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Methodological Developments towards Quantitative Short TE *in vivo* ^{1}H NMR Spectroscopy without Water Suppression

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Contents

Abbreviations and Symbols

Abbreviations

ADC: Analog-to-digital converter

ACQ: Acquisition

AMARES: Advanced method for accurate, robust and efficient spectral fitting

Asp: Aspartate

a.u.: Arbitrary unit

CHESS: Chemical selective saturation

Cho: Choline

Cr: Creatine

CRLB: Cramer Rao lower bound

CV: Coefficient of variation

CWT: Continuous wavelet transformation

dB: Decibel

DWT: Discrete wavelet transformation

FFT: Fast Fourier transformation

FID: Free induction decay

FWHM: Full width at half maximum

FM: Frequency modulation

GABA: ν-aminobutyric acid

Glc: Glucose

Gln: Glutamine

Glu: Glutamate

Glx: Glu + Gln

GSH: Glutathione

Ins: Myo-inositol

ISIS: Image-selected *in vivo* spectroscopy

IWT: Inverse wavelet transformation

LCModel: Linear combination model

LPSVD: Linear prediction singular value decomposition

MC: Monte Carlo study

mM: Millimole

MPM: Matrix Pencil method

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

MRSI: Magnetic resonance spectroscopic imaging

NA: Number of accumulations

NAA: N-acetylaspatate

NAAG: N-acetylaspartylglutamate

NMR: Nuclear magnetic resonance

PCr: Phosphocreatine

PE: Phosphorylethanolamine

PPM: Parts per million

PRESS: Point resolved spectroscopy

QUALTY: Quantification improvement by converting lineshapes to the Lorentzian type

RF: Radio frequency

SD: Standard deviation

SNR: Signal-to-noise ratio = 20log(Signal amplitude/SD of noise) (in dB)

STEAM: Stimulated echo acquisition mode

SVD: Singular value decomposition

SW: Spectral width

T: Tesla

Tau: Taurine

TE: Echo time

TR: Repetition time

VARPRO: VARiable PROjection method

WS: Water suppression

WT: Wavelet transform

WTC: Wavelet transform coefficient

w.w.: Wet weight

Symbols

A, a: Signal amplitude

$B_m(t)$: Time domain model signal of metabolite m

B_0: External magnetic field

C: Concentration

M: Macroscopic magnetization

N, n: Number of spins in the group or in the compound

$\vee$: Real number

S: NMR signal

T_1, T_2: Spin-lattice and spin-spin relaxation times

$\div\zeta$: Difference of Lorentzian decay rates between the model signal and the *in vivo* signal

$\div\eta$: Difference of Gaussian decay rates between the model signal and the *in vivo* signal

$\div\varpi$: Frequency difference between the model signal and the *in vivo* signal

$\div\pi$: Zero order phase difference between the model signal and the *in vivo* signal

ν: Gyromagnetic ratio

ω: Standard deviation of noise; shielding constant of orbiting electrons

ϖ_0: Larmor frequency

…: Mother wavelet

Introduction

Since the first *in vivo* magnetic resonance (MR) spectroscopy (MRS) performed some two decades ago, *in vivo* MRS has proven to be a unique versatile and non-invasive technique in biochemical and biomedical studies and clinic diagnosis. The first *in vivo* MRS was performed on ^{31}P [Gord80, Grif80], but now the technique is used for ^{1}H, ^{31}P, ^{13}C, ^{19}F, ^{23}Na and other nuclei, among which ^{1}H MRS predominates because of the highest natural abundance of protons in human body and the highest NMR detectability, and also due to the wealthy amount of information contained in ^{1}H MRS.

Different from MRI [Laut73], which provides an anatomical map of the normal and pathological distribution of water and fat, MRS provides spectra of compounds in the humans and animals. The potential of *in vivo* MRS is that it can non-invasively detect the concentrations of metabolites in the subject. Therefore, accurate and reliable quantification of the MRS is crucially important for the developments and the applications of *in vivo* MRS.

