JOINT ESTIMATION OF WATER AND FAT IMAGES FROM MAGNETIC RESONANCE SIGNALS

BY

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DISSERTATION

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Fat-water separation is a classical problem for in vivo magnetic resonance imaging, with multiple applications both in cases where the aim is the removal of fat signal, as well as in cases where the fat signal itself is of diagnostic interest. Although many methods have been proposed, robust fat-water separation remains a challenge. The problem presents two key difficulties: (a) the presence of $B_0$ field inhomogeneities, which makes the problem non-linear and ill-posed; and (b) the difficulty of accurately modeling the acquired signal, which can lead to bias in quantitative fat-water separation applications. The research in this thesis has developed joint estimation methods to address the ill-posedness of the problem by simultaneously estimating the complete fat-water images and field inhomogeneity map. The joint estimation formulation developed in this work is able to overcome the complications of voxel-by-voxel separation, and it allows characterization of the resolution properties of its estimates, but results in a challenging optimization problem. To address this complication, optimization algorithms based on graph cuts have been developed and studied. Additionally, this work addresses the modeling issues of fat-water separation by comparing a set of recently proposed models, demonstrating that accurate spectral modeling of the acquired signal is critical for quantitative applications. Simulation, phantom and in vivo results are included to highlight the properties of the proposed methods and compare them to previous approaches. This thesis also contains example applications of the proposed methods, with an emphasis on the characterization of intramyocardial fat.
To my family
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6.7 Fat quantification fat fraction on phantom data including standard deviations, for high SNR. The dashed line shows the desired exact estimates. The arrows highlight the differences among complex-fitting, single-peak fat models: improved estimates for low FF values are obtained with the two-decay model, compared to no-decay and one-decay models. All three complex-fitting, multi-peak models show good performance in this case.

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CRLB</td>
<td>Cramér-Rao Lower Bound</td>
</tr>
<tr>
<td>CSA</td>
<td>Chemical Shift Artifact</td>
</tr>
<tr>
<td>DPE</td>
<td>Direct Phase Encoding</td>
</tr>
<tr>
<td>DW</td>
<td>Diffusion-Weighted</td>
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<tr>
<td>EPI</td>
<td>Echo-Planar Imaging</td>
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<tr>
<td>FF</td>
<td>Fat Fraction</td>
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<tr>
<td>FOV</td>
<td>Field of View</td>
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<tr>
<td>FSE</td>
<td>Fast Spin Echo</td>
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<tr>
<td>GPU</td>
<td>Graphics Processing Unit</td>
</tr>
<tr>
<td>GRE</td>
<td>Gradient-Recalled Echo</td>
</tr>
<tr>
<td>ICM</td>
<td>Iterated Conditional Modes</td>
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<tr>
<td>IDEAL</td>
<td>Iterative Decomposition of water and fat with Echo Asymmetry and Least squares estimation</td>
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<tr>
<td>LP</td>
<td>Linear Prediction</td>
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<tr>
<td>LS</td>
<td>Least-Squares</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>MD</td>
<td>Mean Diffusivity</td>
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<td>ML</td>
<td>Maximum-Likelihood</td>
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<tr>
<td>MRF</td>
<td>Markov Random Field</td>
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<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MSE</td>
<td>Mean Squared Error</td>
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<tr>
<td>MT</td>
<td>Magnetization Transfer</td>
</tr>
<tr>
<td>NLLS</td>
<td>Nonlinear Least Squares</td>
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<tr>
<td>NSA</td>
<td>Number of Signal Averages</td>
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<tr>
<td>PML</td>
<td>Penalized Maximum Likelihood</td>
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<tr>
<td>ROI</td>
<td>Region of Interest</td>
</tr>
<tr>
<td>SE</td>
<td>Spin Echo</td>
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<tr>
<td>SNR</td>
<td>Signal-to-Noise Ratio</td>
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<tr>
<td>SPGR</td>
<td>Spoiled Gradient Echo</td>
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<tr>
<td>SSFP</td>
<td>Steady State Free Precession</td>
</tr>
<tr>
<td>STE</td>
<td>Stimulated Echo</td>
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<tr>
<td>STIR</td>
<td>Short-Tau Inversion Recovery</td>
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<tr>
<td>TE</td>
<td>Echo Time</td>
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<td>TR</td>
<td>Repetition Time</td>
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<td>VARPRO</td>
<td>Variable Projection</td>
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Chapter 1

Introduction

1.1 Problem Formulation

This thesis addresses the problem of fat-water separation in magnetic resonance imaging (MRI). Because of their different electronic environments, protons within water and fat molecules produce signals with slightly different frequencies. This property is known as chemical shift, and it can be encoded into the MRI acquisition. In a chemical shift-encoded imaging experiment, several \( N \) images are acquired with different echo time (TE) shifts, and the signal originating from a given location can be described by the simplified signal model [1–4]:

\[
s(t_n) = e^{i2\pi f_B t_n} \left( \rho_W e^{i2\pi f_F t_n} \right), \quad \text{for } n = 1, \ldots, N, \tag{1.1}
\]

where \( t_n \) is the \( n \)th TE shift, \( f_B \) is the frequency offset due to the local \( B_0 \) (static) field inhomogeneity, \( \rho_W \) and \( \rho_F \) are the amplitudes of the water and fat signals, respectively, and \( f_F \) is the frequency of fat relative to water, which is approximately \(-3.5\) ppm (i.e., nearly \(-220\) Hz at 1.5 T).

Estimation of \( \rho_W \) and \( \rho_F \) presents two key challenges: accounting for the nonlinear effects of field inhomogeneity \( f_B \) in Eq. 1.1, and properly modeling the acquired signal.

In the absence of field inhomogeneity \( (f_B = 0) \), the model is linear and the problem of estimating \( \rho_W \) and \( \rho_F \) is trivial. However, in practice the problem is complicated by the presence of field inhomogeneity, which is often unavoidable due to magnet imperfections and susceptibility artifacts. Field inhomogeneity introduces frequency shifts in the signal, and must be accounted for in order to produce correct fat-water decompositions. Errors in accounting for field inhomogeneity
effects can lead to large errors in fat-water separation, including swaps (regions of the image where the dominant species is mistaken, e.g., water regions estimated as containing mostly fat). Thus, the problem becomes largely one of identification (rather than simply parameter estimation): in voxels containing only one component, it must be decided whether the component is water or fat. A number of methods have been proposed to overcome this complication by seeking a spatially smooth field inhomogeneity map [3, 5, 6]. However, reliable fat-water separation in the presence of large field inhomogeneities remains a challenge.

Additionally, the signal model in Eq. 1.1 contains significant simplifications, as it neglects signal decay due to $T_2^*$ effects, which are often relevant, and models the fat signal as a single resonance, whereas the fat signal actually consists of multiple peaks at different frequencies. Modeling errors can lead to bias in fat-water estimates. In recent years, there has been significant research interest in advanced signal models beyond Eq. 1.1, particularly in the context of quantitative fat-water imaging [7–9].

1.2 Fat-Water Separation in MRI: Background and Motivation

In vivo $^1$H MR images contain signals from water and fat protons. Separation of the water and fat signals is a problem of considerable practical importance. In some cases, the aim is fat suppression. This is particularly important in pulse sequences such as spoiled gradient echo (SPGR) [10, 11], steady-state free precession (SSFP) [1], or fast spin echo (FSE) [12], where fat appears hyperintense and may obscure the underlying pathology. In other cases, the fat signal itself is of diagnostic interest [13]; such cases include: characterization of hyperechoic liver nodules (where fat introduces nonspecific hyperechogenicity on ultrasound scans) [14], adrenal adenoma [15], renal angiomyolipoma [16, 17], and myocardial fatty infiltration [18–21]. Furthermore, the ability to quantitatively measure the presence of fat has a number of applications, including studies of bone marrow [22], breast [23], muscle [24], brain [25], liver [9, 26, 27], and heart [28–30].
A number of methods have been developed to address the fat-water separation problem. A straightforward approach is to suppress the fat signal during excitation. The most common methods for fat suppression are based on the different resonance frequencies of the water and fat signals (either by using fat saturation or spatial-spectral pulses) [31–34]. These methods employ frequency selective excitation pulses and are often used in practice. However, the main drawback is their inherent sensitivity to $B_0$ (and, in some cases, $B_1$) field inhomogeneities. $B_0$ inhomogeneities, which lead to spatially varying frequency shifts in the MR signal, are often unavoidable due to physical reasons (i.e., magnet imperfections and susceptibility artifacts). In the presence of substantial $B_0$ inhomogeneities, spectrally selective methods fail to suppress the fat signal, and may even result in suppression of the water signal. Fat suppression can also be realized by signal nulling using a short-tau inversion recovery (STIR) sequence, based on the short $T_1$ relaxation time of the fat signal [35]. In STIR, the magnetization is prepared by flipping it using an inversion pulse, followed by a relaxation period and excitation at the time when the magnetization of the fat signal crosses the zero point. Even though this method can be made insensitive to $B_0$ and $B_1$ inhomogeneities, it results in a loss of signal-to-noise (SNR) and alters the desired contrast in the imaging sequence [1, 6]. Another method with interesting properties is fat suppression based on exploiting magnetization exchange effects [36]. This method can effectively remove fat signal from all fat resonances, and is insensitive to $B_0$ and $B_1$ inhomogeneities. However, its applicability may be restricted due to the inherent magnetization transfer (MT) contrast [37, 38] and long acquisition times.

An alternative approach to fat suppression that can overcome these limitations is the so-called chemical shift-encoded fat-water imaging, based on separating the water and fat signals by post-processing. This is the crux of the celebrated Dixon method [2] and its many variants. In fat-water imaging, several images are acquired without fat suppression using slightly different imaging parameters (i.e., a simple spectroscopic imaging acquisition). The acquired images therefore contain contributions from both water and fat (Eq. 1.1). Subsequently, separate water-only and fat-only images are estimated by post-processing. The key advantages of fat-water imaging are the ability
to generate water-only images with arbitrary contrast, robustness to $B_0$ and $B_1$ inhomogeneities, as well as its SNR efficiency. Additionally, the resulting fat-only image has several important clinical applications, e.g., in the diagnosis of liver steatosis [26] and fibrofatty infiltration in the myocardium [18–20]. Furthermore, a map of the $B_0$ field inhomogeneity (or “field map”) is typically also generated during the estimation of fat-water images. Even though the field map may be considered as a nuisance parameter, it has several applications, such as correction of fast acquisitions (e.g., EPI and spiral trajectories), and automated shimming [39, 40]. A multitude of methods have been proposed over the past 25 years to solve the fat-water separation problem. These methods, which differ essentially in how they account for the effects of field inhomogeneity, are reviewed in Chapter 2.

1.3 Overview of Contributions

The main contributions of this dissertation are the following:

- **Joint estimation formulation.** This work has developed a formulation for fat-water imaging, based on joint estimation. The water and fat images and field inhomogeneity map are estimated jointly for all the voxels, seeking a solution that both fits the measured data and encourages smoothness in the estimated field map.

- **Graph cut algorithm.** The joint estimation formulation has desirable properties for fat-water separation, but results in a challenging (high-dimensional and non-convex) optimization problem. A novel algorithm based on a graph cut iteration has been developed. This algorithm is able to avoid many suboptimal local optima by considering and updating all voxels simultaneously.

- **Analysis of signal models.** Accurate modeling of the acquired signal is particularly important for quantitative applications. A number of signal models have been proposed in recent years. This work includes a comparison of signal models, based on the bias and standard
deviation of their resulting estimates. The comparison is performed largely through phantom experiments, and also includes analytical results, simulations and *in vivo* data.

- **Removal of olefinic fat signal in diffusion MRI.** A specific extension of fat-water imaging methods has been developed in the context of diffusion imaging, where signal from olefinic fat protons can introduce significant distortions due to the chemical shift artifact and the slow diffusion of fat molecules.

### 1.4 Organization of the Dissertation

The remainder of the dissertation is organized as follows:

- Chapter 2 provides a review of chemical shift-encoded fat-water imaging methods in MRI, including the data acquisition, modeling, and algorithmic components. The most relevant previously proposed methods are reviewed and placed in a common estimation framework. Additionally, this chapter includes an overview of graph cut methods for nonlinear parameter estimation.

- Chapter 3 introduces the proposed formulation for solving the fat-water separation problem. The key feature of this formulation is that the problem is posed as joint estimation of the desired parameters for all the voxels simultaneously. Modeling considerations and extension to the multi-coil case are also discussed in this chapter. Additionally, a simple and efficient alternative method based on linear prediction is described.

- Chapter 4 introduces the methods developed in this work for solving the joint estimation problem, with emphasis on a novel graph cut solution where the optimization is decomposed as a sequence of binary decision problems at each voxel. Simple solutions based on iterated conditional modes (ICM), as well as globally optimal solutions based on a different graph formulation, are also discussed.
• Chapter 5 provides experimental results for the previously described methods, in cases of varying levels of field inhomogeneity. Analytical, simulation and in vivo results are provided, with an emphasis on cardiac imaging. Example applications are also shown, specifically for the characterization of intramyocardial fat.

• Chapter 6 contains a comparison of different signal models for fat-water imaging. The key choices for modeling/fitting the acquired signal are: modeling of $T_2^*$ decay, spectral modeling of the fat signal and whether to fit the complex-valued signal or its magnitude. These choices lead to a set of models that are analyzed using experiments on a custom-built phantom, as well as theoretical analysis, simulations and in vivo data.

• Chapter 7 introduces an extension of chemical shift-encoded fat-water imaging methods to the case of diffusion-weighted imaging, where residual signal from the olefinic protons may result in significant distortions of the acquired signal. Separation of water and olefinic fat is performed within the constraints of diffusion-weighted echo-planar imaging (namely, unreliable phase and large chemical shift artifact). The proposed method is evaluated using simulations, phantom and in vivo data.

• Finally, Chapter 8 provides the concluding remarks and outlines several suggestions for future extensions of this research.
Chapter 2
Preliminaries

2.1 Introduction

In $^1$H MR, protons contained in different molecules produce signals with slightly different frequencies. The frequency of the MR signal originating from a given nucleus depends on the gyromagnetic ratio of the nucleus (an intrinsic property, e.g., 42.576 MHz/T for protons), as well as on the magnetic field observed by the nucleus. This magnetic field is affected by the electronic environment surrounding the nucleus, which results in nuclei within different molecules observing slightly different magnetic fields, and thus giving rise to different spectral components in the MR signal, with frequencies typically separated by a few parts per million (ppm).

In the presence of multiple spectral components, the signal measured in an MR experiment can be modeled as:

$$d(k(t), t) = \int \int \rho(r, f) e^{-i2\pi r \cdot k(t)} e^{i2\pi ft} dr df,$$

where $\rho(r, f)$ is the desired spatial-spectral distribution of spins, and $k(t)$ is the k-space (spatial) encoding measured at time $t$. If sufficient spatial encodings are acquired, Fourier transformation along the spatial dimensions produces the spatial-temporal signal $s(r, t)$, defined as:

$$s(r, t) = \int f \rho(r, f) e^{i2\pi ft} df.$$

If sufficient samples are acquired in the temporal dimension, Fourier transformation along this dimension will provide the desired $\rho(r, f)$. This method is very general and has the advantage that it can simultaneously map a very large number of spectral components. However, acquisition of
fully sampled spatial-spectral distributions is time-consuming and typically low spatial resolutions are used (e.g., 32×32 spatial encodings for 2D imaging) [41].

This chapter provides a review of the chemical shift-encoded acquisition methods used to acquire data with high spatial resolution, in the presence of relatively simple spectral information (as is the case in fat-water separation). Next, the previously proposed methods and signal models used to obtain separated water and fat images from chemical shift-encoded acquisitions are reviewed using a common estimation framework. Finally, this chapter also includes an overview of graph cut methods for solving problems of regularized estimation of nonlinear parameters.

2.2 Chemical Shift-Encoded MR Acquisitions

For in vivo $^1$H MR experiments, signals originating from water and fat are typically several orders of magnitude larger than those of other spectral components. Fat-water imaging acquisitions can be performed with high spatial resolution and moderate acquisition time by exploiting the simple (and known) spectrum produced by the water and fat components.

In a chemical shift-encoded fat-water separation acquisition, a sequence of images is obtained with different echo time (TE) shifts, $t_1, t_2, \ldots, t_N$ (typically $N = 3$). An example of such acquisition is shown in Fig. 2.1, based on a spin-echo (SE) pulse sequence. By shifting the refocusing pulse by $\Delta TE/2$ while keeping the rest of the pulse sequence fixed, the fat and water components will not refocus exactly at the center of the readout gradient, but this refocusing will be shifted by $\Delta TE$. Acquiring several images with different values of $\Delta TE$ will result in different phases between the water and fat components due to their chemical shifts or, in other words, an encoding of the chemical shift in the acquisition.

Another example is shown in Fig. 2.2, based on a gradient-echo (GRE) pulse sequence, where placing the readout gradients at different times results in encoding the chemical shift. Note that by including multiple readout gradient lobes (in combination with “fly-back” gradients in between) after a single excitation pulse, this sequence allows the acquisition of an echo train during each
Figure 2.1: Spin-echo chemical shift-encoded pulse sequence. Several images are acquired with different shifts of the refocusing pulse while leaving the rest of the timings unmodified.

Figure 2.2: Gradient-echo pulse sequence using an echo-train acquisition for chemical shift-encoded imaging. A train of echoes can be acquired, limited by the desired TR as well as the $T_2^*$ decay of the signal. Note the use of monopolar readouts to avoid eddy current-related artifacts.
repetition. This type of sequence is commonly used for fat-water imaging due to its speed and the lack of phase errors between the different echoes. However, echo-train GRE acquisitions also present several drawbacks: (a) increase of the minimum TR due to the need to collect several echoes; and (b) relatively long TE spacings, due to the use of a monopolar readout with flyback gradient. This increased TE spacing is more problematic at higher fields (e.g., at 3 T), because of the increased frequency difference between the water and fat components. Bipolar readout-based sequences have also been proposed [42, 43], but require careful correction of eddy current-related artifacts and are not as common as monopolar readout sequences.

In a chemical shift-encoded acquisition such as the examples shown in Figs. 2.1 and 2.2, the signal at an individual voxel $q$ can be described by the simplified model:

$$s_q(t_n) = e^{i(2\pi f_{B, q} t_n + \phi_{0,q})} \left( \rho_{W,q} + \rho_{F,q} e^{i2\pi f_{F} t_n} \right), \text{ for } n = 1, \ldots, N,$$

(2.3)

where $f_{B, q}$ (in Hz) is the local frequency shift due to $B_0$ field inhomogeneity, $\phi_{0,q}$ is the initial phase of both water and fat signals, $\rho_{W,q}$ and $\rho_{F,q}$ are the magnitudes of the water and fat components, respectively, and $f_{F}$ (in Hz) is the frequency shift of fat relative to the water, which is assumed to be known a priori [1–3]. In this simplified model, $T_2^*$ effects are ignored and the fat signal is considered to have a single spectral line [7, 44]. These simplifications can be removed if needed, as described in Chapter 3.

One of the key properties of chemical shift-encoded fat-water imaging is its ability to be combined with a variety of pulse sequences and $k$-space trajectories. Pulse sequences used include fast spin echo (FSE) [12, 45–47], steady-state free precession (SSFP) [18, 48, 49], and spoiled gradient echo (SPGR) [4, 8, 11, 20, 50]. Proposed $k$-space trajectories include Cartesian [2, 3], radial [51], spiral [44], and concentric rings [52].
2.3 Previously Proposed Methods

The unknowns in the signal model of Eq. 2.3 are the parameters \( \{ f_B, \phi_0, \rho_W, \rho_F \} \) at each voxel. Generally, \( \phi_0 \) is considered a nuisance parameter, and estimation of the desired \( \{ \rho_W, \rho_F \} \) is simple if \( f_B \) is known. However, estimation of \( f_B \) is complicated by the nonlinearity of the signal model and the presence of phase wraps in the acquired images [1, 6]. Next, the most relevant prior fat-water separation methods are reviewed, highlighting their fundamental differences: the number of TE shifts (or “points”) they require, and the way in which they account for the effects of field inhomogeneity in the acquired signal.

**Single-point methods**

In the absence of phase errors (\( \phi_{0,q} = 0 \)) and field inhomogeneity (\( f_{B,q} = 0 \)), it is possible to separate water and fat from a single image. According to the signal model in Eq. 2.3, such acquisition would provide one complex data point, sufficient to estimate the two real-valued parameters \( \rho_{W,q} \) and \( \rho_{F,q} \). This can be achieved, e.g., by a “quadrature” acquisition, where the relative fat-water phase is \( \pi/2 \); i.e., water is in the real channel and fat in the imaginary channel.

This method would provide extremely efficient fat-water separation. Unfortunately, phase errors are generally unavoidable. In practice, a single-point quadrature acquisition will produce a signal:

\[
s_q(t_1) = e^{i(2\pi f_{B,q} t_n + \phi_{0,q})} (\rho_{W,q} + i\rho_{F,q}) \tag{2.4}
\]

\[
= e^{i\phi_q} (\rho_{W,q} + i\rho_{F,q}) \tag{2.5}
\]

where \( \phi_q = 2\pi f_{B,q} t_n + \phi_{0,q} \) is the unknown phase error at voxel \( q \). Note that this signal model results in three real-valued unknowns (\( \phi_q, \rho_{W,q} \) and \( \rho_{F,q} \)) and only one complex-valued data point.

In order to overcome these phase errors, multiple methods have been proposed for single-point fat-water separation. These methods typically rely on an additional reference scan to estimate the
phase $\phi_q$ [53–56]. Alternatively, methods have been proposed where the phase is calibrated from the data itself by introducing a small water tube next to the desired object [57], or by modeling the phase distributions [58]. Other autocalibrated methods based on smoothed versions of the data or region growing techniques have also been proposed [4, 59–61].

**Dixon’s original two-point method**

Dixon proposed the original “simple proton spectroscopic imaging” method for fat-water separation [2]. In Dixon’s method, two images are acquired: the first one (“in-phase”) at the spin echo (i.e., $t_1 = 0$), and the second one (“opposed-phase”) with a TE shift:

$$t_2 = -\frac{1}{2f_p},$$

where $f_p \approx -50$ Hz in the original work in Ref. [2] (where experiments were performed at 0.35 T), leading to $t_2 \approx 10$ ms. This TE shift was obtained by shifting the refocusing pulse by $-5$ ms, while maintaining the readout gradient fixed, in a spin echo sequence. Subsequently, water-only and fat-only images are obtained at each voxel $q$ by adding and subtracting the two acquired images, respectively:

$$\hat{\rho}_{w,q} = \frac{1}{2}|s_q(t_1) + s_q(t_2)|$$

$$\hat{\rho}_{f,q} = \frac{1}{2}|s_q(t_1) - s_q(t_2)|,$$

where the key assumption is the absence of field inhomogeneity, i.e., $f_{n,q} = 0$ in Eq. 2.3. If this assumption is incorrect, then Dixon’s simple method results in fat-water separation errors, where the estimated water image contains part of the fat signal, and vice versa.

**Advanced two-point methods**

It is well known that, for the signal model in Eq. 2.3, two points are enough to recover the water and fat images, even in the presence of field inhomogeneities [62, 63]. In fact, two points are the minimum that allows estimation of the fat-water images from Eq. 2.3 without additional as-
assumptions: the problem becomes estimating four real-valued parameters from two complex-valued measurements.

Two-point methods usually require the acquisition of two images with fat-water phases 0 and $\pi$. Multiple methods have been proposed that directly apply a phase unwrapping algorithm to the acquired images [62–64]. Subsequent fat-water separation (once the phase of the acquired images is unwrapped) is trivial, but direct phase unwrapping is complicated, e.g., in regions where there are signal cancellations because of the presence of similar magnitudes of water and fat [6]. Several methods have also been proposed for fat-water separation without explicit phase unwrapping of the acquired images [65]. More recently, Ma introduced an improved 2-point method where phase errors due to field inhomogeneities are corrected using a region-growing algorithm that considers both the amplitude and phase of neighboring voxels in the region-growing process [66].

