

Advances in Quantitative MRI: Acquisition, Estimation, and Applications

by

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LIST OF ABBREVIATIONS

ABSTRACT

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We show that it is possible to get approximate solutions to analytically intractable equations using iterative methods. Thus we show that the author could pass an undergraduate class in numerical analysis. In addition, a unique extension to Brent's method is proposed that results in slight improvements in convergence.

CHAPTER 1

Introduction

{c,intro}

Magnetic resonance imaging (MRI) is a non-invasive tool that has earned widespread clinical adoption due (among other factors) to its potential for excellent soft tissue contrast, its avoidance of ionizing radiation, and its flexibility to characterize many physical phenomena. Despite its numerous advantages, MRI requires highly specialized hardware, ongoing liquid-helium cooling of its superconducting main magnet, and comparably long scan times. For these reasons, MRI is (somewhat inherently) expensive relative to other medical imaging modalities. Accordingly, one broad initiative recently advocated by the MR community is to increase the *value* of MRI examinations.

Two reasonable measures of an acquisition’s value are its sensitivity to a given disorder and its specificity in distinguishing it from others. The field of *pathology* seeks to ascribe physical processes to disorders of interest with high sensitivity and specificity. The field of *quantitative MRI* (QMRI) seeks to build MRI biomarkers that measurably describe such physical processes and thereby provide indirect information about the onset and progression of underlying conditions.

QMRI poses several challenges beyond those of commonplace anatomical MRI and thus remains yet to be widely adopted clinically. For example, latent parameter “maps” that describe relevant physical processes are often related to the received MR signal through complicated, highly nonlinear relationships. Furthermore, practical MR pulse sequences produce signals that are usually functions of not only desired but also nuisance parameters. Scan repetition is often necessary for accurate estimation of multiple desired and nuisance parameters, which can increase scan times. Mitigating these challenges (and likely others) is essential to furthering widespread clinical adoption of QMRI techniques.

1.1 Thesis Overview

{s,intro,over}

In this thesis, we seek to build a systematic framework towards QMRI. We borrow tools from optimization, statistics, and machine learning to construct time-efficient workflows for quantifiably characterizing physical processes of interest. We apply this framework to challenging QMRI problems that are motivated by pathological studies. Our goal is to introduce tools that aid in identifying clinical tasks for which QMRI should (or should not) be part of a targeted, high-value MRI examination.

We consider two distinct subproblems in our framework. Questions in *acquisition design* (Chapters 4,6) ask how to assemble fast collections of scans that yield data rich in information about physical processes of interest. Questions in *parameter estimation* (Chapters 3,5) ask how to quickly and reliably quantify parameters associated with these relevant physical processes. The overall framework seeks to first design fast and informative scans based on the application, and to then accurately and precisely estimate application-specific parameters of interest.

1.2 Thesis Organization

{s,intro,org}

The main body of this thesis is organized as follows:

- Chapter 2 reviews relevant background MR material about DESS,SPGR,blahblah...
- Chapter 3 discusses methods for MRI parameter estimation from likelihood models and applies these methods for model-based MR relaxometry, (*i.e.*, estimation of relaxation parameters T_1, T_2), of interest for many neurological applications. It derives some content (especially regarding applications) from conference papers [1, 2].
- Chapter 4 introduces a minimax optimization approach to aid robust and application-specific MR scan selection and optimization for precise latent parameter estimation. It optimizes several practical acquisitions and uses the likelihood-based estimation techniques introduced in Chapter 3 to assess the utility of scan optimization through simulations, phantom studies, and *in vivo* experiments. It derives content mainly from journal paper [3] and conference paper [4].
- Chapter 5 describes MRI parameter estimation using kernel ridge regression. It derives content from conference paper [5].
- Chapter 6 introduces a multi-compartmental model for relevant MR pulse sequences and proposes a new acquisition useful for myelin water fraction estimation, of in-

terest in white matter disorders. It applies kernel-based MR parameter estimation to estimate myelin water fraction, in simulations and *in vivo* experiments. It derives some content from conference paper [6].

