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Optimized multiple-quantum filter for robust selective excitation of metabolite signals

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ABSTRACT

The selective excitation of metabolite signals *in vivo* requires the use of specially adapted pulse techniques, in particular when the signals are weak and the resonances overlap with those of unwanted molecules. Several pulse sequences have been proposed for this spectral editing task. However, their performance is strongly degraded by unavoidable experimental imperfections. Here, we show that optimal control theory can be used to generate pulses and sequences that perform almost ideally over a range of rf field strengths and frequency offsets that can be chosen according to the specifics of the spectrometer or scanner being used. We demonstrate this scheme by applying it to lactate editing. In addition to the robust excitation, we also have designed the pulses to minimize the signal of unwanted molecular species.

1. Introduction

In vivo ^{1}H-MRS spectra of mammalian brain tissue contain information about ≈20 metabolites resonating in a very narrow chemical shift range. The majority of the metabolite signals appear between 1.2 and 4.4 ppm [1]. This leads to considerable signal overlap, which is most severe for signals from coupled spins and from molecules whose concentrations are small. In addition macromolecules and lipids overlap with the metabolite signals. As an example, the lactate methyl resonance at 1.3 ppm can be obscured by a broad lipid peak. Unambiguous detection of metabolite signals *in vivo,* therefore, often requires selective excitation techniques.

Selective detection of metabolite signals can be achieved by spectral editing techniques that use differences in the scalar couplings to simplify the spectra [1]. Widely used methods are J-difference editing [2–5] and multiple-quantum-filters (MQF). While J-difference editing requires two scans that are subtracted, multiple-quantum-filter sequences allow spectral editing in a single scan and, therefore, reduce artifacts, e.g. from motion of the patient.

Many *in vivo* studies require absolute quantification of metabolite signals related to a disease or disorder. In these studies, co-edited or poorly suppressed undesired signals that contribute to the measured signal distort the real value of the desired metabolite concentration. Therefore, improved selective excitation techniques are desirable that allow reliable quantification.

Early work on the detection, quantification and imaging of lactate *in vivo* based on double quantum coherence transfer was reported e.g. in [6,7]. Single-shot lactate editing and simultaneous lipid suppression is also possible with a zero-quantum-filter, as described in [8]. Here we investigate the performance of multiple-quantum filters using the example of the sequence Sel-MQC from He et al. [9]. Current work on the basis of this sequence can be found e.g. in [10–19]. Pickup et al. developed a robust method for generating lactate maps *in vivo* in selected regions with a sequence that is a combination of the Sel-MQC technique with longitudinal Hadamard slice selection and chemical shift imaging [10]. In [11] the clinical feasibility of this technique was demonstrated. On the basis of the sequence in [10] early and patient-specific markers of therapeutic response in cancer treatment can be monitored [12,13]. The Sel-MQC sequence was also combined with fast spectroscopic imaging methods like spiral MRSI [14] or multi-spin-echo-readout [15]. Enhancement of *in vivo* lactate signal was achieved by a refocused version of the sequence [16] or in combination with binomial spectral-selective pulses [17]. A variant of the sequence for relaxation measurements was developed in [18].

In spite of these improvements, selective excitation with multiple quantum filters in the presence of experimental non-idealities like field inhomogeneities is challenging for low concentrated metabolites with overlapping signals. In general B_1-inhomogeneity in high field MRI systems and also at clinical field strengths poses

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one of the major problems for *in vivo* measurements. It is known that the performance of MQF sequences degrades rapidly in inhomogeneous magnetic fields [9,16]. Especially in the *evolution period* where double quantum coherences are manipulated by radio-frequency (RF) pulses, imperfect flip angles or off-resonance conditions have a significant effect on the outcome of the sequence. This may result in severe signal loss of the edited signal or in suboptimal selectivity, e.g. inefficient suppression of unwanted signals. As under *in vivo* conditions and in MRI-scanners the B_1- and B_0-inhomogeneities are much larger than in NMR-systems the poor performance of multiple-quantum filters is very critical and may prohibit lactate editing with this method in large volumes with considerable field inhomogeneities and for relatively small lactate concentrations. The unwanted co-excitation of the metabolites alanine or threonine may be a problem for an unambiguous lactate quantification. To avoid these problems small volumes and preferably homogeneous B_1- and B_0-fields can be used. As an example Melkus et al. [15] used a 17.6 T animal scanner with a small birdcage resonator. Several mechanisms can cause lactate signal loss in lactate editing sequences. 'NMR-invisible lactate' is one problem that was reported recently in [19] but was also observed previously e.g. in [20]. It seems that this phenomenon is associated with binding of the lactate molecule to large molecules which involves a change of the T_2-relaxation time for the lactate and therefore a broadening in the line width.

