Advanced Brain Spectroscopy at High Field Strength
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Summary

One of the most interesting fields of *in-vivo* magnetic resonance is spectroscopy (MRS). This field enables the direct investigation of the human metabolism, hence providing insights into the underlying physiological processes. Despite its great potential for valuable applications, MRS is limited due to low sensitivity, heavy overlap of resonances and other experimental restrictions. In this regard, there is a great challenge to increase the information obtainable by MRS. In this thesis, several methods are combined in order to achieve this goal and increase detection capabilities of spectroscopy.

The localisation in MRS requires shaped radio-frequency (RF) pulses. Traditionally, these are obtained by non-linear optimisation. This kind of optimisation is neither intuitive nor flexible. A more elegant and semi-analytic method is the Shinnar-Le Roux (SLR) transformation, which reversibly transforms an RF pulse into two finite-impulse response (FIR) filters. This reduces the pulse design problem to that of designing FIR filters, which is a highly advanced discipline with many methods existing. In this work, an improved strategy for the design of quadratic-phase RF pulses is proposed. The required FIR filters are directly and flexibly designed with the complex Remez exchange algorithm, ensuring an equi-ripple error function. It is argued, that these pulses are near optimal in terms of minimising the $B_1$ amplitude, hence yielding the maximal bandwidth for a given $B_1$. Various parameter relations are derived to provide an insight into the trade-offs in the design. The effectiveness for localisation as well as suppression is demonstrated both *in vivo* and *in vitro*. Besides various possible applications in both MRI and NMR, quadratic-phase RF pulses can be used for improving the PRESS volume localisation in MRS. This can be achieved by saturating the region of chemical-shift displacement, thereby improving the general quality of the spectra.

Special editing techniques are generally required to increase the amount of detectable metabolites beyond the predominant singlets of N-acetyl aspartate (NAA), creatine (Cre) and choline (Cho). An effective and robust way is multi-dimensional spectroscopy. A promising technique is the chemical-shift-selective filter (CSSF), which is the constant-time version of localised 2D $J$-resolved spectroscopy. This filter is an acquisition based technique, and requires only the chemical-shifts but not the whole multiplet structures to be resolved from each other. The chemical shift is encoded in the indirect dimension by successively shifting the last echo pulse, but leaving the reference of the reconstruction constant. Localisation is achieved through PRESS, thus making the method similarly robust. CSSF is applied to the detection of $J$-coupled metabolites in the human brain, specifically glutamate (Glu) and myo-inositol (mi) and yields good separation from the predominant singlets.

Another sequence for gaining more information in MRS is $J$-resolved spectroscopy, also known as JPRESS. The $J$-evolution is encoded in the indirect dimension by multiple echo times. This provides an additional separation of the $J$-coupled metabolites, which is highly desired due to the heavy overlap of regular 1D spectra. A maximum-echo sampling scheme is presented for increasing the sensitivity and tolerance to strong signals (e.g., residual water or fat) by a tilt of the 2D peak tails. This tilt reduces the overlap and hence contamination. The sensitivity between different 1D and 2D experiments is compared analytically, showing that the sensitivity of 2D JPRESS compared to 1D PRESS is similar or even higher for metabolites with long $T_2$. The effects of eddy currents on the 2D JPRESS experiment is elucidated and possible correction schemes are proposed.

The full amount of information present in the 2D JPRESS spectrum is extracted by a 2D fitting procedure, dubbed ProFit. This procedure is based on two complementary 1D approaches, namely LCMRModel for including the maximal prior knowledge and VARPRO for increasing robustness and speed of the fit. The parameters lineshape, shifts and phase are optimised in a non-linear outer fit, while the con-
Summary

Concentration is determined by linear least squares in the inner step. The degrees of freedom are increased during a three-fold iteration of the non-linear optimisation, which improves convergence and provides accurate starting values. ProfIt is extensively validated both in vitro and in vivo in 27 healthy volunteers. The results suggest, that the amount of detectable metabolites in the brain can be increased to 15 at the current field strength of 3 T.
Zusammenfassung


Um mehr als nur die dominanten Singlets von N-Acetyl-Aspartate (NAA), Kreatin (Cre) und Cholin (Cho) zu detektieren sind normalerweise spezielle Editingsequenzen erforderlich. Ein effektiver und robuster Ansatz ist multidimensionale Spektroskopie. Besonders hervorzuheben ist hierbei ein auf die chemische Verschiebung selektives Filter (CSSF). Dieses Filter ist die Konstantzeitversion der 2D $J$-aufgelösten Spektroskopie. CSSF ist eine akquisitionsbasierte Methode, welche die Anforderungen an die benötigte Auflösung reduziert. Es muss nunmehr nicht die gesamte, oft sehr breite Multiplettstruktur aufgelöst werden, sondern nur noch die chemische Verschiebung. In der indirekten Dimension wird die chemische Verschiebung durch Varieren der Echozeit bei konstantgehaltenem Akquisitionsstart kodiert. Die Lokalisierung wird durch PRESS erreicht, was diese Technik robust macht. Anwendungen für CSSF sind $J$-gekoppelte Systeme, im Speziellen Glutamat (Glu) und myo-Inosit (mI), die sich mit dieser Technik gut von den dominierenden Singlets separieren lassen.


Introduction

In-vivo Proton Magnetic Resonance Spectroscopy (MRS) is an invaluable tool for the non-invasive study of various disorders. Hundreds of metabolites are present in the human brain, which give rise to often complex spectra. In total, there are about twenty substances possibly detectable with proton MRS at the currently typical field strength of 3 T [1, 2, 3]. These substances play an essential role in the metabolism and the determination of individual concentrations gives an insight into the underlying processes of the brain. Most metabolites are however difficult to detect due to low sensitivity and complicated spectral appearance from J evolution. In general, many different methods have to be combined in order to achieve the goal of accurately quantifying individual concentrations. The aim of this thesis was to advance both the experimental and post-processing parts, for improving the detection and quantification of metabolites.

One of the most popular ways to advance spectroscopy is increasing the magnetic field strength $B_0$. The typical field strength increased to 3 T over the years and even 7 T systems are becoming more widely available. Increasing $B_0$ improves sensitivity and chemical shift separation [2], both of which are of paramount importance for spectroscopy. However, it comes along with certain drawbacks, namely a hampered localisation. The maximum transmitting field strength of the coil $B_{1\text{max}}$ typically decreases on MR systems with higher field strengths, while the chemical shift increases, thus aggravating the localisation problem. For example, the chemical-shift displacement in PRESS volume localisation [4] is about half a voxel on the 3 T Philips Intera scanner with the transmit/receive head coil. This is 4.5 times larger than with the comparable setup on the 1.5 T scanner.

These localisation problems can be effectively alleviated by quadratic-phase RF pulses [5], which exhibit an extraordinary broad bandwidth. These kind of pulses can be used to pre-saturate the region of chemical shift displacement in PRESS localisation [6]. A novel design method for quadratic-phase pulses is presented in Chapter 1. The design is based on the Shinnar-Le Roux transformation [7], which reversibly transforms RF pulses in finite impulse response (FIR) filters. The required FIR filters with an overlaid quadratic phase are directly calculated with the complex Remez exchange algorithm [8, 9]. Manifold parameter relations are derived to give an insight into the trade-offs of the design of such pulses, hence enabling the flexible and specific design of quadratic-phase pulses. The underlying theory is semi-analytic, hence extraordinary elegant for both design and understanding. It is shown, that overlaying a quadratic phase leads to near optimality in terms of reducing $B_{1\text{max}}$. Furthermore, the method is extended to include higher order phase terms, showing that the near optimality of the quadratic phase can be further increased by combining different phase terms.

In spectroscopy, the main goal is the accurate detection and quantification of individual metabolite concentrations. Multiple resonances of these substances are often strongly coupled by chemical bonds, giving rise to an overcrowded spectrum consisting of complex multiplet structures. One way to extend detection capabilities beyond the predominant singlets of N-acetyl-aspartate (NAA), creatine (Cre) and choline-containing compounds (Cho) is spectral editing [3]. Indeed, these techniques enabled various interesting and elaborate clinical studies [3]. However, editing techniques are often complicated to perform and the data are usually quantified manually, leading to subjective and inaccurate results. Quality measures to exclude poor spectra are difficult to establish. In conjunction with low concentrations, these factors give rise to great variances of the determined concentrations.

Multi-dimensional spectroscopy methods dominate the in-vitro NMR field, due to their superior information content. Over the years, many attempts have been made to show practicality in in-vivo MRS, also at the Institute for Biomedical Engineering (University and ETH Zurich) [10, 11]. However, these techniques have never been widely applied to in-vivo MRS, mainly because of the lack of appropriate
post-processing techniques and to some extent to the long scan duration.

In Chapters 2 and 3, two $J$-resolved spectroscopy methods are presented. The first one is a chemical-shift-selective filter (CSSF) \[12, 13\], capable of filtering out certain chemical shifts. CSSF has the great advantage that only the chemical shifts, but not the entire multiplet structures have to be resolved. Common 1D post-processing techniques can be applied for further extraction of information from the obtained spectra.

The second method is $J$/PRESS \[14\], and provides an additional distinction of $J$-coupled metabolites (Chapter 3). The robustness of this technique is considerably increased by two methodological improvements, namely a maximum-echo sampling scheme and a two-dimensional eddy current correction scheme. Reconstruction issues are discussed and the sensitivity of $J$/PRESS is compared to regular PRESS.

The last chapter is devoted to extracting the maximal information from the $J$/PRESS spectra by fitting directly in two dimensions. The fitting procedure is based on a combination of two existing 1D techniques; VARPRO \[15, 16\] provides numerical robustness and efficiency and LCModel \[17\] allows the inclusion of the maximal possible prior-knowledge. The newly developed program was dubbed ProFit, standing for two-dimensional Prior-knowledge Fitting. The resulting optimisation problem is considerable and therefore several strategies were combined in order to achieve a convergence of the fit close to the global optimum. ProFit yields the individual concentrations of several metabolites in a single experiment. Cramér-Rao lower bounds \[18\] give an estimate of the quality of the result. The combination of $J$/PRESS with fitting is easy to apply, even under clinical conditions, and greatly enhances detection capabilities in spectroscopy.
Chapter 1

Equi-ripple Design of Quadratic-Phase RF Pulses

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Abstract

An improved strategy for the design of quadratic-phase RF pulses with high selectivity and broad bandwidths using the Shinnar-Le Roux (SLR) transformation is proposed. Unlike previous implementations, the required quadratic-phase finite impulse response (FIR) filters are generated using the complex Remez exchange algorithm, which ensures an equi-ripple deviation from the ideal response function. It is argued analytically that quadratic-phase pulses are near-optimal in terms of minimising the $B_1$-amplitude for a given bandwidth and flip angle. Furthermore, several parameter relations are derived, providing practical design guidelines. The effectiveness of the proposed design method is demonstrated by examples of excitation and saturation pulses applied in vitro and in vivo.

**Keywords:** quadratic-phase pulses; Shinnar-Le Roux transformation; broad bandwidth; very selective saturation pulses; frequency modulation.

1.1 Introduction

Most magnetic resonance imaging (MRI) methods rely on frequency selective radio-frequency (RF) pulses, which become spatially selective with the application of magnetic field gradients. The quality and usefulness of such pulses is determined by several criteria, including the excitation profile, the maximum RF field strength $B_{1\text{max}}$, the deposited energy and the length of the pulse. The ideal slice profile is a rectangular function for high selectivity. In other words, the excitation should be uniform within a chosen region and negligible outside this region. Furthermore, a broad excitation bandwidth is desired to reduce problems like the chemical shift displacement or the sensitivity to $B_0$ inhomogeneities.

In general, trade-offs have to be made among the various criteria mentioned above in order to obtain practically useful pulses. For common linear-phase pulses, which are essentially sinc-pulses, high selectivity requires a long pulse duration with many side lobes. For a broad excitation bandwidth, pulses of this type require high maximum RF field strength $B_{1\text{max}}$, which is ultimately limited by the RF amplifier. For example, a typical limit for the $B_1$ amplitude is about 10 µT on a whole-body MRI scanner. At this RF field strength, linear-phase pulses achieve about 1 kHz for a 90° flip angle and 500 Hz for 180°. However, much larger bandwidths are required for many applications, especially at higher $B_0$ field strengths. As shown in Ref. [19, 5, 20], overlaying RF pulses with a quadratic phase in the frequency domain results in the RF energy of the main lobe being distributed more evenly over the pulse. Hence, for a given $B_{1\text{max}}$ restriction, it is possible to achieve a broader bandwidth and improved selectivity by using quadratic-phase pulses.

However, the quadratic phase of these pulses limits their application as general pulses, since they cannot be refocused through linear gradients. Therefore, these pulses are most useful for purposes that do not require refocusing, such as the saturation and inversion of magnetisation. For these purposes, the phase distribution is irrelevant, while high selectivity, good agreement with the target profile and broad bandwidth remain essential. For instance, good outer volume suppression enables scanning with a reduced field of view and therewith reduced scan time in imaging [5]. Furthermore, the chemical shift displacement in PRESS can be reduced by saturating the region of displacement [6].

A straightforward way of obtaining pulses with an approximately quadratic phase is to rescale adiabatic full passage pulses with offset independent adiabaticity [21]. However, pulses with improved characteristics, such as higher selectivity or error functions with constant error ripples, can be obtained by designing them from scratch. De novo design of RF pulses amounts to inverting the Bloch equations. This is particularly convenient in the small-tip-angle approximation [22], where the RF wave form and the pulse response can be approximated by a Fourier pair. For the design of pulses with large flip angles, several methods of non-linear optimisation have been proposed, using for instance optimal control theory [23, 24] and simulated annealing [25].

An elegant and more analytical approach is the Shinnar-Le Roux (SLR) transformation [7, 26], which reversibly transforms RF pulses into two complex finite impulse response (FIR) filters. The frequency response of these filters corresponds closely with the excitation profile of the RF pulse. Hence, the problem of RF pulse design reduces to that of designing low pass FIR filters. In case of linear-phase filters, this is a standard procedure for which many methods exist. The SLR transform is frequently used to design linear-phase pulses, which are purely amplitude-modulated. Nevertheless, the SLR concept
is equally applicable for the design of RF pulses with frequency modulation, such as quadratic-phase pulses. However, FIR filters with a quadratic phase are more intricate to design.

FIR filters are represented in the z-transform domain as finite-order polynomial functions of a complex variable \( z \). Quadratic phase requires complex polynomial coefficients, which are generally more difficult to determine than real-valued coefficients for linear-phase pulses due to increased algebraic complexity and possible ill-conditioning of the problem [8, 9]. A simple solution is to determine real and imaginary parts of the coefficients independently as though they were real-valued coefficients. This simplifies the problem, but does not generally yield the optimal solution [8].

Two methods have been previously proposed for determining the complex coefficients of approximately quadratic-phase FIR filters. The first one commences by designing a minimum-phase FIR filter with the desired magnitude response, whose phase pattern is then modified by root inversion [27]. The maximum frequency bandwidth achievable with this method is small due to numerical constraints and imprecise phase approximations. The second method is to calculate the polynomial coefficients of the desired FIR filter through a complex least-squares algorithm [5]. This optimisation minimises the deviation from the ideal response in terms of the 2-norm, which typically results in error overshoots at the band edges. A more favourable solution is the equi-ripple solution, where all error ripples are minimised to achieve equal magnitude. This is obtained by minimising the \( \infty \)-norm (Chebyshev norm) of the error function. An approximately equi-ripple error can also be obtained by introducing a proper weighting function in the least-squares optimisation. The implementation of this approach, as described in [5], performs a weighted least-squares fit to a pre-tailored target profile. With this method, the authors obtained an almost equi-ripple solution with broad bandwidth and high selectivity. Nevertheless, they report restrictions to the range of feasible quadratic-phase patterns.

In this work, we propose to obtain the equi-ripple solution directly, using the complex Remez exchange algorithm [8, 9]. This permits determining quadratic-phase pulses with a wide range of quadraticity from zero (linear-phase) up to a critical maximum value. In the first part of the paper, the motivation for quadratic phase is reviewed. A simple heuristic reasoning is followed by a mathematical argument, which illustrates the near-optimality of quadratic phase pulses in terms of minimising \( B_{1\text{max}} \). Then several parameter relations are described, providing design guidelines and illustrating trade-offs among the various pulse properties. In the subsequent sections, the actual design algorithms are described and validated by both simulations and MR experiments.

1.2 Motivation for Quadratic-Phase Pulses

The advantage of quadratic-phase pulses can be appreciated by comparing them to linear-phase pulses. Most of the magnetisation in the selected band is rotated simultaneously with a linear-phase pulse. This requires a short main lobe, as its width is inversely-proportional to the bandwidth. The maximum \( B_1 \)-amplitude of such pulses increases with the bandwidth, as the integral underneath the main lobe remains approximately constant for a given flip angle. Therefore, the \( B_{1\text{max}} \) and power limitations of the transmit coil and the RF amplifier restrict the bandwidth achievable with linear-phase pulses.

The key idea for reducing RF peak power is to excite the spins successively at their individual frequencies rather than all at once [27]. By sweeping through the desired frequencies sequentially, the pulse energy does not need to be confined to a single main lobe. Thus, the maximum RF amplitude can be significantly reduced. The most straightforward option, a linear frequency sweep, corresponds to multiplying the pulse envelope with a quadratic phase term. Interestingly, such a modulation also results in an approximately quadratic phase pattern in the spectral response of the pulse. Thus, the quadratic-phase response forms a suitable design goal for RF pulses with reduced peak power, enabling higher bandwidths. However, simply combining a linear frequency sweep with constant RF amplitude, forming a so-called chirp pulse, results in a poor excitation profile. Thus, more sophistication is needed to combine a quadratic phase response with a proper rectangular amplitude profile.

The motivation for quadratic-phase pulses can also be argued from a more mathematical perspective, employing the Fourier transformation (FT), which approximates the solution of the Bloch equation for pulses with small flip angles [22]. This approximation holds strictly only for pulses with small flip angles \( \theta \) with \( \sin \theta \approx \theta \), but it holds sufficiently well to qualitatively describe the behaviour of pulses with a flip angle of up to about 90°.
The ideal excitation profile \(|F(\omega)|\) is rectangular

\[
|F(\omega)| = \text{rect}(\omega), \quad \text{where} \quad \text{rect}(\omega) = \begin{cases} 
0, & \text{for } |\omega| > BW/2, \\
\sin \theta, & \text{for } |\omega| \leq BW/2,
\end{cases}
\]  

(1.1)

where \(\omega\) denotes the frequency, \(BW\) the bandwidth and \(\theta\) the flip angle. If \(F(\omega)\) has a linear phase, the RF wave form \(f(t) = \mathcal{F}(F(\omega))\) is a sinc-function with a sharp peak and a large number of significant side lobes. Here, \(\mathcal{F}(\cdot)\) denotes the Fourier transform. In contrast, for efficient RF energy transfer in a limited time, the envelope \(f(t)\) should ideally be rectangular as well. That is, the pulse envelope should be approximately rectangular in both the time and the frequency domain. These two seemingly conflicting requirements can be fulfilled only with a quadratic phase, as shown by Papoulis [28].