- Chapter 7 presents some relatively immature ideas on steady-state radiofrequency (RF) pulse design as well as associated challenges. This work is presently unpublished and may offer avenues for further research.
- Chapter 8 summarizes several items of possible future work (on both short- and long-term timescales) and presents a timeline for completion of this thesis.

The appendices are organized as follows:

- Appendix A proposes an algorithm for combining multiple MRI datasets (as is necessary for many parameter estimation problems), when each dataset is acquired using multiple receiver coils.
- Appendix B presents an analysis of DESS in the presence of diffusion, shows that neglecting diffusive effects during T_2 estimation from DESS can cause significant bias, and suggests acquisition modifications for mitigating this bias.

CHAPTER 2

Background

{c,bkgrd}

This chapter focuses only on background information pertinent to multiple subsequent chapters. We present further topic-specific information at the beginnings of corresponding chapters. Section 2.1 places emphasis on reviewing necessary MR fundamentals, and Section 2.2 proceeds to a shorter discussion regarding optimization as it pertains to QMRI.

2.1 Relevant MR Physics

{s,bkgrd,mri}

This section begins with the fundamental Bloch equations and derives the signal models associated with two MR pulse sequences used extensively in this thesis. Our coverage of MRI is far from comprehensive, and omits fundamental but tangential topics such as signal localization. We refer the interested reader to books such as [7, 8, 9].

2.1.1 Bloch Equations

{ss,bkgrd,mri,bloch}

The Bloch equations [10] describe the magnetization dynamics of *spins*, or (loosely) atomic nuclei with nonzero angular momentum and thus nonzero magnetic moment, *e.g.* ^1H . If the dominant source of magnetic flux arises (as is typical in MRI) from a main magnetic field that is oriented along the z -axis, the equations read

{eq:bloch-mxy}
$$\frac{\partial}{\partial t} m_{xy}(\mathbf{r}, t) = i\gamma(m_z(\mathbf{r}, t)b_{xy}(\mathbf{r}, t) - m_{xy}(\mathbf{r}, t)b_z(\mathbf{r}, t)) - \frac{m_{xy}(\mathbf{r}, t)}{T_2(\mathbf{r})}; \quad (2.1)$$

{eq:bloch-mz}
$$\frac{\partial}{\partial t} m_z(\mathbf{r}, t) = \gamma(m_x(\mathbf{r}, t)b_y(\mathbf{r}, t) - m_y(\mathbf{r}, t)b_x(\mathbf{r}, t)) - \frac{m_z(\mathbf{r}, t) - m_0(\mathbf{r})}{T_1(\mathbf{r})}. \quad (2.2)$$

Here, $m_{xy}(\mathbf{r}, t) := m_x(\mathbf{r}, t) + im_y(\mathbf{r}, t) \in \mathbb{C}$ and $m_z(\mathbf{r}, t) \in \mathbb{R}$ are the transverse and longitudinal components of the magnetization vector at position $\mathbf{r} \in \mathbb{R}^3$ and time $t \geq 0$; $b_{xy}(\mathbf{r}, t) := b_x(\mathbf{r}, t) + ib_y(\mathbf{r}, t) \in \mathbb{C}$ and $b_z(\mathbf{r}, t) \in \mathbb{R}$ are the transverse and longitudinal components (in an inertial reference frame) of the applied magnetic field; $T_1(\mathbf{r})$ and $T_2(\mathbf{r})$

are spin-lattice and spin-spin relaxation time constants; $m_0(\mathbf{r})$ is the equilibrium magnetization and is proportional to the density of spins per unit volume as well as the main field strength; γ is the gyromagnetic ratio; and $i := \sqrt{-1}$. As written, equations (2.1)-(2.2) only model dominant temporal dynamics; later chapters consider second-order effects such as multiple magnetization compartments (Chapter 6) and diffusion (Appendix B).

