Inaccurate Radiofrequency Field Amplitudes in Quantitative Magnetization Transfer Imaging

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Preface

The original research presented in this Ph.D. thesis is composed of the following three journal articles:

1. **Mathieu Boudreau**, Christine L. Tardif, Nikola Stikov, Wayne Lee, John G. Sled, G. Bruce Pike, “*B1 Mapping for Bias-correction in Quantitative T1 Imaging of the Brain at 3 Tesla Using Standard Pulse Sequences*”, Journal of Magnetic Resonance Imaging, doi:10.1002/jmri.25692 (2017)
2. **Mathieu Boudreau**, Nikola Stikov, G. Bruce Pike, *“B1-Sensitivity Analysis of Quantitative Magnetization Transfer Imaging”*, Magnetic Resonance in Medicine, doi:10.1002/mrm.26673 (2017).
3. **Mathieu Boudreau** and G. Bruce Pike, *“B1-Sensitivity Analysis of Quantitative Magnetization Transfer Imaging”*, Submitted to Magnetic Resonance in Medicine.

This thesis was written with the assumption that its readers already have a good foundation of MRI physics, the details of which are not presented here. Additional material to bridge the gap between basic MRI physics and the advanced quantitative MRI concepts required for understanding the original research work done in this thesis is presented in the Background chapter.

Contribution of Authors

I am the first author of the three manuscripts included in this thesis. As such, I designed the studies, acquired the data, processed and analyzed the data, wrote (or adapted) the majority of the simulation and analysis code needed, and wrote the manuscripts. The contributions of my co-authors of these articles are listed below.

* **Christine L. Tardif, PhD:** Previously implemented some of the pulse sequence protocols used (Actual Flip angle Imaging and spoiled Variable Flip Angle) as well as some data analysis code (Bloch-Siegert shift). Provided guidance during the planning stage of the study (Chapter 3). Edited the manuscript prior to submission (Chapter 3).
* **Nikola Stikov, PhD:** Provided general guidance during throughout the studies (Chapters 3 and 4). Provided some data analysis code (Variable Flip Angle and Actual Flip angle Imaging). Edited the manuscripts prior to submission (Chapter 3 and 4).
* **John G. Sled, PhD:** Assisted in the implementation of the echo-planar imaging B1 mapping sequence on our scanner (Chapter 3). Edited the manuscript prior to submission (Chapter 3).
* **Wayne Lee, MSc:** Assisted in the implementation of the echo-planar imaging B1 mapping sequence on our scanner (Chapter 3). Edited the manuscript prior to submission (Chapter 3).
* **G. Bruce Pike, PhD:** Overall supervision, mentorship, guidance, assistance, and feedback throughout all the stages of the projects presented in this thesis. Edited all manuscripts and the thesis prior to submission.

Other Publications

The following list of peer-reviewed articles and conference presentations were also produced over the course of this Ph.D. degree, but are not included in the thesis. In addition to the three first-authored manuscripts included this thesis, these other publications total five co-authored journal articles, five first-authored conference presentations, and three co-authored conference presentations.

* J.S.W. Campbell, I.R. Leppert, S. Narayanan, **M. Boudreau**, T. Duval, J. Cohen-Adad, G.B. Pike, N. Stikov, *“Promise and pitfalls of g-ratio estimation with MRI”*, Neuroimage, doi:10.1016/j.neuroimage.2017.08.038 (2017).
* M. Mclean, M.E. MacDonald, R.M. Lebel, **M. Boudreau**, B. Pike, *“Accelerated z-Spectrum Imaging”*, Oral, International Society for Magnetic Resonance in Medicine Meeting (2017).
* J. Campbell, I.R. Leppert, **M. Boudreau**, S. Narayanan, T. Duval, J. Cohen-Adad, G.B. Pike, N. Stikov, *“Myelin g-ratio imaging: promises and pitfalls”*, Poster, International Society for Magnetic Resonance in Medicine Meeting (2016).
* J.-F. Cabana, Y. Gu, **M. Boudreau**, I.R. Levesque, Y. Atchia, J.G. Sled, S. Narayanan, D.L. Arnold, G.B. Pike, J. Cohen-Adad, N. Stikov, *“Quantitative Magnetization Transfer Imaging Made Easy with qMTLab: a Software for Data Simulation, Analysis and Visualisation”*, Concepts in Magnetic Resonance Part A, 44A: 263–277 (2016).
* N. Stikov, J.S.W. Campbell, T. Stroh, M. Lavalée, S. Frey, J. Novek, S. Nuara, M.-K. Ho, B.J. Bedell, R.F. Dougherty, I.R. Leppert, **M. Boudreau**, S. Narayanan, T. Duval, J. Cohen-Adad, P.-A. Picard, A. Gasecka, D. Côté, G.B. Pike, *“In vivo histology of the myelin g-ratio with magnetic resonance imaging”*, NeuroImage, 118:397-405 (2015).
* N. Stikov, J.S.W. Campbell, T. Stroh, M. Lavalée, St. Frey, J. Novek, S. Nuara, M.-K. Ho, B.J. Bedell, R.F. Dougherty, I.R. Leppert, **M. Boudreau**, S. Narayanan, T. Duval, J. Cohen-Adad, P.-A. Picard, A. Gasecka, D. Côté, G.B. Pike, *“Quantitative analysis of the myelin g-ratio from electron microscopy images of the macaque corpus callosum”*, Data in Brief, 4:368-373 (2015).
* N. Stikov, **M. Boudreau**, I.R. Levesque, C.L. Tardif, J. Barral, G.B. Pike, “*On the Accuracy of T1 Mapping: Searching for Common Ground.*” Magnetic Resonance in Medicine, 73:514-522 (2015).
* **M. Boudreau**,N. Stikov, G.B. Pike, *“B1-Sensitivity Analysis of qMT”*, Poster, International Society for Magnetic Resonance in Medicine Meeting (2015).
* N. Stikov, J. Campbell, **M. Boudreau**, S. Narayanan, T. Stroh, S. Nuara, J. Novek, S. Frey, M.-K. Ho, B. Bedell, G.B. Pike, “*In vivo histology of the myelin g-ratio”*, Poster, OHBM Annual Meeting (2014).
* **M. Boudreau**, N. Stikov, G.B. Pike, *“A B1-Insensitive qMT Protocol”*, Poster, International Society for Magnetic Resonance in Medicine Meeting (2014).
* **M. Boudreau**, C. Tardif, N. Stikov, G.B. Pike, *“A Comparison of B1 Mapping Methods for T1 Mapping at 3T”*, E-Poster, International Society for Magnetic Resonance in Medicine Meeting (2014).
* **M. Boudreau**, N. Stikov, G.B. Pike, *“Effect of Different T1 Mapping Techniques on a Quantitative Magnetization Transfer MRI Biomarker for Myelin Density”*, Poster, endMS Conference (2013).
* **M. Boudreau**,N. Stikov and G.B. Pike, *“T1 Mapping: Should We Agree To Disagree?”*, Poster, International Society for Magnetic Resonance in Medicine (2013).

Abstract

* Paragraph 1
  + Quantitative MRI promise more specificity relative than conventional imaging techniques for several diseases.
  + MS is a disease that has benefited significantly from the advent of MRI, both for diagnostic purposes and to study the disease in a research setting.
  + Quantitative MT improves on conventional imaging by probing the myelin content typically unobservable, providing quantitative measurements (pool-size ratio) that correlate strongly with myelin density.
* Paragraph 2
  + The focus of this thesis was exploring the sensitivity of one of these supplementary quantitative maps required in qMT, B1, and how qMT’s sensitivity to this parameter can be minimized or potentially eliminated.
  + Aim of paper 1 and quick overview.
  + Aim of paper 2 and quick overview
  + Aim of paper 3 and quick overview.
* Paragraph 3
  + Overall conclusion and impact.
  + Future work

Résumé

* Traduction française.

Original Contributions

The original contributions of the thesis are:

1. Demonstration that rapid whole-brain B1 mapping using a standard product sequence provides sufficient quality B1 maps to produce accurate variable flip angle T1 maps in white matter, of similar quality to other widely used advanced B1 mapping methods that require pulse sequence programming implementations.
2. Characterization of the sensitivity of quantitative magnetization transfer (qMT) imaging to B1-inaccuracies, and its dependence on the choice of T1 mapping method.
3. Discovery and demonstration that a robust measurement of the qMT biomarker for myelin density (pool-size ratio) can be maintained in the presence of large B1 inaccuracies if the variable flip angle T1 mapping method is used in the qMT processing pipeline.
4. Development and validation of an iterative optimization strategy of qMT acquisition protocols for minimized sensitivity to B1-inaccuracies, potentially eliminating the requirement of B1 maps from qMT acquisition protocols.

# *Introduction*

## Motivation

* Paragraph 1
  + Quantitative MRI is a subset of MRI techniques which measure information on physical sample or system quantities.
  + Unlike most clinical MRI data, which only provides qualitative images in which to make some conclusion image intensities must be compared in contrast to other image regions or the same region in an image acquired at a different time, quantitative MRI provides voxel-wise information about tissues or physical properties, which can then be used to infer information about biological properties in that voxel.
  + Although the majority MRI images are qualitative in nature, meaning that the signal intensity of a pixel are due to a combination of several factors which aren’t all precisely known and likely vary between scanners or acquisition protocols, quantitative MRI promises more specificity, accuracy, and reproducibility of biological or system parameters, which is particularly of interest in a research setting.
  + If clinical MRI is said to be a camera capable of taking pictures inside the brain, quantitative MRI is the scientific instrument analogue of such a comparison.
* Paragraph 2
  + Most diseases which widely use clinical MRI as a diagnostic tool could benefit from quantitative MRI to study their biological origin and progression. One disease which has widely benefited from the development of MRI is multiple sclerosis (MS), an autoimmune disease of the central nervous system resulting in the destruction of myelin surrounding axons. The loss of myelin, which acts as an electrical insulator, inhibits signal transmission between neurons, resulting in a physical or cognitive impairments.
  + MS is a disease that has benefited significantly from the advent of MRI, both for diagnostic purposes and to study the disease in a research setting. However, clinical image data of MS is not specific to myelin loss, and can have confounding factors such as edema [1].
  + Quantitative MT improves on conventional imaging by probing the myelin content typically unobservable, providing quantitative measurements (pool-size ratio) that correlate strongly with myelin density.
* Paragraph 3
  + To be able to estimate quantitative values (e.g. pool-size ratio) from quantitative MT data, several MT images must be acquired (~10+) to fit the data for all the parameters in the model (~3-5 independent parameters).
  + Three additional calibration measurements are also necessary: a B0 map to account for main field inhomogeneity, a B1 map for radio-frequency inhomogeneity, and a T1 map to constrain a subset of the fitting parameters.
  + In a general sense, the absence or inaccurate estimate of any of these measurements will likely result in an error in the estimate of one or more quantitative MT fitting parameters.
  + Since the calibration measures do not have perfect accuracy and can be sensitive to different error sources (which varies between the techniques used to measure these maps), it is desirable to reduce the sensitivity of the qMT fitting method to inaccuracies in calibration techniques (e.g. from noise or small artifacts).
  + However, qMT is not the only technique which require these calibration measurements. Some of the calibration methods can also require other calibration maps. For example, the widely used whole-brain T1 mapping technique Variable Flip Angle (VFA) also depends on B1 maps as a calibration measurement, unlike the gold standard for T1 mapping, inversion recovery (IR), which is typically limited to be a single-slice technique due to long acquisition times. Therefore, the error propagation due to inaccuracies in B1 maps will propagate to the qMT fitting parameters differently depending on if the T1 map is B1-dependent (e.g. VFA) or B1-independent (e.g. IR).

## Objectives

* Paragraph 1
  + Broad objectives of this thesis (in bold)
  + What this work proposes
  + Rationale?
* Paragraph 2: bullet points
  + Action description of paper 1
  + Action description of paper 2
  + Action description of paper 3

## Thesis Outline

* Paragraph 1
  + Description of Chapter 2
  + Description of Chapter 3 (i.e. This chapter contains the first manuscript titled “\_\_”, which was submitted and accepted to the Journal of Magnetic Resonance Imaging, and is currently published in Early View. This work presents \_\_\_.
  + Description of Chapter 4
  + Description of Chapter 5
  + Description of Chapter 6 (summary & future work)

# *Background*

## Multiple Sclerosis

### Overview

* Paragraph 1: Overview of the disease from a medical perspective
  + Population/risk information (Canada/geography, gender, rate)
  + Disease symptoms (typical initial symptoms at diagnosis, lifelong progression)
  + Treatments (drugs/therapy, no cure)
* Paragraph 2: Overview of the disease from a biological perspective
  + Basics (very) of the autoimmune inflammatory response
  + Resulting damage due to this inflammatory response (demyelination, axonal loss, etc).
  + Current big-picture open questions (inside-out vs outside-in, grey matter lesion origin).

### Role of MRI in MS

## Quantitative MR Imaging

### Tissue Properties (T1, T2)

*Longitudinal Relaxation Time (T1)*

* Paragraph 1: Very brief overview of what T1 is, and how it can change.
* Paragraph 2: Inversion Recovery and Look-Locker
* Paragraph 3: Actual Flip angle Imaging and Bloch Siegert

### Field Properties (B0, B1)

* Paragraph 1: Very brief overview of what B1 is, and how it can change.
* Paragraph 2: Double Angle imaging based methods.
* Paragraph 3: Whole-brain methods: Actual Flip angle Imaging and Bloch Siegert.

## Magnetization Transfer Imaging

### Two-Pool Model of MT



Figure 2‑1. Two-pool model of the magnetization transfer effect. (\*\*From Henkelman 2001. Placeholder, will make new figure with the correct variables that will match those in later equations\*\*).

### MTR and MTsat

*Magnetization Transfer Ratio (MTR)*

* Paragraph 1
  + MTR, most commonly used MT technique for clinical applications/research



Figure ‑. Pulsed MT-weighted spoiled gradient echo (SPGR) pulse sequence for a Gaussian MT pulse shape. (\*\*From Sled 2001. Either make a similar figure or get Wiley rights for thesis use\*\*).

* + Calculated using On-Off subtraction/normalization

|  |  |
| --- | --- |
|  | **(2-1)** |

* + Disadvantages
    - Not specific to the pool-size ratio/quantifying the restricted pool size
    - Will also vary with T1, which can vary due to other biological processes, such as edema [1].
    - Can be affected by other pulse sequence-related parameters (B1 inaccuracy/profile, through both RF pulses). However some work has proposed ways to correct for this [2,3].
* Paragraph 2: Applications
  + Despite some drawbacks.

*Magnetization Transfer Saturation (MTsat)*

* Paragraph

### Quantitative Magnetization Transfer Imaging

* Paragraph 1

|  |  |
| --- | --- |
|  | **(2-2)** |
|  | **(2-3)** |
|  | **(2-4)** |
|  | **(2-5)** |
|  | **(2-6)** |

* Where G is a spectral line shape function.
* The two line shape typically used are Gaussian for solids and gels (e.g. used for imaging phantoms) and super-Lorentzian for tissues [4].
* Paragraph 2
  + An exact analytical solution to Eqs. (2.2-2.6) cannot be derived, unless a very long MT pulse (5+ seconds) is used to drive (Eqs. 2.4) and (2.5) to a steady state within a single TR [5]. High SAR and scan time does not make this feasibly in vivo.
  + To make the imaging sequence feasible in vivo, a pulse MT-Weighted SPGR approach is typically used, as for MTR.
  + Solving these equations are too numerically difficult,

# *B1 Mapping for Bias-Correction in Quantitative T1 Imaging of the Brain at 3T Using Standard Pulse Sequences*

## Preface

* Paragraph 1
  + Why VFA T1 mapping needs whole-brain B1 maps
  + Mini-history of whole-brain B1 maps
  + General technical challenges encountered between implementing different B1 maps.
* Paragraph 2
  + Where manuscript was submitted/published.
  + One-line description of what is done in the paper
  + Reasoning behind objectives the paper
    - To compare how a whole-brain B1 method implement without pulse-sequence programming compared.
    - Target audience is different than other two manuscripts, however results are useful to a broader quantitative MR audience.
  + Impact of this paper
    - First two compare the 2 major rapid whole-brain B1 mapping methods with one easily implementable on scanners.
    - Only known manuscript that compares these methods both with and without B1 filtering, which may reduce and/or increase voxel-wise/regional inaccuracies. The different artifacts observed in these implementation also show examples of potential inaccuracies that can occur in the context qMT later on, even though it is not explicitly mentioned in this manuscript.