A rectangular function with an overlaid quadratic phase can be written as

\[
f(t) = \frac{1}{\sqrt{-4\pi k^4}} \text{rect} \left( \frac{t}{2k} \right) e^{-\frac{u^2}{2\pi}},
\]  

(1.2)

where \(k\) is a scaling constant and \(\text{rect}\) is defined as in Eq. [1.1]. Eq. [1.2] is expressed in the frequency domain as

\[
F(\omega) = \frac{1}{\sqrt{-4\pi k^4}} \cdot \mathcal{F} \left( \text{rect} \left( \frac{t}{2k} \right) \right) \otimes \mathcal{F} \left( e^{-\frac{u^2}{2\pi}} \right).
\]  

(1.3)

The convolution in Eq. [1.3] can be developed into an asymptotic series, as shown in Ref. [28]. For a sufficiently large \(k\) and a sufficiently smooth envelope, this series can be approximated by

\[
F(\omega) \approx e^{i k \omega^2} \text{rect}(\omega).
\]  

(1.4)

In this expression, \(k\) specifies the amount of quadratic phase applied in the frequency domain. Generally, the Fourier transform of a smooth envelope function with a quadratic phase yields the same envelope in the other domain, again with a quadratic phase. In the desired rectangular profile, the smoothness criterion is violated at the two discontinuities. As a consequence, the ideally rectangular envelope in the time domain will deteriorate at its edges. Incidentally, by swapping \(t\) and \(\omega\), the same reasoning explains why chirp pulses, which have the ideal rectangular profile in the time domain, have such poor excitation profiles.

According to Parseval’s theorem

\[
\|f(t)\|_2 = \sqrt{\int_{-\infty}^{\infty} |f(t)|^2 \, dt} = \frac{\|F(\omega)\|_2}{2\pi} \propto \sqrt{BW \sin \theta}.
\]  

(1.5)

Hence, the 2-norm is fixed for a given bandwidth \(BW\) and flip angle \(\theta\). In turn, for a fixed norm and pulse duration, the smallest peak amplitude is achieved by a pulse with a constant envelope (i.e., \(f(t) = \text{const}\)), which is accomplished precisely with quadratic phase in the limit of large \(k\). In other words, practical quadratic-phase pulses are almost optimal in terms of minimising the peak RF amplitude for a given pulse duration, bandwidth and flip angle.

### 1.3 Parameter Definitions and Relations

Successful design of quadratic-phase pulses that match the target specifications closely requires trade-offs among the design parameters. The main parameters include the bandwidth

\[
BW = \frac{\omega_s + \omega_p}{2}
\]  

(1.6)

and the fractional transition width

\[
\text{FTW} = \frac{\omega_s - \omega_p}{BW},
\]  

(1.7)

which is a relative expression for the selectivity. \(\omega_s\) and \(\omega_p\) are the stop and pass band frequencies. Further key parameters are the flip angle \(\theta\), the filter length \(n\) and the amount of quadratic phase \(k\).
1.3 Parameter Definitions and Relations

Figure 1.1: Effect of different amounts of quadratic phase $k$ on the magnitude of the RF pulse (Remez pulse with $n = 512$, $\theta = 90^\circ$, $\omega_p = 0.1\pi$ and $\omega_s = 0.11\pi$). The pulse at $k = 0$ corresponds to a regular linear-phase pulse. For increasing $k$ the RF energy is spread out further and further away from the original central main lobe.

Figure 1.2: The square of the $B_1$ amplitude of Fig. 1 times $k$ is plotted against $k$, showing that Eq. [1.18] holds well in a wide range of $k$ values. The dashed line denotes the maximum $B_1$ value, the solid line is the mean value over the bandwidth calculated through Eq. [1.14] and the default value from Eq. [1.17] $\frac{\pi}{16}$ with $\theta = \frac{\pi}{2}$ is plotted with a dash-dotted line.
Equi-ripple Design of Quadratic-Phase RF Pulses

**Figure 1.3:** The pulse design error as a function of the parameter setting (varying $k$, $BW$, $FTW$). The error plotted here is the maximum error ripple, including the ripple in the transition band exceeding the value of the pass band. In series a, b and c, the fractional transition width is held constant ($FTW = 0.1$) and the bandwidth is varied (a: $BW \cdot n = 80.4$, b: $BW \cdot n = 160.8$, c: $BW \cdot n = 241.3$). In the other series 1, 2 and 3, the bandwidth is held constant ($BW \cdot n = 241.3$), while the fractional transition width is varied (1: $FTW = 0.05$, 2: $FTW = 0.1$, 3: $FTW = 0.125$). Each series contains three lines, corresponding to three different filter lengths ($n = 256$, $n = 512$, $n = 1024$). Beyond a critical value of $k \cdot BW^2 \cdot FTW \approx 3.6$ (vertical line), the pulse design error increases sharply due to the emergence of an overshoot in the transition band.

**Figure 1.4:** Unfavourable parameter selection (i.e., too high ($kBW^2 FTW$) product) can lead to high overshoots inside the transition band. As this band is not considered during the fitting procedure, one has to choose a different parameter set. Here: $kBW^2 FTW = 14$. 
The parameter settings lead to certain pulse properties, such as the maximum RF amplitude $B_{1\text{max}}$, the energy of the pulse and the resulting error function, which is defined as the deviation from the target profile. In the following, several relationships among pulse parameters and properties are established as design guidelines.

To clarify the subsequent description, it is important to distinguish between normalised and physical quantities. In FIR filter design, the frequency $\omega$ is usually normalised to the range $[-\pi, \pi]$. The inverse SLR transformation can be used to convert such filters into an RF pulse shape with normalised time, whose duration is equal to the filter length $n$. This pulse can then be scaled to any physical duration, thus rescaling frequency and time to physical units. Throughout this paper, physical frequency and time will be distinguished from their normalised counterparts by the tilde symbol. The quantities in physical units are given by:

\begin{align*}
\tilde{\omega} &= \frac{\omega}{\Delta \tilde{t}}, \\
\tilde{T} &= n \Delta \tilde{t}, \\
\tilde{k} &= k \Delta \tilde{t}^2, \\
\tilde{B}_1 &= \frac{B_1}{\gamma \Delta \tilde{t}},
\end{align*}

where $\Delta \tilde{t}$ denotes the sample spacing, $\tilde{T}$ the total duration of the pulse and $\gamma$ the gyromagnetic ratio. With these relationships it is straightforward to scale an RF pulse to different pulse durations.

### 1.3.1 Time-Bandwidth Product

The physical bandwidth of the RF pulse is given by

$$B\tilde{W} = \frac{BW}{\Delta \tilde{t}}.$$  \hfill (1.12)

With Eq. [1.9] this leads to the time-bandwidth product of the RF pulse

$$\tilde{T} B\tilde{W} = n \, BW,$$  \hfill (1.13)

which is invariant under time and frequency scaling and thus is a key characteristic of an RF pulse. This product is fundamentally limited by digitisation. For quadratic-phase pulses, an estimate of this limitation can be derived from Eqs. [1.2] and [1.4] for moderate flip angles. Ideally, the cutoff values of the rectangular functions in the two domains are related through $\omega = \frac{t}{2\pi}$, leading to

$$BW = \frac{n}{2k}.$$  \hfill (1.14)

As mentioned, when enforcing a good rectangular shape in the frequency domain, the corresponding profile in the time domain will degrade at its edges and extend beyond the idealised pulse duration. In order to still capture the entire pulse, Eq. [1.14] must allow for some slack in the time domain. This results in

$$BW \ll \frac{n}{2k}.$$  \hfill (1.15)

Combined with Eq. [1.13], this yields

$$\tilde{T} B\tilde{W} \ll \frac{n^2}{2k}.$$  \hfill (1.16)

That is, for achieving a high time-bandwidth product with a given $k$ value, $n$ must be sufficiently large. Note that $k$ needs to be large as well in order to justify the series expansion underlying Eq. [1.4] and to reduce $B_{1\text{max}}$, as discussed in the following.
1.3.2 Amount of Quadratic Phase

The amount of quadratic phase $k$ is an important design parameter, which needs to be chosen carefully. The desired effect of the quadratic phase is to distribute the RF energy more evenly across the pulse duration, thus reducing $B_{1\text{max}}$ as illustrated in Fig. 1.1. For small $k$-values, $B_{1\text{max}}$ is not sufficiently reduced. On the other hand, there is also an upper limit for $k$, beyond which errors in the profile increase disproportionately. This limit for $k$ is difficult to assess analytically, yet can be estimated as follows.

In the small-tip-angle approximation, the function $f(t)$ in Eq. (1.2) is equal to the RF field strength $B_1(t)$. For constant $|B_1|$ and sufficiently large $k$, the flip angle $\theta$ in the pass band can be derived from Eq. (1.2) through

$$\theta = |B_1| \sqrt{4\pi k}.$$  

(1.17)

For a constant $\theta$, this leads to the following proportionality:

$$k \propto \frac{1}{B_1^2}.$$  

(1.18)

Thus, $k$ must be large in order to reduce $B_1$ effectively. The product $kB_1^2$ stays approximately constant when varying the amount of quadratic phase, as illustrated in Fig. 1.2.

However, increasing value of $k$ also leads to increased error of the pulse profile, as shown in Fig. 1.3. The error is defined here as the maximum deviation from the target profile. To account for undesired overshoots in the transition bands, values in the transition bands that exceed the target pass band value were rated as errors as well. The error for $k = 0$ (i.e., linear-phase pulses) is related to an empirically derived performance measure given by $(n \ BW \ FTW)$ [7]. The increase of this error when applying quadratic phase can be best understood in connection with Eq. (1.15). When increasing $k$, the envelope in the time domain widens, as shown in Fig. 1.1. As the finite pulse length $n$ remains the same, the beginning and the end of the idealised pulse become more and more truncated, leading to gradually increasing errors. Thus, $k$ is ultimately limited by the pulse length, as previously observed in Eq. (1.15).

Another limitation to the degree of quadracity was found empirically. As shown in Fig. 1.3, the maximum error in the fitted FIR filter grows slowly as a function of $k$ for moderate $k$ values. Yet, beyond some critical degree of quadracity, the error tends to rise sharply. This effect is due to the onset of an overshoot in the transition band, as depicted in Fig. 1.4. As shown in Fig. 1.3, this overshoot tends to occur when the product $kB_1^2 \ FTW$ reaches a certain threshold, suggesting that $k$ should generally fulfil

$$k \lesssim \frac{3.6}{BW^2 \ FTW}.$$  

(1.19)

The critical value of 3.6 is a rough guideline and subject to slight changes depending on the specific parameter configuration. In practice, a more precise maximum value for $k$ is readily found by a few design iterations. The upper bound expressed in Eq. (1.19) tends to be more limiting than that expressed in Eq. (1.15). Generally, for robust quadratic-phase pulse design both inequalities should be fulfilled.

1.3.3 Filter Length $n$

The number of samples $n$ of the RF pulse is not ultimately significant [7], as long as $n$ is large enough for the chosen time-bandwidth product and $k$ value. Above a certain limit, a higher $n$ while retaining the same time-bandwidth product and fractional transition width will only lead to a finer discretisation in the time domain, while leaving the error in the frequency response largely unaffected. On the other hand, insufficient $n$ leads to a violation of Eq. (1.15) and thus an erroneous fit. Furthermore, the rotations represented in the individual segments of the pulse become larger as $n$ decreases. This leads to an increasing violation of the hard pulse approximation, which underlies the SLR transformation. As a result, the actual frequency response of the RF pulse will deviate from the frequency response of the FIR filter. In these respects, choosing a large $n$ is advisable, although excessive filter lengths $n$ should be avoided as they increase computation times and may lead to numerical instabilities.
1.3.4 Energy

In the context of in vivo application another main design restriction is the energy deposited by the RF pulse in the tissue. The energy deposited per unit time is commonly referred to as specific absorption rate (SAR), which is subject to rigid safety regulations. The pulse energy is proportional to the square of the 2-norm of $\tilde{B}_1$ [5], which in turn is proportional to $\tilde{B}W$ and $\theta^2$ in the small-tip-angle regime (Eq. 1.5)

$$Q \propto \int_{-\tilde{T}/2}^{\tilde{T}/2} |\tilde{B}_1(\tilde{t})|^2 d\tilde{t} \propto \tilde{B}W \theta^2.$$  \hspace{1cm} (1.20)

Frequency modulation can be neglected here, as it is far lower than the precession frequency.

For low flip angles, the pulse energy $Q$ depends solely on the flip angle and the bandwidth $B\tilde{W}$ as derived in Eq. (1.20). Thus, pulses with the same bandwidth and flip angle deposit the same energy [5]. In other words, quadratic-phase pulses behave like regular linear-phase pulses in this respect, at least in the small-tip-angle regime.

1.4 Methods

The SLR transformation converts the problem of inverting the Bloch equations into that of designing two complex polynomials $A(z)$ and $B(z)$, which represent regular FIR filters. Hence, it is possible to use the comprehensive methodology of FIR filter design for RF pulse design. $A(z)$ and $B(z)$ are $(n-1)$th order
polynomials that represent the frequency-dependent Cayley-Klein parameters of the rotation effected by the corresponding RF pulse. For instance, the transverse magnetisation created by a pulse from initial z-magnetisation of $M_0$ is given by [7]

$$M_{xy} = 2A(z)^*B(z)M_0,$$

(1.21)

where the asterisk denotes complex conjugation and $z = e^{i\omega}$ is the argument of the polynomials. In the following, “$A(z)$” and “$B(z)$” will be used interchangeably with “$A(\omega)$” and “$B(\omega)$” for notational convenience. Since the Cayley-Klein polynomials represent rotations, they satisfy the following constraint

$$A(z)A^*(z) + B(z)B^*(z) = 1,$$

(1.22)

for all values of $z$, which leads to

$$|M_{xy}(\omega)| = 2\sqrt{1 - |B(\omega)|^2} \cdot |B(\omega)|M_0.$$

(1.23)

Hence, if $|B(\omega)|$ describes a rectangular profile as a function of $\omega$, the excited transverse magnetisation $|M_{xy}(\omega)|$ will also exhibit a rectangular envelope. For the design of low pass pulses, it is thus possible to first design a suitable $B$ polynomial and then generate a matching $A$ polynomial that satisfies Eq. (1.22). Typically, and in the current work as well, the $A$ polynomial is created through the Hilbert transform, leading to a minimum-phase frequency response of $A$, as described in Ref. [7]. When the phase of $A$ is negligible, the phase of $M_{xy}$ will be similar to that of the $B$ polynomial. Therefore, an RF pulse with a quadratic-phase frequency response can be generated on the basis of a $B$ FIR filter with a quadratic phase and a corresponding minimum-phase $A$ polynomial. The relationship between the RF pulse and the $A$ and $B$ polynomials is depicted in Fig. 1.5.

In the following, two methods are described for creating FIR filters with complex coefficients. The first method is least-squares optimisation, which employs a weighting function for obtaining an approximately equi-ripple error function, as previously suggested in Ref. [5]. The second one is the proposed
1.4 Methods

Method, which uses the complex Remez exchange algorithm [8,9] to directly achieve a truly equi-ripple error function without the need for heuristic spectral weighting. This algorithm is a generalisation of the Remez/Parks-McClellan algorithm [29], which permits approximating arbitrary magnitude and phase response functions.

1.4.1 Target Filter Response

The desired frequency response, to which \( B(\omega) \) will be fitted, is expressed as

\[
D(\omega) = R(\omega)e^{i\varphi(\omega)},
\]  

(1.24)

where \( R(\omega) \) and \( \varphi(\omega) \) are real-valued functions, describing the desired magnitude and phase responses, respectively. For a low pass quadratic-phase response, they are expressed as:

\[
R(\omega) = \begin{cases} 
0, & \text{for } |\omega| \geq \omega_s, \\
\sin\left(\frac{\theta}{2}\right), & \text{for } |\omega| \leq \omega_p,
\end{cases}
\]

\[
\varphi(\omega) = k\omega^2,
\]

(1.25)

where \( \theta \) is the desired flip angle and \( \omega_s, \omega_p \) are the pass and stop band frequencies. The gaps between the pass and the stop bands are referred to as the transition bands. The \( \sin(\theta/2) \) originates from the SLR transformation and is derived from Eq. [1.23] by setting \( |M_{xy}| \) to \( (M_0 \sin \theta) \) for \( 0 \leq \theta \leq \pi \). It should be noted, that \( \omega \) is the symmetric and normalised frequency in the range \([-\pi, \pi]\). In the literature, the range of \( \omega \) is frequently defined as \([0, 2\pi]\) with a centre frequency of \( \pi \). This only refers to a shift of reference, and in that case \( \varphi(\omega) \) would include a linear phase term as well. Note also, that it is easily possible to extend this target to an asymmetric function, for instance to obtain one sharper side.

1.4.2 Error Function

The FIR filter to be designed is a polynomial of the form

\[
B(\omega) = \sum_{j=0}^{n-1} b_j e^{-ij\omega},
\]

(1.26)

where \( b_j \) denotes the complex \( j \)th polynomial coefficient. The difference between this filter and the desired response function \( D(\omega) \) is expressed by the error function

\[
E(\omega) = W(\omega) (D(\omega) - B(\omega)),
\]

(1.27)

where \( W(\omega) \) is a real and non-negative weighting function. In the transitions bands, \( W(\omega) \) is generally set to zero.

1.4.3 Least-Squares Fit

As described in [5], a least-squares fit of the target filter response is obtained by minimising the 2-norm of the error function

\[
\|E(\omega)\|_2 = \sqrt{\int_{-\pi}^{\pi} |E(\omega)|^2 d\omega}.
\]

(1.28)

With uniform error weighting this approach leads to overshoots at the band edges. However, the weighting function \( W(\omega) \) can be adjusted to place more emphasis in these areas and thus reduce overshoots. A feasible weighting function for an approximately equi-ripple solution was found to be

\[
W(\omega) = \frac{1}{d(\omega)} \sqrt{1 + 10 \left( \frac{1}{(\omega - \frac{1}{2}(\omega_s + \omega_p))^2 + (\omega + \frac{1}{2}(\omega_s + \omega_p))^2} \right)},
\]

(1.29)
where $\delta(\omega) = \delta_1$ is the relative target ripple of the polynomial in the pass band, $\delta(\omega) = \delta_2$ in the stop band and $\delta(\omega) = \infty$ (i.e., $W(\omega) = 0$) in the transition band.