It is often convenient to study Bloch dynamics in a non-inertial reference frame rotating clockwise about the z -axis at Larmor frequency $\omega_0 := \gamma B_0$, where $B_0 \hat{k}$ is the (nearly uniform) main magnetic field. In these coordinates, the apparent transverse magnetic field $b'_{xy}(\mathbf{r}, t) = b'_x(\mathbf{r}, t) + ib'_y(\mathbf{r}, t) := b_{xy}(\mathbf{r}, t)e^{i\omega_0 t}$ transforms only in phase, but the apparent longitudinal magnetic field $b'_z(\mathbf{r}, t) := b_z(\mathbf{r}, t) - B_0$ is greatly reduced in magnitude. The magnetization components transform more simply as $m'_{xy}(\mathbf{r}, t) = m'_{xy}(\mathbf{r}, t) + im'_y(\mathbf{r}, t) := m_{xy}(\mathbf{r}, t)e^{i\omega_0 t}$ and $m'_z(\mathbf{r}, t) := m_z(\mathbf{r}, t)$. Remarkably, inserting these coordinate transformations into (2.1)-(2.2) does not change the form of the dynamical equations:

$$\text{\textcolor{blue}{\{eq:bloch-mxyp\}}} \quad \frac{\partial}{\partial t} m'_{xy}(\mathbf{r}, t) = i\gamma(m'_z(\mathbf{r}, t)b'_{xy}(\mathbf{r}, t) - m'_{xy}(\mathbf{r}, t)b'_z(\mathbf{r}, t)) - \frac{m'_{xy}(\mathbf{r}, t)}{T_2(\mathbf{r})}; \quad (2.3)$$

$$\text{\textcolor{blue}{\{eq:bloch-mzp\}}} \quad \frac{\partial}{\partial t} m'_z(\mathbf{r}, t) = \gamma(m'_x(\mathbf{r}, t)b'_y(\mathbf{r}, t) - m'_y(\mathbf{r}, t)b'_x(\mathbf{r}, t)) - \frac{m'_z(\mathbf{r}, t) - m_0(\mathbf{r})}{T_1(\mathbf{r})}. \quad (2.4)$$

It thus suffices to consider how perturbations $\mathbf{b}'(\mathbf{r}, t)$ to main field $B_0 \hat{k}$ influence rotating-frame magnetization $\mathbf{m}'(\mathbf{r}, t)$ via Eqs. (2.3)-(2.4). The inertial-frame magnetization $\mathbf{m}(\mathbf{r}, t)$ is then easily constructed via $m_{xy}(\mathbf{r}, t) = m'_{xy}(\mathbf{r}, t)e^{-i\omega_0 t}$ and $m_z(\mathbf{r}, t) = m'_z(\mathbf{r}, t)$.

It is challenging to explicitly solve Eqs. (2.3)-(2.4) for arbitrary field perturbations $\mathbf{b}'(\mathbf{r}, t)$. We discuss relevant special cases in the following.

2.1.1.1 Non-Selective Excitation

Here, we derive solutions to Eqs. (2.3)-(2.4) in the case of short, spatially non-selective excitations. We take the following common assumptions:

- We assume negligible spatial variation in the longitudinal magnetic field, so $b'_z(\mathbf{r}, t) \approx 0$. This lack of spatial variation is reason for non-selective excitation.
- We assume that the duration T_P of RF excitation (often $T_P \sim 1\text{ms}$) is much shorter than relaxation time constants (typically $T_1 \sim 1000\text{ms}$ and $T_2 \sim 50\text{ms}$ in brain tissue) and thus neglect relaxation effects during excitation.
- We assume the transverse field separates in position and time; oscillates at the Larmor frequency (commonly in the radiofrequency (RF) range); and aligns at initial

time $t \leftarrow t_0$ with the x -axis. Together, these assumptions restrict the so-called RF excitation to take form $b'_{xy}(\mathbf{r}, t) \approx s^t(\mathbf{r})b'_{1,x}(t)\hat{i} + 0\hat{j}$, where $s^t(\mathbf{r}) \in \mathbb{R}$ is the RF transmit coil spatial variation and $b'_{1,x}(t) \in \mathbb{R}$ is the RF excitation envelope.

