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Echo-time independent signal modulations using PRESS sequences: A new approach to spectral editing of strongly coupled AB spin systems ☆

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Abstract

In clinical MR spectroscopy, double spin-echo point resolved spectroscopy (PRESS) sequences are routinely used for volume selection. For strongly coupled AB spin systems under PRESS excitation, the dependence of the signal on the echo time TE has been thoroughly investigated, whereas less attention has been paid to the signal modulation which occurs at constant TE with varying interpulse delays. A substantial TE-independent J modulation is here predicted from analytical solutions of the Liouville equation and density matrix simulations, and verified with experiments on citrate at 1.5 and 3 T. It is also shown that this modulation effect could be exploited for editing of strongly coupled AB resonances or for removal of singlets in spectra—by means of difference spectroscopy—just using a standard PRESS sequence. The applicability in vivo of this new spectral editing approach is also demonstrated, with selective detection of citrate resonances in the human prostate. This novel approach has the advantages of being simple, and directly applicable on standard clinical MR scanners, provided that the exact behavior of the resonance is known.

Keywords: PRESS; Citrate; AB; Strongly coupled spin system; Difference spectroscopy; Density matrix

1. Introduction

In the past few years, various proton MRS methods have been proposed for detecting resonances of strongly coupled spin systems, with a particular attention to resonances which lie underneath singlets [1–6]. Traditionally, these methods are based either on difference spectroscopy editing or on multiple quantum coherence editing. Many of these methods work at magnetic field strengths higher than typical field strengths of clinical MR scanners; furthermore, they involve complex pulse sequences not commonly available on clinical systems. In clinical MR spectroscopy, in fact, only basic sequences such as stimulated acquisition mode (STEAM) [7,8] and double spin-echo point resolved spectroscopy (PRESS) [9] are routinely used for localization. The signal dependence on the echo time TE in the PRESS sequence (90°–[t_1/2]–180°–[t_1/2]–[t_2/2]–180°–[t_2/2]–Acq) has been thoroughly investigated for strongly coupled spin systems, in particular for the AB spin system [10–17]. Recently, new methods based on the PRESS sequence have been proposed [18,19]; however, little attention has been paid to the signal dependence of such strongly coupled spin systems on the interpulse delay t_1/2, at constant total echo time TE (TE = $t_1 + t_2$). Here we investigated analytically and with density matrix simulations [20,21] the t_1/2 dependence of the signal of the AB system, with the goal of developing a new method of difference spectroscopy editing. In fact, in the case of a

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significant $t_1/2$ dependence—at constant TE—of the signal of strongly coupled AB resonances, the use of two different $t_1/2$ delays (Fig. 1) will result in two different spectra because of the J modulation. Thus, by subtracting one spectrum from the other, resonances of strongly coupled spin systems which lie underneath singlets can be resolved, since the shape and intensity of singlets depend exclusively on TE and not on the interpulse delay $t_1/2$, assuming ideal behavior of the pulses.

To confirm the results obtained analytically and with density matrix simulations, we performed measurements in phantoms. Furthermore, in order to elucidate the magnetic field strength dependence of this phenomenon, we performed density matrix simulations and experiments both at 1.5 and 3 T. Moreover, we showed the in vivo applicability of this new MR difference spectroscopy method, with selective detection of citrate resonances in the human prostate.

2. Materials and methods

Quantum mechanical simulations, based on the density matrix formalism, were performed to investigate the exact behavior of the signal shape of the strongly coupled AB spin system under PRESS excitation. At both 1.5 and 3 T, the proton spins of citrate behave as a strongly coupled AB spin system. In fact, the J-coupling constant is equal to 16 Hz and the chemical shift difference (Δ) is equal to 0.146 ppm, resulting in a ratio of Δ/J of 0.58 and 1.16, at 1.5 and 3 T, respectively.

In the density matrix simulations, ideal pulses were considered and T_2 relaxation effects were assumed negligible. All the angular momentum and rotation operators were represented by matrices with complex elements in the spin-product basis; the operators were obtained by taking the Kronecker products of the corresponding single spin operators. The simulations generated signals of 1024 points over an acquisition time of 1 s, from which spectra were obtained by fast Fourier transform, using a 5-Hz line broadening factor. To identify the optimal echo time and interpulse delays for difference editing, 3D plots of the signal intensity as a function of $t_1/2$ and TE ($\mathrm{TE} = t_1 + t_2$) were generated. For each $t_1/2$ and TE, the value of the first point of the signal was taken to determine the signal intensity.