**Analytical three-point methods**

The advanced two-point methods described above require relatively sophisticated techniques to remove the effects of field inhomogeneity in the acquired signal. In order to overcome the sensitivity to field inhomogeneity of Dixon’s two-point method, Glover and Schneider proposed a three-point Dixon technique ($N = 3$) that allows direct estimation of $f_{b,q}$ and removal of its effects from the acquired signal [3]. To avoid the nonlinearity of the general estimation problem, the TE shifts are chosen such that $f_{b,q}$ can be estimated from just two of the images prior to fat-water separation. Specifically, three images are acquired in a spin echo experiment, with TE shifts $t_1 = 1/2f_v$, $t_2 = 0$, and $t_3 = -1/2f_v$, resulting in relative fat-water phase shifts $-\pi$, 0 and $\pi$, respectively. The signal model (Eq. 2.3) from the acquired images becomes:

$$s_q(t_1) = e^{i\pi f_{b,q}/f_v} e^{i\phi_{0,q}} (\rho_{w,q} - \rho_{f,q})$$
$$s_q(t_2) = e^{i\phi_{0,q}} (\rho_{w,q} + \rho_{f,q})$$
$$s_q(t_3) = e^{-i\pi f_{b,q}/f_v} e^{i\phi_{0,q}} (\rho_{w,q} - \rho_{f,q}),$$

(2.8)
where $s_q(t_1)$ and $s_q(t_3)$ can be directly used to estimate $f_{w,q}$, as long as $\rho_{w,q} - \rho_{v,q} \neq 0$. After estimating $\phi_{0,q}$ as the argument of $s_q(t_2)$ ($\hat{\phi}_{0,q} = \angle s_q(t_2)$), the fat-water images can be separated as follows:

$$\hat{\rho}_{w,q} = \frac{1}{2} \left( s_q(t_2)e^{-i\hat{\phi}_{0,q}} + p\sqrt{s_q(t_1)s_q(t_3)e^{-i2\hat{\phi}_{0,q}}} \right),$$

$$\hat{\rho}_{v,q} = \frac{1}{2} \left( s_q(t_2)e^{-i\hat{\phi}_{0,q}} - p\sqrt{s_q(t_1)s_q(t_3)e^{-i2\hat{\phi}_{0,q}}} \right),$$

(2.9)

where $p = \pm 1$ determines the sign of the square root. Under the assumption of small field inhomogeneities ($|f_{B,q}| < f_r/2$), $p$ can be determined uniquely. However, in the presence of large field inhomogeneities this condition is too restrictive. A phase unwrapping-based method was proposed in Ref. [3] to address this issue, under the assumption that the field map varies slowly in space.

An important limitation of Glover and Schneider’s three-point Dixon technique is the requirement that images are acquired with water and fat at very specific phase shifts ($-\pi$, 0 and $\pi$). Xiang and An developed a generalized version of three-point Dixon, termed “direct phase encoding” (DPE), where the three images can be acquired with uniformly spaced TE shifts $t_1$, $t_1 + \Delta t$ and $t_1 + 2\Delta t$ [67]. With this acquisition, solving for the field inhomogeneity $f_{B,q}$ reduces to solving a quadratic equation in $e^{i2\pi f_{B,q}\Delta t}$. As in the original three-point Dixon method, an ambiguity arises in DPE through the presence of two possible solutions to this quadratic equation. Again, this ambiguity in field map estimation leads to potential errors in fat-water separation. These errors are removed by imposing spatial smoothness in the resulting image phase $\hat{\phi}_{0,q}$ and field map $f_{B,q}$, through a technique denoted “orientation filters.”

**Basic maximum-likelihood methods**

The three-point methods described above contain several limitations: (a) they are limited to acquisitions that consist of three TE shifts ($N = 3$), (b) they are intended to separate only two chemical species (e.g., water and fat), but cannot directly address the presence of multiple species (e.g., water, fat and silicone). These limitations (and several others) can be overcome by posing the fat-water separation problem using an estimation framework.
Under the common assumption of i.i.d. Gaussian noise, the maximum-likelihood (ML) estimate for the unknown parameters in Eq. 2.3 is given by the least-squares (LS) fit of the model to the data. An and Xiang introduced a method termed “chemical shift imaging with spectrum modeling” (CSISM), for fitting multiple spectral components using nonlinear least-squares (NLLS) [68]. This method works for an arbitrary number \( M \) of spectral components, and an arbitrary number \( N \) of uniformly spaced TE shifts (as long as \( 2N - 1 \geq M + 1 \) and one of the TEs is exactly in phase), and models the signal by extending Eq. 2.3 to the multiple-component case:

\[
s_q(t_n) = e^{i(2\pi f_{B,q}(n-1)\Delta t + \phi_{0,q})} \left( \sum_{m=1}^{M} \rho_{m,q} e^{i2\pi f_m t_n} \right), \text{ for } n = 1, \ldots, N, \quad (2.10)
\]

where \( \Delta t \) is the TE spacing, \( \rho_{m,q} \) for \( m = 1, \ldots, M \) are the real-valued magnitudes of each of the spectral components at voxel \( q \), and \( f_m \) are their frequency offsets due to chemical shift (e.g., for separation of water, fat and silicone at 1.5 T, these frequencies are approximately 0 Hz, \(-220\) Hz and \(-310\) Hz, respectively). In CSISM, the phase \( \phi_{0,q} \) is first estimated from the in-phase image and removed from the data. The remaining unknowns are the nonlinear parameter \( f_{B,q} \) and the linear parameters \( \rho_{m,q} \), for \( m = 1, \ldots, M \). Instead of directly estimating \( f_{B,q} \), the phasor \( P_1 = e^{i2\pi f_{B,q}\Delta t} \) is considered. The possible values for \( P_1 \) are quantized (e.g., 360 values for a \( 1^\circ \) discretization). For each value of \( P_1 \), the solution for \( \rho_{m,q} \) is obtained immediately by linear LS, and so the fit error is recorded.

In voxels with balanced amplitudes of several spectral components, it suffices to pick the best fit to the data. In voxels with a single component (or insufficient number of components, depending on their frequencies), there will be several global minimizers of the fit error. To overcome this ambiguity, CSISM performs a region growing process guided by the reliability of the pixels themselves (since there is no ambiguity for pixels containing a sufficiently balanced mixture of spectral components).

The assumption that the initial phase of the different spectral components is zero is valid in many cases. However, this is not always the case; e.g., the phase may not be zero in steady...
state free precession (SSFP) acquisitions. Additionally, the TE requirements in CSISM (uniformly spaced, and one of the images is acquired in phase) are somewhat restrictive. To overcome these limitations, Reeder et al. introduced a novel method for iterative decomposition of water and fat with echo asymmetry and least squares estimation (IDEAL) where \( \{f_B, \rho_w, \rho_f\} \) are estimated at each voxel by an iterative nonlinear least-squares fitting procedure [1]. The signal model used in IDEAL is slightly different from Eq. 2.3, and can be expressed in terms of complex-valued amplitudes:

\[
s_q(t_n) = e^{i2\pi f_B t_n} \left( \sum_{m=1}^{M} \rho_{m,q} e^{i2\pi f_m t_n} \right), \quad \text{for } n = 1, \ldots, N, \tag{2.11}
\]

where \( \rho_{m,q} \) are now allowed to take complex values (and consequently the phase parameter \( \phi_{0,q} \) becomes redundant and is removed). The unknown parameters are fitted in the NLLS sense using an iterative procedure based on subsequent linearizations: for a given \( f_{B,q} \) estimate, the amplitudes \( \rho_{m,q} \) are estimated simply by linear LS; for given amplitudes, the signal model is linearized about the current \( f_{B,q} \) value, and the next \( f_{B,q} \) estimate is obtained by solving a linear problem. This iterative procedure is initialized with a field map value of zero at each voxel and guarantees convergence to a locally optimal solution.

Because estimating the field map one voxel at a time will often result in noisy estimates, a smoothing step is added after voxel-independent estimation. The IDEAL algorithm can be summarized as follows:

1. Each voxel is processed independently, reaching a locally optimal field map estimate, which is implicitly assumed to have field inhomogeneity close to zero. In the presence of noise, this step may result in a rough field map.

2. Smoothness is imposed separately, by subsequently convolving the voxel-by-voxel estimated field map with a smoothing filter (e.g., a \( 3 \times 3 \) boxcar filter).

3. Given the smoothed field map, the water and fat amplitudes are obtained at each voxel by
solving the corresponding linear LS system (Eq. 2.11).

The original IDEAL method has several desirable properties: (a) it can result in the optimal fat-water decomposition in the ML sense (in the absence of the smoothing step 2), (b) it works for arbitrary TEs and arbitrary numbers of spectral components (as long as sufficient echo times are acquired), and (c) by using complex-valued amplitudes for the spectral components, one of the nonlinear parameters in Eq. 2.3 (the initial phase) is removed, so the IDEAL signal model (Eq. 2.11) contains a single nonlinear parameter (the frequency offset $f_{u,q}$).

**Improved maximum-likelihood methods**

Even though smoothing the voxel-independent field map (step 2 in the original IDEAL method) is able to ameliorate small errors due to noise, it is not able to undo the large errors due to convergence to the wrong local minimizer during voxel-by-voxel estimation. This is demonstrated in Fig. 2.3. Errors in the estimated field map result in incorrect fat-water separation. If the correct field map is known, water fat separation is trivial, as it reduces to a linear LS problem at each voxel. However, field map estimation is difficult because it reduces to a non-convex optimization problem at each voxel, with multiple global and local minimizers (see Fig. 2.4). Because of its local convergence properties and initialization with $f_{u,q} = 0$, IDEAL fails in the presence of large field inhomogeneities (on the order of $f_u \approx f_u/2$). In other words, the original IDEAL method resolves ambiguities in the estimation problem by the implicit assumption that the field inhomogeneity is close to zero. If this assumption is not correct, severe errors in water fat separation may occur.

To overcome this limitation, several algorithms have been proposed in recent years, with improved performance in cases of larger field inhomogeneity. The basis of all these algorithms for overcoming the ambiguities in the signal model is the use of smoothness as a constraint for field map estimation. Specifically, these methods are largely based on imposing field map smoothness using two key concepts: region-growing and multiresolution; and they are designed to maintain the advantages of IDEAL, while addressing its shortcomings. These improved methods are reviewed next.
Figure 2.3: Voxel-independent fat-water decomposition in the presence of high field inhomogeneity. (Left) Estimated water image. (Center) Fat image. (Right) Field map. Errors in field map estimation result in fat-water separation errors (see arrows).

Figure 2.4: Non-convexity of residue at individual voxel, for different choices of TEs. (Left) Combined image (water and fat), showing voxel location within myocardium. (Top right) Residue (as a function of estimated frequency offset $f_B$) for an acquisition using 5 non-uniformly spaced TEs. (Bottom right) Residue for an acquisition using 4 uniformly spaced TEs. In general, the residue may contain multiple local and global minimizers, leading to several different fat-water decompositions.
Yu et al. proposed a region-growing extension of IDEAL (RG-IDEAL) where field map smoothness is imposed by a region growing process initialized with an automatically selected seed voxel [5]. In this work, it was recognized that the result of the original IDEAL algorithm depends heavily on the “valley” of the residue (see Fig. 2.4) where it is initialized. Thus, if IDEAL can be initialized at the correct valley for each voxel (instead of simply initializing with $f_B = 0$), accurate fat-water separation is achievable even in the presence of large field inhomogeneities. Specifically, the voxel-independent estimation in Step 1 of the IDEAL algorithm described above is substituted by a region-growing algorithm.

The key components of a region-growing algorithm are the selection of the seed voxel (or voxels), and the growing strategy. In RG-IDEAL, these components are designed as follows [5]:

- **Selection of seed voxel.** The complex-valued acquired images are smoothed and downsampled to low-resolution (32×32 voxels). Voxel-independent IDEAL is performed on this low-resolution dataset. Within the low-resolution dataset, noisy background voxels are discarded by thresholding the signal amplitudes. From the remaining (non-noise) voxels, those 14 voxels with field map values closest to the median are chosen and the one closest to the center of mass of the low-resolution dataset is picked as seed. Effectively, this method will typically result in an initialization with a moderate field map value (since the original IDEAL algorithm is initialized with field map values of zero at each voxel) near the center of the imaged object (due to the use of the center of mass). This choice will be effective in most cases, as long as the center frequency is set close to the water resonance. Additionally, the use of low-resolution voxels may have the additional benefit of removing some of the ambiguities (since these voxels are likely to contain both water and fat). If the field map varies rapidly within a low-resolution voxel, the signal model (Eq. 2.11, which assumes the field map is constant over a voxel) will no longer be valid. However, the approximation is typically valid for most regions, particularly near the center of the FOV (where the field variations are not extremely rapid).
• **Region-growing strategy.** The high-resolution voxels corresponding to the (low-resolution) seed voxel are processed first, by initializing the IDEAL algorithm with the estimated value for the seed voxel. Subsequently, region-growing is performed following a square-spiral trajectory, where the initial guess for each new encountered voxel is computed by linearly extrapolating the estimated field values of the visited voxels within a neighborhood (e.g., 41×41 voxels) around the new voxel.

Multiresolution methods have also been proposed recently to help guide the selection of the correct decomposition at each voxel [69]. Lu and Hargreaves developed a method that combines region-growing and multiresolution, by using region-growing at the coarsest resolution, and propagating the resulting estimates to the finer resolutions [70]. This algorithm was proposed for acquisitions with uniformly spaced TEs, although it can be readily extended to general acquisitions without fundamental modifications (other than computational efficiency). The algorithm can be summarized as follows:

• **Processing at coarse resolution.** At the coarsest resolution, the local minimizers of the residual are found at each voxel using a golden section search. This step takes advantage of the periodicity of the residue for acquisitions with uniformly spaced TEs (a spacing of Δt in the acquisition leads to a period of 1/Δt in the residue). Next, a seed voxel is selected with criteria similar to RG-IDEAL, and the complete coarse-resolution field map is estimated by region-growing using a nearest-neighbor criterion (simpler than RG-IDEAL).

• **Propagation to finer resolutions.** Given the field map at a certain resolution, the field map at the next resolution (finer by a factor of 2 in each dimension) is obtained by using bilinear interpolation, followed by a correction step (determined by the fit residue of the interpolated estimate). This approach has the advantage of its computational efficiency if most estimates do not need to be corrected during the propagation steps (few corrections will typically be needed if the field map is very smooth).
Additionally, improved ML-based methods have been proposed based on belief-propagation [71], and on a regularized formulation solved using optimization transfer [72].

To compensate for the increased sophistication of the algorithms, enhanced versions of IDEAL have also been implemented on graphics processing units (GPUs) for improved computational efficiency [73].

2.4 Previously Proposed Signal Models

Quantitative fat-water imaging requires accurate signal modeling in order to avoid severe bias in the estimation. In addition to the basic signal model (Eq. 2.3), multiple fat-water imaging signal models have been proposed. These models can be classified according to three criteria:

- **Magnitude vs. complex fitting.** Most of the methods described above use the complex-valued acquired signal, which contains *a priori* unknown phase distortions due to the presence of field inhomogeneity. Fitting the magnitude of the signal has been proposed as a means of simplifying the estimation, since it removes the effects of field inhomogeneity [8, 74, 75], arguably resulting in a simpler problem. However, magnitude fitting has several well-known drawbacks, such as the non-Gaussian distribution of the noise in magnitude MR images, and an inability to correctly detect fat fractions above 50%.

- **Single peak vs. multi-peak fat models.** MR signals from water have a simple spectrum consisting of a single peak, located at about 4.7 ppm. However, signals from fat present a more complicated spectrum, consisting of multiple peaks, due to the presence of protons ($^1$H) at different locations within the fat molecule (see Fig. 2.5) [76]. The basic signal model described in Eq. 2.3 ignores the presence of multiple spectral peaks in the fat signal, which leads to bias in quantification. This can be overcome by using a more sophisticated, multi-peak fat model. If the frequencies of these peaks are assumed known, then the fat-water separation problem can be generalized as simply separating multiple chemical species,
which is already accounted for, e.g., in the IDEAL signal model (Eq. 2.11). However, this direct approach requires the acquisition of a large number of images (high $N$) in order to separate multiple species. Additionally, the conditioning of the problem will suffer because of the presence of peaks with similar frequencies. For instance, the olefinic fat peak (located at approximately 5.35 ppm) is separated by less than 50 Hz from the water peak at 1.5 T. An alternative that has been used effectively in recent works is to assume that the relative amplitudes of the fat peaks are fixed throughout the dataset, which leads to a problem with the same number of unknowns as the standard fat-water separation. The relative amplitudes of the different fat peaks can either be pre-calibrated or auto-calibrated [9, 77].

![Figure 2.5: MR spectrum obtained at 1.5 T from an oil-water phantom.](image)

- **Modeling of $T_2^*$ decay.** In general, the amplitudes of the water and fat components of the signal will decrease with TE, due to $T_2^*$ decay (which appears as peak broadening in the spectral domain, as shown in Fig. 2.5). It has been shown that ignoring this decay may result in significant bias, and a number of groups have developed methods for including $T_2^*$ in the model. In general, water and fat will have different $T_2^*$ decays (and even the different fat peaks will have different decays, although this is typically ignored, as it would result in significant complication in the estimation [6]), so these should be estimated separately, adding two nonlinear parameters to the estimation [78]. As a simplification of this general
model, a single $T_2^*$ has been proposed for both water and fat [7]. Intermediate models have also been proposed, where the decay rates of water and fat are different, but the difference is assumed known [8].

Furthermore, quantitative measurement of fat content is complicated by several factors, such as the presence of bias due to $T_1$ weighting and noise [11].

### 2.5 Overview of Graph Cut Methods

The key component for fat-water separation is estimation of the field inhomogeneity map. This component constitutes an ill-posed, nonlinear estimation problem, where regularization using spatial smoothness constraints is typically required. This section provides a brief overview of a set of algorithms based on graph cuts, for solving problems consisting on the regularized estimation of nonlinear parameters.

Graph cut methods are a set of discrete energy minimization algorithms that have received a great deal of attention in recent years, particularly in the computer vision community. For instance, many of the top performing algorithms for solving the so-called stereo problem in computer vision are based on graph cuts [79–81]. Graph cuts have also been recently applied to solve other challenging problems of importance in MRI, such as image denoising and restoration [82, 83], phase unwrapping [84] and regularized image reconstruction [85].

A number of problems in different fields (e.g., image reconstruction and processing, computer vision), can be recast as energy minimization problems. In the discrete setting, many of these can be generally viewed as labeling problems, i.e., assign a label $\xi_q$ (from a label set $\Omega$ of finite size $|\Omega| = L$) to each voxel $q$ such that a given energy functional $E$ is minimized:

$$\hat{\xi} = \arg \min_{\xi \in \Omega^Q} E(\xi),$$

(2.12)

where $\xi = [\xi_1, \xi_1, \ldots, \xi_Q]^T$. For general energy functionals $E$, the only way to solve Eq. 2.12 is
to examine all $L^Q$ candidate labelings. However, for many important problems (e.g., in computer vision applications), the energy functional $E$ contains significant additional structure. Specifically, one can often decompose $E$ into a summation of terms that depend on few voxels, e.g. only voxel-independent and pairwise terms:

$$E(\xi) = \sum_{q=1}^{Q} D_q(\xi_q) + \sum_{q=1}^{Q} \sum_{j \in \delta_q} V_{q,j}(\xi_q, \xi_j),$$

where $D_q$ are voxel-independent terms, $V_{q,j}$ are pairwise terms, and $\delta_q$ is a neighborhood of voxel $q$. Typically, $D_q$ enforce data consistency according to the appropriate signal and noise model, and $V_{q,j}$ enforce spatial smoothness by penalizing large differences in the estimates of neighboring voxels.

In the context of graph cut methods, the “data terms” $D_q(\xi_q)$ can be arbitrary. The “smoothness terms” $V_{q,j}(\xi_q, \xi_j)$ are typically a function of the differences of neighboring labels, i.e., with some abuse of notation they can be written $V_{q,j}(\xi_q, \xi_j) = V_{q,j}(|\xi_q - \xi_j|)$. In most computer vision applications, non-convex discontinuity-preserving regularization is often preferred, with terms of the form $V_{q,j}(\xi_q, \xi_j) = \min(K, |\xi_q - \xi_j|)$ or $V_{q,j}(\xi_q, \xi_j) = \min(K, |\xi_q - \xi_j|^2)$, but convex choices are also possible, e.g., $V_{q,j}(\xi_q, \xi_j) = |\xi_q - \xi_j|$ or $V_{q,j}(\xi_q, \xi_j) = |\xi_q - \xi_j|^2$.

Multiple different algorithms can be applied to solve this type of labeling problem. Until recently, many of these energy minimization problems were viewed as intractable due to the lack of an efficient computational solution. Previous algorithms, such as iterated conditional modes (ICM) [86], are simple to implement and provide local convergence, but fail to escape a multitude of local optima. The reason for this is that in ICM only one voxel is considered at a time, and the algorithm is forced to always descend, thus getting trapped in locally optimal “valleys.” Another possibility is to resort to “simulated annealing,” which overcomes the local convergence properties of ICM [87]. Annealing is based on a cooling schedule, where it will converge to a local minimum once the “temperature” is low. It is simple to implement, and can guarantee global convergence asymptotically. However, in order to reach the global minimum extremely slow cooling
is usually needed, resulting in a very high computational cost which makes it impractical for most applications.

In recent years, there has been growing interest in a set of graph cut-based algorithms that can overcome the limitations of previous algorithms for minimizing energy functions of the form of Eq. 2.13. Graph cut algorithms have much stronger convergence properties than ICM, as well as a provably efficient computation (low order polynomial complexity) and fast practical implementation [88]. First, there exist a set of cases where graph cut methods can directly find the global minimizer of Eq. 2.13:

- **Binary labeling problems.** When there are only two possible labels (L=2), the problem becomes a particular instance of the Ising model, and can be globally optimized by mapping it to the appropriate graph computation [89].

- **Multi-label problems with convex regularization.** If $V_{q,j}(\xi_q, \xi_j) = V_{q,j}(|\xi_q - \xi_j|)$ is a convex function, the global optimum can also be found efficiently by formulating the problem in terms of graph cuts, as was shown (constructively) in Ref. [90]. Interestingly, the form of the data term $D_q(\xi_q)$ is irrelevant in this formulation. Note that this result has limited importance in computer vision applications, due to the advantages of non-convex penalties (for which global optimization is not attainable) in these applications.

However, graph cut methods have had a large impact even in cases where direct global optimization is not possible. In fact, many of the most successful applications of graph cuts are in applications where global convergence is not guaranteed, but a “good” solution (sometimes provably good) can still be achieved. This is the case with multi-label problems using a non-convex regularization term. These algorithms are based on decomposing the original multi-label problem into a sequence of binary problems. The current estimate at voxel $q$ is denoted as $\xi_{q}^{\text{cur}}$. At each iteration, a binary choice is made at each voxel, between maintaining the current estimate $\xi_{q}^{\text{cur}}$ or switching to an alternative estimate $\xi_{q}^{'}$. Therefore, there are $2^Q$ candidate labelings at each iterations, and the best one (in terms of minimizing the energy function Eq. 2.13) is picked and becomes
the current estimate. The key to these algorithms is that, even though each iteration requires the choice among an exponentially large set of alternative labelings, the iteration can be solved very efficiently by mapping it to a graph cut problem. Note that this approach leaves considerable freedom for designing the iteration, which reduces to choosing the alternative labeling \( \xi'_q \) at each step.

Next, some of the most popular choices for graph cut iterations are reviewed:

- **Jump move.** In this iteration, the alternative labeling is the current labeling plus a constant at each voxel [91]:
  \[
  \xi'_q = \xi_{\text{cur}} + \beta
  \]

- **\(\alpha\)-expansion.** In this iteration, the alternative labeling is a constant at each voxel [88]:
  \[
  \xi'_q = \alpha
  \]

- **\(\alpha\)-\(\beta\)-swap.** In this iteration, the alternative labeling is defined as [88]:
  \[
  \xi'_q = \begin{cases} 
  \alpha, & \text{if } \xi_{\text{cur}} = \beta \\
  \beta, & \text{if } \xi_{\text{cur}} = \alpha \\
  \xi_{\text{cur}}, & \text{else}
  \end{cases}
  \]

Not all binary decision problems can be solved efficiently using an equivalent graph representation. The necessary and sufficient condition for graph-representability (i.e., the existence of an equivalent graph cut problem that can be efficiently solved) of the above-described iterations was derived in Ref. [79] and can be stated as:

\[
V_{q,j}(\xi_{\text{cur}}, \xi_{\text{cur}}) + V_{q,j}(\xi'_q, \xi'_j) \leq V_{q,j}(\xi'_q, \xi_{\text{cur}}) + V_{q,j}(\xi_{\text{cur}}, \xi'_j)
\]

for \( q = 1, \ldots, Q, \ j \in \delta_q \). Clearly, graph-representability depends only on the regularization penalty function \( V_{q,j}(\cdot, \cdot) \) and the choice of \( \xi'_q \).
Figure 2.6: Example of graph used for solving a binary iteration, including a graph cut. The number of vertices in the graph is $Q + 2$, i.e., one vertex per voxel in the corresponding image, and two additional vertices $s$ (source) and $t$ (sink). The edge weights $d_{qj}$ are determined by the cost function and the set of candidate labelings under consideration.

To construct the equivalent graph for Eq. 2.13 (see Fig. 2.6), each voxel gets assigned one vertex $v_q$, plus two additional vertices are created: source ($s$) and sink ($t$) vertices. Thus, the total number of vertices is $Q + 2$. The edges of the graph, accounting for the data term (called data edges) and the regularization term (called regularization edges) in Eq. 2.13, are defined as follows [79]:

- **Data edges.** $D_q(\xi^c_q)$ generates one edge for each voxel $q$. This edge is $(s, v_q)$ with weight $d_{sq} = D_q(\xi^c_q) - D_q(\xi'_q)$ if $D_q(\xi^c_q) - D_q(\xi'_q) > 0$, and $(v_q, t)$ with weight $d_{qt} = D_q(\xi'_q) - D_q(\xi^c_q)$ otherwise.