In the past decade or so, various methods have been developed to quantify *in vivo* MRS, with algorithms ranging from simple spectral peak integration to sophisticated parametric non-linear spectral fits, and with different degrees of success. Some of the methods are the Maximum Likelihood method (ML) [Prie81], the Linear Prediction Singular Value Decomposition method (LPSVD) [Bark85a, Kölb92], the Variable Projection method (VARPRO) [Veen88] and the Advanced Method for Accurate, Robust and Efficient Spectral fitting (AMARES) [Vanh97], Linear Combination of Model spectra (LCModel) method [Prov93], and the Wavelet Transform (WT) based method [Serr97], to name just a few. Some recent review articles are found in [Krei97], [Mier01] and [Vanh01].

Although proton MRS is the most popular, widely used and extensively investigated *in vivo* NMR technique, it is also the most difficult to quantify because of the intrinsic complexities associated with it. The *in vivo* proton MRS have all the common problems of *in vivo* MRS, such as low signal-to-noise ratio, lineshape distortion, spectral overlapping and baseline distortion, among which the latter two are more pronounced with short TE (echo time) ^{1}H

MRS. For instance, the ^{1}H MR spectra of human brain consist of more than 20 NMR detectable compounds crowded in a spectral region of about 4 ppm. Short TE *in vivo* ^{1}H MRS features a well structured baseline from macromolecules and lipids. The unique feature of *in vivo* ^{1}H MRS is the dominant water signal which is 3 to 5 orders of magnitude larger than metabolite signals. The dominant water signal constitutes serious problems to *in vivo* ^{1}H MRS: (i) it is the source of strong artifacts severely distorting the baseline, which can be larger than the metabolite signals, making reliable spectral analysis and estimation impossible; (ii) its broad resonance line extends far into the spectral region of interest making the spectral post-processing a challenging task; (iii) the large dynamic range of the signal means demanding requirements both for hardware data acquisition and software signal quantification. Therefore, water suppression (WS) technique, which saturates water signal prior to data acquisition, is traditionally used as a routine in *in vivo* ^{1}H MRS to avoid these problems.

However, WS has several disadvantages [Hurd98, Dong00a]: (i) Signals with small chemical shift differences to water are also partially suppressed; (ii) Some WS methods may cause magnetization transfer effects to metabolites and thus cause systematic quantification errors; (iii) RF pulses used for WS increase the total RF power deposition and require additional adjustments; (iv) Additional measurements are necessary, if water is used as an internal reference for absolute quantification; (v) Spoiler gradients pulses increase the acoustic noise level.

Because of this, *in vivo* proton MRS acquired without WS has attracted increasing attention in recent years. Efforts have been made to address these difficulties in order to measure and quantify *in vivo* ^{1}H MRS acquired without WS [Hurd98, Veen00, Dong00a, b, 02, Clay01, [Serr01a]. However, to the best knowledge of the author, until now only 3 metabolites with prominent singlets, namely NAA (3.01 ppm), tCr (3.04 ppm) and tCho (3.24 ppm), could be quantified by Matrix Pencil (MPM) based method (Dong00b), singular value decomposition (SVD) based method [Clay01] and wavelet transform (WT) based method [Serr01a], performed on spectra acquired at TE's > 40 ms [Dong00b] and TE = 288 ms [Clay01, Serr01a].

The objective of this thesis is the methodological developments to quantify short TE *in vivo* ^{1}H MRS acquired without WS. A fast, automatic, robust and accurate quantification method was developed, which combines experimental approaches, prior knowledge and sophisticated software algorithm to tackle the common problems of *in vivo* ^{1}H MRS and the special

problems associated with MRS acquired without WS. The method is able to quantify more than 10 metabolites from signals acquired on a 4.7 Tesla spectrometer and with TE = 20 ms. This method can also be used to quantify signals acquired with WS.

The thesis is structured as follows:

Chapter 1 gives a brief introduction to the basics of NMR and *in vivo* proton MRS, in which the topics closely related to the present work, such as the basic principle of localization and the metabolite MR spectra, are introduced and reviewed.

Chapter 2 describes the general aspects of spectral quantification including the common problems, preprocessing approaches and quantification strategies. Some of the well established and widely used quantification methods are also briefly reviewed. This chapter sets the direction and the goal, the reference and the benchmark for the new method developed in chapter 3.