To provide more insight into the evolution of the spin states, the density matrix formalism was also employed to evaluate the temporal evolution of the coherences of the strongly coupled AB spin system, in the Cartesian product operator basis. The amplitude of relevant coherences—the in-phase y and x magnetization $\{I_{y1} + I_{y2}\}$ and $\{I_{x1} - I_{x2}\}$, and the corresponding antiphase magnetization $\{2I_{x1}I_{z2} + 2I_{z1}I_{x2}\}$ and $\{2I_{y1}I_{z2} - 2I_{z1}I_{y2}\}$—was assessed during PRESS excitation [22].

The analytical solution of the Liouville equation for the AB spin system under PRESS excitation was considered to investigate the $t_1/2$ signal dependence. Also in the analytical calculations, ideal pulses were considered. In practice, however, the modulation may be more complicated due to the pulse shape, deviating pulse angles, etc. [12,23]. The analytical solution provided the functional dependence of the signal oscillations on the coupling constant J, chemical shift difference Δ and echo time TE. The signal intensity can be written as

$$S = A\cos\left(\Omega\frac{t_1}{2} + \varphi\right) + f(J, \Omega, \mathrm{TE}), \tag{1}$$

where the amplitude (A), frequency (Ω), and phase (φ) of the oscillation are:

$$A = 8pq(p^2 - q^2)^2 \sin\left(\frac{\Omega\mathrm{TE}}{4}\right)\sin\left(J\frac{\mathrm{TE}}{2}\right), \tag{2}$$

$$\Omega = \sqrt{(J^2 + \Delta^2)}, \tag{3}$$

$$\varphi = -\frac{\Omega TE}{4}, \tag{4}$$

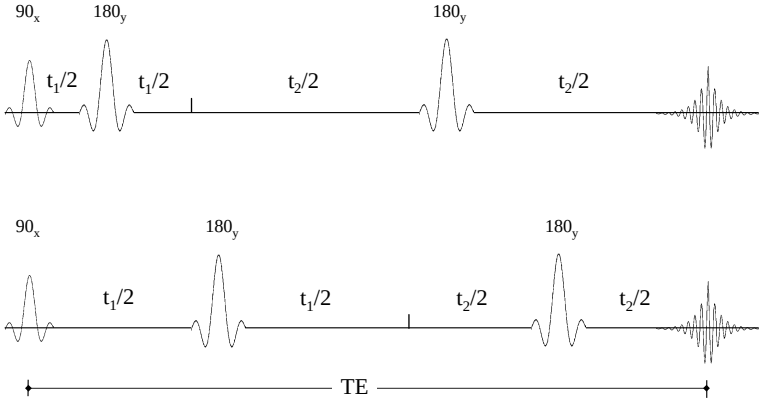

Fig. 1. PRESS pulse schemes used for difference spectroscopy editing of strongly coupled AB resonances. Two spectra from a voxel of interest are acquired with identical TE, but different interpulse delays. The timings are optimized to maximize the modulation in the signal intensity of strongly coupled spin systems. By subtracting one spectrum from the other, the resonances from the coupled spin system are enhanced, while the resonances from singlets are removed, since the signal intensity of singlets is dependent exclusively on TE.

with $p = \cos(\zeta/2)$, $q = \sin(\zeta/2)$, and $\zeta = \arctan(J/\Delta)$. Furthermore, the oscillation has an offset f which is a sum of sinusoidal functions having J, Ω, and TE as arguments.

In vitro MRS experiments were performed at 1.5 and 3 T (Siemens Sonata and Trio, respectively, Siemens Medical Solutions, Erlangen, Germany) on a phantom containing 90 mM citrate, 9 mM choline, and 12 mM creatine. A standard PRESS sequence, with optimal values for $t_1/2$ and TE found from the simulations, was employed. For the in vitro experiments at 1.5 T, the measurements parameters were the following: repetition time (TR) of 1500 ms, $20 \times 20 \times 20$ mm voxel size, 1200 Hz bandwidth, 1024 data points, 64 averages, slice selective 7 lobe MAO pulses [24] at γB_1 of 1000 Hz. For the in vitro experiments at 3 T, the measurements parameters were: TR of 2000 ms, $20 \times 20 \times 20$ mm voxel size, 2000 Hz bandwidth, 2048 data points, 32 averages, slice selective 7 lobe MAO pulses at γB_1 of 2000 Hz. On a patient with prostate cancer, two single-voxel spectra were acquired at 1.5 T, to show the in vivo feasibility of the current technique. The body radiofrequency coil of the system was used for excitation and a disposable endorectal coil (MRInnervu: Medrad, Pittsburgh, PA, USA) was used for signal reception. High resolution T_2-weighted images were acquired with a turbo spin echo sequence in three orthogonal directions, for anatomical identification of the prostate. Two spectra from a voxel of interest positioned within the prostate were acquired with a PRESS sequence ($t_1/2 = 15$ and 45 ms, TE = 160 ms, TR = 1 s, voxel size 15 mm × 15 mm × 15 mm, acquisition bandwidth 1250 Hz, 1024 spectral data points, 128 averages).

