contrast, for $1 \leq \sigma \leq 50$ mm.

2.3.5 Comparison Between IEV-SWI, HPH-SWI, and SVD-SWI

For all comparisons, the skull was removed from the 3D images by applying a mask generated using the FSL brain extraction tool (BET, Functional MRI of the brain Software Library, University of Oxford, Oxford, England) [24].

Quantitative comparison between the three pipelines was performed by identifying five vessels on each of four axial slices throughout the brain of each volunteer, for a total of 100 vessels (20 vessels per volunteer, five volunteers). The four slices were selected to cover different regions of the brain, from near the sinuses to those superior to the lateral ventricles, to ensure that comparison of the three pipelines was performed in clinically significant areas and areas susceptible to large inhomogeneity-related artifacts. For each of the four regions, stacks of SW images processed by each of the optimized pipelines were generated (HPH-SWI, followed by SVD-SWI, and IEV-SWI). To ensure objectivity, the vessels were identified on the HPH-SWI images, because they represent the most commonly used SWI approach. CNR was calculated for each vessel as the average CNR of three line profiles drawn across the vessels described above. For the CNR calculation, noise was calculated as the standard deviation of the pixels comprising the tails of each profile. The techniques were also compared in terms of absolute contrast, to remove sensitivity to the effect of filtering on the SWI process.

A single observer with 3 years of experience in neurological application of MRI qualitatively evaluated the SW images generated through the three pipelines on a slice-by-slice basis. For each dataset, the magnitude image and the corresponding SWI from each of the three pipelines were viewed simultaneously using a 3D viewer (Microview, Parallax Innovations, London, Ontario, Canada). Simultaneous inspection of the SW images from all three pipelines was possible because all images were inherently registered to the corresponding magnitude. The simultaneous slice-by-slice evaluation was performed in reference to the magnitude image.
to ensure that vessels delineated in the SWIs are not artifacts caused by remnant wraps and/or singularity-related artifacts in the LPS maps. Vessel conspicuity and continuity in the different regions of the brain (particularly the veins in the cortex and the frontal region near the sinuses) were compared. In areas where images from the three pipelines differed, the SWI processes were traced back through the pipeline to the LPS maps and the individual channel phase data. Note that the observer could not be blinded to the pipeline used to process the data because of the requirement to access the intermediate phase images and individual channel data. The in-depth assessment of the intermediate images was conducted through the course of 5 days, each day for data from a single volunteer. The computation time for the three pipelines was also compared by running each pipeline on a single processor.

2.3.6 Statistical Analysis

Following confirmation of normality, using the D’Agostino test, changes in contrast between single-slice and mIP images of different thickness were analyzed using one-way repeated measures analysis of variance (ANOVA) for each pipeline. Comparisons of contrast and CNR of the three SWI pipelines were performed using the Friedman nonparametric test, followed by Dunn’s multiple comparison test; this analysis was performed on a per-vein basis (i.e. no averaging was performed). In all cases a p-value < 0.05 was considered as significant. All statistical analyses were performed using GraphPad Prism 6.0e (GraphPad Software, La Jolla, CA).

2.4 Results

2.4.1 IEV-SWI Filter Kernel Size Optimization

Individual-channel phase unwrapped and filtered data, as well as IEV-SWI were successfully generated for all volunteers. Quantitative contrast analysis presented in Figure 2.2 clearly illustrated that optimum contrast is achieved in a relatively narrow band of Gaussian filter kernel with $4mm \leq \sigma \leq 10mm$. While the sampling after $\sigma = 7$ mm is sparse, the graph demonstrates a clear decreasing pattern after $\sigma = 7$ mm. A filter with $\sigma = 7$ mm was used for
all further image analyses.

2.4.2 IEV-SWI: Echo Combined, Single Slice, and mIP

Figure 2.3 depicts single echo and echo-averaged SW images from the IEV pipeline; images are shown for each of the five volunteers together with representative magnified regions to better illustrate the improvement in signal to noise ratio.

![Normalized contrast for the IEV-SWI pipeline as a function of Gaussian filter kernel size; normalization against corresponding magnitude contrast.](image)

To highlight the performance of IEV-SWI in regions of large background field variation, the axial slices presented in Figure 2.4 were selected from regions that are just superior to the sinuses to regions superior to the lateral ventricles. Of interest is the ability to visualize veins clearly throughout the brain, including veins in the cortex and the frontal regions, near the sinuses. Similarly excellent image contrast and vein conspicuity are observed in the inferior axial slices near the base of the brain (first row of Fig. 2.4).

The effect of the minimum intensity projection process on the SW images is seen in Figure 2.5, where single-slice echo-combined axial IEV-SWI are compared with the corresponding magnitude, 3-, 5-, and 7-slice mIPs. As expected, contrast decreases with increasing mIP thickness. Quantitatively, significantly higher contrast was measured in the single-slice images compared with the three-slice mIPs ($p = 0.03$); the contrast difference was more highly significant when the mIP thickness was increased above five slices ($p < 0.01$). Therefore, for the remainder of the manuscript all images presented are single-slice.
2.4. Results

Figure 2.3: (a) Single-echo (echo 5) and echo-averaged IEV-SWI for a single slice from all five volunteers; magnified representative regions (white boxes) are also presented in (b, echo averaged on bottom). Structure conspicuity and signal-to-noise ratio are clearly higher in the echo-averaged images.

2.4.3 Effect of Phase Channel Combination on Susceptibility Weighted Images

The contrast analysis for the HPH-SWI pipeline shows that maximum contrast was achieved with a filter size corresponding to 30% of the field of view (graph not shown). Gaussian filter optimization for the SVD-SWI pipeline demonstrated the same trend as the IEV-SWI, i.e., optimum contrast was achieved with $\sigma = 7$ mm. The optimal contrast in the HPH-SWI data was found to be less sensitive to the homodyne filter kernel size, which was observed to have a broader contrast curve, compared with images processed using the Gaussian filter implementation.

SW images from all three optimized pipelines are presented in Figure 2.6. Axial slices are shown for four regions, each from a different volunteer. The figure clearly demonstrates that IEV-SWI processing results in robust performance and excellent contrast throughout the brain; areas where IEV-SWI performs markedly well are highlighted by the ellipses in Figure 2.6.
Figure 2.4: Example IEV-SWI slices from different regions of the brain for each volunteer. The pipeline robustly generates high contrast images throughout the brain, including near the air/tissue interfaces of the sinuses and the peripheral cortex.

While HPH-SWI and SVD-SWI have similar appearance, some vessels appear "broken" into segments (squares in Fig. 2.6b-d) and some vessel segments near the periphery and close to the sinuses are also missing (arrowheads in Fig. 2.6a,b).

Representative magnified regions from Figure 2.6 (identified by *M1-M4) are shown in Figure 2.7. It is clear in these images that IEV-SWI processing pipeline successfully preserves the visibility and contrast of the vessels even in regions where remnant background noise is
Figure 2.5: A representative single slice magnitude image is compared with the single slice IEV-SWI and the corresponding three, five, and seven-slice mIP images (top). Quantitative analysis shows that the single slice IEV-SWI has the highest normalized contrast compared with the mIP images (bottom; mean ± SEM)

more noticeable compared with HPH-SW and SVD-SW images due to large phase gradients (near air/tissue interface as shown in *M1).

Vessels that are seen on all three images for each region have noticeably lower contrast (*M2-*M4) on HPH-SWI and SVD-SWI. Furthermore, continuity and contrast of the vessels in the cortical regions of the brain is particularly preserved in the IEV-SWI results. Quantitative analysis of the final SW images resulting from each pipeline (Fig. 2.8) showed significantly higher CNR in the IEV-SWI processed images (mean ± SEM : 5.8 ± 0.3), compared with both HPH-SWI (mean ± SEM : 5.4 ± 0.3) and SVD-SWI (mean ± SEM : 5.3 ± 0.3; p < 0.01). On average, IEV-SWI CNR was 7% and 9% higher than the CNR of HPH-SWI and SVD-SWI, respectively. No statistically significant differences between HPH-SWI and SVD-SWI were observed for CNR (p > 0.99). Absolute contrast in the IEV-SW images was also significantly greater than that of the other two pipelines (mean±SEM : 136.0±7.0 for HPH-SWI, 132.0±6.8 for SVD-SWI, and 142.5±7.3 for IEV-SWI; p < 0.01 for IEV-SWI versus both HPH-SWI and SVD-SWI and p = 0.05 for HPH-SWI versus SVD-SWI absolute contrast comparison).

The significantly higher contrast in the IEV-SWI results compared with the outputs of the HPH-SWI and SVD-SWI techniques was traced back through the different processing pipelines. Figure 2.9 represents an example of open-ended fringeline in the third echo of the
Figure 2.6: Representative images from the three SWI pipelines; the axial slices (a-d) are from different volunteers. Regions identified by squares highlight areas where vessels are represented as "broken" or missing; the arrowheads point to areas with obscured vessels. The ellipses highlight areas where IEV demonstrates improved vessels conspicuity, by means of improved susceptibility-related contrast or reduced background noise/artifact level. Regions labeled *M1-*M4 are magnified in Figure 2.7 to better illustrate the differences between the processing pipelines.

tenth channel phase image, which if not handled appropriately in the channel-combination process would result in a singularity artifact. Both HPH-SWI and SVD-SWI pipelines reference the multi-echo dataset to the first echo image and it can be seen that this process removes the open-ended fringeline (Fig. 2.9b) but excess noise is observed in the area where the open-ended fringeline crossed the original channel phase image (Fig. 2.9a, referenced channel phase). This noise was seen to propagate to the final channel combined LPS map (Fig. 2.9c), where white matter and gray matter appear smoothed and vessels have lower contrast conspicuity.
2.4. Results

Figure 2.7: Magnified representative regions (*M1-*M4) from Figure 2.6. IEV-SW images preserve contrast and conspicuity of vasculature even in regions near air/tissue interface where removal of field gradient contribution to the images is difficult (*M1 arrows). Vessel continuity is also better preserved in IEV-SWI (*M2). Challenging regions in the cortical regions of the brain (*M1-*M4) that are processed with IEV-SWI result in easy identification of vessels, while HPH-SWI and SVD-SWI processing result in difficult-to-trace vessels.

Figure 2.8: Comparison of vessel CNR from the three pipelines. The values are mean ± S.E.M of CNR from 100 vessels identified on the HPH-SWI images throughout the brain. Strong significant differences are observed between IEV-SWI and both HPH-SWI and SVD-SWI pipelines (***p<0.01); the difference between HPH-SWI and SVD-SWI was not significant (p>0.99).

when compared with the IEV-LPS map. Figure 2.10 shows the intermediate steps of the three pipelines for a representative vessel; it can be seen that the susceptibility related vessel signal is lost at the channel combination step for both HPH-SWI (Fig. 2.10b) and SVD-SWI (Fig.
2.10c). IEV-SWI, on the other hand, maintains the vessel signal through both the unwrapping and filtering steps (Fig. 2.10a). The vessel signal, visible on the IEV-LPS map, enhances the visibility and contrast of the IEV-SWI, whereas the HPH-SWI and SVD-SWI results merely show contrast from the magnitude image.

Figure 2.9: Open-ended fringelines outlined on the channel 10 phase image (yellow arrows in a) are removed on the corresponding channel phase image of echo 3 image, which was referenced to echo 1 data; however, noise is amplified in these regions (yellow arrows in reference image). Due to referencing, the open-ended fringelines do not result in singularities in the HPH- and SVD-channel combined phase images (b). Nonetheless, the excess noise resulting from this process leads to poorer contrast and structure visibility, both for vessels (yellow arrows on IEV-LPS maps) and for gray/white matter contrast (white arrows on IEV-LPS maps) as shown in (c).

Quantitative slice-by-slice analysis identified differences between the three methods, particularly in the periphery and areas of large inhomogeneity. Four representative regions (different volunteers) where differences were observed are shown in Figure 2.11, where the SWI results from each pipeline are presented along with the corresponding LPS map. It can be seen that while the structures clearly seen in the IEV-LPS maps are also clearly visible in the IEV-SWI images, the presence of phase-related artifacts (arrowheads in Fig. 2.11a,c) and residual background fields (arrows in Fig. 2.11b,d) corrupt the HPH-SWI and SVD-SWI data.
Figure 2.10: Demonstration of the effect of the order of processing steps within the three SWI pipelines. In each panel a whole-brain image and a magnified region are shown (white rectangles on the channel phase images indicate the magnified region). The channel phase data are shown for the three channels that contribute to the visualization of the example vessel. The vessel is seen in each of the channel phase images (white arrows in a) and its appearance is maintained throughout all stages of the IEV-SWI processing pipeline (a). The vessel integrity is lost in both HPH and SVD channel combined phase images (in b and c, respectively) resulting in poor vessel visibility in the corresponding LPS maps. Unlike IEV-SWI, the final HPH-SWI and SVD-SWI appear to demonstrate contrast primarily derived from the magnitude images (top right).

As expected, the HPH-SWI pipeline was fastest, completing the processing in a few minutes, while the SVD-SWI pipeline required over 5 hours to complete channel combination, unwrapping and filtering of the entire image volume. IEV-SWI processing (102 slices, 16 channels, six echoes) required 10 hours to complete the unwrapping, filtering, and channel combination.
Figure 2.11: Examples of differences in SWI generated from each of the three processing pipelines from four different regions (a-d). HPH-SWI data often show residual phase wraps, which mimic the appearance of vessels in some areas (arrowheads). Remnant background in the SVD-SWI data corrupts the visibility of vessels at interfaces (arrows). IEV-SWI successfully maintains vessel signal in these regions enabling the visualization of continuous and high-contrast vessels. For each SWI, the corresponding LPS map is presented to identify the apparent cause of the differences arising from the processing pipeline. To minimize clutter, not all differences between the techniques are highlighted.

2.5 Discussion

This study presented a new pipeline for generating high contrast susceptibility weighted images from multi-echo GRE images acquired with multi-channel receiver coils. We demonstrated that the IEV-SWI process robustly and consistently generates high quality SWI throughout the
2.5. Discussion

brain and in comparison to two common SWI processing pipelines (HPH-SWI and SVD-SWI) resulted in images with improved background removal and significantly higher vessel contrast. The IEV-SWI pipeline processes individual channel phase data before channel combination, and it was shown that this process preserves the details in the LPS-maps that may be cancelled-out or corrupted by noise through pre-processing channel combination.

It has been shown previously that phase wraps often remain following the application of Homodyne filtering [10]; in this study, we showed evidence of vessel-like appearance of the remnant phase wraps in HPH-SWI. While phase unwrapping based techniques are generally more robust, this performance is gained at the price of longer processing times. Both IEV-SWI and SVD-SWI pipelines involve phase unwrapping followed by high-pass filtering; however, the SVD-SWI results showed evidence of remnant background resulting in poor vessel conspicuity and the appearance of interrupted/broken vessels. The IEV-SWI pipeline resulted in images with higher contrast and CNR compared with both HPH-SWI and SVD-SWI; recall that the vessels used in the contrast quantification were identified on the HPH-SWI to remove apparent observer bias toward IEV-SWI. The root of the significantly higher contrast in IEV-SWI was traced back to the channel combination step and two contributing elements were identified: first, the vessel signal apparent in individual channel phase data was lost due to the early application of channel combination in both HPH-SWI and SVD-SWI, which resulted in phase cancellation. Second, the referencing of multi-echo data to the first echo resulted in apparent noise amplification in the channel phase data, which in turn resulted in phase images with overly smoothed white matter/gray matter as well as vessel/tissue contrast. Consideration of this noise amplification is important in quantitative and noise sensitive applications, such as quantitative susceptibility mapping. The IEV-SWI process appears immune to this noise amplification because IEV weighting factor minimizes the contribution of fringelines, which tend to propagate over time.

Previous work has reported on unwrapping and filtering channel phase images before application of channel combination for SWI processing [25, 26] and more recently for quantitative susceptibility mapping [27]. These studies did not evaluate the effect of the order of channel combination and other post-processing techniques on the quality of the LPS maps or SWI. The results presented here demonstrate that phase processing before channel combination preserves
vessel conspicuity and results in higher SWI contrast. As pointed out by Koopmans et al [25] a consequence of SWI processing is that the negative phase mask, not only will enhance the signal difference between the tissue and vessel, but also between sources of negative phase values like the boundaries of the brain. We have shown here that by processing individual channel data and appropriately weighting the information from each channel during data combination, the IEV-SWI processing pipeline results in LPS maps that illustrate the vessels in the cortical regions of the brain more robustly and clearly compared with the processing pipelines that rely on post-channel combination processing (HPH-SWI and SVD-SWI). The previous work often weights the channel combination by information found in the magnitude [25, 28]. The IEV channel combination takes advantage of the propagation of phase wraps over time to account for variations that result in lower weighting for a given channel. In this way, removal of spatiotemporal-dependent artifacts (such as open-ended fringelines), which may not be resolved in the unwrapping step, can be ensured.

Susceptibility weighted images are often presented in the literature as minimum intensity projections. While this process allows for the visualization of longer vessel paths, minimum intensity projection results in loss of contrast and a reduced ability to localize vessels and structures in 3D. It should be remembered that mIP processing is quite sensitive to brain shape changes and, therefore, discriminates against regions where the central slice is placed near the sinuses, where the changing geometry of the tissue interface with air will corrupts the mIP image. Single-slice IEV-SWI enables visualization of continuous vessels of different sizes in different regions of the brain. The results presented suggest that HPH-SWI and SVD-SWI are less robust, compared with IEV-SWI, in maintaining visualization of continuous vessels over the entire brain in single-slice mode, thereby necessitating the use of mIPs. The ability to accurately localize vessels benefits applications such as the localization of venocentric lesions in patients with multiple sclerosis [29].

Compared with HPH-SWI, the improved vessel conspicuity and contrast of IEV-SWI comes at an increased computational cost because of the requirement for phase unwrapping and filtering on a channel-by-channel basis. While the 10-hour processing time reported here is long for routine studies, parallelized and optimized processing will result in reduction of computation time. Recent implementation of IEV-SWI pipeline using C++ has demonstrated the ability to
perform the processing in less than 10 minutes. This dramatic reduction in computation was made possible by the fact that the PUROR unwrapping technique used in IEV-SWI processing pipeline is non-iterative and can be easily parallelized [14].

The filter kernel optimization was performed on a single slice processed with several filter kernel sizes; the results suggest that the resulting optimized kernel size leads to high contrast IEV-SW images throughout different regions of the brain. While this method may have affected the findings from the comparative pipelines, it can be viewed as evidence of the stable performance of IEV-SWI processing pipeline. The IEV-SWI pipeline, and comparison to HPH-SWI and SVD-SWI, was performed on a limited number of volunteers scanned at 7T. However, the use of quantitative metrics (contrast/CNR) calculated from intensity profiles along identical line segments provided strong statistical power to the comparisons between techniques. The use of profiles along line segments to quantify contrast and CNR may have resulted in underestimation of the contrast of some vessels, which are surrounded by different tissues on either side (e.g., the periventricular veins have the ventricle on one side and corpus callosum on the other, each with a different mean tissue intensity), but such underestimation of contrast is not specific to any of the processing techniques. While no patients were included in this study, the findings of the current chapter are expected to translate directly to clinical studies. Chapter 3 reports on a study involving a cohort of patients with multiple sclerosis. The time-consuming in-depth analysis of the large number of slices and intermediate images evaluated was performed by an experienced observer who was not a radiologist. A study involving qualitative assessment from several radiologists could provide additional credence to the results but is beyond the scope of the current work.

In conclusion, the IEV-SWI processing pipeline preserves susceptibility related signal present in individual channel phase images, resulting in high-contrast SWI and enabling the visualization of continuous vessels within a single slice. In comparison to other commonly used processing pipelines, IEV-SWI illustrated performance that is robust against phase-related artifacts such as remnant background fields and open-ended phase wraps. This work presents evidence of the importance of the order in which post-processing techniques are applied to multi-channel MR image data on the quality of susceptibility-weighted images.
2.6 Conclusions

In this chapter a channel-by-channel processing approach was presented using the previously reported IEV channel combination weights proposed by our lab. By implementing two representative conventional approaches for multi-channel phase image processing, specifically for susceptibility weighted imaging, the proposed method was compared in terms of quality of the phase information preserved. Additionally, it was demonstrated that the proposed IEV-SWI approach results in images with significantly higher contrast when compared to the conventional approaches which apply the channel combination first.

Thus far, the research in the area of multi-channel image processing have solely focused on the design of better channel combination approaches that minimize artifacts in the resulting channel-combined phase map. The idea of channel-by-channel processing was proposed for the first time by the IEV channel combination approach and investigated for its impact for the first time through the work presented in this chapter.

While the quantitative differences in contrast is an affirmative finding, the qualitative difference found between the conventional approaches and the IEV-SWI approach is of a higher clinical significance. There is a number of reasons for this; presence of artifacts, which may mimic the appearance of vessels or microbleeds will interfere with a diagnostic assessment of these images. Additionally, the poor visibility of structures, such as venous vasculature, will corrupt the information that may be of interest. The potential clinical impact that these suboptimal MR phase image processing may have can be demonstrated using an appropriate application. Chapter 3 presents a clinical study of such cohort, highlighting the role of a high quality phase processing pipeline in the diagnostic value and inter- and intra-reader agreement.
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Chapter 3

MS White Matter Lesion
Characterization using CVS at 7T

In this chapter the clinical impact of the work of Chapter 2 is demonstrated using a clinical cohort of multiple sclerosis patients and an age- and gender-matched control subjects. A version of this chapter has been submitted to American Journal of Neuroradiology in February 2018.

3.1 Overview

Imaging, specifically MRI, has an undeniably important role in many neurological applications from both the diagnostic and treatment standpoints. Among these applications, the role of MR imaging has been established across many centers worldwide as a tool for diagnosis and treatment monitoring of multiple sclerosis. The commonly used imaging sequence for this purpose is the T2-weighted fluid attenuated inversion recovery (FLAIR), in which the demyelinating lesions in the white matter appear hyperintense. Using FLAIR images, the dissemination of lesions in space and time can be evaluated, thereby enabling a definitive MS diagnosis after a number of clinical visits. With the availability of MS-specific imaging biomarkers it may be possible to diagnose the patients at an earlier time point and start disease-modifying therapies.

One of these imaging biomarkers is the central vein sign. In early histological studies it was demonstrated that many of the MS white matter lesions have a central vein. This finding was
later observed in vivo using MR imaging. While several studies have investigated the ability of MR imaging, at various field strengths, in differentiating white matter lesions in MS from its mimics, the imaging protocols used in the published literature varies, which prevents a reliable cross-study comparison. A new set of guidelines and criteria has been published by the North American Imaging of Multiple Sclerosis, which aims to provide the grounds for cohesive study of central vein sign.