**B1 Mapping for Bias-Correction in Quantitative T1 Imaging of the Brain at 3T Using Standard Pulse Sequences**

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## Abstract

**Purpose:** B1 mapping is important for many quantitative imaging protocols, particularly those that include whole-brain T1 mapping using the variable flip angle (VFA) technique. However, B1 mapping sequences are not typically available on many magnetic resonance imaging (MRI) scanners. The aim of this work was to demonstrate that B1 mapping implemented using standard scanner product pulse sequences can produce B1 (and VFA T1) maps comparable in quality and acquisition time to advanced techniques.

**Materials and Methods:** Six healthy subjects were scanned at 3.0T. An interleaved multislice spin-echo echo planar imaging double-angle (EPI-DA) B1 mapping protocol, using a standard product pulse sequence, was compared to two alternative methods (actual flip angle imaging, AFI, and Bloch-Siegert shift, BS). Single-slice spin-echo DA B1 maps were used as a reference for comparison (Ref. DA). VFA flip angles were scaled using each B1 map prior to fitting T1; the nominal flip angle case was also compared.

**Results:** The pooled-subject voxelwise correlation (*ρ*) for B1 maps (BS/AFI/EPI-DA) relative to the reference B1 scan (Ref. DA) were *ρ* = 0.92/0.95/0.98. VFA T1 correlations using these maps were *ρ* = 0.86/0.88/0.96, much better than without B1 correction (*ρ* = 0.53). The relative error for each B1 map (BS/AFI/EPI-DA/Nominal) had 95th percentiles of 5/4/3/13%.

**Conclusion:** Our findings show that B1 mapping implemented using product pulse sequences can provide excellent quality B1 (and VFA T1) maps, comparable to other custom techniques. This fast whole-brain measurement (~2 min) can serve as an excellent alternative for researchers without access to advanced B1 pulse sequences.

## Introduction

Radiofrequency transmit field (B1+) maps, typically termed “B1 maps” for brevity, are necessary in several quantitative magnetic resonance imaging (MRI) applications, such as specific absorption rate (SAR) estimation, magnetization transfer (MT) imaging, and quantitative T1 mapping. Electrical properties tomography (EPT) relies on quantitative B1 maps to calculate the conductivity (*σ*) and permittivity (*ε*) of tissue in vivo [6], and is an essential step in the estimation of local SAR [7]. MT techniques probe the macromolecular content of tissue, and are often used as an index of myelination in diseases such as multiple sclerosis [8]. Unaccounted B1 inhomogeneity in certain MT experiments can be an important source of error. For example, B1-correction has been shown to improve the quality of MT ratio (MTR) maps [2], due to the sensitivity of MTR to the MT preparation RF pulse power. The longitudinal relaxation time (T1), one of the fundamental quantities in MRI, is an important input for several other data processing pipelines, such as dynamic contrast enhancement (DCE) imaging [9,10] and quantitative MT [11]. Although some whole-brain T1 mapping methods boast first-order insensitivity to RF field inhomogeneities [12], others—notably the variable flip angle (VFA) method [13]—are inherently sensitive to inaccuracies in the excitation flip angles (FA). B1 maps can greatly benefit the accuracy and precision of VFA T1 maps at high clinical field strengths, (eg, 3T), where large B1 amplitude variations are typical in loaded coils [14] (eg, ±30% for the human brain). The broad range of B1 applications highlights the need for accurate B1 mapping techniques, while also balancing other competing interests such as acquisition speed and ease of implementation, particularly in the context of multisite studies.

Substantial efforts have been made to develop rapid whole-brain B1 mapping techniques in the last decade. Previously, conventional B1 mapping was done using some variations of the double angle (DA) method, which consists of two separate gradient-echo or spin-echo measurements with longitudinal magnetization recovery in which the second measurement is performed with double the excitation pulse flip angle [15]. However, conventional DA requires very long repetition times, and was mostly used for single-slice imaging. Advanced pulse sequences have been developed to accommodate whole-brain B1 mapping. Two of the most popular techniques are actual flip angle imaging (AFI) [16] and Bloch-Siegert shift (BS) mapping [17]. AFI is a steady-state 3D spoiled gradient echo (SPGR) B1 mapping method based on a dual-TR acquisition (TR2 = N\*TR1, where N is typically an integer on the order of 5), and has been shown to be T1-insensitive for most tissues. BS is a phase-sensitive slice-selective B1 mapping method using a modified SPGR sequence; a high amplitude off-resonance RF pulse between the excitation and readout events induces a phase-shift proportional to the B1 amplitude. Currently, an important limitation of these methods is their lack of widespread availability as a standard product sequence on clinical scanners. These pulse sequences are typically implemented onsite, a time-consuming process that require pulse sequence programming expertise, and is susceptible to site-specific implementation issues.

The lack of a readily available whole-brain B1 mapping pulse sequence is a challenge to many researchers, particularly in the context of multi-center studies, resulting in the omission of B1 mapping in quantitative imaging protocols that would significantly benefit from its inclusion. One such quantitative MRI method is VFA T1 mapping, which estimates T1 by fitting the gradient echo images to a function of flip angles, making it inherently sensitive to B1 inaccuracies. For example, using a VFA sequence with a 15 msec TR and two flip angles (3° and 20°) [18], an underestimation of the nominal flip angles by 1/5/10/20% results in an overestimation of the fitted T1 by 2/11/24/57%. Thus, errors in B1 induce at least twice as large errors in T1, and the error increases nonlinearly. Notably, DCE imaging protocols that use VFA T1 mapping often omit B1 correction [9,19], even though B1 maps have been shown to substantially improve the accuracy of DCE [10,20]. Citing the unavailability of advanced B1 mapping sequences at their site, other researchers have developed techniques to simulate B1 maps by normalizing the VFA T1 image [21] using postprocessing image analysis algorithms [22]. However, a systemic bias in B1 values (of unknown size) could still be present using this type of image analysis approximation, so measuring B1 directly should improve the accuracy of the T1 maps.

The purpose of this work was to evaluate the quality of a fast and simple whole-brain B1 mapping protocol implemented using a standard EPI pulse sequence. An interleaved multislice spin-echo EPI readout standard product pulse sequence was used to map B1 with the DA method (EPI-DA) [23-25] in a group of healthy human subjects. EPI-DA has not gained as much attraction in comparison to AFI and BS, due to their demonstrated robustness against specific characteristics (eg, large T1 values, B0 inhomogeneity) and their compatibility with higher fields systems that use parallel transmit coils. Yet the ease of implementation of EPI-DA or other similar techniques (eg, fast spin-echo DA [3]) may make them a good alternative to advanced B1 methods, which require custom implementations and pulse sequence programming expertise.

## Materials and Methods

All measurements were performed on a 3.0T whole-body MRI scanner (Magnetom TIM TRIO, Siemens, Erlangen, Germany) using a 32-channel phased-array receive-only head coil and whole-body transmit coil.

### Measurements

Healthy adult volunteers were scanned in compliance with the guidelines of the Institutional Ethics Committee, and gave written informed consent prior to being scanned for this study. Six healthy adult volunteers were scanned (three females, three males, 29 ± 3 years old). Axial slices were acquired (for 2D measurements) or extracted (from 3D/multislice measurements, with orientations matching the single-slice 2D measurements) parallel to the anterior and posterior commissure (AC-PC) plane, superior to the corpus callosum.

Quantitative analyses of the B1 and T1 maps were limited to voxels comprised of white matter (WM), consistent with previous work [3,26]. Two reasons factored into this decision. First, as B1 maps are typically acquired at low resolution, partial volume effects occur near cortical gray matter (GM) regions and areas adjacent to ventricles. Therefore, there is an insufficient number of voxels that contain pure GM. Second, the partial volume effects in regions containing cerebrospinal fluid (CSF) result in substantially longer mean T1 values (2–5 sec), so T1-sensitive artifacts will vary in severity between B1 methods that have different intrinsic sensitivity to long T1 and CSF flow. Adequately comparing B1 methods in GM and CSF is a specialized topic that requires higher resolution and/or longer scan-times, which is beyond the scope of this work.

Whole-brain T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) 3D volumes (1 × 1 × 1mm3) were acquired: repetition time (TR) = 2300 msec, echo time (TE) = 3.32 msec, inversion time (TI) = 900 msec, iPAT factor = 2 (GRAPPA), bandwidth (BW) 5230 Hz/Px, 5 min 30 sec scan time. Tissue classification maps (WM, GM, CSF) were obtained via Intensity Normalized Stereotaxic Environment for the Classification of Tissue (INSECT)24 using the MP-RAGE data with the ICBM-152 atlas. All necessary preprocessing steps (nonuniformity correction, skull-stripping, etc.) were done using the standard pipeline of the MINC Tool Kit (v. 1.9.11, McConnell Brain Imaging Center, Montreal Neurological Institute, Montreal, Canada). Tissue percentage maps (WM, GM, CSF), at the low resolution (2 × 2 × 5mm3) for which the quantitative maps (B1, T1) were acquired, were estimated by calculating the ratio of high-resolution INSECT tissue-classified voxels (1mm3) that had the center of their voxels located within the corresponding 2 × 2 × 5mm3 voxels. using a majority voting analysis (75% threshold). Figure 3‑1 shows a tissue classification maps of WM, GM, and CSF for a healthy subject. The classification maps show that for a 2 × 2 × 5mm3 resolution, very few voxels consisted of single-tissue GM or CSF, reaffirming our reasoning to exclude these areas in our study. To generate the WM masks for each subject, a >75% binary threshold was applied to the tissue percentage maps; since there can be 20 high-resolution voxels (1mm3) that have their centers located in a low-resolution voxels (2 × 2 × 5mm3), a >75% threshold represents the case that no more than four non-WM INSECT tissue classified voxels (out of 20) are located within a voxel of the WM mask. Lastly, note that the WM mask were only used to mask-out non-WM voxels after the B1 maps were calculated, and are not required to calculate any of the B1 maps described in the following section.



Figure ‑.Tissue classification maps (black = 0%, gray = 100%) of a healthy subject calculated from INSECT [27] using MP-RAGE T1w data (1 × 1 × 1mm3) and resampled to 2 × 2 × 5mm3. Tissue percentages were estimated by calculating the ratio of INSECT tissue-classified voxels (1mm3) for a given tissue type (WM, GM, CSF) that were located inside the corresponding low-resolution voxels (2 × 2 × 5mm3), for which the quantitative maps (B1, T1) were acquired.

### B1 Mapping

Three rapid B1 mapping techniques (Bloch-Siegert shift, BS; actual flip angle imaging, AFI; echo planar imaging double angle, EPI-DA) were acquired with acquisition protocols that matched their original publications values as closely as possible. A single-slice double angle B1 map was acquired as a reference (Red. DA), as is typical [17,28]. Lastly, a uniform B1 map of value 1 normalized units (n.u.), noted in short-hand as “Nominal,” was generated to represent the case when VFA T1 values are fitted using the nominal flip angles of its acquisition protocol.

*BLOCH-SIEGERT (BS).* Single-slice BS B1 maps [17] were acquired using an in-house-developed pulse sequence: TE/TR = 15/100 msec, excitation flip angle (*α*) = 25°, field-of-view (FOV) = 25.6 × 17.6 cm2, 2 × 2mm2 in-plane resolution, 128 × 88 matrix (readout/phase), 5mm slice thickness, 1 slice, 8 msec Fermi Pulse of 500° at 64 kHz off-resonance and phase-shift constant KBS = 74.01 rad/G2, 19 sec scan time.

*ACTUAL FLIP ANGLE IMAGING (AFI).* AFI B1 maps were acquired using an in-house-written slab-selective 3D AFI pulse sequence with optimal RF and gradient spoiling [16,29]: TE/TR1/TR2 3.53/20/100 msec, *α* = 60°, BW = 260 Hz/pixel, FOV = 25.6 × 17.6 × 16.0 cm3, 2 × 2 × 5mm3 resolution, 128 × 88 × 32 matrix (readout/phase/3D), spoiling gradient moment (AG) = 450 mT∙ms/m and RF phase increment (*ψ*) = 39°, 5 min 38 sec scan time.

*EPI DOUBLE ANGLE (EPI-DA).* Interleaved multislice spin-echo EPI-DA B1 maps with whole-brain coverage were acquired using a standard product EPI pulse sequence with a protocol similar to that of Wang et al [23], except with 180° refocusing pulses (the scanner default for this sequence). Since our sequence used (*α*, 180°) and (2*α*, 180°) excitation-refocusing pulses, instead of (*α*, 2*α*) and (2*α*, 4*α*) in the original article, the equation used to calculate EPI-DA B1 was [3,15]:

|  |  |
| --- | --- |
|  | **(3-1)** |

where *α* is the nominal flip angle (double for the second measurement), *α*corr is the true flip angle experienced by the tissue at that voxel location, *I1* and *I2* are the image voxels magnitudes for *α* and 2*α* acquisition, respectively. The EPI-DA acquisition protocol was: TE/TR = 46/4000 msec, *α*/2*α* = 60°/120°, FOV = 25.6 × 25.6 cm2, 2 × 2mm2 in-plane resolution, 128 × 128 matrix (readout/phase), 5mm slice thickness, 27 slices, EPI factor = 9 (15 shots of 9 k-space readout line acquisitions), echo spacing = 4.18 msec, fat saturation on, BW = 250 Hz/px, 2 min 16 sec scan time. Standard automated shimming was performed as with all other sequences (shim currents adjusted using a 3D phase map); no additional adjustments of the static or gradient fields were necessary.

Fast EPI sequences, such as the widely used single-shot implementations, can be susceptible to a wide range of artifacts that lead to a degradation of image quality. Several strategies are incorporated in this protocol to mitigate these artifacts, while still using a readily available scanner sequence and maintaining rapid overall acquisition. A segmented multishot EPI approach increases the effective BW in the phase-encode direction, which reduces distortion artifacts that are typically prevalent in areas of high B0 inhomogeneity such as near the sinuses. Blurring is also reduced, due to decreased T2\* modulation in each acquired echo train. Acquiring the B1 map at a low in-plane resolution (2 × 2mm2) also means smaller readout gradient amplitudes are used, reducing potential eddy current artifacts (eg, ghosting). Other fast imaging techniques, such as fast spin-echo, have also been adapted for whole-brain double angle B1 mapping [3]. These methods could offer different imaging benefits as alternatives to EPI; however, such a comparison is outside the scope of the present work.

*REFERENCE DOUBLE ANGLE (REF. DA).* Single-slice double angle B1 maps were acquired using a spin-echo sequence as a reference measurement for the other B1 mapping techniques: TE/TR 12/1550 msec, *α* = 60°/120°, FOV = 25.6 × 17.6 cm2, 2 × 2mm2 in-plane resolution, 128 × 88 matrix (readout/phase), 5mm slice thickness, 1 slice, slice-selective excitation and 180° refocusing pulses, and BW = 130 Hz/pixel, 4 min 28 sec scan time. The flip angles were chosen to match the EPI-DA sequence. As Ref. DA is the most time costly of all the compared methods (4 min 38 sec), a shorter TR was chosen to reduce the acquisition time of the entire protocol while maintaining sufficient accuracy in WM [18]. The TR is sufficiently long to allow almost complete relaxation of the WM signal, which we are evaluating.

Overall, each pulse sequence had the following effective acquisition time per slice: Ref. DA: 4 min 38 sec/slice, BS: 19 sec/ slice, AFI: 11 sec/slice (3D measurement), EPI-DA: 5 sec/slice (interleaved multislice sequence produced 27 slices in 68 sec per flip angle acquisition).

### T1 Mapping

VFA is a widely used T1 mapping technique; spoiled gradient echo images are acquired using multiple (usually 2–5) excitation flip angles, each using the same TR. VFA T1 maps were acquired using a standard product spoiled 3D gradient echo pulse sequence: 2 × 2 × 5mm3 resolution, 128 × 88 × 32 matrix (readout/phase/3D), TE/TR 2.89/15 msec, *α* = 3°/20°, BW = 390 Hz/pixel, default manufacturer slab-selection and RF spoiling modes, 1 min 28 sec scan time.