Chapter 3 is devoted to the methodology developments towards quantitative short TE *in vivo* ^{1}H NMR spectroscopy without WS. The main scheme of the method is to integrate the metabolite spectral prior knowledge, experimental techniques and software approaches in the quantification to treat the difficulties associated with the short TE *in vivo* ^{1}H MRS acquired without WS. Full prior knowledge of chemical shifts and J-coupling constants of the metabolites are used to obtain the model signals, which are incorporated in the spectral fitting. The experimental approaches eliminate the first order phase errors and the frequency modulation artifacts caused by gradient pulses. The software approaches employ sophisticated water signal extraction technique, spectral simulation technique, WT technique and non-linear least squares technique to overcome the problems of large signal dynamic range, severe spectral overlapping and heavy baseline distortion, and to accurately fit the signal. This method can be represented by the acronym of "metabolite **S**ignal **P**rior knowledge and **E**xperimental approaches **C**ombined spectral **F**itting **I**n the **T**ime domain (**SPECFIT**)".

After an introduction to this chapter, Section 3.2 describes the MPM based parametric spectral fitting scheme including water signal extraction, spectral zoom and lineshape transformation. This method is shown to have a high frequency resolution, to be good at signal separation and to be able to accurately estimate signals with large dynamic range. It can be used as an independent method to quantify metabolites with prominent singlets from *in vivo* MRS acquired at medium and long TE's [Dong00b, Alth02]. In this thesis its advantages with respect to water signal extraction and lineshape transform are used as a part of SPECFIT for quantification of short TE *in vivo* ^{1}H MRS in Section 3.7.

Sections 3.3 and 3.4 describe the experimental approaches to eliminate first order phase errors and frequency modulation (FM) artifacts caused by gradient pulses. The former can limit the first order phase errors to within 0.5 degree in the spectral range of interest, while the latter can perfectly eliminate the FM artifacts associated with ^{1}H MRS without WS, resulting in virtually artifact-free spectrum comparable to the intrinsically artifact-free one with WS. These approaches greatly improve the quality of the spectra and improve the performance of the spectral fitting.

Model spectra of the metabolites are used in the spectral fitting, which are obtained by spectral simulation instead of phantom measurements. Section 3.5 describes the simulation technique using the GAMMA (General Approach to Magnetic resonance Mathematical Analysis) [Smit94], a C++ library facilitating the simulation of NMR experiments.

Baseline characterization is performed by WT technique with a scheme initiated by Young et al [Youn98]. In section 3.6 the discrete WT (DWT) is briefly introduced as it is relatively new to the NMR community and the basic properties of DWT and the principles behind the DWT based baseline characterization and signal denoising are exploited.

Section 3.7 is devoted to the SPECFIT spectral fitting scheme. In the first three subsections the model function, the spectral fitting algorithm and its implementation are introduced. The SPECFIT method is evaluated and validated in the next two subsections by Monte Carlo studies and phantom experimental data under various conditions. Applications of the method to *in vivo* ^{1}H MRS acquired from rat brains at short TE without WS are given in Section 3.7.6. Intra-individual and inter-individual results are presented and compared with the literature values. Factors affecting the performances of the method are discussed.

Chapter 4 contains the discussions and an outlook.

1 Basics of *in vivo* ^{1}H MRS

The *in vivo* MR spectra provide wealthy information on the metabolites of the subject, including the structures and the concentrations of the metabolites and their interactions with the environments. This property of the *in vivo* MRS makes it a versatile and unique technique of *in vivo* biochemical and biomedical studies and a potential non-invasive tool of clinical diagnosis.

The information of *in vivo* MRS is reflected by the parameters of *in vivo* MR spectra: the amplitudes, frequencies and relaxation rates of the resonance lines. The objective of quantification of *in vivo* MRS is to determine the concentrations of metabolites from the amplitudes of the corresponding components of MR signal. Other parameters also influence the accuracy of the quantification. In this chapter, the basic aspects concerning the characteristics and quantification of *in vivo* ^{1}H MRS are reviewed.