Under these assumptions, Eqs. (2.3)-(2.4) reduce to the linear system

$$\frac{\partial}{\partial t} \begin{bmatrix} m'_x(\mathbf{r}, t) \\ m'_y(\mathbf{r}, t) \\ m'_z(\mathbf{r}, t) \end{bmatrix} = \begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & \gamma s^t(\mathbf{r})b'_{1,x}(t) \\ 0 & -\gamma s^t(\mathbf{r})b'_{1,x}(t) & 0 \end{bmatrix} \begin{bmatrix} m'_x(\mathbf{r}, t) \\ m'_y(\mathbf{r}, t) \\ m'_z(\mathbf{r}, t) \end{bmatrix}. \quad (2.5)$$

Eq. (2.5) admits the simple solution (for $t \geq t_0$)

$$\begin{bmatrix} m'_x(\mathbf{r}, t) \\ m'_y(\mathbf{r}, t) \\ m'_z(\mathbf{r}, t) \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \cos(\alpha(\mathbf{r}, t; t_0)) & \sin(\alpha(\mathbf{r}, t; t_0)) \\ 0 & -\sin(\alpha(\mathbf{r}, t; t_0)) & \cos(\alpha(\mathbf{r}, t; t_0)) \end{bmatrix} \begin{bmatrix} m'_x(\mathbf{r}, t_0) \\ m'_y(\mathbf{r}, t_0) \\ m'_z(\mathbf{r}, t_0) \end{bmatrix}, \quad (2.6)$$

where $\mathbf{m}'(\mathbf{r}, t_0) := [m'_x(\mathbf{r}, t_0), m'_y(\mathbf{r}, t_0), m'_z(\mathbf{r}, t_0)]^\top$ is the initial magnetization and

$$\alpha(\mathbf{r}, t; t_0) := \gamma s^t(\mathbf{r}) \int_{t_0}^t b'_{1,x}(\tau) \, d\tau \quad (2.7)$$

is the nutation (or “flip”) angle at time t . Eq. (2.6) reveals that on-resonance RF excitation causes the magnetization vector to rotate clockwise about an axis parallel to the direction of excitation. The nutation angle accumulated over an RF pulse of duration T_P is often decomposed as $\alpha(\mathbf{r}, t_0 + T_P; t_0) =: \alpha_0 s^t(\mathbf{r})$, where α_0 is a prescribed nominal flip angle.

For deriving signal models in later sections, it is convenient and intuitive to define matrix operators that summarize relevant dynamics. Here, we rewrite Eq. (2.6) as

$$\mathbf{m}'(\mathbf{r}, t) = \mathbf{R}_{x'}(\alpha(\mathbf{r}, t; t_0))\mathbf{m}'(\mathbf{r}, t_0), \quad (2.8)$$

where $\mathbf{R}_{x'}(\alpha(\mathbf{r}, t; t_0))$ denotes a clockwise rotation of angle $\alpha(\mathbf{r}, t; t_0)$ about the x' -axis.

2.1.1.2 Free Precession and Relaxation

Next, we derive solutions to the rotating-frame Bloch equations when no RF excitation is present, *i.e.* $b'_{xy}(\mathbf{r}, t) \approx 0$. In this case, Eqs. (2.3)-(2.4) decouple, yielding separate

dynamical equations for the transverse and longitudinal magnetization components:

$$\{\text{eq:bloch-free-mxyp}\} \quad \frac{\partial}{\partial t} m'_{xy}(\mathbf{r}, t) = -i\gamma m'_{xy}(\mathbf{r}, t) b'_z(\mathbf{r}, t) - \frac{m'_{xy}(\mathbf{r}, t)}{T_2(\mathbf{r})}; \quad (2.9)$$

$$\{\text{eq:bloch-free-mzp}\} \quad \frac{\partial}{\partial t} m'_z(\mathbf{r}, t) = -\frac{m'_z(\mathbf{r}, t) - m_0(\mathbf{r})}{T_1(\mathbf{r})}. \quad (2.10)$$