- **Regularization edges.** Each term $V_{q,j}(\xi_q, \xi_j)$ generates three edges (if a data edge already exists, the new weight is added to the existing weight). Defining $A_q = V_{q,j}(\xi'_q, \xi^c_j) - V_{q,j}(\xi^c_q, \xi'_j)$ and $A_j = V_{q,j}(\xi^c_q, \xi'_j) - V_{q,j}(\xi^c_q, \xi^c_j)$, the following edges are added:
  - Edge $(s, v_q)$ with weight $d_{sq} = A_q$ if $A_q > 0$, or edge $(v_q, t)$ with weight $d_{qt} = -A_q$ otherwise.
  - Edge $(s, v_j)$ with weight $d_{sj} = A_j$ if $A_j > 0$, or edge $(v_j, t)$ with weight $d_{jt} = -A_j$
otherwise.

- Edge \((v_q, v_j)\) with weight

\[
d_{qj} = V_{q,j}(\xi'_q, \xi'_j) + V_{q,j}(\xi'_{\text{cur}}, \xi'_j) - V_{q,j}(\xi'_q, \xi'_{\text{cur}}) - V_{q,j}(\xi'_q, \xi'_j).
\]

As formulated, the solution to Eq. 4.8 is given by the minimum cut problem [79]. Note that cut \(C\) of a graph is a partition of the vertices of the graph into two disjoint subsets, \(S\) and \(T\), such that \(s \in S\) and \(t \in T\). Every remaining vertex is either in \(S\) or in \(T\) (see Fig. 2.6). The cost \(|C|\) of \(C\) is defined as:

\[
|C| = \sum_{q \in S, j \in T} d_{qj}.
\]  

(2.15)

The minimum cut problem is defined as solving:

\[
C_{\text{min}} = \arg \min_C |C|,
\]  

(2.16)

which can be solved with worst-case complexity \(O(Q^3)\) for the graph defined above [92].
Chapter 3

Joint Estimation of Fat-Water Images and Field Map

3.1 Introduction

As discussed in Chapter 2, estimation of the water and fat images is trivial if the field map is known, as it reduces to a small linear LS problem at each voxel. However, field map estimation is a difficult problem due to the nonlinearity and ambiguity in the signal model. This ambiguity appears in different forms in the different fat-water separation algorithms, but it originates from the fact that, in the context of single-peak fat modeling, a water signal in a voxel with frequency offset $f_B$ is indistinguishable from a fat signal with frequency offset $f_B - f_F$. For ML estimation, the ambiguity appears in the non-convex form of the cost function (fit residue) to be minimized, which contains multiple local and global minimizers.

An effective way to overcome the ambiguity in the estimation is to seek a solution where the field map is spatially smooth. Indeed, field map smoothness is the underlying assumption in all previously proposed methods (except for those basic methods where the separation is performed one voxel at a time). Specifically, previously proposed ML-based methods impose field map smoothness by region-growing or multiresolution techniques to guide the selection of the correct “valley” of the fit residue at each voxel. In this work, a different approach is proposed, based on joint estimation. The key idea is to directly seek a solution for the complete field map and fat-water images (i.e., for all voxels simultaneously) that satisfies two conditions: (a) the solution fits the acquired data, and (b) the resulting field map is spatially smooth. Figure 3.1 illustrates the ambiguity for fat-water separation at a single voxel, as well as the ability of the field map smoothness constraint to overcome this ambiguity. The joint formulation is described in the following sections.
Figure 3.1: Ambiguity in voxel-independent estimation. (Left) Plot of the fit residue as a function of field map estimate. The residue is also shown with color code, for a more compact representation. Note the presence of multiple local and global minimizers. When attempting to separate water and fat at an isolated voxel, there are often several equally good solutions for the field map. Some of these solutions correspond to assigning mostly water to the voxel, and some correspond to assigning mostly fat. (Right) Performing the estimation jointly for all voxels, in combination with the constraint that the field map be spatially smooth, can resolve this ambiguity without the need for additional assumptions or sophisticated initialization strategies.

Additionally, this chapter introduces an alternative method for rapid fat-water separation using linear prediction (LP). The LP-based method is extended to include field map smoothness constraints and a multi-coil formulation.

### 3.2 Regularized Problem Formulation

This work is based on the following model for the chemical shift-encoded signal acquired at voxel $q$ with TE shift $t_n$:

$$s_q(t_n) = e^{i2\pi f_{\text{w},q} t_n} (\rho_{w,q} + \rho_{f,q} e^{i2\pi f_f t_n}) , \text{ for } n = 1, \ldots, N,$$

(3.1)
where $\rho_{w,q}$ and $\rho_{v,q}$ are the complex-valued amplitudes of water and fat, respectively, $f_v$ is the fat frequency offset due to chemical shift, and $f_{n,q}$ is the local frequency offset due to $B_0$ field inhomogeneities [1].

Under the usual assumption of white additive Gaussian noise, the ML estimate of the desired parameters $\{\rho_{w,q}, \rho_{v,q}, f_{n,q}\}$ in Eq. 3.1 is obtained by minimizing the following cost function at each voxel $q$ (as previously proposed in Refs. [1, 68]):

$$R_0(\rho_{w,q}, \rho_{v,q}, f_{n,q}; s_q) = \sum_{n=1}^{N} |s_q(t_n) - e^{i2\pi f_{n,q}t_n(\rho_{w,q} + \rho_{v,q}e^{i2\pi f_v t_n})}|^2, \quad (3.2)$$

where $s_q = [s_q(t_1) \cdots s_q(t_N)]^T$ is a column vector containing all the acquired signal samples at voxel $q$.

If the value of $f_{n,q}$ is approximately known (or it can be assumed to be close to zero), and the noise is moderate, the minimizer of Eq. 3.2 provides an effective (and optimal in the ML sense) solution to the fat-water separation problem. In general, minimizing $R_0(\rho_{w,q}, \rho_{v,q}, f_{n,q}; s_q)$ voxel-by-voxel (as is done in conventional voxel-based fat-water separation methods) is undesirable because: (a) $R_0(\rho_{w,q}, \rho_{v,q}, f_{n,q}; s_q)$ has multiple local and global minimizers [5,70], and (b) the ML estimates from Eq. 3.2 are sensitive to noise and often require post-estimation smoothing of the field map [1]. To address both of these issues, the residues for all the voxels, $R_0(\rho_{w,q}, \rho_{v,q}, f_{n,q}; s_q)$ for $q = 1, \ldots, Q$, can be minimized jointly. This joint approach allows the introduction of spatial smoothness constraints on the field map. Invoking the penalized ML (PML) framework, estimation of the complete field map $f_u = \{f_{n,q}\}_{q=1}^{Q}$, and fat-water images $\rho_u = \{\rho_{w,q}\}_{q=1}^{Q}$ and $\rho_v = \{\rho_{v,q}\}_{q=1}^{Q}$, can be reformulated as:

$$\{\hat{\rho}_w, \hat{\rho}_v, \hat{f}_u\} = \arg\min_{\rho_u, \rho_v, f_u \in \mathbb{C}^Q} \sum_{q=1}^{Q} R_0(\rho_{w,q}, \rho_{v,q}, f_{n,q}; s_q) + \mu \sum_{q=1}^{Q} \sum_{j \in \delta_q} w_{q,j} V(f_{n,q}, f_{n,j}), \quad (3.3)$$

where $\delta_q$ is the local neighborhood of voxel $q$, $\mu$ is a regularization parameter balancing data
consistency and smoothness of the solution, \( w_{q,j} \) are spatially dependent weights, and \( V(f_{w,q}, f_{w,j}) \) penalizes the roughness of the field map. In this work, \( \delta_q \) is the second-order neighborhood (which, in 2D, includes the eight voxels surrounding \( q \)) [87], and a quadratic \( V(f_{w,q}, f_{w,j}) = (f_{w,q} - f_{w,j})^2 \) is chosen to promote field map smoothness [72, 93].

The PML formulation in Eq. 3.3 has two important properties:

1. It can overcome the ambiguities present in voxel-independent estimation, i.e., solve the identification problem in voxels containing only one component (see Fig. 3.1). Note that solving Eq. 3.3 can remove the ambiguity in the estimation problem without need for sophisticated initializations or additional assumptions (e.g., assuming that the field map is known at a seed voxel), and also without need for explicit phase unwrapping of the acquired images.

2. By posing the problem as the explicit minimization of a cost function, Eq. 3.3 allows characterization of the spatial resolution properties of the resulting estimates using local methods [94]. This is useful for the selection of the regularization parameters \( \mu \) and \( w_{q,j} \) to avoid over-smoothing the field map (which could result in significant bias in the fat-water images). The spatial resolution properties of these estimates are characterized in Chapter 5.

### 3.3 Variable Projection Reformulation

Joint estimation of \( \{\rho_w, \rho_v, f_B\} \) using the PML formulation in Eq. 3.3 has several significant computational challenges:

- **High dimension.** The space of all possible solutions has \( 5Q \) dimensions, because each voxel contains two complex-valued parameters \( (\rho_w, q, \rho_v, q) \) and one real-valued parameter \( (f_{w,q}) \). In practice, the solution space has on the order of \( 10^5 \) dimensions for the datasets considered in this work.

- **Non-convexity.** The cost function is non-convex, and presents the usual difficulties of non-convex optimization (e.g., gradient-based methods only guarantee local convergence and
depend heavily on the initialization) [95].

- **Multiple local minima.** The cost function has a very large number of local (and often global) minima, due to the complex exponential form of the signal model (Eq. 3.1). Convergence to suboptimal local minima typically results in inaccurate fat-water separation [5].

\[ R_0(\rho_{w,q}, \rho_{v,q}, f_{B,q}; s_q) \] has a particular mathematical structure that lends itself to the Variable Projection (VARPRO) formulation [96, 97]. Specifically, the nonlinear parameter \( f_{B,q} \) can be estimated equivalently by minimizing:

\[
R(f_{B,q}; s_q) = \left\| \left[ I - \Psi(f_{B,q}) \Psi^\dagger(f_{B,q}) \right] s_q \right\|^2_2,
\]

where \( \Psi(f_{B,q}) \) is a \( N \times 2 \) matrix with \( [\Psi(f_{B,q})]_{(n,1)} = e^{i2\pi f_B t_n} \) and \( [\Psi(f_{B,q})]_{(n,2)} = e^{i2\pi (f_F + f_{B,q}) t_n} \), for \( n = 1, \ldots, N \), and \( \dagger \) denotes pseudoinverse.

Note that VARPRO effectively isolates the key component of fat-water separation: field map estimation. Thus, the field map estimate for the regularized problem in Eq. 3.3 can be equivalently expressed as:

\[
\hat{f}_n = \arg \min_{f_{B,q} \in \mathbb{R}^Q} \sum_{q=1}^{Q} R(f_{B,q}; s_q) + \mu \sum_{q=1}^{Q} \sum_{j \in \delta_q} w_{q,j} V(f_{B,q}, f_{B,j}),
\]

where the dimension of the problem is now reduced to \( Q \). Estimation of \( \{\rho_w, \rho_v\} \) is performed subsequently by solving a linear least-squares (LS) problem. Given the field map estimate \( \hat{f}_n \), the closed-form LS solution at each voxel \( q \) is given by:

\[
\left( \hat{\rho}_{w,q}, \hat{\rho}_{v,q} \right) = \Psi^\dagger(\hat{f}_{B,q}) s_q,
\]
which can be computed very efficiently. Computation of $\Psi^\dagger(f_B)$ for the values $\{f_{Bi}\}_{i=1}^L$ can be performed efficiently by rewriting $\Psi(f_B) = \Lambda(f_B)\Phi$, where

$$
\Phi = \begin{pmatrix}
1 & e^{i2\pi f_{B1}} & 0 \\
1 & e^{i2\pi f_{B2}} & 0 \\
\vdots & \vdots & \vdots \\
1 & e^{i2\pi f_{BN}} & 0
\end{pmatrix}, \quad \text{and} \quad \Lambda(f_B) = \begin{pmatrix}
e^{i2\pi f_{B1}} & 0 & \ldots & 0 \\
0 & e^{i2\pi f_{B2}} & \ldots & 0 \\
\vdots & \vdots & \vdots & \vdots \\
0 & 0 & \ldots & e^{i2\pi f_{BN}}
\end{pmatrix}.
$$

(3.7)

Therefore, the desired pseudoinverse is simply $\Psi^\dagger(f_B) = \Phi^\dagger \Lambda(-f_B)$, noting that $\Lambda(f_B)$ is a unitary matrix and also $\Lambda^{-1}(f_B) = \Lambda(-f_B)$. Furthermore, only one pseudoinverse needs to be computed for the entire decomposition, even if $\rho$ is estimated for many different values of $f_B$ at each voxel, since $\Phi$ does not depend on $f_B$ or $s$. If $\Phi$ has full column rank (which is needed in order to distinguish the water and fat signals), this pseudoinverse computation reduces to $\Phi^\dagger = [\Phi^H \Phi]^{-1} \Phi^H$.

Equation 3.5 shows the final form of the proposed formulation using VARPRO. In this formulation, fat-water separation is expressed as its key component: the regularized estimation of a non-linear parameter map (the field map $f_B$). Relative to the original formulation (Eq. 3.3), VARPRO results in an optimization problem of lower dimension (only one parameter per voxel). However, the cost function is still non-convex, and the optimization requires careful consideration. In Chapter 4, several optimization algorithms are described. These algorithms take advantage of this formulation to overcome the non-convexity and escape local minima where standard algorithms would be trapped.

**Selection of the regularization parameters $\mu$ and $w_{q,j}$**

Selection of the regularization parameter $\mu$ and the spatial weights $w_{q,j}$ is based on the resolution properties of the estimated field map. In this work, the weights are set to:

$$
w_{q,j} = \min \left( \left| \frac{\partial^2 R(f_{B,q}, s_q)}{\partial f_{B,q}^2} \right|_{f_{B,q} = f_{B,q}^{\min}}, \left| \frac{\partial^2 R(f_{B,j}, s_j)}{\partial f_{B,j}^2} \right|_{f_{B,j} = f_{B,j}^{\min}} \right),
$$

(3.8)
where \( f_{\text{min}} \) is the minimizer of \( R(f_{b,q};s_q) \), for \( q = 1, \ldots, Q \). This choice is obtained by approximating \( R(f_{b,q};s_q) \) by a quadratic function near its minimizer, and results in approximately uniform spatial smoothing of the field map [94]. The second derivatives in Eq. 3.8 are easily approximated by quantizing the values of \( f_{b,q} \). The degree of smoothing is then determined by \( \mu \), which is empirically set to 0.02 in this work. The effect of varying \( \mu \) and \( w_{q,j} \) is analyzed in Chapter 5.

### 3.4 Advanced Signal Models

In addition to the standard signal model (Eq. 3.1), the proposed method can easily be extended to handle more advanced signal models:

- **\( T_2^* \) decay.** The presence of significant \( T_2^* \) decay can severely bias the estimates of the fat-water images, if not included in the signal model. Generally, the water and fat components in a given voxel experience different \( T_2^* \) decay rates. However, estimating two separate decay rates significantly increases noise sensitivity. Even though separate rates can be estimated with more images [74], it is common to model the decay by a single decay rate \( R_{2,q}^* = 1/T_2^* \) at each voxel \( q \). The corresponding signal model becomes [7, 8, 77, 98, 99]:

\[
\begin{align*}
  s_q(t_n) &= e^{-R_{2,q}^*t_n} e^{i2\pi f_{b,q}^* t_n} \left( \rho_{w,q} + \rho_{v,q} e^{i2\pi f_{b,q}^* t_n} \right),
  &\text{for } n = 1, \ldots, N. 
\end{align*}
\]  

(3.9)

The above signal model can easily be included in the proposed method, by redefining \( R(f_{b,q};s_q) \) as:

\[
R(f_{b,q};s_q) = \min_{R_{2,q}^* \in \mathbb{R}} \sum_{n=1}^{N} \left| s_q(t_n) - e^{-R_{2,q}^*t_n} e^{i2\pi f_{b,q}^* t_n} \left( \rho_{w,q} + \rho_{v,q} e^{i2\pi f_{b,q}^* t_n} \right) \right|^2, 
\]  

(3.10)

where \( \{\rho_{w,q}, \rho_{v,q}\} \) can be removed using VARPRO, and the minimization with respect to \( R_{2,q}^* \) is performed by discretizing the \( R_{2,q}^* \) values. Therefore, the field map estimation algorithm, which depends only on \( R(f_{b,q};s_q) \), remains unchanged.

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- **Multi-peak fat model.** This model allows the fat signal to have \( M \) distinct peaks (often with \( M \) between 3 and 6). As a result, the signal at voxel \( q \) can be expressed as [8, 100]:

\[
s_q(t_n) = e^{i2\pi f_{B,q}t_n} \left( \rho_{w,q} + \rho_{F,q} \sum_{m=1}^{M} \alpha_{m,q} e^{i2\pi f_{F,m}t_n} \right), \text{ for } n = 1, \ldots, N, \tag{3.11}
\]

where \( |\alpha_{1,q}| + |\alpha_{2,q}| + \cdots + |\alpha_{M,q}| = 1 \) for \( q = 1, \ldots, Q \), and \( \{f_{F,m}\}_{m=1}^{M} \) are the (known) frequency shifts of the \( M \) individual fat peaks.

This model requires \( N \geq M + 2 \) acquisitions to estimate \( f_{B,q}, \rho_{w,q} \) and \( \{\rho_{F,q}\alpha_{m,q}\}_{m=1}^{M} \), which may not be practical. Alternatively, it may be assumed that \( \{\alpha_{m,q}\}_{m=1}^{M} \) are known (or calibrated from the data itself) and spatially uniform, i.e., \( \alpha_{m,q} = \alpha_{m} \) for \( q = 1, \ldots, Q \). Under this assumption, the multi-peak model (Eq. 3.11) contains the same number of unknown parameters as the original signal model in Eq. 3.1, so \( N = 3 \) acquisitions are sufficient to perform the separation [44, 77, 101]. Since the only nonlinear parameter in the multi-peak model is the field map, the proposed method applies naturally to this model. The only modification necessary is substituting the second column in \( \Psi(f_{B,q}) \) by the corresponding linear combination of fat peaks from Eq. 3.11.

### 3.5 Multi-Coil Acquisitions

This work considers a multi-coil acquisition with \( P \) distinct coils, which produce \( P \) images with independent amplitude weightings and phase offsets. Thus, the signal at a given voxel \( q \) corresponding to coil \( p \) with TE shift \( t_n \) can be modeled as

\[
s_{p,q}(t_n) = e^{i2\pi f_{B,q}t_n} \left( \rho_{w,p,q} + \rho_{F,p,q} e^{i2\pi f_{F}t_n} \right) \tag{3.12}
\]
where $\rho_{W,p,q}$ and $\rho_{F,p,q}$ are the water and fat signal intensities, respectively, observed by coil $p$ at voxel $q$.

The proposed VARPRO formulation can be extended to optimally (in the ML sense) estimate the field map as well as the $P$ sensitivity-weighted fat-water images. According to the signal model in Eq. 3.12, the new cost function is

$$R_{MC,0}(\rho_1, \ldots, \rho_P, f_B; s_{1,q}, \ldots, s_{P,q}) = R_0(\rho_1, f_B; s_{1,q}) + \cdots + R_0(\rho_P, f_B; s_{P,q}) \quad (3.13)$$

where $\rho_p = [\rho_{W,p}, \rho_{F,p}]^T$ and $R_0(\rho_p, f_B; s_{p,q})$ is the single-coil cost function for the signal $s_{p,q}$, as defined in Eq. 3.4. Clearly, $f_B$ is the only nonlinear parameter under consideration and thus the VARPRO approach discussed above can be naturally extended by simply minimizing the sum of the individual cost functions. Since for each value of $f_B$ all the linear parameters $\{\rho_1, \ldots, \rho_P\}$ are obtained immediately by solution of $P$ linear LS problems, the combined cost function in the VARPRO formulation can be expressed as $R_{MC}(f_B)$ (similarly to Eq. 3.4), and again a global one-dimensional search is possible to find the optimal $f_B$ estimate.

As in the single-coil case, the fat-water amplitudes can be determined efficiently once $f_B$ is estimated, by solving the corresponding linear problem (Eq. 3.6) for each coil. After the $P$ sensitivity-weighted fat-water images are obtained, they can be combined using standard multi-coil combination techniques [1, 102–104].

Here, the coil sensitivities are assumed unknown. If they are known, the VARPRO formulation can still be used, with the difference that only two component amplitudes, $\rho_W$ and $\rho_F$, and the field inhomogeneity, $f_B$, need to be estimated at each voxel.

Alternatively to the proposed multi-coil method, the acquired images can be combined before fat-water separation, using an eigenvector-based filter [105]. This approach has the advantage of reduced computation (since the initial image combination can be performed very efficiently), and has been shown to work well in practice.
3.6 Linear Prediction-Based Method

If the images are acquired at uniformly spaced TEs, a computationally simpler fat-water separation method is possible. Assuming the TEs are \( t_n = t_0 + n \Delta t \), \( n = 1, \ldots, N \), the signal model in Eq. 3.1 can be rewritten as follows:

\[
s(t_n) = \sum_{m=1}^{2} a_m z_m^n, \quad n = 1, \ldots, N \quad (3.14)
\]

where \( a_1 = \rho_w e^{i2\pi f_w t_0}, a_2 = \rho_f e^{i2\pi (f_f + f_B) t_0}, z_1 = e^{i2\pi f_B \Delta t} \) and \( z_2 = e^{i2\pi (f_f + f_B) \Delta t} \).

This signal, in the absence of noise, is linearly predictable with coefficients \( \{g_1, g_2\} \), i.e.

\[
s(t_n) = g_1 s(t_{n-1}) + g_2 s(t_{n-2}), \quad n = 3, \ldots, N \quad (3.15)
\]

and, since \( |z_1| = |z_2| = 1 \), it is also backward-predictable with the same prediction coefficients:

\[
s^*(t_n) = g_1 s^*(t_{n+1}) + g_2 s^*(t_{n+2}), \quad n = 1, \ldots, N - 2. \quad (3.16)
\]

Furthermore, it can be shown that the polynomial

\[
G(z) = 1 - g_1 z^{-1} - g_2 z^{-2} \quad (3.17)
\]

has its roots at \( z_1 \) and \( z_2 \) (see, e.g., [106] for details).

This formulation enables an efficient determination of the parameters in the signal model (Eq. 3.1). Similarly to the VARPRO method described above, the problem is solved by estimating the linear and nonlinear parameters in two separate steps. First, the prediction coefficients \( \{g_1, g_2\} \) are estimated using the so-called forward-backward LP by simultaneously solving Eqs. 3.15 and 3.16 [107]. Next, the estimates for \( z_m \) are computed as the roots of \( G(z) \), and the linear parameters \( a_m \) are obtained by solving the corresponding linear problem (Eq. 3.14).

In the absence of noise, the parameters \( \{\rho_w, \rho_f, f_B\} \) are obtained directly from the LP estimates.
\{a_m, z_m\}, as long as \(a_1 \neq 0\) and \(a_2 \neq 0\). Denoting \(\phi_m = \angle z_m/(2\pi \Delta t)\), then either \(\phi_2 = \phi_1 + f_F\) or \(\phi_2 = \phi_1 - f_F\). Without loss of generality, the values \(\{\phi_m\}\) can be sorted so that the former is satisfied. Thus, the signal parameters are obtained as follows: \(f_B = \phi_1, \rho_w = a_1 e^{-i2\pi f_B t_0}\) and \(\rho_F = a_2 e^{-i2\pi(f_B + f_F)t_0}\).

If one of the components is absent, the signal model becomes ambiguous [5] and assigning the observed component to water or fat requires some prior knowledge. Similarly, in the presence of noise, the frequency separation of the observed components will not be exactly \(f_F\). Assuming a limited range on the field inhomogeneity, \([f_{B,\text{MIN}}, f_{B,\text{MAX}}]\), water and fat can be assigned the component with estimated frequency \(\phi_m\) closest to 0 and \(f_F\), respectively. Specifically, the component minimizing

\[
\phi_w = \arg \min_{\phi \in \{\phi_1, \phi_2\}} |\phi|, \text{ s.t. } \phi \in [f_{B,\text{MIN}}, f_{B,\text{MAX}}]
\]  

(3.18)

is assigned to water (with corresponding amplitude \(\rho_w = a_1 e^{-i2\pi f_B t_0}\)), and the component minimizing

\[
\phi_F = \arg \min_{\phi \in \{\phi_1, \phi_2\}} |\phi - f_F|, \text{ s.t. } \phi \in [f_F + f_{B,\text{MIN}}, f_F + f_{B,\text{MAX}}]
\]  

(3.19)

is assigned to fat (with amplitude \(\rho_F = a_2 e^{-i2\pi(f_B + f_F)t_0}\)).

If no estimated frequency \(\phi_m\) lies within the specified bounds for a given component, this component is assumed not present at the current voxel. Subsequently, the field map value can be estimated at each voxel by weighted averaging of the individual estimated field inhomogeneities:

\[
f_{B,v} = \frac{\phi_w |\rho_w| + (\phi_F - f_F) |\rho_F|}{|\rho_w| + |\rho_F|}.
\]  

(3.20)
3.6.1 Imposing Spatial Constraints

In the presence of noise, the voxel-by-voxel LP-based method may produce spatially non-smooth field map estimates. Thus, the LP field map estimate can benefit from spatial regularization. However, the LP formulation does not provide the same flexibility as VARPRO for incorporating spatial constraints. Instead, field map smoothness can be imposed in a separate step, by penalizing deviations from the voxel-by-voxel estimates as well as field map roughness. This can be formulated effectively as a regularized LS problem:

\[
\hat{f}_b = \arg \min_{f_B} \left[ \|W(f_B - f_{B,v})\|^2 + \lambda \|Df_B\|^2 \right]
\] (3.21)

where \(f_B\) is the complete field map (a length-\(Q\) vector corresponding to the \(Q\) voxels in the image), \(f_{B,v}\) is the rough field map estimated independently at each voxel (Eq. 3.20), \(W\) is a diagonal weighting matrix used to place more weight on field map estimates from voxels where the signal level is higher, \(D\) computes spatial finite differences in the field map, and \(\lambda\) is a regularization parameter controlling the tradeoff between field map smoothness and data fidelity.