The evaluation of central vein sign is affected by the quality of the images used; specifically, when using susceptibility weighted imaging for imaging the veins, it is essential to eliminate any sources of phase-related artifacts that may result in artifactual vessel-like signals. Using the tools developed as part of Chapter 2, high-contrast single slice SWI images can be generated to assist in accurate quantification of central vein sign. This chapter aims to utilize the IEV-SWI processing pipeline proposed in Chapter 2 in tandem with a robust implementation of FLAIR at 7T to arrive at a data-driven radiological definition for central vein sign.

3.2 Introduction

Multiple sclerosis is an autoimmune disease, which affects the central nervous system. While the use of conventional MRI to detect white matter lesions (WMLs) can support and supplement the McDonald criteria for diagnosis of MS based on dissemination in time and space [1], using more advanced imaging biomarkers may enable diagnosis based on a single-time-point assessment. Such early diagnosis of MS could improve patient outcome, as it would enable earlier application of disease modifying therapies [2, 3, 4, 5].

White matter lesions in MS are detectable on $T_2$-weighted fluid attenuated inversion recovery (FLAIR) images. However, a pitfall of using such MRI-visible WMLs is that the presence of non-specific WMLs is known to increase with age and with certain risk factors even in healthy control subjects. The presence of non-specific WMLs can, thus, confound a confirmatory diagnosis of MS. A number of studies have proposed methods to address this problem. For example, perivenous WML count (herein referenced as a percentage of total lesion count - %PVWML), as detected by SWI or $T_2^*$-weighted magnitude images, is a promising imaging biomarker for differentiation of MS lesions from other WMLs [6, 7, 8, 9]. However, the
lack of a cohesive practice in evaluating perivenous lesions has led to some uncertainty in evaluating %PVWML as an imaging biomarker. The recently published consensus statement by the North American Imaging in Multiple Sclerosis (NAIMS) committee promotes a more controlled evaluation of the perivenous lesion [10] by identifying several exclusion criteria in defining the central vein sign (CVS). Specifically, the NAIMS consensus proposes exclusion of lesions that are \(< 3\, \text{mm}\) in diameter in any plane, are confluent, have multiple distinct veins, or have poor visibility. Additionally, the consensus statement calls for the investigation of a standard radiological definition of central vein sign.

Initial study of the radiological definition of CVS may benefit from high-field MRI, as in other neurological applications [11, 12, 13, 14]. While generally advantageous due to the associated higher signal to noise ratio, imaging at high field also presents challenges [15]. Susceptibility artifacts near the air/tissue interfaces are amplified at higher field, rendering information in the phase images unusable in extreme cases. Incomplete phase processing prior to SWI mask generation can result in subtle phase artifacts, which may have vessel-like appearance, much like those demonstrated in Chapter 2 [16]. Phase artifacts may lead to inaccurate calculation of %PVWML. The work of Chapter 2 showed that, by processing individual receiver coil complex image data separately (the IEV-SWI processing pipeline), phase information can be better preserved [16]. This approach, which is employed in our study, allows for generation of high-contrast, artifact-free SWIs. For accurate WML identification at 7T, it is also advantageous to collect 3D FLAIR images with efficient fluid suppression and $T_2$-contrast, which is accomplished through the addition of magnetization preparatory pulses to the conventional FLAIR sequence (MP-FLAIR) [15].

In this study, we have performed a thorough evaluation of features included in the NAIMS consensus statement. Using IEV-SWI and MP-FLAIR images acquired at 7T, we sought to identify morphological characteristics of WML to enable the sensitive and specific differentiation of clinically definite MS WMLs from benign WMLs in controls.
3.3 Materials and Methods

3.3.1 Study Design and Patient Population

The study was approved by our Institutional Research Ethics Board. Written informed consent was obtained from each subject. Seventeen relapsing-remitting MS (RRMS) patients and eighteen age and gender matched healthy control (HC) subjects were selected from a large study population [17]; the subjects were selected from [17] based on the availability of raw image data. There is no overlap between the subject matter of the previously published work and the current study. HC subjects had no known neurological conditions, but were incidentally found to have WMLs. Clinical data, including extended disability status scale (EDSS), were collected for all RRMS subjects.

3.3.2 Imaging Protocol

Imaging was performed on a 7T MRI system (Agilent Technologies, Santa Clara, CA) using a 23-channel transmit/receive head coil. A six-echo GRE dataset was collected from each subject with the following acquisition parameters: resolution: $0.5 \times 0.5 \times 1.25 \text{ mm}^3$; $TR/TE_1 : 40/3.77\text{ms}$; echo spacing: $4.1 \text{ ms}$, flip angle $= 13^\circ$, acceleration factor $R = 2$ in first phase encode direction; the total imaging time for this sequence was 15 minutes 55 seconds. Accompanying MP-FLAIR images (for hyperintense lesion identification) were also collected, as described previously [15]. The MP-FLAIR images were acquired with $1.0 - \text{mm}^3$ isotropic resolution in the sagittal orientation. Other MP-FLAIR acquisition parameters were as follows: $TR/TE: 2000/242.8 \text{ ms}$; total imaging time 13 minutes 52 seconds.

3.3.3 Image Processing and Registration

The complex channel data of the multi-echo GRE acquisition was processed offline using the channel-by-channel IEV-SWI pipeline [16]. All SWI processing was performed using parallel computing on a system with 16 cores using MATLAB software (R2014a, The MathWorks Inc., Natick, MA).

IEV-SWI and MP-FLAIR images were registered using FSL tools (FSL, Oxford Center for
3.3. MATERIALS AND METHODS

Functional Magnetic Resonance Imaging of the Brain, University of Oxford, UK) [18, 19, 20, 21]; the IEV-SWIs were viewed as single-slice images.

3.3.4 White Matter Lesion Assessment

A neuroradiologist with 9 years of experience in MR imaging of neurodegenerative and demyelinating disorders performed white matter lesion assessment. Lesion counting was repeated one month after the initial evaluation by the same reader to enable intra-reader variability assessment. For inter-reader variability assessment, two radiology residents (year 4 and year 5) performed the same evaluations. For each RRMS and HC subject, the registered pair IEV-SWI and MP-FLAIR images was anonymized and randomized by a non-reader. Images were then imported into Osirix (v5.8.1) [22] for viewing. Each reader had a training session where they were introduced to the procedures and requirements for WML assessment. Readers were able to view co-registered, coronal, axial and sagittal views of IEV-SWI and MP-FLAIR images. White matter lesions were defined as abnormal hyperintensities on MP-FLAIR images. Veins were defined as hypointensities on IEV-SWI extending over several voxels either in or through the axial plane of the images.

In-line with the hypergeometric model validated previously to accelerate radiological brain white matter lesion assessment [12], readers were asked to identify the 10 largest lesions for each subject based on the MP-FLAIR image data. They were then asked to assess morphological information for each lesion (outlined in Section 3.3.5 below). For subjects who had less than 10 lesions, readers recorded information for as many lesions as they could identify on the MP-FLAIR images.

3.3.5 Metric of Assessment

The following assessments were incorporated into a paper form to enable easy recording of the observations by each reader (i.e. the possible responses were outlined in the form to control the range of variation in the responses).

The lesion location was recorded as being in one of the following brain regions: 1. Infratentorial - below the tentorium, 2. Juxtacortical - within one voxel from the cortex, 3. Periventric-
ular - within one voxel of the ventricles, or 4. Subcortical/deep - between the ventricles and the cortex.

Preliminary lesion size assessment was performed using the Osirix length measurement tool. If the lesion length along its longest axis was smaller than 3 mm, this was noted and area was not measured. This was done because the NAIMS consensus statement excludes lesions that are \(< 3\text{mm}\) in any of the viewing planes. For lesions \(> 3\text{mm}\) the closed polygon tool of Osirix was used to measure the area of the lesion on its largest axial cross section.

Additionally, all readers recorded the presence or absence of central veins within the lesions based on the registered IEV-SWI. If central veins were present, the number of distinct veins was noted. The presence or absence of an iron rim around the lesions was also noted. Finally, the time required for assessment of each dataset was recorded.

### 3.3.6 Metrics of Analysis

**Assessment of Diagnostic Value:**

For each scan the following metrics were calculated:

For each HC and RRMS subject \(S_k\) scan, \(\%\text{PVWML}\) was calculated for each of the three readers \((R_i)\) throughout the brain volume and for each of the four lesion locations \((\text{loc}_j)\) as follows:

\[
\%\text{PVWML}_{R_i,S_k} = \frac{\sum \text{lesions with central vein}(s)_{\text{brainvol.}}}{\text{total lesions}} \tag{3.1}
\]

\[
\%\text{PVWML}_{R_i,\text{loc}_j,S_k} = \frac{\sum \text{lesions with central vein}(s)_{\text{loc}_j}}{\text{total lesions}} \tag{3.2}
\]

Data from subjects with fewer than 3 lesions were eliminated from the analyses.

The location-specific \(\text{Average}\%\text{PVWML}\) for each reader was calculated for the RRMS and HC groups using Equation 3.2 as follows:

\[
\text{Average}\%\text{PVWML}_{R_i,\text{loc}_j} = \frac{\sum_{k} \%\text{PVWML}_{R_i,\text{loc}_j,S_k}}{K} \tag{3.3}
\]

where \(K\) is the total number of subjects for each group.

The \(\%\text{PVWML}\), as calculated by 3.2, was averaged over all readers, for each subject and
at each location, for the HC and RRMS group:

\[
\text{Average}\% PVWML_{loc, S_k} = \frac{\sum_{i} \% PVWML_{R_i, loc, S_k}}{I}
\]  

(3.4)

where \( I \) is the total number of readers.

The global average \( \% PVWML \) was calculated as follows:

\[
\text{Average}\% PVWML_{S_k} = \frac{\sum_{i} \% PVWML_{R_i, S_k}}{I}
\]  

(3.5)

where \( \% PVWML_{R_i, S_k} \) is calculated by 3.1.

These assessments were repeated for three different lesion pools of: (i) large lesions > 3mm (LL pool), (ii) non-confluent > 3mm (NC pool), and (iii) non-confluent > 3mm with a single central vein (SV pool). Note that NC and SV pools are subsets of LL pool.

### 3.3.7 Statistical Analysis

Statistical analysis was performed using GraphPad Prism v7.0a (GraphPad Software, La Jolla, CA). Average lesion size in each anatomical region was compared between the RRMS and HC groups, using multiple measures two-way ANOVA. Lesion size differences in each of the four regions within the RRMS group were compared using the non-parametric paired Friedman test. The average time taken by each reader to complete the review of each dataset was compared between RRMS and HC groups using the Mann-Whitney test.

\text{Average}\% PVWML_{R_i, loc, S_k} (Eq. 3.3) was used to assess inter- and intra-reader agreement using Bland-Altman analysis. \text{Average}\% PVWML_{loc, S_k} (Eq. 3.4) and \text{Average}\% PVWML_{S_k} (Eq. 3.5) were used to calculate sensitivity and specificity of location-specific \%PVWML and average \%PVWML over the brain volume as a means of differentiating MS from non-MS WMLs, respectively, using the area under the receiver operating characteristic (AUC) curve analysis.

The correlation between \text{Average}\% PVWML_{S_k} and the average lesion size and \%confluency (number of confluent lesions divided by the total number of lesions for each subject) were evaluated. Additionally, the correlation between EDSS and \text{Average}\% PVWML_{S_k} was evaluated. All correlation analyses were performed using the Spearman correlation test.
For all statistical analyses \( p < 0.05 \) was considered as significant.

3.4 Results

3.4.1 Clinical Data

Clinical and demographic information (including EDSS) are provided in Table 3.1. The mean age of RRMS and HC cohorts was not statistically different. Gender distribution was also not different between the two groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>HC Subjects</th>
<th>RRMS Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Subjects</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>No. of females</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>37.4 ± 5.8(26 – 46)</td>
<td>39.4 ± 5.4(26 – 46)</td>
</tr>
<tr>
<td>EDSS</td>
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<td>2.2 ± 1.6(0 – 6)</td>
</tr>
<tr>
<td>Time between EDSS and scan (days)</td>
<td>NA</td>
<td>297 ± 49</td>
</tr>
</tbody>
</table>

Note: Data are mean ± standard deviation. Data in parentheses present the range. NA=not applicable. EDSS = Expanded Disability Status Scale.

\(^a\) \( p=0.23 \), not significant, t-test following D’Agostino & Pearson omnibus normality test

Table 3.1: The demographic information and the clinical data of RRMS and HC participants are presented.

3.4.2 Visualization of Perivenous Lesions

For all subjects, IEV-SWI images were successfully registered to the MP-FLAIR images. Examples are shown for three different RRMS and HC subjects in Figure 3.1 and Figure 3.2. MP-FLAIR images demonstrate lesion boundaries, while the IEV-SWI examples identify submillimetre veins. Figure 3.3 shows examples of perivenous lesions in different regions of RRMS-patient brains. Regardless of lesion location and size, the IEV-SWI approach reliably identified veins co-localized with lesions. Additionally, in three of the examples presented in Fig. 3, a hypointense rim is evident (around the lesion in the periventricular white matter and the lesion in the subcortical region).

Figure 3.4 shows two representative WML examples in HC subjects. No infratentorial lesions were found in HCs.
3.4. Results

Figure 3.1: Three examples of MP-FLAIR and IEV-SWI slices and selected magnified regions are shown for three RRMS patients. Several sub-cortical and periventricular lesions are demonstrated. (a) The white arrows on the magnified IEV-SWI images (right-most column) identify a vein running through the body of a white matter lesion. (b) The arrow on the magnified regions points to a "coffee bean" shaped lesion with a vessel running through it. (c) The arrows point to small, sub-millimeter, vessels running through very small WMLs in the subcortical white matter region.

3.4.3 White Matter Lesion Assessment

A total of 626 lesions were identified in RRMS patients (median<sub>readers</sub>: 156, range: 154-160); 13 infratentorial (median<sub>readers</sub>: 3, range: 3-4), 86 juxtacortical (median<sub>readers</sub>: 20, range: 18-29), 190 periventricular (median<sub>readers</sub>: 49, range: 37-55), and 337 subcortical (median<sub>readers</sub>: 88, range: 66-96). A total of 169 lesions were identified in the HC group (median<sub>readers</sub>: 43, range: 34-49); 9 juxtacortical (median<sub>readers</sub>: 2, range: 0-5), 7 periventricular (median<sub>readers</sub>: 1, range 1-4) and 153 subcortical (median<sub>37</sub>, range: 31-48).

Mean lesion size in each brain region was significantly larger in RRMS than HC (<i>p < 0.01</i>) (the infratentorial region was excluded from this analysis). The mean RRMS lesion sizes were also different between brain regions (<i>p < 0.01</i>) with periventricular lesions being the largest (average: 43.6 mm<sup>2</sup>), followed by subcortical lesions (average: 29.7 mm<sup>2</sup>), juxtacortical lesions (average: 23.5 mm<sup>2</sup>) and infratentorial lesions (average: 18.1 mm<sup>2</sup>).
Figure 3.2: Three example MP-FLAIR and IEV-SWI images of HC subjects. Magnified views of lesions are presented in the two right-most columns. Note the central vessel running through the subcortical lesion in (a). The lesion in (b), a subcortical lesion, is situated between two veins. This is also observed in (c). The IEV-SWI image shows clear delineation of these vessels.

Figure 3.3: Magnified lesion views taken from axial slices of RRMS patients enrolled in our study. CVS lesions are shown for each brain region: (a) infratentorial, (b) juxtacortical, (c) periventricular, and (d) subcortical lesions. For the lesions in the periventricular and subcortical regions, a hypointense rim is observed around the lesion on the IEV-SWI image. Yellow arrows point to select lesions and the central vessels running through them. Panels are, on average, 3 cm wide.

The average image assessment times, which included the performance of area measurements, for the RRMS and control subjects were 12 minutes 10 seconds (SD: ±3 minutes 47 seconds) and 4 minutes 33 seconds (SD: ±2 minutes 5 seconds), respectively ($p < 0.01$).
3.4. Results

Figure 3.4: Examples of juxtacortical, periventricular, and subcortical lesions for HC participants. Yellow arrows identify central veins running through the body of WMLs. IEV-SWI allows for the visualization of CVS sub-millimeter vessels enabling accurate definition of %PVWML. Panels are, on average, 2 cm wide.

3.4.4 Diagnostic Value of %PVWML

The results of Bland-Altman analysis are presented in Table 3.2 for the three lesion pools analyzed. Overall, agreement between the readers improved when confluent lesions were removed (NC pool). However the inter- and intra-reader agreement degraded for the SV pool.

<table>
<thead>
<tr>
<th>LL lesion pool</th>
<th>NC lesion pool</th>
<th>SV lesion pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SD of bias</td>
<td>95% LoA</td>
</tr>
<tr>
<td>R1R2</td>
<td>8.5</td>
<td>−12.3 : 21.1</td>
</tr>
<tr>
<td>R1R3(1)</td>
<td>9.8</td>
<td>−2.9 : 35.6</td>
</tr>
<tr>
<td>R1R3(2)</td>
<td>6.8</td>
<td>−11.3 : 15.1</td>
</tr>
<tr>
<td>R2R3(1)</td>
<td>11.5</td>
<td>−10.5 : 34.5</td>
</tr>
<tr>
<td>R2R3(2)</td>
<td>11.1</td>
<td>−24.2 : 19.3</td>
</tr>
<tr>
<td>R3(1)R3(2)</td>
<td>3.8</td>
<td>−21.9 : −7.1</td>
</tr>
</tbody>
</table>

Table 3.2: Results of Bland-Altman test for reader agreements. Agreement between individual readers (R1, R2, R3(1), R3(2)). The most consistently good agreement between readers was observed for the analysis of the non-confluent lesions > 3-mm (the NC pool). Removal of the lesions with multiple distinct vessels (the SV pool in the table), results in an increase in the bias and the standard deviation of the bias.

Table 3.3 summarizes the location-specific %PVWML (Eq. 3.4) and the average %PVWML (Eq. 3.5). The difference in %PVWML between the RRMS and HC groups is significant ($p < 0.01$). Figure 3.5 presents the average %PVWML results over the brain volume for the three lesion pools. Many of the MS WMLs that are classified as perivenous have multiple distinct veins within them. The removal of these lesions results in a spread of the MS data (Fig. 3.5c). Meanwhile, the HC plots don’t change from (b) to (c).
Table 3.3: Summary of location-specific and averaged %PVWML (averaged over the three readers’ data) are presented together with the average %PVWML in the brain volume, for each of the lesion pools. All differences between RRMS and HC statistics were significant as per Mann-Whitney test ($p < 0.01$).

<table>
<thead>
<tr>
<th>Variable</th>
<th>RRMS At each location</th>
<th>Average$^\psi$</th>
<th>HC At each location</th>
<th>Average$^\psi$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LL lesion pool</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{infratentorial}$</td>
<td>10 ± 18%</td>
<td></td>
<td>0 ± 0%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{juxtacortical}$</td>
<td>59 ± 31%</td>
<td>83 ± 14%</td>
<td>3 ± 8%</td>
<td>5 ± 6%</td>
</tr>
<tr>
<td>Average%PVWML$_{periventricular}$</td>
<td>68 ± 35%</td>
<td></td>
<td>4 ± 10%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{subcortical}$</td>
<td>82 ± 16%</td>
<td></td>
<td>12 ± 17%</td>
<td></td>
</tr>
<tr>
<td><strong>NC lesion pool</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{infratentorial}$</td>
<td>3 ± 8%</td>
<td></td>
<td>0 ± 0%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{juxtacortical}$</td>
<td>50 ± 34%</td>
<td>91 ± 15%</td>
<td>3 ± 8%</td>
<td>18 ± 23%</td>
</tr>
<tr>
<td>Average%PVWML$_{periventricular}$</td>
<td>47 ± 31%</td>
<td></td>
<td>1 ± 6%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{subcortical}$</td>
<td>84 ± 17%</td>
<td></td>
<td>16 ± 21%</td>
<td></td>
</tr>
<tr>
<td><strong>SV lesion pool</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{infratentorial}$</td>
<td>2 ± 6%</td>
<td></td>
<td>0 ± 0%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{juxtacortical}$</td>
<td>52 ± 39%</td>
<td>76 ± 24%</td>
<td>3 ± 8%</td>
<td>17 ± 23%</td>
</tr>
<tr>
<td>Average%PVWML$_{periventricular}$</td>
<td>20 ± 23%</td>
<td></td>
<td>0 ± 0%</td>
<td></td>
</tr>
<tr>
<td>Average%PVWML$_{subcortical}$</td>
<td>78 ± 22%</td>
<td></td>
<td>16 ± 21%</td>
<td></td>
</tr>
</tbody>
</table>

Note: Data are mean ± standard deviation
$^\dagger$ Calculated using Eq. 3.4
$^\psi$ Calculated using Eq. 3.5.

Figure 3.5: Average %PVWML$_{S_4}$ presented for the RRMS and HC groups in the (a) LL lesion pool, (b) NC lesion pool, and (c) SV lesion pool. A large number of WMLs with central veins were observed to have multiple central veins. The removal of lesions with multiple central veins results in wider spread in the data. This yielded reduced diagnostic value of %PVWML for the NC lesion pool (c). The average %PVWML was found to be significantly different between the RRMS and HC groups for all lesion pools as per the Mann-Whitney test ($p < 0.01$).

Table 3.4 summarizes the sensitivity and specificity for %PVWML calculated for lesions belonging to each brain region. Separation of RRMS and HC based on the infratentorial lesions results in poor sensitivity (29% for the LL pool). The LL and NC pools, on average, demonstrate high sensitivity (94%) and specificity (100%). The sensitivity and specificity results for
Average%PVWML_{P_4} are presented in Fig. 3.6. This, together with the Bland-Altman results, suggests that the removal of non-confluent lesions reduces the bias between different readers. Overall sensitivity was lower in the SV pool (77%). Cut-off thresholds of 30% PVWML and 67% PVWML allow for differentiation of RRMS and HC with sensitivity of 94% and a specificity of 100% in both the LL and NC pools, respectively.

Figure 3.6: The diagnostic accuracy of the Average%PVWML_{S_1}, as analyzed by ROC test, presented for the pool of all the lesions > 3mm (LL pool), the pool of non-confluent lesions > 3mm (NC pool), and the pool of non-confluent lesions > 3mm with a single central vessel (SV pool).

Significant correlation was found between %PVWML and both average lesion size (r=0.6, p=0.02) and %confluency (r=0.7, p=0.003). EDSS scores did not correlate strongly with the location-specific %PVWML (r=0.04, p=0.88).