1.1 Bloch equation and relaxation

The object of NMR is nuclear macromagnetic momentum ***M*,** which is the vector sum of the micromagnetic momentums of nuclear spins in the sample volume. Bloch [Bloc46] proposed an equation, the Bloch Equation, which is the basic equation of NMR, to describe the motion of magnetic momentum in a magnetic field. The Bloch equation is given as,

$$\frac{d}{dt}\boldsymbol{M} = \nu \boldsymbol{M} \Delta \boldsymbol{B} - \frac{(M_x - M_x^0)}{T_2}\boldsymbol{i} - \frac{(M_y - M_y^0)}{T_2}\boldsymbol{j} - \frac{(M_z - M_z^0)}{T_1}\boldsymbol{k} \qquad \text{Eq. 1.1-1}$$

The first term of the equation describes the action of magnetic fields on the magnetic momentum. If the magnetic field is static, that is $\boldsymbol{B} = \boldsymbol{B}_0$, which is in the z direction, the above equation has an analytical solution, called the stationary solution. Suppose, the system is initially in the thermal equilibrium state, that is, $M_{x,y}^0 = 0, M_z^0 = M_0$, then Eq.1.1-1 gives

$$M_{x,y} \mid 0, M_z \mid M_0. \qquad \text{Eq. 1.1-2}$$

When an RF field $2\boldsymbol{B}_1\cos(\varpi t)$ is applied along the x direction superimposed on $\boldsymbol{B}_0$, the linearly polarized RF field can be decomposed into two circularly polarized RF fields with opposite angular frequencies ϖ and $-\varpi$. Given that $\varpi - \varpi_0$, where ϖ_0 is the Larmor frequency, it is shown that only the right hand circular polarized field has significant effects on the magnetic momentum. The total effective field is given by,

$$\begin{aligned} \boldsymbol{B} &= \boldsymbol{B}_0 + 2\boldsymbol{B}_1\cos\varpi t \\ &= (\boldsymbol{B}_1\cos\varpi t, \boldsymbol{B}_1\sin\varpi t, \boldsymbol{B}_0). \end{aligned} \qquad \text{Eq. 1.1-3}$$

The effect of RF field is best illustrated in the rotating frame of reference with angular frequency ϖ around z. In this case, the total effective field reads,

$$\boldsymbol{B} = (B_1, 0, B_0 - \frac{\varpi}{\nu_I}) \qquad \text{Eq. 1.1-4}$$

Fig.1.1-1 illustrates the effective total field $\mathbf{B}_{eff}$ and its effect on the magnetic momentum: **M** rotates around B_{eff}. On resonance, i.e. $\varpi = \varpi_0$, $B_{eff} = B_1$, M rotates around B_1 with angular frequency $\varpi_1 = \nu_I B_1$. If the duration of RF field B_1 is t_p, termed the RF pulse width, the flip angle is given by,

$$\zeta \mid \nu B_1 t_p. \qquad \text{Eq. 1.1-5}$$

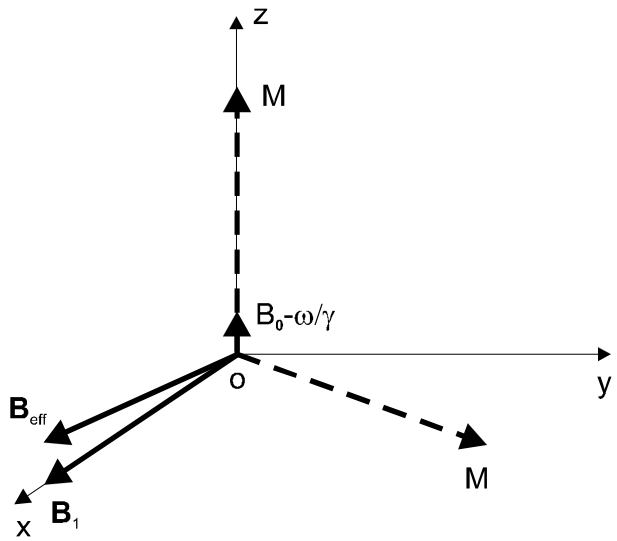

Fig.1.1-1 Effects of total magnetic field B_{eff} in the presence of RF field B_1.