This minimization reduces to a linear problem:

\[
(W^HW + \lambda D^HD) \hat{f}_b = W^HWf_{B,v}
\] (3.22)

and can be solved efficiently using, e.g., a conjugate-gradient method [108]. This method is similar to the one proposed in [1], where the fat-water images and field map are estimated point by point and field map smoothing is performed separately. Decoupling both steps simplifies the algorithm and reduces the computational burden. It must be noted that this “two-step” method is suboptimal, and is expected to perform well only in cases of moderate field inhomogeneity. Specifically, the smoothing step will generally not be able to correct large errors in the field map estimate, e.g., in voxels where water and fat are swapped during voxel-by-voxel processing [5, 93]. Finally, the water and fat components should be re-estimated at each voxel using the regularized field map \(\hat{f}_b\).
by solving the corresponding linear problem (Eq. 3.6).

The following parameters for LP have been used in this work: the weighting matrix $W$ was set to the sum of the signal amplitudes at each voxel, normalized to have a maximum value of 1 (thus assigning more weight to the field map estimates from voxels containing higher signal amplitude). The regularization parameter $\lambda$ was set to 1. Similarly to VARPRO, the parameters for LP were fixed throughout the results.

Since the proposed regularization of the field map will place very little weight on estimates from voxels that contain only noise (e.g., voxels where the signal amplitude is below a noise threshold), these voxels may be skipped (and their field inhomogeneity set to zero) during the voxel-by-voxel estimation, for increased computational efficiency.

The LP-based algorithm for regularized estimation of fat-water images and field map can be summarized as follows:

1. At each voxel with signal amplitude above a noise threshold, perform forward-backward LP to obtain $z_k$ and $a_k$ following Eqs. 3.15, 3.16 and 3.14. Assign the estimated components to fat-water using Eqs. 3.18 and 3.19.

2. Obtain the regularized field map $\hat{f}_B$ by imposing spatial smoothness (Eq. 3.21).

3. Re-estimate the fat-water components $\rho_w$ and $\rho_v$ at each voxel using the regularized field map (Eq. 3.6).

### 3.6.2 Multi-coil Acquisitions

The single coil LP algorithm can easily be extended to handle multi-coil acquisitions. According to the multi-coil signal model in Eq. 3.12, the field inhomogeneity effect is the same for all coils, and furthermore the signals detected at a particular voxel by the different coils are different linear combinations of the same complex exponentials. Thus, the prediction coefficient vector is the same for all coils, which can simply be enforced by solving Eqs. 3.15 and 3.16 simultaneously.
for all coils. Once the prediction coefficients (and thus the \( z_k \)) are obtained, the amplitudes of the different chemical species can be estimated independently for each coil using Eq. 3.14.
Chapter 4

Solution of the Joint Estimation Problem

4.1 Introduction

The proposed PML formulation (Eq. 3.5) has two important properties for solving the fat-water separation problem: (1) it can overcome the ambiguities in voxel-independent estimation by imposing field map smoothness, and (2) it allows characterization of the properties of the resulting estimates (as will be described in Chapter 5). However, Eq. 3.5 also results in a difficult optimization problem, due to its non-convexity and high dimension. Gradient-based methods have been proposed for solving a similar formulation [72], but converging to the correct valley of $R(f_{b,q}; s_q)$ remains a challenge. This chapter introduces the proposed strategies for solving Eq. 3.5, based on a discretization of the problem (obtained by quantizing the possible field map values), followed by a solution of the resulting discrete problem. First, an algorithm providing the globally optimal solution of the discretized problem is reviewed. This solution is interesting, but too computationally expensive for practical use. To overcome this limitation, a simple coordinate descent approach is described, where voxels are updated one at a time. Next, a novel graph cut-based iterative algorithm is introduced, where all voxels are considered simultaneously. Finally, alternative choices of regularization strategies with globally optimal graph cut solutions are described.

4.2 Problem Discretization

The residue $R(f_{b,q}; s_q)$, defined in Eq. 3.4, contains multiple local and global minimizers at each voxel, so gradient-based methods may converge to a suboptimal solution. This limitation can be
effectively overcome by discretizing the problem [68]. The proposed method constrains $f_{n,q}$ to a discrete set of possible values $\Omega = \{\psi_l\}_{l=1}^L$, where the $\psi_l$ are uniformly spaced with spacing 2-4 Hz over a range $\pm 1500$ Hz. This spacing was found to introduce only negligible errors in fat-water separation. The wide range of $\Omega$ accounts for the potentially very large field inhomogeneities that often appear near the edges of the field of view (FOV), particularly in short, wide bore scanners. Note that, for the usual acquisitions with uniformly spaced TEs ($t_n = t_0 + n\Delta t$) [1, 109], $R(f_{n,q};s_q)$ is periodic with period $1/\Delta t$. In this case, even though $\Omega$ spans $\pm 1500$ Hz, it suffices to evaluate $R(f_{n,q};s_q)$ on the interval $[0, 1/\Delta t]$ [70]. Limiting $f_b \in \Omega^Q$ yields the following discrete optimization problem:

$$\hat{f}_b = \arg\min_{f_b \in \Omega^Q} \sum_{q=1}^Q R(f_{n,q};s_q) + \mu \sum_{q=1}^Q \sum_{j \in \delta_q} w_{q,j} V(f_{n,q}, f_{n,j}).$$ (4.1)

This discretization introduces a critical advantage in the formulation: it allows the algorithm to choose solutions from arbitrary valleys in the non-convex function $R(f_{n,q};s_q)$ at each voxel. For instance, one can consider a single voxel where there are several suboptimal solutions and only one globally optimal solution. In this case, descent-based methods may be trapped in the wrong valley, whereas by considering a discrete grid of possible field map values, the solution from the best valley (assuming the discretization is fine enough) can be directly picked without need for descent.

An important requirement for the minimizing solution to be meaningful is that the spacing between quantized values is small enough relative to the variability of $R(f_b)$. In other words, we need to guarantee that $R(f_b)$ does not contain abrupt changes which are not captured by the discretized version $\{R(f_{n,t})\}_{t=1}^L$. For this purpose, the derivative of $R(f_b)$ can be evaluated. From Eq. 3.4,

$$\frac{dR(f_b)}{df_b} = -i \sum_{m,n, m \neq n} s^*(t_n)s(t_m)\Gamma_{n,m} e^{i2\pi f_b(t_n-t_m)} 2\pi(t_n-t_m),$$
where $\Gamma = \Phi (\Phi^H \Phi)^{-1} \Phi^H$. The following bound follows readily:

$$\left| \frac{dR(f_B)}{df_B} \right| \leq \max_k |s(t_k)|^2 \sum_{m \neq n} |\Gamma_{n,m}| 2\pi |t_n - t_m| = B.$$  \hspace{1cm} (4.2)

Given the discretization spacing $\Delta f_B = f_{B,l+1} - f_{B,l}$, this provides a bound on the maximum difference of the global optimum of the continuous function $R(f_B)$ from the discretized version $\{R(f_{B,t})\}_{t=1}^T$:

$$\left| \min_{f_B} R(f_B) - \min_{t=1,2,\ldots,L} \{R(f_{B,t})\}_{t=1}^L \right| \leq \frac{\Delta f_B}{2} B,$$ \hspace{1cm} (4.3)

which produces a useful criterion to ensure that the cost function $R(f_B)$ is smooth with respect to $\Delta f_B$.

In cases of true ambiguity, e.g., voxels containing only water or only fat, this discretization will not be enough to resolve the ambiguity – regularization is still needed – but it allows the use of a set of powerful optimization algorithms to solve the discretized problem. These algorithms are described next.

### 4.3 Global Optimization

The discretized problem in Eq. 4.1 involves choosing the best among $L^Q$ possible field maps. This number, e.g., $1,000^{256 \times 256} \approx 10^{197,000}$ is much too large for exhaustive search. It is, therefore, perhaps surprising that Eq. 4.1 can be solved globally with a computational cost polynomial in the number of voxels $Q$. This solution follows the constructive proof given in Ref. [90]. Sufficient conditions for discretized cost functions (where the discretization is obtained by restricting the field map values to a uniformly spaced set of values over a certain range) of the form shown in Eq. 4.1 to be globally solvable using graph cuts are the following [90]:

1. The non-convex term is voxel-independent (i.e., it is the sum of independent terms defined
at each voxel). In the context of fat-water separation, the non-convexity appears only in the data term:
\[
\sum_{q=1}^{Q} R(f_{b,q}; s_q),
\]
but this term is simply the sum of the fit residues at each of the \(Q\) voxels.

2. The pairwise terms are a convex function of field map differences. In the context of fat-water separation, the pairwise terms correspond to the smoothness term of the cost function:
\[
\mu \sum_{q=1}^{Q} \sum_{j \in \delta_q} w_{q,j} V(f_{b,q}; f_{b,j}),
\]
which are convex if \(V(\cdot, \cdot)\) is a convex function of the difference (as is normally the case for field map estimation, where edge-preserving regularization is not common).

The corresponding graph required to solve the problem has the structure shown (with two examples) in Fig. 4.1. The graph contains \(QL + 2\) nodes, where \(Q\) is the number of voxels in the image and \(L\) is the number of quantization levels; i.e., there is one node for each possible pair of voxel and field map value, plus the source and sink nodes. Note that this is a larger graph than those used in binary optimization (as reviewed in Chapter 2), which contain only \(Q + 2\) nodes.

The edge structure of these graphs is relevant, as it determines which problems can be solved in practice. One can define the penalty function in terms of the indices of the quantized field map values \(g(l - m) = V(\psi_l, \psi_m)\). Then, the edge between the nodes corresponding to voxel \(q\), field value \(\psi_l\), and voxel \(j\), field value \(\psi_m\) has weight given by the second order finite differences of \(g\) [90]:
\[
d_{\{q,l\},\{j,m\}} = \frac{g(l - m + 1) - 2g(l - m) + g(l - m - 1)}{2},
\]
where it must be noted that the edge structure is the same between the nodes corresponding to any pair of neighboring voxels. For the quadratic (\(\ell_2\)) penalties introduced in Chapter 3, all the nodes corresponding to a given voxel \(q\) will have edges to all the nodes corresponding to all the voxels.
Figure 4.1: Global optimization graph structure for a hypothetical 2-voxel dataset, with quadratic regularization. The edge directions are omitted for simplicity. The graph contains $QL + 2$ nodes, and on the order of $QL^2$ edges.

$j \in \delta_q$ in the neighborhood of $q$. This results in a graph with a very large number of edges: on the order of $QL^2$ (see Fig. 4.1), which makes it impractical for large problems because the graph structure is difficult to store and manipulate in computer memory. For instance, for a problem with $Q = 128^2$ voxels, $L = 300$ field map values, MRF neighborhood of size 8, the corresponding graph will contain approximately $4.9 \times 10^6$ nodes and over $2.3 \times 10^{10}$ edges.

In the next sections, we study computationally tractable alternatives to the global optimization approach.

### 4.4 Iterated Conditional Modes

The regularized problem in Eq. 4.1 can be locally solved efficiently using the well-known iterated conditional modes (ICM) algorithm [86, 87]. ICM iterates several times through all the voxels,
updating the field map one voxel at a time, while holding the estimates at the remaining voxels fixed. This algorithm results in the following update for voxel $q$ (with neighborhood $\delta_q$):

$$f_{B}^{q,\text{new}} = \arg \min_{f_{B}^{q}} R(f_{B}^{q}) + \mu \sum_{j \in \delta_q} w_{q,j} |f_{B}^{q} - f_{B}^{j,\text{cur}}|^2,$$  \hspace{1cm} (4.5)

where $f_{B}^{j,\text{cur}}$ is the current field inhomogeneity estimate at neighboring voxel $j$.

For the case of VARPRO-ICM, more conservative parameters are used compared to those described in Chapter 3. The field inhomogeneity bounds are set to almost the chemical shift between water and fat, i.e. $\pm 200$ Hz for 1.5 T acquisitions and $\pm 400$ Hz for 3T acquisitions. The number of discretized field values used in the optimization is $L = 300$, which provides a good tradeoff between estimation accuracy and computational efficiency. The MRF neighborhood employed is the square of size $5 \times 5$ voxels centered at each voxel (excluding the center). The weights $w_{q,j}$ are set to the inverse of the distance between voxels $q$ and $j$. Finally, the regularization parameter $\mu$ is set to $\sigma^2/30$, where $\sigma^2$ is the estimated noise variance. The value of $\sigma^2$ can be estimated from the data itself, or alternatively from pre-scan noise only data [110]. According to the MRF model, the value of $\mu$ is the ratio between the noise variance in the acquired images and a measure of the variability of the field map.

The VARPRO-based method with MRF prior is summarized below:

1. Initialize the field map estimate $f_{B}$ (e.g., all zeros).

2. Pre-compute the cost function $\{R(f_{B,l})\}_{l=1}^{L}$ (Eq. 3.4) for a set of field inhomogeneity values $f_{B,l} \in [f_{B,\text{MIN}}, f_{B,\text{MAX}}]$, for all voxels.

3. For each voxel, update the field map estimate using Eq. 4.5.

4. Repeat step (3) until the overall field map change falls below some small threshold $\varepsilon > 0$:

$$\sum_{q=1}^{Q} |f_{B}^{q,\text{new}} - f_{B}^{q,\text{cur}}| < \varepsilon.$$  \hspace{1cm} (4.6)
5. For each voxel, estimate $\rho_w$ and $\rho_s$ given the estimated field map using Eq. 3.6.

### 4.5 Graph Cut-Based Iterative Optimization

The main limitation of ICM is that only one voxel is updated at a time, which is problematic in cases of large field inhomogeneities. In these cases, the field value at multiple voxels should be updated simultaneously in order to correctly track the field map. On the other extreme, global optimization using the large graph from Ref. [90] is too computationally demanding for practical applications. An algorithm is presented next, that subdivides the problem in Eq. 4.1 into a sequence of binary decision problems and solves each of them efficiently (and jointly for all the voxels) using a graph cut algorithm at each iteration. Specifically, let $\Gamma$ be a subset of $\Omega^Q$, defined as:

$$\Gamma = \hat{\Omega}_1 \times \hat{\Omega}_2 \times \cdots \times \hat{\Omega}_Q,$$

where $\hat{\Omega}_q = \{\hat{f}_{n,q}, \hat{f}'_{n,q}\}, q = 1, \ldots, Q$ are binary sets. Denote $\hat{f}_{n,q}$ as the current field map estimate at voxel $q$, and $\hat{f}'_{n,q}$ as a potential update of $\hat{f}_{n,q}$ for the next iteration. Limiting $f_n \in \Gamma$ yields the following discrete optimization problem at each iteration:

$$\hat{f}_n = \arg\min_{f_n \in \Gamma} \sum_{q=1}^{Q} R(f_{n,q}; s_q) + \mu \sum_{q=1}^{Q} \sum_{j \in \delta_q} w_{q,j} V(f_{n,q}, f_{n,j}).$$

Even though $\Gamma$ is still too large (with size $2^Q$) for exhaustive search, Eq. 4.8 can be solved very efficiently by mapping it to an equivalent graph cut problem [79,83,85,88,92,111]; details on how to perform the mapping are provided in the following subsection.

With the graph cut algorithm guaranteeing the global minimum of Eq. 4.8, the key to solving Eq. 4.1 is the design of $\Gamma$ at each iteration, (i.e., choosing $\hat{f}'_{n,q}$). In this work, three different
constructions for $\Gamma$, corresponding to different choices of $\hat{f}^n_{b,q}$ are used:

\begin{align*}
\Gamma_{\beta}^+ & : \hat{f}^n_{b,q} = \hat{f}^n_{b,q} + \beta \\
\Gamma^+ & : f^n_{b,q} = \min_m \{ f^{\min,m}_{b,q} \} \quad \text{s.t.} \quad f^{\min,m}_{b,q} > f^n_{b,q} \\
\Gamma^- & : f^n_{b,q} = \max_m \{ f^{\min,m}_{b,q} \} \quad \text{s.t.} \quad f^{\min,m}_{b,q} < f^n_{b,q},
\end{align*}

(4.9)

where $\beta$ is a constant, and $\{ f^{\min,m}_{b,q} \}$ is the set of local minimizers of $R(f^n_{b}; s_q)$ at voxel $q$. In noise-only voxels (identified using a threshold on the signal amplitude), the locations of local minima are meaningless, and thus the “jumps” corresponding to the separation between local minimizers in a voxel with a single component are used in $\Gamma^+$ and $\Gamma^-$. Note that $\Gamma_{\beta}$ corresponds to a uniform “jump” with step size $\beta$ applied to all the voxels [84, 91], whereas $\Gamma^+$ and $\Gamma^-$ correspond to voxel-dependent jumps (see Fig. 4.2). In practice, iterations based on $\Gamma^+$ and $\Gamma^-$ provide rapid convergence to the correct “valley” of $R(f^n_{b}; s_q)$ at each voxel. Their role is similar to the search for the correct local minima performed in Ref. [70]; in practice, the first few (e.g., 15) iterations can be fixed to be of these kinds. Iterations based on $\Gamma_{\beta}$ perform fine-tuning. A simple proof of the equivalence of the proposed iterations to a graph cut problem [79] is given in Section 4.5.1.

In this work, a randomized scheduling of the proposed iterations is used, where, at each iteration, $\Gamma_{\beta}$ (with random step size $\beta$ in the range $\pm 20$ Hz), $\Gamma^+$ or $\Gamma^-$ is used [80]. Upon convergence, the solution $f^n_b$ is optimal with respect to an exponentially large set [80]. An example of the evolution of $\hat{f}^n_b$ in the proposed algorithm is shown in Fig. 4.3. A key advantage over previous methods is the ability to simultaneously update $\hat{f}^n_b$ for arbitrary sets of voxels, thus enabling the proposed algorithm to escape suboptimal solutions, where methods that consider one voxel at a time may be trapped.

### 4.5.1 Conversion of Eq. 4.8 to a Graph Cut Problem

Recall the definition of the subset $\Gamma \subset \Omega^Q$ for the optimization problem in Eq. 4.8: $\Gamma = \hat{\Omega}_1 \times \hat{\Omega}_2 \times \cdots \times \hat{\Omega}_Q$, where $\hat{\Omega}_q = \{ \hat{f}^n_{b,q}, \hat{f}^n_{b,q} \}, q = 1, \ldots, Q$. The necessary and sufficient condition for graph-representability (i.e., the existence of an equivalent graph cut problem that can be efficiently
Figure 4.2: Example of $R(f_b; s_q)$ at an individual voxel. Note the non-convexity of $R(f_b; s_q)$, which contains multiple local minimizers, and no unique global minimizer. Given $\hat{f}_{n,q}$ as the current field inhomogeneity estimate at voxel $q$, $\hat{\Omega}_q = \{\hat{f}_{n,q}, \hat{f}'_{n,q}\}$ is the binary set for $\Gamma$ in the proposed algorithm. There are three choices for $\hat{f}'_{n,q}$, corresponding to $\Gamma_+, \Gamma_-$ and $\Gamma_\beta$ (with $\hat{f}'_{n,q} = \hat{f}_{n,q} + \beta$).

Solved) of Eq. 4.8 was derived in Ref. [79] and can be stated as:

$$V(\hat{f}_{n,q}, \hat{f}_{n,j}) + V(\hat{f}'_{n,q}, \hat{f}'_{n,j}) \leq V(\hat{f}'_{n,q}, \hat{f}_{n,j}) + V(\hat{f}_{n,q}, \hat{f}'_{n,j})$$  \hspace{1cm} (4.10)

for $q = 1, \ldots, Q, j \in \delta_q$. Clearly, in this problem graph-representability depends only on the regularization penalty function $V(f_b, f_{b,j})$ and the choice of $\hat{f}'_{n,q}$.

For a quadratic penalty $V(f_b, f_{b,j}) = (f_b - f_{b,j})^2$, it is easy to show that any choice of $\Gamma$ where $\hat{f}'_{n,q} - \hat{f}_{n,q}$ has the same sign for all voxels $q = 1, \ldots, Q$ (as is the case for the proposed iterations $\Gamma_\beta, \Gamma_+$ and $\Gamma_-$) is graph-representable. Denoting $\Delta_0 = \hat{f}_{n,q} - \hat{f}_{n,j}, \Delta_q = \hat{f}'_{n,q} - \hat{f}_{n,q}$, and $\Delta_j = \hat{f}'_{n,j} - \hat{f}_{n,j}$, then Eq. 4.10 will be satisfied if

$$\left(\Delta_0 + \Delta_q\right)^2 + \left(\Delta_0 - \Delta_j\right)^2 - \Delta_0^2 - \left(\Delta_0 + \Delta_q - \Delta_j\right)^2 > 0,$$  \hspace{1cm} (4.11)

i.e., if $\Delta_q \Delta_j > 0$ (or equivalently, if $\Delta_q$ and $\Delta_j$ have the same sign). Therefore, the iterations
Figure 4.3: Results to illustrate convergence of the proposed method. (Top) Estimated field map at several iterations. (Center) Corresponding water images. (Bottom) Corresponding fat images. The ability of the graph cut algorithm to update a large set of voxels at any iteration results in rapid convergence of the proposed method, even in the presence of large field inhomogeneities. Additionally, no complicated initialization heuristics are necessary (the field inhomogeneity map can simply be initialized to zero).
employed in this work are graph-representable.

To construct the equivalent graph for Eq. 4.8 (see Fig. 2.6), each voxel gets assigned one vertex \( v_q \), and there are two additional vertices: source \((s)\) and sink \((t)\). Thus, the total number of vertices is \( Q + 2 \). The edges of the graph, accounting for \( R(f_{b,q}; s_q) \) (called data edges) and the regularization term (called regularization edges) in Eq. 4.8, are defined as follows [79]:

- **Data edges.** \( R(f_{b,q}; s_q) \) generates one edge for each voxel \( q \). This edge is \((s, v_q)\) with weight 
  \[ d_{sq} = R(\hat{f}_{b,q}; s_q) - R(\hat{f}'_{b,q}; s_q) \text{ if } R(\hat{f}_{b,q}; s_q) - R(\hat{f}'_{b,q}; s_q) > 0, \]
  or \((v_q, t)\) with weight 
  \[ d_{qt} = R(\hat{f}_{b,q}; s_q) - R(f_{b,q}; s_q) \text{ otherwise.} \]

- **Regularization edges.** Each term \( V(\hat{f}_{b,q}, \hat{f}_{b,j}) \) generates three edges (if a data edge already exists, the new weight is added to the existing weight). Defining \( A_q = V(\hat{f}_{b,q}, \hat{f}_{b,j}) - V(\hat{f}_{b,q}, \hat{f}_{b,j}) \) and \( A_j = V(\hat{f}_{b,q}, \hat{f}_{b,j}) - V(\hat{f}_{b,q}, \hat{f}_{b,j}) \), the following edges are added:
  - Edge \((s, v_q)\) with weight \( d_{sq} = A_q \) if \( A_q > 0 \), or edge \((v_q, t)\) with weight \( d_{qt} = -A_q \) otherwise.
  - Edge \((s, v_j)\) with weight \( d_{sj} = A_j \) if \( A_j > 0 \), or edge \((v_j, t)\) with weight \( d_{jt} = -A_j \) otherwise.
  - Edge \((v_q, v_j)\) with weight
  \[ d_{qj} = V(\hat{f}'_{b,q}, \hat{f}_{b,j}) + V(\hat{f}_{b,q}, \hat{f}'_{b,j}) - V(\hat{f}_{b,q}, \hat{f}_{b,j}) - V(\hat{f}'_{b,q}, \hat{f}'_{b,j}). \]

As formulated, the solution to Eq. 4.8 is given by the minimum cut problem, which can be solved very efficiently for the graph defined above [79,92].
4.6 Alternative Regularization Strategies with Global Solutions

In this section, we revisit the topic of (noniterative) global optimization using graph cuts. The ability of graph cut methods to globally solve the regularized field map estimation problem is remarkable. However, the quadratic regularization proposed in Chapter 3 leads to a very large graph (with many edges). As an alternative, regularization of the field map using an $\ell_1$-based penalty has been explored, i.e., $V(f_{n,q}, f_{n,j}) = |f_{n,q} - f_{n,j}|$. This formulation presents a significant advantage in terms of the edge structure of the equivalent graph (see Fig. 4.4), because the weights $d_{\{q,l\},\{j,m\}}$ as given by Eq. 4.4 become nonzero only for $l = m$.

The global optimization graph structure shown in Fig. 4.1 highlights the difficulties of performing global optimization for quadratic regularization. On the other hand, $\ell_1$-based regularization (see Fig. 4.4a) results in a much more manageable graph, but is typically not the desired regularization for field map estimation (since $\ell_1$ regularization tends to produce blocky, rather than smooth, results).