### Data Analysis

B1 and T1 maps were processed from the MRI data using custom MATLAB code (MathWorks, Natick, MA). Each B1 map was used to scale the VFA nominal flip angles voxelwise prior to fitting for T1. T1 maps were estimated from linear least square fitting to the SPGR equation [18].

The B1 amplitude is expected to be a smooth slowly varying function, particularly in the brain [22]. As such, B1 maps are commonly filtered to reduce noise and minor artifacts [16,28]. Subjective assessment of the images was performed by two of the coauthors (coauthors #3 and #6) who were blinded to the acquisition method used for each dataset. They provided a brief subjective evaluation of any artifacts they observed. A consensus opinion was then formed via discussion between all coauthors. In addition to comparing unfiltered (raw) B1 maps (as well as in the VFA T1 analysis), we repeated the data analysis using filtered B1 maps. Single slice B1 maps were filtered (prior to WM masking) using the MATLAB function *roifilt2* and skull-stripped brain masks (all tissues). A Gaussian kernel (*fspecial*) was used with a full-width-half-maximum of 10 × 10mm2 (sigma = 4.2466) and a 7 × 7 voxel kernel matrix.

The voxelwise WM B1 and T1 data for each method (Ref. DA, BS, AFI, EPI-DA) and the nominal flip angle case (Nominal) were pooled together (all subjects) for data analysis. Histograms of the unfiltered B1 maps and accompanying fitted T1 values were calculated to investigate the presence of potential systemic biases or spreading between methods [3,18]. Linear regression analysis of B1 and T1 (Pearson correlation and linear fit values) was performed for each B1 method relative to the Ref. DA B1 values. The linear regression analysis was performed using both the unfiltered and the Gaussian filtered B1 data.

## Results

Pooled-subject histograms of unfiltered B1 map values from WM regions are shown in Figure 3‑2a. There is an overlap between the different B1 histograms; the differences in statistical modes (ΔMode) for each method relative to Ref. DA were 3.6/1.5/3.8% (BS/AFI/EPI-DA). EPI-DA is the only method for which a small B1 histogram shift is qualitatively observable, which suggests the presence of a small systemic bias. The unfiltered B1 maps for a single subject are shown in Figure 3‑3b, along with their accompanying acquisition images in Figure 3‑3a. The signal-to-noise ratio (SNR) in a region-of-interest of WM was estimated across all subjects to be 240 ± 45 for Ref. DA, 98 ± 11 for BS, 170 ± 35 for AFI, and 130 ± 30 for EPI-DA. Linear regression statistics computed using the pooled voxelwise data for each unfiltered B1 map (BS, AFI, EPI-DA) relative to the Ref. DA measurement is presented in Table 3‑1. EPI-DA had the highest Pearson correlation coefficient relative to Ref. DA (*ρ* = 0.96) and a near-unity slope (*β* = 0.99); the BS B1 maps had the lowest correlation out of the three (*ρ* = 0.88). Table 3‑2 lists the mean and SD of voxelwise differences (%) in WM for each B1 method relative to Ref. DA. Overall, EPI-DA had a lower voxelwise percent differences SD than other methods for all subjects, except subject #6, where BS had a lower value.



Figure ‑. Normalized histograms of single-slice unfiltered B1 (a) and T1 (b) map values masked for WM in six healthy subjects. The abbreviation “n.u.” stands for normalized units.



Figure ‑. a: Acquisition images for each acquired B1 method: Ref. DA (reference single-slice double angle), AFI (actual flip angle imaging), BS (Bloch-Siegert shift), and EPI-DA (double-angle using an interleaved multislice EPI acquisition). b: Unfiltered single-slice B1 maps, and corresponding WM-masked VFA T1 maps fitted using flip-angles scaled voxelwise using each B1 map. The “Nominal” column represents VFA T1 fitting using no B1 correction (B1 = 1 n.u.).

The pooled-subject histogram analysis of WM T1 values is shown in Figure 3‑2b. Each measured B1 map resulted in narrower WM T1 histograms than for the Nominal case. The differences in statistical modes (ΔMode) for WM T1 between Ref. DA and BS/AFI/EPI-DA/Nominal were 2.5/ 1.0/5.0/5.0%, respectively. The width of the WM T1 distributions had more relative variation between methods than observed for the B1 histograms. EPI-DA had the largest ΔMode value (5%), but did not experience noticeable broadening relative to Ref. DA. However, BS clearly did suffer from broadening, yet much less severe than the Nominal case. The small reduction in EPI-DA WM T1 histogram statistical mode (Figure 3‑2b) is attributed to the small increase in the corresponding B1 histogram statistical mode (Figure 3‑2a). T1 correlations were lower relative to their respective B1 correlations, which was to be expected due to the B1-sensitivity of the VFA technique. Overall, EPI-DA T1 maps had the highest correlation relative to Ref. DA (*ρ* = 0.92), which was substantially better than for the Nominal case (*ρ* = 0.53). WM-masked T1 maps are shown for a single subject in Figure 3‑3. Large overestimations of T1 at the center of the slice are clearly seen for the Nominal case, unlike those using each measured B1 map.

Table ‑. Linear Regression Analysis of the Pooled WM-Masked B1 and T1 Values (Six Subjects) for Each Rapid B1 Method Relative to the Ref. DA Method

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | Unfiltered B1 Maps | | | Gaussian Filtered B1 Maps | | |
|  |  | Ref. DA | Nominal | BS | AFI | EPI-DA | BS | AFI | EPI-DA |
| B1 | **Pearson *ρ*** | --------- | N/A | **0.88** | **0.92** | **0.96** | **0.92** | **0.95** | **0.98** |
| Slope *β* | --------- | N/A | 0.97 | 1.01 | 0.99 | 0.96 | 0.99 | 1.01 |
| Intercept *y0* | --------- | N/A | 0.04 | -0.01 | 0.03 | 0.05 | 0.00 | 0.01 |
| T1 | **Pearson *ρ*** | --------- | **0.53** | **0.79** | **0.81** | **0.92** | **0.86** | **0.88** | **0.96** |
| Slope *β* | --------- | 0.95 | 0.99 | 0.89 | 0.94 | 0.97 | 0.92 | 0.98 |
| Intercept *y0* | --------- | 0.07 | 0.00 | 0.12 | 0.02 | 0.00 | 0.09 | -0.02 |

Table ‑. Mean and Standard Deviations of Voxelwise Percent Differences (%) of B1 and T1 Values in WM Relative to the Ref. DA Method for All Subjects

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Mean ± SD Voxel-wise Percent Differences (%) in White Matter | | | | | | |
|  | Subject # | Ref. DA | Nominal | BS | AFI | EPI-DA |
| B1 | 1 | --------- | N/A | 0.31 ± 3.47 | 0.47 ± 1.83 | 1.67 ± 1.43 |
| 2 | --------- | N/A | 3.34 ± 2.46 | -1.46 ± 2.40 | 2.41 ± 1.32 |
| 3 | --------- | N/A | 0.95 ± 2.24 | -0.44 ± 2.22 | 1.87 ± 1.49 |
| 4 | --------- | N/A | 1.57 ± 2.43 | -1.28 ± 3.12 | 0.15 ± 1.66 |
| 5 | --------- | N/A | -0.01 ± 3.61 | 0.63 ± 2.09 | 2.37 ± 1.45 |
| 6 | --------- | N/A | 2.07 ± -0.69 | -0.69 ± 3.07 | 1.76 ± 2.08 |
| T1 | 1 | --------- | -2.11 ± 12.12 | -0.30 ± 6.83 | -0.85 ± 3.78 | -3.27 ± 2.70 |
| 2 | --------- | 2.86 ± 10.96 | -6.25 ± 4.67 | 3.17 ± 5.07 | -4.64 ± 2.50 |
| 3 | --------- | 0.46 ± 10.64 | 2.10 ± 4.69 | 1.03 ± 4.66 | -3.72 ± 2.59 |
| 4 | --------- | 10.27 ± 14.19 | -3.01 ± 4.84 | 2.69 ± 6.60 | -0.54 ± 2.60 |
| 5 | --------- | 3.40 ± 11.01 | 0.32 ± 7.02 | -1.09 ± 4.16 | -4.53 ± 2.72 |
| 6 | --------- | -2.70 ± 10.54 | -3.86 ± 4.93 | 1.56 ± 6.70 | -3.39 ± 4.36 |

Artifacts in the unfiltered B1 maps differ between methods due to their differing acquisition pulse sequences (Figure 3‑3b). The sulci are visible in the B1 maps of both DA methods (Ref. DA and EPI-DA), unlike BS and AFI. In the ventricles, lower B1 values are present for Ref. DA and EPIDA relative to the other methods (Figure 3‑3b, Figure 3‑5). An open-ended fringe line (pole) was present in the Bloch-Siegert phase maps (Figure 3‑3a), due to out-of-phase multichannel image recombination [30], and may have caused some inhomogeneity in the Bloch-Siegert B1 maps in the posterior left hemisphere (Figure 3‑3b). This phase image artifact was present in all subjects. For BS, the inhomogeneities near the phase pole along with noisier B1 maps were likely contributing factors in the broadening of the WM T1 distribution (Figure 3‑2b). A ringing artifact affected the AFI B1 maps (Figure 3‑3b), although it is not easily seen in the raw AFI acquisition images themselves (Figure 3‑3a). However, by carefully adjusting the window/level (not shown), a small ringing artifact is present in both AFI MRI images. We observed this ringing in both the raw data and B1 maps of all subjects. If the ringing between both images is out-of-phase, the resulting B1 artifact may be amplified due to the nature of the AFI calculation, which requires a division of the two images. The original AFI work only presents their B1 maps postfiltering (8 × 8 × 16mm3 median filter); however, ringing can also be seen in their axial and coronal TR1 images (fig. 10a in Ref. [16]). Overall, these artifacts and noise in the unfiltered B1 maps likely contributed to lower correlations of B1 and T1 relative to the reference maps.



Figure ‑. Unfiltered (a) and Gaussian filtered (b) B1 maps of a single subject. (c) Relative differences between unfiltered and filtered maps shown as percent difference maps.

The unfiltered and Gaussian filtered B1 maps are shown for a subject in Figure 3‑4a,b, and the relative difference (%) between the two is shown in Figure 3‑4c. The Gaussian filter was effective at reducing noise in the maps, as well as in attenuating minor artifacts (eg, sulci in DA maps, “ringing” in AFI). The correlations and linear regression analysis of B1 (and VFA T1) relative to the reference (Ref. DA) were recalculated using the filtered B1 maps (Table 3‑1). The correlations improved postfiltering; for BS/AFI/EPI-DA, B1 correlations (*ρ*) were 0.92/0.95/0.98, and for T1 they were 0.86/0.88/0.96. The 95th percentiles of the absolute relative differences between the reference B1 map and BS/AFI/EPIDA (in WM) were equal or lower than 5% (5/4/3%, respectively), while the nominal flip-angle case had a relative difference (to Ref. DA) 95th percentile of 13%.



Figure ‑. Whole-brain coverage of axial MP-RAGE T1w slices, unfiltered AFI B1 maps, and unfiltered EPI-DA B1 maps in one subject.

The raw images used to calculate an EPI-DA B1 map for a subject are shown in Figure 3‑3a. The image quality of the EPI images is comparable to the Ref. DA method, and no observable distortions or ghosting were present in the brain for either the acquisition images or the B1 map. This observation was consistent in all subjects for the slice used in the data analysis. In addition to the single-slice measurements, two of the B1 mapping protocols were acquired with whole-brain coverage (AFI and EPI-DA). Axial slices for both B1 methods are shown in Figure 3‑5. EPI-DA B1 maps throughout the brain were free of severe susceptibility-induced distortions. However, the ventricles can be clearly identified in the EPI-DA maps (lower values) unlike for AFI, as AFI is well known to be very robust for a wide range of T1 values [16].

## Discussion

Our findings demonstrate that B1 mapping implemented using a standard product EPI pulse sequence (EPI-DA) can provide quality whole-brain B1 maps with a short acquisition time (~2min). The B1 maps were comparable or superior in WM to other well-regarded rapid acquisition B1 methods (AFI and BS) at 3T. Unfiltered B1 maps correlated with our reference single-slice measurement (Ref. DA), and we observed an improvement in those correlations after applying a Gaussian filter to the images to reduce noise and attenuate small artifacts. Pooled-subject voxelwise B1 correlation values (relative to Ref. DA) ranged between 0.88 ≤ *ρ* ≤ 0.96 for unfiltered maps, and 0.92 ≤ *ρ* ≤ 0.98 for filtered maps. The 95th percentile of the relative errors of filtered B1 maps (compared to Ref. DA) were ≤ 5%, nearly three times lower than for the nominal flip-angle case (13%). VFA T1 maps using Gaussian filtered B1 maps correlated with those using Ref. DA (0.88 ≤ *ρ* ≤ 0.96,), unlike for the case using uncorrected (nominal) flip-angles (*ρ* = 0.53). The peak of the WM T1 histograms varied slightly between methods (1 to 5%), much less than the differences reported between different T1 [18] mapping techniques themselves (20–30%). Our results demonstrate that double angle B1 mapping using a standard product EPI sequences can produce whole-brain B1 maps comparable in quality to rapid techniques (eg, AFI and BS) in a clinically acceptable scan time (~2min). While our work was based on a multishot EPI protocol [23], double angle imaging using other fast k-space acquisition strategies could also be considered (eg, double angle using a fast spin-echo readout [3]). Implementing standard product pulse sequence protocols for B1 mapping avoids time-consuming on-site pulse sequence programming (sequences similar to the one used in our study are commonly offered by other manufacturers [23]), improves accessibility of whole-brain B1 mapping to researchers without access to custom pulse sequences, and could facilitate protocol standardization between sites.

Other groups have also presented comparison studies of existing B1 methods. Lutti et al [28] optimized and compared the following methods at 3.0T: AFI, a 3D stimulated-echo B1 mapping method with EPI readouts, a 2D stimulated echo acquisition mode (STEAM) B1 mapping method, and single-slice DA as a reference. The two stimulated-echo-based methods required additional quantitative pulse sequences for calibration: the 3D stimulated-echo with single-shot EPI B1 mapping technique used B0 maps to correct for distortions, and the 2D STEAM method was calibrated against AFI using a separate measurement on a gel phantom to correct for nonlinearities of the slice-selective pulse. Each method demonstrated good reproducibility, and the largest deviation relative to the reference (DA) was observed with the stimulated-echo EPI method (4%), which is in the range of deviation we observed with our standard product EPI-DA pulse sequence (5% relative to Ref. DA for WM). Despite the benefits of these optimized rapid B1 methods, wide-scale use is limited, as all methods require pulse sequence programming expertise and additional quantitative measurements. Another important source of B1 inaccuracies, noise, has been characterized for different B1 methods (Ref. DA, AFI, and BS) using Monte Carlo simulations and phantoms [31,32]. The authors demonstrated that SNRs as low as 50 can be sufficient for accurate flip angle estimation for the range observed in the brain at 3T, and all of the methods compared in our work had SNRs above this threshold in WM.

Optimal flip angles for VFA are in the low FA range (1–30°) due to short TRs required for whole-brain VFA T1 mapping.21 All B1 methods compared in this work used larger flip angles to map the B1 intensity (Ref. DA and EPIDA: 60°/120°; AFI: 60°; BS: 25° and 500°), consistent with the published values in the original articles. Thus, RF amplifier nonlinearities could result in inaccurate low FA estimations. RF amplifier nonlinearity can vary substantially between scanner hardware manufacturers, which may lead to a bias of the corrected low flip angles used for VFA [33]. VFA pulse sequence optimization techniques have been proposed to minimize the impact of RF nonlinearity on T1 mapping [34]. A modified DA B1 method has also been proposed to map low flip angles accurately [33], which could possibly be adapted to use fast k-space readout acquisition pulse sequences, such as EPI or fast spin-echo.