3.5 Discussion

In this study we identified morphological characteristics of WMLs and associated cerebral venous vasculature from combined MP-FLAIR [15] and IEV-SWI [16]. Through simultaneous visualization of WML and veins, we demonstrated that, with a threshold of > 67% perivenous non-confluent WMLs of > 3mm in length, the RRMS group can be differentiated from HC...
### Table 3.4: The results of ROC analysis (sensitivity, specificity, and 95% CI) are presented for the analysis performed for the three lesion pools. It can be noted that the diagnostic value of regional and average %PVWML generally remains the same in terms of sensitivity and specificity when the non-confluent lesions are removed. With the removal of lesions with multiple central vessels the diagnostic value of this approach drops considerably (values highlighted in red).

<table>
<thead>
<tr>
<th>Region</th>
<th>Threshold:</th>
<th>LL lesion pool</th>
<th>NC lesion pool</th>
<th>SV lesion pool</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 13%</td>
<td>&gt; 13%</td>
<td>&gt; 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td>12%</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>10% – 56%</td>
<td>2% – 36%</td>
<td>0% – 29%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.65</td>
<td>0.56</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 19%</td>
<td>&gt; 7%</td>
<td>&gt; 29%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>82%</td>
<td>82%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>57% – 96%</td>
<td>57% – 96%</td>
<td>38% – 86%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>89%</td>
<td>100%</td>
<td>100%</td>
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<td>95% CI:</td>
<td>65% – 99%</td>
<td>65% – 99%</td>
<td>82% – 100%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.93</td>
<td>0.89</td>
<td>0.86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 13%</td>
<td>&gt; 13%</td>
<td>&gt; 13%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>88%</td>
<td>82%</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>64% – 99%</td>
<td>57% – 96%</td>
<td>28% – 77%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>83%</td>
<td>94%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>59% – 96%</td>
<td>73% – 100%</td>
<td>82% – 100%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.93</td>
<td>0.90</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 51%</td>
<td>&gt; 61%</td>
<td>&gt; 61%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>94%</td>
<td>94%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>71% – 100%</td>
<td>71% – 100%</td>
<td>57% – 96%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.99</td>
<td>0.99</td>
<td>0.96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 30%</td>
<td>&gt; 67%</td>
<td>&gt; 66%</td>
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<tr>
<td></td>
<td>94%</td>
<td>94%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>71% – 100%</td>
<td>71% – 100%</td>
<td>50% – 93%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>95% CI:</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td>82% – 100%</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>0.99</td>
<td>0.99</td>
<td>0.95</td>
<td></td>
</tr>
</tbody>
</table>

The AUC: Area Under the receiver operating Characteristic curve.

This study used high-field (7T) acquisition and a custom image post-processing protocol to assess the global and morphological characteristics of WMLs in MS and matched healthy control subjects. Previous studies have examined longitudinal changes in the volume of central

with a sensitivity of 94% and a specificity of 100%.
veins [23] using 7T SWI/FLAIR images. However, the assessment of %PVWML in anatomically distinct brain regions using IEV-SWI and MP-FLAIR at 7T has never been performed. Furthermore, our study demonstrates the ability to visualize CVS in the infratentorial lesions. Specifically, the IEV-SWI method enabled generation of venography images in the infratentorial region of the brain, where 7T phase data may be corrupted. Readers in this study did not report corrupted phase information affecting %PVWML assessment in the infratentorial brain. The poor sensitivity of the infratentorial lesions identified in Table 3.4 must be interpreted while considering other known factors, such as Fazekas’ inclusion criteria [24].

Our proposed %PVWML threshold (67%) is higher than the threshold of 40% previously reported [12] and used in the literature [9]. This difference can be attributed to the quality of IEV-SWI venography images, which enabled the visualization of sub-millimeter sized veins and a proportionally higher %PVWML in both groups.

Our work has also demonstrated the ability of the IEV-SWI approach to identify hypointense rims around some MS lesions, while no hypointense rims were observed in the HC group. The hypointense rim has previously been attributed to iron-laden macrophages [25] and may be an imaging biomarker for MS.

The cohort in our study was selected from a pool of age-matched, self-reported healthy individuals, with no known neurological disorders. Incidental findings of WMLs in these individuals (a total of 63 lesions > 3mm and range of 0-17 lesions in each HC subject) may be indicative of undocumented risk factors, such as risk factor for small vessel disease. Incidental findings of white matter lesion hyperintensities have been reported previously [26], even in young cohorts [27].

Strong inter- and intra-reader agreement was observed (Table 3.2), particularly when confluent lesions were not included in the analysis. Agreement between readers was reduced when lesions with multiple central veins were excluded. This can be explained by the spread of data in the HC plot from Fig. 3.5a to Fig. 3.5b and the lack of change from Fig. 3.5b to Fig. 3.5c, which suggest that non-confluent benign lesions are likely to have a single vessel. On the other hand, the spread of the RRMS subjects’ data (Fig. 3.5c) suggests that the morphology of the majority of MS (confluent and non-confluent) WMLs include multiple veins. The data presented in Table 3.2 demonstrates the first reader (R1, the most junior reader) as an outlier
compared to R2 and R3. The consistent superior agreement between R2 and R3 as compared to the agreement of R1 data with either of R2 or R3 raises a potential question about the contribution of readers’ experience to the consistency of the findings.

Visualization of lesions and corresponding venograms on two separate datasets may have added uncertainty to the readings performed in this study. In a previous study employing the FLAIR* approach [28], a $T_2^*$-weighted image was multiplied with a FLAIR image on a pixel-by-pixel basis, which facilitated assessment of co-localized WMLs with vessels. Adopting the approach of superposition of FLAIR and SWI would allow for simultaneous assessment of the IEV-SWI information and MP-FLAIR images but requires precise registration and re-sampling. Neurodegenerative disorders mimicking MS may exhibit benign WMLs with unique morphological characteristics. The proposed radiological definition for CVS is strictly for separating MS WMLs from benign WMLs. The guidelines of the NAIMS criteria should be investigated further for other mimics of MS. While this study was performed at 7T, the radiological definition of CVS defined here is expected to hold at 3T but the threshold to separate RRMS and HC may need to be validated through further investigation.

In conclusion, based on the investigation of the NAIMS consensus criteria we have identified a sensitive and specific radiological definition for CVS: our work suggests that $\%PVWML$, as calculated for non-confluent lesions > 3mm in length with one or more central veins observed on 7T MP-FLAIR and IEV-SWI, can be used as a sensitive and specific discriminator of RRMS patients from control subjects with benign WMLs.

3.6 Conclusions

The technical methods developed in Chapter 2 enabled the generation of high contrast single slice venography images using susceptibility contrast from the phase component of MRI data. All data belonging to the 35 subjects participating in this study were successfully processed using the IEV-SWI approach to enable the visualization of venous vasculature of sub-millimeter size throughout the volume of the brain.

With no artifacts reported by the expert readers, it may be concluded that the IEV-SWIs in conjunction with the MP-FLAIR image data may be reliably incorporated into acquisition and
post-processing of ultrahigh-field MR imaging practice in order to provide clinically useful information. Using the IEV-SWI approach it was possible to propose a data-driven radiological definition for MS white matter lesions. Extension of this definition to mimics of MS other than benign white matter lesions remains a topic for future research.
References


Chapter 4

Single Acquisition Multi-Parametric
Myocardial Mapping at 3T

The third development of this dissertation presented in this chapter is the design and validation of the post-processing methods that enable multi-parametric quantitative maps of the tissue using a single multi-echo GRE acquisition. A version of this chapter has been submitted to Magnetic Resonance in Medicine in March 2018.

4.1 Overview

Chapters 2 and 3 presented evidence that lend support to the hypothesis pertaining to the benefits resulting from channel-by-channel processing of MR phase images acquired using multi-echo GRE imaging. Several considerations must be made when imaging in the body, which are not necessary in neurological MRI applications. The present chapter develops the necessary post-processing steps to translate the channel-by-channel processing approach into cardiac imaging.

The challenge of preserving phase information is intensified when imaging in the torso and even the extremities. The main challenge is presented by the large region of interface between tissue and air (lungs). Furthermore, the presence of fat (different chemical environments) leads to an additional bias phase term. The natural body motion (e.g. peristalsis in the digestive tract, cardiac motion), which is added to the possibility of the patients global motion present further
challenges, imposing the requirement of short or ultrashort acquisition time.

The clinical feasibility and high quality results presented in Chapter 3 provide support for the potential impact that the methods of Chapter 2 may have outside of the brain. It may even be hypothesized that the extent to which channel-by-channel processing of MRI complex data improves the final quantitative maps is more pronounced in applications outside of the brain where the abovementioned challenges present themselves.

In this chapter, the methods of Chapter 2 are modified and translated into cardiac imaging. The cardiac MRI application is selected in order to represent a range of image acquisition and post-processing challenges commonly faced outside of the brain. Furthermore, a cohort of heart failure patients are selected in this work in order to enable preliminary validation against the accepted standard of myocardial scar imaging (i.e. LGE).

4.2 Introduction

Myocardial tissue characterization using magnetic resonance imaging has emerged as a promising tool in predicting the response of patients to interventional procedures such as cardiac resynchronization therapy for heart failure (HF) [1, 2] and pulmonary vein ablation procedures for atrial fibrillation [3]. The current standard of practice involves the use of presence and quantification of late gadolinium enhancement (LGE) [4] as assessed by cardiac MRI to differentiate between healthy myocardium (hypointense appearance on the image) and scar tissue, with hyperintense contrast on the image.

Quantitative tissue mapping is a well-established technique in the body. Specifically, native and post-contrast $T_1$-mapping, as well as native $T_2$- and $T_2^*$-mapping have been applied in various clinical applications such as diffuse myocardial fibrosis [5, 6], edema [7, 8], iron overload [9] and many more. All of these quantitative approaches utilize the magnitude component of MR data. MR phase data, obtained from gradient echo imaging, contain tissue magnetic susceptibility sensitive information as well. Multi-echo GRE (ME-GRE) acquisition protocols provide the means of computing multiple quantitative maps (fat fraction (FF), $R_2^*$, $B_0$, and local frequency shift (LFS) map) from a single imaging session. Taviani et al. [10] demonstrated the application of a novel cardiac- and respiratory-gated 3D ME-GRE sequence for chemical shift
encoding, however they did not explore the information provided by the field map. Similarly, Liu et al. [11] demonstrated the value of dual echo GRE imaging at 1.5T for accurate FF-mapping. The masks obtained from the filtered phase images have been used in two studies at 1.5T (ME-GRE) and 3T (single echo GRE) to assess the feasibility of susceptibility weighted imaging (SWI) for detection of intramyocardial haemorrhage [12, 13]. SWI, however, is not quantitative and is sensitive to the specific mask, the imaging parameters, namely the product of field strength and echo time (TE), and may not be easily translated to other cardiac applications.

Quantitative mapping of B0 field is challenging, particularly in tissue structures close to areas of large inhomogeneity. The large phase gradients near the air/tissue interface, such as those between the heart and lungs, cause severe loss of local phase information. In the work completed as part of Chapter 2 [14] and Chapter 3, it was demonstrated that channel-by-channel processing of complex MR data, successfully preserves phase information. While channel-by-channel analysis can be computationally intensive, particularly in iterative applications [15], a non-iterative B0-mapping technique exists for unipolar and bipolar acquisitions, which can be parallelized in order to speed up the image processing [11].

In the current work, we present a new approach for integrating channel-by-channel quantitative mapping with gated 2D ME-GRE acquisitions and evaluate the ability to measure quantitative myocardial maps (FF, \( R^*_2, B_0, \) LFS) at 3T using these methods. Specifically, we implement a pipeline for processing individual channel data by non-iterative correction of phase errors (IC-NICE), which receives reconstructed complex data for each channel and calculates a series of quantitative cardiac maps prior to combination. We present the detailed pipeline required to accurately calculate these quantitative maps, demonstrate the robustness of the approach in healthy volunteers, and compare the non-contrast quantitative maps against LGE in heart failure patients.

### 4.3 Theory

The quantitative LFS-mapping approach presented in this work employs the non-iterative B0-NICE technique [16]. Channel-by-channel quantitative phase data processing introduces unique
4.3. Theory

Challenges requiring modification of the B0-NICE pipeline. Specifically, phase processing must occur on a channel-by-channel basis and a magnitude-based mask must be introduced to define the high signal-to-noise ratio (SNR) regions of each phase image. In addition, for most fat/water imaging applications requiring short (and specific) echo spacing, bi-polar gradients must be used and, therefore, correction for the phase error due to opposite gradient polarity must be incorporated. To address these challenges, the IC-NICE algorithm includes the following additional steps: (i) a phase correction block for removal of phase errors due to coil-specific bias and bipolar acquisition, (ii) a local frequency shift mapping block, and (iii) a channel combination block to generate full field-of-view (FOV) maps of the heart. The details of these blocks are presented below and illustrated in Fig. 4.1.

Figure 4.1: Flow chart presents the steps taken in the IC-NICE algorithm to generate quantitative maps for each channel using the magnitude ($M_i$) and phase ($\phi_i$) information. The gray box outlines the modified B0-NICE algorithm, which enables channel-by-channel processing of the complex MR data. The key additional steps for IC-NICE are highlighted with the dashed border.

The GRE signal equation includes the relaxation term, B0-inhomogeneity term as well as a model for chemical species within the FOV. Whereas a single peak fat model was used in the earlier work concerned with water/fat separation, for a thorough evaluation of chemical shift phase term, a multi-peak fat spectrum should be used. This model includes six peaks, each
of which are observed at a unique frequency shift, with respect to water. When the 6-peak fat model is used, the MRI signal for the \(j^{th}\) echo is given by the equation below:

\[
S_{TE_j} = (\rho_W + \rho_F \sum_{m=1}^{M} \alpha_m e^{i2\pi \Delta f_m T E_j}) e^{-R^*_E T E_j} e^{i2\pi f_{b0} T E_j}
\]  

(4.1)

where \(\rho_W\) and \(\rho_F\) are the water and fat signal amplitude, respectively, \(\alpha_m\) is the amplitude of the \(m^{th}\) hydrogen peak in the fat spectrum \((M = 6)\) and \(\Delta f_m\) is the frequency shift of the \(m^{th}\) peak. To extract a quantitative B0 map, a few processing steps are required. First, the phase component of the signal contains linear bias terms, which are generally modelled with zeroth and first order terms as follows:

\[
\phi = \phi_0 + \phi_\epsilon
\]  

(4.2)

The \(\phi_0\) term is a constant while \(\phi_\epsilon\) is a linearly varying phase term in the frequency encode direction due to bipolar gradients. Ma et al. [17] proposed a technique based on the earlier work of Ahn and Cho [18] for calculating and correcting these linear phase terms. This approach has previously been shown to correct for phase errors introduced by opposite gradient polarity for two-point water/fat separation [11] and is therefore employed in this work to correct the bipolar phase error term. As suggested by Ma et al. the zeroth phase term does not affect water/fat separation (since it is a constant offset and does not introduce a bias between water and fat) and therefore can be ignored. However, for signal processing on a channel-by-channel basis, the \(\phi_0\) term varies between channels and must be corrected for (subscript \(i\) in all expressions denotes the \(i^{th}\) channel). For the case where \(2TE_2 \approx TE_1 + TE_3\), this constant phase term \(\phi_{0,i}\) can be calculated for each channel \(i\) using the following equation [19]:

\[
\phi_{0,i} = \frac{1}{4} \angle \frac{S^2_{TE_2(i)}}{S_{TE_1(i)} S_{TE_3(i)}}
\]  

(4.3)

where \(\angle\) is the symbol representing the angle (phase) of the expression that follows it. For the entire field of view, \(\phi_0\) can be calculated as:

\[
\phi_0 = \sum_{i=1}^{C} \phi_{0,i}
\]  

(4.4)
4.3. Theory

where $C$ is the total number of channels in the receiver array. The error term $\phi_0$ can then be subtracted from the original phase and, using any unwrapping technique, an initial $B_0$, map ($B_{0\text{init},i}$ in Fig. 4.1) can be calculated.

Chemical-Shift Bias Removal:
Initial $B_0$, maps ($B_{0\text{init},i}$) can be calculated using any phase unwrapping technique. This initial estimate of the field map still includes chemical-shift bias terms, which must be removed. The B0-NICE algorithm calculates the bias term in $B_{0\text{init},i}$ using a matching criterion imposed on two separate fat masks, one of which is derived from the magnitude data and the other derived from the phase component of the complex image (we will refer to these as the "magnitude-based fat mask" and "phase-based fat mask", respectively); the gray block in Fig 4.1 summarizes these steps. The reader is referred to the original publication for details of this the B0-NICE algorithm [16]. To implement the IC-NICE algorithm, channel-specific phase-based fat masks must be generated; this is achieved by defining a magnitude threshold for each channel that allows for the inclusion only of the high-SNR regions in the phase-based fat masks. Because magnitude information is not lost in the sum-of-squares [20] combination process, a single magnitude-based fat mask may be used in the IC-NICE processing. The output of this stage of the IC-NICE algorithm is in the form of three quantitative maps, $B_{0i}$, $FF_i$, and $R2^*_{i}$-maps for each channel.

Local Frequency Shift mapping:
The $B_{0i}$ and $FF_i$ quantitative maps are then used to extract quantitative LFS maps for each channel. To ensure that fat and water are in phase, $LFS_i$ is calculated only from the in-phase echoes, as follows:

$$LFS_i = \frac{S_{in-phase,i}^* e^{-\Delta \phi_{cs,i}} e^{-i2\pi f_{B_{0,i,\text{filt}}} \Delta T E_{in-phase}}}{2\pi \Delta T E_{in-phase}}$$ (4.5)

where $^*$ is the complex conjugate operator, and $\Delta T E_{in-phase} = T E_3 \text{ } T E_1$. The $f_{B_{0,i,\text{filt}}}$ term is the filtered field map calculated for the $i^{th}$ channel; filtering is necessary to minimize loss of phase contrast in the final LFS map. The $\Delta \phi_{cs,i}$ term in Eq. 4.5 is the chemical shift phase term,
which is calculated, based on the computed $FF_i$ map, as follows:

$$\Delta \phi_{cs_i} = \angle ((1 - FF_i) + FF_i \sum_{m=1}^{M} \alpha_m e^{2\pi f_m \Delta T \text{in-phase}})$$  \hspace{1cm} (4.6)

**Channel Combination:**

The quantitative maps of the full FOV are finally calculated using the individual channel magnitude images for weighting during channel combination.

### 4.4 Methods

#### 4.4.1 Imaging and Participants

**Imaging and Participants**

All data acquisition was performed in accordance to the requirements of the research ethics board at our institution. Informed consent was obtained from all participants. All imaging studies were performed at 3T (Prisma, Siemens Healthineers, Erlangen, Germany). The body coil was used for excitation and the built-in spine coil and a 16-channel torso coil were used for image acquisition; complex channel data (reconstructed using GRAPPA) were saved from 20 to 34 receiver coils. All acquisitions were 2D, breath-held, and gated to end-diastole.

**Healthy volunteers**

Five healthy volunteers (all male, age range: 25-28 years, median age: 26 years) were scanned with a four-echo multi-slice dark blood ME-GRE imaging sequence using bipolar readout gradients to enable acquisition with shorter echo spacing. The acquisition parameters were as follows: $\text{TEs/TR (ms)} = [2.23, 3.5, 4.87, 6.14]/940$; trigger time (ms) = 902.5; flip angle = $20^\circ$; $\text{BW (Hz/px)} = 1150$; GRAPPA factor $R=2$; in-plane resolution ($mm^2$) = $1.5 \times 1.5$; $FOV_{FE} (mm) = 384$; the FOV in phase encoding direction ranged between 230 mm and 384 mm to optimize resolution while avoiding aliasing. Left ventricular (LV) short axis (SAX) images were
acquired (6 mm thick) for all volunteers. Three volunteers also underwent an additional scan with the same imaging parameters but a slice thickness of 3.5 mm. Two- and four-chamber long axis (LAX) views (6 mm thick) were also acquired for two of the volunteers.

**Heart failure patients**

To compare the proposed non-contrast quantitative mapping technique to LGE, five patients with previously diagnosed systolic heart failure (all male, ages 56-78, median of 74) were enrolled in a sub-study of a trial evaluating the potential role of LGE MRI in guiding resynchronization therapy. Patients 1 and 2 had no history of myocardial infarct (MI), patients 3 and 4 had an MI within a year of imaging, and patient 5 had an MI 11 years prior to the scan. As part of the main study protocol [1], these patients underwent LGE imaging 6 minutes following the intravenous administration of Gadovist (0.1 mmol/kg). 2D LGE images were acquired with a 2D turbo flash inversion recovery sequence and the following imaging parameters: TE (ms) = 1.02; trigger time (ms) = 617.5; slick thickness (mm) = 8.0; in-plane resolution ($mm^2$) = 2.0 × 2.0; BW (Hz/px) = 1530; flip angle = 40°; $FOV_{FE}$ (mm) = 384; the FOV in phase encoding direction ranged between 280 mm and 350 mm to optimize resolution while avoiding aliasing. The inversion time (TI) was identified using an initial TI scout and adjusted throughout the scan to ensure appropriate nulling of myocardial signal. ME-GRE images (short axis and long axis, as described above for the healthy participants) were acquired immediately prior to contrast administration; for these subjects the slice thickness of 6.0 mm was used and the FOV and the first slice location in the stack matched that of the first 2D LGE image.

### 4.4.2 Quantitative Cardiac Mapping

All ME-GRE data were processed following the pipeline described in Fig. 4.1, which summarizes the different processing blocks of the IC-NICE technique. The channel-dependent static phase term was removed for each channel and the resulting phase images were subsequently corrected for phase error due to bipolar acquisition. The corrected channel phase images were unwrapped using a 2D implementation of a non-iterative technique (PUROR [21]) to calculate channel phase maps. The channel phase maps were filtered with a 10 × 10 pixel (24 × 24 $mm^2$)
averaging filter to allow for the removal of the background fields for LFS mapping. Using the separate magnitude- and phase-based fat and water masks, errors in the field map were corrected and a final $B_0$- and $FF$-map were generated for each channel. Finally, the relaxation maps ($R_2^*$) were computed as described by Liu and Drangova [16]. This process resulted in three primary maps for each channel, $B_0$-, $FF$-, and $R_2^*$-maps, and a single relaxation map for the channel-combined data, $R_2^*$ map; for each of the participants, the $B_0$- and the $FF$-maps were then used to compute $LFS$ maps for each of the channels as per Eq. 4.5. The quantitative maps for each channel were then combined using the weighted average approach, where the channel magnitude images were used as the weighting factor.

To assess the potential benefit of IC-NICE processing approach, all maps were also calculated from the channel-combined complex images. For clarity, we will refer to the individual channel maps as ”channel maps”, denoting them with subscript $i$, the combined channel maps as IC-NICE maps, and the maps obtained from channel-combined complex data as simply ”combined maps”.