For numerical treatment, the normalised frequency $\omega$ must be discretised. An equi-distant discretisation of the frequency is given by

$$\omega_l = \Delta \omega \left( l + \frac{1}{2} \right) - \pi ,$$

(1.30)

where $\Delta \omega = 2\pi / m$ denotes the sampling frequency and the index $l$ counts from 0 to $(m - 1)$. The number of sampling points $m$ needs to be much larger than the filter length $n$ for sufficient accuracy.

Using this discretisation, the minimisation problem can be reformulated in terms of matrix notation. The actual and desired filter responses $B$ and $D$, and the error function $E$ are transformed into the vectors $B$, $D$, $E$ by sampling along $\omega_l$. By assembling the polynomial coefficients $b_j$ from Eq. [1.26] in a similar fashion, the actual filter response can be expressed as

$$B = Ub ,$$

(1.31)

where the entries of the $m \times n$ matrix $U$ are given by

$$u_{l,j} = e^{-ij\omega_l} .$$

(1.32)

The weighting function from Eq. [1.29] can be incorporated as an $m \times m$ diagonal matrix $W$, with its diagonal elements given by

$$w_{l,l} = W(\omega_l) .$$

(1.33)

Hence, Eq. [1.27] can be restated as

$$E = W (D - Ub) ,$$

(1.34)

and the optimal coefficient vector $b$ is characterised by a minimum of the 2-norm of $E$. The minimum-norm solution can be calculated with the Moore-Penrose $^\dagger$ pseudo-inverse

$$b = (WU)^\dagger WD .$$

(1.35)

### 1.4.4 Complex Remez for Chebyshev-Norm

In the proposed method, the truly equi-ripple solution is obtained by finding filter coefficients that minimise the Chebyshev (i.e., maximum) error norm

$$\|E(\omega)\|_\infty = \max_{\omega} \{|E(\omega)|\} ,$$

(1.36)

with $E(\omega)$ defined as in Eq. [1.27]. The major advantage of Chebyshev optimisation is that it does not require a particular weighting function for approximating equi-ripple behaviour. It minimises the maximum error, which forces the magnitudes of the error ripples to be the same everywhere. Therefore, the weighting function $W(\omega)$ is now constant everywhere apart from the transition bands, which are exempt from optimisation. Nevertheless, one may also choose to apply different constant weights on the pass and stop bands in order to individually alter the magnitude of the error ripples in the different bands.

Chebyshev optimisation of FIR filters with complex coefficients can be accomplished with the complex Remez exchange algorithm. For a detailed description of the algorithm, the reader is referred to Refs. [8, 9]. Briefly, to minimise the Chebyshev norm efficiently, the main strategy is to sample $E(\omega)$ only at a sparse, finite subset $S$ of frequencies and iteratively adapt these frequencies such that they sample the extreme values of the error ripples. This basic approach consists of two steps, which are depicted on the right in Fig. [1.6]. In a first step, the best approximation in terms of $\|E_S(\omega)\|_\infty$ (Eq. [1.36]) on the sparse subset is calculated. In a second step, this subset is altered such that the maximum error norm $\|E_S(\omega)\|_\infty$ of this subset increases. The optimal solution is found iteratively repeating both steps until the subsets remain the same.

The complex Remez algorithm (Fig. [1.6], top left) performs these steps with subsets of $n + 1$ points, where $n$ is the filter length. In this case, the minimisation problem on each subset reduces to a linear system of equations, which can be solved very efficiently. The optimal solution is found when the
error norm on the subset, $\|E_T(\omega)\|_\infty$, converges toward the actual error norm on the continuous set, $\|E(\omega)\|_\infty$. This is generally the case for parameter sets that comply with the relations described in Sect. 1.3. For the case of non-convergence of the complex Remez algorithm, a more advanced method was described in [9]. This method, a generalised multiple-exchange ascent algorithm, forms the optional second stage of the optimisation procedure (Fig. 1.6 bottom left). It performs the same steps as described above, yet samples the error function more densely and uses a more intricate method for subset iteration. Using the result of the first stage as an initial estimate, the second stage converges safely, yet at the expense of drastically increased computation time. However, it was found empirically that the second algorithm needs to be invoked only in cases with unfavourable parameter relations. In these cases, even the optimal solution must typically be discarded due to high error levels. For the present work, the complex Remez and multiple-exchange ascent algorithms were performed under MATLAB (The MathWorks, Inc., Natick, MA, USA), using an implementation available in the signal processing toolbox.

1.4.5 Validation Study

To validate the proposed methods, an exemplary RF pulse was designed with a time-bandwidth product of 330 (in radians), a fractional transition width of 0.073, a flip angle of $\theta = 90^\circ$, $k = 120$, and $n = 512$ samples. For comparison, two pulses with the same specifications were additionally designed using the least-squares approach with either the weighting function given by Eq. 1.29 or constant weights.

The excitation profiles of these pulses were verified by numerical integration of the Bloch equations employing a fourth-order Runge-Kutta method [31]. Additionally, the pulses were verified experimentally on a Philips 1.5 T Intera whole-body MR scanner equipped with a transmit/receive birdcage resonator (Philips Medical Systems, Best, The Netherlands). Both excitation and saturation capabilities were shown on a phantom containing one litre of doped water solution ($T_1 = 360$ ms; $T_2 = 320$ ms). Furthermore, the saturation of magnetisation was demonstrated in vivo in an axial section through the human brain. Written informed consent was obtained from the healthy volunteer prior to imaging.

All experiments were based on regular spin echo imaging sequences. In the excitation experiments, the quadratic-phase RF pulse was used for $90^\circ$ excitation, with a selection gradient in the same direction as the readout gradient. The $180^\circ$ refocusing pulse was then used to select the image plane ($T_E = 40$ ms, $T_R = 800$ ms). In the saturation experiments, the quadratic-phase pulse was used for exciting the magnetisation, again in a perpendicular slice, followed by spoiler gradients and the full spin-echo sequence with normal slice selection ($T_E = 30$ ms, $T_R = 800$ ms).

1.5 Results

The amplitude and frequency modulation of the exemplary pulse (see Sect. 1.4.5) is shown in Fig. 1.7. For a duration of $\bar{T} = 5$ ms it has a maximum RF field strength of $\bar{B}_{1\text{max}} = 20\mu$T. For comparison, the maximum RF field strength of a linear-phase pulse with the same specifications is more than three-fold at $\bar{B}_{1\text{max}} = 68\mu$T. The complex Remez design is compared to the alternative design methods in Fig. 1.8. The upper row shows the magnitude of the deviation between the desired and the achieved profiles designed with the complex Remez, weighted least-squares and plain least-squares algorithms. These results illustrate that direct Chebyshev optimisation yields an exact equi-ripple error function, while some variation in the error level is obtained with either weighted or plain least-squares. From the $A$ and $B$ polynomials, the transverse magnetisation was calculated through $M_{xy} = 2A^*BM_0$ and the longitudinal magnetisation through $M_z = (\bar{A}A^* - BB^*)M_0$ [7], setting $M_0$ to one. In the middle and lower row of Fig. 1.8 the deviation of $M_{xy}$ and $M_z$ from their ideal profiles are plotted for the complex Remez, weighted least-squares and plain least-squares methods. The error level in $M_{xy}$ and $M_z$ is different between pass and stop bands, reflecting the non-linear relationship between $B(\omega)$ and the components of the magnetisation. This effect can be readily compensated for by appropriate weights applied to the pass and stop bands [7], as shown in Fig. 1.9.

In case of the complex Remez, the transverse magnetisation has a truly equi-ripple error function in the stop band. However, in the pass band, the error shows some modulation, falling below the equi-ripple level in small intervals. This is due to the fact that $M_z$ and $|M_{xy}|$ depend only on the modulus.
of $B(\omega)$ (see Eq. [1.23]). As a consequence, only errors that are in phase with $B(\omega)$ do actually propagate into $M_z$ and $|M_{xy}|$. Out-of-phase errors get masked, causing said incisions in the error plots. The same also applies to the least-squares methods, which additionally show variation in the error envelope. In case of weighted least-squares these variations have been found to significantly depend on the chosen parameter settings, making it difficult to choose an optimal weighting function a priori. The plain least-squares fitting procedure with constant weighting is generally unfavourable as errors increase significantly near the transition band.

The effect of scaling $\tilde{B}_1$ to different flip angles is depicted in Fig. 1.10 for both transverse and longitudinal magnetisation. By rescaling the applied RF field, the bandwidth remains unchanged, but the profile deteriorates. Hence, for each target flip angle a specific RF pulse should be designed rather than rescaling an existing pulse.

The results of the experimental validation study are shown in Figs. 1.11 and 1.12. Fig. 1.11 shows the \textit{in vitro} experiments on the phantom, for both excitation and saturation. Note the quadratic phase of the magnetisation, which is only slightly distorted by the minimum-phase $A(z)$ polynomial. When used for selective saturation, the designed pulse leaves only little magnetisation remaining. Fig. 1.12 demonstrates the selective saturation \textit{in vivo} in the brain of a healthy human.

The complex Remez algorithm is relatively fast for properly chosen parameters. For instance, designing the RF pulse shown in Fig. 1.7 required 10 seconds on a current CPU (Intel Pentium 4, 2.53 GHz), running MATLAB 6.5 R13 (without JAVA) under a Linux operating system. The algorithm converged in the first stage after 18 iterations. While conceptually simpler than the complex Remez approach, the least-squares algorithm has not proven to be significantly faster than the latter. The main reason for this is the fine discretisation required for sufficient accuracy.

High time-bandwidth products rely on large filter lengths $n$ and are thus practically limited by computing power. A time-bandwidth product in the range of 1000 (in radians) and above has been found to be readily feasible with current equipment. However, the application of such pulses \textit{in vivo} may be restricted due to excessive power deposition.
Figure 1.8: Comparison of FIR filter design with least-squares (left), weighted-least-squares (middle), and complex Remez (right), based on the pulse specifications given in Fig. 1.7. The top row shows the error in the FIR filter response $|B(\omega) - D(\omega)|$. The structure of the error ripples is illustrated in the magnified insets. The two major peaks in each plot correspond to the transition bands and do not represent actual errors. Only the complex Remez algorithm yields error ripples of constant magnitude throughout the pass and stop bands. The middle and bottom rows show the resulting error in the transverse and longitudinal magnetisation, respectively. For the magnetisation the error levels differ between the pass and stop bands, reflecting the non-linear relationship between $B(\omega)$ and the components of the magnetisation (Eq. 1.23).
Figure 1.9: Error in the transverse (|M_{xy}| - |M_{xy}^{\text{ideal}}|); left) and longitudinal (|M_z - M_z^{\text{ideal}}|; right) magnetisations, obtained with a quadratic-phase complex Remez pulse. The pulse specifications were the same as for Figs. 1.7 and 1.8. However, different error weighting was applied in the pass and stop bands to match the ripple magnitude in all three bands. For equi-ripple transverse magnetisation (left), the weight on the stop bands was exaggerated 140-fold. For equi-ripple longitudinal magnetisation (right), the weight on the pass band was exaggerated 300-fold.

Figure 1.10: Pulse profiles of quadratic-phase pulses generally deteriorate as $\tilde{B}_1$ is simply scaled to different flip angles. 0% denotes the original $\tilde{B}_1$ for a flip angle of 90°. Scaling the RF field by the indicated percentage alters the pulse profile as shown. For high profile quality, quadratic-phase pulses must be designed specifically for the target flip angle.
1.6 Discussion and Conclusion

In this work, we propose the use of the complex Remez algorithm for determining the complex filter coefficients in SLR design of quadratic-phase RF pulses. Although it is possible to obtain qualitatively similar results with the weighted least-squares approach, the key advantage of the Remez method is that it is straightforward to apply. Since it directly minimises the Chebyshev error norm, it obviates the need for a heuristic weighting function and directly achieves solutions with truly equi-ripple error function. While this work has focused on quadratic-phase low pass pulses, the general design method is applicable to pulses with arbitrary magnitude and phase response functions. Nevertheless, with any desired response function, it has been found that solutions with acceptable errors generally require proper choices of the design parameters.

This work also illustrates the specific benefits of quadratic phase modulation in a semi-analytic fashion (Sect. 1.2) and suggests parameter relations that may serve as guidelines for the design of these pulses (Sect. 1.3). In particular, a critical maximum value for the amount of quadratic phase $k$ was obtained empirically. This limit and several further rules need to be observed in order to achieve markedly reduced $B_{1\text{max}}$ without significant sacrifice in profile quality. It has been observed that for parameters
chosen within the suggested limits, the resulting error level will be similar to the error of the correspond-
ing linear-phase pulse.

The profile quality of the quadratic-phase Remez pulses has been demonstrated by simulations and
experiments. In vivo application has confirmed the usefulness of such pulses for a highly selective sup-
pression of magnetisation and in vitro experiments have illustrated their applicability for both excitation
and saturation. Nevertheless, in Fig. 1.11 some residual signal is still observed in the saturated band.
The main reasons for the residual signal are noise and $T_1$ relaxation. The latter effect could be addressed
by adjusting the flip angle for a given $T_1$ value. Some further deviation from perfect suppression may
arise from slight mismatches between the analytical pulse description and the actual execution of the
amplitude and frequency modulations by the MR system.

Numerous applications may benefit from the quadratic-phase pulses, which exhibit large bandwidth
and high selectivity. Reduced field-of-view imaging and non-echo volume selection in spectroscopy
are two applications already mentioned. Another prime application is the inversion of magnetisation.
Currently, this task is often performed with adiabatic pulses. However, two factors favour the use of
specifically designed quadratic phase pulses: for given time and $B_{1\text{max}}$ restrictions better profiles can be
achieved and the pulse energy will generally be lower than for adiabatic pulses. Such pulses will find
use in many inversion-prepared sequences, in particular arterial spin labelling, where high selectivity is
crucial.

While less intuitive, quadratic phase RF pulses may indeed also be used for selective excitation,
e.g., in 3D imaging [32, 33]. Here, the additional phase encoding and Fourier reconstruction along the
selection direction can make the quadratic phase variation negligible at the voxel scale. For common 2D
imaging, quadratic phase modulation across a selected slice is usually a problem because it cannot be
unwound with linear external gradients. Alternatively, phase compensation can be done by consecutive
pulses with quadratic phase, where each pulse cancels the phase of the previous one [34]. Another
way is to combine multiple pulse segments into a composite pulse [35], as originally done to create an
adiabatic spin-echo pulse [36]. The downsides of these approaches are higher power deposition and
longer pulse duration.

Finally, non-linear through-plane modulation may as well be exploited as a beneficial effect. Ex-
amples for such applications are spatial encoding by quadratic phase [37] and various methods for
compensating $B_0$ inhomogeneity by quadratic- and tailored-phase RF pulses [38, 39, 40]. Requiring RF
pulses with specific target phase responses, these methods will benefit from the flexibility and accuracy
of complex Remez design.

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1.7 SLR Design of Broad Bandwidth RF Pulses using Higher Order Phase Functions

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Abstract

The achievable bandwidth of RF pulses is limited by the maximum feasible $B_1$ amplitude of the system. For reducing the $B_{1\text{max}}$ requirements of pulses, quadratic phase envelopes can be argued to be near-optimal. In this work, it is demonstrated that further $B_{1\text{max}}$ reduction and hence higher bandwidths can be achieved by combining quadratic phase with higher order phase functions. Exemplary RF pulses with up to tenth order phase functions were designed using the Shinnar-Le Roux transform, yielding $B_{1\text{max}}$ reductions by up to 71% with respect to linear-phase design.

Introduction

Radio-frequency (RF) pulses with high bandwidth are often required in MRI/MRS applications. However, the achieved bandwidth is limited by the $B_{1\text{max}}$ of the system. For reducing the $B_{1\text{max}}$ requirements of high bandwidth pulses, quadratic (i.e., 2nd order) phase envelopes can be argued to be near-optimal [41]. In this work we show that further reduction of $B_{1\text{max}}$ and hence increased bandwidth is still possible by combining second- with higher even-order phase functions.

<table>
<thead>
<tr>
<th>Order</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>linear</td>
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</tr>
<tr>
<td>2nd</td>
<td>36%</td>
</tr>
<tr>
<td>2nd + 4th</td>
<td>33%</td>
</tr>
<tr>
<td>2nd + 6th</td>
<td>32%</td>
</tr>
<tr>
<td>2nd + 8th</td>
<td>29%</td>
</tr>
<tr>
<td>2nd + 10th</td>
<td>31%</td>
</tr>
</tbody>
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Table 1.1: Different reductions achieved by higher order phase functions.
1.7 Higher Order Phase Functions

Figure 1.14: Error in the longitudinal magnetisation ($M_L$) plotted on logarithmic scale for linear (left), 2nd order (middle) and the optimal combination of 2nd and 8th order phase functions.

Figure 1.15: Map of $B_{1\text{max}}$ (colour axis) for different amount of 2nd ($k_2$; x-axis) and 8th ($k_8$; y-axis) order phases. Due to symmetry, only positive $k_2$ are shown. The blue outer region is excluded because of excessive fitting errors (>0.5). The minimal $B_{1\text{max}}$ with acceptable error (0.0025) is marked with a cross and was selected.

Figure 1.16: Profile of exemplary 2nd + 8th order phase pulse used for suppression. The yellow line shows a numerical integration of the Bloch equation, whereas the red line and the image depict the measurement of a phantom on a Philips Intera 1.5T using a spin echo sequence.
Methods

RF pulses are obtained from finite impulse response (FIR) filters through the Shinnar-Le Roux transformation \[22\]. FIR filters that minimise the Chebyshev (i.e., maximum) error norm are generated with the complex Remez exchange algorithm \[41, 8\]. The fitting target for these FIR filters is specified by

\[
D(\omega) = R(\omega)e^{i\varphi(\omega)},
\]

(1.37)

\[
R(\omega) = \begin{cases} 
0, & \text{for } |\omega| \geq \omega_s, \\
\sin\left(\frac{\theta}{2}\right), & \text{for } |\omega| \leq \omega_p,
\end{cases}
\]

(1.38)

\[
\varphi(\omega) = \sum_\alpha k_\alpha \omega^\alpha,
\]

(1.39)

where \(-\pi \leq \omega \leq \pi\) is the normalised frequency, \(\omega_s\) and \(\omega_p\) are the stop and pass band frequencies, \(k_\alpha\) a scaling constant and \(\alpha\) the order of the phase function. All pulses shown here have a time-bandwidth product of 180° (in radians), a fractional transition width of 0.1 and a flip angle of 90°. For 256 samples, this translates into \(\omega_s = 0.315\) and \(\omega_p = 0.385\). In this work, integer-valued orders of up to ten were investigated. For finding the minimal \(B_{1\text{max}}\), quadratic-phase functions were systematically combined with higher orders. As shown in Fig. 1.15, the optimal \(k_\alpha\) was determined by iterating through different phase functions. The selection criterion for the optimal pulses was a minimal \(B_{1\text{max}}\) with a fitting error below 0.0025 (instead of 0.0015 for the linear phase pulse).