The graph structures for quadratic- and $\ell_1$-based regularization suggest alternative regularization strategies that combine the benefits of the two, while overcoming their limitations. Specifically, this work has considered two forms of the penalty function $V(\cdot, \cdot)$, shown graphically in Fig. 4.5. These choices impose a quadratic penalty for small field map differences (i.e., in smoothly varying regions), and either a linear penalty or a very large penalty for larger differences (i.e., either “allow” large steps at certain locations, or essentially forbid them).

The edges needed to represent these alternative regularization strategies are shown in Fig. 4.4b. Note that the node for a given voxel and field map value will not have edges to the nodes for all field map values of neighboring voxels, but only to “nearby” field map values. Specifically, assuming the cutoff point for quadratic penalty corresponds to a difference of $K$ in the index of quantized field map values, the edge weights needed to represent the Huber function penalty (shown in
Figure 4.4: Global optimization graph structure for alternative regularization penalties. (Left) Graph structure for \(\ell_1\)-based regularization. This graph contains the same number of nodes \((QL + 2)\) as required for quadratic regularization. Note that quadratic regularization requires on the order of \(L\) times more edges. In this sense, solving the quadratic-regularized problem is harder than solving the \(\ell_1\)-regularized problem. (Right) Graph structure for “mixed” regularization penalties. These choices require fewer edges than quadratic regularization, although more than \(\ell_1\).

Fig. 4.5a) are:

\[
d_{(q,l),(j,m)} = \begin{cases} 
\mu w_{qj}(\Delta f_B)^2, & \text{for } |l - m| \leq K \\
0, & \text{for } |l - m| > K
\end{cases}
\]

(4.12)

where an edge weight of 0 means no edge is needed, and the edge weights needed to represent the quadratic-\(\infty\) penalty (shown in Fig. 4.5b) are:

\[
d_{(q,l),(j,m)} = \begin{cases} 
\mu w_{qj}(\Delta f_B)^2, & \text{for } |l - m| < K \\
\infty, & \text{for } |l - m| = K \\
0, & \text{for } |l - m| > K
\end{cases}
\]

(4.13)

where in practice we can use a very large, but finite, edge weight in place of \(d_{(q,l),(j,m)} = \infty\)

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at the appropriate locations in the graph. Note that this results in a finite penalty approximating the behavior of Fig. 4.5b, but satisfying the Hammersley-Clifford theorem, which requires that all configurations have strictly positive probability [112].

These two choices of penalty function have promising properties in terms of field map regularization, and additionally they lead to global optimization graphs with considerably fewer edges than the original quadratic regularization used in this work (see Fig. 4.4b).

In practice, global optimization of even the $\ell_1$-based formulation is too slow for routine use: the current implementation requires approximately 20 GB of memory and 20 minutes of computation for a typical dataset, on an Intel Xeon-based desktop computer. Thus, this global optimization is only used as a proof of concept in this work. When “graph cut” method is mentioned in subsequent chapters, this refers to the iterative method based on a sequence of binary optimizations unless specified otherwise.
Chapter 5

Experimental Results

5.1 Introduction

This chapter provides experimental results for the fat-water separation methods described in Chapters 3 and 4. First, the noise performance of ML- and LP-based estimation is analyzed for single voxel estimation in the absence of fat-water swaps (i.e., when the field map can be assumed to be approximately known a priori). Second, the performance of ICM and LP is demonstrated in cases of moderate field inhomogeneities (when the field offsets are at most on the order of the fat chemical shift). Third, the performance of graph cuts is demonstrated and compared to previous methods in the presence of large field inhomogeneities (several times larger than the fat chemical shift). Fourth, the spatial resolution properties of the estimated field map using the proposed regularized formulation are studied, and the implications regarding systematic errors in fat-water separation are analyzed. Finally, the properties of the proposed formulation and optimization methods are discussed in more detail.

5.2 Noise Performance of ML and LP Estimation

A simulation study was done to test the performance of several methods for single-voxel decomposition in the presence of noise. Figure 5.1 shows a comparison of the Cramér-Rao lower bound (CRLB, a lower bound on the variance of any unbiased estimator [109, 113]) and mean squared error (MSE) simulation results for amplitude estimation using three samples ($N = 3$) with phase shifts $\{-\pi/6, \pi/2, 7\pi/6\}$. This choice of phase shifts is optimal for all fat-water ratios, as shown
in [109]. The simulated signal contains two components with amplitudes $\rho_w = \rho_v = 1$. Complex Gaussian noise with a range of different variances was added to the signal. The ML estimate appears to be efficient (i.e., unbiased and with MSE matching the CRLB) for all SNR values. The LP estimate becomes more robust as the SNR increases. Figure 5.1 shows that, at lower SNR, the ML approach is preferable. On the other hand, at higher SNR, LP provides a competitive and computationally efficient solution to the fat-water imaging problem.

![Figure 5.1: Comparison between theoretical bounds (CRLB) and empirical MSE for amplitude estimation. The solid line indicates the CRLB, while the circles and asterisks represent the empirical results obtained from ML (using VARPRO) and LP, respectively.](image)

**5.3 Moderate Field Inhomogeneities**

A quantitative comparison of the accuracy of the proposed methods including spatial regularization of the field map, and an iterative voxel-independent ML method followed by field map filtering (i.e., the original IDEAL algorithm [1]) was performed using synthetic data. Three synthetic datasets were generated, based on brain, abdominal and cardiac acquisitions, respectively. The water and fat images were obtained by wavelet denoising the estimated fat-water components (obtained using VARPRO with no spatial regularization on the field map) from each *in vivo* dataset.
The synthetic field maps were obtained by smoothing the corresponding voxel-by-voxel estimated field maps. This was done by applying a Hamming window in the Fourier domain. Note that the field map smoothing step in our implementation of the original voxel-independent ML algorithm was performed with the same Hamming window used to generate the synthetic field maps [1]. Several field maps, simulating increasing severity of field inhomogeneity, were obtained in each case by scaling each synthetic field map. The fat-water images were then combined with each field map according to the signal model in Eq. 3.1 to obtain datasets with increasing levels of field inhomogeneity. The fat-water chemical shift was 215 Hz and the the TEs produced fat-water phases \{- \pi/6, \pi/2, 7\pi/6\}. Finally, complex Gaussian noise was added to each of the datasets (SNR = 20). The noisy datasets were then processed using voxel-independent ML, VARPRO-ICM and LP, and the resulting decompositions compared to the true images. Figure 5.2 shows the relative norm of the error (averaged for the brain, abdominal and cardiac simulated datasets) in the resulting water image produced by voxel-independent ML, VARPRO-ICM and LP. Note how VARPRO-ICM performs almost uniformly well for all levels of field inhomogeneity, whereas the errors of LP and voxel-independent ML increase sharply as the maximum field inhomogeneity becomes larger than |fF|/2. This is due to the misclassifications that occur in the voxel-by-voxel decomposition, which are only partially removed in the field map smoothing step. Also, for low field inhomogeneities, LP performs nearly as well as VARPRO-ICM and voxel-independent ML.

To test the proposed methods on in vivo data, several brain images were obtained using optimal echo spacings [12], with TE values \{3.38, 4.17, 4.97\} ms, which give rise to fat-water phases \{\pi/2, 7\pi/6, -\pi/6\}. Data were acquired on a 3 T Siemens Allegra head scanner in accordance with the local institutional review board. Figure 5.3 shows the fat-water decomposition and field map obtained with voxel-independent ML [1] and the proposed VARPRO-ICM and LP methods, respectively. The fat-water decompositions using all three methods are very similar. The differences observed in the estimated field map are due to the different strategies for imposing field map smoothness: (a) voxel-independent ML filters the raw field map with a smoothing kernel [1], and thus the estimates from voxels where the signal is mostly noise are preserved; (b) VARPRO-
ICM imposes a smoothing MRF prior on the field map (Eq. 4.5), automatically assigning more weight to field inhomogeneity estimates from voxels with higher signal intensity; (c) LP applies a weighted LS smoothing (Eq. 3.21) which has a similar effect to the MRF-based approach, since the weights applied on the field map estimates are proportional to the amplitudes of the corresponding components.

To test the multi-coil version of the proposed methods, a multi-coil acquisition of the abdomen was performed using 6 TEs, \{1.5, 2.0, 3.6, 5.1, 6.6, 8.2\} ms, corresponding to fat-water phases \{-7\pi/5, -7\pi/6, -\pi/2, \pi/6, 5\pi/6, 3\pi/2\}. Data were collected on a GE 1.5 Tesla whole body scanner (GE Healthcare Technologies, Waukesha, WI) using a four-channel torso phased-array receiver coil. The pulse sequence used was a 3D fast spoiled gradient echo sequence. Each 3D data set (for a corresponding TE) was acquired in a single but separate breath hold. All data were collected in accordance with the local institutional review board.

The multi-coil results are shown in Fig. 5.4. Figures 5.4a-c show the “gold standard” decomposition obtained from VARPRO-ICM using all six shifts. Figures 5.4d-f show the results from
Figure 5.3: Fat-water decomposition from a brain acquisition. The first column contains the estimated water component using the different algorithms. The second column contains the estimated fat component. The third column contains the regularized field map. (a)-(c) voxel-independent ML estimates. The smooth field map is obtained by filtering the raw field map (resulting from voxel-by-voxel estimation) with a smoothing kernel [1]. (d)-(f) VARPRO-ICM estimates. The smooth field map is obtained directly by applying an MRF prior. (g)-(i) LP estimates. The smooth field map is obtained by weighted LS regularization of the raw field map.
VARPRO-ICM using only three different TEs (with fat-water phases \([-7\pi/6, -\pi/2, \pi/6]\)). Figures 5.4g-i show the resulting decomposition from the same three TEs, using the LP method. Note the high quality of the decompositions obtained with both methods using just three TEs.

Figure 5.4: Fat-water decomposition from a multi-coil abdominal acquisition. The first column contains the estimated water component using the different algorithms. The second column contains the estimated fat component. Both components are displayed using sum of squares combination of the multi-coil signal. The third column contains the regularized field map. (a)-(c) VARPRO estimates using all 6 TE shifts. (d)-(f) VARPRO-ICM decompositions using fat-water shifts \([-7\pi/6, -\pi/2, \pi/6]\). (g)-(i) LP decompositions using shifts \([-7\pi/6, -\pi/2, \pi/6]\).

Figure 5.5 shows a comparison of voxel-independent ML and the proposed VARPRO method in the presence of higher field inhomogeneities. The images were acquired with fat-water phases \([7\pi/6, \pi/2, -\pi/6]\) on a 3 T Siemens Allegra head scanner in accordance with the local institutional review board. The field inhomogeneity reached approximately 360 Hz. The VARPRO-ICM method included spatial regularization using ICM. Note how voxel-independent ML swaps the different components in part of the image, whereas the proposed method is able to correctly separate the water and fat signals. This increased robustness is due to the global optimality of the VARPRO-
ICM approach, regardless of the non-convexity of $R(f_u)$, and the improved method for imposing spatial smoothness on the field map (which is performed jointly with the fat-water estimation, instead of in a separate step).

Figure 5.5: Comparison of voxel-independent ML and VARPRO-ICM results in the presence of high field inhomogeneity. (a)-(c) voxel-independent ML estimates for water, fat and field map, respectively; (d)-(f) VARPRO estimates for water, fat and field map, respectively.

5.4 Large Field Inhomogeneities

Data for quantitative evaluation were acquired on a Siemens MAGNETOM Espree (Siemens AG Medical Solutions, Erlangen, Germany) 1.5 T scanner. This is a short, wide bore MRI scanner (70 cm inner diameter, 125 cm length), which results in greater patient comfort and the ability to image obese subjects. However, because of its short, wide bore, it contains larger magnetic field inhomogeneities compared to conventional scanners, particularly near the edges of the field of view.

Data were acquired using a phased-array coil, in accordance with the local institutional review board. Twenty-five cardiac datasets were acquired (from 21 subjects), of which 15 were short axis slice orientation, and 10 were long axis orientation. Imaging was performed with an ECG-triggered
GRE sequence, using an echo-train with monopolar readout. Typical parameters included: Field of view (FOV) = 36 cm × 27 cm; bandwidth = 977 Hz/pixel; TR = 11.2 ms; flip angle = 20° to 25°; matrix size = 256 × 126, TE spacing between 1.9 ms and 3.07 ms [20]. Usually 4 echoes were collected (often selected to provide nearly optimal noise properties [109]), but only 3 are used in this work, to conform more closely to the common conditions used in fat-water separation [1, 3]. One additional dataset, not included in the quantitative results, was acquired on a Siemens Avanto 1.5 T scanner with TEs \{3.6, 5.8, 7.9\} ms.

The proposed graph cut algorithm was run on each of the acquired 2D slices, for 50 iterations in all cases, at which point the changes in the estimated field map were negligible. Multi-coil data were processed jointly, as described in Chapter 3. In order to evaluate the reliability of the proposed method, fat-water separation was performed on 25 cardiac datasets acquired with various slice orientations. Three echoes ($N = 3$) were used for each dataset. For comparison, the same datasets were also processed using VARPRO-ICM, where the voxels are updated one at a time. Both methods included $T_2^*$ decay in the signal model. By visual inspection of the resulting decompositions, the number of images containing errors (e.g., localized fat-water swaps) were counted. These swaps are defined as estimation errors where the main signal component in a voxel is assigned to the wrong chemical species (e.g., identifying as mostly fat a voxel that contains mostly water). Additionally, some of the datasets were processed using our own implementation of the voxel-independent ML algorithm (without region growing or any other advanced features that may have been added to the current commercial implementation) [1]. Note that the data used in the comparison have a different set of TEs from those suggested in Refs. [1, 109]. The TEs employed in this work are not SNR optimal (which would require a TE spacing of nearly 1.6 ms at 1.5 T) due to the monopolar readout with gradient flyback.

For short, wide bore scanners, the field variation at the edge of the FOV was found to be on the order of ±1000 Hz. The central FOV excluding the border was more well behaved. Nevertheless, the frequency variation across the heart was in the range of 100-150 Hz. This variation may be due to tissue-air interfaces [114], or the presence of deoxygenated blood in large epicardial veins [115].
The central FOV was identified on a per-slice basis as the region having field inhomogeneities in the range \( \pm 300 \) Hz. Fat and water swaps using the ICM method were observed in 18 of the 25 cases with 5 occurring in the central FOV. Fat and water swaps using the graph cut method were observed in 2 of the 25 cases, with a single fat/water swap in the central FOV, in a region of low signal.

Figure 5.6 shows representative results from a sagittal view of the heart, comparing the proposed method, ICM and voxel-independent ML. Images were acquired with TEs \( \{4.2, 6.7, 9.2\} \) ms. Since the original IDEAL method did not include \( T_2^* \) decay, the modified algorithm \( T_2^*-\text{IDEAL} \) was used [7]. It must be noted that the fat-water images obtained with voxel-independent \( T_2^*-\text{IDEAL} \) were similar to a voxel-independent VARPRO where ambiguities are resolved by forcing the field map to be in the range \( (-f_F/2, f_F/2) \). For this reason, these results are denoted simply “voxel-independent” in the figures. The proposed method provided significantly improved results, particularly in regions with rapid field variations, where previous methods produced fat-water swaps. Even though the heart was the region of interest in this application, artifacts in other areas of the FOV are undesirable since they may erroneously lead to incidental findings.

Figure 5.7 shows another case, acquired on a Siemens Avanto 1.5 T scanner with the following TEs: \( \{3.6, 5.8, 7.9\} \) ms. Note that both ICM and the voxel-independent method produced fat-water swaps in the central FOV (see arrows), whereas the proposed method produced correct fat-water decomposition throughout the FOV.

Figure 5.8 shows multi-peak fat modeling results from a 13-point acquisition with echo spacing 1.9 ms (with the first TE at 1.4 ms), using \( M = 3 \) fat peaks with known frequency shifts \( \{-210, -159, 47\} \) Hz at 1.5 T. An independent decomposition of the 3 fat peaks and the water peak was performed using all 13 TEs. Fat-water decompositions with multi-peak and single peak fat modeling, respectively, were obtained from the first 5 TEs. All cases were processed accounting for \( T_2^* \) decay. For the multi-peak decomposition, the relative amplitudes \( \alpha_m \) were estimated from the data itself (as proposed in [77] under “self-calibration for 6-point \( T_2^*-\text{IDEAL} \) acquisitions”), and were found to be \( \alpha_1 \approx 0.77, \alpha_2 \approx 0.13e^{-i0.08\pi} \) and \( \alpha_3 \approx 0.10e^{-i0.04\pi} \). Additionally, the \( \alpha_{m,q} \)
Figure 5.6: Comparison of the proposed method with two previously proposed methods (ICM and voxel-independent ML). This dataset contains large field inhomogeneities near the edges of the FOV. (Top) Estimated field maps (in Hz). (Center) Water images. (Bottom) Fat images. The proposed method produced accurate field map estimation throughout the FOV, providing uniformly good fat-water separation. Previous methods were not able to track the field variations in the regions of high inhomogeneity, resulting in incorrect fat-water separation (indicated by arrows). Note that the field inhomogeneity reached +/- 1000 Hz, but the color scale was kept in the range +/- 600 Hz to show better contrast throughout most of the image.
Figure 5.7: Comparison of the proposed method with two previously proposed methods (ICM and voxel-independent ML). In this dataset, field inhomogeneities near the edges of the FOV are relatively moderate, because it was not acquired on a wide bore scanner. (Top) Field maps. (Center) Water images. (Bottom) Fat images. ICM and pixel-independent methods resulted in water fat swaps (indicated by arrows) in the liver under the dome of the diaphragm, as well as in the subcutaneous fat, but the proposed method produced good fat-water separation.
Figure 5.8: Multi-peak fat modeling. Data were acquired at 13 TEs, with uniform spacing 1.9 ms. The presence of several fat peaks in the signal is shown by performing an independent fit (without fixing $\alpha_{m,q}$) using all 13 TEs. The data corresponding to the first 5 TEs are then processed using a multi-peak model and the standard single peak model (both including $T_2^*$ decay). Multi-peak modeling results in better fat-water separation, particularly in the regions with high fat signal such as the subcutaneous layer (see arrows in single peak water image). Additionally, the multi-peak model helps resolve ambiguities in isolated signal regions (see arrow in single peak fat image).
obtained with the independent peak model were averaged over the fat region, and the results were in good agreement with the multi-peak estimates (the averages of the independent peak model produced \( \alpha_1 \approx 0.77, \alpha_2 \approx 0.13e^{0.06\pi} \) and \( \alpha_3 \approx 0.10e^{-0.12\pi} \)). Multi-peak modeling has two main advantages over single peak modeling (see the arrows in Fig. 5.8): (a) improved fat-water separation, which is clearly noticeable in fat-only regions (e.g., the subcutaneous fat layer), and (b) reduced ambiguity in the estimation [77].

Fat-water separation is useful for tissue characterization in cardiac MRI, where it has been shown to allow robust detection of fibrofatty infiltration of the myocardium [18, 20], as well as characterization of tumors and masses, including lipomas. Figure 5.9 shows results from a patient with intramyocardial fat [20], reconstructed here using the proposed method. Images were acquired with TEs \( \{1.5, 3.6, 5.7\} \) ms. The separation was performed including multi-peak modeling of the fat signal, as well as \( T_2^* \) decay. The intramyocardial fat is clearly visible in the fat-only image (Fig. 5.9b), which has positive contrast (i.e., fat against dark background), but is difficult to detect in the conventional fat-saturated turbo spin echo (TSE) image (Fig. 5.9d), which has negative contrast [20]. Figure 5.10 shows another example application. Images were acquired from a 3-chamber view using TEs \( \{2.5, 4.7, 7.0, 9.2\} \) ms. The fat-water separated images (Figs. 5.10a and 5.10b, respectively) clearly show a large lipoma.

In the proposed algorithm, the bulk of the computation time is spent solving Eq. 4.8 (via the equivalent graph cut problem) at each iteration. On an Intel Xeon-based desktop PC with 48 GB of RAM and a 3.16 GHz CPU, solving this problem at each iteration requires 0.3 s for images of size \( 192 \times 144 \), and 0.9 s for images of size \( 192 \times 256 \) (image sizes from the results shown in this section). A moderate number of iterations suffices to produce good results: the field map estimate converges rapidly and the improvements are negligible after 50 iterations for all the datasets processed in this work. The total processing time for the proposed algorithm is typically around 60 seconds (90 seconds if the model includes \( T_2^* \)).
Figure 5.9: Results showing the application of the proposed method for the detection of fatty infiltration in the myocardium. (a)-(b) Fat-water images obtained with the proposed method. The fatty infiltration is clearly visible in the fat image. (c) Standard TSE acquisition, without fat saturation. (d) TSE including conventional fat saturation. The fatty infiltration appears as a decrease in intensity in the fat saturated image, but is difficult to discern due to the negative contrast.

Figure 5.10: Example of lipoma in the anteroseptal region of the myocardium, seen clearly in cardiac 3-chamber view. (a) Water image. (b) Fat image.
5.5 Spatial Resolution Analysis

One desirable feature of the proposed PML formulation is the ability to characterize the spatial resolution properties of the estimates. This is important in order to interpret the results, as well as to provide a criterion for choosing the regularization parameter. In the case of field map estimation, it is desirable to know the amount of smoothing introduced by the spatial regularization. Even though a complete characterization is challenging due to the nonlinearity of the signal model, one can analyze the local properties of the estimation by calculating the local impulse response (LIR), as derived in Ref. [94]. The LIR\(^q(f_B)\) is defined as the change in the mean estimated field map caused by a perturbation in the true field map \(f_a\) at voxel \(q\). The expression for the LIR\(^q(f_B)\) is given in Eq. [16] of Ref. [94]. The true fat-water images are assumed fixed here for simplicity. Substituting the cost function in Eq. 3.5 into the formula derived in Ref. [94], the following expression follows:

\[
\text{LIR}^q(f_a) = \left[ \nabla^{20} \left( \sum_{q=1}^{Q} R(\hat{f}_{u,q}, s_q) \right) + \mu D^T D \right]^{-1} \nabla^{11} \left( \sum_{q=1}^{Q} R(\hat{f}_{u,q}, s_q) \right) \frac{\partial}{\partial f_{u,q}} s(f_a), \tag{5.1}
\]

where \(s(f_a)\) is the noiseless signal obtained for all voxels and TEs, expressed as a vector, the \((q,j)\) element of \(\nabla^{20}\) is \(\partial^2/\partial f_{u,q}\partial f_{u,j}\) and the \((q,j)\) element of \(\nabla^{11}\) is \(\partial^2/\partial f_{u,q}\partial s_j\), \(D\) is the finite differences matrix that equivalently expresses the quadratic spatial regularization:

\[
\|Df_u\|^2 = \sum_{q=1}^{Q} \sum_{j \in b_q} w_{q,j}(f_{u,q} - f_{u,j})^2, \tag{5.2}
\]

and \(\hat{f}_a\) is the field map estimate obtained from noiseless data. It must be noted that this characterization disregards the field map quantization. However, simulation results indicate that the LIR accurately describes the local properties of the proposed solution.

Exact computation of \(\hat{f}_a\) would in principle require solving Eq. 3.5. Note that, for moderate values of \(\mu\), this solution can be approximated by its linearized form, using a quadratic approxima-
tion of $R(f_b; s_q)$ at each voxel (since the regularization is also quadratic, this leads to a closed-form solution). The quadratic approximation is shown in Fig. 5.11a. Figure 5.11b shows an example of the LIR for the dataset shown in Fig. 5.8.

To study the field map smoothing introduced by the spatial regularization, a dataset was simulated where the field map contained an abrupt transition. Subsequently, field map estimation was performed using several values of the regularization parameter $\mu$. Results demonstrating different levels of smoothing as a function of $\mu$ are shown in Figs. 5.11c-d. As can be seen from the figures, spatial regularization with $\mu = 0.02$ (the value used in this work) results in only moderate smoothing, which is important in regions of rapid field variation. Errors in the field map result in inaccurate fat-water separation, which is shown quantitatively by simulation in Fig. 5.11d. Note that the abrupt field map transition used in the simulation is more severe than the field maps observed in practice across the heart [115]. It is expected that even with a worst case gradient of 15 Hz/pixel based on experimental measurements within the heart, a frequency error < 3 Hz would result using regularization with parameter $\mu = 0.02$, corresponding to an erroneous fat signal with amplitude equal to 2% of the water signal (Fig. 5.11e). In this case, with a water SNR in the range of 20, the artifactual fat signal would be below the noise level.