All post-processing steps were implemented in MATLAB (R2015a, The MathWorks Inc., Natick, MA) on a MAC OS workstation with 3.5 GHz Intel Core i7 processor, and 16 GB RAM.

### 4.4.3 Qualitative Assessment

Channel, IC-NICE and combined $B_0$-, $FF$-, $R_2^*$-, and $LFS$-maps were qualitatively assessed, by an imaging researcher with four years of experience in MR imaging, on a slice-by-slice basis. Specifically, the ability to identify and track myocardium, coronary vessels, and pericardial fat was assessed throughout the image volume. The presence of susceptibility-related artifacts and fat/water swaps was also noted.

For each of the HF patients, the correspondence of tissue scar on the LGE and the non-contrast quantitative maps was evaluated by a cardiologist. This assessment was performed in Osirix (v5.8.1) [22] - co-registered slices were viewed simultaneously. For identification of scar, the LGE image was first assessed against the cine image data for a given patient to ensure presence of scar; in other words, the hypointense myocardium as seen on the cine images was
compared against the nulled myocardial region on the LGE, thereby enabling the confident identification of hyperintense scar region(s) on LGE. Once this assessment was completed, comparison of scar was made on the quantitative maps against the LGE.

4.4.4 Quantitative Assessment

Quantitative assessments were performed for the IC-NICE and combined $LFS$- and $R_2^*$-maps for all volunteers. Three short-axis co-registered IC-NICE and combined maps were loaded into Osirix, sequentially. Slices in the basal, mid, and apical segments of the myocardium, as defined by the American Heart Association were selected. The 3.5 mm thick IC-NICE $R2^*$ map was used to define regions of interest (ROI) for analysis; these ROIs were then transferred to all other maps. Three myocardial regions were selected within each of the basal and mid slices in the anterolateral, inferior, and septal zones. For the apical slice, four regions were selected in the anterior, lateral, inferior, and septal sections of the myocardium. The signal in the $R2^*$ maps was calculated as the mean of each ROI, and the noise in each of the $R2^*$- and $LFS$-maps was calculated as the standard deviation of the ROI.

The effect of slice thickness on IC-NICE maps was evaluated from 30 segments (3 volunteers × 10 segments each), while 40 segments (4 volunteers × 10 segments each) were included in the comparison of the IC-NICE to combined maps. Statistical analyses were performed using GraphPad Prism 7.0a (GraphPad Software, La Joya, CA). All comparisons (i.e. the effect of slice thickness as well as the employed processing pipeline) were non-parametric paired t-tests and a $p < 0.05$ was considered significant.

4.5 Results

4.5.1 Quantitative Cardiac LFS Mapping

The quantitative $B_{0\gamma}$-, $FF_\gamma$-, $R_{2\gamma}^*$-, and $LFS_\gamma$-maps were successfully generated for each of the participants. Channel map combination using magnitude weighting resulted in IC-NICE maps with preserved details throughout the imaging volume. Particularly, when compared to the quantitative maps generated from the channel-combined complex datasets, the signal in the re-
regions of high susceptibility at the air/tissue interface and small structures such as the coronary vessels were spared. While the main aim of the application of the IC-NICE approach to volunteer and patient data was to demonstrate the robust performance of this technique in generating phase-based quantitative maps, IC-NICE $R2^*$ maps were also found to have significantly higher SNR ($p < 0.01$ for maps of 3.5- and 6.0-mm slice thickness - see "Quantitative Assessment" section), suggesting a benefit for processing magnitude images on a channel-by-channel basis.

Figure 4.2(a) shows the channel-combined phase and magnitude images of volunteer 1 at four echo times for SAX and LAX cardiac views. The figure illustrates the extent to which the phase information is lost in the channel-combined images, in the regions of air/tissue interface as well as in the regions of rapid blood flow (orange arrows), despite the application of a phase-sensitive channel combination [23]. Figure 4.2 (b) and (c) provide evidence of high signal in the regions of high susceptibility in the phase and magnitude data acquired by three representative channels for the SAX and LAX views, respectively. Figure 4.2 (d) and (e) show the quality of the quantitative $B0^{-}$, $FF_{i}^{-}$- and $R2_{i}^{-}$-maps generated for each of these channels. The observations of Fig. 4.2(b-e) lends support to the hypothesis that the signal loss seen on Fig 4.2(a) is due to imperfect channel combination.

Figure 4.3(a) presents the IC-NICE maps for the same volunteer as shown in Fig. 4.2 along with the combined maps (Fig. 4.3 (b)). This figure provides a clear demonstration of the improvements that result from the proposed quantitative mapping approach. The yellow arrows point out the preserved signal in the challenging myocardial regions, where cross sections of the coronary vessels are clearly visible (three coronary vessels in the interventricular groove on the SAX view and the coronary sinus on the LAX view). The orange arrows on Fig. 4.3 (b) point to several regions where the maps provide unreliable values and where potentially valuable information is lost. The robustness of the proposed approach was tested in different SNR conditions by applying it to images acquired with 3.5- and 6.0-mm slice thicknesses. Figure 4.4 shows that there are minimal differences in the resulting quantitative maps. Despite degradation of the phase values at air/tissue interface seen on channel combined phase image, the proposed IC-NICE processing successfully extracts the tissue information in this region.
Figure 4.2: (a) The magnitude and phase of the channel-combined images are shown at four echo times for volunteer 1 in the short- and long-axis views (6.0 mm slices). Phase artifacts in regions of large susceptibility differences are identified by the orange arrows. Individual channel data (3 channels) are shown for the short (b) and long (c) axis acquisitions for echo 3, demonstrating that the individual channel phase data are preserved in the regions of high susceptibility identified by the arrows in (a). As expected, when the individual channel phase data are processed, quantitative channel maps of $B_0$, $FF$, and $R^*_2$ are successfully generated for both short (d) and long (e) axis orientations.

Figure 4.5 presents additional examples of the quantitative maps for image slices in the basal, mid, and apical regions of the heart for volunteer 3. The images demonstrate the robust performance of the IC-NICE approach in atrial, atrioventricular and ventricular regions of the heart. Examples of two-chamber and four-chamber long-axis views of the heart are presented.
Figure 4.3: IC-NICE quantitative maps (a) and combined maps (b) are shown for the same short and long axis slices as Fig. 4.2. The blood pool is masked (based on the magnitude images) in the R2*- and LFS-maps for improved visualization of the myocardium. While the R2* maps are similar in (a) and (b), the B0, FF and LFS maps (all derived from phase) are extensively corrupted in the regions identified by the orange arrows. In contrast, the IC-NICE maps in (a) enable the assessment of all regions of myocardium and cardiac structures; interventricular vessels and the coronary sinus are highlighted by the yellow arrows on the SAX and LAX images, respectively.

Figure 4.4: The effect of slice thickness is assessed qualitatively using a set of closely matched image slices of volunteer 1; channel-combined magnitude and phase, as well as IC-NICE maps are presented. Signal loss is evident in the 3.5 mm phase image (orange arrows). In contrast, the IC-NICE approach preserves the information in the quantitative phase-derived maps (e.g. yellow arrows point to coronary vessels visible on both 3.5- and 6.0-mm LFS maps). The expected increase in SNR is evident in the 6.0 mm maps, particularly in the R2*- and LFS-maps. For clarity, the R2* and LFS maps were blanked using the blood pool from the magnitude images as a mask.

in Figure 4.6 for volunteers 3 and 5, where the white arrows point to the cross-section of the coronary sinus on the different views.
4.5. Results

Figure 4.5: Short axis quantitative maps are shown for four contiguous 3.5 mm slices (basal to apical) of volunteer 3. A suspicious hypointense signal is seen on the basal myocardial LFS map, which should be interpreted with care and while considering the anatomical region illustrated in these panels; the atrioventricular region of the myocardium involves rapid changes in the anatomy of the heart, which in turn leads to signal changes influenced by partial volume effects.

4.5.2 Qualitative Assessment

The quantitative maps were successfully generated for all HF patients. The LGE data of patients 1, 2 and 5 did not demonstrate any scar tissue leaving the data from patients 3 and 4 for assessment of the correspondence between LGE and the non-contrast IC-NICE maps.

Figure 4.7 shows examples of the IC-NICE maps and a closely matched LGE image slice of patient 3. The LGE clearly shows the region of scarred myocardium in the septal and the lateral walls of the LV, while each of the quantitative maps show specific signal in this same myocardial regions; the $R^*_2$ map clearly shows the region of septal scar and the FF and LFS
map demonstrate the scar in both septal and lateral regions. The FF map shows fatty infiltration within the scar, $R_2^*$ map reflects an increase in the relaxation time in the scar relative to the healthy myocardium, consistent with the hypothesis of extracellular collagen I. Otherwise, this signal may be due to deoxygenated blood, which is also expected to increase $R_2^*$ values. Finally, the LFS map shows a decrease in the local frequency shift values, which could be attributed to the network of collagen fibres, within the scar, oriented in various directions causing the observed dephasing. As with the $R_2^*$ observations, this dephasing may be due to deoxygenated blood.
Figure 4.7: Quantitative FF-, $R_2^*$- and LFS-maps are shown (patient 3) along with the closely matched LGE image. Regions of late Gd enhancement are seen in the septal and lateral myocardial wall (black arrows) on the LGE image. The non-contrast quantitative maps suggest the presence of fatty infiltration (FF map) and collagen (LFS map) in the scar regions. The $R_2^*$ map clearly demonstrates increased $R_2^*$ in the septal wall but little increase in the lateral wall.

Figure 4.8 shows sample image slice in patient 4 with the magnitude and phase images shown in Fig. 4.8 (a) for reference. The signal loss due to a sternal wire is clearly noticeable on the magnitude and phase images as well as the IC-NICE maps (Fig. 4.8 (b)); in order to demonstrate the extent to which signal is preserved in IC-NICE maps, Fig. 4.9 provides a direct comparison with the corresponding combined maps. The LGE image of a closely matched slice is also presented (Fig. 4.8 (b)). Notice that the slice thickness for the ME-GRE data is 6.0 mm, while that of the LGE data is 8.0 mm, and therefore there is a slight difference in the appearance of the quantitative maps and the LGE images. A hyperintensity is clearly seen on the subendocardial myocardium on the LGE; corresponding regions on the IC-NICE maps demonstrate slightly increased $R_2^*$ and a region of decreased frequency shift values on the LFS maps. Increased FF (> 50%) is observed on the FF maps and the LGE for better visualization of the scar (Fig. 4.8 (c)). Note that the signal pointed to by the yellow arrow on the LFS maps (Fig. 4.7 and Fig. 4.8) cannot be due to fat as these maps are calculated using only the in-phase image data.
Chapter 4. Single Acquisition Multi-Parametric Myocardial Mapping at 3T

Figure 4.8: Phase and magnitude images (a) are shown together with the corresponding IC-NICE maps and the closely matched LGE image slice (b) for patient 4. A region of subendocardial fat is highlighted by the yellow arrow on the FF map. The $R^*_2$- and LFS-maps also demonstrate signal differences in this region (yellow arrows). The corresponding hyperintensity is seen on the matched LGE image slices. Magnified images of the scar regions are presented in (c). (Note that this patient had a sternal wire, which is distorting the image as seen on the magnitude and phase images in (a); despite the large local inhomogeneity, IC-NICE processing is able to resolve the cardiac tissue with minimal degradation in the signal - Fig. 4.9 shows the corresponding combined maps, for comparison.

Figure 4.9: Quantitative maps obtained from processing the image data of Patient 4 using the coil-combined complex images (Adaptive channel combination) as source images (bottom row) are compared to the same maps generated using the IC-NICE approach (reproduced on the top row). It is clear that much of the tissue signal in the combined maps is compromised due to the susceptibility artifacts generated by the sternal wire and the lung/tissue interface.

4.5.3 Quantitative Assessment

The $R^*_2$ values obtained from ROI analysis of the anterolateral wall, inferior wall, and septal wall from the IC-NICE maps were compared to those obtained from the combined maps; the
first two columns of Table 4.1 summarize these findings and presents the mean and standard deviation of the $R^*_2$ values as measured from the combined data and the IC-NICE approach; no significant difference was found in the $R^*_2$ values for any of the myocardial regions for 3.5-mm maps ($p = 0.63$, $p = 0.15$, and $p = 0.85$, respectively). Small, but statistically significant, differences were observed in the values calculated for the anterolateral wall and the septal wall on the 6.0-mm maps ($p < 0.01$, and $p = 0.043$). The differences in $R^*_2$ values in the inferior wall was not significant ($p = 0.52$).

SNR was also quantified for the $R^*_2$ maps. It was demonstrated that the SNR in the IC-NICE maps was significantly higher in all regions of the heart compared to the maps obtained from the combined data (Fig. 4.9, $p < 0.01$). This improvement in SNR performance could be a contributing factor to the differences observed in the mean $R^*_2$ values reported in Table 4.1. The IC-NICE maps generated from the 6.0-mm data were found to have higher SNR compared to the maps obtained from 3.5-mm data ($p = 0.022$), as expected.

<table>
<thead>
<tr>
<th></th>
<th>3.5 mm slices</th>
<th>Noise in LFS maps$^c$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$R^*_2$ values ($s^{-1}$)</td>
<td>conventional</td>
</tr>
<tr>
<td>Anterolateral wall</td>
<td>22.3 ± 7.2</td>
<td>24.3 ± 7.9</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>22.6 ± 8.7</td>
<td>26.2 ± 9.1</td>
</tr>
<tr>
<td>Septal wall</td>
<td>19.2 ± 5.8</td>
<td>19.9 ± 3.1</td>
</tr>
<tr>
<td>6.0 mm slices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterolateral wall</td>
<td>28.8 ± 6.7$^c$</td>
<td>25.8 ± 5.7</td>
</tr>
<tr>
<td>Inferior wall</td>
<td>29.9 ± 10.8</td>
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<tr>
<td>Septal wall</td>
<td>25.9 ± 5.4$^c$</td>
<td>23.7 ± 8.6</td>
</tr>
</tbody>
</table>

$^c p = 0.0013$, $^p = 0.043$

$^c$ all ROI measurements resulted in significantly lower noise in the maps generated through the proposed approach.

Table 4.1: The mean $R^*_2$ values are presented demonstrating similar values in the maps calculated from the proposed approach as from the conventional method of fitting the combined magnitude data. The standard deviation of the LFS values within the identical ROIs are also presented providing evidence of the outperformance of the proposed approach in terms of minimizing noise in the final LFS maps.

In addition, the noise in the LFS maps calculated from each processing pipeline is presented in Table 4.1. The noise level in every region of the myocardial wall for both 3.5- and 6.0-mm maps was significantly lower in the IC-NICE maps compared to the combined maps, demonstrating the extent of information preserved on the LFS maps obtained through the proposed method. Additionally, the IC-NICE maps calculated from the 6.0-mm data had lower noise than the maps generated from the 3.5-mm data ($p < 0.01$).
The scar region of Figure 4.7 was separately segmented. The mean $R_2^*$ value of $57.8 \pm 16.1 \, s^{-1}$ was measured for the segmented ROI, which is outside the mean $\pm 2\sigma$ of the measured value for the healthy participants in the septal myocardium ($23.7 \pm 8.6 \, s^{-1}$). The mean LFS value was $-6.4 \, Hz$, which is outside of the noise level for the septal myocardium ($3.8 \pm 1.8$) and can be presumed detectable through the presented processing approach.

![Figure 4.10: SNR performance of IC-NICE $R_2^*$ maps was consistently higher than that of the combined $R_2^*$ maps for data acquired at (a) 3.5-mm slice thickness and (b) 6.0-mm ($p < 0.01$).](image)

### 4.6 Discussion

In this work, we presented the IC-NICE approach to effectively extract quantitative maps of myocardial tissue using a conventional multi-slice ME-GRE imaging sequence. We demonstrated the robustness of this technique using image data from five healthy volunteers as well as five HF patients. We showed that the IC-NICE approach results in $R_2^*$ maps with significantly higher SNR and LFS maps with significantly lower noise than equivalent maps generated from channel-combined data. Additionally, through qualitative assessments we demonstrated that IC-NICE processing preserves tissue information at air/tissue interfaces and areas susceptible to rapid phase degradation (e.g. atrioventricular regions with rapid blood flow). Finally, using the accepted standard (LGE) as a validation tool, we were able to extract information about the sub-structures in chronic scar, specifically fat and collagen contents (Fig. 4.7 and 4.8).

Importantly, the IC-NICE technique has enabled quantification of local frequency shift values following correction for background $B_0$ and additional errors introduced by opposite gradient polarities; LFS-mapping was made possible by the ability to calculate a high quality $B_0$ map even in regions prone to susceptibility artifacts near the lungs. LFS-mapping using ME-GRE is challenging [24, 25], particularly at higher field strengths, limiting practical acquisition
4.6. Discussion

Recent work has reported on the role of SWI for visualizing myocardial haemorrhage at 3T using a single echo GRE sequence [13] and at 1.5T using a ME-GRE [12]. As the results presented in these reports show, $T_2$-weighted magnitude image can also be used to distinguish myocardial haemorrhage. With the IC-NICE technique, several quantitative maps are generated from a single acquisition, which provide complementary information, thereby resulting in enhanced diagnostic value.

The quantitative ROI analysis showed that by processing the complex data from the individual receiver coils the resulting LFS map benefits from significantly lower noise (Table 4.1). The noise performance analysis was done for different regions of the myocardium to demonstrate that the improvements resulting from IC-NICE technique enable analysis of all myocardial regions and analysis is not limited to the septal myocardium, which is most immune to susceptibility artifacts [26]; therefore both magnitude- and phase-based quantitative maps can be calculated throughout all myocardial regions using the IC-NICE technique. Recent studies have shown that different hyperintensity LGE patterns can be used to identify the cause of HF [27]. With the robust performance of IC-NICE throughout the different regions of the myocardial wall, this approach may be used to further investigate the potential of non-contrast characterization of myocardial scar in HF patients. We additionally demonstrate that the $R_2^*$ maps obtained from the IC-NICE approach result in significantly higher SNR, regardless of the prescribed slice thickness. Finally, the low noise of the IC-NICE LFS maps and the higher SNR of the IC-NICE $R_2^*$ maps obtained for both 3.5- and 6.0-mm data is promising, as high-performing processing pipelines for smaller slice thickness would be desirable for applications in the atria (e.g. scar identification in atrial fibrillation).

The quantitative maps obtained from Patient 3 (Fig. 4.7) demonstrate several key potential benefits of the IC-NICE processing technique. A clear decrease in LFS is seen in the septal wall, along with a corresponding increase in $R_2^*$. Both effects are consistent with an increase in collagen fibre, which is typically laid down anisotropically and results in greater dephasing and low MR signal [28]. As changes in myocardial contractility in HF have been attributed to increased type I collagen [29], it is highly plausible that the observed variations of $R_2$ and LFS are consistent with collagen deposition within the scar. Alternatively, these signal changes in both $R_2^*$ and LFS maps may be attributed to deoxygenated blood. The certain clarification of
these hypotheses can be accomplished through histological validations and is subject to future research. The appearance of fat within the septal wall in Fig. 4.7 and in the subendocardial wall in Fig. 4.8, is consistent with prior observations of lipomatous metaplasia in patients with chronic scar in both histological and in-vivo studies [30, 31, 32, 33]. It could be hypothesized that the mismatch in scar-related signal on the different maps may reflect regional differences that are indicative of scar age. If this is the case, the IC-NICE approach is a vast improvement to previous imaging approach to identify lipomatous metaplasia, where two images (one with and one without fat suppression) are acquired to identify fat within the scar [31].

The patients showed signal differences in LFS, $R_2^*$ and FF values within the scar versus the normal appearing myocardium; of course, the observations are limited to 2 out of the 5 patients, which does not represent a sufficient sample size for comprehensive conclusions but the data suggest that these maps can provide additional valuable information. In the present study, the data were acquired with a 2D multi-slice breath held acquisition protocol, which poses some limitations including the coverage and inconsistent breath-holds between slices. Clearly a 3D free-breathing acquisition, such as the 3D free-breathing chemical shift encoding imaging sequence proposed by Taviani et al. [10] would alleviate most of these concerns. The ME-GRE images in this study were acquired at 3.5 mm and 6.0 mm slice thicknesses while the LGE images were acquired at 8.0 mm, which is the commonly used slice thickness in clinical setting. This resulted in imperfect registration of the images. The use of large slice thickness increases the possibility of artifacts due to partial volume effects, which compromises the ability to separate water and fat from the ME-GRE data. The phase at a given voxel is the sum of phase of the underlying tissue within that voxel. The values of the quantitative phase-based maps, therefore, depends on the size of the imaging voxel, which ideally should be minimized.

In conclusion, a new approach was presented, which enables the extraction of non-contrast quantitative maps of the heart using a conventional ME-GRE imaging sequence. The IC-NICE quantitative maps appear to provide information about the sub-structures within myocardial scar of heart failure patients, potentially indicative of scar age. As part of future work, this finding will need to be validated in a larger clinical study. The preliminary clinical results presented suggest that the proposed IC-NICE approach for quantitative cardiac tissue mapping could potentially provide additional information about myocardial scar tissue and potentially
be a surrogate for LGE scans for patients with poor kidney function for whom injection of contrast agents is a contraindication.

4.7 Conclusions

The IC-NICE approach presented in this study enabled the robust extraction of multi-parametric cardiac maps from a single conventional multi-slice ME-GRE acquisition protocol. The robust performance of IC-NICE further validated the efficacy and the benefits of channel-by-channel MR complex data processing. The immediate application of these maps was shown in a small cohort of HF patient, two of whom showed chronic scar on their LGE images. The IC-NICE approach not only allowed for identification of myocardial scar, but also enabled the characterization of sub-components of the scar. This finding may result in a non-invasive in vivo means for assessing the age of the scar. Of course, this can only be achieved by validating the findings of this study in a large controlled cohort of HF patients with chronic MI.

Poor kidney function is the primary reason for exclusion of HF patients from pre-procedural MRI studies such as that for device implantation (LGE-MRI). The availability of a non-contrast means for acquiring the same pathophysiological information (and perhaps more) enhances the quality of care for these patients.
References


Chapter 5

Conclusions and Future Directions

This chapter will conclude this document by presenting a summary of the accomplished goals as part of the work of this dissertation. Section 5.1 presents a summary for the advances resulting from the completed research and their corresponding impacts. Section 5.2 presents the potential future research directions that can be taken using the completed work of this dissertation as a base knowledge; additionally the section presents a number of preliminary results enabling the easier translation forward for future studies. Finally, Section 5.3 presents the limitations for the work completed here and provides recommendations and considerations necessary for future research.