Results

Different order phases can be combined to further reduce \(B_{1\text{max}}\) beyond the reduction achieved with a pure quadratic phase. As in the case for quadratic phase \[41\], the design parameters for these higher-order phase pulses are subject to certain restrictions, so not all parameter specifications result in acceptable pulses with a lower fitting error. The best combination was found to be 2\textsuperscript{nd} and 8\textsuperscript{th} order phases \((k_2 = 189.8, k_8 = -18586)\). Odd-order phase functions are generally not capable of reducing \(B_{1\text{max}}\) significantly, since they are purely amplitude modulated with asymmetric pulse shapes. Various pulses are shown in Fig. 1.13. For a pulse duration of 5 ms, \(B_{1\text{max}}\) was reduced by 71% from 37.3 \(\mu\)T (linear phase) to 10.8 \(\mu\)T (2\textsuperscript{nd} + 8\textsuperscript{th} order phase). The error in \(M_z\) did not increase significantly, as depicted in Fig. 1.14. Figure 1.16 shows the experimental verification of the pulse.

Discussion and Conclusion

The 2\textsuperscript{nd} order phase is near optimal if the desired selection profile is smooth with a sufficient amount of quadratic phase. In practise, both conditions are somewhat violated. As a result, \(B_{1\text{max}}\) can be further reduced by combining the 2\textsuperscript{nd} order phase with higher even-order phase functions. The optimal choices for \(k_\alpha\) could be found more efficiently by non-linear optimisation instead of an exhaustive search, since the parameter landscape (Fig. 1.15) is relatively smooth.
1.8 Appendix: SLR Transformation

The Shinnar-Le Roux (SLR) transformation converts the problem of inverting the Bloch equations into that of designing two complex polynomials, which can be tackled by standard FIR filter methods. The different domains and their interdependencies are depicted in Fig. 1.5. Following is a brief overview of the method described in [7].

The first step in the forward SLR transformation is to describe an RF pulse as a series of piecewise constant segments. The whole transformation can be made arbitrarily accurate by increasing the number of subdivisions. The effect of every segment on the spins can then be described in the spinor notation by a $2 \times 2$ unitary rotation matrix $Q_j$. The effect of applying successive segments of the pulse can be represented by the matrix product

$$Q = Q_n Q_{n-1} \ldots Q_1,$$

which corresponds to the net rotation of $n$ sub-pulses. The key step of the SLR algorithm is the hard-pulse approximation in which every single rotation matrix is split up into two distinct rotations: the nutation about an axis inside the $xy$-plane induced by the RF pulse and the free precession about the $z$-axis. Translated into rotational states of spins, the forward recursion is given by

$$
\begin{pmatrix}
A_j(z) \\
B_j(z)
\end{pmatrix}
= 
\begin{pmatrix}
C_j & -S_j^z \\
S_j & C_j
\end{pmatrix}
\begin{pmatrix}
1 & 0 \\
0 & z^{-1}
\end{pmatrix}
\begin{pmatrix}
A_{j-1}(z) \\
B_{j-1}(z)
\end{pmatrix}
$$

with the initial condition being no rotation

$$A_0 = 1, \\
B_0 = 0.$$

In Eq. (1.41), $C_j$ and $S_j$ describe the rotation due to the RF pulse and $z$ the free precession under a

---

\[3\] This section is not part of the original publication.
gradient $G$ along the spatial direction $x$

\[
C_j = \cos \left( \gamma \left| \mathcal{B}_{1,j} \right| \Delta \tilde{t} \right),
\]

\[
S_j = i e^{i \mathcal{B}_{1,j}} \sin \left( \gamma \left| \mathcal{B}_{1,j} \right| \Delta \tilde{t} \right),
\]

\[
z = e^{i G x \Delta \tilde{t}} = e^{i \omega}.
\]

In this equation, $\gamma$ is the gyromagnetic ratio, $\mathcal{B}_{1,j}$ the radiofrequency pulse in one time step $\Delta \tilde{t}$. The normalised frequency $-\pi \leq \omega \leq \pi$ is unitless and corresponds to the spatially dependent off-resonance frequency. $A_j$ and $B_j$ are polynomials at the $j$th step of the RF pulse

\[
A_j(z) = \sum_{k=0}^{j-1} a_{j,k} z^{-k},
\]

\[
B_j(z) = \sum_{k=0}^{j-1} b_{j,k} z^{-k}.
\]

It should be noted that the incremental precession $z(x)$ varies with the spatial position $x$ (Eq. 1.43). Therefore, the polynomials $A_j(z)$ and $B_j(z)$ provide a complete description of the rotation at all positions along $x$. The final polynomials for a pulse of length $n$ are equal to the Cayley-Klein parameters $\alpha$ and $\beta$ with the reference shifted to the middle of the pulse

\[
A_n(z) = z^{n/2} \alpha_n(x),
\]

\[
B_n(z) = z^{n/2} \beta_n(x),
\]

with

\[
\alpha(x) = \cos \left( \frac{\phi(x)}{2} - i n_x(x) \sin \frac{\phi(x)}{2} \right),
\]

\[
\beta(x) = -i (n_y(x) + i n_y(x)) \sin \frac{\phi(x)}{2}.
\]

In this equation, $\alpha(x)$ and $\beta(x)$ represent the net rotations of the entire RF pulse and they are spatially dependent. $\phi(x)$ is the rotation angle and $\tilde{n}(x)$ the rotation axis. This leads to the rotation matrix $Q$

\[
Q = \begin{pmatrix}
\alpha^* & -\beta^*
\end{pmatrix}.
\]

Since $Q$ represents a rotation, the determinant is equal to 1

\[
\alpha \alpha^* + \beta \beta^* = 1.
\]

From these rotations it is possible to calculate the magnetisation by

\[
\begin{pmatrix}
M^+_{xy} \\
M^+_{yz} \\
M^+_{xz}
\end{pmatrix} = \gamma \begin{pmatrix}
(\alpha^*)^2 & -\beta^2 & 2 \alpha^* \beta \\
-\beta^2 & \alpha^2 & 2 \alpha \beta^* \\
-\alpha^* \beta^* & -\alpha \beta & \alpha \alpha^* - \beta \beta^*
\end{pmatrix} \begin{pmatrix}
M^-_{xy} \\
M^-_{yz} \\
M^-_{xz}
\end{pmatrix},
\]

where $M^+_{xy} = M^+_{x} + i M^+_{y}$ denotes the magnetisation afterwards and $M^-_{xy}$ beforehand. All the preceding steps represent the forward SLR transformation. For design purposes, it is necessary to transform the polynomials into RF pulses, the so-called inverse SLR transformation. The core step is the inverse recursion, which is derived in a similar fashion as in Eq. 1.41 by inverting the unitary rotation matrix (i.e., the matrix containing $C_j$ and $S_j$)

\[
\begin{pmatrix}
A_{j-1} \\
B_{j-1}
\end{pmatrix} = \begin{pmatrix}
C_j & S_j^t \\
-S_j z & C_j z
\end{pmatrix} \begin{pmatrix}
A_j \\
B_j
\end{pmatrix}
\]

\[
= \begin{pmatrix}
C_j A_j + S_j^t B_j \\
z(-S_j A_j + C_j B_j)
\end{pmatrix}.
\]

In this matrix multiplication, the low order coefficients of the term must drop out, since $B_{j-1}$ is a lower order polynomial. Hence, the RF pulse segment can be calculated by

\[
\frac{b_{j,0}}{a_{j,0}} = \frac{S_j}{C_j} = e^{i \mathcal{B}_{1,j}} \tan \left( \gamma \left| \mathcal{B}_{1,j} \right| \Delta \tilde{t} \right).
\]

This inverse recursion repeats to decompose the entire polynomials into a series of pulse segments. Hence the polynomials $A_0$ and $B_0$ provide a complete and reversible description of any RF pulse. Both the forward and inverse recursion process is depicted in Fig. 1.17.
Chapter 2

Chemical-Shift-Selective Filter for the In Vivo Detection of $J$-Coupled Metabolites at 3T

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Abstract

A chemical-shift-selective filter (CSSF) was applied to the detection of \( J \)-coupled metabolites in the human brain. This filter is an acquisition-based technique that requires the chemical shifts (CS’s) of different metabolites, but not their whole multiplet structures, to be resolved. The sequence is based on the 2D constant-time spin-echo experiment, which yields pure CS spectra in the indirect dimension. Localisation is achieved through point-resolved spectroscopy (PRESS). The method enables unequivocal detection of glutamate and \textit{myo}-inositol, both \textit{in vitro} and \textit{in vivo} in the human brain, at 3T.

\textbf{Keywords:} chemical-shift-selective filter; CSSF; 2D \( J \)-resolved spectroscopy; constant-time experiments; CT-PRESS.

2.1 Introduction

The challenges of \textit{in vivo} proton magnetic resonance spectroscopy (\( ^{1} \)H MRS), particularly in brain tissue, include low sensitivity and heavy overlapping of resonance lines caused by a small chemical shift (CS) range together with broad lines. The splitting of resonance lines into often complex multiplet structures further complicates the interpretation of spectra. The extraction of quantitative information about one specific metabolite from \textit{in vivo} brain spectra is therefore generally difficult and typically requires sophisticated fitting procedures [17, 42]. However, this approach is often not sufficient to reliably quantify low-concentration metabolites covered by other stronger signals. Therefore, many studies restrict themselves to the observation of the predominant singlets of N-acetyl aspartate (NAA), total creatine (Cre) and choline-containing compounds (Cho), while a vast amount of information about other metabolites contained in the spectrum is discarded. These “hidden” signals arise, for instance, from neurotransmitters such as \( \gamma \)-aminobutyric acid (GABA) and glutamate (Glu), or substances whose function is not yet well understood (e.g., \textit{myo}-inositol (mI) or taurine) [1]. They contain invaluable information about the normo- and pathophysiological state of the brain.

A complementary approach to information extraction through fitting procedures is the use of acquisition-based methods. The purpose of these methods is to simplify the appearance of overloaded spectra and thus make them more accessible to post-acquisition data analysis. This simplification can be achieved in two ways. One approach is to reduce the information content of spectra through spectral editing techniques, such as multiple-quantum-coherence (MQC) filtering and difference editing [43, 3]. Ideally, edited spectra contain exclusively the lines of interest, whereas unwanted signal is suppressed. However, these techniques have not found widespread application in clinical research, mainly because of tedious optimisation, difficult handling, inherent signal loss and/or sensitivity to experimental conditions.

The second approach is based on spreading the signal information into multiple spectral dimensions. Two-dimensional (2D) acquisition schemes can be extraordinarily simple, as in case of \( J \)-resolved spectroscopy or correlation spectroscopy (COSY) [43, 10]. Techniques that rearrange the information contained in the 1D spectrum are potentially more interesting for \textit{in vivo} MRS than methods that provide additional information, such as connectivities. In general, multi-dimensional spectroscopy is more universal than filtering techniques. The most prominent example of methods that separate interactions into two dimensions is \( J \)-resolved spectroscopy [43]. The combination with spatial localisation is straightforward. In the pioneering work by Ryner et al. [14], the pulse sequence is identical to point-resolved spectroscopy (PRESS) [4] and therefore is equally robust and efficient. This method was consequently dubbed J-PRESS. Recent applications focused mainly on the detection of glutamate [44, 45] and GABA [46]. In general, encoding spectral information into multiple dimensions leads to a longer experiment duration. However, in the case of low-concentrated metabolites, the time required for signal averaging can be efficiently used to encode a second dimension.

Dreher and Leibfritz [47] combined J-PRESS with a constant-time element and named the sequence CT-PRESS. The acquisition always starts at the same constant time after excitation; therefore, the \( J \) evolution depends only on the time the acquisition begins. The experiment can thus be tuned such that the metabolites of interest show mainly in-phase signal, leading to a considerable gain in SNR [48]. Applications include the detection of various metabolites in rat brain [47] and glutamate in the human brain [49].
Figure 2.1: CT-PRESS spectrum of a phantom containing 100-mM GABA solution. Nicely visible are the alignment of resonances on the diagonal (blue throughout line), and the splitting up into multiplets in the $f_2$ dimension. The red dashed line ($f_1 = 2.35$ ppm) depicts the cross-section, which is equivalent to a CSSF spectrum.

An experiment closely related to CT-PRESS is the chemical-shift-selective filter (CSSF) [12, 13]. This filter is a constant-time experiment in which different time increments are summed up and then Fourier transformed. A CSSF spectrum therefore corresponds to a cross-section through the 2D CT-PRESS spectrum. CSSF requires only the CS’s of different metabolites, not their whole multiplet structures, to be resolved from each other. This offers a significant advantage, since multiplet structures are broad and often overlap with other resonances. Originally, CSSF was implemented by Hall and Norwood [12, 13] on an NMR spectrometer in a basic spin-echo sequence without volume localisation. In this work, we present the application of PRESS-localised CSSF [50] to the *in vivo* detection of coupled resonances, specifically glutamate and myo-inositol.

2.2 Theory

The basic acquisition scheme for CSSF [12, 13] is a spin-echo sequence with varying echo times (TEs). In principle, this is the same as a 2D $J$-resolved constant-time experiment. In this work, the 2D view is used to illustrate the underlying principles. Different CS evolution times are encoded in the indirect $t_1$ dimension, whereas echoes are acquired in the direct $t_2$ dimension.

The evolution of weakly coupled spin systems can be split into a $J$ part and a CS part. A $180^\circ$ echo pulse refocuses only the CS evolution and does not alter the $J$ evolution. When the acquisitions of different spin echoes are started at the same time, the $J$ evolution will always be identical, but the CS evolution will differ. This leads to a cancellation of the $J$ evolution upon Fourier transform along $t_1$. Therefore, the resonances appear at the pure CS positions in $f_1$. The $t_2$ domain still contains both $J$ and CS evolution. A 2D Fourier transform yields a 2D spectrum with its resonances aligned on the diagonal and split into multiplets in the $f_2$ direction, as shown in Fig. 2.1 for a typical spectrum of GABA. The projections onto the $f_2$ and $f_1$ axes correspond to the conventional and a broadband decoupled PRESS spectrum, respectively (Fig. 2.2). The elimination of the $J$ evolution in $t_1$ holds strictly only in the weak
Figure 2.2: Projections of the CT-PRESS spectrum as shown in Fig. 2.1 onto $f_2$ (left) and $f_1$ (right) axes, respectively. The projection onto the $f_2$ axis corresponds to a regular PRESS spectrum, whereas the projection onto the $f_1$ axis corresponds to a decoupled PRESS spectrum. The linewidth of the decoupled spectrum is fairly broad because of the strong filtering required in the $f_1$ direction to remove truncation artefacts. Both spectra are displayed in complex mode.

Figure 2.3: A strong coupling effect is demonstrated on the aspartate moiety of NAA. This part forms an ABX spin system resonating at 2.49 (A), 2.67 (B) and 4.38 ppm (X). Clearly visible is an additional set of resonances located at the mean CS along $f_1$ (i.e. 2.58 ppm). Also visible is the tail originating from the strong singlet peak at 2.01 ppm.
Figure 2.4: CSSF spectrum of the 2.31 ppm GABA triplet. This spectrum corresponds to a cross-section through the CT-PRESS spectrum (Fig. 2.1) with a constant $f_1$ frequency.

coupling limit. Strongly coupled spin systems show a spurious response at the mean CS frequency [43, 48]. In the 2D $J$-resolved constant-time experiment, this leads to additional resonances along the $f_1$ direction, as depicted for the strongly coupled aspartate group of NAA in Fig. 2.3.

The CSSF spectrum is equivalent to a cross-section through the 2D spectrum along a constant $f_1$ frequency. One CSSF spectrum consists of a multiplet from a single chemical-shift frequency (Fig. 2.4). All other frequencies are filtered out (hence the term “chemical-shift-selective filter”). Coupled resonances must be resolved only by their difference in CS, and not by their whole multiplet structure. In the original CSSF implementation [12, 13], the authors set up the experiment for one specific CS frequency and added the FIDs directly. This saves memory space, which was precious during the time of that study (1988). However, a more flexible method is to store the whole 2D FID and process it subsequently. One can reconstruct different CS frequencies by shifting the frequency along $f_1$, hence selecting different cross-sections of the 2D spectrum. A frequency shift corresponds to a modulation in the time domain.

This means that before adding up the rows of the 2D FID, one has to select the desired CS frequency by multiplying the rows of the FID with the appropriate exponential kernel. The process is equivalent to a Fourier transformation along $f_1$ at a certain frequency, and we refer to it as reconstructing a CSSF spectrum to one specific CS frequency.

The 2D line-shapes in $J$-resolved constant-time experiments are phase-twisted, i.e., they are asymmetric with partial signal cancellation [43]. 2D spectra are conveniently displayed in magnitude mode, despite the unfavourable long dispersion tails of the peaks. However, this undesired line-shape complicates only the 2D spectrum. The CSSF spectra can still be properly phased and displayed in complex mode, which is a considerable advantage of this technique over a direct quantification of the 2D spectrum, i.e., taking the integral underneath the magnitude peak.
Figure 2.5: Basic PRESS sequence used for this 2D experiment. All RF pulses are used for spatial localisation. The first echo time, $T_E_1$, is always set to the same minimal possible duration. The last pulse is shifted to varying TEs ($T_E = T_E_1 + T_E_2$), with $T_E_2$ denoting the varying second echo time. This is used to encode the indirect $t_1$ dimension with $t_1 = T_E - T_{ct}$. The time $T_{ct}$ is constant and denotes the reference of the Fourier transform. In the direct $t_2$ dimension the sampling time is given by $t_2 = t_{acq} + T_{ct} - T_{as}$. The acquisition starts at $T_{as} = (T_E + T_{E_{min}})/2$ directly after the last crusher gradient. The data are reconstructed to a constant-time experiment during post-processing by shifting the times by $T_{ct} - T_{as}$.