### 5.6 Discussion of Graph Cut Method

Field map estimation is a critical step for accurate fat-water separation. However, the problem is severely ill-posed when voxels are considered individually, which makes spatial regularization necessary. This has led to a variety of methods that impose field map smoothness, e.g., using multiresolution or region-growing algorithms [5, 66, 69, 70]. The proposed method has two main desirable properties: (i) the use of a PML formulation, which allows a local characterization of the spatial resolution (smoothing) properties of the resulting field map; and (ii) the introduction of a novel optimization algorithm based on graph cuts, which allows the update of field map estimates at all the voxels simultaneously. This is quite different from algorithms where voxels are visited
Figure 5.11: Analysis of the spatial resolution properties of the proposed regularized field map estimate, and the associated errors in the fat-water decomposition. (a) Residue $R(f_n, q_s)$ at an individual voxel and local approximation using a quadratic function. (b) LIR for field map perturbations at different locations (shown in logarithmic scale over the true field map). (c) Simulation demonstrating the field map smoothing that results from different values of $\mu$. The true field map contains a sharp jump in the center of the image. In this work, $\mu = 0.02$ is used. (d) Absolute field map errors corresponding to varying values of $\mu$ in the previous example. (e) Errors in the estimation of the fat-water magnitudes at a single voxel, as a function of the error in the field map (in the absence of noise). The simulated TEs are {6.76, 8.36, 9.96} ms. The true fat-water amplitudes are $\rho_w = 1$, $\rho_r = 0$. 

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one at a time, even if information from previously visited voxels is used to constrain/initialize the estimate at the current voxel.

For the datasets considered in this work, it is important that the regularization term is spatially varying (through the $w_{q,j}$’s in Eq. 3.3), because of the widely varying signal intensities observed in different regions of the image. If the $w_{q,j}$’s were constant, then it would not be possible to achieve regularization in the high signal regions without over-smoothing the field map in the low signal regions. The effect of spatially varying regularization can be well characterized using the LIR.

The performance of the proposed method depends on the accuracy of the signal model. For instance, the presence of $T_2^*$ decay or multiple fat peaks can, if not accounted for, result in not only small perturbations on the fat-water estimates, but also fat-water swaps. Additionally, multi-peak fat modeling reduces the ambiguity in fat-water separation, because the water and fat signals become different in this improved model (instead of being the same signal model with different frequency shift) [77]. These effects are observed clearly in Fig. 5.8.

The proposed method has several limitations. Firstly, it provides a locally (as opposed to globally) optimal solution to Eq. 4.1 (it is optimal with respect to an exponentially large set). As previously discussed, graph cut methods can also provide a global solution to the (discretized) regularized problem. However, this solution requires a very large graph and is currently not practical for clinical application unless significant accelerations can be achieved.

Secondly, the discretization required for applying the proposed graph cut algorithm imposes a limit on the accuracy of the estimated field map. Even though the discretization is fine enough that it is usually not significant for qualitative applications, it can be overcome by running a descent algorithm (such as the one proposed in Ref. [72]), initialized with the outcome of the proposed method.

Thirdly, the proposed method uses a PML formulation (Eq. 3.3) to regularize the field map estimate by penalizing non-smooth solutions. This regularization is useful and has desirable properties in terms of characterizing its resolution properties, as discussed above. However, it is only a crude model if viewed as imposing a prior distribution on the field map. For instance, in regions
of extremely rapid field variation (such as when imaging near metal implants), this smoothness assumption would not be adequate, and the corresponding image distortions would make the current signal model inaccurate.

In MRI, there are a variety of applications requiring the regularized estimation of nonlinear parameters (e.g., relaxation rates, $B_1$ field) [116, 117]. The method presented in this report, based on VARPRO followed by a graph cut optimization algorithm, may also prove useful in these scenarios. The most important restriction on the proposed method is that the data term of the cost function is defined voxel-by-voxel (or, at least, that the interactions between different voxels are very limited [85]). In this case, the proposed optimization method provides a powerful tool for overcoming the nonlinearity of the model and the non-convexity of the cost function [83].

5.7 Global Optimization Results

The graph cut-based global optimization methods described in Section 4.3 have been implemented and tested on several datasets. These methods map the discretized optimization problem (Eq. 4.1) directly to a single minimum cut problem on a large graph. This graph contains a node for each combination of voxel and field map value (i.e., $QL + 2$ total nodes) [90]. The number of edges depends heavily on the choice of penalty function.

Results from global optimization using an $\ell_1$-based regularization are shown in Fig. 5.12. The dataset was a short-axis view of the heart, imaged in a 1.5 T wide bore scanner (Siemens Magnetom Espree), in the presence of substantial field inhomogeneities, particularly near the edges of the FOV. This implementation requires approximately 20 GB of memory and 20 minutes of processing on an Intel Xeon-based desktop computer. The method results in good field map, water and fat estimates throughout the field of view.

Global optimization results using the alternative penalty functions discussed in Section 4.3 are shown in Fig. 5.13. These methods discourage field map roughness using a quadratic penalty for small field map differences between neighboring voxels (up to a threshold), and using a lin-
Global optimization results on a cardiac short-axis acquisition. (a) Water image; (b) Fat image; (c) Field map (Hz). This implementation requires approximately 20 GB of memory and 20 minutes of processing, so it is currently not practical, but it highlights the ability of graph cut methods to solve the problem of regularized estimation of nonlinear parameters.

ear ("quadratic-linear" method) or high penalty ("quadratic-∞" method) for field map differences above the threshold. A simple oil-water phantom acquisition was used to demonstrate these methods. The threshold was purposefully set to a low value (5 Hz) in order to highlight the differences between the two methods. Additionally, the spatial regularization parameters $w_{q,j}$ were set spatially homogeneous, to prevent the spatially varying regularization proposed in Chapter 3 from obscuring the differences in the estimates using these two methods. The matrix size was kept very reduced ($72 \times 72$ voxels) in order to allow processing in moderate time. Each of these methods required 20 minutes of processing.

Global optimization based on Ishikawa’s graph construction [90] requires manipulation of a very large graph and needs significantly more processing time and memory compared to other methods (e.g., methods based on binary graph iterations). Therefore, global optimization using this implementation is currently not practical, but it serves to highlight the remarkable abilities of graph cut methods to solve the problem of regularized estimation of nonlinear parameters.
Figure 5.13: Global optimization results on an oil-water phantom, using mixed penalty functions.
(Top) Field map estimates, highlighting the different behavior of the two penalties to sharp field map variations. Profiles are shown as indicated by the dashed lines on the field map images. (Bottom) Corresponding water-fat images, where the differences are concentrated on the regions of susceptibility differences, where $B_0$ may vary sharply. These results were obtained using a small threshold of 5 Hz for the penalty functions (transition from quadratic to linear or from quadratic to high penalty), to emphasize the different behavior.
5.8 Separation of Multiple Spectral Components

The proposed methods are not specific to the separation of water and fat, but rather can be generally used to separate multiple spectral components as long as these resonate at different frequencies [1, 118]. The introduction of additional components only requires additional linear parameters (amplitudes) into the signal model. Therefore, the methods developed in Chapters 3 and 4 apply essentially unchanged (since all amplitude parameters are removed from the formulation using VARPRO). An example of separation of silicone-fat-water (from a subject with breast implants) is shown in Fig. 5.14. Data were acquired using an SPGR sequence on a Siemens Avanto 1.5 T scanner at TEs $1.36 + 1.89n$, for $n = 0, \ldots, 7$.

![Figure 5.14: Silicone-fat-water separation from chemical shift-encoded data. (Left) Water image. (Center) Fat image. (Right) Silicone image. The resonance offset of fat and silicone was $-220$ Hz and $-310$ Hz, respectively.](image)

Chapter 6

Comparison of Fitting Models

6.1 Introduction

The ability to quantitatively measure fat content in tissues has multiple important applications in MRI, including studies of bone marrow [22], breast [23], muscle [24], brain [25], liver [9, 26], and heart [28, 29]. In recent years, chemical shift-encoded fat-water separation methods have become increasingly popular for quantitative fat measurement. This popularity is largely due to the ability of chemical-shift encoded methods to overcome the limitations of alternative techniques: lack of spatial information in single-voxel spectroscopy, sensitivity to $B_0$ and $B_1$ inhomogeneities in conventional fat saturation, or loss of SNR and inherent $T_1$-weighting in short-tau inversion recovery (STIR) [1, 6, 18].

There are four key issues with chemical shift-encoded fat-water separation. First, the presence of large $B_0$ magnetic field inhomogeneities can result in large errors in fat-water separation if the $B_0$ effects are not adequately addressed [3, 5]. Second, the commonly used spoiled gradient echo (SPGR) sequences may result in considerable residual $T_1$-weighting, typically leading to bias (overestimation) in the estimated fat component, which has a shorter $T_1$ relaxation time than the water component [11]. Third, the presence of noise can introduce bias in the estimation of the minority component of the signal (whether it is water or fat), particularly in cases where the minority component is very small compared to the majority component, i.e., fat fractions (FFs) close to 0% or 100% [11]. Fourth, inaccurate modeling of the acquired chemical shift-encoded signal also results in considerable bias in fat quantification [8, 9, 77].

Complications due to $B_0$ field inhomogeneities, $T_1$ bias and noise have been thoroughly ad-
dressed in the literature. Field inhomogeneities can be addressed by region-growing or regularized estimation methods (as shown in the previous chapters) [5, 67, 70, 72, 119]. $T_1$ bias in SPGR acquisitions can be avoided by using a small flip angle, or corrected by using a dual flip angle acquisition [11]. Noise bias also can be corrected effectively by using magnitude discrimination or phase-constrained reconstruction [11], or by using a look-up table bias correction over a region-of-interest [120]. However, signal modeling for quantitative fat-water separation remains largely an unresolved issue. Specifically, there are three key decisions to make when modeling the acquired signal:

- **Magnitude vs. complex fitting**
- **Single peak vs. multi-peak fat models**
- **Modeling of $T_2^*$ decay**

In this chapter, a comparative analysis of multiple models is presented, based on these three choices. The analysis focuses on two key properties of the estimates for each model: bias and standard deviation. These properties capture the behavior of different models regarding model mismatch (bias) and noise sensitivity (standard deviation). The analysis is based on theoretical properties of the different models, simulations and phantom data, and the conclusions derived from this analysis are verified qualitatively with an in vivo dataset. Additionally, the case of inhomogeneous fat-water mixtures at individual voxels is also considered using a multi-resolution approach on a separate ex vivo dataset.

The results presented in this chapter can be viewed as an extension of previous studies that focused on a subset of the models considered here. For instance, in Ref. [7], the authors proposed to include a single $T_2^*$ decay in the signal model and showed its advantage over a no-decay model. In Ref. [8] the authors performed a comparison of different magnitude-based fitting models, with an emphasis on modeling the $T_2^*$ decay. In Refs. [9, 77], the authors demonstrated the advantages of multi-peak fat modeling relative to single-peak fat modeling. In [78, 121], the authors compared the use of a single $T_2^*$ or different $T_2^*$s for water and fat, in the context of complex fitting. Relative
to these works, this study includes a more comprehensive set of models as well as a thorough analysis ranging from the theoretical characterization of different models to phantom and in vivo results.

6.2 Methods

6.2.1 Signal models

A total of 12 signal models were evaluated, by considering the main alternatives proposed in the literature, in terms of the following choices:

- **Magnitude and complex fitting (2 alternatives).** All the models were implemented in two versions: fitting the magnitude of the acquired data, and fitting the complex-valued data.

- **Single peak and multi-peak fat models (2 alternatives).** In addition to the model based on a single-peak fat spectrum, a six-peak fat model was calibrated and implemented. Even though a larger number of fat peaks can be found by spectroscopy, six fat peaks is the most that has been used in the fat-water separation literature. If more peaks are used, some of the peaks will have very similar frequencies, resulting in considerably more unstable calibration.

- **Modeling of $R_2^*$ decay (3 alternatives).** No-decay, one-decay (with a single $R_2^*$, common for water and fat), and two-decay (with independent $R_{2,W}^*$ and $R_{2,F}^*$ for water and fat) models were implemented. Intermediate models, e.g., where water and fat have different decay rates but the difference $R_{2,F}^* - R_{2,W}^*$ is assumed known, were not considered in this work, due in part to the difficulty of estimating this difference and also to the dependence of the apparent difference $R_{2,F}^* - R_{2,W}^*$ on whether a single-peak or multi-peak fat model is used [8]. Similarly, even more sophisticated fat models, where different peaks within the fat spectrum have different decay rates, were also not considered due to their significant increase in complexity and noise sensitivity.
The 12 models used in this study are summarized in Table 6.1. All model fitting was done voxel-by-voxel in Matlab (The MathWorks, Natick, MA) using a standard gradient-based least-squares fitting procedure (lsqnonlin). Magnitude fitting was also least-squares (even though the noisy magnitude data does not follow a Gaussian distribution), because this is a good approximation (except at very low SNRs), and this is the approach taken in practice in most previous works [8].

6.2.2 Theoretical analysis

The well-known Cramér-Rao lower bound (CRLB) provides a bound on the variance of any unbiased estimator. In the context of fat-water separation, it has been used to effectively characterize different models and acquisition strategies [7, 109]. The CRLB for each of the 12 models under consideration was computed for a range of water/fat ratios, assuming a fixed set of 8 TEs: $1.43 + (n - 1)2.23$ ms, for $n = 1, \ldots, 8$ (the same TEs used in the simulations and phantom experiments). Computation of the CRLB for the complex fitting models was done as described in Ref. [122], and for the magnitude fitting models as described in Ref. [123].

6.2.3 Simulations

Even though the CRLB provides an elegant characterization (bound) of the variance of any unbiased estimator, it does not capture the effects of bias (e.g., due to model mismatch) or the practical performance of a given estimator. To address these issues, chemical shift-encoded data were simulated, using the following model, which employs representative values measured in the phantom experiments (as will be described in the Multi-peak calibration subsection):

- The fat has 6 peaks, with frequencies $[-244.3, -221.7, -175.4, -119.3, -32.1, 34.0]$ Hz, and relative amplitudes $0.01 \cdot [9.45e^{-i\pi0.181}, 64.66, 9.67e^{i\pi0.046}, 2.26e^{-i\pi0.567}, 2.22e^{-i\pi0.244}, 8.83e^{-i\pi0.089}]$. These were the same frequencies and relative amplitudes obtained by pre-calibration on the phantom.
Table 6.1: Models considered in this study. The multi-peak fat signal model $s_{t}(t_n)$ is defined as $s_{t}(t_n) = \sum_{m=1}^{M} \alpha_{m} e^{i 2 \pi f_{m} t_n}$.

<table>
<thead>
<tr>
<th>Magnitude fitting</th>
<th>Complex fitting</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-peak</strong></td>
<td><strong>Multi-peak</strong></td>
</tr>
<tr>
<td>$R_2^*$</td>
<td>$\rho_W + \rho_p e^{i 2 \pi f_p t_n}$</td>
</tr>
<tr>
<td>$2 R_2^*$</td>
<td>$\rho_W e^{i 2 \pi f_p t_n} + \rho_p e^{i 2 \pi f_p t_n} e^{-R_2^*}$</td>
</tr>
<tr>
<td>$1 R_2^*$</td>
<td>$e^{-R_2^*} (\rho_W + \rho_p e^{i 2 \pi f_p t_n})$</td>
</tr>
</tbody>
</table>
• Water and fat have different $R^*_2$ values: $R^*_2,W = 42 \text{ s}^{-1}$ and $R^*_2,F = 54 \text{ s}^{-1}$.

• Two sets of 21 true water/fat ratios were chosen: covering the range of water/fat ratios $[0.01, 100]$ (equally spaced on a logarithmic scale), and covering the range of fat fractions $[0\%, 100\%]$ (equally spaced in a linear scale).

The simulations used the same TEs as the CRLB analysis. Noise was added to the simulated data, resulting in two different regimes: moderate SNR (SNR=30) and high SNR (SNR=100). A total of 1024 noisy instances were generated for each water/fat ratio and each SNR. These data were then fitted with the 12 models described above, using all combinations of the following choices: magnitude or complex fitting (two options); single-peak or multi-peak fat modeling (two options); no-decay, one-decay or two-decay models (three options).

6.2.4 Experimental studies

Phantom construction

A fat-water phantom was constructed based on the methods described in Refs. [124–126]. The phantom consisted of 11 vials containing fat-water mixtures at FFs ranging from 0% to 100% in increments of 10%. In order to obtain stable emulsions with biologically relevant $T_1$ and $T_2$ parameters, appropriate volumes of vegetable oil were mixed in vials with a solution of saline, agarose (2% mass/volume concentration), CuSO$_4$ (0.5 mM), and sodium dodecyl sulfate (43 mM). The CuSO$_4$, agarose and sodium dodecyl sulfate were dissolved in saline. The resulting saline solution was heated until it boiled for 30 seconds. The vegetable oil and saline solution were placed in a water bath at 50 °C, and then carefully poured in the appropriate proportions into the 11 vials. After filling each vial, it was immediately mixed by gentle inversion to obtain a homogeneous emulsion [125], and placed in ice for the gel to form. The vials up to 60% FF formed homogeneous gels. The vial at 70% FF did not gel, but the mixture remained homogeneous. The vials at 80% and 90% FFs contained severe inhomogeneities in the mixture, and were not used for the quantitative study.
Data acquisition

Data for quantitative evaluation were acquired on a Siemens Avanto (Siemens AG Medical Solutions, Erlangen, Germany) 1.5 T scanner using a phased array coil. Phantom experiments were performed with an SPGR sequence, using an echo-train with monopolar readout: FOV = 36.0 cm × 14.3 cm; bandwidth = 977 Hz/pixel; matrix size = 256 × 102, 8 and 32 TEs with spacing 2.23 ms and initial TE 1.43 ms. Separate acquisitions were used, in order to obtain moderate SNR (SNR≈30) and high SNR (SNR≈90). The moderate SNR acquisition was performed with flip angle 8° and TR 500 ms, and the high SNR acquisition was performed with flip angle 25° and TR 2000 ms. These long TR values were chosen in order to avoid $T_1$ bias [11], which results in a bias under 1% for the $T_1$ values of water and oil measured in the phantom (953 ms and 207 ms, respectively) [11]. This choice of acquisition parameters was made purposefully to isolate the desired component (signal modeling) from the other complicating factors involved in fat quantification.

The phantom data were acquired using a Monte Carlo strategy. In order to perform a quantitative evaluation of bias and standard deviation for the different fitting models, each 8-echo acquisition was performed 128 times. This way, statistics from the estimated parameters can be obtained on a voxel-by-voxel basis (without the need for additional spatial homogeneity assumptions on the sample or the receive coils’ sensitivity). Therefore, the phantom experiments correspond closely to the analytical and simulation-based results.

Additionally, data for measuring $T_1$ and $T_2$ were acquired on the phantom from the same slice. For the $T_1$ measurements, an inversion-recovery sequence was used with an echo-train with monopolar readout. This allowed fat-water separation at each inversion time (which ranged from 100 ms to 1000 ms). For the $T_2$ measurements, a spin-echo sequence was used with TEs ranging from 11 to 200 ms.

In vivo imaging was performed on a healthy normal volunteer under a research protocol approved by the local Institutional Review Board, with written informed consent. Data were obtained using an ECG-triggered SPGR sequence, acquiring 8 echoes with spacing 2.11 ms and initial TE
1.47 ms. Other parameters are: FOV = 40.0 cm × 40.0 cm; bandwidth = 977 Hz/pixel; TR = 18.03 ms; flip angle = 10°; matrix size = 256 × 156 with 13 views per segment. These imaging parameters result in < 4% bias in fat amplitude estimation in the liver, given typical relaxation parameters of fat and liver water at 1.5 T [127]. For low FFs, this bias results in very small systematic errors in FF estimation: for instance, if the true FF is 3.00%, a 4% positive bias in fat signal amplitude relative to water will lead to a 3.12% estimated FF in the absence of noise (i.e., an error typically well below the noise level). An additional in vivo dataset with 16 echoes was obtained to calibrate the relative amplitudes of the fat peaks in vivo.

All images were reconstructed using SNR-scaled reconstruction [120]. This allows convenient evaluation of SNR at each voxel. Multi-coil data was combined prior to fat-water separation using the eigenvector filter method described in Ref. [105].

**Multi-peak calibration**

The 32-echo dataset was used for pre-calibration of the multi-peak fat model (frequencies and relative amplitudes of the fat peaks). A 6-peak model was used in this work. The calibration was performed in two steps:

1. From the vial containing 100% fat, the relative frequencies and relative amplitudes of 6 fat peaks were estimated by nonlinear least-squares fitting. Note that this step provides a good calibration of the relative amplitudes of the fat peaks (due to the absence of a water peak to interfere with the calibration of fat peaks near the water peak). However, their frequency shifts (with respect to the water peak) can only be estimated up to a common shift.

2. From the vial containing 50% fat: by fixing the relative frequencies and relative amplitudes of the fat peaks, the absolute frequency shift of the fat peaks was estimated (with respect to the water peak). This was done by estimating a common shift for the fat relative frequencies using nonlinear least-squares fitting.
The calibration resulted in fat peaks located at frequencies $[-244.3, -221.7, -175.4, -119.3, -32.1, 34.0]$ Hz, with the associated complex-valued relative amplitudes (where the phase of the main fat peak at $-221.7$ Hz is kept at zero): $0.01 \cdot [9.45e^{-i\pi0.181}, 64.66, 9.67e^{i\pi0.046}, 2.26e^{-i\pi0.567}, 2.22e^{-i\pi0.244}, 8.83e^{-i\pi0.089}]$. The nonzero phase of the smaller peaks is likely due to the fact that even this relatively sophisticated 6-peak fat model is only an approximation, and some of the calibrated peaks in fact consist of several peaks at nearby frequencies.

Multi-peak pre-calibration for *in vivo* fitting was performed on a 16-echo *in vivo* dataset [9]. The frequencies of the six fat peaks were kept constant, and their calibrated relative amplitudes were, respectively: $0.01 \cdot [7.98e^{-i\pi0.142}, 70.0, 8.38e^{i\pi0.121}, 1.52e^{-i\pi0.892}, 5.04e^{i\pi0.112}, 7.09e^{-i\pi0.162}]$.

### 6.2.5 Comparison strategy: bias and standard deviation

The estimated bias and standard deviation are used to compare the performance of the different signal models. Intuitively, the bias reflects the model mismatch, whereas the standard deviation reflects the noise sensitivity. Two different quantities were considered: the estimated fat amplitude and the estimated FF. These were evaluated as follows:

- The fat amplitude was analyzed in terms of the standard deviation of the estimates, as well as the root mean squared error (RMSE), which is due to both bias and standard deviation. The resulting standard deviation was compared to the CRLB for each model. For the phantom data, averaged estimates (from 8 measurements) obtained using a 2-decay multi-peak model on the 32-echo acquisition were used as gold standard.

- The FF was analyzed in terms of mean $\pm$ standard deviation for each true FF (both in simulation and in the phantom data). Since the FFs were measured when building the phantom, the known (volume) FF was used as gold standard for the observed (signal) FF [128].

The noise performance of the amplitude estimates for different models was compared using the square root of the effective number of signal averages $\sqrt{\text{NSA}} = \sigma_n/\sigma_F$ where $\sigma_n$ is the standard
deviation of the noise in the acquired images, and $\sigma_F$ is the standard deviation of the fat amplitude estimates [3,109]. $\sqrt{\text{NSA}}$ was used instead of NSA to reflect SNR more directly, and also because of its decreased range, in order to allow better visualization and comparison of the different models. NSA values for multi-peak models were adjusted for the Euclidean norm of the fat signal model (since the relative amplitudes were normalized so that their magnitudes add up to 1, the Euclidean norm was $< 1$, which needs to be accounted for when computing NSA).

### 6.2.6 Assumptions and fixed parameters

The present study includes several assumptions and constraints:

- Multi-peak fat modeling is limited to a 6-peak model, even though more peaks can be found by spectroscopy. Previous works have also used 3-peak fat models, for ease of calibration [77].

- This work uses a fixed set of TEs, similar to those used in previous works [8]. The effect of varying the choice of TEs on the different models is not analyzed, but is not expected to alter the conclusions of this work.

- For the computation of fat amplitude estimation errors using different models, the gold standard was an 8-averaged estimate from the 32-echo acquisition using a complex, multi-peak, 2-decay model (i.e., the most sophisticated among all the models under consideration).

- This work does not focus on the ability of different models to prevent fat-water swaps. Thus, the $B_0$ field map is first estimated using a spatially regularized formulation (see Chapter 3), and subsequently the different models are applied voxel-by-voxel. The complex fitting methods use the regularized field map as initial estimate at each voxel for the descent procedure. The magnitude fitting methods are initialized with the fat-water amplitudes obtained from the corresponding complex fitting methods (similarly to Ref. [129]).
6.3 Results

Figure 6.1 shows the phantom setup used in this work, including an in-phase image as well as separated water and fat images. The average estimated relaxation parameter values in the water component (water-only vial) were $T_{1,W} = 953$ ms and $T_{2,W} = 82$ ms; in the fat component (fat-only vial), these values were $T_{1,F} = 207$ ms and $T_{2,F} = 43$ ms. It must be noted that $T_{1,W}$ seemed to decrease in the mixed vials (e.g., it was measured to be 813 ms in the vial containing 50% fat) [130]. However, this range of values does not affect the results of bias and standard deviation comparison, as the sequence parameters were chosen to avoid $T_1$-weighting.

Figure 6.1: Image of the phantom used in this study, including in-phase image (generated by combining the estimated water and fat images) and fat-water separated images.

Results are shown in the form of sets of 12 plots/images (one for each of the 12 models under study). First, the standard deviation of the fat amplitude estimates is examined, without regard for bias. Figure 6.2 shows $\sqrt{\text{NSA}}$ for SNR=100 and a range of water/fat ratios. Note that the maximum $\sqrt{\text{NSA}}$ attainable by any unbiased estimator is $\sqrt{8}$. Figure 6.2 includes both CRLB-based predictions, as well as results on simulated data. CRLB and simulations provide similar results, but not equal, largely due to model mismatches (which are not accounted for in the CRLB). In other words, only the multi-peak, two-decay signal models are fitting the correct model to the data.