For the purpose of our study, a simple single-slice DA method measurement was considered to be our “reference” method, as is often the case in B1 mapping studies. The Ref. DA acquisition is itself sensitive to sources of inaccuracies, as the typical pulse sequence protocols for Ref. DA render the B1 maps sensitive to long T1, particularly in voxels containing CSF. The TR used for this pulse sequence was shorter than conventional implementations; however, it was validated against another robust DA method [35] using a TR = 3000 msec and demonstrated very high voxelwise correlation in WM (*ρ* = 0.98, y = 0.99x + 0.03). Longer TRs could be used for improved accuracy; however, such a protocol requires 20+ min for a single slice scan [17], and motion would become an increasing concern with longer TRs. Slice-select RF pulse profiles may also impact B1 map accuracy, as nonrectangular RF profiles result in a range of flip angles within a slice (and voxel), particularly for large flip angles. Some techniques have been developed to correct for slice profile effects [36]; however, they add additional complexity in postprocessing and require RF pulse waveform information, which may not always be accessible from the scanner. Single-slice DA imaging can mitigate slice profile inaccuracies by using nonselective excitation pulses [35] or refocusing pulses, yet undesired signal from outside the slice can be a problem if incompletely crushed [37]. All B1 methods compared in this work used pulse sequences that differ greatly in their mechanism and analysis (saturation recovery: DA; steady-state: AFI; phase: BS), yet still produced voxelwise B1 values highly correlated with the reference measurement (Ref. DA). Each B1 method, even considering their imperfections, produced much better T1 maps than for the case of omitting B1 correction altogether (Nominal).

Smoothing or blurring filters are typically applied to B1 maps [16,28,38], as the B1 variation in the brain is expected to be smooth and spatially slowly varying [22]. There is no well-established consensus on which filter is ideal for B1 maps. The types of filters used in the literature are numerous: Gaussian convolution, median filters, spline interpolation, etc. In addition, the size of the blurring kernel used varies widely between studies; ranging from 3mm [16] to 10 mm [38]. Although filtering the B1 map is often considered a good practice when used in subsequent B1-correction applications, unfiltered B1 maps should also be reported when using, developing, or comparing new B1 methods. B1 methods are often only compared postblurring [16,28], thus not all artifacts (or noise level) may be clearly identifiable, only those not fully attenuated by the filters. Unfiltered B1 maps display valuable information about scanner and pulse sequence artifacts, which is particularly useful when developing or evaluating new methods. For example, even though the ringing artifact in our AFI measurements can be attenuated in the B1 maps using filtering methods, it may be preferable to use preprocessing techniques to eliminate the ringing in the acquisition images before the B1 map is calculated [39]. Although blurring B1 maps can attenuate local artifacts, it can also spread inaccuracies (eg, ventricles in our EPI-DA maps). If tissue masks are available, specific tissues known to produce inaccurate B1 values (eg, for the multislice EPI-DA case, cerebrospinal fluid) could be masked, and B1 values could be interpolated in these regions to approximate the missing values.

The specific scope of this work is limited to applications at clinical field strengths. B1 mapping at ultrahigh field strengths must be robust against more B0 inhomogeneity, longer T1 values, and faces additional hardware challenges, such as parallel transmit [40]. Accelerating B1 mapping methods using an EPI-based acquisition scheme can be prone to significant susceptibility distortions and signal dropouts at ultrahigh fields [41]. However, Bloch-Siegert at 7T requires additional acceleration techniques like EPI due to its high SAR RF pulses [42]. Supplementary scans (eg, B0 map) can be used in EPI-based B1 mapping to correct the distortions [43], but at the cost of a longer total scan time. Investigating structural characteristics of the cortex is also a topic of great interest in high-field MRI, due to its capability to image at very high resolutions (≤1mm3). High-resolution VFA T1 mapping of the cortex must use B1 maps acquired using a method that has a good robustness against the long T1 of CSF that neighbors the cortical regions [44], such as AFI, BS, or other advanced B1 mapping techniques.

This study had some limitations. The decision to use single-slice B1 for a reference limited the quantitative comparison between methods to a single slice of the brain. Although using a single-slice DA B1 map as a reference is common for validating whole-brain methods [17,28], one solution could be to acquire two more slices in perpendicular planes. Another limitation was that the low resolution of the reference scan restricted the quantitative assessment of B1 and T1 values to WM. To quantitatively compare B1 maps in the cortex, a faster reference acquisition allowing for higher resolution (~1mm3) is needed.

In conclusion, we report that B1 mapping at 3T implemented using standard product pulse sequences (eg, interleaved multislice EPI double angle) can serve as a sufficient alternative to advanced B1 methods (eg, actual flip angle imaging, Bloch-Siegert), which are not readily available on most MRI systems. The EPI double angle protocol produced whole-brain B1 maps in a clinically acceptable scan time (~2min), shorter than the AFI and BS’s protocols that were compared (although these methods can be further accelerated by implementing fast acquisition strategies, eg, EPI, fast spin-echo, or spiral). All investigated B1 mapping methods correlated well with a reference measurement, and produced substantially better VFA T1 maps than in the absence of B1 correction. The agreement between B1 maps and resulting T1 maps were improved by filtering the B1 maps to reduce noise and minor artifacts. B1 mapping implemented with standard product pulse sequences can provide an excellent alternative for researchers without custom rapid whole-brain B1 methods and is much preferred to omitting B1 correction altogether.

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# *B1-Sensitivity Analysis of Quantitative Magnetization Transfer Imaging*

## Preface

* Paragraph 1
  + Chapter 3 presented potential sources of errors in B1, and the impact inaccurate or the absence of a B1 map may have on VFA T1 maps.
  + Since qMT depends on both T1 and B1 maps, inaccuracies in B1 values will propagate to the qMT fitting parameters differently depending on if the T1 mapping method used is B1-independent (e.g. Inversion Recovery) or B1-dependent (e.g. Variable Flip Angle). For the B1-independent T1 case, errors in B1 value will propagate to qMT fitting parameters through the calibration of the nominal MT pulse and excitation flip angles; for the B1-dependent T1 case, errors in B1 value will propagate to qMT through this same pathway, but also through errors in T1 (used as a constraint for qMT parameters) as a result of B1-errors.
  + The purpose of this chapter is to explore the differences in B1-sensitivity of qMT for these two categories of T1 mapping, and to determine which T1 mapping method case leads to the least B1-sensitivity for qMT parameters, particularly for the parameter-of-interest called the pool-size ratio.
* Paragraph 2
  + Where manuscript was submitted/published.
  + One-line description of what is done in the paper
  + How it was studied (simulations, sensitivity analysis, in vivo, etc)
  + Impact of this paper

**B1-Sensitivity Analysis of Quantitative Magnetization Transfer Imaging**

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## Abstract

**Purpose:** To evaluate the sensitivity of quantitative magnetization transfer (qMT) fitted parameters to B1 inaccuracies, focusing on the difference between two categories of T1 mapping techniques: B1-independent and B1-dependent.

**Methods:** The B1-sensitivity of qMT was investigated and compared using two T1 measurement methods: inversion recovery (IR) (B1-independent) and variable flip angle (VFA), B1-dependent). The study was separated into four stages: 1) numerical simulations, 2) sensitivity analysis of the Z-spectra, 3) healthy subjects at 3T, and 4) comparison using three different B1 imaging techniques.

**Results:** For typical B1 variations in the brain at 3T (±30%), the simulations resulted in errors of the pool-size ratio (F) ranging from -3% to 7% for VFA, and -40% to>100% for IR, agreeing with the Z-spectra sensitivity analysis. In healthy subjects, pooled whole-brain Pearson correlation coefficients for F (comparing measured double angle and nominal flip angle B1 maps) were *ρ* = 0.97/0.81 for VFA/IR.

**Conclusion:** This work describes the B1-sensitivity characteristics of qMT, demonstrating that it varies substantially on the B1-dependency of the T1 mapping method. Particularly, the pool-size ratio is more robust against B1 inaccuracies if VFA T1 mapping is used, so much so that B1 mapping could be omitted without substantially biasing F.

## Introduction

Quantitative magnetization transfer (qMT) imaging is a powerful MRI technique used to investigate macromolecular content not typically detectable with conventional MRI. MR properties of macromolecular hydrogen are measured with qMT by indirect means: the magnetization of the macromolecular pool is saturated, and energy is exchanged with nearby water molecules via cross-relaxation processes and chemical exchange [5,45]. In imaging brain white matter (WM), the pool-size ratio (F), the ratio between the equilibrium magnetization of hydrogen in macromolecules versus hydrogen in water, has been shown to be a good marker of myelin density [8,46]. In particular, the pool-size ratio has been used to study multiple sclerosis lesions [47-49]. Several methods have been developed to estimate qMT parameters from the mathematical model that describes the exchange processes [50-54].

Commonly, off-resonance qMT imaging uses a magnetization transfer (MT)-prepared spoiled gradient (SPGR) echo pulse sequence [55]. It is a standard SPGR sequence preceded by an off-resonance radiofrequency (RF) pulse that varies in amplitude and frequency offset between measurements; 10 measurements or more are generally required to fit this Z-spectrum (normalized MT signal vs. off-resonance frequencies) [56], and one additional measurement without the MT-preparation for signal normalization. These qMT techniques also require three additional measurements: B0, B1, and T1. In postprocessing, B0 maps calibrate the off-resonance frequency of the MT pulse in each voxel. B1 maps are used to scale the SPGR excitation flip angle and MT-pulse saturation power. A T1 map is necessary to constrain certain fitting parameters of the two-pool MT fitting model [5]. For a given voxel, the measured T1 (T1,meas) is a function of the T1 of the water molecules (T1,f, “f” is for “free pool”) and of the T1 of the macromolecules (T1,r, “r” is for “restricted pool”), and two other parameters (F, ratio of the two pool sizes in the voxel, and kf, the exchange rate constant). The large number of measurements required to sample the Z-spectrum and additional quantitative maps make qMT a time-costly technique.

Increasingly, whole-brain qMT imaging has been achieved via a reduction in qMT measurements [57,58] and new rapid techniques to measure the required quantitative calibration maps [16,17,29]. However, integrating new methods into quantitative imaging studies can introduce unintended effects. For example, transitioning from single-slice T1 mapping techniques (i.e., inversion recovery [IR]) to three-dimensional [3D] techniques, variable flip angle [VFA]) also results in transitioning from B1-insensitive [18,59] to B1-sensitive [21] T1 mapping. If VFA is used in the qMT imaging protocol, inaccuracies in B1 will propagate into fitted qMT parameters through two pathways instead of just one (Figure 4‑1): from errors induced in T1, used to restrict the fitting parameters, and from errors in scaling the MT saturation powers with the B1 maps. The potential effect of B1-uncorrected qMT on the fitted parameters has been noted in previous work [11,60]; however, these were limited in scope to B1-insensitive T1 techniques. To our knowledge, no comprehensive characterization of the B1- sensitivity of qMT (and notably, comparing different T1 mapping methods) has previously been performed.

This work focuses on answering the following three questions: 1) How sensitive is each qMT parameter to B1-inaccuracies? 2) How does the B1-sensitivity of qMT parameters differ between protocols using B1-independent (IR) and B1-dependent (VFA) T1 mapping methods?; and 3) Which T1 mapping method results in the most robust measure of the pool-size ratio in the presence of B1-inaccuracies? To explore these questions, we first focused on simulations under ideal measurement conditions for a single tissue type, and then used this framework to perform a sensitivity analysis of the signal curves. We then measured qMT maps in healthy human volunteers using both T1 mapping methods (IR and VFA), and compared measured B1 maps with fictitious maps generated to have a large range of potential inaccuracies. Finally, we compared the relative agreement of qMT fits between three different B1 mapping methods (double angle, actual flip angle imaging, Bloch-Siegert) using both T1 mapping methods (IR and VFA).

## Methods

All measurements were performed with a 3.0T whole-body MRI scanner (Magnetom TIM TRIO; Siemens, Erlangen, Germany) using a 32-channel phased-array receive-only head coil and whole-body transmit coil. Healthy volunteers were scanned after providing informed consent, in compliance with and approved by the institutional ethics committee. The total scan time for the entire acquisition protocol described in the B1-Sensitivity of qMT in Healthy Subjects and B1 Method Comparison sections was 28 minutes and 58 seconds.

### Simulations

The coupled Bloch-McConnell differential equations describing two-pool magnetization exchange were solved numerically (MATLAB 2011a; MathWorks Inc., Natick, MA) for a pulsed MT-prepared SPGR pulse sequence using the Sled and Pike model [11,61]. The pulse sequence was decomposed into event blocks of instantaneous saturation of the free pool, constant irradiation of the restricted pool, and free precession. Prior to simulating exchange, the fractional saturation of the longitudinal magnetization induced by direct saturation was computed numerically in the absence of exchange and T1 recovery. The steady-state solution was approximated analytically using the assumption that the magnetization at an arbitrary time t should be equal to that of time *t*+prepetition time (TR), as described in detail in the appendix of Sled and Pike [52]. The signal was simulated with the following pulse sequence parameters [56,57]: TR = 25 ms, excitation flip angle (FA) = 7º, MT pulse flip angle = 142 º and 426 º, MT pulse duration = 10 ms, 10 offresonance frequencies ranging between 423.9Hz and 17.2354 kHz in logarithmic steps. The envelope of the MT-preparation RF pulse was a Gaussian-Hanning function, and a super-Lorentzian lineshape function was used for the transition rate of the restricted pool to approximate the behavior observed in tissues [61]. qMT tissue parameters for all simulations were set to healthy white matter values measured in a previous scan: F = 0.122 n.u. (normalized units), magnetization exchange rate (kf) = 3.97 s-1, free-pool longitudinal relaxation rate (R1,f = 1/T1,f) = 1.12 s-1, restricted-pool longitudinal relaxation rate (R1,r = 1/T1,r) = 1.00 s-1, free-pool transverse relaxation time (T2,f) = 27.2 ms, restricted-pool transverse relaxation time (T2,r) = 10.96ms.

SPGR qMT experiments require three additional quantitative measures: B0, B1, and T1. B0 measurement methods typically do not require B1 or T1 calibration; thus, ideal B0 homogeneity was used in the simulations. MT signal values were simulated using B1 (to scale the MT saturation powers and excitation flip angles) and T1,meas (to constrain the fitting parameters) that were fixed to their ideal values (1 n.u. and 0.9 s respectively). The MT signal was subsequently fitted using the Sled and Pike method [11]. As per convention, R1,r was fixed to 1 s-1. R1,f was calculated during the fitting algorithm from an analytical expression of F, kf, R1,r, and T1,meas. To investigate the effect of inaccuracies in B1 and T1,meas on the fitted qMT parameters, the simulated MT signal values were fitted using a large range of B1 and T1,meas values. Four qMT parameters (F, kf, T2,f, T2,r) were explicitly fitted for each pair of 100 B1 and 100 T1,meas values (10,000 combinations). The set of B1 values varied linearly from 0.5 to 2 n.u., and T1,meas varied from 0.1 s to 4 s. For this stage, B1 and T1,meas varied independently of each other. We investigated the qMT parameter sensitivities due to B1 inaccuracies for two T1 mapping techniques: IR, approximately B1 independent [18], and VFA, inherently B1-dependent [21]. The IR case was interpreted to be a linear subset of the B1-T1 combination discussed above by a fixed T1 (T1,IR = 0.9 s, constant). The VFA signals from a two flip angle experiment were calculated for T1 = T1,true =0.9 s from the analytical steady-state SPGR equation (TR = 25 ms, FA = 3º and 20 º). T1,VFA values were subsequently estimated by linear least-square fitting of the VFA data with flip angle calibration [62] using the set of 100 B1 values (0.5 to 2 n.u.). The fitted VFA T1,meas values were then used in conjunction with their respective B1 values to fit the qMT parameters to the simulated MT signal.

### Sensitivity Analysis

To provide further insight into the behavior of fitted parameters in the presence of B1 inaccuracy, a sensitivity analysis of the qMT signal was performed [63]. For each qMT parameter, the following definition of sensitivity was used (cf. Appendix A):

|  |  |
| --- | --- |
|  | **(4-1)** |

where the index *i* describes a specific qMT acquisition point, *Mi* is the normalized signal of the ith qMT measurement, and *Sp,i* is the sensitivity of the MT signal with respect to *p* for the *i*th qMT acquisition. The sensitivity *Sp,i* represents the change in normalized MT signal induced by a slight change in fitting parameter value or model input value (e.g., B1). A large absolute *Sp,i* value signifies that, to a linear approximation, a large change in MT signal will occur (at that Z-spectrum value) for a small variation of *p*. In the context of fitting data to measurements using an inaccurate B1 value, the following relationship can be shown (cf. Appendix A):

|  |  |
| --- | --- |
|  | **(4-2)** |

Thus, the sensitivity values can provide an insight as to why certain fitting parameters are more likely to have large errors due to inaccurate B1 values. When comparing two measurement protocols, the following metrics can be expected to provide insight into which fitting parameters *p* are more/less sensitive to B1 inaccuracies (cf. Appendix A):

|  |  |
| --- | --- |
|  | **(4-3)** |
|  | **(4-4)** |

where ***S*** is the vector of sensitivity values for a set of N measurements, is its norm, and is its unit vector. If the sensitivity values of a parameter *p* and B1 have very similar curves (Eq. (4-3) ≈ 1), then *p* is likely to be most sensitive to B1 inaccuracies compared to other parameters. The relative error of *p* will then be proportional to the ratio in Eq. (4-4).