Figure 2.6: The original (above) and reconstructed constant-time FIDs (below). The latter FID is required for CSSF and was obtained by time shifting the rows to the same constant acquisition beginning.
2.3 Materials and Methods

All experiments were performed on a Philips Intera 3.0 T whole-body scanner equipped with a transmit/receive birdcage head coil. The number of samples along $t_2$ was 2048 with a bandwidth of $f_{S2} = 2$ kHz. Echo times ranged from 31 ms to 229 ms in steps of $\Delta T_E = 2$ ms, leading to a total of 100 acquisitions and a bandwidth of $f_{S1} = 500$ Hz. A four-step phase cycle was applied for eliminating experimental imperfections. With a repetition time of $TR = 2$ s, this results in a total experimental duration of 13 minutes. Second-order shimming based on $B_0$ field maps [51] was applied, and water suppressed using CHESS [52].

Spatial localisation is achieved through PRESS [4], as depicted in Fig. 2.5. The first echo time, $T_{E1}$, is always minimal and the indirect dimension is encoded by shifting the second 180° pulse, thus varying the second echo time $T_{E2}$. The maximal information is acquired by starting the sampling of the echoes immediately after the last crusher gradient (Fig. 2.5). The obtained data set can be subsequently reconstructed in different ways, such as JPRESS or, as shown in this work, CSSF.

It is necessary to shift the rows of the FID to the same constant acquisition time, $T_{ct}$, by post-processing to obtain a constant-time FID required for CSSF (Fig. 2.6). This shift in $t_2$ is conveniently done in the frequency domain by multiplying a linear phase. This retains complete flexibility in the choice of the dwell time in $t_2$ and $\Delta T_E$ in $t_1$. The bandwidth $f_{S1} = 1/\Delta T_E$ must be sufficiently large for minimising foldover artefacts of peaks, and particularly their long tails. Here, a sampling frequency of $f_{S1} = 500$ Hz (i.e., $\Delta T_E = 2$ ms) was chosen, adapted to the spectral dispersion at $B_0 = 3$ T. A Lorentz-to-Gauss transformation was applied ($t_2$ domain: exp.: -3 Hz, gauss.: 4 Hz; $t_1$ domain: exp.: -1 Hz, gauss.: 0.8 Hz). All post-processing was performed in MATLAB (The MathWorks, Inc.) with in-house written code.

The $T_E$s are arranged symmetrically around the optimal constant acquisition time, $T_{ct}$, which was determined experimentally with pure phantom solution. The criteria for selection of $T_{ct}$ were an evolution yielding mostly in-phase signal and a time long enough to encode sufficient steps in $t_1$, but not too long to control loss due to $T_2$ relaxation. The minimal $T_E$ of 31 ms is given by the duration of RF pulses and gradients.

We measured phantoms to validate the proposed technique. Pure metabolite solutions with a concentration of 100 mM were prepared for NAA, Cre, Glu, Gln (glutamine), GABA and GSH (glutathione). Another phantom contained approximate in vivo concentration ratios [1] (24 mM NAA, 16 mM Cre, 18 mM Glu, 9 mM Gln, 3 mM GABA and 4 mM GSH). The contamination of the target resonances with other metabolites was determined experimentally. Pure solutions with DSS (3-(trimethylsilyl)-1-propanesulfonic acid) and sodium formate as reference were measured and reconstructed for the respective CS frequencies of the target resonances. The signals were normalised with respect to sodium formate. An empirical correction factor was introduced to partially account for signal loss from relaxation and other sources. This factor was obtained by normalising the integral of the corresponding metabolites to the sodium formate reference, and was subsequently used to correct the concentration ratios of the in vivo data. The correction factor is an approximation, because the relaxation times are different in vitro and in vivo. Five healthy volunteers (two males and three females; age 24.4 ± 2.7 years), who provided written informed consent, were measured in the prefrontal cortex for in vivo validation; the voxel size was $(25$ mm)$^3$.

2.4 Results

The optimal target for glutamate proved to be the 2.35 ppm multiplet with a reconstruction time of $T_{ct} = 130$ ms. Other possible targets have CS’s too close to those of Gln, NAA and GSH, and are thus not separable through CSSF. The Glu resonance at 2.35 ppm appears as a single peak with a widened base for typical in vivo shims of 7 Hz (Fig. 2.7). The contamination of Gln from 2.44 and 2.12 ppm was 8.3 % for a typical in vivo concentration ratio Glu:Gln of 2:1. GABA contamination reduces the signal by 5.0 % (Glu:GABA ≈ 6), and the contamination of NAA (Glu:NAA = 0.8) is negligible (1.5 %). The corrected in vivo concentration ratio Glu:Cre was 1.24 ± 0.08.

The most suitable target for the other example, myo-inositol, was the 3.64 ppm triplet (Fig. 2.7), with the same reconstruction time of $T_{ct} = 130$ ms. The triplet at 3.27 ppm is covered by Cho, and the
Figure 2.7: CSSF spectra measured \textit{in vivo} (blue solid) and in phantoms with pure solutions of the corresponding metabolite (red dash-dotted).
2.5 Discussion and Conclusions

CSSF simplifies quantification and improves the unequivocal detection and quantification of $J$-coupled resonances as compared to regular 1D spectroscopy. Two prominent examples are glutamate and myo-inositol. Furthermore, the information of singlets such as NAA, Cre, and Cho is preserved, and contamination of other metabolites is reduced. The method is robust, and different metabolites are readily observable within a single experiment. This is a considerable advantage over MQC filtering, which requires cumbersome optimisation for each metabolite and field strength, and reveals in general only one metabolite at a time. Furthermore, CSSF has no inherent signal loss as opposed to MQC filtering. However, certain metabolite resonances, such as GABA and GSH, are still too close to stronger signals and the detection is more reliable with other forms of editing, such as difference editing or MQC filtering.

The sensitivity of CSSF (defined here as SNR per unit time) is comparable to that of 1D PRESS spectroscopy. It is decreased through $T_2$ relaxation and $t_1$ noise. To minimise the loss to $T_2$, sampling was restricted to shorter TEs, hence confining linewidth in the $t_1$ direction. The $t_1$ noise originates from experimental imperfections and can be minimised with the use of a sufficiently long repetition time (TR) [43], crusher gradients and phase cycling. In this work, we improved the sensitivity by starting the sampling of the FID as soon as possible. The total acquisition time of 13 min is rather long for $in vivo$ applications; however, such a duration is not an experimental precondition and was chosen here for improved sensitivity. One can readily shorten the time by using fewer steps in the phase cycle or entirely omitting it. Another possibility is to reduce the number of time steps in the $t_1$ domain by increasing $\Delta T_E$, hence decreasing the bandwidth in $f_1$. Acquisition-based filtering techniques, as performed for JPRESS [53], obviate the filtering along $t_1$ during post-processing. However, the universality of the experiment is lost with such techniques, and thus they were not considered for the current work.
Figure 2.10: Impulse response function from two reconstruction possibilities. The FIDs are shown above, and the corresponding spectra are shown below. The diagonal, where the resonances are located, is depicted in the spectra through a blue dashed line. In the case of a tilted peak tail (left) little contamination is spread into contiguous resonances. Truncation of the FID (right) restores an orthogonal peak tails, albeit at the cost of lost information and hence worse SNR.
Sampling the maximum information leads to FIDs with different starting points of the acquisition, as depicted in Fig. 2.6. This results in a tilt of the peak tail in $f_2$ direction (Fig. 2.10). Truncation of the FID will restore the orthogonality of the peak tails, though at the cost of reduced information content and hence reduced sensitivity. One must ensure that the tail of another peak is not leaking too much into the metabolite of interest. The tilt angle away from the $f_1$ axis in clockwise manner is $\alpha = \arctan 2 \approx 63.4^\circ$. This is sufficiently different from the diagonal ($\alpha = 45^\circ$), where all resonances are located. The fact that the tails of the water peak are tilted away from the diagonal can be exploited for spectroscopy without water and/or fat suppression, as shown for $J$-resolved spectroscopy in vivo [44, 54, 55].

The baseline of CSSF spectra is flat, primarily for two reasons: Only few short TEs are encoded in CSSF, and therefore macromolecules are usually relaxed. Another source of baseline instability in 1D spectra is the water suppression. In CSSF the tail of the water is tilted away from contiguous resonances, and thus contamination is much reduced.

The chosen implementation differs from the CT-PRESS implementation described in Refs. [47, 49] in that no additional 180° pulse was added. It is possible to use the last slice-selective refocusing pulse because there are sufficient spoiler gradients surrounding this pulse. Otherwise, an incomplete refocusing will transfer magnetisation to cross peaks in a COSY-like manner. The major advantage of not adding another pulse is a shorter minimal TE, which increases the number of possible encoding steps. Because of the long pulse duration on the 3 T whole-body scanner, this minimal TE is quite long. In the CT-PRESS implementation described in Ref. [49], the authors chose to shorten the sequence by lowering the flip angle of all refocusing pulses to 167°. This led to an increased bandwidth of the RF pulses, but also a considerable sensitivity loss.

A 1D fitting algorithm can be applied to the CSSF spectra to decrease variability and user interdependence. A promising method is to use a linear combination of model spectra, such as done in LCModel [17], since the line-shapes are not optimal Lorentzian singlets but are more complex. For this purpose, one has to acquire model spectra for all metabolites and reconstruct them for the various CS frequencies. The contribution of other metabolite peaks leaking into the CSSF spectrum can be completely eliminated by the fitting procedure.

CSSF reveals more information than normal 1D spectroscopy, and compares well with other forms of spectral editing. Because it offers ease of handling and applicability to various metabolites, it is a promising candidate for clinical use. Since extensive averaging is required for sufficient sensitivity, 2D spectroscopy does not considerably increase the experiment duration, and therefore a wealth of additional information is obtained at minimal cost.

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CSSF for the *In Vivo* Detection of *J*-Coupled Metabolites at 3T
Chapter 3

Improved Two-Dimensional $J$-Resolved Spectroscopy

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Abstract

Localised two-dimensional J-resolved spectroscopy (JPRESS) is optimised for the in-vivo detection of J-coupled metabolites by magnetic resonance spectroscopy at 3 T. The acquisition of echo signals starts as early as possible (i.e., maximum-echo sampling). This sampling scheme increases sensitivity and decreases overlap of peak tails, hence alleviating baseline problems. Reconstruction issues are discussed and the sensitivity is compared analytically with 1D PRESS. The qualitative behaviour of eddy currents in JPRESS is outlined and a 2D eddy current correction procedure based on the 1D phase deconvolution method is proposed. The reconstructed spectra are subsequently fitted in two dimensions for extracting the maximal information and obtaining more accurate quantification results.

Keywords: 2D J-resolved spectroscopy; JPRESS; maximum-echo sampling; eddy current correction; ProFit.

3.1 Introduction

In-vivo 1H magnetic resonance spectroscopy (MRS) offers great opportunities for the study of various disorders due to its non-invasive nature and avoidance of ionising radiation. Various metabolites contribute to a generally complex and overcrowded spectrum. The inherently low sensitivity of MRS experiments limits the number of detectable substances in the human brain to at most twenty for a typical field strength of 3 T [3]. A major objective in spectroscopy is the determination of individual metabolite concentrations. Normal proton spectra of the human brain are dominated by four easily detectable singlets, namely N-acetyl aspartate (NAA), total choline (Cho) and two singlets from total creatine (Cre). Special acquisition and/or post-processing techniques are generally required for the investigation of further metabolites.

Many fitting routines have been developed for extracting spectroscopic information. An overview of the various methods can be found in Refs. [56, 57]. Fitting can improve the quantification considerably, especially for the predominant singlets. However, many J-coupled metabolites are difficult to detect because of heavy overlap and insufficient signal-to-noise ratio (SNR). This renders fitting often insufficient, thus requiring different sequences for a more specific acquisition. The methods of choice for detecting J-coupled metabolites are often spectral editing techniques [3, 43, 2]. In multiple quantum coherence filtering or difference editing, the signal is selectively filtered in order to simplify the overcrowded spectra. The signal of interest remains and is directly accessible for quantification. These filters have to be specifically tuned to the metabolite of interest and often reduce sensitivity. Typical in-vivo applications of spectral editing include the detection of lactate (Lac), γ-aminobutyric acid (GABA), glutamate (Glu) and glutathione (GSH) [3]. Although useful for clinical studies, these techniques have not found widespread application in clinical routine. This can be attributed to difficult handling, low SNR and sensitivity to motion and other experimental imperfections.

Another promising approach to increase specificity is multi-dimensional spectroscopy, where indirect dimensions are encoded by varying the lengths of evolution periods. This class of sequences greatly dominate the in-vitro NMR field, yielding a wealth of information such as connectivities (COSY [43]) or molecular distances (NOESY [43]). However, the application of multi-dimensional spectroscopy to in-vivo MRS is rather unpopular due to several reasons. Time, hardware and other constraints only permit the application of the most basic multi-dimensional sequences, such as J-resolved spectroscopy [14] or COSY [10]. The post-processing is not as advanced as in regular 1D spectroscopy; no appropriate fitting procedures exist for extracting the maximal information from the 2D spectra.

Two-dimensional J-resolved spectroscopy [58, 43, 2] is one of the simplest 2D sequences and well suited for in-vivo application. It consists of a series of spin-echo experiments with different echo times encoding the indirect \( t_1 \) dimension. The equivalent in-vivo MRS sequence is dubbed JPRESS [14], since it employs point-resolved spectroscopy (PRESS) [4] for volume localisation. As the name “2D J-resolved spectroscopy” suggests, the experiment provides an additional resolution of the J-coupled metabolites. One of the main limitations in 1D MRS is the overlap especially of coupled spins, and thus JPRESS is a powerful approach to alleviate this problem.

JPRESS has been applied for in-vivo MRS on humans only in a few studies. The most common application is the human brain [14, 59, 60, 44, 65, 61, 62, 45, 43], which is generally the most studied organ in MRS. Nevertheless, several other organs have been studied with JPRESS as well, such as muscle [64, 65].
3.2 Theory

Localized two-dimensional J-resolved spectroscopy (JPRESS) is a simple spin-echo experiment with different echo times encoding the J coupling in the indirect t\textsubscript{1} dimension. The echo top is used as reference point for the reconstruction along t\textsubscript{1} so that no chemical-shift (CS) evolution takes place in that dimension. The J evolution is not influenced by the 180° pulses and is hence resolved along t\textsubscript{1}. The acquisition is the direct t\textsubscript{2} dimension and contains both CS and J evolution. After Fourier transformation of the data in two dimensions, a spectrum is obtained with its resonances aligned on the horizontal (0 Hz) axis. J-coupled spin systems are split up into multiplets tilted by 45°, as depicted for GABA in Fig. 3.1. The preceding considerations hold strictly only in the weak coupling limit. Strongly-coupled spins systems give rise to additional resonances at the mean chemical-shift frequency [14, 43].

The JPRESS implementation used for this work is derived from the regular, asymmetric PRESS sequence [4] (Fig. 3.2). The first echo time (TE\textsubscript{1}) is always as short as possible and only the second refocusing pulse is shifted for encoding t\textsubscript{1}. The sampling of the echo signals starts immediately after the final crusher gradient of the last 180° pulse [68, 70], and is henceforth called maximum-echo sampling. This acquisition scheme has several advantages over the traditional half-echo sampling, where the acquisition starts at the echo top. Highly beneficial, as described later, is the resulting tilt of the peak tails. Furthermore, the sensitivity is increased by acquiring more signal. This gain in sensitivity is calculated analytically in the appendix by integrating over the damping curves in the time domain, which corresponds to the peak height in the frequency domain. The noise is the same for both experiments. Experiments of the same duration and repetition time can be compared by calculating the ratio of peak heights. Analytical forms of this ratio are derived in the appendix for shortest-echo-time PRESS and JPRESS with the two different sampling schemes (i.e., maximum and half echo).

The reconstruction of JPRESS spectra from the maximum-echo data is straightforward. The different rows are shifted to the same reference point (i.e., the echo top; Fig. 3.3) in the time domain. This is
Figure 3.1: *In-vitro* spectrum of GABA plotted in magnitude mode (top) and phased complex mode (bottom). Two triplets are visible at 3.01 and 2.28 ppm and one quintet at 1.89 ppm. The CS evolution is only effective in the direct $f_2$ dimension. One multiplet is therefore located at one CS frequency along $f_2$. $J$ coupling is effective in both $f_1$ and $f_2$ and therefore the resonances are split up into multiplets tilted by 45°. The minimum echo time was 31 ms and therefore the multiplets already exhibit some anti-phase evolution (bottom). Almost all structure is lost in the magnitude spectrum (top) due to the broad dispersion tails. (100 mM GABA; 2 Hz Gaussian line broadening in both $t_1$ and $t_2$)

Figure 3.2: Principle functioning of the applied $J$PRESS sequence. The crusher gradients around the 180° pulses are depicted in green. The acquisition starts at $T_{AS}$ directly after the final crusher gradient. The indirect dimension is given by $t_1 + T_{E_{\text{min}}}$ = $T_E$ = $T_{E_1} + T_{E_2}$, with a varying second echo time $T_{E_2}$ (blue arrow) and a constant first echo time $T_{E_1}$. $T_{E_{\text{min}}}$ is the minimum echo time of the corresponding PRESS sequence.
most flexibly performed in the frequency domain by multiplication with a linear phase. A JPRESS spectrum is obtained after a two-dimensional Fourier transformation of the time-domain data. The reference for this transformation is the minimum echo time (TE\textsubscript{min}) and the echo top for the t\textsubscript{1} and t\textsubscript{2} dimension, respectively (Fig. 3.3). The TE\textsubscript{min} is identical to the minimum echo time of the corresponding PRESS sequence and governed mainly by the duration of the RF pulses and gradients. For every echo time increment \(\Delta TE\), the maximum-echo sampling starts the acquisition \(\Delta TE/2\) earlier with respect to the echo top. In the shifted JPRESS time domain data, the echo truncation line is therefore tilted by \(\arctan(1/2) \approx 26.6^\circ\) against the vertical t\textsubscript{1}-axis (Fig. 3.4). This truncation line directly translates into the frequency domain, where the peak tails along f\textsubscript{2} are tilted by the same angle against the horizontal f\textsubscript{2}-axis. The angle is independent of the sampling frequencies in f\textsubscript{1} and f\textsubscript{2}. However, the f\textsubscript{1} dimension should be oversampled sufficiently in order to prevent folding of the residual water peak tail back into the spectral region of interest. These additional acquisitions usually come at no extra cost, because oversampling amounts to averaging, and the main limitation for the detection of J-coupled metabolites is the sensitivity.