3. Results

Density matrix simulations provided the behavior of the AB spin system of citrate as a function of $t_1/2$ and TE, at 1.5 T (Fig. 2, left panel) and 3 T (not shown). The signal intensity obtained by PRESS excitation, as a function of $t_1/2$ and TE, shows a $t_1/2$-dependent J modulation at various TEs. In particular, at certain TEs (e.g., TE = 160 ms, at 1.5 T, Fig. 2, center panel) these simulations predicted substantial changes in the AB signal intensity as a function of $t_1/2$. At other echo times, on the other hand, smaller changes were predicted (e.g., TE = 100, 200 ms, see Fig. 2, center panel). No signal modulations occurred at certain TEs (for example, TE = 125 ms). Simulated and experimental spectra, all acquired at the same TE = 160 ms, provide evidence of the $t_1/2$-dependent modulation of the spectral shape (Fig. 2, right panel).

The analytical solution of the Liouville equation for the AB spin system under PRESS excitation (Eq. (1)) confirmed the results obtained with density matrix simulations, specifically, the $t_1/2$ sinusoidal dependency of the signal intensity. Let us examine the characteristic parameters of the signal oscillations, that is, the frequency (Eq. (3)) and amplitude (Eq. (2)) of the oscillations. A series of citrate spectra with $t_1/2 = 5$, 15, 25, 35, 45, 55, 65, 75 ms and a fixed TE = 160 ms (at 1.5 T) and with $t_1/2 = 5$, 10, 15, 20, 25, 30, 35, 40, 45, 50 ms and TE = 275 ms (at 3 T) were acquired (data not shown). The variation of the signal intensity as a function of $t_1/2$ was then fitted to a cosine function and the period of the oscillation T was found to be 52.2 ms (at 1.5 T) and 41.9 ms (at 3 T). The period of the oscillation $T = (2\pi/\Omega)$, calculated from the analytical solution, is 54 ms (at 1.5 T) and 40 ms (at 3 T). Thus, the shortest time interval between maxima and minima, $T/2$, is ~27 ms at 1.5 T and 20 ms at 3 T. These values represent the increment values in $t_1/2$ which provide the highest modulation in the signal intensity. With respect to the amplitude of the oscillations at constant TE, from the analytical solution we observe that the amplitude is given