Figure 6.3 shows similar results, but comparing the CRLB predictions with $\sqrt{\text{NSA}}$ based on
Figure 6.2: Fat quantification $\sqrt{\text{NSA}}$ on simulated data, for SNR=100. The stars show the $\sqrt{\text{NSA}}$ values obtained by simulation (including model mismatch), and the solid line shows the $\sqrt{\text{NSA}}$ values predicted by CRLB analysis (without model mismatch). The arrow highlights the fact that the CRLB-based NSA provides a good indication for observed noise performance (particularly for complex fitting methods), even in the presence of model mismatch.

Figure 6.3: Fat quantification $\sqrt{\text{NSA}}$ on phantom data, for SNR=90. The arrow highlights the fact that the CRLB-based NSA provides a good indication for observed noise performance.
the measured standard deviation for fat amplitude estimation in the actual phantom experiments. Note that the phantom results closely follow the simulations (shown in Fig. 6.2), with the largest difference arising in the magnitude fitting using a single peak and no decay, where the phantom estimates often converged to zero at low fat fractions, thus showing very low standard deviation (and very high NSA). Aside from that effect, magnitude fitting models result in lower NSA than their complex fitting counterparts, both in theory (CRLB) and in practice (simulations and phantom data).

Figures 6.4 and 6.5 show the standard deviation $\sigma_F$ and the root mean squared error (RMSE) for fat amplitude estimation using the 12 models, both for the simulation (Fig. 6.4), and for the phantom data (Fig. 6.5). Note the close correspondence of simulation and phantom results for most models. Several of the magnitude fitting models present a larger discrepancy between simulation and phantom data. This discrepancy might be due to residual model mismatches in the phantom case. A more detailed discussion of this effect will be deferred to the description of FF estimation results. The simpler models (e.g., without accounting for $R^*_2$ or multi-peak fat) produce significant bias in the estimation of fat amplitudes, resulting in RMSE much higher than $\sigma_F$. For these models, the bias dominates the errors. Therefore, an analysis of these based only on CRLB (or standard deviations) will not give an accurate assessment of the quality of the estimates.

Figures 6.6 and 6.7 show FF results (mean ± standard deviation) for simulated and phantom data, for a range of true FFs between 0% and 100%. All single-peak models result in considerable bias. For the multi-peak, no-decay model, the bias in fat amplitude estimation seems to be approximately compensated by the bias in water amplitude estimation, resulting in good estimates except at very low or very high FFs. Generally, complex fitting models perform significantly better (smaller bias and standard deviation) than their magnitude fitting counterparts. Furthermore, complex fitting phantom results show better agreement with simulation results. Magnitude fitting phantom results show somewhat different behavior (most notably an increased bias) with respect to the simulations. One possible explanation is that the cause is the sensitivity of magnitude fitting to model mismatches. To test this hypothesis, a second set of simulated data was generated,
Figure 6.4: Fat quantification standard deviation (stars) and RMSE (circles) on simulated data, for high SNR (SNR=100). Arrows with different labels highlight different aspects of these results: ‘2’) In the presence of model mismatch, the bias component of the RMSE can be significantly larger than the standard deviation; ‘4’) Complex fitting generally results in better estimates (lower standard deviation and RMSE), compared to magnitude fitting; ‘5’) For one- and two-decay complex fitting, multi-peak models largely remove the bias present in single-peak models.

Figure 6.5: Fat quantification standard deviation (stars) and RMSE (circles) on phantom data, for high SNR (SNR=90). The arrows highlight the bias incurred by single-peak fat modeling. For single-peak fat modeling, a two-decay model is able to reduce bias over a range of fat fractions by allowing the estimated fat signal to decay faster than the water signal, approximately accounting for the multi-peak nature of the fat signal.
Figure 6.6: Fat quantification fat fraction on simulated data including standard deviations, for high SNR. The dashed line shows the desired exact estimates.

Figure 6.7: Fat quantification fat fraction on phantom data including standard deviations, for high SNR. The dashed line shows the desired exact estimates. The arrows highlight the differences among complex-fitting, single-peak fat models: improved estimates for low FF values are obtained with the two-decay model, compared to no-decay and one-decay models. All three complex-fitting, multi-peak models show good performance in this case.
where the multi-peak (6-peak) fat model is not exactly correct, but instead the peaks at $-175$ Hz and $-119$ Hz were each split into two peaks separated by 10 Hz, with the same amplitude as the original peak. Noise was added to the resulting simulated data, as described in Section 6.2, and the resulting signals were fitted using all 12 models, where the multi-peak model still consisted of the original 6 peaks. The resulting FF plots are shown in Fig. 6.8. The complex-fitting results are similar to the ones shown in Fig. 6.6. However, the magnitude-fitting results have increased bias and standard deviation, due to the model mismatch. These results correspond well with the observed phantom results (Fig. 6.7).

In vivo liver imaging results are shown in Fig. 6.9. The SNR was approximately 20. The FF maps shown in Fig. 6.9 are provided to illustrate the differences in bias and standard deviation for the various signal models used for fat and water fitting. The low SNR of the fat in the liver region leads to a noise bias [11]. Estimates of FF were calculated from the mean values of fat and water signal intensities within a circular ROI rather than from the FF map which is noisier. Furthermore, the complex fat images were filtered to improve the SNR. Using a 7x7 filter yielded an SNR for fat signal of approximately 5 for the complex fitting, multi-peak, one-decay estimates, which results in noise bias error under 5%. All signal models are affected similarly by noise bias, which was not the objective of this work. It must be noted that there is no available ground truth for the in vivo data, but rather it serves to compare the relative estimates of the different models. The single-peak models (with the exception of the complex-fitting, single-peak, two-decay model) result in lower FF estimates relative to the multi-peak models. This is in good agreement with simulation and phantom results. Additionally, the two-decay estimates are noisier compared with the no-decay and one-decay models (with the exception of the magnitude-fitting, multi-peak, one-decay model, which produces unstable results due to model mismatch).

Based on these results, the following key observations can be highlighted (arrows are marked in the figures with the corresponding observation number):

1. Despite the model mismatch, the CRLB provides a useful approximation of the standard deviation obtained with the different models. However, the CRLB does not take model
Figure 6.8: Fat quantification fat fraction on simulated data including calibration error, for high SNR (SNR=100). Magnitude fitting models are more heavily perturbed by calibration error, compared to complex fitting (see arrows).

mismatch-related bias into account.

2. The bias component of the RMSE can be significantly larger than the standard deviation component.

3. The relative importance of the bias component with respect to the standard deviation component is a function of the SNR. This is shown in Fig. 6.10, where complex fitting, multi-peak fat models are compared. For low SNRs, the standard deviation component of the error, which is larger in the two-decay model, dominates the (approximate constant with SNR) bias component of the error, which is larger in the one-decay model.

4. Complex fitting results in better estimates than magnitude fitting. This is true for the standard deviation (as shown by the CRLB, simulation and phantom results), as well as for the bias (as shown by the simulation and phantom results). Additionally, complex fitting is less sensitive to model mismatch.

5. Multi-peak modeling has significantly reduced bias error compared to single-peak modeling.
Figure 6.9: In vivo liver FF estimates using all 12 models. (Top) Full FOV. (Bottom) Zoomed view of liver, with gray scale adapted to highlight the differences between the models. The quantified FF shown for each model was calculated using mean estimates for fat and water magnitudes over the shown ROI (dashed circumference), after smoothing to improve SNR and reduce noise bias.
Figure 6.10: Difference in RMSE for fat fraction estimation with complex-fitting, multi-peak models including two decay rates and a single decay rate. The contour shows the region where both models result in the same RMSE. For low SNR or fat fractions close to 0% or 100%, the one-decay model results in lower errors. For high enough SNR and fat fractions close to 50%, the two-decay model results in lower errors. There is some discrepancy between simulation and phantom results, particularly for FF=20%, where in the phantom data the one-decay model resulted in higher bias than for neighboring values of FF, thus compensating for its reduced variance. Currently, this effect is not understood.
Furthermore, single-peak models perform worse when there is more fat.

6. The no-decay models result in very large bias for fat amplitude estimation. In this particular case the large errors in fat amplitude estimation appear to be compensated by similar errors for water amplitude estimation, resulting in approximately unbiased FF estimates. For single-peak fat modeling, the two-decay model is needed in order to approximately account for the multi-peak nature of the fat signal.

7. For multi-peak fat modeling, the two-decay model typically results in lower bias than the one-decay model, but the increased standard deviation results in higher errors except at high SNR and fat fractions close to 50%. For SNRs < 30, the increased standard deviation in the two-decay model dominates the improvement in bias with respect to the one-decay model. This is in good agreement with Ref. [78, 121], and is demonstrated in Fig. 6.10 with simulation and phantom results for a range of SNR and FF values.

In short, in order to minimize the RMSE for the fat amplitude and fat fraction estimates, it is necessary to account for the multi-peak nature of the fat signal, and preferable to directly model the complex-valued signal. The optimal modeling of $R_2^*$ decay depends on the experimental conditions, specifically, SNR, true (expected) FF and the true difference in the $R_2^*$ of water and fat.

6.4 Inhomogeneous Fat-Water Mixtures

As a complement to the phantom- and simulation-based studies provided in this chapter, where the fat-water mixtures were assumed homogeneous within each voxel, the case with inhomogeneous mixtures was also studied.

In this case, the estimated FF from a high-resolution dataset (where the voxels are assumed to be approximately homogeneous) is compared with the estimated FF from low-resolution datasets, at different spatial resolutions (where there are significant spatial inhomogeneities within each voxel). The comparison method is shown in Fig. 6.11.
Figure 6.11: Process for validation of FF estimation in the presence of inhomogeneous mixtures. The FF estimates obtained from a low-resolution dataset (with in-plane resolution $1.0 \times 1.0$ mm, $2.0 \times 2.0$ mm, or $4.0 \times 4.0$ mm) are validated using FF estimates from a high-resolution dataset (in-plane resolution $0.5 \times 0.5$ mm).
A piece of meat with significant fat content (pork belly) was used for these experiments. Images were acquired on a Siemens Trio 3 T scanner, with the following imaging parameters: FOV=250×70 mm, slice thickness=3 mm, 10 TEs (interleaved acquisition to achieve closer TE spacing). Several datasets with different resolutions were acquired, using matrix sizes=512×144, 256×72, 128×36 and 64×18, with in-plane resolutions 0.5×0.5 mm, 1.0×1.0 mm, 2.0×2.0 mm, and 4.0×4.0 mm, respectively. The lower resolution datasets were obtained by discarding k-space samples from high resolution datasets, but the images at each resolution were acquired separately. Images were acquired using a phased-array coil and combined prior to fat-water separation.

All datasets were processed using a complex-fitting, multi-peak fat, single-decay model. The high resolution dataset (0.5×0.5 mm in-plane resolution) was assumed to contain approximately homogeneous voxels, and thus the fat-water separation was assumed unbiased as shown earlier in this chapter. The high-resolution results were used to validate the results from the lower-resolution datasets. In order to do this, the fat-water separated images obtained from the high-resolution dataset were filtered and downsampled to each of the lower resolutions, and the resulting FF maps were compared to the FF maps obtained directly from each of the low-resolution datasets.

The results for FF estimation from inhomogeneous mixtures are shown in Fig. 6.12 in the form of scatter plots obtained from signal regions. The Pearson correlation coefficients of the FF estimates at 1.0×1.0 mm, 2.0×2.0 mm, and 4.0×4.0 mm compared to the corresponding filtered high-resolution estimates (as described in Fig. 6.11) were 0.9913, 0.9915 and 0.9836, respectively.

These results show that the FF estimates obtained with chemical shift-encoded fat-water imaging are consistent across multiple spatial resolutions. This is to be expected, as long as the signal observed at one voxel can be well approximated as being affected by a single $B_0$ field offset. If this approximation is not valid (i.e., because the $B_0$ field varies rapidly relative to the voxel size), then the signal model used in this work may no longer be a valid approximation. However, for most practical scenarios and imaging resolutions, this assumption will indeed be valid. Note that this is also relevant in the region growing methods that use low-resolution (filtered) versions of the original dataset to initialize the process [5].
Figure 6.12: Results from FF estimation using data at multiple resolutions. (Left) FF map obtained from a high-resolution acquisition (in-plane resolution $< 0.5 \times 0.5$ mm). (Right) Scatter plots of the FF values obtained from datasets with varying resolutions (voxel size increasing by 2, 4 and 8, respectively, in each dimension), compared to the FF obtained from the high-resolution dataset, after filtering and downsampling the high-resolution fat-water images to each resolution.
6.5 Discussion

This chapter has shown a systematic comparison of signal models for fat-water separation from chemical shift-encoded acquisitions. The analysis was based on comparing the bias and standard deviation resulting from the different models. This study can be viewed as an extension of previous works, e.g., where the standard deviation was studied for different acquisition strategies using the CRLB [109], or different sets of models were compared empirically [8, 9].

The present study has several limitations. First, the study assumes that the signal phase is reliable. Under these conditions, complex fitting is uniformly superior to magnitude fitting. In the presence of phase distortions (e.g., due to eddy currents), magnitude fitting [8] or a mixed approach [129] may become more attractive. However, phase distortions were not found to be significant in the experimental data. Similarly, ghosting due to motion may complicate the fitting, but it was not observed in the in vivo data. Second, the study assumes that a suitable calibration is available for multi-peak fat models. Third, in order to limit the complexity of the study, several parameters, such as the choice of TEs, were fixed. The present set of 8 TEs allowed stable application of even the more complicated, two-decay models. Using fewer TEs (e.g., 4) is expected to result in increased noise sensitivity, particularly in the more sophisticated, two-decay models. This choice was made to approximately follow the usual sets of TEs in recent fat quantification literature [8]. Fourth, varying differences in the true \( R^*_2 \)'s of water and fat are not examined. It is expected that a two-decay model will become more attractive if the \( R^*_2 \)'s of water and fat are very different [121]. Fifth, this study does not take computation time into account. Generally, increasing the number of parameters (especially nonlinear parameters) in a model will result in increased computation. For instance, computation times to process 1024 voxels with the three complex multi-peak models (no-decay, one-decay, and two-decay models) were 8.9, 9.6 and 16.4 seconds, respectively, in the non-optimized Matlab implementation.

Multi-peak fat modeling has been shown in this and previous works to result in reduced bias in fat quantification, relative to single-peak fat modeling [9]. However, the present results seem to
indicate that even the 6-peak fat model with separate $R_2^*$ decays for water and fat does not completely describe the fat signal. This residual model mismatch appears in two ways: (a) the multiple fat peaks are not all in phase in the calibration, and (b) magnitude fitting contains significant bias. However, incorporating more peaks into the model results in more difficult calibration, due to the complication of calibrating peaks with very similar resonant frequencies.

The decay constant $R_2^*$ for each species can be approximated as a combination of an intrinsic component due to spin-spin interactions, and an extrinsic component due to field inhomogeneities and susceptibility effects: $R_{2,W}^* = R_{2,W} + R_2'$ and $R_{2,F}^* = R_{2,F} + R_2'$, where $R_{2,W} = 1/T_{2,W}$, $R_{2,F} = 1/T_{2,F}$, $R_2' \sim \gamma \Delta B$, and $\Delta B$ is the amount of $B_0$ field variation within the voxel [116, 131]. Thus, $R_{2,W}^*$ and $R_{2,F}^*$ will generally be different, which is observed in the phantom data using a multi-peak, two-decay model, where the estimated difference was $R_{2,F}^* - R_{2,W}^* \approx 12 \, \text{s}^{-1}$. This is in good agreement with the $T_2$ relaxation parameters measured in the phantom (using a spin-echo sequence with varying TEs), where $T_{2,W} \approx 82 \, \text{ms}$, and $T_{2,F} \approx 43 \, \text{ms}$, resulting in $R_{2,F} - R_{2,W} \approx 11 \, \text{s}^{-1}$. Furthermore, according to this approximation, the difference $R_{2,F}^* - R_{2,W}^* = R_{2,F} - R_{2,W}$ can be approximately known a priori if $T_{2,W}$ and $T_{2,F}$ are assumed known. However, it has been suggested that $R_{2,F}^*$ and $R_{2,W}^*$ may behave differently, e.g., as a function of iron concentration [121]. If a single-peak fat model is used, the apparent $R_{2,F}^*$ will be higher as it has to account for the dephasing due to interference between multiple fat peaks at frequencies near the the main peak. Moreover, assuming that all the fat peaks share a single $R_{2,F}$ (or $R_{2,F}^*$) is also an approximation, but estimating independent decay constants for each fat peak would result in greatly increased computational complexity and noise sensitivity, likely making it impractical. Furthermore, if the relative differences between the decay rates of the different fat peaks can be assumed known a priori, this information can also be incorporated into the model.

According to these results, finding the optimal model for fat-water separation reduces to a choice between complex, multi-peak fitting including either two decays ($R_{2,W}^*, R_{2,F}^*$) or a single decay rate $R_2^*$. This choice presents a clear tradeoff of bias and standard deviation: the two-decay model can represent the acquired signal more accurately (reduced bias), but the estimation of an
additional decay rate increases the noise sensitivity (increased standard deviation). This increased standard deviation is particularly significant in the estimates of the “minority” component of the signal: in the one-decay model, the minority component “gets to share” the $R_2^*$ parameter of the majority component, resulting in very stable (although somewhat biased) estimates of the minority component. In the two-decay model, estimation of the decay parameter for the minority component must be done independently, resulting in noisy decay rate estimates and in turn noisy amplitude estimates. As shown on Fig. 6.10, the choice between one or two decays depends on the SNR and the (expected) true FF. In several important applications, low FFs (e.g., 0-20%) are expected [9, 26, 29, 78, 121], which makes the one-decay model preferable unless very high SNR can be achieved.
Chapter 7

Removal of Olefinic Fat in Diffusion MRI

7.1 Introduction

This chapter examines a specific application of fat-water separation, in the context of diffusion-weighted (DW) MRI, a technique that allows characterization of the microstructure of intracerebral and extracerebral tissues by probing the diffusion properties of water molecules [132–134].

The presence of diffusion-weighting gradients in DW MRI pulse sequences makes this technique very sensitive to macroscopic tissue motion. This sensitivity has made single-shot echoplanar imaging (EPI) the most widely used imaging technique in diffusion-weighted experiments. Although single-shot EPI acquisitions minimize the sensitivity to motion, they suffer from high sensitivity to off-resonance effects, which are caused by field inhomogeneities, susceptibility and chemical shift differences. Specifically, the low EPI bandwidth along the phase-encoding direction can cause the fat signal to be shifted into the tissue region, resulting in chemical shift artifact (CSA) [135]. Since the diffusion properties of the fat are in general different from the diffusion properties of the tissue, the estimated diffusion parameters can be biased when applying diffusion-weighted imaging in tissues surrounded by fat. An example of this sort of bias is the contamination of the diffusion tensor parameters in skeletal muscle due to subcutaneous and bone marrow fat chemical shift artifacts [136, 137].

Fat suppression is thus critical in DW MRI acquisitions. Multiple techniques have been pro-

\[^{1}\text{This chapter describes joint work with Dimitrios Karampinos. The definition of the problem is a result of discussion with D. Karampinos on the presence of residual chemical shift fat artifact in skeletal muscle diffusion-weighted images. The author developed the proposed reconstruction method, performed its theoretical evaluation and analyzed the phantom and in vivo results. D. Karampinos implemented the proposed acquisition scheme and ran the experiments. The discussion of the results was performed jointly.}\]
posed to achieve fat suppression, including chemical shift-selective RF pulses [31, 32], STIR [35, 138], and slice selection gradient reversal [139]. In the case of diffusion-weighted single shot EPI, chemical shift-selective RF pulses are typically used for suppression of aliphatic protons (0.8-3.0 ppm). However, there is also significant fat signal due to the olefinic protons (which constitute approximately 5 – 10% of all fat protons). The chemical shift of the olefinic protons (5.4 ppm) is close to that of water protons (4.7 ppm) [140]. The signal from olefinic protons can result in significant contamination of the estimated diffusion parameters because of the combination of the following effects. First, the signal from the slower-diffusing olefinic protons becomes significant in the presence of diffusion-weighting, which greatly attenuates the water signal. Second, the olefinic fat shift can be of the order of less than 5 voxels, depending on the employed readout length, because of the low frequency separation between olefinic fat and water (5.4 – 4.7 = 0.7 ppm). This olefinic fat shift can contaminate the boundary between water and fat in the typical low resolution diffusion-weighted images, making the identification of the chemical shift artifact difficult in certain cases.

Recently proposed water-fat separation techniques are capable of separating fat at multiple frequencies [77], but they suffer from long acquisition times, and are difficult to apply to diffusion-weighted single shot EPI. Hybrid techniques incorporating a form of fat suppression in an echo-shifted acquisition can be time efficient. Specifically, it has been proposed that the fat signal can be suppressed by a technique combining chemical shift selective fat suppression for nulling signal from aliphatic fat protons and chemical shift-encoded imaging for suppressing the signal from the olefinic fat protons [141].

In this chapter, a method is proposed based on an olefinic fat-water separation approach for removal of olefinic fat signal from DW-EPI acquisitions. This method adapts the chemical shift-encoded approach for the separation of water and olefinic fat signals in a DW acquisition with chemical selective suppression of aliphatic fat. The proposed method addresses two important complications encountered when incorporating fat-water separation in diffusion imaging. First, the implementation of a multiple-point fat-water separation method considerably lengthens the to-
tal scan time. In the present work, we propose to substitute the averaging commonly employed in DW acquisitions (typically 2-6 averages are needed to improve the inherently low SNR in DW acquisitions) by a fat-water separation acquisition using a set of different echo time (TE) shifts, which allow separation of the water and olefinic fat signals. Second, DW images have inherently unreliable phase, due to the sensitivity to small motions introduced by the DW gradients. This complicates fat-water separation, compared to standard, non-DW acquisitions [1], where the image phase is typically consistent. The proposed method performs the separation based on the magnitude DW images [142, 143]. In this chapter, the method is described and validated using phantom data, as well as in vivo data from the skeletal muscles of healthy volunteers.

7.2 Methods

7.2.1 Acquisition

The proposed method is based on replacing the averaging in standard DW-EPI by a TE-shifted acquisition [1–3, 67, 144]. As is the practice with fat-water imaging, the TE shifts are obtained by time-shifting the refocusing pulses in a spin echo (SE) or a stimulated echo (STE) DW-EPI sequence. The proposed acquisition scheme is shown in Fig. 7.1.

Due to the relatively small chemical shift between water and olefinic protons (approximately 89 Hz at 3 T), longer TE shifts compared to standard fat-water imaging methods [109] are needed in order to attain sufficient phase shifts for separating the two components. In this work, 6 values of \( \Delta T_{E_n} \) are used, equally spaced between 0 and 10 ms, which result in accumulating nearly one full cycle in the relative phase between water and olefinic protons. The SNR properties of this choice of TE shifts are analyzed theoretically and empirically in the Results section.
Figure 7.1: Proposed acquisition scheme, based on a stimulated echo DW-EPI acquisition. Shifting the shown block (dashed box) to the left by $\Delta T_{E_n}/2$ results in an effective TE shift of $\Delta T_{E_n}$. The shaded gradient pulses depict diffusion-weighting gradients. A similar acquisition is of course possible based on spin echo DW-EPI.

### 7.2.2 Post-processing

Because of the phase distortions typical of body DW-EPI, which are caused by the motion-probing DW gradients and complicate standard fat-water separation processing, the proposed method performs olefinic fat-water separation using magnitude images. The signal magnitude measured at an individual voxel in a DW-EPI acquisition with a diffusion weighting $b$ and TE shift $\Delta T_{E_n}$ (as shown in Fig. 7.1) can be modeled as:

$$|s(x; b, \Delta T_{E_n})| = \left| W(x; b) e^{j2\pi f_w(x) \Delta T_{E_n}} + F(x - \Delta x; b) e^{j\phi_F(x - \Delta x; b)} e^{j2\pi (f_w(x - \Delta x) + f_F) \Delta T_{E_n} + \nu} \right|$$  \hspace{1cm} (7.1)

where $W(x; b)$ is the magnitude of the water signal, $F(x - \Delta x; b)$ is the amplitude of the olefinic fat signal, $\Delta x$ is the spatial displacement of the olefinic fat signal due to the CSA (e.g., approximately 4 voxels in the acquisitions used in this work), $\phi_F(x - \Delta x; b)$ is the initial (i.e., with zero TE shift) phase of the fat signal relative to the water signal, $f_F$ is the chemical shift of the olefinic fat signal ($f_F \simeq 89$ Hz at 3 T) [140], $f_w(x)$ is the local frequency offset due to $B_0$ field inhomogeneity, and $\nu$
represents complex Gaussian noise with distribution $N(0, \sigma^2)$.

The field map $f_b(x)$ is estimated from the complex-valued $b = 0$ data along with the $b = 0$ water and fat images. This is done using a version of the ICM algorithm described in Chapter 4, modified here to account for the olefinic fat CSA (as described in the next subsection).