The qMT measurement protocol and tissue parameters from the Simulations section were used to simulate normalized MT signal values. Partial derivatives with respect to qMT parameters (and B1) of the MT signal were evaluated at each point of the Z-spectrum [64]. B1 sensitivity values were calculated for two cases: T1,meas independent of B1 (which for consistency with the other sections we designate as IR), and T1,meas with VFA B1-dependency. As T1,meas is primarily used to constrain R1,f, R1,f was modified in addition to B1 accordingly for the VFA case. The derivative steps were fixed to a 10-5% relative increase of the parameter denominator value, sufficient for the convergence of the partial derivative at each Z-spectrum point of our qMT protocol.

### B1-Sensitivity of qMT in Healthy Subjects

Three healthy adult volunteers were scanned (two males, one female, 30 ± 4 years old). All quantitative imaging sequences were acquired at a resolution of 2 × 2mm2 in-plane × 5mm slice thickness. Single slices were acquired parallel to the anterior commissure–posterior commissure (AC-PC) line, superior to the corpus callosum.

*T1 Maps:* VFA T1 maps were acquired using a spoiled 3D gradient echo sequence [29]: echo time (TE) = 2.89 ms, TR = 15 ms, FA = 3º and 20 º, spoiler gradient moment (AG) = 280 mT ∙ ms/m, RF phase increment (*φ*) = 169º, 1 m 28 s scan time. Prior to fitting the data for T1, the nominal flip angles were scaled voxel-wise with each B1 map. The VFA T1 values were then estimated from linear least-square fitting. Inversion recovery T1 data were collected from a four-inversion-time (TI) spin-echo sequence [18]: TE/TR = 11/1550 ms, TI = 30, 530, 1030, 1530 ms, 9 m 16 s scan time. An open-source software package for robust inversion recovery fitting was used to fit the IR T1 maps [59].

*qMT Maps:* qMT data were acquired according to the 10-point MT-prepared SPGR acquisition protocol described in the Simulations methods section, which for our single slice has a 2 m 38 s scan time. B0 maps were acquired for off-resonance frequency correction using a two-point phase-difference gradient measurement [65]: TE1/TE2/TR = 4/8.48/25 ms, FA = 7º, 30 s scan time. qMT parameter maps were produced by fitting the normalized qMT data voxel-wise using the Sled and Pike fitting model [66].

*B1 Maps:* Two categories of B1 maps were compared: 1) in vivo measured B1 maps and 2) B1 maps that had a single value assigned to all voxels (B1,Flat). B1,Flat maps were used to investigate the sensitivity of qMT to B1 inaccuracies for in vivo conditions (e.g., noise, tissue partial volume, a broad range of qMT tissue parameter values). Single-slice double angle (DA) B1 maps (B1,DA) were acquired using a spin-echo readout: TE/TR = 12/1550 ms, FA = 60º/120º, with slice-selective excitation and 180º refocusing pulses, 4 m 28 s scan time. A set of B1,Flat maps were generated for a range of values (B1,Flat = 0.5, 0.75, 0.9, 1, 1.1, 1.25, 1.5, 2 n.u.), where B1,Flat = 1 n.u. represents the nominal flip angle case. Prior to fitting the qMT data, each B1 map (B1,DA and the set of B1,Flat) was used as a corrective factor for the VFA nominal flip angles, MT excitation flip angles, and MT saturation powers.

*Data Analysis:* qMT parameter maps (F, kf, T2,f, T2,r) were fitted voxelwise using four sets of B1 and T1 combinations: B1,DA and B1,Flat used with IR and VFA T1 maps (Figure 4‑1). Voxel data of each qMT parameter map were pooled (across all subjects) for each B1 and T1 set, and linear regression analysis was performed (comparing B1,DA and each B1,Flat).



Figure ‑. Quantitative measurements used in our magnetization transfer (MT)-prepared spoiled gradient quantitative MT study. Solid arrows are used for required measurements; dotted arrows are used for specific methods of a particular measurement. The double angle (DA) method is an explicitly measured B1 map. B1,Flat maps are generated using a single value in all voxels. Variable flip angle (VFA) is a T1 mapping methods that also requires B1 as a support measurement, unlike inversion recovery (IR).

### B1 Method Comparison

Several techniques exist to measure B1 maps, and each method can be prone to unique sources of systemic biases or local artifacts [43]. To probe the robustness of the B1-sensitivity of qMT between different B1 measurement techniques, two additional B1 maps were acquired and compared against the DA B1 maps in all three subjects from the B1-Sensitivity of qMT in Healthy Subjects section. Actual flip angle imaging (AFI) [16], a two-TR steady-state SPGR-based pulse sequence, was applied to produce B1 maps with a 2 × 2 × 5mm3 whole-brain 3D spoiled acquisition (19): TE/TR1/TR2 = 3.53/20/100 ms, FA = 60º, AG = 450 mT ∙ ms/m, *φ* = 39º, 5 m 38 s scan time. Bloch-Siegert shift (BS) B1 mapping [17], an SPGR-based method with an off-resonance RF preparation pulse, produced B1 maps using a single-slice 2 × 2 × 5mm3 acquisition: TE/TR = 15/100 ms, *α* = 25º, 8 ms Fermi Pulse of 500º at 64 kHz off-resonance, phase-shift constant (KBS) = 74.01 rad/G2, 19 s scan time.

At the resolution of our data (2 × 2 × 5mm3), partial volume effects near cortical grey matter (GM) and adjacent to ventricles can be significant. The partial volume effects can make the analysis of in GM challenging. Preliminary data (not shown) suggested that an insufficient number of voxels exist containing only GM, for a reliable analysis to be performed, and including all voxels containing at least some GM would include a significant bias in the qMT parameters from cerebrospinal fluid (CSF). As such, the images were masked solely for WM. Whole-brain T1-weighted magnetization-prepared rapid gradient-echo (MP-RAGE) 3D volumes (1 × 1 × 1mm3) were acquired: TE/TR/TI = 3.32/2300/900 ms, parallel imaging acceleration factor = 2, bandwidth (BW) = 230 Hz/Px, 5 m 30 s scan time. Tissue classification maps (WM, GM, CSF) were estimated via Intensity Normalized Stereotaxic Environment for the Classification of Tissue [27] using the MPRAGE data with the International Consortium for Brain Mapping-152 atlas. WM tissue masks were resampled to match the AC-PC 2 × 2 × 5mm3 single slices using a majority voting analysis (75% threshold). The histograms of WM qMT parameters were calculated for all three B1 maps, using both VFA and IR T1 maps in the processing pipeline. Chi-square (*χ*2) of the histogram differences was calculated to quantify how well the histograms matched between the DA case versus AFI and BS.

## Results

### Simulations

The error (%) in F calculated after fitting the simulated qMT signal using each B1 and T1 value-pair is displayed in Figure 4‑2. T1 curves as a function of B1 inaccuracies are superimposed with solid (IR) and dotted (VFA) lines. The error in F (%) is a smooth nonlinear function of B1 and T1, with some speckling in values occurring far from the true B1 and T1 intersection (where they are both grossly inaccurate). IR T1 is set to be constant, resulting in a wide range of errors in F (<-100% to 50%) for the B1 inaccuracy range evaluated. B1 underestimation resulted in an overestimation of VFA T1, and the error in F for this case overlaps near the 0% error contour line (green).



Figure ‑. Simulated differences (%) in fitted quantitative magnetization transfer (qMT) F values in the presence of a wide range of B1 and T1 errors (B1,true = 1 n.u., T1,true = 0.9 s). The superimposed lines plot the T1 distribution for a B1-independent T1 mapping method (inversion recovery [IR], solid line, and variable flip angle [VFA], dashed line). n.u. = normalized units.

At 3T, the B1 amplitude varies approximately ±30% in the brain. The errors in the four qMT fitted parameters are shown for this range of B1 inaccuracy in Figure 4‑3, for both the IR and VFA T1 cases. Note that Figure 4‑3a corresponds to the values superimposed by the IR and VFA T1 lines in Figure 4‑2. Relative to IR, errors in F due to B1 inaccuracies are substantially reduced using VFA. For VFA, the errors in F ranged between -3% and 7% (blue line) for ±30% B1 inaccuracy; for IR, the errors ranged between -40% and >100% (red line). kf exhibits the inverse trend; errors in kf are larger for VFA relative to IR (Figure 4‑3b) for all B1 values. No advantage in either T1 method is identified for T2,f; the slopes of the curves flip between both T1 methods with approximately the same magnitude. T2,r is insensitive to B1 inaccuracies for both T1 mapping method (Figure 4‑3d).



Figure ‑. Simulated errors (%) in fitted quantitative magnetization transfer (qMT) parameters for ±30% B1 errors (a: pool size ratio [F], b: magnetization exchange rate [kf], c: free pool T2 [T2,f], d: restricted pool T2 [T2,r]). Fits using a B1-independent T1 measure (inversion recovery [IR]) are shown in red, and those using variable flip angle (VFA) T1 mapping are shown in blue. The IR curve in d) is underneath the VFA line. Note: The solid and dashed lines in Figure 4‑3 to show the dependence of IR and VFA T1 on B1. n.u. = normalized units.

For IR, a 10% underestimation in B1 produced a 23% error in F, 6% error in kf, 12% error in T2,f, and 0.78% error in T2,r. For VFA, a 10% underestimation in B1 produced a 1.5% error in F, 25% error in kf, 6.7% error in T2,f, and 0.78% error in T2,r. Thus, switching from IR to VFA reduces B1-sensitivity of F by a factor of 15 for a 10% error in B1. The error in F for the IR case (23%) produced from a 10% error in B1 is consistent with the value calculated by Sled and Pike using a 60-point protocol (20%) [11].

### Sensitivity Analysis

The plots of the sensitivity values for our qMT protocol are shown in Figure 4‑4, and the sensitivity metrics (from Eqs. (4-3) and (4-4)) are calculated in

Table 4‑1. The curve similarity metric informs us of how well changing a particular fitting parameter *p* (F, kf, T2,f, and T2,r) can correct the expected signal change due to an error in B1. For a B1-independent T1 measurement (e.g., IR), we see from

Table 4‑1 that the values have the following trend: (F ≈ 1) > kf > T2,f ≫ T2,r, for VFA: (kf ≈ 1) > F ≈ T2,f ≫ T2,r. This suggests that F has a higher sensitivity to B1 inaccuracies for IR than VFA, with a reverse relationship expected for kf, both in agreement with the simulations results from the Simulations section. Figure 4‑4 illustrates these relationships; the sensitivity curves for B1IR (Figure 4‑4a) have a similar pattern to those for F (Figure 4‑4c), whereas the sensitivity curves for B1VFA (Figure 4‑4b) have a similar pattern to those for kf (Figure 4‑4d). For these respective cases, is greater for kf than F (

Table 4‑1), suggesting that larger relative errors in kf are required to compensate B1VFA inaccuracies than F for B1IR, consistent with our simulation observations. Lastly, note that the minima observed in is due to a zero-crossing of , a characteristic that was also reported in a previous study [67].

Table ‑. qMT Z-Spectra Sensitivity Comparison Metrics for B1 (Accounting for the B1-Sensitivity of Each T1 Method, IR, and VFA) and Each Fitted qMT Parameter

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  | |  | |
|  |  |  |  |  |
|  | **0.975** | 0.754 | **2.05** | 1.07 |
|  | 0.815 | **0.951** | 6.02 | **3.12** |
|  | 0.704 | 0.776 | 4.67 | 2.43 |
|  | 0.482 | 0.552 | 3.08 | 1.61 |

**Note: corresponds to the qMT sensitivity values relative to B1 assuming a B1-independent measure of T1, whereas considers a qMT protocol using a VFA T1 measurement, which inherently is B1-dependent. IR = inversion recovery; qMT = quantitative magnetization transfer; VFA = variable flip angle.**

****

Figure ‑. Sensitivity analysis of the magnetization transfer signal relative to B1 (a, b) and fitting variables (c–f). The plots (note scale changes) show the magnitudes of the sensitivity values (Eq. (4-2)).

### B1-Sensitivity of qMT in Healthy Subjects

Noise, partial volume effects of tissue, and a wide range of different qMT tissue parameters were not considered in the previous sections, all of which could potentially impact the B1-sensitivity of the qMT fits. In vivo data were acquired to investigate whether the B1-sensitivity features identified in our simulations hold under real-world conditions. Single-slice qMT parameter maps are shown in Figure 4‑5, fitted using VFA (a) and IR (b), for either DA B1 maps or the nominal flip angle assumption (B1,Flat = 1). For VFA and B1,Flat, the elevated T1 at the center of the brain counteracts the underestimated B1 values, resulting in minimal errors in the qMT F maps relative to the IR F maps. At the perimeter of the brain where B1,Flat overestimates the measured values, the VFA case results in nearly no qMT F bias. Regions of very high T1, suggesting presence of CSF, do exhibit speckling of large errors in F. qMT F fitted with the combination of IR and B1,Flat resulted in large errors, where the B1 profile is clearly distinguishable in map of errors in F.

Table 4‑2 lists the correlation and linear regression slope (B1,DA vs. B1,Flat = 1) for all fitted qMT parameters, using both T1 methods. qMT F using VFA had the best correlation (*ρ* = 0.97, slope = 0.97), as opposed to IR (*ρ* = 0.81, slope = 0.57). T2,f also demonstrated good correlations (*ρ* = 0.97), but with an underestimation of the slope (slope = 0.86). Based on our simulations, the low correlation of kf for the IR case (*ρ* = 0.26) was unexpected. Upon further investigation of the raw kf scatter plots (not shown), the linear assumption for fitting the kf scatter plot was violated. Thus, for conditions exhibited in vivo (i.e., noise, multi-tissue voxels), the kf parameter fits were not stable in the presence of large B1 errors, resulting in kf voxel values diverging substantially in the scatter plot data.

Table ‑. Pooled (All Subjects) Pearson Correlation Coefficients and Linear Regression Slopes for qMT Values Comparing Measured DA B1 Maps and Fictitious B1,Flat = 1 Mapsa

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **(B1,DA) vs. (B1,Flat = 1)** | | | |
|  | **T1,VFA** | | **T1,IR** | |
| **qMT** | **Pearson *ρ*** | **Slope** | **Pearson *ρ*** | **Slope** |
| F | **0.97** | **0.97** | 0.81 | 0.57 |
| kf | 0.27 | 0.24 | 0.26 | 0.25 |
| T2,f | 0.97 | 0.86 | 0.93 | 0.90 |
| T2,r | 0.81 | 0.78 | 0.89 | 0.82 |

**aB1,Flat = 1 is equivalent to the nominal flip angle assumption DA = double angle; qMT = quantitative magnetization transfer.**

****

Figure ‑. Single-subject comparison of quantitative magnetization transfer parameter maps fitted using double angle and B1,Flat = 1 maps using (a) variable flip angle (VFA) T1 maps corrected using the corresponding B1 map, and (b) inversion recovery (IR) T1 maps independent of B1.

Expanding the correlation analysis of F to a larger B1,Flat set of values (ranging from 0.5 to 2 n.u.), F was more robust against B1 overestimations than underestimations (Figure 4‑6a). The correlations break down rapidly for B1,Flat values below 0.75, yet are near unity for most values ranging between 1 and 2. The same trend is true for the fit slope for F; it is near unity for slight B1 underestimations and for large B1 overestimations (Figure 4‑6b).



Figure ‑. Pooled (all subjects, voxel-wise) whole brain Pearson correlation coefficients (a) and linear regression slopes (b) for qMT F values between the measured double angle B1 maps and generated B1,Flat maps. IR = inversion recovery; n.u. = normalized units; VFA = variable flip angle.