5.1 Advances Resulting from Current Work

The work of the present dissertation has exploited the multi-channel MR phase and magnitude images, to allow for utilization of multi-echo gradient echo image data for tissue characterization. While the practice of multi-channel image acquisition, for the purpose of accelerating the acquisition, has been explored extensively and a large body of research articles focused on such specific research topics exists, multi-channel image combination practices all employ the same approach of combining the channel images prior to applying any post-processing steps. The benefits gained from channel-by-channel processing approach of MR images, especially for the phase component of the data, has not received sufficient attention. In this section, the advances in knowledge are summarized for each of the specific chapters.
5.1.1 Channel-by-Channel MR Phase Image Processing

The work presented here was initiated by the investigation of channel-by-channel MR phase image processing and comparison to other widely adapted post-processing pipelines. Specifically, in Chapter 2 I presented in depth experiments to assess and quantify the value of extracting information from the individual channel images prior to application of channel combination. The extensive investigation of the advantages of processing the individual channel data prior to application of channel combination was not explored prior to the work of Chapter 2. The only phase image combination approach published to-date that specifically requires the complex channel data be processed before the weighting factor for combination can be calculated is the inter-echo variance channel combination approach [1], on which the work of Chapter 2 was based. In the original published manuscript, improvements in the resulting high-pass filtered phase images are reported, which triggered more in-depth investigation of the advantages of such approach. With thorough analysis of quantitative and qualitative differences between the currently adapted approaches and the IEV-SWI approach (Fig. 5.1), it was shown that by processing the channel phase image data prior to the application of channel combination much more detailed phase maps can be generated with significantly higher contrast compared to phase maps obtained from conventional approaches [2, 3]. Additionally, the proposed channel-by-channel processing approach was shown to ameliorate the artifacts and signal loss often seen in the images resulting from the conventional processing approaches [4].

The work of Chapter 2 was completed at the same time as other scientific groups were adapting the practice of channel-by-channel processing. In 2015, Bollmann et al. [5] showed that by positioning the channel-combination step in the last stage of post-processing for quantitative susceptibility mapping better quality QS maps, with fewer artifacts and noise, can be obtained. The benefits of channel-by-channel processing of phase data has since been shown to result in better phase maps and QS maps [6, 7]. The work of Chapter 2, therefore, marks a new chapter in enhancing the integrity and utility of the phase component of MR images.

The immediate follow-up step to enable the translation of these proposed methods to clinical practice is to implement a parallel computing pipeline for handling the large volume of the data that results from multi-channel acquisition. A recent pipeline has been proposed to
5.1. Advances Resulting from Current Work

efficiently handle and process the image data from multiple receiver coils [8].

Figure 5.1: Channel-by-channel (IEV-SWI) processing proposed in Chapter 2: The extensive quantitative analysis of conventional approaches to phase image processing against the proposed channel-by-channel approach demonstrated the ability of the latter in preserving phase information, thereby enabling more robust means of generating SW images and deeming the added acquisition time for post-processing worth-while.

5.1.2 Characterizing MS-Specific White Matter Lesion Morphology

In Chapter 3 I demonstrated the benefit of channel-by-channel local phase shift mapping by employing the IEV-SWI processing, presented in Chapter 2, to generate high-contrast single slice SWIs for a cohort of multiple sclerosis (MS) patients and matched controls. The value of central vein sign (CVS) as a diagnostic tool for MS has been debated and extensively studied in the scientific and clinical communities, however with different approaches for defining the morphological characteristics of white matter lesions and the venous vasculature. The ability to standardize a radiological definition for CVS will prove advantageous for appropriately evaluating it as an imaging biomarker of MS. The work of Chapter 3 aims to accomplish this goal by evaluating the morphological characteristics specific to MS white matter lesions as per the guidelines published in the 2016 consensus statement by the North American Imaging in Multiple Sclerosis (NAIMS) [9]. Using the phase information in conjunction with magnitude data in susceptibility weighted imaging, offers an undeniable advantage in terms of accurate
and reliable definition of structures as compared to using mere magnitude data. In fact, the improvement in contrast and the enhancement of the identification of CVS at higher field strengths and using SWI was demonstrated as early as 2009 [10]; this early work highlights the need for a robust SWI processing pipeline, such as that presented in Chapter 2. Using the IEV-SWI approach, it is possible to accurately characterize white matter lesion morphology and specifically CVS, avoiding the inaccuracies introduced by vessel-like artifacts and/or poorly visible vessels resulting from the conventional approaches. The work presented in Chapter 3 establishes a definition for CVS that enables the sensitive and specific separation of MS white matter lesions from the benign white matter lesions in otherwise healthy volunteers.

The work of Chapter 3 implemented the criteria presented in the NAIMS consensus in a clinical setting and evaluated the radiological definition of CVS. Using the previously presented IEV-SWI together with MP-FLAIR images it was possible to perform morphological assessment of white matter lesions in MS and otherwise healthy individuals (Fig. 5.2). The main impact of the work of Chapter 3 is this validation of the radiological definition of CVS for specific, sensitive, and reproducible differentiation of MS lesions from the benign white matter lesions. Future studies will benefit from this definition for differentiation of MS from this specific mimic, while other studies should be similarly implemented to accomplish a radiological definition for other mimicking neurodegenerative disorders.

Figure 5.2: Radiological assessment of white matter lesion morphology presented in Chapter 3: Representative images of white matter lesions as seen in data belonging to different MS patients and different healthy subjects. The MP-FLAIR images (top row) enable the visualization of lesions while the high quality IEV-SWIs (bottom row) provide an effective means of visualizing venous vessels, regardless of the brain region. The MS lesion panels are on average 3 cm wide and the benign lesion panels are on average 2 cm wide.
5.1.3 Myocardial Tissue Characterization using Multi-parametric MRI

Chapter 4 developed the technical tools to translate and implement the ideas presented and tested through the work of Chapters 2 and Chapter 3 for cardiac imaging. Cardiac MR applications were selected to account for the different image acquisition and post-processing challenges that arise when imaging in the body. The work of this chapter was completed using a 2D ECG-gated multi-echo, multi-slice imaging sequence, which required the participants to hold their breath repeatedly during acquisition. The multi-echo acquisition was set up with four echoes in such a way to avoid acquisition to be pushed into the early systolic period of the cardiac cycle. The dark-blood option was turned on together with the flow-compensation in the slice-orientation, and together these acquisition options resulted in lack of any signal from the blood pool, inside the different chambers of the heart or any of the coronary vessels. These acquisition parameters enabled the shortening of the acquisition time for an imaging slice to a single breathhold (\(\sim 17\) s). The challenges of post-processing, on the other hand, included identification and separation of signal from water and fat. Therefore, the acquisition process also required carefully selected TE to correspond to, roughly, in- and out-of-phase water and fat signal.

The main contribution of the work of Chapter 4 was the demonstration of the reproducible multi-parametric cardiac maps throughout the heart of healthy volunteers and heart failure patients. Additionally, the feasibility of the proposed processing approach to delineate fatty infiltration and fibrosis within the scar was demonstrated; the fatty infiltration is consistent with the previous histological findings of ex-vivo myocardial scar constituents [11]. It has been shown using histology that as myocardial scar ages, fatty infiltration can be observed in the scar region; a biological phenomenon referred to as lipomatous metaplasia. The in vivo approaches to visualization of lipomatous metaplasia involve water/fat separation approaches [12] and dual acquisition imaging with a double and a subsequent triple inversion recovery acquisition to firstly remove the blood signal but retain the fat signal, and secondly remove both the blood and fat signal to validate the signal seen inside the scar tissue as fat [13]. The thorough post-processing tools presented in Chapter 4 enable the generation of several quantitative maps from a single acquisition, which enable the assessment of the constituents of myocardial scar
tissue (Fig. 5.3). The approaches do not require the injection of external contrast agents, which removes the operator-dependence of the successful of the imaging techniques (as is the case for LGE) and, moreover, provides the means of imaging in cases where external contrast agents are contraindications (e.g. for patients with poor renal function or at risk of renal failure). It should be noted that, while the results reported in Chapter 4 are quite promising, this work is a preliminary feasibility study and a large clinical trial need to be initiated to validate these clinical findings.

Figure 5.3: Quantitative maps generated as a result of the methods presented in Chapter 4: The conventional LGE and the phase-matched CINE images are shown for a heart failure patient. The quantitative LFS maps demonstrate the regions of scar, numbered with 1 through 3 on the LGE; FF map demonstrate fatty infiltration in 2 of the three scar regions. $R^*_2$ map is also shown demonstrating an increase in $R^*_2$ values in two of the three scar regions.

5.2 Future Directions

Several pilot studies have been initiated and/or completed as part of the work completed in Chapters 2-4, which have been or will be presented at the International Society of Magnetic Resonance in Medicine. This section provides a summary of these preliminary results.
5.2. Future Directions

5.2.1 Towards a Specific Radiological Definition for MS WMLs

The development of a sensitive and specific definition of central vein sign as part of the work of Chapter 3 has created the grounds for extension of this imaging biomarker to other mimics of MS. The primary work should be focused on validating this definition, or otherwise developing a sensitive and specific data-driven definition, for each specific mimicking neurodegenerative disorder. This would then ensure a cohesive clinical practice in using CVS as an imaging biomarker, which in turn would move us towards a more definitive and earlier diagnosis of MS.

The longitudinal multi-parametric MRI studies may provide additional information about MS and non-MS white matter lesions and MS-specific prognosis. A pilot study was designed to investigate the role of multi-parametric MRI in identifying the differences between the changes in MS WMLs and benign WMLs over a short-term follow-up [14]. In doing so, normalized changes detected using four different MR image contrasts were measured over a period of four months: T1-weighted images, T2-weighted images, QSM, and $R_2^*$ maps. The short-term results are demonstrated qualitatively in Fig. 5.4 and quantitatively in Fig. 5.5. While qualitative differences are evident in Fig. 5.4, it can be seen clearly (Fig. 5.5) that the differences between the two groups are most prominently detected using the normalized $T_1$-weighted MPRAGE images. These results are in agreement with the results of a larger study [15] that concluded at the same time as this work was submitted to the ISMRM meeting.

Figure 5.4: Multi-parametric MRI provides complementary information about the white matter lesions found in MS patients (a) compared to otherwise healthy participants with incidental findings of white matter lesions (b).
Figure 5.5: Quantitative analysis of the normalized changes found in $T_1$ weighted MPRAGE images was shown to provide the most sensitive means of identifying the differences in MS lesions (MSL) and age-related lesions (ARLs).

Finally, as is the current advancing trend in medical imaging with the integration of artificial intelligence and automated algorithms based on machine learning, detection and differentiation of MS and non-MS lesions can be ultimately accomplished using a trained computer algorithm. However, for such approaches to succeed, it is essential to have a large dataset for training, and a separate body of image dataset for testing. This was not possible for the duration of the tenure of this dissertation, but should be explored in the future.

5.2.2 Non-contrast Myocardial Scar Imaging

A potential future translation of the methods proposed in Chapter 4 is in atrial fibrillation; it was shown that the results achieved by the IC-NICE methods are robust regardless of the imaging slice thickness. Imaging the atria requires thinner slices and preferably 3D acquisition in order to enable visualization of the atrial wall, which is thinner than the ventricular myocardium. The preliminary results of applying the IC-NICE processing to high-resolution 3D data (acquired using the 3D chemical shift encoded sequence proposed by Taviani et al., [16]) are presented in Fig. 5.6 - data belongs to a healthy volunteer. As a working version of this 3D pulse sequence was not available, all the cardiac multi-echo GRE images in this dissertation are acquired using an ECG-gated 2D pulse sequence.

A semi-automatic 3D atrial modelling toolbox (Cardiac MRI Toolkit Slicer extension, Comprehensive Arrhythmia Research & Management Center, University of Utah) has been
developed, which is currently used to generate models of atrial scar using MR angiography and LGE images in tandem. An example of such model is presented in Fig. 5.7 where normal myocardium appears white in the 3D model, while the shades of green correspond to the atrial regions with higher likelihood of scar. These colormaps are generated based on the mean signal intensity on the atrial wall as obtained by semi-automatic segmentation of the angiography image. The black arrow points to a region of atrial wall on the 3D model, which may indicate scar. However, the regions highlighted by shades of green extend most of the atrial wall. This demonstrates the sensitivity of such approach to the threshold used to separate normal versus scarred atrial wall. By taking a non-contrast-based quantitative approach to atrial mapping, more consistent results may be achieved; in this way, the threshold can be determined experimentally and, as it is not subject to biases introduced by the concentration of contrast agent and acquisition time, it can result in a consistent means of classifying and differentiating scar from healthy myocardium.

![Figure 5.6: Successful extraction of quantitative maps (B₀ map, FF map, and R² map) from 3D GRE images acquired using the chemical shift encoded imaging sequence [16] are demonstrated in the axial (first row) and coronal (second row) views and their respective magnified regions (third and fourth rows, respectively) - Raw image data courtesy of Karl Vigen, University of Madison, Wisconsin](image)

Figure 5.8 demonstrates the successful application of the IC-NICE pipeline to generate multi-parametric quantitative maps of the atria (the data belong to the same patient whose
LGE data are shown in Fig. 5.7. In addition, the RDF as computed by the application of a SHARP [17] filter to the IC-NICE $B_0$-map and the dipole inverted QSM are shown on the right-most panels of the figure. No suspicious signal is seen along the posterior wall of the atria on any of the quantitative maps, where the presumed scar signal appears on the 3D model of Fig. 5.7. This raises further concerns about the validity of the 3D model, demonstrating the extent of subjective information drawn from such a semi-automatic approach of determining a threshold to differentiate scar and healthy myocardium.

Figure 5.7: The MR angiography and late gadolinium enhancement images are shown for an atrial fibrillation patient. Semi-automated segmentation based on these images (below) allows for generation of 3D models of the patient’s atrium, using the Cardiac MRI Toolkit Slicer extension, where regions of scar are intensity-encoded: in this case, the darker the green the more likely it is that atrial region is composed of scar tissue (black arrow on the 3D model).

It is noteworthy that in Fig. 5.8 the images are acquired with the flow-compensation removed. This imaging practice makes it difficult to distinguish the wall of the left atrium from the blood pool. Additionally, as is the common practice in quantitative mapping of susceptibility, part of the tissue (in this case the left atrial wall) may be removed through the mask erosion process. This must be considered when interpreting the IC-NCIE quantitative maps of Fig. 5.8 with respect to Fig. 5.7. Future work may focus on developing mask erosion approaches that merely remove the epicardial fat, sparing the atrial wall.

The application of flow compensation makes the delineation of coronary vessels more effective. Nevertheless, complete nulling of blood signal will also eliminate any susceptibility
signal that may otherwise be useful. For instance, the removal of flow compensation can enable the assessment of blood oxygenation, similar to the recently reported work by Wen et al. [18]. As the results of the IC-NICE LFS mapping demonstrated (e.g. Fig. 4.3), the application of flow compensation in the slice direction, in addition to the dark blood preparatory pulse, prevents the differentiation of venous and arterial coronary blood vessels.

![Image](image.png)

Figure 5.8: The axial GRE magnitude and phase images of the same atrial fibrillation patient as in Fig. 5.7 are shown together with the quantitative maps obtained from the IC-NICE processing pipeline; axial slice corresponds to the Angiography and LGE slices shown in Fig. 5.7. In addition, the RDF and QSM are calculated through processing the IC-NICE B0-map with the SHARP filter [17] and subsequent dipole inversion.

Quantitative mapping of susceptibility may offer the means of more definite in vivo assessment of cardiac structures. For instance, slice 1 in Fig. 5.9 demonstrates the possibility of mapping the susceptibility values within the anterior interventricular vein (yellow arrow). The same would be possible for the inferior vein (also pointed to by the yellow arrow on the LFS-map), however, due to mask erosion step in QSM, this vein is excluded from the dipole inversion step and therefore the QS map. Additionally, slice 2 in Fig. 5.9 demonstrates the same septal scar of the patient shown in Fig. 5.3. The hyperintensity of the scar on the QSM, signifying a more paramagnetic tissue compared to normal myocardium (yellow arrow), may indicate that the non-fat constituent may be deoxygenated blood; the reader is reminded that the $B_0$-map obtained from the IC-NICE pipeline does not include the chemical shift phase term.
Figure 5.9: Two image slices (a) magnitude and phase at echo 1 and echo 2 are shown for the same heart failure patient. (b) The IC-NICE quantitative maps corresponding to slice 1 and 2 demonstrate the tissue information about the inter-ventricular vein and scar in the septal myocardium (yellow arrows), respectively. Note that slice 2 corresponds to the image slice shown in Fig. 5.3.

### 5.2.3 Beyond Neurological and Cardiac Imaging Applications

In the present dissertation I demonstrated the feasibility of channel-by-channel MR image processing. Moreover, through the clinical studies, the benefits of the proposed approaches (specifically IEV-SWI and IC-NICE) became evident. By using images acquired from brain and cardiac anatomy I was able to study a wide range of challenges presented during MR image acquisition including increased relaxation rate (magnitude images) and dephasing (phase image data) around the sinuses in the brain images and at lung/heart interface in the cardiac data, requirement for fast imaging to enable rapid acquisition for cardiac imaging where breathhold
is an essential part of the acquisition, and introduction of additional dephasing and signal loss due to medical instruments (i.e. sternal wires).

While the work of this dissertation focused on the neurological and cardiac applications, it is expected that the developed technical tools would prove to benefit any other imaging applications. The technical development of this dissertation have been tested extensively on images acquired using GE and Siemens scanner systems and have been found to be robust regardless of the specific platform and the specific receiver coil used. The range of receiver coils that have been tested are 8 to 36 receiver channel arrays (including head and neck coils, spine coils, cardiac coils, and abdominal coils). Additionally, image processing tools developed were shown to benefit acquisition protocols at both 3T and 7T. The consistent results obtained from these tests support the notion that processing the images acquired by the individual coils would benefit the quality and the details preserved in the final phase-based and magnitude-based images.

5.3 Limitations

The methods developed throughout the present dissertation are not without limitations and several key considerations should be accounted for in the future studies implementing these methods. In this final section I will outline these limitations and considerations.

The clinical utility of the MR magnitude and phase data processing tools developed in this work were demonstrated in limited number of subjects. In the clinical neurological applications, the application of IEV-SWI and FLAIR data to achieve a radiological definition for MS-specific white matter lesion must be extended to other mimics of this disorder. Only at that point can we make complete use of the central vein sign and investigate the feasibility of its application for earlier and more definite diagnosis of MS. In the clinical cardiac application the feasibility and the utility of the IC-NICE approach was demonstrated in a small cohort of heart failure patients. It is possible that the application of IC-NICE in other cardiac disease models would benefit the patients and physicians more. Nonetheless, the limited number of patients recruited during the tenure of the dissertation allowed only for feasibility studies in a specific cohort. The potential of this approach to replace contrast based LGE imaging should be studied in a larger cohort of HF patients. Additionally, other disease models should be considered
and relevant clinical trials should be designed to further implement and assess the utility of the
IC-NICE approach.

In the clinical cardiac studies, the LGE slice thickness was 8.0-mm while the matching ME-
GRE images had a slice thickness of 6.0-mm; this resulted in a mis-registration between the
two images in the validation study. Future studies should implement identical slice thickness
between the LGE and ME-GRE acquisitions; otherwise, as the results of 3.5-mm acquisitions
were of high quality, 4.0-mm slice thickness could be used to match each slice of LGE to two
slices of the IC-NICE maps obtained from the ME-GRE acquisition.

The 2D multi-slice acquisition enabled imaging with short breathheld durations. The 2D
nature of the imaging protocol, however, resulted in slight shift in the location of the heart
between subsequent breath-holds. This may be avoided if a respiratory and cardiac gated 3D
ME-GRE sequence is available. A 3D imaging sequence will also enable more reliable cal-
culation of quantitative susceptibility maps, if that is desired.

The clinical neurological images were acquired at 7T, which is not clinically available.
However, in 2017 the high-field (7T) MRI systems were approved by FDA in North America
for clinical use. It is noteworthy that high-field MRI systems have been approved for clinical
use for years prior to this in Europe. Whether the FDA approval in North America will result
in an increased clinical availability of 7T systems is open for discussion; regardless, there is
evidence that imaging at higher field strength enables a more accurate characterization of the
pathology, which could then be translated into lower field strength that are clinically available.

Finally, the computation time is a concern when applying the post-processing techniques
to individual channels prior to the application of channel combination. As it was mentioned
earlier, by using non-iterative techniques it is quite possible to significantly minimize this pro-
cessing time. Orders of magnitude reduction in time resulted when the non-iterative meth-
ods of IEV and IC-NICE were implemented on GPU (≈60 times faster for the IEV approach
and ≈97 times faster for the IC-NICE). Nevertheless, it is acknowledged that many of the
well-established approaches for phase unwrapping [19, 20], water/fat separation [21, 22] and
quantitative susceptibility mapping [23] are iterative and a motion toward adapting the channel-
by-channel MRI post-processing approach proposed here should consider this.
References


Appendix A

Theory

This appendix presents the theory behind the topics discussed in the Introduction Chapter of this document.

The unique advantage of MR imaging is its exquisite soft tissue contrast, which is the result of its inherent design and the way that the imaging signal is formed. MRI pulse sequences are choreographs of different imaging parameters, which control the extent to which each tissue property will play a role in the final image contrast.