Nuisance gradients, caused mainly by eddy currents, lead to a line-shape distortion. Knowledge of the qualitative behaviour of these gradients is important for devising correction strategies. Eddy currents are space and time dependent and induced by switching the gradients of the MR system [2]. They decay in a multi-exponential fashion and lead to additional gradients, which also decay multi-exponentially. A specific voxel at a single echo time always shows the same decay, as long as the experimental settings are not altered by any intermediate preparations. To correct PRESS spectra, it therefore suffices to measure the reference signal with an identical experiment, but omitting the water suppression. The phase of the echo in the time domain is ideally constant (for water being on-resonant) and any deviation reflects the additional nuisance gradient. Symmetric and undistorted line-shapes can be restored by subtracting the phase of the reference signal from the data under analysis, which amounts to a phase deconvolution [72].

The eddy currents in a 2D JPRESS experiment are induced mainly by the last pair of crusher gra-
Figure 3.4: Traditional half-echo sampling (a+c) in comparison to maximum-echo sampling (b+d). The acquisition of the echo starts either at the echo top (a) or as soon as possible (b). The tilt of the truncation line for the acquisition begin (b) translates directly into a tilt of the peak tails away from $f_2$-axis (d). In the traditional sampling, both tails are rectangular to each other. The reference point of the 2D Fourier transformation is shifted to the middle in both domains. The echo signals are additionally zero-padded to twice the number of rows in $t_1$. 
Figure 3.5: Effect of eddy currents on the echo signal, depicted here by plotting all echo times in lines with different colours. The top row shows the magnitude of the echo, the middle row the phase of the echo and the bottom row the corrected phase. The echo is acquired in a phantom (15 mM Cre) without water-suppression and the phase should be ideally zero. Any phase distortion is due to experimental imperfections, mainly eddy currents. Different echo times always give rise to the same phase distortion (middle) despite the shifted echo top (top). Therefore, it is sufficient to acquire a reference spectrum for only one echo time and subtract its phase from all signals acquired with other echo times (bottom).  

Phase-sensitive J\textit{PRESS} spectra exhibit phase-twisted 2D line-shapes arising from the product of two complex signals (Fig. 3.6). Each domain contains absorption (A) and dispersion (D) components. The
Figure 3.6: Phase-twisted line-shape in half- (left) and maximum-echo sampling (right) plotted on a logarithmic colour scale.

Figure 3.7: TE-averaged spectrum of GABA. This is equivalent to a 0 Hz cross-section through the complex mode JPRESS spectrum (Fig. 3.1, bottom).
real part of the (phased) spectrum is given by

\[
\text{Re}((A_1 + iD_1)(A_2 + iD_2)) = A_1A_2 - D_1D_2. \tag{3.1}
\]

Phase-twisted line-shapes are inherent to this kind of experiment due to phase-modulation in \(t_1\) [43, 2]. However, the cross-section through the centre of the peak still exhibits a pure (1D) absorption line-shape and can therefore be processed in complex mode (Fig. 3.7). The 2D line-shape is further complicated by the tilt of the peak tails due to the maximum-echo sampling scheme (Fig. 3.4). Because of this tilt, the 1D line-shape in the cross-section is not purely Lorentzian, but has a somewhat reduced peak tail. Additionally, the \(t_1\) dimension starts at the minimum echo time and thus some \(J\) evolution has already taken place. The 2D peaks of \(J\)-coupled metabolites therefore exhibit a small anti-phase component (Fig. 3.1, bottom). Nevertheless, all these effects are deterministic and do not really hamper quantification through fitting. The advantages of quantifying the real part of the spectrum (i.e., less overlap) greatly exceed its disadvantages (i.e., strange line-shape with negative components).

### 3.3 Materials and Methods

All experiments were performed on a Philips Intera 3 T whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with a transmit/receive head coil. The echo times ranged from 31 to 229 ms in steps of 2 ms and the bandwidths in \(f_1/f_2\) were 0.5/2 kHz with 100/2048 sampling points, respectively. Four-step phase cycling for each echo and a repetition time of \(TR = 2.5\) s amount to a total scan duration of 17 minutes. Twenty-seven healthy volunteers (age 35.4 ± 7.5 years; 20 female, 7 male) who provided written informed consent were scanned in the parietal lobe.

Quantification was performed with ProFit [71], a semi-automatic 2D fitting program, which only requires the confirmation of the initial automatic referencing and phase correction. The concentrations were determined in the form of ratios to creatine and no attempt for absolute quantification was made. The quality of the fitting results was assessed by means of Cramér-Rao lower bounds, excluding all metabolites with a value larger than 20 %, and a quality factor, reflecting the fit residual over the noise. Ideally this quality factor approaches one and an appropriate threshold for exclusion proved to be 1.7. The quality factor includes a small part of the water peak tail and the macromolecular signal at around 1 ppm. Therefore, this threshold mainly excludes data of generally poor spectral quality and not necessarily with a bad fit.

### 3.4 Results and Discussion

The presented \(J\)PRESS sequence is comparably robust and easy to apply as standard PRESS. Accurate quantification is possible even for suboptimal experimental conditions, such as poor shimming and insufficient water suppression. Out of the 27 acquired datasets, only two spectra were discarded due to a too high quality factor (>1.7), stemming mainly from signal contributions of macromolecules. The concentrations of the singlets in the two discarded spectra perfectly matched the concentrations determined in the other volunteers, but the low-concentrated metabolites were not accurately quantified. A typical \(J\)PRESS spectrum of a healthy volunteer is shown in Fig. 3.8. The inter-subject concentration ratios (to creatine) and standard deviations for the included spectra are given in Table 3.1. Metabolites included in the fit, which did not yield reliable values, were glutamine and taurine. These substances generally had too high Cramér-Rao lower bounds. The inter-subject standard deviations reflect natural concentration differences and a varying tissue composition of the voxel, as well as systematic errors of the experiment and the quantification. A more thorough discussion of the specific results, including the \(T_2\) relaxation times and phantom experiments, is given in [71]. The results indicate that \(J\)PRESS effectively decreases the spectral overlap.

The maximum-echo sampling scheme has several advantages. Highly beneficial for the robustness of the experiment is the tilt of the peak tails. The contamination from the only partially suppressed water resonance is greatly reduced. Figure 3.9 shows the effect of poor water suppression on the spectrum. In the traditional half-echo sampling, the spectrum is heavily contaminated and quantification is impaired.
Figure 3.8: Typical *in-vivo* JPRESS spectrum plotted on a logarithmic colour scale. Directly visible are the predominant singlets from NAA, Cre and Cho, but also some of the $J$-coupled metabolites.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>$inc$</th>
<th>Cre ratio</th>
<th>ISSD [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/NAAG</td>
<td>25</td>
<td>1.63</td>
<td>6.8</td>
</tr>
<tr>
<td>NAA</td>
<td>25</td>
<td>1.27</td>
<td>8.6</td>
</tr>
<tr>
<td>NAAG</td>
<td>25</td>
<td>0.351</td>
<td>20.3</td>
</tr>
<tr>
<td>total Cho</td>
<td>25</td>
<td>0.282</td>
<td>10.5</td>
</tr>
<tr>
<td>glutamate</td>
<td>25</td>
<td>2.02</td>
<td>24.5</td>
</tr>
<tr>
<td><em>myo</em>-inositol</td>
<td>25</td>
<td>1.26</td>
<td>26.9</td>
</tr>
<tr>
<td>glutathione</td>
<td>25</td>
<td>0.304</td>
<td>24.8</td>
</tr>
<tr>
<td>GABA</td>
<td>16</td>
<td>0.216</td>
<td>33.1</td>
</tr>
<tr>
<td>alanine</td>
<td>19</td>
<td>0.193</td>
<td>37.9</td>
</tr>
<tr>
<td>glucose</td>
<td>17</td>
<td>0.322</td>
<td>33.3</td>
</tr>
<tr>
<td>glycine</td>
<td>22</td>
<td>0.143</td>
<td>29.3</td>
</tr>
<tr>
<td><em>scyllo</em>-inositol</td>
<td>22</td>
<td>0.0523</td>
<td>34.8</td>
</tr>
<tr>
<td>phosphorylethanolamine</td>
<td>21</td>
<td>0.516</td>
<td>42.8</td>
</tr>
<tr>
<td>lactate</td>
<td>20</td>
<td>0.188</td>
<td>35.5</td>
</tr>
<tr>
<td>aspartate</td>
<td>22</td>
<td>0.888</td>
<td>64.8</td>
</tr>
</tbody>
</table>

Table 3.1: Fit results for the 27 healthy volunteers in table form. The ratio to creatine is listed together with the inter-subject standard deviation (ISSD). The second column states the number of included spectra $inc$. Taurine and glutamine are excluded due to too high Cramér-Rao lower bounds (i.e., more than 20 %).
Figure 3.9: In-vivo JPRESS spectrum with poor water suppression. In the traditional half-echo sampling (top), the tail of the water peak leaks into the other metabolites, hence impeding quantification. The maximum-echo sampling (bottom) allows for accurate quantification despite this poor water suppression.

However, the maximum-echo sampled spectrum allows for accurate quantification, although this is typically restricted to Cre, NAA, Cho, Glu, myo-inositol (ml) and GSH.

In maximum-echo sampling, more of the signal is acquired as compared to half-echo sampling. This naturally increases sensitivity. An analytical sensitivity comparison is given in the appendix. Some actual examples with typical values are given in Fig. 3.10. PRESS and JPRESS, both with maximum and half-echo sampling, are compared for a line-width of 6.4 Hz ($T_2^* = 50$ ms), the actual $t_1$ sampling range of $T_{S1} = 200$ ms and $T_2$ relaxation times of 100, 150, 200 and 250 ms. The maximum-echo sampling generally leads to a considerable gain in sensitivity as compared to half-echo JPRESS. For longer $T_2$ relaxation times, the sensitivity between PRESS and maximum-echo sampled JPRESS is approximately the same. This is the case for the predominant singlets Cre, NAA and Cho, which have rather long $T_2$ relaxation times [71]. The signal loss is aggravated for many of the $J$-coupled metabolites, which tend to have shorter $T_2$ relaxation times than the predominant singlets. It is therefore important to restrict the sampling time along $t_1$. However, $J$ evolution needs to be sufficiently resolved and therefore the chosen maximum echo time of 229 ms seems to be a good compromise.

The sensitivity calculations (appendix) take only non-coupled spins into account. Although $J$ coupling can be included in the calculations, this is not particularly helpful and intuitive as it must be done
Figure 3.10: Sensitivity comparison between PRESS and JPRESS with both maximum and half-echo sampling for $T_2^* = 50$ ms and $T_{S1} = 200$ ms. The maximum-echo sampling scheme is highly beneficial for gaining sensitivity in 2D experiments.

Figure 3.11: Zero-Hertz cross-section through JPRESS spectrum of water with (red dashed) and without (blue solid) eddy current correction. Symmetry is increased, hence increasing also the peak height.
individually for each metabolite. Most brain metabolites are strongly coupled at typical field strengths of $B_0 \leq 3$ T, hence impeding analytical calculations. However, some insight might be delivered by comparing the experiments. The $J$ evolution depends in both PRESS and $J$PRESS on the minimal echo time. A PRESS spectrum can be reconstructed from $J$PRESS by building the projection onto the $t_2$ axis. This projection can lead to signal loss when anti-phase terms are summed up. Regular 1D PRESS always suffers from these destructive interferences and therefore performing a 2D experiment is advantageous.

Closely related to the sensitivity issue is the scan duration. The relatively long scan time of 17 minutes was mainly chosen to increase sensitivity. The scan time can be readily shortened by decreasing the phase-cycling steps or the amount of oversampling in the indirect dimension. Favourable for the sensitivity would be the reception with surface coils. This option was not considered here, because of the reduced bandwidths of the radio-frequency pulses when transmitting with the body coil instead of the transmit/receive head coil. As a consequence, the chemical-shift displacement is large, giving rise to localisation errors and anomalous $J$ evolution \[73\].

The effect of the eddy current correction is best examined in Figs. 3.5 and 3.11, where in-vitro experiments without water suppression are shown. The strength of the last pair of crusher gradients is increased from 12 to 20 mT/m in order to increase the eddy currents. The observable distortion induced by eddy currents is usually small, because the gradient systems of modern scanners are highly optimised. Important is the measurement of the reference signal in the same scan, omitting intermediate preparations. This was however not possible in the current implementation and the separately measured reference scan showed slightly different eddy current effects compared to the actual measurement. In general, it is difficult to see the spectral distortions from eddy currents in the in-vivo spectra with modern hardware, due to the broad line-widths of typically 6-9 Hz.

The acquired data can also be reconstructed differently, for instance as CSSF \[68\]. Other options are $J$PRESS with different $J$ evolutions, which can be achieved by moving the reference of the 2D Fourier transformation along $t_1$. Sensible positions for the reference are the beginning, as chosen for the current implementation, the middle or the end of the different echo acquisitions. The end and the beginning is identical due to the periodicity in the signal. The middle often implies more in-phase evolution for some metabolites, however at the cost of greatly increased truncation wiggles. Shifting the data in either domain does not alter the information content of the spectra, when filtering is omitted. For a subsequent fit of the spectra, the way of reconstruction is mainly governed by ease of implementation, thus favouring $J$PRESS over CSSF.

### 3.5 Conclusions and Outlook

$J$PRESS generally increases the specificity in MRS and alleviates the effects of high fat and water signal. The combination with the 2D fitting procedure ProFit \[71\] enables the detection and quantification of a whole range of metabolites in a single experiment. Two major limitations in proton MRS are the overlap of peaks and sensitivity. The former is greatly alleviated by $J$PRESS, while the latter remains and has to be addressed by other measures such as signal acquisition by surface coils. The outlined sensitivity considerations give an idea about the strengths and limitations of $J$PRESS, thus helping the experimental design. Most favourable for sensitivity and robustness is the maximum-echo sampling scheme. The qualitative description of the eddy current effects helps to devise appropriate correction strategies. Furthermore, 2D spectroscopy gives a much more intuitive insight into various spectroscopic artefacts, which are often less disturbing in 2D. Examples include poor water suppression, as demonstrated in this work, or spurious water and lipid sidebands \[44, 55\].

Methodological improvements can tackle the localisation problem of spectroscopy occurring at higher fields strengths ($B_0 > 1.5$ T). This will enhance measurements in smaller organs or closer to adjacent fat (in the brain), but it will also prevent anomalous $J$ evolution \[73\]. The region of chemical-shift displacement can be saturated with highly selective quadratic-phase pulses \[5, 6, 41\]. Another possibility is the localisation with adiabatic pulses, providing a two-dimensional version of LASER \[55\], which has the additional advantage of yielding more in-phase signal at short echo times for strongly coupled spin systems. The phase sensitive $J$PRESS spectra will therefore also exhibit more in-phase signal. Other interesting future directions include numerous applications of $J$PRESS/ProFit to various clinical studies. It is possible to omit water suppression \[44, 54\] and use the water signal for referencing and miscella-
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neous corrections. $J$PRESS also enables spectroscopy in organs with high fat content, such as the breast

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3.6 Appendix: Sensitivity Comparison

A common definition of the sensitivity is the signal-to-noise (SNR) ratio per unit time [43]. For identical experimental durations, the noise will remain the same and it is sufficient to compare the signal only. The signal is commonly defined as the peak height in the frequency domain, which is equivalent to the integral of the time domain signal. For singlets it suffices to integrate over the exponential damping curve of the echo along the times $t_1$ and $t_2$. The digitisation does not fundamentally change the signal and therefore it suffices to take the continuous integral. The 1D PRESS experiment can be compared to 2D experiments simply by integrating over the indirect $t_1$ axis with always the same intensity. The signal from PRESS is therefore given by

$$\int_0^{T_{S1}} \int_0^{\infty} \exp \left( -\frac{t_2}{T_2^*} \right) dt_2 dt_1 = T_2^* T_{S1}, \quad (3.2)$$

where $T_{S1}$ is the sampling time along $t_1$. The PRESS sequence with the shortest possible echo time is used for an equitable comparison. The echo time of this PRESS sequence is also equivalent to the shortest echo time of $J$PRESS.

The signal of $J$PRESS can be split up into two halves. The damping curves in the traditional half-echo sampling is equivalent to the right half and given by

$$\int_0^{T_{S1}} \int_0^{t_1/2} \exp \left( \frac{t_2}{T_2^*} \right) \exp \left( -\frac{t_1}{T_2} \right) dt_2 dt_1 = T_2^* T_2 \left( 1 - \exp \left( -\frac{T_{S1}}{T_2^*} \right) \right), \quad (3.3)$$

The left half of the maximum-echo signal can be calculated by

$$\int_0^{T_{S1}} \int_{-t_1/2}^0 \exp \left( \frac{t_2}{T_2^*} \right) \exp \left( -\frac{t_1}{T_2} \right) dt_2 dt_1 = T_2^* T_2 \left[ 1 - \exp \left( -\frac{T_{S1}}{T_2} \right) \right] - T_2^* t_x \left( 1 - \exp \left( -\frac{T_{S1}}{t_x} \right) \right), \quad (3.4)$$

where $t_x = \frac{2T_2 T_{S1}^*}{T_2^* + T_{S1}^*}$ is introduced for notational convenience. Adding both halves together, yields the total signal of the maximum-echo sampled $J$PRESS

$$2T_2^* T_2 \left[ 1 - \exp \left( -\frac{T_{S1}}{T_2^*} \right) \right] - T_2^* t_x \left( 1 - \exp \left( -\frac{T_{S1}}{t_x} \right) \right), \quad (3.5)$$

These formulae can now be used to compare the various experiments with each other.

The ratio maximum-echo $J$PRESS (Eqn. 3.5) to PRESS (Eqn. 3.2) is given by

$$\frac{2T_2}{T_{S1}} \left[ 1 - \exp \left( -\frac{T_{S1}}{T_2^*} \right) \right] - \frac{t_x}{T_{S1}} \left( 1 - \exp \left( -\frac{T_{S1}}{t_x} \right) \right), \quad (3.6)$$

and half-echo $J$PRESS (Eqn. 3.3) to PRESS (Eqn. 3.2) by

$$\frac{T_2}{T_{S1}} \left( 1 - \exp \left( -\frac{T_{S1}}{T_2^*} \right) \right), \quad (3.7)$$

Examples with typical values are given in Fig. 3.10.
Chapter 4

Two-Dimensional Prior-Knowledge Fitting: ProFit

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Abstract

A two-dimensional fitting procedure is introduced, capable of extracting the full amount of information present in 2D $J$-resolved magnetic resonance spectroscopy data. The fitting procedure uses a linear combination of 2D model spectra. For reducing the degrees of freedom and increasing robustness, it is split up into a non-linear outer loop and an inner linear-least squares fit for the concentrations. Validation on brain spectra of 27 healthy volunteers and several phantom experiments show the detectability of a wide range of metabolites. In-vivo $T_2$ relaxation times are a direct by-product of the 2D fitting procedure.