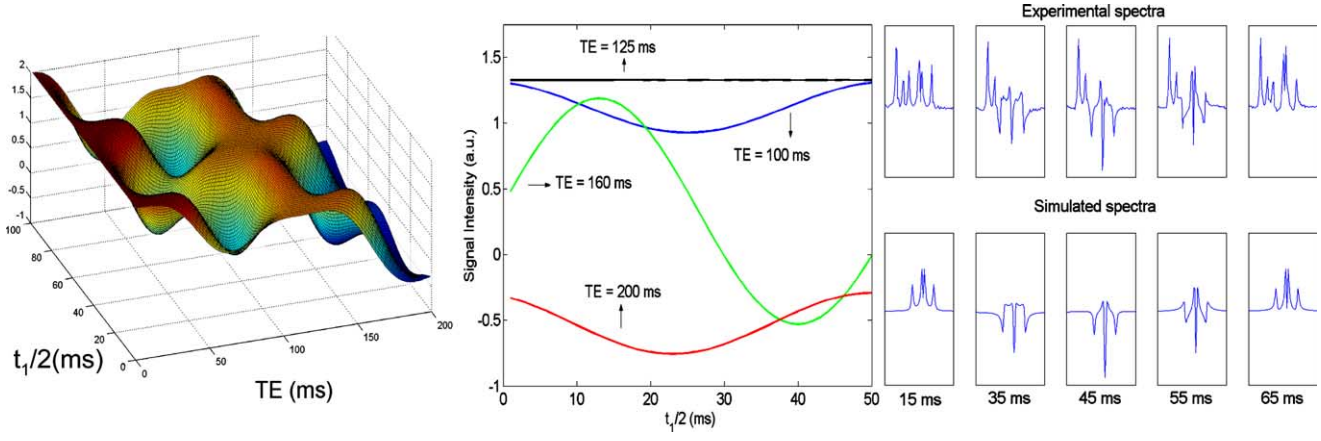

Fig. 2. (Left panel) Simulated citrate signal intensity from PRESS at 1.5 T as a function of $90x$–$180y$ interpulse delay $t_1/2$ and total echo time TE (TE = $t_1 + t_2$). Note the $t_1/2$-dependent signal J modulation at various values of the total echo time TE. At TE ~125 ms the citrate signal appears independent of $t_1/2$. For most other values of TE, there is a clear modulation in the signal intensity, as a function of $t_1/2$. (Center panel) Simulated signal modulation plotted as a function of $t_1/2$, at various values of the total echo time TE. (Right panel) Simulated and experimental signal modulation of the spectral shape. The simulated (bottom) proton MR spectra of citrate and experimental (top) proton MR spectra of a phantom containing citrate obtained from PRESS excitation at 1.5 T, at a fixed TE (TE = 160 ms) and different $t_1/2$ (15, 35, 45, 55, and 65 ms) are shown. Note the remarkable differences in spectral shape at different $t_1/2$. Note also the constant singlets of the methyl protons of creatine and choline in the experimental spectra.

by the product of three factors, one polynomial term and two sinusoidal terms (Eq. (2)). In particular, the argument of one of the sinusoidal terms is field independent (JTE/2) while the argument of the other (ΩTE/4) is a function of the chemical shift and, as such, field dependent. In other words, some of the zeros of the oscillation amplitude are field dependent while others are field independent. The total amplitude as a function of TE is shown in Fig. 3, left panel, for the field strength of 1.5 T (dashed line) and 3 T (continuous line). Since the amplitude of the two sinusoidal terms can only oscillate between 0 and 1, the polynomial term plays an important role in characterizing the total amplitude of oscillation. The amplitude of the polynomial term is dependent on the magnetic field strength. It reaches a maximum between 3 and 4 T (Fig. 3, right panel) and slowly decreases as a function of the magnetic field strength until, in the limit of a weakly coupled system, the polynomial term vanishes all together. This result shows that both for uncoupled systems (equivalent to 0 T) and for weakly coupled systems (e.g., very high field strengths for citrate), the $t_1/2$ modulations vanish. Finally, the amplitude as derived from the analytical solution agrees well with that obtained with the density matrix simulations (not shown).

The assessment of the relevant coherences for the strongly coupled AB spin system, under PRESS excitation, provides additional insight into the characteristics of the $t_1/2$-dependent signal oscillations. The temporal evolution of the coherences for the citrate spin system at 3 T, at values of TE where the $t_1/2$ modulations vanish, is shown in Fig. 4. Following excitation, the transverse magnetization evolves into a mixture of the y and x in-phase and antiphase coherences. At TE = 81 ms (which corresponds to a field dependent zero of the amplitude of the signal oscillations, see Eq. (3) and Fig. 3, left panel) all four coherences at the onset of the acquisition are independent of $t_1/2$ (Fig. 4, left panel). This means that changing $t_1/2$ has no effect on the spectrum. On the other hand, at TE = 125 ms (which corresponds to a field independent zero of the amplitude of the signal oscillations) only $\{I_{y1} + I_{y2}\}$ is independent of $t_1/2$ at the onset of the acquisition. Since $\{I_{y1} + I_{y2}\}$ represents the signal intensity, changing $t_1/2$ will not affect the spectral area, but it will affect the spectral shape. Thus, the temporal evolution of the coherences indicates that: (i) at those TEs which correspond to the field dependent zeros, the spectral area and the spectral shape of the citrate multiplet do not change with $t_1/2$ and (ii) at those TEs which correspond to the field independent zeros, the spectral area does not change with $t_1/2$, but the spectral shape does change. It should also be noted that in the weakly coupled system only the y in-phase $(I_{y1} + I_{y2})/2$ and antiphase $(\mathrm{I}_{x1}\mathrm{I}_{z2} + \mathrm{I}_{z1}\mathrm{I}_{x2})$ coherences are generated during PRESS excitation. Further, the temporal evolution of the coherences for the citrate spin system at 3 T, at the value of TE where the $t_1/2$-dependent modulation is maximal (TE = 280 ms), is shown in Fig. 5. At the onset of the acquisition, the large difference in signal intensities obtained by changing the value of $t_1/2$ is noticeable. The values of the in-phase y and x magnetization and antiphase y and x magnetization, at the onset of the acquisition, are in perfect agreement with the values calculated using the analytical formulae provided by Trabesinger et al. [22]. For example, for the citrate spin system at 3 T, with $t_1/2 = 10$ ms and TE = 280 ms, the values of the in-phase y and x magnetization and antiphase y and x magnetization obtained with our simulation were (0.838, 0.187, −0.129, and 0.495), which are equal to the values (0.838, 0.187, −0.129, and 0.495) calculated using the analytical formulae.