### B1 Mapping Method Comparison

Three B1 maps (DA, AFI, BS) are shown for one subject in Figure 4‑7. The DA B1 map, which was used in the previous section, was set as the reference measurement that the two other methods are compared against. AFI and BS displayed heterogeneous inaccuracy patterns relative to DA; voxel-wise relative errors were ±10%. In this subject, B1 in the frontal lobe was overestimated by both methods, whereas the left and right posterior regions showed different bias patterns for both techniques. Relative to DA, the voxelwise Pearson correlation and linear regression coefficients for all three subjects were *ρ* = 0.904 (y = 1.035 x – 0.034) for BS and *ρ* = 0.912 (y = 0.960 x + 0.038) for AFI. Despite variations in voxelwise accuracy between B1 methods, the histograms of WM qMT F matched very well for the VFA case (Figure 4‑8b, same subject as Figure 4‑7). The excellent overlap of histogram curves for this case resulted in low *χ*2 values for this subject (*χ*2AFI = 1.24, *χ*2BS = 1.41), unlike to the IR case for F (*χ*2AFI = 5.45, *χ*2BS = 6.40). Consistent with our simulations, the inverse relationship was true for kf in WM (Figure 4‑8c,d). The mean *χ*2 values of F for all subjects also had low standard deviations for VFA (*χ*2AFI = 1.24 ± 0.33, *χ*2BS = 1.41 ± 0.12) relative to IR (*χ*2AFI = 9.25 ± 5.81, *χ*2BS = 9.17 ± 3.94; Figure 4‑8a). For kf, the means for all subject for VFA were *χ*2AFI = 6.10 ± 1.81, *χ*2BS = 9.00 ± 3.45, and for IR were *χ*2AFI = 1.44 ± 0.42, *χ*2BS = 2.44 ± 1.21. These results demonstrate the robustness of VFA for qMT F, even in the presence of local inaccuracies acquired in similar B1 maps, and that B1 maps containing minor artifacts can be used without degradation in quantitative F value precision.



Figure ‑. B1 map comparison in a single subject using three different acquisition techniques: double angle method, actual flip angle imaging (AFI), and Bloch-Siegert shift. n.u. = normalized units.



Figure ‑. Single-subject white matter pool-size ratio (F) (a, b) and magnetization transfer (MT) exchange coefficient (kf) (c, d) distributions for three B1 mapping methods, using inversion recovery (IR) T1 mapping (a, c) or variable flip angle (VFA) T1 mapping (b, d). *χ*2 values of the actual flip angle (AFI) and Bloch-Siegert shift (BS) histograms were calculated relative to double angle.

## Discussion

Our findings demonstrate that the B1-sensitivity of off-resonance MT-prepared SPGR qMT parameters is strongly influenced by the T1 mapping method used. We showed that the robustness of the fitted qMT parameters is impacted by the choice between a B1-independent and a B1-dependent T1 mapping method impacts. Overall, the pool-size ratio F was shown to be most robust against B1 errors when VFA T1 mapping is used. Using simulations, we found that a 10% overestimation in B1 results in a 1.5% error in F if VFA is used for T1 mapping. This B1-induced error in F was 15 times less than for B1-independent methods such as IR (23% error in F). Although possibly a counter-intuitive prediction, the increased robustness in F against errors in B1 for a B1-dependent T1 method is made possible due to other fitting parameters (particularly kf) being more compatible to compensate the expected signal errors for this case. In vivo measurements were in agreement with our simulations; the F maps fitted using the nominal flip angle assumption (B1 inaccuracy ranging between -10% and 25%) and VFA T1-mapping correlated strongly with the case using a measured B1 map (*ρ* = 0.97). Histogram comparisons of WM qMT F between three different B1 mapping methods showed that VFA could result in four to five times better histogram matching (*χ*2 values) in the presence of B1 inaccuracies compared to IR.

Although most B1 mapping methods are designed to be robust to common sources of potential artifacts (i.e., tissues with long T1), there is no well-accepted gold standard method for accurately imaging B1. Our comparison between three well-accepted B1 imaging methods showed that ±10% in voxel-wise differences between B1 maps can be reasonably expected, resulting in inevitable B1 inaccuracies regardless of which technique is chosen. In addition, B1 maps are typically filtered with large blurring kernels (10mm3) [16,28,38], because B1 maps are expected to have a smoothly varying profile [22]. In the presence of local highly inaccurate voxels, blurring filters can have the unintended effect of biasing nearby voxels. Blurring filters can also be less effective in cortical grey matter due to edge effects, an area that is already sensitive to inaccuracies due to partial volume effects with CSF. Resampling low-resolution B1 maps for higher resolution qMT applications means that some inaccurate B1 information will inevitably be used in qMT postprocessing. Overall, some inaccuracies in B1 maps must be considered when planning the qMT acquisition protocol to minimize the sensitivity of the qMT parameter(s) of interest to this source of error.

The B1-sensitivity characteristics reported here are limited to the qMT imaging method and model that were used. Several other qMT techniques could benefit from a similar analysis; well-established pulsed SPGR qMT alternatives include the Ramani [54] and the Yarnykh [16] models. A key difference between these three MT models is in how they approximate the MT pulse power [61]. As B1 is primarily used as a corrective factor for the MT pulse power, B1-sensitivity will likely vary between these methods and could be explored in future work. Our sensitivity analysis results may also suggest that the B1-sensitivity will vary depending on certain key Z-spectrum acquisition choices, particularly dependent on how many MT powers are used. The number of MT powers is conventionally limited to two; however, optimized acquisition schemes have used anywhere between one [67,68] and eight MT pulse powers [56].

Despite the fact that VFA T1 mapping benefits qMT by improving the robustness of F, even for the extreme case of no B1 correction at all, certain limitations must be carefully taken into consideration prior to integration into a protocol. As shown with simulations and in vivo, the increase in robustness of one qMT parameter for a certain choice of T1 method (e.g., IR or VFA) results in a reduction in robustness of the other fitted parameters. For instance, a study whose aim is to compare all the qMT parameters should refrain from omitting B1 mapping, even if VFA is used, as kf will be inaccurate in several regions. Accurate T1 maps, which are valuable to many studies because they correlate with disease characteristics, would also be compromised if measuring B1 is omitted in a qMT protocol that uses VFA. However, for circumstances where the certain qMT parameters have been well-characterized for the disease of interest (e.g., multiple sclerosis), choosing to improve the accuracy and robustness of one parameter (e.g., F) at the expense of others may be justified. Reducing the number of measurements to benefit one qMT parameter at the expense of others has been reported previously; for example, constraining multiple fitting parameters was used to achieve a single off-resonance qMT measurement technique of the pool-size ratio [67,68].

## Conclusion

In summary, our work revealed the strong dependency of qMT B1-sensitivity on the choice of T1 mapping. Choosing carefully between a B1-independent and B1-dependent T1 mapping method can greatly improve the precision of certain qMT parameters. Our results showed that, for a pulsed SPGR qMT sequence with uniform Z-spectrum sampling, using VFA T1 mapping is preferable if the parameter of interest is the pool-size ratio F parameter. The robustness against B1 inaccuracy is so strong for this case, that B1 mapping could be omitted altogether without resulting in large differences in fitted qMT F maps. Omitting this measurement could help accelerate lengthy qMT acquisition protocols, at the expense of losing quantitative T1 information. B1-sensitivity of qMT could be further improved by optimizing the Z-spectrum sampling scheme, similar to how qMT acquisition schemes have been optimized for noise performance [56].

## Appendix A

Let us assume an experiment consisting of N measurements *M*i,meas (i = 1, 2 ..., N). Fitting the data to a mathematical model, the algorithm is expected converge to a state where |*Mi,meas - Mi,fi*t| is minimized at each point, such that ideally:

|  |  |
| --- | --- |
|  | **(4-A1)** |

*Mi,fit* depends on a set model parameters (k = 1, 2, .., L). For a small error in an measured model parameter (i.e., a calibration measurement, such as B1 in qMT), the change in each *Mi,fit* is approximated by a Taylor expansion:

|  |  |
| --- | --- |
|  | **(4-A2)** |

The fitting algorithm will nonetheless aim at producing a good fit (Eq. (4-A1)); thus, the following approximations are expected:

|  |  |
| --- | --- |
|  | **(4-A3)** |
|  | **(4-A4)** |

A first order approximation of the Taylor series for small and substituting for *Mi* condenses Eq. (4-A2) to:

|  |  |
| --- | --- |
|  | **(4-A5)** |

The *Mi* terms cancel, thus any error caused by must be compensated by errors propagated to the remaining fitting parameters for k ≠ j:

|  |  |
| --- | --- |
|  | **(4-A6)** |

For the Sled and Pike model of qMT, the calibration measurement we are interested in as a possible source of error in this work is B1, and the explicitly fitted parameters are F, kf, T2f and T2r:

|  |  |
| --- | --- |
|  | **(4-A7)** |

The sensitivity of a measurement *Mi* relative to a model parameter pk is defined as [63]:

|  |  |
| --- | --- |
|  | **(4-A8)** |

For a set of N measurements, Eqs. (4-A7) and (4-A8) simplify to matrix form:

|  |  |
| --- | --- |
|  | **(4-A9)** |

For a given error in B1 (), Eq. (4-A10) could be minimized to estimate the errors in each fitting parameter (, , , ) having known sensitivity values, which can be calculated analytically or through numerical simulations. However, to simplify the analysis, we chose to compare each fitting parameter *pk* independently to find possible easy-to-understand metrics to compare fitting parameter sensitivity to B1 inaccuracies. For each fitting parameter of interest (, we set all other values to 0. Equation (4-A9) now simplifies to a vector equation:

|  |  |
| --- | --- |
|  | **(4-A10)** |

where is the column vector for the parameter of interest *p* in Equation (4-A9), similar to . This equation is solved for by doing the scalar product of on both sides of the equation, and separating the norm of the vectors ( and their unit vectors (. Also, because and are absolute errors, they are scaled by the parameter values (, where is the relative error). To better compare each parameter, the relative error is preferred:

|  |  |
| --- | --- |
|  | **(4-A11)** |

Thus, for a given relative error in B1 , the parameter *p*, which maximizes for a given measurement protocol, will likely have larger inaccuracies than the other fitting parameters. This can be visualized easily, because ≈ 1 means that the sensitivity curves for B1 and *p* nearly match, and any change in the Z-spectrum expected by an inaccurate B1 can be nearly completely compensated solely by adjusting that fitting parameter. The error induced () will then proportional to the ratio of overall sensitivities .

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# *Sensitivity-Regularization of the Cramér-Rao Lower Bound to Minimize B1 Nonuniformity Effects in Quantitative Magnetization Transfer Imaging*

## Preface

* Paragraph 1
  + In the last chapter, we investigated the differences in sensitivity of qMT fitting parameters to B1 inaccuracies between different T1 mapping methods, using a fixed acquisition protocol.
  + We concluded that VFA T1 mapping provides more robustness of the qMT pool-size ratio to B1-inaccuracies.
  + The next logical step is to ask how will the B1-sensitivity change for a fixed T1 mapping method between different qMT acquisition protocols.
  + Or more broadly, how can the qMT acquisition protocol be optimized to reduce B1-sensitivity of certain qMT parameters.
* Paragraph 2
  + Where manuscript was submitted/published.
  + One-line description of what is done in the paper
  + How it was studied.
  + Impact of this paper

**Sensitivity-Regularization of the Cramér-Rao Lower Bound to Minimize B1 Nonuniformity Effects in Quantitative Magnetization Transfer Imaging**

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## Abstract

**Purpose:** To develop and validate a regularization approach of optimizing B1-insensitivity of the quantitative magnetization transfer (qMT) pool-size ratio (F).

**Theory and Methods:** An expression describing the impact of B1-inaccuracies on qMT fitting parameters was derived using a sensitivity analysis. To simultaneously optimize for robustness against noise and B1-inaccuracies, the optimization condition was defined as the Cramér-Rao lower bound (CRLB) regularized by the B1-sensitivity expression for the parameter-of-interest (F). qMT protocols were iteratively optimized from an initial search space, with and without B1-regularization. Three 10-point qMT protocols (Uniform, CRLB, CRLB+B1-regulatization) were compared using Monte Carlo simulations for a wide range of conditions (SNR, B1-inaccuracies, tissues).

**Results:** The B1-regularized CRLB optimization protocol resulted in the best robustness of F against B1-errors, for a wide range of SNR and for both white and grey matter tissues. For SNR = 100, this protocol resulted in errors of less than 1% in mean F values for B1-errors ranging between -10 to 20%, the range of B1 values typically observed in vivo in the human head at field strengths of 3 T and less. Both CRLB-optimized protocols resulted in the lowest σF values for all SNRs, and did not increase in the presence of B1-inaccuracies.

**Conclusion:** This work demonstrates a regularized optimization approach for improving the robustness of auxiliary measurements (e.g. B1) sensitivity of qMT parameters, particularly the pool-size ratio (F). Predicting substantially less B1-sensitivity using protocols optimized with this method, B1 mapping could even be omitted for qMT studies primarily interested in F.

## Introduction

Quantitative magnetization transfer (qMT) imaging is a class of techniques that indirectly probe tissue macromolecular content, which is not directly observable using conventional MRI due to their inherently short T2\*. Most qMT techniques quantify properties of macromolecular hydrogen (“restricted pool”) relative to nearby liquid water molecules (“free pool”) by solving the Bloch-McConnell equations, which describes the magnetization exchange between these two interacting pools [52]. Particularly, the pool-size ratio F (ratio of equilibrium magnetization between both pools) is a qMT parameter that correlates strongly with myelin content [8,46]. As such, the pool-size ratio has been proposed as a potential biomarker for lesion monitoring in multiple sclerosis (MS) patients [48,49], and has been shown to correlate with de- and remyelination in a mouse model of MS [69].

Several techniques have been developed to acquire and model qMT data. Most commonly, qMT data are acquired using pulsed off-resonance MT-prepared spoiled gradient echo (SPGR) pulse sequences [11], however techniques using inversion recovery [51] and balanced steady-state free precession have also been proposed [50]. Analytically solving the Bloch-McConnell equations is challenging unless a long continuous-wave MT pulse is used [5], which is impractical for in vivo measurements. Several fitting models have been developed to estimate quantitative parameters from pulsed SPGR qMT data [11,53,54], each with unique sets of experimental assumptions and approximations. In addition, SPGR qMT techniques require several additional quantitative measurements, such as main field (B0) mapping, transmit radiofrequency (RF) field (B1) mapping, and longitudinal relaxation time (T1) mapping. In this context, B0 mapping is used to calibrate the off-resonance frequency values in the presence of main field inhomogeneity [65], B1 mapping to correct the RF field amplitude variations [70,71], and T1 mapping to constrain the magnetization transfer fitting parameters [5,11,72]. These three measurements, in addition to the 10+ qMT measurements typically required to fit the full set of model parameters [56], makes it a challenge to acquire qMT data in a clinically feasible acquisition time.

Several strategies have been developed to shorten the SPGR qMT acquisition time, which originally consisted of over 60 qMT measurements [11] and limited the technique to single slice acquisitions. The first three-dimensional qMT brain scan was achieved using a “uniform” acquisition protocol by reducing the number of off-resonance frequencies (Δ) to 5 (uniformly ranging between 400 Hz and 20 kHz) and MT flip angles (FAMT) to 2 (high and low values), for a total of MT-weighted 10 measurements [57]. Other studies went further, optimizing the protocol Δ and FAMT values using the Cramér-Rao lower bound (CRLB) as an optimization condition to minimize estimated parameter variances, using simulated annealing [73] or an iterative protocol reduction algorithm from an initial search space [56]. Rapid k-space readout techniques such as echo planar imaging have also been proposed to improve acquisition times [74]. The choice of B0/B1/T1 mapping techniques have evolved over time, with researchers typically choosing the most rapid and reliable technique available at their disposal. For example, the evolution from single-slice qMT imaging to whole-brain imaging required a switch from single-slice T1 mapping techniques (e.g. inversion recovery – IR, Look-Locker – LL) to 3D techniques (e.g. Variable Flip Angle – VFA). However, recent work has shown that this transition may impact the robustness of the fitting parameters, since IR is a B1-insensitive technique [59], whereas VFA is a B1-sensitive technique [21]. For a uniform 10-pt SPGR qMT protocol, it has been demonstrated that the pool-size ratio F is much less sensitive to B1-inaccuracies if the qMT protocol uses VFA T1 mapping, relative to B1-insensitive T1 mapping techniques [75]. Since that work used a fixed “uniform” qMT sampling protocol to demonstrate the benefit of using VFA T1 mapping for F, it raises an interesting question: is it possible to further improve the robustness of F against B1 inaccuracies by optimizing the qMT acquisition protocol itself for B1-insensitivity?