Keywords: ProFit; prior knowledge model fitting; LCModel; VARPRO; JPRESS; 2D J-resolved spectroscopy.

4.1 Introduction

Magnetic Resonance Spectroscopy (MRS) allows the non-invasive examination of metabolite concentrations. Many studies investigated the underlying processes of the brain, especially in conjunction with various disorders [1]. In total, about 20 metabolites are possibly detectable in the human brain on current MR scanners, with four singlets dominating the spectra. These stem from N-acetyl-aspartate (NAA), total creatine (Cre) with two singlet peaks and choline-containing compounds (Cho) [1][3]. Special techniques such as spectral editing [3][4][2] have to be applied to detect further metabolites at the currently typical field strength of $B_0 \leq 3$ T. Editing, however, is often difficult and therefore rarely applied for clinical studies. At present, a great potential for improving the detection and quantification of $J$-coupled metabolites lies in spectral fitting. As a result, many different fitting routines have been developed over the years [56][57]. In this work, two specific techniques are combined and will be briefly introduced, namely LCModel (“linear combination of model spectra”) [17] and VARPRO (“variable projection”) [16][15].

LCModel works in the frequency domain and requires metabolite basis spectra [17]. A non-linear optimisation fits the magnitudes, line-widths and other parameters of the basis spectra to approximate a measured spectrum. The baseline is modelled by including a spline function into the fit. LCModel is robust and generally converges to a suitable solution. It is possible to extract most of the information present in the data, because the whole amount of prior knowledge is included in the fit. On the other hand, VARPRO is a parametrised fit in the time domain [15]. Prior knowledge can be incorporated by providing expected resonance frequencies and constraining the complex amplitudes of metabolites with multiple peaks. In general, parametrised fitting routines are more complex and providing all available prior knowledge is cumbersome if not impossible, especially for strongly coupled metabolites with complicated multiplet structures. However, the great benefit of VARPRO lies in the algorithmic implementation. The fit is a mixture of non-linear and linear optimisation. The line-widths and frequency shifts are optimised in an outer loop by non-linear fitting. In the inner step, the complex amplitudes (i.e., concentrations and phases) are calculated by linear least-squares optimisation. This improves efficiency and robustness of the whole fit. While proper procedures can considerably improve quantification, many $J$-coupled metabolites are still undetectable and one has to resort to different acquisition methods.

One promising concept to increase specificity, and hence detectability of overlapping metabolites, is multi-dimensional spectroscopy. One of the simplest and most useful sequences for in-vivo MRS is localised 2D $J$-resolved spectroscopy (JPRESS) [14][24]. The $J$ evolution is encoded in an additional indirect dimension by shifting the last 180° refocusing pulse. The overcrowded 1D spectra are disentangled, yielding a better separation of the resonance lines. JPRESS spectra are typically quantified by either integration of the 2D magnitude peaks or by applying common 1D methods to a cross-section through the spectrum [24]. However, such a quantification is inaccurate, subjective and time consuming. This is probably one of the main reasons why JPRESS could not find widespread clinical application. The maximal information can be extracted from JPRESS spectra by fitting directly in two dimensions. The additional benefits of such a fit as compared to other forms of editing are its objectiveness and the possibility to calculate quality measures, for example in the form of Cramér-Rao lower bounds (CRLB) [18].

A first attempt to fit 2D spectra was made with the 2D Hankel singular value decomposition (SVD) by De Beer et al. [75]. The signal is decomposed in the time domain by an SVD, yielding directly the corresponding damping factors and frequencies individually for each projection onto the $f_1$ and $f_2$ axes. Subsequently, concentrations and phases are obtained by a linear least-squares fit spanning a basis with
these parameters. The whole optimisation is linear, thus the global minimum is reached. However, the fit cannot be constrained to physically sensible values by prior knowledge and only Lorentzian line-shapes are possible. Probably, the biggest drawback stems from fitting only projections. In JPRESS, only the $J$ coupling is encoded along $f_1$ and therefore a heavy overlap of many different resonances is observed at $f_1 = 0$ Hz [74]. Together with the remaining water signal, this gives rise to an imprecise frequency determination in the indirect dimension, rendering the technique not particularly suitable for 2D $J$-resolved spectroscopy.

Another attempt to fit 2D spectra was undertaken by Slotboom et al. [76]. An existing 1D routine, named “TDFD fitting” [77], was extended to pseudo 2D by constrained 1D fits. The procedure is based on non-linear iterative optimisation in the frequency domain and allows the inclusion of prior-knowledge constraints. The authors used a multi-echo sequence, similar to JPRESS, with the main difference of Fourier transforming the data only along the direct $f_2$ dimension. The second dimension is included in the fit by additional constraints on the different echo times. Feasibility was shown on glutamate and glutamine phantoms and the authors concluded, that this 2D fitting does not improve quantification compared to pure 1D routines [76].

In this work, a genuinely two-dimensional fitting procedure is presented, capable of applying the complete prior knowledge. *In-vivo* transverse relaxation times ($T_2$) are obtained directly for a wide range of metabolites. In principle, the fitting can be applied to all kinds of 2D experiments, with JPRESS being especially well suited due to its robustness and high sensitivity [74]. A maximum-echo sampling scheme helps to further improve experimental robustness and increase sensitivity [74]. The proposed fitting procedure is dubbed ProFit, which stands for Prior-Knowledge Fitting.

### 4.2 Methods

ProFit is based on two complementary approaches; the concept of LCModel [17] provides the maximal prior-knowledge constraint, while VARPRO [16, 15] reduces the degrees of freedom of the non-linear fit. The underlying JPRESS spectra are reconstructed from maximum-echo data as described in [74]. The oversampled spectra are then truncated to the region of interest in both $f_1$/$f_2$ to reduce the numerical burden. ProFit combines several different strategies (Fig. 4.1) in order to enable convergence of the fit close to the global minimum.

In general, spectroscopic fits are complex and must be constrained for obtaining physically sensible values. Allowing too many degrees of freedom to be adjusted might yield mathematically excellent, but physically meaningless fits. Prior knowledge can be included in the form of basis spectra. These can be either measured in pure phantom solutions [78] or simulated [79]. In this work, the metabolite basis spectra are calculated numerically by evolving the complete density matrix with the GAMMA library [80], using the chemical shift and $J$ coupling values from Govindaraju et al. [1]. The simulation assumes ideal experimental conditions.

The underlying principle of ProFit is a linear combination of model spectra [17]. The optimisation problem is to find the best combination of basis spectra to approximate the spectrum under analysis. LCModel [17] solves this problem completely with non-linear optimisation, despite its linear nature. The baseline of JPRESS spectra is generally flat and therefore not considered in the fit. ProFit determines the following global parameters for the whole spectrum under analysis: a Gaussian line-broadening in $f_2$, a zeroth-order phase, a line-shape distortion function and a shift in $f_1$ to account for small assignment errors. Individual parameters for each basis metabolite include the concentrations, exponential line-broadenings in both $f_1$ and $f_2$ and small shifts in $f_2$. The latter shift is important because of often imprecise frequencies in $f_2$ and assignment errors. All of this amounts to quite a few parameters (i.e., degrees of freedom) for the fit and aggravates the convergence of the optimisation to the global minimum. Several strategies have to be applied for assisting the non-linear optimiser in getting close to the global minimum.

ProFit is split up into a non-linear outer optimisation and an inner linear-least squares fit (Fig. 4.1), similar to VARPRO [16,15]. The outer loop adapts the parameters line-broadening, small shifts, global phase and a line-shape distortion function. In the inner step, the basis spectra are updated with the parameters given from the outer loop. The spectrum under analysis is approximated with this basis by a linear least-squares fit yielding the individual concentrations. Since these concentrations are not
Figure 4.1: Principle functioning of ProFit. The non-linear fitting procedure (yellow box) is repeated thrice, each time with an increase in the degrees of freedom. The first non-linear fit is initialised with typical values for the lineshape and separately determined shifts and global phase. The second and third non-linear fit is initialised with previous fit results. Each non-linear optimisation implies numerous evaluations of the cost function, where the basis spectra are updated and then fitted by linear least squares to the spectrum under analysis.
optimised in the outer loop, the degrees of freedom of the non-linear fit are reduced by the number of metabolites. This increases the speed and robustness as compared to a complete non-linear fit. In contrast to the original VARPRO method, only the real parts are fitted linearly in order to constrain the individual phases. All basis spectra are stored with the correct phase and only the spectrum under analysis is phase corrected.

A good initialisation of the non-linear fitting routine is of paramount importance for a successful optimisation. Non-linear fitting routines often get stuck in local minima. The likelihood of getting close to the global minimum is often small when starting far away from the optimum. Basically, all parameters of the non-linear optimisation need to be initialised. The spectrum under analysis is first shifted to the right frequencies in $f_1/f_2$ by detecting the maxima of the predominant singlets NAA, Cre and Cho in the magnitude spectra. All additional relative shifts, originating from assignment errors, are small and thus initialised with zero. The global phase is also determined from the predominant singlets by averaging over four different methods. The first two maximise the 2D peak area and maximum, whereas the remaining ones exploit the symmetry of the negative parts of the 2D peaks, stemming from the phase-twisted line-shape [74] by equalising the two minima and the integral of the two negative parts. The line-widths are initialised with typical values and the line-shape distortion function with zero.

A further strategy for successful fitting is a three-fold iteration of the non-linear optimisation (Fig. 4.1). The number of parameters taken into account increases with each iteration. This helps to achieve convergence to an acceptable minimum, since the most important parameters are optimised first. The subsequent fits can be initialised with appropriate starting values from the previous fit. The first iteration considers only the predominant singlets with a global Gaussian line-broadening in $f_1$ and an individual exponential line-broadening for each metabolite in both $f_1$ and $f_2$. Iteration two adds a line-shape distortion function, while in the last iteration all metabolites are fitted.

The cost function of the non-linear optimisation is the sum of the squares fit residual plus the sum of squares of certain penalty factors for regularisation. This additional penalty factor permits the inclusion of soft constraints, necessary to guide the fit to converge to a physically sensible solution [17]. Water and lipids are excluded from the optimisation by truncating the fit residual to the spectral region of interest. The differences in line-widths and chemical shifts (in $f_2$) in between the basis metabolites are obliged to be small, which will lead to some bias towards the mean values in case of low-concentrated metabolites. The search space is limited to physically sensible values (i.e., positive concentrations and line-widths) directly by the optimisation routine. Gradients of the cost function are provided in analytic form.

Nuisance gradients, caused mainly by eddy currents, lead to an additional distortion of the line-shape [74]. Therefore, the fit includes a line-shape distortion, similar to most conventional 1D fitting routines [17, 77, 81]. The distortion function should describe the effect accurately while adding only few extra degrees of freedom. The most feasible model turned out to be a bi-exponential phase decay multiplied on all rows of the original time domain data. This bi-exponential phase is given by

\[ \varphi = \phi_1 \exp \left( -\frac{t_2}{T_{\phi_1}} \right) + \phi_2 \exp \left( -\frac{t_2}{T_{\phi_2}} \right), \]  

where $\phi_1, \phi_2$ and $T_{\phi_1, \phi_2}$ are the amplitudes and positive decay time constants, respectively. The decay times are fixed and only its amplitudes are fitted. This introduces only two additional parameters to the non-linear fit. It is possible to use the same distortion function for all echo times because of a similar behaviour of the nuisance gradients for all echoes [74].

The two-dimensional data is reshaped into vector form for the inner linear least-squares fit. The spectrum under analysis therefore becomes a vector with length $n_1 \cdot n_2$, where $n_1$ and $n_2$ stand for the sample points in the indirect and direct dimension, respectively. The basis set forms a matrix of size $n_1 \cdot n_2$ times the number of metabolites. Afterwards, the fit residual is reordered into a $n_1$ by $n_2$ matrix and then truncated to exclude the remaining water and fat signal. The cost function is the sum of the squares fit residual plus some regularisation, as described above.

The quality of the fit can be evaluated with the Cramér-Rao lower bounds (CRLB) [18]. This gives a statistical lower bound for the achievable standard deviation of the estimated parameter. The underlying assumptions for this theory include white noise of the data, the correct fitting model and an optimal fit. The CRLB provides information about the accuracy limits, governed by sensitivity and overlap. The
quality of the spectra and the fit can be further assessed by a quality factor reflecting the non-truncated fit residual over the noise. Ideally, this factor is one and increases with a poor fit, but also includes the lipid signal and a small part of the water tail. The CRLB and the quality factor can be used as exclusion criteria for unreliable metabolite concentrations.

4.3 Materials

All post-processing routines were implemented in MATLAB V7.0 (R14) (The MathWorks, Inc., Natick, MA, USA). The non-linear optimisation is based on a gradient-descent algorithm (MATLAB function “fmincon”), which enables a constrained search. A medium-scale optimisation is performed with the sequential quadratic programming method [82] (see MATLAB manual for details). The linear least-squares algorithm of the inner step calculates the Moore-Penrose pseudo-inverse [82] (Matlab function “pinv”). Typical execution times for fitting a spectrum are in the order of several minutes (Pentium 4 CPU with 2.53 GHz).

All experiments were performed on a Philips Intera 3 T whole-body scanner (Philips Medical Systems, Best, The Netherlands), equipped with a transmit/receive head coil. The echo times ranged from 31 ms to 229 ms in steps of 2 ms and a repetition time of 2.5 s. The bandwidths were $BW_1 = 0.5$ kHz and $BW_2 = 2$ kHz with $n_1 = 100$ and $n_2 = 2048$ sampling points in the $f_1$ and $f_2$ direction, respectively. To
### Table 4.1: Phantom measurements with a varying amount of GABA and GSH, and most standard metabolites in approximate *in-vivo* concentrations. One row represents the measurement of one phantom with two different concentrations of GABA and GSH, given in the column “con.” in mM. The column “Cre ratio” denotes the ratios to creatine and “norm. ratio” the concentrations normalised to the actual concentrations and then normalised to the mean value thereof. The column “CRLB” lists the Cramér-Rao lower bounds of the corresponding fit (in %). The concentration of creatine was 10 mM. The concentration changes are accurately determined and the errors in quantification are in the order of the CRLBs, indicating the appropriateness of the CRLB for estimating the accuracy of the fit. The value for 0 mM GSH would be excluded because of a CRLB of more than 20 %.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>con. [mM]</th>
<th>inc</th>
<th>Cre ratio</th>
<th>ISSD [%]</th>
<th>CRLB [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>10</td>
<td>10</td>
<td>0.908</td>
<td>2.8</td>
<td>0.24±0</td>
</tr>
<tr>
<td>NAAG</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cho</td>
<td>2</td>
<td>10</td>
<td>0.193</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Glu</td>
<td>10</td>
<td>10</td>
<td>0.771</td>
<td>15.4</td>
<td>1.3±0.2</td>
</tr>
<tr>
<td>mI</td>
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<td>10</td>
<td>0.576</td>
<td>17.1</td>
<td>1.3±0.2</td>
</tr>
<tr>
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<td>0.111</td>
<td>13.7</td>
<td>2.9±0.5</td>
</tr>
<tr>
<td>GABA</td>
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<td>13.6</td>
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<td>10</td>
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<td>10.4</td>
<td>7.3±1.6</td>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gly</td>
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<td>10</td>
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<td>15.9</td>
<td>2.2±0.5</td>
</tr>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PE</td>
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<tr>
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<td>0.0679</td>
<td>-</td>
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</tr>
<tr>
<td>Cre 3.03</td>
<td>10</td>
<td>10</td>
<td>1</td>
<td>0</td>
<td>0.2±0</td>
</tr>
<tr>
<td>Cre 3.91</td>
<td>10</td>
<td>10</td>
<td>1.04</td>
<td>3.7</td>
<td>0.4±0.1</td>
</tr>
</tbody>
</table>

### Table 4.2: Phantom verification with metabolites in approximate *in-vivo* concentrations. The reproducibility of the *in vitro* quantification is shown by repeating the measurements ten times. *J*PRESS was recorded with a repetition time of TR = 7 s to minimise $T_1$ relaxation effects. “Con.” is the actual concentration in the phantom in mM, “inc” denotes the number of included spectra in the analysis, “ISSD” stands for the inter-scan standard deviation of the ten measurements and quantifications and “CRLB” is the Cramér-Rao lower bound of the fit.
Table 4.3: Results of various mixed phantoms. The columns “C” denote the LCModel fit, as recommended in [78].

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>basic</th>
<th>comb. 1</th>
<th>comb. 2</th>
<th>comb. 3</th>
<th>comb. 4</th>
<th>comb. 5</th>
<th>all</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>2.04</td>
<td>2.02</td>
<td>2.03</td>
<td>2.05</td>
<td>2.04</td>
<td>2.01</td>
<td>2.01</td>
</tr>
<tr>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>PCh/GPC</td>
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<td>0.15</td>
<td>0.14</td>
<td>0.14</td>
<td>0.14</td>
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<tr>
<td>Glu</td>
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<td>20.69</td>
<td>20.73</td>
<td>20.82</td>
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<tr>
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<td>0.83</td>
<td>0.82</td>
<td>0.78</td>
<td>0.89</td>
</tr>
<tr>
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<td>0.01</td>
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<td>0.05</td>
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<td>0.01</td>
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<td>0.00</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<td>0.04</td>
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<td>0.03</td>
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<td>0.00</td>
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<td>0.03</td>
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<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
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<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Lac</td>
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<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
<td>0.03</td>
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<tr>
<td>Asp</td>
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<td>0.00</td>
<td>0.06</td>
<td>0.02</td>
<td>0.16</td>
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<td>20</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

Table 4.4: Fit results for the 27 healthy volunteers for both ProFit and LCModel. The ratio to creatine (3.03 ppm) is italic and red. The columns “R” denote the in-vitro concentration of this metabolite in mM and the columns “C” the concentration ratio to creatine (3.03 ppm). The numbers in italic and red exhibit a Cramér-Rao lower bound greater than 20 % and would be excluded from quantification.