Eqs. (2.9)-(2.10) admit simple solutions with no further assumptions:

$$\{\text{eq:mxy-fp}\} \quad m'_{xy}(\mathbf{r}, t) = m'_{xy}(\mathbf{r}, t_0) e^{-(t-t_0)/T_2(\mathbf{r})} e^{-i\phi'(\mathbf{r}, t; t_0)}; \quad (2.11)$$

$$\{\text{eq:mz-fp}\} \quad m'_z(\mathbf{r}, t) = m'_z(\mathbf{r}, t_0) e^{-(t-t_0)/T_1(\mathbf{r})} + m_0(\mathbf{r}) (1 - e^{-(t-t_0)/T_1(\mathbf{r})}), \quad (2.12)$$

where $m'_{xy}(\mathbf{r}, t_0)$ and $m'_z(\mathbf{r}, t_0)$ are the initial magnetization components and

$$\{\text{eq:ph-def}\} \quad \phi'(\mathbf{r}, t; t_0) := \gamma \int_{t_0}^t b'_z(\mathbf{r}, \tau) d\tau \quad (2.13)$$

denotes the phase accumulation due to main field inhomogeneity (often called off-resonance effects). Eq. (2.11) reveals that without RF excitations, the transverse magnetization $m'_{xy}(\mathbf{r}, t)$ relaxes to zero exponentially fast with time constant $T_2(\mathbf{r})$, while accruing phase due to off-resonance effects. Eq. (2.12) similarly reveals that without RF excitations, longitudinal magnetization $m'_z(\mathbf{r}, t)$ recovers to $m_0(\mathbf{r})$ exponentially fast with time constant $T_1(\mathbf{r})$.

As in Section 2.1.1.2, we rewrite Eqs. (2.11)-(2.12) for $t \geq t_0$ using matrix operators:

$$\{\text{eq:mtx-pr}\} \quad \mathbf{m}'(\mathbf{r}, t) = \mathbf{R}_{z'}(\phi'(\mathbf{r}, t; t_0)) \mathbf{E}(\mathbf{r}, t; t_0) \mathbf{m}'(\mathbf{r}, t_0) + \mathbf{m}_0(\mathbf{r}, t; t_0) \quad (2.14)$$

where $\mathbf{m}_0(\mathbf{r}, t; t_0) := m_0(\mathbf{r}) (1 - e^{-(t-t_0)/T_1(\mathbf{r})}) \hat{k}$;

$$\{\text{eq:op-rotz}\} \quad \mathbf{R}_{z'}(\phi'(\mathbf{r}, t; t_0)) := \begin{bmatrix} \cos(\phi'(\mathbf{r}, t; t_0)) & \sin(\phi'(\mathbf{r}, t; t_0)) & 0 \\ -\sin(\phi'(\mathbf{r}, t; t_0)) & \cos(\phi'(\mathbf{r}, t; t_0)) & 0 \\ 0 & 0 & 1 \end{bmatrix} \quad (2.15)$$

denotes a clockwise rotation of angle $\phi'(\mathbf{r}, t; t_0)$ about the z' -axis; and

$$\{\text{eq:op-relax}\} \quad \mathbf{E}(\mathbf{r}, t; t_0) := \begin{bmatrix} e^{-(t-t_0)/T_2(\mathbf{r})} & 0 & 0 \\ 0 & e^{-(t-t_0)/T_2(\mathbf{r})} & 0 \\ 0 & 0 & e^{-(t-t_0)/T_1(\mathbf{r})} \end{bmatrix} \quad (2.16)$$

is an exponential relaxation operator. Section 2.1.2 (and later chapters) use matrix dynamical representations (2.8) and (2.14) to succinctly describe pulse sequence signal models.