The simulated and experimental proton MR spectra of citrate at a fixed TE, for two different $t_1/2s$, as well as the

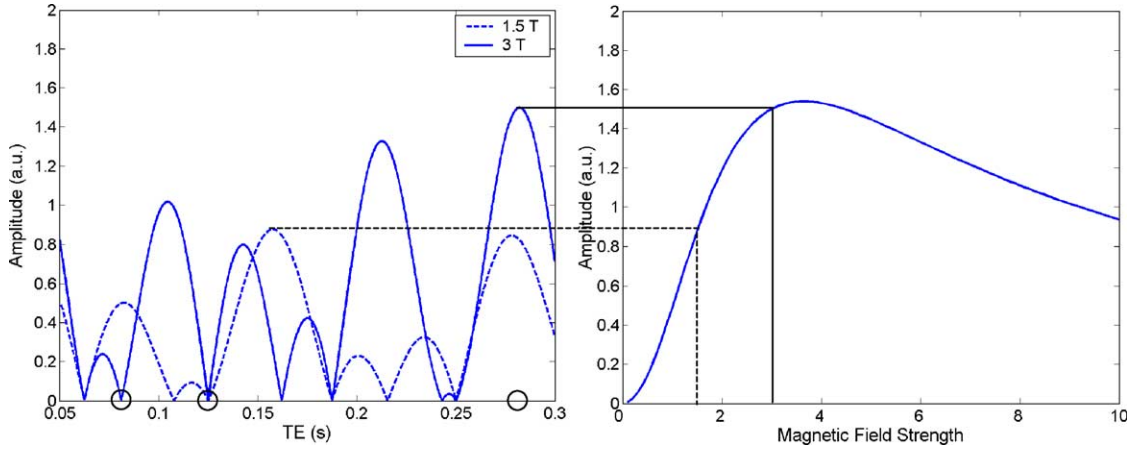

Fig. 3. The amplitude of the $t_1/2$-dependent signal modulation, obtained from the analytical solution for the strongly coupled AB spin system under PRESS excitation. (Left panel) Total signal amplitude, as a function of TE, for the spin system of citrate, at 1.5 T (dashed line) and at 3 T (continuous line). Note a maximum at TE ~160 ms, for 1.5 T (dashed horizontal line), and at TE ~280 ms, for 3 T (continuous horizontal line). The circles indicate the values of TE which are employed in the simulations of the temporal evolution of coherences (see Figs. 4 and 5). (Right panel) The amplitude of the polynomial term (see Eq. (2)) of the signal modulation, as a function of magnetic field strength. The amplitude reaches a maximum at a magnetic field strength of ~3 T.