A.1 Tissue Characterization Using MRI

MRI signal depends on the many available imaging parameters as well as tissue properties. With the ability to manipulate tissue signal by varying the acquisition parameters, MRI allows for generation of images with outstanding contrast between different tissues and allows for characterization and differentiation of the diseased versus healthy tissue. Tissue characterization has many applications including but not limited to scar tissue imaging in interventional cardiac [1] and neurological procedures [2], white matter lesion identification and diagnosis of multiple sclerosis [3], perfusion assessment in stroke [4], and many more. Tissue assessment can be enhanced by using exogenous contrast agents, especially for motion sensitive applications such as coronary angiography [5]. In the following sections an overview of contrast mechanisms using the intrinsic tissue properties and exogenous contrast agents is presented.
A.1.1 Intrinsic Tissue Properties as a Source of Contrast

MRI systems can detect an atom with an odd atomic number. The odd atomic number results in a magnetic moment ($\mu$). While quantum mechanics describes the behavior of the individual spin states when placed in a magnetic field, it is common practice to represent the spin isochromats with a single arrow. The sum of all the magnetic moments in a spin isochromat gives the resulting magnetization $M$. For a given proton with specific gyromagnetic ratio $\gamma$, the relationship between the magnetization and its angular momentum $L$ is given by:

$$M = \gamma L$$ (A.1)

When these atoms are exposed to an external magnetic field $B$, a torque $\tau$ results, which causes the atoms to precess counter-clockwise (in a right-handed system) around the vector of the main field, as expressed by the following equation:

$$\tau = \frac{dL}{dt} = M \times B$$ (A.2)

This interaction between the magnetization and the main magnetic field can be expressed in terms of the magnetization by using Eq. A.1:

$$\frac{dM}{dt} = \gamma \frac{dL}{dt} = \gamma M \times B$$ (A.3)

This expression is the main differential equation, the solutions of which make up Bloch’s equations given in A.4-A.6, listed below. The equations of A.4-A.6 must be modified when considering a complete MR experiment with excitation pulse. The application of an RF pulse with a frequency that closely matches the Larmor frequency of a given atom will result in excitation. Once the RF pulse is removed, the absorbed energy during excitation is released back into the system and can be detected and used to formulate a signal, which represents relaxation back towards equilibrium.

$$\frac{dM_x}{dt} = \gamma(M_yB_z - M_zB_y)$$ (A.4)

$$\frac{dM_y}{dt} = \gamma(M_zB_x - M_xB_z)$$ (A.5)
\[
\frac{dM_z}{dt} = \gamma (M_x B_y - M_y B_x) \quad (A.6)
\]

The return of the signal to equilibrium is described using two time constants, one of which describes the dephasing of the spin isochromats in the transverse plane (the so-called \(T_2\) time constant) and the other describes the longitudinal recovery of the spin isochromats to align with the main field (the so-called \(T_2\) time constant). With the inclusion of relaxation terms, the solutions to Bloch equations will take the following forms:

\[
\frac{dM_x}{dt} = \gamma (M_y B_z - M_z B_y) - \frac{M_x}{T_2} \quad (A.7)
\]

\[
\frac{dM_y}{dt} = \gamma (M_z B_x - M_x B_z) - \frac{M_y}{T_2} \quad (A.8)
\]

\[
\frac{dM_z}{dt} = \gamma (M_x B_y - M_y B_x) - \frac{(M_z - M_0)}{T_1} \quad (A.9)
\]

More formally, \(T_1\) (the longitudinal relaxation time constant) is defined as the time it takes for 66.6% of the magnetization to recover to its original value \(M_0\). \(T_2\) (the transverse relaxation time constant) is defined as the time it takes for transverse magnetization to decay to 33.3% of its initial value.

The equations A.7-A.9 map any pattern of excitation and relaxation and enable us to predetermine the acquisition parameters, which we need to generate an image with controlled contrast between the different tissues. Note that the details of the derivation of these solutions and the subsequent signal equations are beyond the scope of this thesis and the reader is referred to MRI physics textbooks that thoroughly cover the topic [6].

While hydrogen makes \(\approx 10\%\) of the human body by weight, it is the most abundant element in the human body (62% by atomic percent) and is present in almost all tissues [7]. Therefore it is the ideal target for MR imaging. The work of this thesis is completely based on conventional proton-MRI and therefore no other nuclei are discussed in the Introduction Chapter, or in this Appendix. Depending on the water (or hydrogen) content of each tissue, a differentiable relaxation pattern will form as the result of the RF excitation pulses. Additionally, depending on the chemical environment of hydrogen, the local field perceived by the atom...
can be slightly different from the main field applied by the magnet. The tissue-specific relaxation behaviors within a magnetic field are the reason MR imaging performs well in generating images with exceptionally good soft tissue contrast.

**Image Weighting in MRI**

MRI pulse sequences fall under the category of spin-echo (SE) and gradient recalled echo (GRE), depending on the way the RF pulses are utilized to generate a detectable signal. The conventional SE utilizes two separate RF pulses, one is a $90^\circ$ RF pulse for excitation and the second pulse is a $180^\circ$ refocusing pulse that removes the effect of field inhomogeneity related dephasing of the signal. It can be deduced from this intrinsic nature of SE that the sequence takes a relatively long time to complete for a given imaging plane. This approach in imaging, however, is insensitive to field inhomogeneities since the $180^\circ$ pulse refocuses any dephasing that is introduced by such effects. On the other hand, GRE does not utilize a refocusing pulse and is therefore affected by field inhomogeneities. This sensitivity to field inhomogeneities results in a change in transverse relaxation time constant in GRE imaging from $T_2$ to $T_2^*$ as defined by the following equation:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \quad (A.10)$$

where $T_2'$ denotes the field inhomogeneity related relaxation time constant.

The generic GRE signal equation for an MRI experiment (Eq. A.11) demonstrates the role of relaxation and acquisition parameters in the imaging sequence. The signal equation can represent a SE experiment by simply replacing the $T_2^*$ parameter with $T_2$.

$$S_{GRE}(TE_i) = \rho_0 (1 - e^{\frac{-TR}{T_1}}) e^{\frac{-TE_i}{T_2^*}} \quad (A.11)$$

Note that the simplistic expression of Eq. A.11 merely models the magnitude component of MR images. By using different imaging parameters, specifically repetition time (TR) and echo time (TE), images with different weighting can be generated. **Weighting** in MRI signifies the level of contribution of each relaxation parameter, and therefore allows for enhancement of differences in one specific parameter (*i.e.* $T_1$, $T_2$, $T_2^*$ or proton density $\rho$). The so-called $T_1$-weighted, $T_2$-weighted, and $T_2^*$-weighted imaging are the most basic methods of image
weighting. Others include susceptibility weighted imaging [8], magnetization transfer imaging [9], and diffusion weighted imaging [10]. Examples of images with different contrasts are shown in Fig. A.1. Susceptibility contrast will be discussed in section A.3.2, but others are beyond the scope of this thesis. The reader is referred to appropriate literature on each topic.

From the signal expression of A.11, a $T_1$-weighted image can be obtained using a TE that is much shorter than the shortest $T_2/T^*_{2}$ in the tissues of interest, and a TR that is in the same range as the $T_1$ of the tissues of interest. While a $T_2$-weighted image can be generated using a longer TE (in the range of $T_2/T^*_{2}$ relaxation time constant of the underlying tissue) and a TR that is much longer than the longest $T_1$ in the tissues of interest. A $\rho$-weighted image can also be obtained by using a long TR and a short TE. A specific experiment that enhances the weighting based on one parameter minimizes the contributions of the other parameters (with the exception of $\rho$, which plays a part in any experiments).

The above discussion provides a qualitative way of designing an imaging experiment. Using the signal equation, contrast can be optimized by solving for the optimum TE and TR for a given experiment. Contrast between tissue A and B can be expressed as follows:

$$C_{AB} = |S_A(TE) - S_B(TE)| = |\rho_A(1 - e^{-TR/T^*_1,A})e^{-TE/T^*_2,A} - \rho_B(1 - e^{-TR/T^*_1,B})e^{-TE/T^*_2,B}|$$  (A.12)

As per the description above, this equation will change depending on the weighting desired for the image. Once the right signal equation is setup for a given experiment, the contrast expression can be used to solve for the optimize TE or TR.

In addition to the different image weighting that can be generated by varying MR imaging parameters, quantitative relaxation images (referred to as maps in MRI literature) can be computed using multiple temporal imaging frames. The following sections present an overview of relaxation mapping approaches.

**Native $T_1$-mapping**

The term native $T_1$-mapping is used to refer to non-contrast mapping of the longitudinal relaxation time constant for a given tissue. $T_1$-mapping can be performed using saturation recovery (SR) and inversion recovery (IR) imaging sequences. The first requires the combination of
a 90° RF pulse followed by a subsequent RF pulses to flip the recovering magnetization into the transverse plane and sample the recovery curve at multiple time points. Inversion recovery approach employs a 180° (an inversion) pulse in place of the 90° pulse. This approach will allow for phase sensitive reconstruction [11]. Signal-to-noise ratio in a $T_1$-map can be shown to be directly dependent on the dynamic range of the signal; as a result the $T_1$-map resulting from the IR experiment outperforms SE or SR in terms of signal-to-noise ratio (SNR).

It is important that after each TI the magnetization be given enough time to evolve back to $M_0$ before the next excitation pulse is delivered in order to ensure that the same recovery curve is sampled. A rule of thumb is to use five times the longest $T_1$ of the underlying tissue being imaged as the prescribed value of TR. Clearly, the imaging time for these $T_1$-mapping approaches is unrealistically long for many clinical applications.

There are alternative approaches to the time-consuming conventional $T_1$-mapping methods, which can be broadly divided into two approaches:

*Multiple flip angle:* The first category of fast $T_1$-mapping is one that utilizes steady state imaging and the application of multiple flip angles in one TR interval. This approach maintains the SNR while decreasing the total measurement time required for estimation of $T_1$ over a large volume of interest.

*Small flip angle:* This method was first proposed by Look and Locker [12], the so-called Look-Locker (LL) approach, which was later modified for fast 3D $T_1$-mapping [13]. As opposed to applying a 90° pulse to sample during each repetition time, N pulses with small flip
angle are used during one repetition time. This approach was shown to manipulate the spins in the same way as when using an IR experiment [12]. Look-Locker results in a new steady state, which is lower than that obtained using traditional $T_1$-mapping approaches. However, by observing the rate of change of the signal amplitude, the $T_1$ of the underlying tissue can be estimated all the same. The obvious downside of this approach is low SNR that is the consequence of the small flip angle. Nonetheless, this approach has become very popular in the in-vivo $T_1$ measurement applications.

The main interest in fast $T_1$-mapping approaches is for cardiac imaging. The Look-Locker $T_1$-mapping approach is the basis of the more recently proposed techniques for tissue mapping, particularly in the cardiac applications where the cardiac phase and respiratory motion must be considered concurrently [14, 15].

$T_2$-mapping

The second quantitative tissue map is that of the spin-spin relaxation time or the more commonly known $T_2$-map. $T_2$-map is the measure of signal decay (as opposed to recovery) in the transverse plane. To measure this time constant, it is important that a SE imaging sequence be utilized. In this way the effect of extra field inhomogeneity-related signal decay will be refocused and the true value of $T_2$ can be measured. The idea of the traditional $T_2$-mapping approach is the same as that described for $T_1$-mapping in the previous section.

With respect to equation A.11, a long TR will ensure that the signal equation is $T_2$-weighted and therefore by collecting multiple temporal samples the $T_2$ values of the underlying samples can be computed. For both, the $T_1$ and $T_2$-mapping, it is important to note the spin density $\rho$ always plays a part in the signal equation; therefore in fitting the data, a nonlinear model should be used.

As mentioned above, the pulse sequence used for tissue $T_2$-mapping must reverse the effect of the field inhomogeneities at the interfaces of tissues prior to acquisition. The field inhomogeneities are not, however, the only source of signal inconsistencies. One such major problems arise from $B_1$ nonuniformity. The solution to this problem was introduced by Carr, Purcell, Meiboom, and Gill in the so-called CPMG pulse sequence. In this method, a phase shift of $\pi$ is introduced in the refocusing pulse with respect to the excitation pulse.
\textbf{A.1. Tissue Characterization Using MRI}

\textit{T}_2^*-\textbf{mapping}

As discussed earlier, the intrinsic contrast obtained from GRE-based imaging sequences is a \(T_2^*\)-weighting, which includes a reversible relaxation term as well as an additional irreversible decay term due to field inhomogeneity related signal loss. Therefore, with acquisition of multiple points with this imaging sequence the signal can be fit to a decay curve described by the \(T_2^*\) time constant resulting in a \(T_2^*\)-map.

\textbf{A.1.2 Contrast-Based Tissue Characterization}

Despite the outstanding ability of MR imaging to generate soft tissue contrast using the intrinsic properties of the tissue, this modality, much like other imaging tools, can benefits from the use of exogenous contrast agents. Particularly, the applications that involve imaging the moving tissues (\textit{e.g.} blood flow and vascular imaging [5]) benefit immensely from administration of contrast agents. However, the application of contrast agents in MR imaging also includes visualization of tumors [16] anywhere in the body and perfusion studies [4, 17], visualization of white matter lesions [3], and imaging of myocardial scar [18] through a procedure known as the late gadolinium enhancement [19] (discussed later in this section).

Magnetic resonance contrast agents are gadolinium-based. Gadolinium shortens the \(T_1\) time constant of the tissue it is within. As a result, when imaging a structure with a very long \(T_1\), such as the blood, the use of contrast agents will decrease the imaging time.

Currently, the contrast-based imaging techniques have a major advantage over most of the non-contrast imaging techniques that are presented in Section A.1.1; the imaging techniques that utilize contrast agents are validated and well accepted in the clinical practice. This includes the well-established acquisition techniques by the MR imaging technicians, and the ability and experience of reviewing the images by the radiologists and the clinicians. As a result there is a learning curve involved with integration of the previously discussed non-contrast based imaging techniques into clinical workflow.

As is the case with any techniques discussed so far, contrast based imaging is not free of limitations. Firstly, MRI contrast agents are known to be contraindications for patients with renal failure, resulting in devastating conditions such as nephrogenic systemic fibrosis.
Additionally, regardless of the imaging application, the good quality contrast-based images can only be obtained with carefully timed acquisition with respect to contrast injection. If the time is miscalculated, the images may not have the optimal contrast for diagnosis. This may call for repeated injection/acquisition in one imaging session, which increases the exposure of the patient to potentially harmful exogenous agent.

**Late Gadolinium Enhancement MRI**

Magnetic resonance imaging plays an important role in predicting the response of the patients to interventional procedures such as cardiac resynchronization therapy (CRT) [20] and pulmonary vein ablation procedures [21]. Particularly in CRT, multiple studies have correlated the response of patients to therapy with the left ventricular lead location [22, 23, 20]. Contrast based MR imaging, as pointed out earlier enables us to differentiate between viable and diseased myocardium through an imaging procedure called late gadolinium enhancement (LGE).

Myocardial scar tissue contains excess amount of collagen, which has different mechanical properties than healthy myocyte. The structure of scar in myocardium can be divided into one of two classes of *replacement fibrosis* and *interstitial reactive fibrosis*, which shows a diffuse distribution. Fibrous tissue retains exogenous contrast for a longer time compared to healthy tissue. In LGE procedure, contrast agent is injected into the venous circulation of the patient and after a typical delay time of 15-20 minutes images are acquired [19]. At this time point, the healthy myocardium has excreted the contrast while the scar tissue still retains it. As a result, the scar tissue appears hyperintense on the images. LGE is often obtained using a pulse sequence with an inversion preparatory pulse with the inversion time carefully selected to null the signal of myocardium. In this way the contrast between the scar and healthy myocardium is optimized.

It is noteworthy that the application of MR imaging and in particular LGE to tissue characterization in the interventional procedures is a recent development and is not widely adopted yet. The main challenge that impedes this process is the variability of the imaging and the outcomes that result from imaging on different systems and from one clinic to another. Specifically, imaging atrial scar for ablation procedures has been done at 1.5*T* in several studies [24, 25, 26] but translation of this technique to 3*T* becomes a challenge as imaging parameters
A.1. Tissue Characterization Using MRI

are not as well established. Furthermore, studies have shown the variability of imaging findings (e.g. size of the scar tissue) depending on the timing parameters used [27].

It follows from the abovementioned challenges that LGE is an operator-dependent imaging protocol and can become quite prone to requiring repeated imaging and therefore repeated contrast injection. With newer findings reported on the accumulation of gadolinium at the blood brain barrier [28], this is a risk for patients with poor kidney function, which is often the case with heart failure patients.

Post-Contrast \( T_1 \)-mapping

It is not surprising that contrast based imaging is not a quantitative means of tissue characterization. Quantitative T1-mapping as presented in the Section A.1.1 is an effective means of quantifying the tissue relaxation time constant on a voxel-by-voxel basis.

A number of applications combine the two imaging protocols to obtain new set of information about the health status of the tissue. Extracellular volume (ECV) mapping [29, 30] is one such application, which allows for quantification of the changes in the myocardial tissue affected by diffuse fibrosis. For such applications, LGE fails to generate the necessary contrast to enable the differentiation of interstitial reactive fibrosis and \( T_1 \)-mapping cannot generate a strong signal and these changes sometimes remain undetected. Contrast-based \( T_1 \)-mapping can allow for quantification of these changes in the myocardium. In ECV mapping, an image is acquired prior to injection of contrast and a second image is acquired after the contrast is injected. The ECV can then be calculated using the following equation:

\[
ECV = (1 - Htc)\left( \frac{\delta R_{1,myocardium}}{\delta R_{1,blood}} \right)
\]  

(\text{A.13})

In Eq. A.13, the \( \delta R \) terms are the change in relaxation time of the tissue between the time point prior and after contrast administration. There are a number of limitations in ECV method. As can be seen in equation A.13, a sample of the patients blood is required for an accurate estimation of extracellular volume. This does not necessarily interrupt the imaging as a previously connected intravenous system can be used to automatically obtain a sample. ECV mapping requires two images before and 15-20 minutes after contrast injection, which is indicative of
an increase in imaging time. Finally, ECV mapping has not yet been validated thoroughly and is not yet a routine clinical tool.

A Note on the Safety of MR Contrast Agents

As pointed out at the start of this section, contrast-based MR imaging makes up a large number of clinical applications. Nevertheless, the link between gadolinium-based contrast agents and several adverse affects have been shown. Life threatening adverse reactions such as anaphylactic reactions, contrast-induced nephrogenic systemic fibrosis, especially in patients with renal failure and nephrotoxicity can result when using gadolinium-based contrast agents, especially when administered at high doses \((i.e. > 0.3 \text{ mmol/kg})\) [31, 32, 33]. Additionally, recent studies have found accumulated gadolinium at the blood brain interface of patients who underwent repeated Gd-based imaging [34, 35].

The gadolinium ion has nine coordination sites, which are stabilized by a combination of carboxyl groups and other groups, depending on the manufacturer. Carboxylate donor atoms are better able to neutralize and therefore stabilize the molecule and the more stable the molecule the safer it is for usage. Another aspect that determines the stability and safety of the contrast agent is its configuration. Gadolinium contrast agents can take one of two configurations; linear and cyclic. The cyclic configuration is more stable as it allows for a more stable structure, from which the Gd\(^{3+}\) ion does not readily break free. The linear configuration of the molecule can allow for separation of the Gd\(^{3+}\) much more easily.

Regardless of the configuration and the specific brand of the contrast agent used, guidelines require that this imaging technique be classified as a contraindicated scan for patients with glomerular filtration rate smaller than \(15\text{mL/min/1.73m}^2\) [36]. As a result, any patients that are considered for contrast-based scans must undergo renal function screening.

A.2 Signal Contributors

Magnetic resonance imaging systems acquire signal from the vicinity of the receiver coil as far as the sensitivity of the receivers allow. Depending on the anatomy being imaged, different
considerations must be made both regarding the pulse sequence used and also on the post-processing techniques employed to resolve local tissue information from the signal acquired.

MR images are complex valued data and consist of a phase term and a magnitude term. The generic complex signal model of Eq. A.11 can be modified to include the relevant signal contributors as:

$$S_{TE_i} = (1 - FF)\left(\sum_{m=1}^{M} \alpha_m e^{i2\pi\Delta f_m T E_i} \right) e^{i2\pi\Delta f_0 T E_i} e^{R_2^* T E_i}$$  \hspace{1cm} (A.14)

In this equation, the $FF$ term defines the fraction of each voxel that is occupied by fat versus free water. The counter in the summation term, $m$, accounts for the $M$ peaks of fat spectrum. Fat spectra include several peaks, six of which are most prominent and are often used to model MR signal equation. The $\Delta f_m$ term is the resonance frequency of the hydrogen atom corresponding to the $m^{th}$ peak of fat with respect to water peak. $\Delta f_0$ is the $B_0$-offresonance term. Finally the last exponential term in Eq. A.14 is the relaxation term; as can be seen in the equation, this specific signal model belongs to a GRE experiment, where the relaxation term follows the dual decay model of the reversible $T_2$ and the irreversible $T_2'$ (field inhomogeneity related) relaxation.

The above equation holds for images acquired from any parts of the body; however, the contributions from the different terms can be enhanced or diminished depending on the imaging sequence as well as the anatomy being imaged. A short description of the main signal terms follows.

### A.2.1 Relaxation Term

The relaxation term and its utility has been covered in depth in section A.1.1. The main point to be re-iterated here is that the relaxation term affects the magnitude signal and describes the behavior of the magnetization after the excitation pulse and as a function of time. The relaxation term is indicative of the health status of the underlying tissue and any changes in the microstructure of the tissue is expected to have an effect on the voxel-by-voxel value of this parameter.

Relaxation maps also provide an orientation-independent information about the underlying
tissue; this can be quite useful when utilized in conjunction with the phase images, which are heavily orientation dependent. As a result of this orientation-independence, when fitting the multi-echo GRE data for anatomical regions with more than one hydrogen species, it is not necessary to consider utilizing the in-phase images for water and fat, which means neither the acquisition needs to be designed to acquire only in-phase data, nor the post-processing needs to discard the data corresponding to echo times when water and fat are out-of-phase.

### A.2.2 $B_0$-Inhomogeneity Term

The main magnet of an MRI scanner is carefully designed to generate uniform magnetic field and therefore the main field is assumed to be perfectly homogeneous. Once an object, or a subject is placed in this main field, it introduces small, localized changes in the field, the so-called field inhomogeneities. These inhomogeneities in the main field contribute to the detected signal in way of signal dephasing. Somewhat counter intuitively, this is not necessarily a negative effect for the MR images as the effective extraction of the field inhomogeneity phase term can result in valuable information about the underlying object or subject being imaged.

![Figure A.2: The field degradation near the air/tissue interface is detrimental to the phase information and is magnified at longer echo times. The short-axis images (a) display the rapid dephasing in the myocardial region interfacing with the lungs, which results in a field map of poor quality. Similarly, the long-axis images (b) demonstrate the same effect but in addition the dephasing in the atrio-ventricular region is also evident, resulting in sub-optimal field map.](image)

The magnetic field inhomogeneities at the interfaces between the different tissues provide information about the type of environments at each side of the boundary and the local properties of the field in these regions, which in turn can provide useful information about the nature of the underlying tissue and its properties. This boundary-sensitivity of phase can also
A.2. **Signal Contributors**

contribute to MRI artifact, particularly when the interface is between tissue of dramatically different susceptibility properties (*i.e.* a typical example is the air/tissue interface at the heart/lung interface, Fig. A.2 and around the sinuses in the brain, Fig. A.3).

The $B_0$ inhomogeneity map is often computed by unwrapping the phase component of complex MRI data. When this approach is used, the resulting map includes both high and low frequency information about the underlying tissue, which can be extracted separately, depending on the application at hand.