The unknown parameters in Eq. 7.1 are $W(x; b)$, $F(x - \Delta x; b)$, and $\phi_F(x - \Delta x; b)$. The maximum-likelihood (ML) estimates of these parameters are obtained at each voxel, accounting for the Rician distribution of the noisy MR magnitude data [145], by maximizing:

$$\max_{W, F, \phi_F} \prod_{n=1}^{N} \left| s(x; b, \Delta T_{E_n}) \right| e^{-\left| s(x; b, \Delta T_{E_n}) \right|^2 + \left| \hat{s}(W, F, \phi_F; \Delta T_{E_n}) \right|^2 / 2\sigma^2} \times$$

$$I_0 \left( \frac{\left| s(x; b, \Delta T_{E_n}) \right| \left| \hat{s}(W, F, \phi_F; \Delta T_{E_n}) \right|}{\sigma^2} \right),$$

(7.2)

where $s(x; b, \Delta T_{E_n})$ is the measured signal at a given voxel, $\hat{s}(W, F, \phi_F; \Delta T_{E_n})$ represents the signal model, i.e.,

$$\hat{s}(W, F, \phi_F; \Delta T_{E_n}) = W e^{j2\pi f_b(x)\Delta T_{E_n}} + F e^{j\phi_F} e^{j2\pi(f_b(x - \Delta x) + f_F)\Delta T_{E_n}},$$

(7.3)

for known field map values $f_b(x)$, $f_b(x - \Delta x)$, and $I_0$ is the zeroth-order modified Bessel function of the first kind. The estimation is equivalent to minimizing the following negative log-likelihood:

$$\min_{W, F, \phi_F} \sum_{n=1}^{N} \left[ \frac{\left| \hat{s}(W, F, \phi_F; \Delta T_{E_n}) \right|^2}{2\sigma^2} - \log I_0 \left( \frac{\left| s(x; b, \Delta T_{E_n}) \right| \left| \hat{s}(W, F, \phi_F; \Delta T_{E_n}) \right|}{\sigma^2} \right) \right].$$

(7.4)

This minimization is performed using a standard iterative Newton descent-based algorithm available in MATLAB (The MathWorks, Natick, MA) [146]. The proposed method is depicted graphically in Fig. 7.2.

The proposed method results in locally optimal estimates, so it is important to have a good initialization. In this case, the initialization is obtained from the $b = 0$ images. These are also acquired using different TE shifts, and so fat-water separation is possible on them. Note that the
phase was observed to be reliable in the $b = 0$ images due to the lack of DW gradients. From the olefinic fat-water separated $b = 0$ images $(W(x; 0), F(x; 0), \phi_F(x; 0))$, the initial guesses for the parameters $(W, F, \phi_F)$ in Eq. 7.4 are obtained at each location $x$ by using approximated diffusion coefficients for the water and olefinic fat components (conservatively chosen to preserve the water signal). The specific values $(W(x; 0)e^{-0.0005b}, F(x - \Delta x; 0), \phi_F(x - \Delta x; 0))$ are used in this work.

### 7.2.3 Fat-Water Separation from b=0 EPI Images

The complex-valued signal measured at an individual voxel in an EPI acquisition with TE shift $\Delta T_{En}$ can be modeled similarly to Eq. 7.1:

$$s(x; \Delta T_{En}) = W(x)e^{j2\pi f_b(x)\Delta T_{En}} + F(x - \Delta x)e^{j2\pi(f_b(x-\Delta x)+f_F)\Delta T_{En}} + \nu,$$

(7.5)
where \( W(x) \) and \( F(x - \Delta x) \) are the complex-valued amplitudes of water and fat, respectively, observed at location \( x \). The difference of Eq. 7.5 from that employed in the standard chemical-shift encoded fat-water separation [1–3] is that the olefinic fat observed at location \( x \) originates from location \( x - \Delta x \) due to the CSA, and is affected by the \( B_0 \) field at location \( x - \Delta x \). In the EPI acquisitions used in this work, \( \Delta x \) was approximately 4 pixels along the phase-encoding direction. In standard fat-water separation methods (e.g., based on non-EPI Cartesian acquisitions), \( \Delta x \) is usually less than 1 pixel and is typically neglected.

In this work, a modified version of the VARPRO-ICM method described in Chapter 4 was used for joint estimation of the field map and fat-water images. The proposed method is based on finding the field map, water, and fat images that best fit the acquired data in the least-squares (LS) sense, i.e., minimizing at each voxel:

\[
R_0(W(x), F(x - \Delta x), f_B(x), f_B(x - \Delta x); s(x)) = \\
\sum_{\Delta T_E_n} |s(x; \Delta T_E_n) - (W(x)e^{j2\pi f_B(x)\Delta T_E_n} + F(x - \Delta x)e^{j2\pi(f_B(x - \Delta x) + f_F)\Delta T_E_n})|^2. \tag{7.6}
\]

However, simply minimizing \( R_0 \) in Eq. 7.6 is known to be problematic due to the presence of ambiguities and noise [5]. This problem can be addressed by imposing smoothness in the field map. The modified method seeks the solution that minimizes the regularized LS cost function:

\[
\sum_x R_0(W(x), F(x - \Delta x), f_B(x), f_B(x - \Delta x); s(x)) + \sum_x \sum_{x' \in \delta_x} w(x, x') (f_B(x) - f_B(x'))^2, \tag{7.7}
\]

where \( x \) traverses all voxels in the image, and \( R_0(W(x), F(x - \Delta x), f_B(x), f_B(x - \Delta x); s(x)) \) represents the fit residue at voxel \( x \), and \( \delta_x \) is the neighborhood of voxel \( x \) (its 8 surrounding voxels in this work). The first term in Eq. 7.7 imposes data fidelity, whereas the second (regularization) term imposes field map smoothness. The regularization parameters \( w(x, x') \) are chosen as in Chapter 3.

As described in Chapter 4, the linear parameters \( \{W(x), F(x - \Delta x)\} \) can be removed from
the formulation by reformulating the residue:

\[ R(f_u(x), f_u(x - \Delta x); s(x)) = \arg \min_{W(x), F(x-\Delta x)} R_0(W(x), F(x-\Delta x), f_u(x), f_u(x - \Delta x); s(x)). \] (7.8)

This modification leads to an equivalent version of Eq. 7.7, which can be now expressed in terms of \( R \) (i.e., only in terms of the field map), as minimizing

\[ \sum_x R(f_u(x), f_u(x - \Delta x); s(x)) + \sum_x \sum_{x' \in \delta_x} w(x, x') (f_u(x) - f_u(x'))^2. \] (7.9)

The minimization problem in Eq. 7.9 is then solved by iteratively updating the field map one voxel at a time. This simple optimization procedure may result in convergence to a local minimum in the presence of large field inhomogeneities, so a reasonable initialization is necessary. In this work, the field map is initialized with the estimates from the graph cut-based method proposed in Chapter 4 (where the CSA is not taken into account).

### 7.2.4 Experiments

All experiments were performed on a 3 T whole-body scanner (General Electric Healthcare, Waukesha, Wisconsin). Data were acquired by scanning a fat-water phantom as well as the lower extremity muscles of three volunteers, using a single-shot stimulated echo EPI sequence \[147\] with the following parameters: TR/TE=2000/72 ms, FOV=20×20 cm², slice thickness=10 mm, acquisition matrix=64×48 (6/8 partial phase encoding), with 30 diffusion directions and diffusion weighting \( b = 540 \text{s/mm}^2 \). The in vivo scans included data from the right calf muscle of two volunteers and from the right lower thigh musculature of a third volunteer, using in all cases a transmit-receive single channel lower extremities coil. Seven slices were acquired and standard fat suppression (to remove signal from methyl/methylene fat peaks near 1.4 ppm) was performed using a spatial-spectral RF pulse. The proposed acquisition was obtained using 6 values of \( \Delta T E \), equally spaced between 0.0 ms and 10.0 ms. For comparison, a standard acquisition (with TE=72)
was obtained with 6 averages and no echo time shifts.

The calf acquisitions were performed twice, by altering the direction of the phase encoding lines, so that the olefinic fat signal from the subcutaneous fat layer was shifted in a different direction each time, resulting in contamination of a different muscle region. The thigh dataset on the third volunteer was acquired with the proposed method, using the same acquisition parameters but only 6 diffusion directions.

7.3 Results

7.3.1 SNR analysis

An important aspect of the proposed method is its noise performance. This can be well characterized in terms of the effective number of signal averages (NSA), which is the ratio of the noise variance in the acquired images and the noise variance in the resulting water image [3, 109, 123].

Figure 7.3 shows the NSA for different fat-water ratios and different initial relative phases between the two signal components (water and fat). In this work, one cannot assume an initial relative phase of 0 (as is commonly done when analyzing conventional fat-water separation), because an initial relative phase (dependent on the diffusion weighting) is observed, which is unknown a priori. As can be observed, it is not possible to attain constant NSA for all fat-water ratios, unlike in standard fat-water separation [109]. The variability of NSA with fat content is due to the unreliable phase in the acquired images, so that the separation must be performed from magnitude images. Two main observations can be derived from Fig. 7.3:

- NSA approaches its maximum value, 6, for voxels containing mostly water. This results in good SNR for voxels containing only water, where separation is not needed in the first place.

- NSA vanishes for a water/olefinic fat ratio of 1. Note that this does not imply arbitrarily large errors in the amplitude estimates. Given a sufficiently large number of TE shifts, the signal at a voxel containing $W = F$ will have a minimum of approximately 0 and a maximum
Figure 7.3: Effective number of signal averages for water component estimation from magnitude images, using a 6-point acquisition with TE shifts evenly distributed between 0 and 10 ms. (Top) Theoretical NSA (obtained from CRLB). (Bottom) Empirical NSA (obtained from MSE observed in simulation with 10,000 trials using SNR=10). Values are shown for different initial phase shifts between the water and olefinic fat components, and for different water/olefinic fat ratios.

of approximately $2W$. Thus, the estimated amplitudes obtained with the proposed fitting method will both be near the correct value (so that the signal model can fit the measured signal). However, the variance of these estimates will not scale down linearly with decreasing noise variance [148]. Still, it may be preferable to avoid this effect altogether, which in the context of the proposed technique can be achieved by using moderate $b$ values so that the water amplitude is larger than the amplitude of the olefinic fat in the DW images. For instance, in the calf dataset the water/olefinic fat ratio in most of the contaminated region of the $b = 0$ images is nearly 6. Assuming that the diffusivity of water in muscle tissue along any direction is less than $2.3 \times 10^{-3}$ mm$^2$/s, the water/olefinic fat ratio of the $b = 540$ s/mm$^2$ images is higher than $6 \times \exp(-2 \times 10^{-3} \times 540) \approx 1.7$, so the degenerate region of the NSA can be avoided.
7.3.2 Phantom results

Figure 7.4 shows representative results from a phantom scan. The imaged slice contains a circular region of fat surrounded by water. The basis for the proposed method is displayed in Fig. 7.4 (left box): voxels containing both water and olefinic fat components show a variation in signal magnitude with varying TE shifts (due to the varying relative phase), which allows us to separate the two components of the signal. The olefinic fat component is clearly visible in the acquired DW images, with a spatial shift of nearly 4 voxels due to the chemical shift artifact. Note that unsuppressed methylene proton signals would experience a different spatial shift (nearly 18 voxels in the opposite direction), and thus would appear elsewhere in the images. Good separation of water and olefinic fat is achieved from the DW images. Thus, the diffusion parameter estimation errors obtained with a standard acquisition are largely removed with the proposed method.

Based on the proposed separation, two regions were segmented: the region of the image containing only water (“water region”), and the region containing both water and olefinic fat (“mixed region”). Table 7.1 shows the estimated mean diffusivity (MD) in both regions using the standard acquisition as well as the proposed method. The standard acquisition shows severely biased MD estimates in the mixed region. This bias is well removed using the proposed method. MD estimates in both regions using the proposed method are in good agreement with the standard water region estimates. Additionally, the proposed method results in a decrease of the standard deviation in MD estimation. This difference may be due to the presence of unsuppressed aliphatic signal in both acquisitions. In the standard acquisition, this unsuppressed signal appears coherently in all the averages, and results in a small but non-negligible bias in the MD estimates of a region within the image. In contrast, in the proposed acquisition, unsuppressed aliphatic signals introduce rapidly varying distortions of small amplitude to the signal, as a function of TE shift, and are treated as noise during the olefinic fat-water separation. Moreover, MD estimates in the mixed region using the proposed method also show decreased standard deviation compared to the water region. This is somewhat surprising, since according to theory (see Fig. 7.3), the NSA for a fat-water ratio of 4
Figure 7.4: Olefinic fat removal results on a fat-water phantom. (Left box) Acquired images, with and without diffusion weighting. Note the visible signal contamination due to the olefinic fat chemical shift artifact (see arrow). Also shown is the signal magnitude evolution with TE shift at voxels within the water region, olefinic fat region, and mixed region. The proposed separation is based on the magnitude variation observed when both components are present. (Center box) Resulting DW water and olefinic fat images, obtained with the proposed method. The gray scale is common to water and olefinic fat, to highlight their relative amplitudes. (Right box) Estimated MD ($\times 10^{-3}$ mm$^2$/s) maps with a conventional acquisition (6 averages) and with the proposed method (6 TE shifts). The MD estimate obtained with the standard acquisition in the mixed region (see arrow) is significantly biased, due to the slow-diffusing olefinic fat component. This bias is largely removed with the proposed method.

(observed in the mixed region) should be slightly worse than for water-only voxels. This mismatch may be due to the small size of the mixed region sample, which contains 23 voxels.

Table 7.1: Estimated MD ($\times 10^{-3}$ mm$^2$/s) using a standard acquisition (6 averages) and the proposed acquisition (6 TEs), in the region of the phantom containing only water ("water region"), and in the region containing both water and olefinic fat ("mixed region," where olefinic fat appears due to the chemical shift artifact).

<table>
<thead>
<tr>
<th></th>
<th>Standard acquisition</th>
<th>Proposed acquisition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water region</td>
<td>2.14 ± 0.10</td>
<td>2.15 ± 0.08</td>
</tr>
<tr>
<td>Mixed region</td>
<td>2.01 ± 0.03</td>
<td>2.12 ± 0.04</td>
</tr>
</tbody>
</table>
7.3.3 In vivo results

Representative results from a calf DW-EPI imaging experiment are shown in Fig. 7.5. The acquisition was performed twice, reversing the order of the EPI phase encoding lines. This gave rise to different susceptibility-related distortions for datasets acquired with different phase encoding orderings. In order to ameliorate this inconsistency, all datasets were distortion-corrected using the field maps estimated from the $b = 0$ images (field maps estimated with both phase encoding orderings were averaged prior to performing distortion correction) [149].

The acquired images (Fig. 7.5, left box) contain significant olefinic fat signal contamination. Note that, even in the standard acquisition (where no olefinic fat-water phase shifts are purposefully introduced), the relative phase between water and olefinic fat varies with diffusion gradient direction. This can give rise to brighter and darker regions in the acquired images, in cases where the two components are in phase and in opposed phase, respectively. As in the phantom case, the proposed method results in good water-only images (Fig. 7.5, center box), which in turn produce improved estimates of diffusion parameters (Fig. 7.5, right box). The MD maps obtained with the standard acquisition show clear errors in “problematic” regions of olefinic fat contamination. The MD maps obtained with the proposed method for both phase encoding orderings are free of most of these errors. The remaining problematic region in the “phase encoding down” results from the proposed method (see short arrow) is likely due to the higher intensity of olefinic fat signal in that region (originating from the bone marrow), where the water/olefinic fat ratio is nearly 2 in the $b = 0$ images. In the presence of DW, the water/olefinic fat ratio may be close to 1, resulting in poor NSA (see Fig. 7.3). Still, the problematic region is reduced with respect to the standard acquisition even in this case. The eigenvalues of the diffusion tensor are also contaminated in the region of the residual olefinic fat chemical shift artifact (Fig. 7.5) and the bias in the estimation of the eigenvalues is removed by employing the proposed method.

Additional results from a thigh dataset are shown in Fig. 7.6. The olefinic fat contamination is somewhat subtle in the acquired $b = 0$ image, but remains obvious in the $b = 540 \text{ s/mm}^2$
Figure 7.5: Results from a calf dataset. (Left box) Acquired images using the standard acquisition (no TE shifts), with two different diffusion directions. Note the significant olefinic fat signal contamination. Furthermore, the relative phase of water and olefinic fat is not consistent for different DW directions. (Center box) Results from the proposed method for separation of water and olefinic fat from magnitude DW images. (Right box) MD estimates using the standard and proposed methods, and acquired with and without reversal of the EPI phase encoding ordering. Different phase encoding orderings give rise to different directions of the olefinic fat CSA, creating different problematic regions in the MD maps. These regions are largely fixed with the proposed method, for both phase encoding orderings. Bottom box shows the diffusion tensor eigenvalues with the standard and the proposed method, with the phase encoding up.
image. The estimated water-only images obtained with the proposed method show good removal of olefinic fat. The acquired images also contain a small residual contribution from unsuppressed aliphatic fat signal, which is partially (although not completely) removed by the proposed method.

Figure 7.6: Results on a thigh dataset with phase encoding down. Arrows in the acquired images indicate olefinic fat contamination. The $b = 0$ water-only image was obtained with a standard method (relying on the complex-valued data), and the $b = 540$ water-only image was obtained from the magnitude DW data.

### 7.4 Discussion

This chapter describes a novel method for removal of olefinic fat signal in DW-EPI. The proposed method is based on a combined approach for removal of aliphatic fat signals using conventional fat suppression, and removal of olefinic fat signals using a TE-shifted acquisition [141]. The proposed algorithm seeks the ML estimates for water and olefinic fat at each voxel, and it can be viewed as an adaptation of the IDEAL algorithm [1] in the case where the phase of the acquisitions is unreliable, i.e., where optimal separation is obtained from magnitude images [142, 143]. The
proposed method has been applied in vivo in healthy calf and thigh DW imaging applications. In these applications, the olefinic fat results in significant image contamination due to the presence of fat in the subcutaneous layer and the bone marrow region near the tissue of interest.

The proposed acquisition scheme involves replacing averages with multiple shifts of the refocusing pulses in a spin echo- or stimulated echo-based DW-EPI pulse sequence. This scheme places certain constraints on the sequence timing. First, the timing must allow shifting the refocusing pulses (see Fig. 7.1) by nearly 5 ms at 3 T. Second, the partial Fourier factor may need to be increased to ensure that the echo is captured within the acquisition even in the TE-shifted case. Both constraints result in an increase of the minimum TE achievable, with the corresponding SNR loss. However, the SNR loss of the water signal induced by the echo shifting is lower than the SNR loss of the water signal induced by using STIR to suppress olefinic fat. Specifically, if the T1/T2 of muscle are 1420/32 ms [150] and the T1 of olefinic fat is 537 ms [151], the required increase in the TE (by 10 ms) of the echo-shifted acquisition results in a water SNR reduction by 27% and the T1 relaxation over the inversion recovery interval (372 ms) in STIR acquisition results in a water SNR reduction by 46%.

Two important assumptions are made in the present signal model. First, even though the phase in DW-EPI images is inconsistent (so no standard fat-water separation is possible), the phase inconsistencies are assumed to be spatially smooth, so that the relative phase between olefinic fat and water signals (which originate from nearly 4 voxels apart with the current acquisition parameters) is consistent. Although motion and eddy current effects could affect the relative phase between olefinic fat and water, the approximation of consistent relative phase appears to be good enough in the presented phantom and in vivo data to enable separation using the proposed signal model (Eq. 7.1). Second, the proposed method assumes the presence of two components in the signal (water and olefinic fat), and thus, requires the use of standard fat suppression techniques to remove the aliphatic fat components. In the case of incomplete aliphatic fat suppression, the proposed method has demonstrated a moderate ability to remove residual aliphatic fat signal from the water image during the olefinic fat-water separation stage. However, a thorough characterization of this ability
(e.g., to determine what levels of residual aliphatic fat signal can be tolerated) is outside the scope of this work.

An alternative approach to reduce the chemical shift artifact in EPI acquisitions is the reduction of the gradient readout duration by employing parallel imaging or reduced-FOV techniques. Although these techniques reduce the spatial misregistration shift of the olefinic fat, they do not remove the olefinic fat signal. Therefore, they can reduce the olefinic fat shift in regions close to the subcutaneous fat and the bone marrow, but they cannot suppress the olefinic fat signal in fatty infiltrated muscles and in the fascia of the intermuscular fat, where the discrimination of water from fat is more challenging. However, complete fat suppression is essential in tissues with increased fat content to monitor the mobility of the water molecules only [137]. The proposed technique has the advantage of enabling water and olefinic fat separation. Therefore, the proposed technique might be preferable for suppression of the olefinic fat signal in diseased muscular tissues with homogeneous fatty infiltration or increased intermuscular adipose tissue.
Chapter 8

Future Work and Conclusions

8.1 Directions for Further Research

8.1.1 Accurate Spectral Modeling: Further Characterization

A number of research works have recently shown that accounting for the multi-peak nature of the fat signal allows improved estimation of fat fractions. This has been shown both in phantom studies, as well as \textit{in vivo} (e.g., liver). Multi-peak fat modeling has two important advantages: it removes bias associated with ignoring the secondary fat peaks, and it helps reduce the estimation ambiguity associated with modeling the water and fat components simply as frequency-shifted versions of each other. However, perfect calibration of the multiple fat peaks is rarely possible. The sensitivity of fat-water separation with multi-peak fat modeling to calibration errors in the multi-peak model needs to be further addressed. Preliminary simulation results (see Chapter 6) seem to indicate that multi-peak fat modeling performs well even in the presence of moderate calibration errors. Ideally, this needs to be tested and quantified using theoretical analysis, phantom experiments and \textit{in vivo} data.

8.1.2 Study Optimum TEs: Beyond CRLB

One of the key aspects of experimental design for fat-water imaging is the selection of echo times (TEs) that allow accurate separation of water and fat. The works of Pineda et al. [109], and more recently Wen et al. [148], provide an elegant characterization of the noise performance associated with different choices of TEs in the context of single-peak fat modeling. These works are largely
based on Cramer-Rao lower bound (CRLB) analysis and focus on a set of three “IDEAL” TEs that provide optimal noise performance for any fat-water ratio. However, these IDEAL TEs are not always attainable due to hardware constraints. Additionally, in the presence of large field inhomogeneities, large errors can be made, including fat-water swaps, related to the non-convex nature of the ML cost function, which are not captured by the CRLB. It would be desirable to develop tools for analysis and selection of experimental parameters (specifically TEs) in the presence of hardware constraints and possibly large field inhomogeneities.

8.1.3 Other Applications

The methods developed in this work (VARPRO-based penalized ML formulation solved using a tailored graph cut algorithm) are not specific to the fat-water imaging problem, but rather constitute a general approach to solving problems of regularized estimation of nonlinear parameters. Other applications of these methods may arise, both in the context of spectroscopic MR imaging (e.g., hyperpolarized $^{13}$C imaging), as well as in other imaging scenarios.

8.2 Conclusions

The ability of MRI to simultaneously map multiple chemical species based on their different chemical shifts is of great practical importance. Specifically, separating signals originating from water and fat has a number of important applications, both in cases where the goal is to remove the fat signal, as well as in cases where the fat signal itself is of diagnostic relevance. However, fat-water separation is difficult in the presence of large field inhomogeneities, due to the distortions introduced in the acquired signal by a rapidly varying $B_0$ field. Additionally, quantitative fat-water imaging requires careful modeling of the acquired signal. This dissertation has studied the problem of fat-water separation in MRI, including formulation, modeling and optimization aspects. The proposed methods have been characterized theoretically, and validated using simulations, phantom and in vivo experiments.
The main contributions of this dissertation are:

1. **Novel joint estimation-based formulation for the fat-water imaging problem.** The problem of fat-water separation presents severe ambiguities when addressed at an individual voxel; i.e., it constitutes an identification problem. By posing the problem simultaneously for all the voxels using a regularized joint formulation, two important properties are obtained: (1) the ambiguities are addressed and the identification problem solved by seeking a solution where the $B_0$ field varies smoothly in space; and (2) the spatial resolution properties of the resulting estimates are characterized.

2. **Graph-cut algorithm for solving the regularized formulation.** The joint estimation formulation results in a difficult high-dimensional and non-convex optimization problem. However, the structure of this problem, where the non-convexity appears only in the (voxel-independent) data term of the cost function, makes it suitable for a graph cut-based solution. A novel iterative graph cut algorithm has been developed that is able to escape suboptimal solutions where previous algorithms would be trapped. An efficient implementation has been developed by mapping each iteration to a standard graph max-flow/min-cut problem.

3. **Systematic comparison of signal models.** A comparison of 12 relevant signal models has been performed, based on theoretical predictions (using Cramer-Rao lower bounds), simulations, phantom studies and *in vivo* validation. This comparison shows that complex-fitting, multi-peak fat models have superior performance, and a model with a single $R_2^*$ (common for the water and fat components) is preferable over a clinically relevant range of fat fractions and SNRs.

4. **Removal of olefinic fat signals in diffusion MRI.** An extension of fat-water imaging methods to the challenging case of diffusion MRI has been proposed and studied. The proposed method is based on a combination of spatial-spectral pulses for the suppression of signal from aliphatic fat protons, and on a chemical shift-encoded method for the suppression of signal from olefinic protons.
References