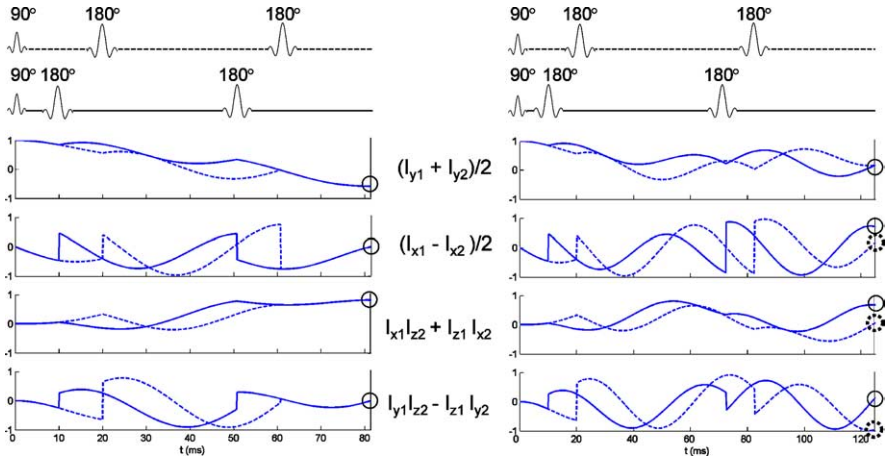

Fig. 4. Time evolution of the coherences for the spin system of citrate, at 3 T, during PRESS excitation, for echo times where the $t_1/2$ modulation vanishes. (Left panel) Normalized amplitude of the y and x in-phase and antiphase coherences for an echo time (TE = 81 ms) which correspond to a field dependent zero of the oscillation amplitude. Dashed lines represent the evolution of coherences for $t_1/2 = 10$ ms, while continuous lines represent the evolution for $t_1/2 = 20$ ms. At the onset of the acquisition, the signal intensity ($I_{y1} + I_{y2}$) and the other coherences are independent of the position of the refocussing pulses. The circles indicate the values of coherence amplitudes at the onset of the acquisition. The timings of the pulse sequences are displayed on top of the evolution graph. (Right panel) Normalized amplitude of the y and x in-phase and antiphase coherences for an echo time (TE = 125 ms) which correspond to a field independent zero of the oscillation amplitude. At the onset of the acquisition, the signal intensity is independent of the position of the refocussing pulses, while the values of the other coherences depend on the sequence timings.

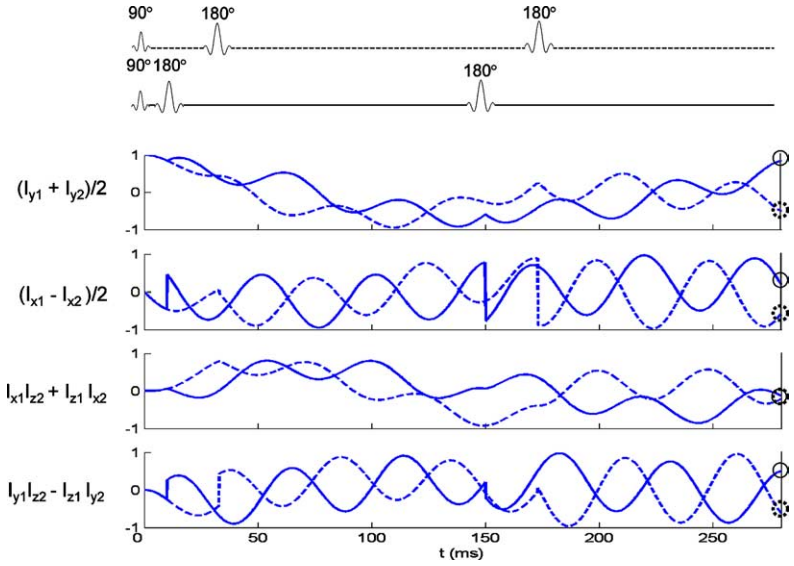

Fig. 5. Time evolution of the coherences for the spin system of citrate during PRESS excitation, for the echo time (TE = 280 ms) which corresponds to the maximum of the $t_1/2$ modulation at 3 T. Continuous lines represent the evolution of coherences for $t_1/2 = 10$ ms, while dashed lines represent the evolution for $t_1/2 = 33$ ms. At the onset of the acquisition, a substantial difference between the signal intensity ($I_{y1} + I_{y2}$) of citrate is noticeable. The circles indicate the values of coherence amplitudes at the onset of the acquisition. The timings of the pulses are displayed on top of the evolution graph.

difference spectra are shown in Fig. 6. At 3 T, the $t_1/2$-dependent J modulation at TE = 280 ms generated a quasi-inverted spectrum when $t_1/2$ was changed from 10 to 33 ms (that is, when $t_1/2$ is increased by the value of $T/2 \sim 20$ ms at 3 T). At 1.5 T, MR spectra were also acquired from a single voxel in the prostate of a patient with prostate cancer, to test the in vivo applicability of this method. The in vivo proton MR spectra [TE = 160 ms, $t_1/2 = 15$ ms (A), and TE = 160 ms, $t_1/2 = 45$ ms (B)] are shown in Fig. 6. The difference spectra obtained in vivo (C) and in vitro (D) display the same spectral pattern for the citrate signal. Resonances for lipids at ~1.3 ppm and choline compounds at 3.2 ppm are efficiently suppressed. Note that no additional lipid signal suppression was used in the PRESS localization.