![Figure A.3: Effect of field inhomogeneity at the air/tissue interface is evident in the brain near the sinuses. Two approaches to phase image processing, Homodyne filtering (left) and unwrapping followed by high-pass filtering (right) fail to resolve the tissue information in this region of the brain.](image)

**A.2.3 Chemical Shift Term**

As mentioned previously, the conventional MR imaging systems acquire signal from protons, which make up $\approx 62\%$ of the human body by atomic percent. However, protons within the body are attached to different substrate molecules and depending on their chemical environment experience different extent of electronic shielding [37]. This difference in chemical shielding results in a spectral shift between the hydrogen of the water and that of the fat molecule, a phenomenon referred to as chemical shift effect. Fat molecule in particular is of interest in many clinical MR imaging applications as it may interfere with the identification of some physiological conditions such as edema [38]. As such the characterization and differentiation of fat signal from that of water on MR images is of importance.
Fat spectrum is more complex than the water spectrum in that aside from the main peak, it also consists of a number of smaller peaks at slightly different frequencies. The main spectral peak of fat, however, has an amplitude $\approx 10$ times larger than the rest. As such this peak is sometimes the only peak that is modelled. In quantitative applications, such as water/fat mapping, however, it is important to take all the peaks into account.

One of the means of differentiating fat from the pathologies of interest in the clinical applications is to suppress the fat signal using spectrally selective RF pulses in the preparatory block of the acquisition [39]. Often an additional acquisition is required without this spectrally selective RF pulse to ensure correct interpretation of the clinical data. This naturally increases the acquisition time and provides added incentive for methods that intrinsically characterize fat and water spectra.

The main fat peak is observed with a 3.5 ppm shift from the water peak. The conversion of this shift in units of ppm to frequency can be accomplished using equation A.15.

$$\Delta f_{cs} = \frac{\gamma}{2\pi} B_0 \Delta \delta [ppm] 10^{-6}$$

which is derived from the Larmor equation ($\omega_0 = \gamma B_0$). As can be seen from equation A.15, the amount of shift in frequency is a function of main magnetic field strength ($B_0$), meaning the chemical shift between the water and fat spectra increases as the field strength increases. This can be beneficial since a larger bandwidth can be used during acquisition, resulting in the ability to decrease echo time and maintain the image SNR.

**B0 mapping by Non-Iterative Correction of phase Errors (B0-NICE)**

An overview of available approaches for water/fat imaging was presented in the introductory Chapter 1; for completeness a more in-depth overview of the B0-NICE approach [40], which is used in the work of this dissertation, is discussed here:

The B0-NICE field mapping approach initially corrects the global phase errors by applying a non-iterative phase unwrapping approach [41] to the wrapped images, thereby calculating an initial field map ($B_{0,init}$). The local bias terms are then calculated using information drawn from the phase and magnitude data. The magnitude image is used to calculate a relaxation
map \( (R_2^*-map) \) via a look-up-table method with a range of trial values for each of \( R_2^* \) and FF maps. Each trial \( R_2^* \) value is used to calculate a residual error term \( (RES_t, \text{ where } t \text{ is the trial value}) \) between it and that obtained from the signal equation. This residual term is then used as a weight term for calculation of the fat fraction map, as follows:

\[
FF_{mag} = \frac{\sum_{t=1}^{T} \frac{1}{RES_t} FF_t}{\sum_{t=1}^{T} \frac{1}{RES_t}}
\]  

(A.16)

Once a magnitude-based FF map is calculated in this way, the phase image (with the global phase errors removed) is used to calculate a phase-based FF map. Two masks are then drawn from each of these FF maps and a matching criterion is imposed to allow for calculation of bias term due to imperfections in the acquisition. This bias term is removed from the \( B_{0,init} \) to result in the final bias-corrected field map \( (B_0\text{-map}) \). The bias is also removed from the phase-based FF map to result in the final FF map.

This approach is completely non-iterative and as a result can be implemented on GPU to significantly reduce computation time. As a result it is an ideal method for channel-by-channel processing approach proposed by the work of this dissertation.

### A.3 Quantitative MR Phase Imaging

The physics of MR imaging revolves around the phenomenon of the precessing magnetization vector around the main static field. The information about the orientation of the magnetization vector is in the phase component of MR images, which is the cornerstone of many effective imaging means for differentiating tissues and pathologies.

#### A.3.1 MR Phase Image

Phase is a relative quantity and is defined as the product of angular velocity of the transverse magnetization vector and time:

\[
\phi(t) = \omega t + \phi_0
\]

(A.17)
The term $\phi_0$ is the reference phase at time 0, to which all other phase values in the experiment are referenced. It is clear from the expression that phase, as a cyclic quantity evolves linearly with time. However, the value of phase can be measured accurately within a multiple of $2\pi$; beyond this range phase aliasing occurs where the phase values are wrapped back to the start of the range.

The primary challenge of extracting the tissue information in the phase component of MR data is to unwrap this signal. Several phase processing approaches have been proposed, an overview of which was presented in Chapter 1.

Notice that in equation A.17 phase is expressed as a function of time only. The underlying assumption is that the static magnetic field is the same everywhere within the sample and that the introduction of the imaging subject into the main field does not distort the field. As outlined in the next sections, this underlying assumption is not accurate and in fact, local changes in the field ($\Delta B(r)$) require the expression of equation A.17 to be modified and expressed as a function of both time, $t$ and spatial location, $r$.

### A.3.2 Field Perturbors and Magnetic Susceptibility

When an object is placed in a magnetic field, the microscopic field probes, or the nuclear spins, become aligned with the main field. Additionally the object will become magnetized. This magnetization results in additional field, commonly referred to as the demagnetizing field, which induces local field changes. The changes that are caused by the demagnetizing field are caused by the electronic interactions. By making the assumption that the distance between the observation point ($\vec{r}$) and the atom or molecule is large compared to the spatial extent of its magnetic field, these electronic interactions are modelled using a dipole field term ($\vec{b}_d(\vec{r})$). In this approximation, the demagnetization field $\vec{B}_{demag}$ can be written as the sum of all the dipoles in the volume of interest:

$$\vec{B}_{demag}(\vec{r}) = \sum_j \vec{b}_d(\vec{r} - \vec{r}_j, \vec{m}_j), \vec{r} \neq \vec{r}_j$$  \hspace{1cm} (A.18)
with the dipole term defined as:

\[
\vec{b}_d(\vec{r}) = \mu_0 \frac{3\vec{r}(\vec{m}, \vec{r}) - \vec{m}}{4\pi ||\vec{r}||^3}
\]  

(A.19)

In Eq. A.18 and Eq. A.19, \( \vec{r} \) is the spatial location of the dipole moment. While imaging is performed on a macroscopic scale, the variations that result in detectable changes are caused on a microscopic scale. In order to appropriately interpret the acquired images and derive susceptibility values corresponding to the underlying tissue, the microscopic magnetic environment of the nuclear spin should be accounted for. Macroscopic derivations result in bulk estimation of magnetic moments, and MR measurement does not involve such a spatial averaging process over the microscopic magnetic field. Lorentz proposed that by dividing the environment into near and distant regions a virtual surface (often a sphere) can be defined inside which the magnetic moments are considered as discrete entities with individual dipole fields, corresponding to the near region. On the other hand, outside of this sphere the magnetic moments are treated mathematically as a continuous magnetic moment density [42].

The MRI literature makes the assumption that the magnetic moments are randomly distributed in a sample resulting in the cancelling of the field contributions from all the dipoles inside Lorentz sphere (\( \vec{B}_{LS}^{near} = 0 \)) [43]. This assumption, while true for most imaging applications, is not completely accurate for instances where non-random distribution of dipoles exists (e.g. white matter and myocardial fibers). With this assumption as a cornerstone, susceptibility, the underlying tissue property that causes the field perturbation can be derived from the MR phase data. Magnetic susceptibility, is a macroscopic material property, which relates the magnetization to the applied field:

\[
\vec{M}(\vec{r}) = \chi(\vec{r})\mu_0^{-1}\vec{B}(\vec{r})
\]  

(A.20)

In Eq. A.20, \( \mu_0 \) is the permeability constant (\( \mu_0 = 4\pi \times 10^{-7} H.m^{-1}, H: henries \)). Most tissues are diamagnetic (with negative susceptibility values) or weakly paramagnetic (with positive susceptibility values) with \( |\chi| \ll 1 \). Ferromagnetic material have susceptibility values that are orders of magnitude larger (\( \chi > 1 \)) and are considered MRI-unsafe [44].
We can express the macroscopic unit dipole function as follows:

\[ b_χ(\vec{r}) = \frac{3\chi(\vec{z}, \vec{r}) - \hat{z}}{4\pi||\vec{r}||^3_2} \]  

(A.21)

and \(\hat{z}\) can be expressed in the form of Green’s function of the inverse macroscopic field-to-source problem as:

\[ \hat{z} = \frac{3\cos^2\theta - 1}{4\pi||\vec{r}||^3_2}, \vec{r} \neq 0 \]  

(A.22)

With the definitions of Eq. A.21 and Eq. A.22 we can express the demagnetizing field as follows:

\[ B_{demag}(\vec{r}) = B_{ext}(\vec{r}) \int_{vd} \chi_{app}(\vec{r}) b_χ(\vec{r} - \vec{r}')d^3\vec{r}' \]  

(A.23)

This integral takes the form of a convolution integral except it excludes the near region (i.e. inside the Lorentz sphere). Using calculus principles to add this region to make a continuous integral and subsequently subtracting it we can evaluate the demagnetization field [42]. Under the assumption of random dipole distribution within the Lorentz sphere, the total detected field can be expressed as follows:

\[ B_{random}(\vec{r}) = B_{ext}(\vec{r}) + B_{ext}(\vec{r})\chi_{app}(\vec{r}) \odot b_χ(\vec{r}) \]  

(A.24)

where \(\odot\) is the convolution operator. This equation describes the relationship between an arbitrary spatial variation of magnetic susceptibility and the total magnetic field. Using the Fourier convolution theorem this relationship can be expressed as a multiplication:

\[ FT\left[\frac{B_{random}(\vec{r}) - B_{ext}(\vec{r})}{B_{ext}(\vec{r})}\right] = FT[\chi_{app}(\vec{r})].FT[b_χ(\vec{r})] \]  

(A.25)

The left side of Eq. A.25 is commonly referred to as the relative difference field (RDF). Knowing that \(FT[b_χ(\vec{r})] = \frac{1}{3} - \cos^2(\theta)\), the fundamental challenge of extracting susceptibility values from the measured field (quantitative susceptibility mapping [45, 46]) becomes evident; the dependence of frequency components of the field on the spatial frequency distribution of the susceptibility weakens at low frequencies and diminishes to zero at the origin. Therefore, it becomes impossible to resolve the susceptibility values from the measured field.
Susceptibility differences can be used in one of two ways to generate contrast between different tissues; susceptibility can be mapped on a pixel-by-pixel basis [47]. Additionally, susceptibility differences can be used to generate a specific weighting in the images, similar to that discussed for $T_1$ and $T_2$ weighted imaging, however for susceptibility weighted imaging [8], the weighting is not intrinsic to the imaging sequence and is generated through post-processing of the complex MR data. As the name suggests, susceptibility mapping enables the characterization of all tissues within the field of view that exhibit different behavior in a magnetic field whereas SWI is a convenient means of generating contrast between any two tissues with known susceptibility differences. Both of these techniques require the RDF to be extracted from GRE phase data. The following section presents a brief description of the processing steps involved in each of these applications.

**Susceptibility Contrast**

The relationship between the measured phase and the echo time can be derived from the Larmor equation:

$$\omega = -\gamma B_0$$  \hspace{1cm} (A.26)

$$\phi_{TE} = -\gamma BTE$$  \hspace{1cm} (A.27)

$$\phi_{\Delta TE} = -\gamma B\Delta TE$$  \hspace{1cm} (A.28)

With $\Delta B = \Delta \chi B_0$, where $\Delta \chi$ is the susceptibility difference between the tissues, we can calculate the imaging time for a given field strength at which the phase signals are completely out of phase (i.e. an echo time corresponding to a completely out of phase image with $\Delta \phi = \pi$).

The original means of extracting susceptibility contrast from GRE phase data was through the application of a phase-driven mask to magnitude image for SW imaging. The quantitative mapping of the susceptibility values can be achieved by solving Eq. A.25. However, it is clear from this expression that the inverse problem of calculating the underlying tissue susceptibility from the measured field is an ill-posed problem. As a result a number of approaches have been proposed in the literature to enable calculation of an accurate QS map [48, 49, 50, 51, 52].

For QSM the starting $B_0$ offresonance map must include both the low and the high fre-
quency contents of the MR phase data (i.e. the phase image is merely unwrapped). The back-
ground field, which is part of the information in the phase map, arises from various sources
such as magnetic susceptibility sources outside of the region of interest, the main field inho-
mogeneity and imperfect shimming. For quantitative mapping of tissue susceptibility, we are
interested in removing the background field effects while sparing the low- and high-frequency
contents of the local field. As such, the SWI processing presented in the introductory Chapter
1 is not applicable to QSM. As a result, separation of background and foreground fields is no
longer trivial (i.e. the background fields extend into the local fields the same way as the local
fields extend into the background fields). In other words, the two are not separable in a physical
sense. In mathematical form, Eq. A.25 can be re-written in a more complete form as follows:

\[
RDF = RDF_{\text{local}} + RDF_{\text{background}} = d \odot |\chi_{\text{local}} + \chi_{\text{background}}| \\
(A.29)
\]

It becomes clear that the problem of quantitative mapping of susceptibility is a two-stage prob-
lem. Firstly an accurate RDF must be extracted from the unwrapped phase. Subsequently
dipole inversion can be performed through deconvolution of Eq. A.29 to extract the suscepti-
bility values.

**Background Field Removal Approaches**

The background fields are an order of magnitude stronger compared to the internal field con-
tributions, the extraction of which is desired in QSM [53]. The most basic, yet essential, step
in QSM is to remove the physical regions in the background from the image, which is often
performed by masking out the tissues outside of the tissue of interest (e.g. brain extraction).
Several strategies are available for subsequent background field removal including: (1) in so-
phisticated harmonic artifact reduction for phase data (SHARP) methods [54, 51] the Laplacian
equation is solved for background field, using the spherical mean value property of this field.

\[
\nabla^2 \phi_{\text{background}} = 0 \\
(A.30)
\]
(2) The Laplacian equation can also be solved by assuming a boundary value [55]. (3) Projection onto dipole fields (PDF) method computes a projection of the total magnetic field to the dipole fields generated by the magnetization outside of volume of interest [49]. Both SHARP and PDF approaches assume orthogonality between the dipole fields generated by the sources outside and inside the volume of interest. This assumption breaks down for PDF and results in edge artifact in SHARP. These problems are the topic of current research in this area [51, 50, 56, 48].

![Quantitative susceptibility map of a volunteer at 7T](image)

Figure A.4: Quantitative susceptibility map of a volunteer at 7T is shown with the $T_1$-weighted image as a reference. A consequence of rigorous background field removal is the elimination of the ambiguous tissue boundary regions, which are removed in the QS map.

### Dipole Inversion Approaches

The final step of QSM is the deconvolution, which results in bulk magnetic susceptibility distribution map of the underlying structures. This step is heavily affected by noise, which manifests itself in the form of streaking artifact in the final QSM. The easiest means of addressing this ill-posed problem is to threshold the values as the surface of the double cone is reached. This approach is referred to as the thresholded k-space division (TKD) [57]. Expectedly, the quality and accuracy of the results of this approach depend heavily on the threshold chosen [58]. More sophisticated techniques attempt to regularize this inverse problem by using iterative methods such as conjugate gradient to minimize the difference between the measured field and the calculated field [59]. The necessary prior knowledge about the underlying tissue is extracted from
the magnitude data.

The ideal means of calculating susceptibility maps is to image the object at multiple orientation [60]. However this approach is not practical in clinical situations.

### A.3.3 Field Strengh Considerations

The work of this thesis includes images acquired at 3T and 7T. Therefore, it is beneficial to include a short section on the factors that should be taken into account, not only for the different applications where the work of this thesis focused, but also to address the necessary considerations for imaging at different field strengths.

According to Curie’s law (Eq. A.31), there are two means of increasing the amount of magnetization, and therefore signal; firstly an imaging system with higher magnetic field can be designed, and secondly the temperature of the sample can be lowered. Naturally, in clinical setting decreasing the temperature of the patient is not an option, therefore to achieve better SNR, higher field strengths are desired.

\[
M_0 = C \frac{B_0}{T}
\]  

(A.31)

A direct consequence of increased signal at higher field is the ability to image at finer resolution and to resolve smaller structures. This is generally desirable, regardless of application.

Another benefit of imaging at higher field is shorter scan time, specifically in susceptibility-weighted imaging applications. The physical principles governing the formation of susceptibility contrast were presented earlier in this section. A phase shift of \( \pi \) is simply achieved at an earlier time point when imaging at higher fields. However, it should be noted that imaging time for other applications, such as \( T_1 \)-mapping will increase at higher field strengths, simply because the longitudinal recovery times increase with an increase in field strength.

Imaging at high field strengths presents unique challenges for specific imaging applications. In neurological applications, imaging at high field strength results in rapid phase degradation in the regions near the sinuses rendering the information unusable in the tissue neighboring the air-interface. Imaging at lower field strengths (1.5T) are highly favored for cardiac applications in particular as most of the myocardial wall is situated adjacent to the lungs rendering it
susceptible to rapid signal decay due to large phase gradients at air/tissue interface.

## A.4 Multi-Channel MR Image Acquisition

Magnetic resonance imaging is one of the slowest available medical imaging modalities. This is the direct consequence of the way the image data are acquired. The earliest means of addressing this short-coming was the proposal to acquire the images using multiple receivers, thereby decreasing the number of phase-encoding lines necessary to reconstruct a full field-of-view (FOV) image [61]. An added bonus to this approach to MR image acquisition is the increase in SNR [62], which is made possible by positioning the receiver coils in close proximity to the tissue of interest.

Theoretically, with N coils in an array of receivers, the imaging can be performed N times faster since N phase encode lines can be skipped during acquisition and reconstructed offline [62]. Fast imaging by skipping phase encode lines is referred to as *accelerated image acquisition*, sometimes referred to as *partially parallel imaging* (PPI), and the acceleration factor, represented by the letter $R$, is defined as the number of lines skipped during image acquisition plus 1.

To ensure the best SNR is achieved in multi-channel acquisition, the receiver coils are designed to fit a specific anatomy (*e.g.* head coil, head and neck, knee, etc.). Each coil has a region of sensitivity, which is described by the Biot-Savart law (Eq. A.32) and is known to drop with the square of the radius of the coil. Therefore, depending on the location of the structure of interest, different size coils are appropriate (*i.e.* if the structure of interest is deep inside the tissue, coils of larger diameters can be used as they have a larger depth in their sensitivity, whereas if the structure is more superficial, smaller coils can reliably acquire signal from these regions).

$$d\vec{B}(\vec{r}) = \frac{\mu_0 I d\vec{l} \times \vec{r}}{4\pi r^2} \quad (A.32)$$

Two main consequences of partially parallel imaging are the requirement to resolve the missing K-space data, and subsequently to combine the images from the different receiver coils. Note
that in this thesis, \textit{reconstruction} refers to the process of solving for the missing samples in K-space whereas \textit{channel combination} is used to refer to the mere step of combining the images acquired from the different coils. Section A.4.1 will present an overview of methods available for reconstructing the missing lines of k-space in accelerated acquisition. Section A.4.2 will then discuss the available approaches for channel combination, highlighting their strengths and pitfalls.

\section{A.4.1 Accelerated Image Reconstruction}

The first processing step in PPI is the reconstruction of the missing samples in K-space (or otherwise in image space). Depending on whether the reconstruction is applied in the image domain or the frequency domain, different physical phenomenon are used to guide the reconstruction process.

The MR signal for an imaging plane can be expressed using Eq. A.33.

\begin{equation}
S(k_x, k_y) = \int \int dx dy C(x, y) \rho(x, y) e^{-ik_x x - ik_y y} \tag{A.33}
\end{equation}

Here $\rho(x, y)$ is the spin density and $C(x, y)$ is the coil sensitivity. $k_x = \gamma G_x t_x$ and $k_y = \gamma G_y t_y$ with $\gamma$ the gyromagnetic ratio and $G_x$ and $G_y$ are the $x$ and $y$ gradient amplitudes, respectively. Equation A.33 combines the spin excitation function and the effect of relaxation into the pulse-sequence-specific sensitivity function.

\section{K-Space Domain Reconstruction Techniques}

The K-space based techniques make use of the relationship of the spatial harmonics between the different lines of K-space. The first accelerated image reconstruction technique proposed by Sodickson et al. in 1997 [63] was the simultaneous acquisition of spatial harmonics (SMASH). The main theory of SMASH makes use of the fact that the different regions of the imaging volume generate varying currents in the RF receiver coil, which spatially varies as a consequence of spatial variation in the field produced by the coil over the sample volume. A standard circular surface coil has a monotonic fall-off of sensitivity with distance from the coil in all directions. With an arrangement of surface coils with sinusoidal spatial sensitivity profiles, the MR signal
from these coils will have information content somewhat different from that of the usual coil signal. An appropriate combination of coil outputs may then be configured to have a composite sensitivity in the form of a complex exponential function, giving rise to the complex sensitivity function expressed by:

\[ C^{\text{comp}}(x,y) = \cos \Delta k_y^{\text{comp}} y + i \sin \Delta k_y^{\text{comp}} y = e^{i \Delta k_y^{\text{comp}} y} \] (A.34)

where \( \Delta k_y^{\text{comp}} \) denotes the spatial frequency of the composite complex exponential sensitivity.

Now the expression of Eq. A.33 can be re-written as follows:

\[ S(k_x, k_y) = \int \int dxdy \rho(x,y) e^{-ik_x x - i(k_y \Delta k_y^{\text{comp}}) y} \] (A.35)

The above equation is the spatial Fourier transform of the underlying spin density. The equation is the mathematical representation of the combined MR signal from the inhomogeneous coils, which is apparently shifted in k-space by an amount \(-\Delta k_y^{\text{comp}}\). This shift has the same form as the shift that is produced by evolution in a y-gradient of magnitude \(\gamma G_y t_y = -\Delta k_y^{\text{comp}}\). The appropriate modulation in the amplitude of the spatially varying sensitivity function, can therefore be used to take the place of phase or frequency encoding normally produced by magnetic field gradients.