The aim of this work is to develop a method to incorporate B1-sensitivity considerations into the optimization of qMT data acquisition, by regularizing the CRLB optimization condition with a B1-sensitivity term. We first derived a B1-sensitivity expression that was used to regularize the CRLB condition. Using simulations, we then explored the B1-sensitivity of qMT for several different uniform sampling protocol configurations. The optimal regularization term for the pool-size ratio was determined, and a sample qMT protocol was iteratively optimized using the CRLB condition both with and without the regularization term. The robustness of three protocols (uniform, CRLB, CRLB + B1 regularization) were then investigated using Monte Carlo simulations for a range of signal-to-noise ratios (SNR), B1-inaccuracies, and tissue values. Lastly, the qMT optimization framework developed and presented here is released as an open-source package.

## Theory

In the presence of a small inaccuracy of a measurement parameter, such as B1 in qMT, this error will propagate to the fitting parameters of the model. The behavior of how this propagated error will impact each fitting parameter can be explored through a sensitivity analysis, by expanding the fitted signal in the presence of a ΔB1 with a Taylor expansion [63]. Assuming a small ΔB1 and a good fit (*M*(*B1*+ ΔB1) ≈ *M*(*B1*) ≈ *M*meas, where *M* is the signal generated by the fit), a first-order approximation of the Taylor expansion of the fitted signal results in the following matrix equation [75]:

|  |  |  |
| --- | --- | --- |
|  |  | **(5-1)** |

where *p* are the model fitting parameters (e.g. for the Sled and Pike[52] model of qMT: F, kf, T2,f, T2,r), is the column vector of errors in fitted parameters [ΔF, Δkf, ΔT2,f, ΔT2,r]ʹ, and are matrices with sensitivities values elements relative to *pi* or *B*1 (columns) for each measurement *n* (rows). can also be interpreted as being the Jacobian of the measurement for the fitting parameters, which we’ll call the Jacobian sensitivity matrix.

Given a known ΔB1 value and Jacobian sensitivity matrices for *p* and *B*1, Eq. (5-1) can be solved for . However, since Eq. (5-1) is typically an overdetermined system of linear equations (), the optimal solution is found by minimizing the following 2-norm for :

|  |  |  |
| --- | --- | --- |
|  |  | **(5-2)** |

Although Eq. (5-2) provides an estimate of the error propagated to the fitting parameters by an error in B1, it alone is insufficient to be used for optimal protocol design. qMT protocols must also be designed for robustness against noise that naturally occurs in measured signals. For this purpose, the Cramér-Rao lower bound (CRLB) has been shown to be an adequate and sufficient estimate to minimize the variance in fitted qMT parameters due to experimental noise [73]. Consider the Fisher information matrix (FIM) **J**, which has elements:

|  |  |  |
| --- | --- | --- |
|  |  | **(5-3)** |

where σ is the standard deviation of the noise, and **x***n* is the acquisition protocol for the *n*th measurement out of N unique measurements. The CRLB is defined as the diagonal elements of **J**-1, and the trace of this matrix provides an overall estimate of the minimum variance of a model. However, because the qMT fitting parameters differ largely in their order of magnitudes, the parameter-normalized CRLB (*V*) is defined instead [73]:

|  |  |  |
| --- | --- | --- |
|  |  | **(5-4)** |

In this work, we propose a regularization approach to simultaneously optimize against both noise (Eq. (5-4)) and B1-error propagation (Eq. (5-2)), using an iterative optimization approach for the acquisition protocol design [56]. Particularly, we are interested in minimizing the propagation of B1-error to the pool-size ratio *F* (Δ*F*) because of its demonstrated potential as a biomarker for myelin content. Thus, to optimally reduce an acquisition protocol of N unique measurements to N-1 measurements, each iteration evaluates:

|  |  |  |
| --- | --- | --- |
|  |  | **(5-5)** |

where λ is the regularization parameter constant, and **x**N-1 is the N-1 optimal qMT subset protocol of **x**N for a given iteration. The regularization parameter λ value controls the tradeoff between CRLB (noise) and *F* sensitivity to B1-inaccuracies during the optimization.

## Methods

The core qMT functions and routines used in the simulations and fitting of this work are from qMRLab (http://github.com/neuropoly/qMRLab), an open-sourced quantitative MRI software packaged that evolved from qMTLab [66] and is written in MATLAB (MATLAB 2017a; MathWorks Inc., Natick, MA). The additional source code developed in this work, particularly for numerically estimating the Jacobians matrices of the system, the protocol optimization algorithms, and the Monte Carlo simulations, is released as its own open-source package (http://github.com/mathieuboudreau/qMTLab\_Tabs). The code was developed to wrap around the qMRLab code, so that it may also be easily adaptable with other qMT software packages or in-house code.

### Uniform Protocols

The regularization term in Eq. (5-5) proposed for optimizing qMT parameters against B1-inaccuracies was derived using a first-order approximation of a Taylor series. To test this approximation, **Δ*p*** values (ΔF, Δkf, ΔT2,f, ΔT2,r) were calculated by solving Eq. (5-2) for a range of ΔB1 typically observed in vivo (±30%, with an actual B1 = 1.0 n.u.), and were compared to values estimated by fitting the signal to the Bloch-McConnell equations [11]. A “uniform” qMT measurement protocol was used, meaning a protocol with logarithmically uniform off-resonance frequencies for each MT flip-angle (αMT) preparation pulse. Jacobian sensitivity matrices calculations for Eq. (5-2) (and) were estimated from numerical partial derivatives (10-2 % relative increase in parameter values). Two different qMT cases were considered for : B1-independent T1 measurements (IR) and B1-dependent T1 measurements (VFA). Signal simulation details (protocol and tissue parameters) matched those described in full detail in a recent study [56].

Prior to protocol optimization, we were also interested in investigating values (from Eq. (5-2)) for other uniform qMT protocols with different numbers of MT flip angles and off-resonance values. MT-prepared SPGR (TR = 25 ms, α = 7°) pulse sequence protocols using every combination of three αMT values (150°, 400°, 650°) were used (each unique αMT, each combination of two αMT values, and all three). Logarithmically-uniform offset frequencies for each αMT values ranged between 300 Hz and 20 kHz. To fairly assess all uniform protocols, the total number of acquisitions were limited between 8 and 30 by varying the number of offset values per αMT sets. For example, a single-αMT 10-point protocol would have 10 off-resonance frequencies, and a two-αMT 10-point protocol would have the same 5 off-resonance frequencies for both αMT. qMT signals were simulated for tissue values within the typical white matter range (Table 5‑1). A 5% overestimation in B1 value (ΔB1 = +0.05 n.u.) relative to the expected value (B1 = 1 n.u.) was used for all protocols to solve Eq. (5-2) for , and a VFA T1 mapping method was assumed (TR = 15 ms, α = 3° and 20°).

### Protocol Optimization

qMT protocols were iteratively optimized [56] from a large initial search-space set of potential αMT and Δ protocol values, for fixed TR and α (25 ms and 7°). The most time-intensive component of the optimization algorithm is computing the Jacobian sensitivities ( and ). The Jacobian sensitivities were precomputed using parallel processing and cached for rapid access during the optimization algorithm execution. Note that both terms in Eq. (5-5) require element values from the Jacobian sensitivity matrices (through Eqs. (5-4) and (5-3)). The optimization search-space consisted of 312 points; each combination of 12 αMT values (ranging between 150° to 700°, in 50° increments) and 26 Δ values (ranging between 300 Hz and 20 kHz, with logarithmically uniform steps). A few (<5%) protocol points resulted in outlier numerical partial derivative values (non-smooth Jacobian sensitivity curve at those points), which may be due to signal simulation rounding errors or imprecise free-pool saturation fraction interpolations in the open-source software used. Those protocol points were replaced with the nearest-neighbor points calculated from a higher-resolution search-space (101 Δ values). The Jacobian sensitivity matrices were calculated for white matter tissue values (Table 5‑1).

Prior to protocol optimization, an optimal value for the regularization parameter λ was determined. The iterative optimization algorithm using Eq. (5-5) was executed for a range of λ values (λ = 0, 0.01, 0.1, 0.5, 1, 2, 5), assuming ΔB1 = 0.05 and VFA T1 mapping (TR = 15ms, α = 3° and 15°). Since TR, TE, and α were fixed for all protocol points, the standard deviation of the noise in Eq. (5-3) (σ) was arbitrarily set to 1 during the optimization calculations. The ΔF values and variance-efficiency curves ([variance × # acq. points]-1/2, where the variance is interpreted to be the parameter-normalized CRLB *V*) were compared for each N during the iterative optimization procedure. Two sets of 10-point protocols were optimized by iteratively finding the N-1 protocol subset that minimized Eq. (5-5) for ΔB1 = 0.05 (and assuming the VFA as above) and with and without regularization (CRLB and CRLBλ).

### Monte Carlo Simulations

Ideal (noiseless) MT-prepared SPGR signals were simulated for three 10-point protocols (Table 5‑2: Uniform, CRLB, and CRLBλ) and two tissue types (Table 5‑1: white matter, grey matter). Rician noise was added to each simulated MT signal and an MT-off signal, for normalization (*M*MT/*M*MT-off). Six different SNR levels were considered (SNR = 25, 50, 75, 100, 150, 200). Sets of 10,000 noisy MT signals were independently generated and compared for each combination of qMT protocols, tissues, and SNR. Each dataset was subsequently fitted for qMT parameters (F, kf , T2,f, and T2,r) considering a range of B1 errors (±30% in increments of 5%) and a two-FA VFA T1 mapping method (TR = 15ms, α = 3° and 15°).

Table ‑. qMT tissue parameters used to simulate white matter and grey matter tissue values in the Monte Carlo simulations. The parameter definitions are: F ­ pool-size ratio, kf  – exchange rate constant, T1,f – longitudinal relaxation time of the free pool, T1,r – longitudinal relaxation time of the restricted pool, T2,f – transverse relaxation time of the free pool, T2,r – transverse relaxation time of the restricted pool. The fitting parameters for qMT are F, kf, T2,f, and T2,r; T1,f is calculated from the observed T1 and the fitting parameters, and T1,r is conventionally fixed to 1 s.

|  |  |  |
| --- | --- | --- |
| Parameter | White Matter | Grey Matter |
| F | 0.15 n.u. | 0.075 n.u. |
| kf | 4.0 s-1 | 2.5 s-1 |
| T1,f | 0.9 s | 1.3 s |
| T1,r | 1.0 s | 1.0 s |
| T2,f | 30 ms | 55 ms |
| T2,r | 12 μs | 11 μs |

Table ‑. qMT protocols used in the Monte Carlo simulations. The repetition times, excitation flip angles, and number of acquisitions were matched for all protocols. The Uniform protocol is a two MT flip-angle with logarithmically uniform off-resonance frequencies. The CRLB protocol was optimized using Eq. (5-5) with the regularization parameter set to 0, and CRLBλ=0.5 was optimized using a regularization parameter of 0.5.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Uniform | | | CRLB | | | CRLBλ=0.5 | | |
| Acq. # | TR/α | αMT | Δ (Hz) | TR/α | αMT | Δ (Hz) | TR/α | αMT | Δ (Hz) |
| 1 | 25ms/7° | 142° | 432.9 | 25ms/7° | 200.0 | 300.0 | 25ms/7° | 200.0 | 300.0 |
| 2 | 1 087.5 | 250.0 | 1 903.9 | 250.0 | 1609.5 |
| 3 | 2 731.6 | 700.0 | 1 609.5 | 700.0 | 1609.5 |
| 4 | 6 861.6 | 700.0 | 12 083.6 | 700.0 | 12 083.6 |
| 5 | 17 235.5 | 700.0 | 1 903.9 | 700.0 | 2 252.2 |
| 6 | 426° | 432.9 | 250.0 | 2 252.2 | 200.0 | 1 903.9 |
| 7 | 1 087.5 | 150.0 | 300.0 | 650.0 | 300.0 |
| 8 | 2 731.6 | 700.0 | 1 360.6 | 200.0 | 1 360.6 |
| 9 | 6 861.6 | 200.0 | 1 609.5 | 700.0 | 1 903.9 |
| 10 | 17 235.5 | 700.0 | 2 252.2 | 150.0 | 300.0 |

## Results

### Uniform Protocols

Figure 5‑1 shows the simulated errors in each fitting parameter (ΔF, Δkf, ΔT2,f, ΔT2,r) estimated from the first-order approximation of the Taylor expansion in Eq. (5-2) (solid lines) and from the relative error in fit using the Sled and Pike model (dash line) in the presence of B1 errors (±30%). Data was simulated for a B1-independent T1 measure (IR, red) and a B1-dependent T1 measure (VFA, blue) separately. The overall trends in the error curves produced by model fits reproduced well similar simulations that were reported recently [75] (Boudreau et al 2017, Figure 3) even though they don’t share the same core qMT simulation and fitting software, establishing confidence in the use of this open-source qMTLab software [66] for this work.



Figure ‑. Simulated qMT parameter errors due to B1-inaccuracies (-30% < ΔB1 < 30%) considering a B1-independent T1 measurement (red: IR – inversion recovery) and a B1-dependent T1-measurement (blue: VFA – variable flip angle). Solid lines are parameter errors calculated from minimizing Eq. (5-2) (first-order approximation of the Taylor expansion), and dashed lines are parameter errors calculated from fitting the qMT signal according to the Sled & Pike model. The tissue parameters (white matter) and qMT protocol (uniform) were matched to those presented in Boudreau et al. 2017 (see Fig. 3 of the paper).

For B1 errors within ±5%, the errors in all parameters calculated from Eq. (5-2) approximated well the fitted estimates. For VFA T1 mapping and ΔB1 = 0.05 n.u. (+5 %), the Δ*p* values (Eq. (5-2), Fit) were: ΔF = (-0.94 %, -1.06 %), Δkf = (14.77 %, 16.88 %), ΔT2,f = (-2.56 %, -1.97 %), and ΔT2,r = (-0.51 %, -0.65%). Both ΔF (for VFA) and ΔT2,r showed linear trends for the “Fit” case, which resulted in an overall better agreement with Eq. (5-2). Resulting from these analyses, a ΔB1 of 0.05 n.u. was selected for the iterative optimization calculation (Eq. (5-5)) later in this work.

Figure 5‑2 shows the simulated errors of fitting parameters for a 5% ΔB1 (assuming VFA T1), using a wide range of uniform qMT acquisition protocols varying in number of FAMT, number of off-resonance frequencies per FAMT, and total number of acquisitions points. While most curves (sets of FAMT combinations) trended asymptotically with increasing number of acquisition points, they did not trend towards 0% parameter error values (except for a few ΔT2,r cases, # FA > 1 protocols that contain 650°). For ΔF, the three # FA = 1 curves (dark blue, orange, yellow) resulted in the largest ΔF values overall, demonstrating the benefit of including at least two flip angles in your qMT protocol in the context of lower B1-sensitivity. The three # FA > 1 protocols that included FA=650° (green, light blue, red) resulted in ΔF curves that overlapped and intercepted ΔF = 0 % values near 10 and 15 acquisition points, but increased in error for larger # of acquisition points.



Figure ‑. Simulated qMT parameter errors estimated from Eq. (5-2) for ΔB1=0.05 for a wide range of logarithmically-uniform (offsets) qMT protocols. Single (blue, orange, yellow), dual (purple, green, light blue), and triple (red) flip angle combinations of 150°, 400°, and 600° were compared. The number of offset frequencies were uniformly distributed between 300 Hz and 20 kHz, and matched for the total number of acquisition points (# offsets × # flip angles).