4. Discussion

A significant $t_1/2$-dependent J modulation of the MR signal in the strongly coupled AB spin system, under PRESS excitation, is here predicted from analytical solutions and density matrix simulations. The modulation is

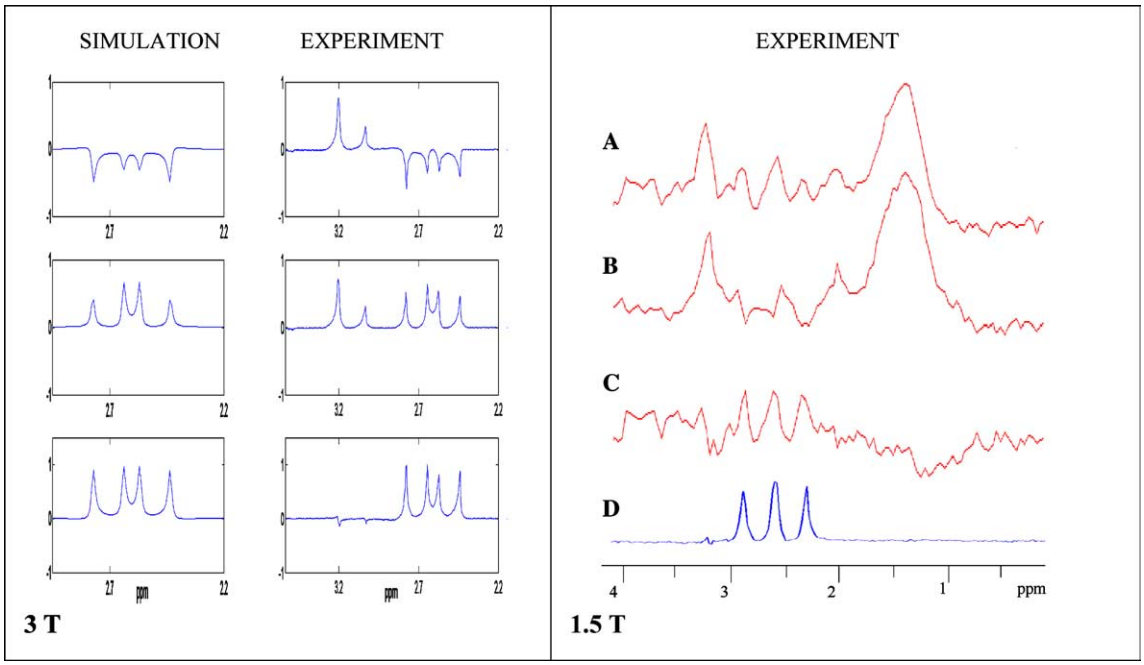

Fig. 6. Difference proton MR spectroscopy of citrate at 3 and 1.5 T. (Left panel) Simulated and experimental proton MR spectra of citrate (TE = 280 ms) at $t_1/2 = 33$ ms (top), $t_1/2 = 10$ ms (middle) and the difference spectra (bottom) at 3 T. (Right panel) Experimental proton MR spectra of citrate in vivo (TE = 160 ms) with $t_1/2 = 15$ ms (A), $t_1/2 = 45$ ms (B) and the difference spectra (C) at 1.5 T, from the prostate of a patient with prostate cancer. In the difference spectrum, note the removal of the resonances of the methyl protons of creatine and choline (3–3.2 ppm), and of the lipid resonances (~1.3 ppm). The in vivo difference spectrum (C) displays the same spectral shape as the in vitro one (D).

such that, at certain echo times, by increasing $t_1/2$ by a few tens of ms, a complete inversion of the spectral lines can be obtained. This effect has been investigated here in detail on the proton spins of citrate—chosen as a model of a strongly coupled AB spin system—at 1.5 and 3 T, and verified experimentally at both magnetic field strengths.

The $t_1/2$-dependent signal modulation could provide a novel spectral editing approach that employs a standard PRESS sequence. The spectral shape of the MR signal of a strongly coupled AB spin system under PRESS excitation—as shown here—depends significantly on the interpulse delay $t_1/2$, at certain TEs. Therefore, by knowing the exact behavior of the strongly coupled spin system as a function of $t_1/2$ and TE, it is possible to identify an echo time such that two different interpulse delays will result in two completely different spectra, because of the J modulation. Thus, by subtracting one spectrum from the other, coupled resonances which lie underneath singlets can be resolved, since the shape and intensity of singlets depend exclusively on TE.