{ss,bkgrd,mri,ss}

2.1.2 Steady-State Sequences

MRI experiments typically involve repeated cycles of (pulsed) RF excitation; signal localization (not discussed here); and transverse T_2 relaxation and free precession, alongside (relatively slow) longitudinal T_1 recovery. We can build models of the received MR signal by considering the magnetization dynamics induced by specific pulse sequences.

Classical pulse sequences use relatively long cycle repetition times T_R to ensure near-complete T_1 recovery of the magnetization vector back to equilibrium state $m_0(\mathbf{r})\hat{k}$ prior to the start of each RF cycle. For such long- T_R sequences, it suffices to approximate the magnetization as fully recovered (*i.e.*, $\mathbf{m}'(\mathbf{r}, t_0 + nT_R) \approx m_0(\mathbf{r})\hat{k}, \forall n \in \{0, 1, 2, \dots\}$) just prior to each RF excitation. This approximation yields a sequence of initial conditions and allows computation of the magnetization at corresponding times of data acquisition via direct application of Bloch dynamics (2.8) and (2.14). Resulting signal models are typically simple expressions of relaxation parameters $T_1(\mathbf{r})$ and $T_2(\mathbf{r})$; however, model accuracy often depends strongly on the long- T_R assumption, which requires long acquisitions.

Steady-state (SS) sequences [11] utilize short T_R , and can thus achieve much faster scan times. Due to short repetition times, SS sequences achieve only partial T_1 recovery in between RF excitations; thus, their magnetization responses do not obey the simple classical initial conditions (for the second RF cycle onwards). Although their transient magnetization dynamics can be complicated, SS sequences produce (under certain assumptions [12]) long-time magnetization responses that eventually¹ achieve a steady-state condition:

{eq:ss-cond}

$$\lim_{t_0 \rightarrow \infty} \mathbf{m}'(\mathbf{r}, t_0 + nT_R) = \mathbf{m}'(\mathbf{r}, t_0), \quad (2.17)$$

where repetition count $n \in \{0, 1, 2, \dots\}$ for fixed RF excitations and off-resonance induced phase increments (as is assumed in the following). Subsections 2.1.2.1 and 2.1.2.2 use SS condition (2.17) and Bloch equation matrix operators introduced in (2.8) and (2.14) to derive long-time signal models for Spoiled Gradient-Recalled Echo (SPGR) and Dual-Echo Steady-State (DESS), two SS pulse sequences useful for quantitative MRI.

¹The progression to steady state takes on the order of $5T_2/T_R$ RF cycles [12], typically a small but not insignificant period during which data acquisition is often foregone. This transition can (in some cases) be accelerated by prepending SS sequences with tailored “magnetization-catalyzing” modules [13].

`{sss,bkgrd,mri,ss,spgr}` **2.1.2.1 Spoiled Gradient-Recalled Echo (SPGR) Sequence**

`{sss,bkgrd,mri,ss,dess}` **2.1.2.2 Dual-Echo Steady-State (DESS) Sequence**

2.2 Relevant Optimization Tools

`{s,bkgrd,opt}`

2.2.1 (Coping with) Non-convex Optimization

`{ss,bkgrd,opt,ncvx}`

2.2.2 Partially Linear Models and the Variable Projection Method

`{ss,bkgrd,opt,vpm}`

CHAPTER 3

MRI Parameter Estimation from Likelihood Models

{c,relax}

CHAPTER 4

Optimizing MR Scan Design for Model-Based Relaxometry

{c,scn-dsgn}

CHAPTER 5

MRI Parameter Estimation via Kernel Regression

{c,krr}

CHAPTER 6

Myelin Water Fraction Estimation from Steady-State Sequences

{c,mwf}

CHAPTER 7

Steady-State RF Pulse Design

{c,ss-rf}

CHAPTER 8

Future Work

{c,future}

APPENDIX A

Coil Data Combination from Multiple Datasets

{a,cc-multi}

APPENDIX B

DESS in the Presence of Diffusion

{a, dess-diff}

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