### Protocol Optimization

Figure 5‑3 displays the values of the Jacobian sensitivity matrices (**a-d** are the columns of , **e** is , and **f** is ). Each plot represents the sensitivity of the Z-spectrum relative to each parameter-of-interest (i.e. the change in Z-spectrum signal value due to a small increase in each parameter). The magnitude of the sensitivity values is shown to simplify interpretations; the sign of the sensitivity curves represents the direction (increase/decrease) that the Z-spectrum changes for small variations of each parameters, while we are mainly concerned in how large of an overall change occurs. A peak of the sensitivity curve for F occurs at off-resonance frequencies an order of magnitude higher for high FAMT (>500°) than for low FAMT values (~150-300°). For all FAMT values, the peak sensitivity for kf remained near Δ = 1-2 kHz. The peak sensitivity of also remained constant near Δ = 1-2 kHz, which may explain why kf has the largest errors due to ΔB1 (Eq. (5-1)) for the VFA case in Figure 5‑1. The higher sensitivity of F at high off-resonance (>10kHz) values (Figure 5‑3a), relative to (Figure 5‑3f), likely contributes to the greater robustness against B1 observed in the previous section.



Figure ‑. Sensitivity values (magnitudes) for each qMT fitting parameters (F, kf, T2,f, T2,r) and B1 measurement values considering a B1-independent T1 measure (IR – inversion recovery) and a B1-dependent T1 measure (VFA – variable flip angle). The 312-point protocol shown (12 flip angles x 26 offset frequencies) represents the initial search-space used for protocol optimization. The sets of sensitivity values for each fitting parameter (a–d) consists of the matrix columns of the Jacobian sensitivity matrix (S*p* in Eqs. (5-2) and (5-5)).

The optimal variance-efficiency and ΔF values (for ΔB1 = 5%) calculated at each iteration of the optimization algorithm using the 312-point initial search-space are shown in Figure 5‑4 for a wide range of regularization parameter (λ) values. The highest-valued variance-efficiency curve occurs for λ=0 (i.e. unregularized parameter-normalized CRLB) and λ = 0.01. For these values, the magnitude of ΔF steadily increased to 1% as the protocol was iteratively reduced to ~150 acquisition points, and then proceeded to decrease to ~0.5% for N < 25. Increasing the regularization parameter by an order of magnitude (λ = 0.1) substantially reduced ΔF values for N > 25 by up to a factor of two, while keeping the variance-efficiency relatively unaffected. However, for this case, ΔF returned to ~-0.5% abruptly for N < 25. A regularization parameter of 0.5 was the lowest value tested which succeeded in ΔF achieving values near 0% for small protocols; for N = 10, λ = 0.5 resulted in ΔF = -0.04% compared to -0.53 % for λ = 0, a factor of 13 in relative improvement of the B1-insensitivity of F. A small reduction in variance-efficiency accompanied the improvement of ΔF for λ = 0.5; for N=10, the variance-efficiency decreased by 6.3% for λ = 0.5 relative to λ = 0. For higher λ values, the regularization term in Eq. (5-5) dominated early in the iterative optimization at the cost of lower variance-efficiencies, which never recover to their unregularized values. For intermediately-high λ values (λ = 1, 2), a second region where the regularization term in Eq. (5-5) dominates the iterative optimization can be seen near N = 60 and 120 respectively, substantially reducing the variance-efficiency. Overall, a λ value of 0.5 showed the best compromise between decreasing ΔF (insensitivity of F against B1 errors) and maximizing variance-efficiency.



Figure ‑. Variance-efficiency (a) and ΔF (b) (Eq. (5-2), ΔB1 = 5%) values during the iterative optimization of the sensitivity-regularized Cramer-Rao Lower-Bound equation (Eq. (5-5)). Variance-efficiency is defined here as (variance × # acq. points)-1/2, where the variance is interpreted to be the parameter-normalized Cramer-Rao Lower Bound (*V*, Eq. (5-3)).

The 10-point protocols optimized using λ = 0 (CRLB) and λ = 0.5 (CRLBλ=0.5) are shown in Figure 5‑5, overlaid on the 312-point protocol search-space (displayed as line plots for better visibility of the optimized protocols). The details of these protocols are listed in Table 5‑2. Overall, both optimized protocols share 7 out of 10 (Δ, FAMT) pairs, with only three acquisition points changing if the regularization term is included in Eq. (5-5) (λ = 0.5). Both protocols have coverage of low, medium, and high off-resonance values, as well as low and high FAMT values.



Figure ‑. Comparison between the 10-point protocols iteratively optimized from a 312-point search space using solely the parameter-normalized CRLB (λ = 0) and regularized CRLBλ=0.5. The different flip angle Z-spectrums of the initial optimization search-space are displayed in blue to emphasize the 10-point protocols. The flip angle Z-spectrums (150° to 700°, in 50° increments) range from the highest MT-signal values curve (150°) to lowest (700°).

### Monte Carlo Simulations

Distributions statistics (mean, σ) of the Monte Carlo simulations of the fitted parameter-of-interest F are shown for a range of ΔB1 values (SNR = 100) in Figure 5‑6 and a range of SNR values (ΔB1 = 0 and 15 %) in Figure 5‑7, for the three protocols listed in Table 5‑2. Figure 5‑6a and b displays the difference (%) in mean F relative to the mean F value for the ΔB1 = 0 case, whereas Figure 5‑7a and b displays the difference (%) in mean F relative to the ideal (noiseless) fitted F value.



Figure ‑. Means (a, b) and standard deviations (c, d) of the distribution of pool-size ratios (F) for sets of Monte Carlo simulations (10,000 runs, SNR = 100) fitted using a range of B1 errors (ΔB1 = ±30%, B1 = 1 n.u.) and for two sets of qMT parameters (white matter – a,c; grey matter – b, d). Mean F values (% error) shown here were compared relative to the accurate B1 value case (ΔB1 = 0), and the grey region represents the region of ±1% relative error. Simulated signal values were generated and fitted for three different 10-point qMT protocols: Uniform (blue) – two-FA protocol with logarithmically-uniform off-resonance frequency values, CRLB (red) – protocol optimized by iteratively minimizing the increase in the parameter-normalized Cramer-Rao Lower-Bound of the system, and CRLBλ=0.5 (yellow) – protocol optimized similar to CRLB, regularized by the estimated error of F (ΔF) in the presence of a B1 error (Eq. (5-5)).



Figure ‑. Means (a, b) and standard deviations (c, d) of the distribution of pool-size ratio values (F) for sets of Monte Carlo simulations (10,000 runs) fitted using a range of SNR values (25, 50, 75, 100, 150, and 200) and for two sets of qMT parameters (white matter – a,c; grey matter – b, d). Mean F values (% error) shown here were compared relative to data fitted for an ideal SNR case (noiseless), and the grey region represents the region of ±1% relative error. Data was fitted assuming ideal B1 values (B1 = 1 n.u., solid lines) and a 15% overestimation in B1 (B1 = 1.15 n.u., dotted lines). Simulated signal values were generated and fitted for three different 10-point qMT protocols: Uniform (blue) – two-FA protocol with logarithmically-uniform off-resonance frequency values, CRLB (red) – protocol optimized by iteratively minimizing the increase in the parameter-normalized Cramer-Rao Lower-Bound of the system, CRLBλ=0.5 (yellow) – protocol optimized similar to CRLB, regularized by the estimated error of F (ΔF) in the presence of a B1 error (Eq. (5-5)).

For the CRLBλ=0.5 protocol, values were less than 1% (grey area) for ΔB1 between -10% and 20% (Figure 5‑6, for both WM and GM). The same was true for ΔB1 between -5% and 10% for the CRLB protocol, and between -5% and 5% for the Uniform protocol. CRLB and CRLBλ=0.5 protocols resulted in standard deviations of fitted F substantially lower (by a factor of ~1.75) than the Uniform protocol. Although CRLBλ=0.5 σF values were slightly different than the CRLB values (6.7% higher), both curves nearly overlapped for all ΔB1 values.

In the absence of B1 errors (ΔB1 = 0), values for both optimized protocols (CRLB and CRLBλ=0.5) were below 1% for datasets with SNR values greater than 75 (Figure 5‑7, WM and GM). The Uniform protocol needed a minimum SNR of 100 to result in values below 1%. In the presence of a 15% overestimation of B1, the vs. SNR curve for CRLBλ=0.5 remained largely unchanged for WM. For GM, the values for CRLBλ=0.5 resulted in slight increase, although remained within 1% for SNR > 100. In contrast, even at high SNR values (>100), values for the CRLB and Uniform protocols resulted in greater bias (>1%) for the ΔB1 = 15% case. The σF curves increased rapidly for SNR values lower than 75 for all protocols. For all cases, σF did not vary substantially between both ΔB1 values evaluated (0% and 15%). For CRLB and CRLBλ=0.5, no substantial differences in their σF vs. SNR curves were observed, and both had lower standard deviations relative to the Uniform protocol.

## Discussion

This work describes a qMT protocol optimization methodology for reduced B1-sensitivity of the pool-size ratio F by regularizing the CRLB with a first-order sensitivity analysis. Using Monte Carlo simulations we found that, for a protocol optimized using regularized CRLBλ=0.5, errors propagated to fitted F were below 1% for B1-errors ranging between -10 and 20%, consistent with the B1 values typically observed in the human brain at 3T [76]. Both regularized and conventional CRLB optimization resulted in an improvement of pool-size ratio B1-insensitivity relative to a two-FAMT uniform protocol. Sensitivity analyses of uniform protocols suggested that, if using VFA T1 mapping, acquiring data at both small and large MT flip angle acquisitions (at mid and high off-resonance frequencies) may be an important contributing factor in designing a B1-insensitive acquisition protocol, where F likely has a higher robustness against B1 errors. These simulations demonstrate for a range of SNRs, B1-inaccuracies, and brain tissues, the effectiveness of a regularized approach of designing qMT for B1-insensitivity. This work suggests that if the pool-size ratio is the primary parameter-of-interest, it may be possible to design a qMT protocol robust enough to omit B1 map acquisition altogether, without substantially biasing estimates of F.

Our study considered a specific qMT fitting model (Sled and Pike[11]) that fitted quantitative MT data for four parameters of the Bloch-McConnell equations (F, kf, T2,f, T2,r). Several other qMT fitting models for MT-prepared SPGR data exist, such as Yarnykh’s model [53], which neglects direct saturation effects, and Ramani’s continuous wave power equivalent model [54]. Each qMT fitting model makes different approximations or assumptions, and differ in fitting parameters. For example, Yarnykh’s model suggests acquiring data only at off-resonance frequencies greater than 1 kHz, and has a different set of fitting parameters (e.g. T2,f is neglected and their pool-size ratio parameter is defined as *f* = M0,r / (1+ M0,r), instead of Sled and Pike’s F = M0,r / M0,f parameter). The different range in off-resonance frequencies will reduce the available Jacobian sensitivity values during optimization, which may impact the optimization against auxiliary measurements (e.g. B1) errors. Different sets of fitting parameters between models could also change the fitting behavior in the presence of B1-error propagation, even if the same SPGR qMT acquisition protocols are used. The single-point qMT fitting model [67,68] may provide additional challenges for optimizing against auxiliary measurement error-sensitivity. This fitting model imposes several fitting parameter restraints, which would provide additional limitations when solving Eq. (5-2). The analysis of uniform protocols and Jacobian sensitivity matrices also suggests that B1-insensitivy of F may be a result of including both small and large MT flip angle acquisitions in a protocol at mid and high off-resonance frequencies, a configuration that cannot be done using single-point measurement protocol.

We proposed a regularization approach to add an auxiliary measurement (e.g. B1) error-sensitivity component to the CRLB in our optimization algorithm. An alternative approach could have been to do a formal statistical analysis of the error propagation using the CRLB instead as the optimization algorithm condition. Lankford and Does [77] recently presented such a treatment and applied it to study T2 mapping. Their statistical analysis of the error propagation from parameter constraints demonstrated that, under certain practical circumstances, it can be beneficial (in terms of variance and full mean-squared error of fitted T2) to include a B1 measurement for multi-echo T2 mapping. Their framework was presented to be generalizable to other quantitative techniques that require auxiliary measurements such as qMT; however, their analysis was only developed for a single-level of parameter constraints. Although this may be applicable for a B1-error propagation analysis of qMT when using a B1-independent T1 mapping method (e.g. IR), a B1-dependent T1 mapping method (e.g. VFA) complicates the error propagation analysis beyond what is presented in Lankford and Does, as there are two interacting constraints within the qMT model (e.g. qMT(B1, T1(B1)). In contrast, one benefit of the sensitivity-regularization approach we presented here is its conceptual simplicity and ease of implementation for optimization applications, particularly for this case. Nonetheless, a formal propagation of error analysis would likely be a good choice moving forward to compare the sensitivity to errors in constraints between different qMT fitting models, as discussed above.

Several limitations should be considered when interpreting this work. An iterative optimization approach was chosen to estimate optimal acquisition protocols from a larger initial search space, however this approach is not guaranteed to result in the global minima of the optimization condition. Global optimization using simulated annealing [73] could have been another valid approach to optimize our qMT protocol using Eq. (5-5). However, iterative optimization approaches benefit from an ease of implementation, rapid computation, and the flexibility to choose the number of measurements in the protocol after the optimization is complete. In contrast, simulated annealing approaches optimize for a fixed pre-determined number of protocol points. We also opted for Monte Carlo simulations instead of an in vivo study to validate the regularized approach to B1-sensitivity protocol optimization. This gave us the flexibility to accurately know and control the system conditions (e.g. tissue values, B1 error values, and noise level). In vivo evidence of the benefits of qMT protocol optimization using CRLB has already been reported in several studies [56,73,74]. In addition, Eqs. (5-1) and (5-2) (used to establish the regularization term) were developed from a recent comprehensive B1-sensitivity analysis of qMT study [75] that compared and validated simulations with in vivo measurements of F in the absence of B1 maps (for a uniform protocol). Lastly, the optimization algorithm investigated here only considered a single tissue type (WM) during the protocol optimization procedure. Although the resulting protocol was also evaluated for another tissue type in the Monte Carlo simulations (GM) and both were restricted to errors below 1%, even though the B1-sensitivity of F in GM varied more than for WM. If desired, the optimization condition (Eq. (5-5)) could be adapted to consider multiple tissue types in a similar manner as proposed by Cercignani et al [73], by instead minimizing for the tissue which results in the maximum value of Eq. (5-5) at each iteration.

Overall, this work presents a framework for designing qMT acquisition protocols optimized for robustness against inaccuracies of auxiliary measurements (e.g. B1) by regularizing the Cramér-Rao lower bound with fitting parameter-sensitivity information. We demonstrated this methodology by optimizing a qMT protocol for robustness of the pool-size ratio (F) against B1-inaccuracies, and studied simulations using this protocol for a wide range of signal-to-noise ratios, B1-inaccuracies, and tissue types. These findings imply that B1 mapping possibly be omitted from such a qMT optimized acquisition protocol with minimal impact to the fitted pool-size ratio (< 1% error). Potential future work may include optimizing protocols for reduced sensitivity of other or multiple auxiliary measurements, and compare this optimization between other qMT fitting models. Another interesting approach could be to combine Z-spectrum compressed sensing [78] with this optimization technique, to maximize the auxiliary measurement insensitivity by increasing the number of measurements while reducing the total acquisition time.

# *Conclusion*

## Summary

* Paragraph 1: Broad overview of thesis
  + Setting up the role of qMT in the context of MS research
  + Setting up the broad question(s) of the thesis.
  + 1-2 line descriptions of each paper.
* Paragraph 2: Paper 1 summary
* Paragraph 3: Paper 2 summary
* Paragraph 4: Paper 3 summary

## Future Work

* Paragraph 1: State what we investigated was subsets of qMT/calibration measurements as a whole (e.g. looked at a single model of qMT => SPGR Sled & Pike, single calibration measurement => B1).
* Paragraph 2: Sensitivity analyses/optimization of the other qMT calibration measurements
  + T1 (refer to Stikov 2015 for differences between methods)
    - VFA shown to typically overestimate T1 relative to IR
    - In this paper we proposed that this may be to not fully spoiled magnetization
    - A very recent paper proposed a correction method to account for the unspoiled magnetization effect for VFA [79], which results in a reduction in T1 estimation relative to the uncorrected values.
  + B0
  + Potentially simultaneously optimizing for all three?
* Paragraph 3: Sensitivity analyses of other qMT fitting models and measurement methods
  + Other SPGR fitting models (Yarnykh, Ramani, Yarnykh single-point)
  + Other MT acquisition methods (bSSFP, inversion preparation)
  + Using Lankford’s theory to compare between these?
* Paragraph 4: Further accelerating qMT measurements
  + Compressed sensing?
  + MR Fingerprinting/Machine learning?
* Paragraph 5: Other applications for qMT
  + g-ratio
  + Other diseases

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