In its simplest implementation, the SMASH technique uses a linear array of surface coils to synthesize multiple sinusoidal sensitivity variations, an approach that is compatible with traditional phased array coil designs. In a linear surface coil array with adjacent components, each coil \( j \) has a distinct but overlapping sensitivity \( C_j(x,y) \). In SMASH approach, signals from the various array components are combined with linear weights, \( n_j \), to produce overall composite sensitivity variations across the image plane of the form:

\[ C^{\text{comp}}(x,y) = \sum_j n_j C_j(x,y) = e^{im \Delta k_y y} \] (A.36)

In the above equation, \( m \) is an integer, and \( \Delta k_y = 2\pi/\text{FOV} \) is the minimum k-space interval corresponding to the desired FOV. The composite sensitivities are arranged to be spatial harmonics of the imaged field of view. By virtue of these sinusoidal spatial modulations, each
The combined data set is shifted in k-space by an amount $-m\Delta k_y$. If a total of $M$ spatial harmonics are generated using linear combinations of component coil signals, then $M$ lines of k-space may be reconstructed for each application of a phase-encoding gradient, which means the full signal matrix may be generated using a fraction $\frac{1}{M}$ of the usual phase-encoding gradient steps and consequently a fraction $\frac{1}{M}$ of the usual time. The SMASH reconstruction is then narrowed down to a least-squares fitting procedure, where the component coil reference image $C_j(x, y)$ in Eq. A.36 are fit to spatial harmonics using complex coefficients $n_j$. The result is a channel-combined full-FOV image.

The next generation of reconstruction was the AUTO-SMASH technique [64], which utilized an additional calibration line, or auto-calibration signal (ACS), to enable calculation of the weights used for reconstruction. Simply, each of the lines in the reduced dataset is fit to the ACS line represented by the following equation:

$$\sum_{j=1}^{J} S_{ACS}^j (k_y - m\Delta k_y) = \sum_{j=1}^{J} n_j(m) S_j^j(k_y)$$ (A.37)

for a line offset by $m\Delta k_y$, where $J$ is the number of coils. Once the weights are calculated, the missing lines in the data can be reconstructed as in the original SMASH technique, discussed above. A slight modification of AUTO-SMASH was the VD-AUTO-SMASH [65], which utilizes more than one ACS lines with variable density in the center of k-space thereby moderating the effects of both noise and coil profile imperfections.

A more practical approach to reconstruction of PPIs was proposed in 2002 by Griswold et al. [66], namely the generalized autocallibration partially parallel acquisition, or the well-known GRAPPA technique. GRAPPA applies multiple block-wise reconstructions to generate the missing k-space lines, separately for each of the coils. A block is defined as a single acquired line and R-1 missing lines of k-space. The data from all the coils are used to fit any given ACS line in any given coil. This can be represented by the following equation given for the $j^{th}$ coil at a line $k_y - m\Delta k_y$ offset from the normally acquired data:

$$S_j^j(k_y - m\Delta k_y) = \sum_{l=1}^{L} \sum_{b=0}^{N_b-1} n(j, b, l, m) S_l^b(k_y - bR\Delta k_y)$$ (A.38)
where \( R \) is the acceleration factor, \( N_b \) is the number of blocks used in the reconstruction process, and \( n(j, b, l, m) \) is the weights that are used in this expanded linear combination. This gives the weights for the \( j^{th} \) coil, which are then used in the reconstruction process of that coil’s full-FOV image. In this way GRAPPA reconstruction technique is unique because it results in the reconstructed images from each individual channel. As a result it is possible to apply any desired channel combination technique to GRAPPA reconstructed data.

**Image Domain Reconstruction techniques**

The sensitivity encoding (SENSE) approach [67] is the most well-known image domain approach to PPI reconstruction. In this technique, firstly, the inverse-Fourier transform of the undersampled k-space images from each of the coils are calculated. From Nyquist theorem, it follows that these images will be aliased due to undersampling, and further processing is required to resolve the full FOV information. The unaliasing of this image will be performed by setting up a linear system of equations constructed with the \( N \) coil images and sensitivity maps. The equations can then be solved in order to resolve the full FOV, unaliased images. Naturally, the information about the coil sensitivity must be known in order to solve for the missing information in the aliased images. This is performed in one of two ways. On rare occasion, the sensitivity functions are known for each of the receiver coils, which makes the remaining steps in reconstruction quite simple. In the common case where the coil sensitivity is unknown, the combination of an image acquired by the body coil and an image acquired by the coil in the array of receivers can enable the calculation of coil sensitivity profile, as per the following equation:

\[
C_j(x,y) = \frac{I_{\text{coil}}}{I_{\text{body coil}}} = \frac{\rho(x,y)C_j(x,y)}{\rho(x,y)} \quad (A.39)
\]

Ensuring no motion between the acquisition using the body coil and the array of receiver coils is crucial in the successful application of this approach. It is also noteworthy that the newer MRI hardware generations do not include a receiver body coil. As a result of this, the above-mentioned process of resolving the coil sensitivity is not a possibility. More recent image domain approaches to PPI reconstruction have aimed to address this challenge by proposing self-calibrating approach to SENSE [68], which similar to AUTO-SMASH and GRAPPA,
Chapter A. Theory

utilizes the information in the image to generate an estimate of the coil sensitivity. In this case, the center of the k-space, which is fully sampled, is converted into image domain, by applying an inverse Fourier transform. The resulting image is a high-SNR, low contrast image, which can be used as the coil sensitivity for the rest of the SENSE reconstruction process.

All of the reconstruction techniques discussed here assume a cartesian acquisition as this is the practice used for the work of the present dissertation. For all other acquisition patterns (e.g. spiral, radial, EPI, etc.) the reader is directed to appropriate literature.

A.4.2 Ideal Multi-Channel Image Combination

Previous discussion highlighted the importance of prior knowledge about coil sensitivity to enable us to model the MR signal equation using Eq. A.33. The ideal channel combination process includes the knowledge of the specific coil sensitivities in absence and presence of the sample. The thorough hardware and signal processing considerations for multi-channel image acquisition was presented by Roemer and colleagues [62]. The method presented by Roemer et al., constitutes an ideal channel combination approach.

In the absence of a sample, the coil sensitivity can be characterized during the design process. However, with the introduction of the sample during imaging, this sensitivity is modified and, therefore, must be characterized prior to imaging with the sample positioned inside the coil. This leads to an increase in image acquisition time, which is not desirable in clinical applications. Nevertheless, if performed accurately, it enables image reconstruction and channel combination with high SNR and no aliasing artifacts.

Roemer et al., also demonstrated that, in the absence of coil sensitivity, magnitude images acquired from multiple receiver coils can be optimally combined using the sum-of-squares technique. With the advent of MR phase imaging, there is more interest in defining an optimal means of phase image combination to address the persisting problem of absence of coil sensitivity information. Many of the approaches for phase image combination have been inspired by Roemer’s proposed (SoS) magnitude combination solution, such as that applied by Hammond et al., [69]. Three key ideas for phase-sensitive channel combination are presented in the following section.
A.4.3 Phase-Sensitive Channel Combination Techniques

Magnetic resonance images are complex valued signal, which give rise to separate magnitude and phase images. Phase component of MR data has shown promising results in diagnosis and longitudinal tracking of changes in the course of diseases, for example [70]. Consequently, it has become a major interest to acquire high quality phase images [71, 69, 72]. Most of the challenges that have been mentioned about multi-channel and partially parallel image acquisition are more pronounced when considered for phase images. A major contributor to this fact is because the phase images for the different channels can experience destructive interference, which results in phase cancellation. In the case of complex summation, this can affect both the phase and magnitude image. However, with more optimal magnitude image combination techniques, such as SoS, it is possible to prevent such phenomenon from negatively affecting the magnitude image. In this section two of the well-established phase image combination techniques, and one high-pass filtered frequency combination techniques are presented. These techniques provide the means of computing more accurate coil-combined phase images, thereby making it possible to, reliably, utilize the information in the phase component of MR data for clinical and otherwise research purposes.

Adaptive Channel Combination

Using eigen-analysis of the sample correlation matrices yields an optimal reconstruction weight vector for the estimated NMR signal process. This mathematical concept has been used both in the adaptive channel combination (ACC) [73] and in singular value decomposition (SVD) [74], discussed in the following subsection.

The signal and noise processes can be modelled in terms of their second-order array correlation statistics, and the optimization formula computes an array filter vector that maximizes the expected SNR for the assumed signal and noise statistics. In brief, both the signal and noise are modelled as stochastic processes and a correlation matrix is computed for each of the coils, separately for noise and signal ($R_n(j, k)$ and $R_s(j, k)$, where $j$ is the given coil and $k$ is the counter for the rest of the coils in the array). The array filter vector that maximizes the SNR in
the array-filtered time-domain signal is the eigenvector of the following matrix product:

\[ P = R_n^{-1} R_s \]  

(A.40)

A proof for this conclusion has been included in [73], and is not reproduced here as it is beyond the scope of the present document. This criteria is met by having the maximum corresponding eigenvector. Notice that in reconstructing the MR images, the correlation matrices for noise and signal are evaluated in two dimension as opposed to the time-dimension which is employed originally by the matched filter algorithm [62]. Therefore, the correlation matrix for the MR signal can be expressed as follows:

\[ R_s(j,k) = \sum_{(x,y) \in S_{ROI}} C_j(x,y)C_k^*(x,y) \]  

(A.41)

\[ j = 1, 2, ..., N, \text{ and } k = 1, 2, ..., N \]

In the above equation, \( S_{ROI} \) is a set of pixel coordinates for estimating \( R_s \). The ACC technique assumes that the noise in a multi-channel acquisition can be modelled as white noise, which is a realistic assumption for the individual receiver channels.

**Singular Value Decomposition**

Singular value decomposition channel combination (SVDCC) is a signal processing tool that provides the dominant mode signal originally proposed for MR spectroscopy applications [74]. It can be used to combine time decay signals from multiple receiver coils by objectively obtaining the optimal coil combination weights. SVDCC utilizes the following equation as a basis for extracting coil sensitivity information from the array of coils at multiple echo times:

\[ \hat{S} = \alpha Q^T \]  

(A.42)

\( \hat{S} \) in the equation above is a \( N_j \times N_k \) matrix, where \( N_j \) is the number of coil elements and \( N_k \) is the number of samples. \( \alpha \) is a \( N_j \times 1 \) vector of coil sensitivity at that voxel and \( Q \) is a \( N_k \times 1 \) vector of spectral component of the sample magnetization in the voxel. Noise can additionally be modeled in Eq. A.42 by adding a white noise term \( (\hat{\psi}) \), making the assumption that the
noise term is multivariate normally distributed with a known covariance. SVDCC begins by applying a $N_j \times N_j$ noise-whitening (decorrelation) matrix $W$ to convert $\hat{S}$ into a matrix of whitened "channel" spectra:

$$S = W\hat{S} \text{ where } W = D^{-1/2}X'XDX' = \hat{\psi} \quad (A.43)$$

Here $D$ contains the eigenvalues and $X$ the eigenvectors of $\hat{\psi}$. The main equation for SVDCC becomes:

$$S = U\Sigma V' \quad (A.44)$$

where $U$ is a $N_j \times N_j$ unitary matrix whose columns are the left-singular vectors, $\Sigma$ is a diagonal matrix of singular values, and $V$ is an $N_k \times N_k$ unitary matrix with columns that are the right singular vectors. The first singular vectors ($U_{*,1}$ and $V_{*,1}$) give the maximum likelihood coil sensitivities and combined spectrum, respectively.

The SVDCC technique requires knowledge of a reference phase and as a result of this the input image to this channel combination technique must be a multi-echo dataset with at least two temporal images. In this way, the phase image at the first echo time is selected as the reference phase and the phase images at the remaining echo times will become measures in reference to the initial echo time. Consequently, the information in the first echo time is lost, which results in a relative decrease in SNR. However, this automatic zero-order phasing can also be considered an advantage. Another advantage of SVDCC, similar to the ACC approach, is that there is no requirement for \textit{a priori} information about the coil sensitivity. Additionally, the signal in low SNR regions can reliably be separated from noise using SVDCC.

**Inter-Echo Variance Channel Combination**

The inter-echo variance channel combination (IEVCC) [72] is used in the work of Chapter 2. This technique utilizes the variance of the high-pass filtered frequency maps over multiple echo times to calculate a weighting factor for each channel (the IEV channel weight maps). Similar to SVDCC, the IEVCC technique requires multi-echo images as input. However, unlike SVDCC, this approach preserves the information acquired at all the echo times. The technique firstly performs phase unwrapping on the individual channel images and subsequently applies
a Gaussian high-pass filter [75].

Naturally any high-pass filtering approach can be used to extract high-frequency contents of the phase image, however inline with the original publication we use Gaussian filter. The channel combination in IEVCC takes into account the theoretical assumption that, given that the temporal contents are removed from the original phase in a high-pass filtered frequency, it should be constant over time. As a result a set of weighting parameters can be calculated for each channel based on the variance between the frequency maps at each pixel over time. These weighting factors will therefore be small for pixels and channels that show high variability over time and, on the other hand, channels that do not show large variability will be assigned larger weighting. Therefore the impact of the more reliable channels will be more pronounced. The application of the IEV weighting approach is represented through the following equation:

\[
LFS_i = \frac{\sum_{j=1}^{C} \frac{1}{\sigma_j} LFS_{ji}}{\sum_{j=1}^{C} \frac{1}{\sigma_j}}
\]

where \(\sigma_j\) is the frequency map variance for the \(j^{th}\) channel, and \(LFS_{ji}\) is the LFS map of the \(j^{th}\) channel at the \(i^{th}\) echo time.

The IEVCC approach is different from the previously discussed phase-sensitive channel combination techniques in two ways; firstly, IEVCC does not concern itself with magnitude information in the complex channel data. Secondly, IEVCC performs what are normally classified as post-channel combination processing prior to combining the phase information from the individual receiver coil. A consequence of the latter is that the channel combined images are high-pass filtered phase images and lack any low frequency phase information.
References


[75] A. Rauscher, M. Barth, K.-H. Herrmann, S. Witoszynskyj, A. Deistung, and J. R. Reichenbach, “Improved elimination of phase effects from background field inhomogeneities,”...
Appendix B

Ethics Forms
Use of Human Participants - Ethics Approval Notice

Principal Investigator: Ravi Menon
Review Number: 18752E
Review Level: Delegated
Approved Local Adult Participants: 85
Approved Local Minor Participants: 0
Protocol Title: Magnetic Resonance Imaging of Multiple Sclerosis at 7 Tesla
Department & Institution: Medical Biophysics, Robarts Research Institute
Sponsor: Canadian Institutes of Health Research

Ethics Approval Date: February 17, 2012
Expiry Date: February 28, 2017
Documents Reviewed & Approved & Documents Received for Information:

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This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The UWO HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB00000920.

Ethics Officer to Contact for Further Information

This is an official document. Please retain the original in your files.
Principal Investigator: Dr. Raymond Yee  
Department & Institution: Schulich School of Medicine and Dentistry\Medicine-Dept of, London Health Sciences Centre  

Review Type: Full Board  
HSREB File Number: 102722  
Study Title: MRI Allocation of Pacing Targets in Cardiac Resynchronization Therapy (MAPIT-CRT)  
Sponsor: Heart and Stroke foundation of Ontario  

HSREB Amendment Approval Date: June 06, 2016  
HSREB Expiry Date: June 19, 2017  

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<td>Revised Western University Protocol</td>
<td></td>
<td>2016/05/18</td>
</tr>
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The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the amendment to the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer: Erika Basile  Katelyn Harris  Nicole Kanuki  Grace Kelly  Vikki Tran  Karen Gopaul

Western University, Research, Support Services Bldg., Rm. 5150  
London, ON, Canada N6G 1G9 t. 519.661.3036 f. 519.850.2466 www.uwo.ca/research/ethics
Appendix C

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Curriculum Vitae

Education

**PhD Candidate**  
09/2013 to Present  
Supervisor: Dr. Maria Drangova.  
Biomedical Engineering Graduate Program,  
Robarts Research Institute, Western University, London, Ontario, Canada.  
*Main dissertation:* Non-contrast tissue characterization using MRI; applications in neurological and cardiac imaging.

**Master of Applied Science**  
09/2011 to 08/2013  
Supervisors: Dr. Gregory R. Wohl, Dr. Shahram Shirani.  
School of Biomedical Engineering, McMaster University, Hamilton, Ontario, Canada.  
*Main dissertation:* Virtual fluoroscopy system for arthroscopic surgical training.  
*Other research contributions:* Study of adverse effects of maternal antidepressant intake on fetal skeletal growth.

**Undergraduate Studies**  
09/2006 to 04/2011  
Bachelor of Engineering,  
Electrical and Biomedical Engineering & Coop, McMaster University, Hamilton, Ontario, Canada.  
*Final Year Capston Project*  
Supervisors: Dr. Michael Noseworthy, Dr. Hubert deBruin & Dr. Alexander Ball.  
McMaster University, Hamilton, Ontario, Canada.  
*Project:* Design and development of an electroretinogram for use in animal research.  
Responsible for design and manufacturing of the signal processing and controller board.

**Honors & Awards**

- Ontario Graduate Scholarship, 2014-2016.  
  $45,000
- Mitacs Scholarship, McMaster University & Torvan Medical, 2012 and 2013.  
  $21,000
- Graduate Scholarship, McMaster University, 2011 and 2012.  
  $21,000
- Top Intern Award, GE Canada, 2010.  
  $1,200
- Top Intern Award, GE Canada, 2008.  
  $1,200
- General Electric Foundation Scholar Leaders Scholarship,  
  $12,000
- Entrance Scholarship, McMaster University, 2006.  
  $1,000

**Special Training**

**Business Acumen.** (Dr. Darren Meister)  
August 28th-September 1st, 2017  
- An introduction to business fundamentals and entrepreneurship.
High-Field MRI Training. March 17th – 20th 2017
- Hands-on training on MRI (3T, 7T, and 9.4T) systems (Winter School at Robarts Research Institute).

Design Driven Innovation. (Dr. Darren Meister) 09/2016 to 11/2016
- Development of innovative solutions through inter-disciplinary collaborative projects (Design Driven Innovation GS 9101).

Teaching and Course Design. (Dr. Aaron Ward) 01/2014 to 04/2014
- Design and development of course material and a curriculum for graduate and fourth year undergraduate students (Practical Medical Imaging BIOPHYS 9520B).

Professional Experience

Software developer 05/2011 to 05/2012
Radio-Frequency Identification Laboratory in collaboration with Bombardier; project: TrackSafe
Supervisor: Dr. Peter Basl
McMaster University, Hamilton, Ontario, Canada.
- C/C++, MATLAB, and microcontroller programming for a controller board.

Quality Assurance Engineer 09/2009 to 08/2010
General Electric-Energy Business
Supervisor: Travis Steinmann
Edmonton, Alberta, Canada.
- Creation and conduction of quality system, successful completion of ISO recertification, facilitation of Root Cause Analyses on customer requests.

Quality Assurance Engineer 05/2008 to 08/2008
General Electric-Energy Business
Supervisor: Tammi Mason.
Stoney Creek, Ontario, Canada.
- Creation and implementation of quality system, successful completion of ISO recertification, and part of an Action Workout team for recreating a business-wide processing pipeline.

Teaching Experience

All teaching assistant experiences included conducting lab and/or tutorial sessions for over 30 students, creating examination questions and marking. All extra activities are listed where relevant.

Teaching Assistant 09/2017 to 12/2017
Design Driven Innovation (graduate).
Ivey Business School & Society of Graduate and Postdoctoral Studies, Western University, London, Ontario, Canada.
**Teaching Assistant** 01/2017 to 04/2017

Programming Fundamentals for Engineers (Undergraduate, yr. 1).
Electrical & Computer Engineering Department, Western University, London, Ontario, Canada.

**Teaching Assistant** 09/2016 to 12/2016

Medical Imaging (Graduate).
Department of Medical Biophysics, Western University, London, Ontario, Canada.

**Teaching Assistant** 01/2016 to 04/2016

Digital Signal Processing (Undergraduate, yr. 4).
Electrical & Computer Engineering Department, Western University, London, Ontario, Canada.

**Teaching Assistant** 09/2015 to 12/2015

Introductory Magnetic Resonance (Graduate).
Physics Department, Western University, London, Ontario, Canada.

- Designed five assignment packages to facilitate the internalization of the concepts covered throughout the course.

**Head Teaching Assistant** 01/2015 to 04/2015

Programming Fundamentals for Engineers (Undergraduate, yr. 1).
Electrical & Computer Engineering Department, Western University, London, Ontario, Canada.

- Designed laboratory activities and quiz and examination material for the course (250 students and 18 TAs).
- Administrative duties including TA and resource allocation and addressing of the concerns raised by the students and the TA.

**Teaching Assistant** 09/2013 to 12/2014

Programming Fundamentals for Engineers (Undergraduate, yr. 1).
Electrical & Computer Engineering Department, Western University, London, Ontario, Canada.

**Teaching Assistant** 09/2012 to 04/2013

Anatomy and Physiology (Undergraduate, yr. 3).
Health Sciences Department, McMaster University, Hamilton, Ontario, Canada.

- Conducted hands-on tutorials and laboratory component of the course using physiological models and cadaveric specimens.

**Teaching Assistant** 09/2011 to 12/2011

Cellular Bioelectricity (Undergraduate, yr. 4).
Electrical & Computer Engineering Department, McMaster University, Hamilton, Ontario, Canada.

- Validated the tutorial and laboratory assignments by developing the solutions.
Publications

Total of 6; 3 published, 2 under review, 1 non-refereed

Published Papers


Papers Under Review


Non-refereed Publications


Conference Proceedings


• Wing Marques dos Santos, A., Hosseini, Z., Drangova, M., Rudko, D.A., Matusinec, J.A., Menon, R., Kremenchutzy, M., Multi-Parametric MRI at 7 T Enables Differentiation of MS and Age-Related White Matter Lesions, (2017), Canadian Neurological Sciences Federation, Vancouver BC, Canada (Poster presentation) June 20-23, 2017


• Hosseini, Z., Liu, J. Drangova, M., Details and Contrast in Local Frequency Shift Maps are Preserved when Post-Processing Individual Channel Phase Images Prior to Channel Combination, (2016), Canadian Arrhythmia Network of Canada, Calgary, Alberta, Canada. (Poster presentation) September 16-18, 2016


• Matusinec, J.A., Hosseini, Z., Liu, J., Rudko, D.A., Quinn, M., Kremenchutzy, M., Menon, R., Drangova, M., High Percentage of MS Lesions Found to Have a Central Vein Using Single Slice


**Organizational Activities**

- Co-coordinator for the second iteration of the Secret Sessions for the 26th Annual meeting of the International Society of Magnetic Resonance in Medicine. **Current**

- Abstract reviewer for the 26th meeting of the International Society of Magnetic Resonance in Medicine. **December 2017**

- Organizer and co-chair of the Employer Panel Session, the inaugural Secret Session, for the 25th Annual meeting of the International Society of Magnetic Resonance in Medicine. **April 2017**

- Abstract reviewer for the 25th meeting of the International Society of Magnetic Resonance in Medicine. **December 2016**

- Founder & host, Reconstruction Club, Robarts Research Institute. **(07/2015 to 07/2016)**

- Founder & organizer, MRI journal club, Robarts Research Institute. **(07/2015 to 07/2016)**

- Graduate Student Representative, Western University. **(05/2014 to 05/2015)**