The amplitude and frequency of the $t_1/2$-dependent signal oscillation depend on the magnetic field strength B_0. In particular, the frequency of the oscillation increases with B_0; this means that, at a higher magnetic field strength, smaller changes in $t_1/2$ are needed to move from a maximum to a minimum of the signal intensity. Further, for the spin system of citrate, the amplitude of the oscillation displays a maximum at a magnetic field strength B_0 just above 3 T, a magnetic field strength becoming more prevalent for clinical use. In general the amplitude of the $t_1/2$ modulations vanishes in the very low field limit, where the chemical shift differences between spins vanish, and also at very high fields where the weak coupling solutions prevail (Fig. 5). Formally, the weak coupling approximation involves ignoring terms in the Hamiltonian that do not commute with the main MR Hamiltonian which is proportional to the total z-angular momentum operator. Under these conditions it is easy to derive expressions for PRESS echo maxima of weakly coupled spin systems AX, AX_2, AX_3, etc., which do not depend on $t_1/2$ but only on the echo time TE, at the condition of using ideal pulses. We conclude that it is only when the non-secular terms which do not commute with the primary MR Hamiltonian are included that $t_1/2$ modulations exist and that these will become quite small as the weak coupling approximation becomes more relevant (e.g., higher field).

Another interesting finding of this study is that, at certain TEs, not only the spectral peak area but also the spectral shape is independent of the position of the RF pulses. It is not obvious yet how to exploit this effect; furthermore, it is not clear yet whether these "magic" TEs are also present in the signal of strongly coupled spin systems more complex than the AB system.

It should be pointed out here that the $t_1/2$ signal dependence investigated in this study does not arise from flip-angle distribution or off resonance effects [12,23]; in both density matrix simulations and analytical solutions, in fact, ideal pulses were considered. The experiments showed also a good agreement with the simulations and analytical solutions, which further indicates that the effects arising

from pulse imperfections were negligible with respect to the significant changes in spectral shape due to different $t_1/2s$.

In this study, the proof of principle of this variant of difference MR spectroscopy for human applications is also given. We applied this method to edit the citrate resonances in vivo in the human prostate. The echo time of 160 ms was selected in order to obtain a substantial inversion of the proton signals. At shorter TEs (e.g., 80 ms) signal loss due to T_2 relaxation is less and editing would still be possible with other combinations of $t_1/2s$. Furthermore, difference MR spectroscopy was performed by acquiring sequentially two signals with different $t_1/2s$; with interleaved acquisition a better performance is expected.

The ultimate potential of this approach could be to acquire rapid MR images of citrate without lipid signal suppression. Although currently robust lipid signal suppression sequences are available for ^{1}H MRS of the prostate [25], field differences may still cause substantial overlap of lipid signals from outside the prostate with citrate signals, in particular close to the prostate capsule. Furthermore, as the T_1 of citrate proton spins is relatively short [26], the selective imaging of citrate could be performed more rapidly or with a higher spatial resolution than spectral mapping.

This editing approach has the advantages of being simple and directly applicable on standard clinical MR scanners, provided that the exact behavior of the resonance is known. For the AB spin system, the Liouville equation has been solved and, thus, the analytical solution is available. For more complex strongly coupled systems, density matrix simulations are needed to predict the signal behavior. We are currently investigating the application of this method to proton MR spectroscopy of brain, where there are a number of metabolite protons that behave as strongly coupled spin systems, at the magnetic field strength of clinical scanners. Preliminary results (density matrix simulations and in vitro experiments) on GABA ($I_2S_2W_2$ spin system) indeed show the $t_1/2$-dependent signal modulation in spectra acquired with the PRESS sequence [27]. Certainly, as the spin systems become more complex, a decrease in spectral editing efficiency is expected; further, the overlap of numerous coupled resonances in the crowded spectra of brain will require detailed analyses for all the resonances, and thus further studies are needed to validate the efficacy of the current editing method in brain spectroscopy.

Finally, the results of this study also indicate that, for spectral shape optimization of strongly coupled spin systems, attention has to be paid not only to TE but also to the $t_1/2$ interpulse spacing, since a more favorable line shape could be obtained by properly choosing the $t_1/2$ interpulse spacing. As the field strength of whole body scanners continues to rise—now 3 T scanners are rapidly getting established in clinical settings—optimization of sequence parameters at new field strengths is particularly important. The rule of thumb of using the shortest possible $t_1/2$ in a PRESS sequence, to minimize propagation of the multiple coherences, might not apply anymore for optimization of spectral shapes, since longer values of $t_1/2$ could provide the most useful spectral shape.

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