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>inc</th>
<th>Cre ratio</th>
<th>ISSD [%]</th>
<th>T1 [ms]</th>
<th>CRLB [%]</th>
<th>inc</th>
<th>Cre ratio</th>
<th>ISSD [%]</th>
<th>CRLB [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/NAAAG</td>
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<td>261±57</td>
<td>0.6±0.1</td>
<td>27</td>
<td>1.5</td>
<td>7.2</td>
<td>1.9±0.4</td>
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</tr>
<tr>
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<td>8.6</td>
<td>28±62</td>
<td>0.6±0.1</td>
<td>27</td>
<td>1.29</td>
<td>11.4</td>
<td>3±1</td>
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</tr>
<tr>
<td>NAAG</td>
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<td>20.3</td>
<td>236±74</td>
<td>2.9±1.3</td>
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<td>0.23</td>
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</tr>
<tr>
<td>PCh/GPC</td>
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<td>1.2±0.8</td>
<td>27</td>
<td>0.24</td>
<td>12.5</td>
<td>3.7±1.1</td>
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</tr>
<tr>
<td>Glu</td>
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<td>91±56</td>
<td>2.8±0.5</td>
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<td>10.8</td>
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</tr>
<tr>
<td>ml</td>
<td>1.26</td>
<td>26.9</td>
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<td>29±0.6</td>
<td>27</td>
<td>0.64</td>
<td>15.1</td>
<td>5.2±1.5</td>
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</tr>
<tr>
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<td>89±39</td>
<td>4±0.8</td>
<td>26</td>
<td>0.28</td>
<td>23.3</td>
<td>10.5±2.3</td>
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<td>33.1</td>
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<td>14.6±2.5</td>
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<td>102±19</td>
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<td>12.8±2.9</td>
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<td>0.314</td>
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<td>1±0.1</td>
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<td>4</td>
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<td>16.3</td>
<td>17.5±0.7</td>
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increase numerical speed, the data was truncated to the spectral region of interest with $32 \times 256$ points before fitting. Furthermore, the fit residual was truncated to the spectral region of interest defined by $-28$ Hz < $f_1$ < 28 Hz and 1.3 ppm < $f_2$ < 4.1 ppm, additionally excluding the tilted water tail (Fig. 4.2 top). The simulated basis spectra were post-processed in a similar fashion as the actual data. That is, the truncation of the data and hence the resulting Gibbs ringing, particularly present in $f_1$, is the same.

The spectra included in the basis set were: N-acetyl aspartate (NAA), N-acetylaspartylglutamate (NAAG), alanine (Ala), $\gamma$-aminobutyric acid (GABA), aspartate (Asp), phosphorylcholine (PCh), glycerophosphorylcholine (GPC), creatine (Cre), phosphorylethanolamine (PE), glucose (Glc), glutamate (Glu), glutathione (GSH), glycine (Gly), myo-inositol (mI), scyllo-inositol (Scy), lactate (Lac) and taurine (Tau). The two creatine peaks were fitted as separate basis spectra without any mutual constraints. The quantification results are given in the form of ratios to the 3.03 ppm Cre peak and no absolute quantification was attempted. The other Cre singlet at 3.91 ppm is close to the water resonance, hence the intensity is influenced by the water suppression.

The proposed method was verified extensively both in vitro and in vivo. Three different sets of phantom experiments investigated the ability of ProFit to determine concentration changes, experimental repeatability and specificity. The first set of measurements (Table 4.1) was on phantoms with varying amounts of GABA and GSH in addition to most standard brain metabolites mixed in approximate in-vivo concentrations [1]: 10 mM NAA, 2 mM choline (Cho), 10 mM Cre, 10 mM Glu, 7 mM ml, 1 mM Ala, 1.5 mM Asp, 1 mM Glc, 3 mM Gln, 1.5 mM Lac, 1.5 mM PE, 1.5 mM Tau, 1 mM Gly. This solution was combined with different combinations of GABA and GSH (mM GABA/mM GSH): 0/0, 1/2, 2/2, 4/2, 2/1 and 2/4. Cho was used instead of GPC and PCh, because the pH value of latter metabolites cannot be neutralised [28]. The in-vivo reproducibility was investigated by measuring the phantom with all in-vivo metabolites, 2 mM GABA and 2 mM GSH ten times (Table 4.2). The latter spectra were recorded in a fully relaxed state with a TR = 7 s to minimise $T_1$ weighting of the results. For each measurement, a completely new scan session was started including the repositioning of the phantom. The third set of phantom measurements evaluated the specificity of the method with phantoms containing the five main metabolites (NAA, Cho, Cre, Glu and ml) in about twice the physiological concentration. $J$-coupled metabolites were added in different combinations with about four times the normal brain concentration (Table 4.3).

In-vivo validation was performed by measuring 27 healthy volunteers, who provided written informed consent (age 35.4 ± 7.5 years; 20 female, 7 male), in the parietal lobe. Both JPRESS and PRESS (TE = 31ms, TR = 2.5 s, 256 averages, spectral width = 2 kHz, 2048 sampling points) spectra were acquired for cross-validation of ProFit with LCModel (Table 4.4).

### 4.4 Results and Discussion

Quantification of JPRESS spectra with ProFit is accurate, robust and yields generally consistent results, both in vivo and in vitro. The range of quantifiable metabolites can be considerably increased at a field strength of 3 T. The fit residual is small (Figs. 4.2, 4.4) and the in-vivo reproducibility is in the order of physiological changes for the predominant singlets (Fig. 4.5 and Table 4.4). Many of the $J$-coupled metabolites are also detectable in the brain, however with an increased scatter of the quantified metabolites (Tables 4.2 and 4.4).

The main objectives in MRS is the detection and quantification of signal changes. The reliability of detecting these changes with ProFit is shown for GABA and GSH in Table 4.1 and Fig. 4.6. A second set of phantom measurements investigated reproducibility by measuring the same phantom ten times (Table 4.2). The inter-scan standard deviation (ISSD) is small for the predominant singlets, in the order of a few percent. Most other metabolites are usually detectable with an ISSD in the range of 10-20%. The last set of phantom measurements show the possible contamination of metabolites by other metabolites (Table 4.3). All these results indicate the reliability of the proposed method. Most important, however, is the consistent quantification of metabolites in the human brain.

The in-vivo fitting results of ProFit and the comparison to LCModel for the 27 healthy volunteers are given in Table 4.4, which shows the concentration ratios to creatine, the inter-subject standard deviations (ISSD), the CRLBs and the in-vivo $T_2$ relaxation times. The ISSD is probably the most important indicator for the accuracy and limits of quantification. This deviation is small for NAA/NAAG (6.8 %) and
Figure 4.3: Same fit as in Fig. 4.2 but plotted in lines. The blue, red and green line represent the spectrum, the fit and the residual, respectively.

PCh/GPC (10.5 %), reflecting probably mainly physiological differences. For most J-coupled metabolites the ISSD is in the order of 30 %, which includes both the individual differences in concentrations and most likely systematic errors from both the experiment (JPRESS) and the fitting (ProFit). The comparison with PRESS fitted with LCModel shows an increased ISSD for Glu and mI, but a decreased ISSD for the predominant singlets. One reason for the discrepancy of Glu and mI is the worse SNR due to their short T$_2$ relaxation times [74]. Furthermore, the glutamate moiety of NAAG is omitted from the simulated basis spectrum due to missing CS and J values. This could also induce small errors in the quantification of Glu.

The in-vivo results (Table 4.4) suggest that the number of quantifiable brain metabolites can be increased from eight with LCModel (Cre, Cho, NAA, NAAG, Glu, mI, GSH and Scy) to 15 with JPRESS/ProFit (additionally: GABA, Ala, Asp, Glc, Gly, PE and Lac). However, in some cases one has to be careful and the phantom validations point out certain limitations. One striking difference of ProFit to LCModel is its higher concentration ratio for certain metabolites (e.g., Glu, mI and GSH). This difference is consistent and does not hamper quantification. Most importantly, as shown by the phantom validation with a varying amount of GSH and GABA (Fig. 4.6 and Table 4.1), ProFit is able to distinguish the different concentrations in the phantom experiments. The lactate and alanine resonances are possibly contaminated by macromolecules and lipids [83] and therefore their concentrations could be overestimated. However, the low ISSD suggests an accurate detection of these metabolites. Glycine overlaps with mI (Table 4.3) and is therefore not accurately resolved. PE seems to be problematic to detect in phantoms (Tables 4.2 and 4.3), while Asp exhibits a quite a large ISSD (Table 4.4). NAAG is more accurately separated from NAA with ProFit as compared to LCModel (Table 4.4). GPC and PCh are still not separable with ProFit, thus the joint concentration is determined. Glu, mI, GSH, GABA, and Glc are accurately quantifiable with ProFit.
Figure 4.4: In-vivo spectrum with very poor quality (i.e., large fat signal (1-1.5 ppm) and water residual (>4 ppm top)). The fit residual is high, mainly due to macromolecules, yielding a quality factor of 2.15. Therefore, this spectrum was excluded from further analysis. The singlets, however, are still accurately fitted and could in principle be used.

The baseline in the maximum-echo sampled JPRESS experiment [74] is generally flat and thus omitted from the fit. The $T_2$ relaxation times of macromolecules are short, hence they are only recorded for shorter echo times. However, when placing the voxel too close to the fat layer in the skull, a considerable fat signal was still observable. It is possible to include these resonances into ProFit, as also shown for LCModel [83, 78]. However, attention needs to be paid considering the fact that fat resonances are often out of phase due to poor localisation [84].

The $T_2$ relaxation times are a direct by-product of ProFit and listed in Table 4.4. The $T_2$s of the predominant singlets are most accurately determined and coincide well with published literature values for 3 T [85, 86]. Furthermore, the $T_2$ values of NAA and Cre are within the range of the standard deviation, but the relaxation time of Cho is slightly shorter with ProFit. The low-concentrated metabolites could exhibit some bias towards the mean $T_2$ value of all metabolites due to regularisation. No values were found for these metabolites in the literature.

Simulation of the basis spectra was necessary due to residual, uncorrectable eddy currents of the measured basis spectra. The line-widths of the basis metabolites must be known for detecting $T_2$ relaxation, which is infeasible in phantoms due to differences in reference and metabolite $T_2$ relaxation. However, the simulations imply ideal conditions. Localisation is problematic at $B_0 \geq 3$ T and the long pulse duration in conjunction with narrow bandwidths of the RF pulses alters the evolution behaviour of $J$-coupled spin systems. The effect is stronger for the weakly coupled spin systems (i.e., Ala and...
Lac) than for strongly coupled ones (i.e., most of the other brain metabolites) and neglecting it in the simulations can induce small systematic errors [87].

4.5 Conclusions and Outlook

The combination of JPRESS with ProFit increases detection capabilities of in-vivo MRS. It is a viable alternative to other forms of editing, yielding a wealth of information in a single experiment. The quality of the spectra and the fit can be assessed more objectively by the Cramér-Rao lower bound and the quality factor. Numerous studies for investigating the metabolism of the brain and other organs are possible. However, the expected signal change should be large (i.e., typically bigger than the inter-subject standard deviation). Inhomogeneous areas should be, as generally the case in editing, avoided and the voxel must be large (e.g., > 15 ml).

Methodological improvements include a further investigation of the line-shape distortion function. Another possibility is the inclusion of macromolecules and lipids into the fit, similar to LCModel [83, 78]. Outer volume suppression can reduce these signals with the added benefit of reducing J evolution effects due to localisation and eliminating the chemical-shift displacement artefact. The J evolution in the measurements will therefore be more similar to that in the simulated basis spectra. Alternatively, the simulation can be extended to include these and other localisation effects [87]. Two-dimensional fitting is not restricted to JPRESS and ProFit can in principle be applied to various 2D experiments; COSY [43], for example, is another promising sequence for in-vivo MRS.
Figure 4.6: Results from phantoms with metabolites in approximate \textit{in-vivo} concentrations and with varying amounts of GABA and GSH. More detailed results are given in Table 4.1. A straight line is fitted to the data points for depicting the accurate determination of the concentration changes. The error bars depict the CRLBs of the corresponding fits.

\section*{Acknowledgements}

The authors would like thank Thomas Lange, Hendrik Mandelkow, Florian Wiesinger, Klaas P. Pruessmann and Jeffrey Tsao for fruitful discussions; Maria Joy Daigo-Schulte, Andreas H. Trabesinger and Thomas Järmann for reviewing the manuscript; Johannes Beck for measuring the healthy volunteers. This work was supported by ETH Zurich (SEP Life Sciences TH7/02-2) and by Philips Medical Systems (Best, The Netherlands).
Conclusions and Outlook

The goal of this thesis was to advance MR spectroscopy by improving both the spatial localisation and the detectability of $J$-coupled metabolites in spectroscopy. Both issues are of paramount importance, especially at higher field strengths $B_0$.

Spatial localisation is problematic at high $B_0$ due to an increased chemical-shift displacement. This problem can be effectively alleviated by saturating the region of chemical shift displacement \cite{5, 6}. The RF pulses used for this saturation must have a broad bandwidth with high selectivity. These desired criteria can be fulfilled with quadratic-phase pulses. In the first two chapters of this thesis, an efficient and powerful design strategy is presented and evaluated. The implementation into the standard scanner software for using these pulses for outer volume suppression is currently under way \cite{88}.

Quadratic-phase pulses are becoming increasingly important in all fields of MR, with a multitude of different applications currently evolving. Applications in imaging include saturating parts of the body to reduce the field of view (FOV) \cite{5}. The scan time (for a given resolution) is proportional to the FOV, and hence considerable gains in speed are possible. Quadratic-phase RF pulses can furthermore be used for 3D imaging, when the non-linear phase distribution is resolved by phase encoding \cite{33, 89, 90}. Besides the broad bandwidth (i.e., less artefacts) and excellent selectivity (reduced FOV), this technique has the additional advantage of spreading out the power in k-space \cite{33, 89}, hence reducing requirements on the dynamic range of the receiver system.

Besides MRI, quadratic-phase RF pulses are also gaining popularity in the *in-vitro* NMR field. In conjunction with magnetic field gradients, this kind of pulses can be used for single-scan two-dimensional spectroscopic sequences \cite{91}. Another interesting application is the suppression of zero-quantum coherence, leaving pure longitudinal magnetisation \cite{92, 93}. Most of these techniques use adiabatic pulses, which are scaled to different flip angles and hence lose their adiabaticity. These pulses have a poor selectivity and only approximately a quadratic phase. Most of these emerging techniques could therefore benefit from specifically designed quadratic-phase pulses.

The other objectives of this thesis was to improve the detection capabilities of *in-vivo* spectroscopy by spectral editing techniques. Editing methods traditionally performed at the Institute for Biomedical Engineering include difference editing \cite{94, 11, 95} and multiple-quantum coherence filtering \cite{10, 96, 97, 98, 3}. Often, these methods have been the only way to detect the metabolites of interest. However, they suffer from reduced sensitivity, being restricted to one metabolite of interest at a time, experimental imperfections and demanding user interaction. Another approach to detect certain $J$-coupled metabolites is multi-dimensional spectroscopy. While conceptually often simpler, these techniques generally lack sufficiently sophisticated post-processing methods.

Two different kinds of $J$-resolved spectroscopy techniques were presented in this work. The usefulness and applicability of the constant-time version of 2D $J$-resolved spectroscopy, called a chemical-shift-selective filter (CSSF; Chapter 2), is presented. Several improvements for traditional localised $J$-resolved spectroscopy, called JPRESS, are presented in Chapter 3. JPRESS allows to perform spectroscopy even under experimentally difficult conditions, like in the presence of high solvent signals (water and/or fat) \cite{44, 54, 66, 55}. Promising future directions can exploit this robustness to investigate various organs where the traditional spectroscopic experiments fail. JPRESS can be combined with chemical-shift imaging (CSI) to additionally yield the spatial distribution of metabolites \cite{57}. The time constraints can be overcome by limiting the number of encoding steps along the spectral dimension. The combination with fast CSI techniques can further alleviate this problem \cite{2, 99, 100}.

Chapter 4 is devoted to the extraction of information from JPRESS by a fitting program named ProFit. The technique is fully automatic, yielding directly the concentrations of a wide range of metabolites. A
quality measure is calculated in the form of the Cramér-Rao lower bounds [18]. ProFit is much more objective than manual post-processing techniques. Two dimensional fitting can in principle be applied to all kinds of different 2D sequences, for example also to COSY [43]. The $J$-coupling is more clearly resolved in this kind of experiment, giving rise to resonances far away from the predominant singlets. However, sensitivity issues might hamper detectability with COSY. JPRESS/ProFit enables a multitude of different spectroscopy studies and requires only an understanding of the general problems in spectroscopy. This, however, remains one of the most demanding fields of in-vivo MR.
References


REFERENCES


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Die vorliegende Dissertation ist das Resultat vieler Jahre Arbeit, welche ohne fremde Hilfe unmöglich gewesen wäre. Ich möchte allen danken, die zum Gelingen dieser Arbeit beigetragen haben. Mein spezielles Dankeschön geht an ...

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Curriculum Vitae

I was born on July 25th 1974 in Münster (Westphalia, Germany) as the fourth child of Sigrid and Dr. Erhard Schulte. In the same place, I attended the Gymnasium Paulinum (High School), the oldest school in Europe. During the 11th grade, I had the opportunity to get acquainted with the American way of life and school system by spending three months at the Clovis High School in Fresno (California, USA). In May 1994, I graduated with a German Abitur. This was followed by a year of mandatory military service in the army orchestra.

In October 1995, I commenced my studies in Electrical Engineering with specialisation in Biomedical Engineering at the University of Karlsruhe (TH) (Germany). An internship in robotics gave me the opportunity to spend some time (October until December 1999) at the Electrotechnical Laboratories, a national research institute, in Tsukuba (Japan). Back in Karlsruhe, I joined the group of Prof. O. Dössel for a student research project on cardiac modelling. From September 2000 until February 2001, I carried out my Diplomarbeit, the German equivalent to the Anglo-Saxon Masters thesis, in the Bioengineering Research group under the supervision of Prof. A. Pullan at the University of Auckland (New Zealand). My thesis topic was on the “creation of a human heart model and its adaption to ultrasound images.” Subsequently, I received my Diplom degree in Electrical Engineering from the University of Karlsruhe (TH).

In June 2001, I joined the group of Prof. P. Bösiger at the Institute for Biomedical Engineering, University and Swiss Federal Institute of Technology (ETH) Zurich (Switzerland), as a PhD student and research assistant. My research was focused on various issues important for magnetic resonance spectroscopy at higher field strengths. Besides radio-frequency pulse design, this included the development of novel sequences and post-processing techniques for the detection of J-coupled metabolites.

During my leisure time, I enjoy hiking, cycling, cooking, babysitting, playing trombone and travelling.