The goal of this work is to develop and implement an improved spectral editing scheme that is robust against inhomogeneous fields and achieves selective excitation of the targeted metabolite over the relevant range of field strengths with minimal loss of signal. At the same time, it prevents co-editing of unwanted molecules and retains a small SAR value. In this study we chose lactate and alanine as an example system where lactate is the metabolite of interest and alanine should be suppressed. Alanine is also a critical metabolite, similar to lactate, e.g. for tumor studies. The method that we present here can also be applied to the other combinations of metabolites, such as the selective excitation of alanine and the suppression of lactate.

1.1. Pulse sequence

To investigate the performance of multiple quantum filter sequences for selective excitation of metabolite signals in the presence of B_1- and B_0-inhomogeneity, we have chosen here the Selective Multiple-Quantum-Coherence Transfer (SSel-MQC) sequence from He et al. [9]. Fig. 1 shows the pulse sequence, which achieves selective excitation of the lactate methyl resonance and suppresses all signals with different coupling topologies in a single scan. In particular, the large signal components from water and lipid are suppressed very effectively.

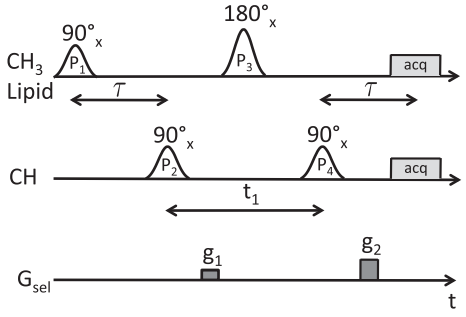

Fig. 1. Pulse sequence SSel-MQC [9]. The relative intensities of the selection gradients (G_{sel}) are $g_1 : g_2 = 1:2$. The pulses in the first row (P_1 and P_3) are selective for the lactate methyl and lipid resonances at 1.3 ppm, the pulses in the second row (P_2 ans P_4) excite the frequencies at 4.1 ppm (lactate methine group and water).

As shown in Fig. 1, the sequence uses selective pulses to excite the CH_3 and CH protons of lactate and consists of three periods. It starts with the *preparation period*, where the first 90°-pulse P_1 excites single-quantum coherence of the lactate methyl spins which evolves under chemical shift and J-coupling during the delay $\tau = \frac{1}{2J}$, where J = 6.9 Hz is the coupling constant between the lactate methyl and methine spins. At the end of this delay, the second 90°-pulse P_2 transforms the antiphase magnetization into double- and zero-quantum coherence. This conversion occurs only for the coupled spins that were excited by the two selective RF pulses. During the following *evolution period* (t_1), chemical shift and J-coupling are refocused by the inversion pulse P_3 while the gradient pulse g_1 labels the double quantum coherence. The last 90°-pulse P_4 initiates the *detection period* by converting the double quantum coherence back into single quantum coherence. The second gradient pulse g_2 has twice the area of g_1 to select coherence that was converted from double to single quantum while dephasing all other (unwanted) signal contributions.

1.2. Optimal control

Improving the performance of the pulse sequence and reducing the effect of experimental imperfections can be achieved by a number of approaches. Their theoretical basis is optimal control (OC) theory, which is a powerful method for steering complex dynamical systems in a desired way. The design and optimization of RF pulses is, therefore, a typical application. Recent work of different groups has shown that OC in NMR and MRI can increase the sensitivity of optimized experiments and make them robust against deviations in instrumental parameters, such as an inhomogeneous distribution of RF amplitudes. This is particularly important for *in vivo* MRI or MRS where OC allows one to design low-power RF pulses that are insensitive to offset and perform the targeted operation with high precision. Recent applications of OC pulse sequence design can be found in [21–23] for liquid NMR and in [24,25] for solid state NMR. In MRI and MRS early work includes [21,26–29] which demonstrated that the improved sequences are also useful under *in vivo* conditions. So far optimized broad bandwidth frequency selective pulses and flip angle homogenizing broadband pulses were developed in [26–28]. In [21,29] spatially selective pulses were optimized.

The use of OC for pulse design enables the optimization of RF pulse shapes that provide (a) the most efficient transfer of coherence from an initial spin state ρ_0 to a desired target spin state C (state-to-state) transfer or (b) a desired effective Hamiltonian [30]. Neglecting relaxation, the dynamics of a nuclear spin system can be described by the Liouville-von Neumann equation

$$\frac{d\rho(t)}{dt} = -i[H(t), \rho(t)] \tag{1}$$

with the Hamiltonian $H(t)$ and the density matrix $\rho(t)$. $H(t)$ can be written as

$$H(t) = H_0 + \sum_k \omega_{1k}(t) I_k, \tag{2}$$

where H_0 is the internal spin Hamiltonian and the second term describes the effect of the RF field. $\omega_{1k}(t)$ are the RF amplitudes coupling to the component I_k ($k = x, y$) of the nuclear spin.

OC is based on the optimization of a function of the type

$$J_j(\omega_{1k}) = \Phi_j - \lambda \int_0^T \sum_k \omega_{1k}^2(t) dt, \tag{3}$$

where Φ_j is the efficiency (the fidelity) to be maximized and the second term penalizes the deposited power scaled with the weighting factor λ, and T is the duration of the pulse.