'Baseline' problems in very short echo-time proton MR spectroscopy of low molecular weight metabolites in the brain

Zenon Starčuk, Zenon Starčuk jr., Jaroslav Horký

Institute of Scientific Instruments, Academy of Sciences of the Czech Republic,
Královopolská 147, 61264 Brno, Czech Republic, e-mail: zenon@isibrno.cz

Abstract: *Accurate and reliable quantification of low molecular weight metabolites in short echo-time proton MR spectra of the brain is usually considerably complicated by an uncharacterized broad baseline extending over the whole frequency range of the metabolite signals of interest. Several sequences providing pure MR spectra of cerebral metabolites were designed, computer analyzed and experimentally tested. In these sequences, precautions have been made to avoid baseline contributions due to experimental imperfections, and signals of low molecular weight metabolites were distinguished from those of macromolecules (lipids), which are substantial contributors to the broad baseline, by utilizing the differences between their T_1 relaxation times.*

Introduction

Short echo-time (*TE*) proton MR spectroscopy is capable of providing substantial quantitative information on many low molecular weight metabolites (MB) present in the brain. However, obtaining accurate and reliable quantitative data of these metabolites is, as a rule, a difficult task. One of the crucial factors introducing errors into the quantitative analysis of metabolites in short *TE* spectra is the broad uncharacterized background underlying the resonances of the metabolites of interest *(1-12)*. Commonly, this baseline is a superposition of several components, which, in principle, can be classified in two different types.

Components of the first type are principally avoidable and originate mainly in various experimental artifacts, such as improper spatial localization, resulting in contamination of the spectrum of interest by signals (mainly of water and extracranial lipids) from outside the volume of interest (VOI), in residual tails of insufficiently suppressed water resonance present inside the VOI, in water modulation sidebands created by acoustic vibrations of the gradient system, in false misregistration and misinterpretation of the first data points, etc. Intrinsic components of the brain tissue are the baseline contributors of the second type. It has been found that short T_2 signals of macromolecules (mobile polypeptides, MM) are the basic intrinsic contribution to the baseline in the healthy brain *(7,11)*. Furthermore, in some pathologies, signals of mobile lipids may appear in the brain and contribute to the baseline as well *(5,8)*.

Mainly components of the first type make the baseline uncharacterized, and are the main reason why in model fitting of the MR spectra of metabolites analytically or iteratively defined baselines have been predominantly employed until now *(2,3)*. However, this approach is in principle inaccurate, arbitrary, and can be a serious source of systematic errors.

A better way is to treat the baseline problem experimentally. In this case, first, baseline components arising from experimental imperfections must be removed. Then, resonances belonging to macromolecules (lipids) and metabolites must be effectively distinguished. For the MB/MM differentiation, especially differences in relaxation times (both T_1 and T_2) of these two species can be exploited. For instance, in a 3 T magnetic field, the relaxation times of metabolites are about 4-5 times longer than those of macromolecules. For several reasons, MB/MM discrimination based on the differences in T_1 is more suitable than utilizing the differences in their T_2 relaxation times *(9-12)*. In T_1 based techniques, inversion-recovery and saturation-recovery provide the desired MB/MM separation effect.

Two different approaches are used for obtaining pure MB spectra. In a single step approach, MB spectra are obtained directly with sequences nulling MM resonances. In a double step approach, MB spectra are obtained indirectly by a scaled subtraction of experimentally determined pure MM spectra from standard MR spectra, containing both MB and MM resonances. In both these approaches, the accuracy of MB spectra determination is complicated by the limited difference between T_1 times of MB and MM resonances and also by the common dispersion of T_1 values of both these species. In

MB/MM discrimination schemes based on inversion-recovery, use of two inversion-recovery episodes in the preparation periods can improve the quality of MB/MM discrimination, albeit at the expense of measurement sensitivity *(9,10,12)*.

The purpose of this work was to evaluate the basic performance of sequences for the determination of pure MB spectra constructed according the above given principles.

Methods

With some prior knowledge of relaxation times of MB and MM (Table 1), sequences for the direct (single-step) and indirect (double-step) determination of pure MB spectra in the brain have been designed, using either one or two inversion-recovery episodes in the preparation periods preceding the volume selection sequence STEAM. For the design of these sequences, simulations based on the numerical solution of the Bloch equations including both T_1 and T_2 relaxation have been employed. With regard to the sensitivity (SNR) and the specific absorption rate (SAR), repetition times $TR < 3$ s have been employed in all studied sequences, whose timing is given in Table 2. The proposed macromolecule-nulling sequences (S_{mb1}, S_{mb2}, and S_{mb3}) and metabolite-nulling sequences (S_{mm1} and S_{mm2}) are described by schemes

S_{mb1}, S_{mm1}: $[P_{I1} - d_{IR1} - \text{Loc} - d_{SR}] - [P_{I1} - \ldots$, and

S_{mb2}, S_{mb3}, S_{mm2}: $[P_{I2} - d_{IR2} - P_{I1} - d_{IR1} - \text{Loc} - d_{SR}] - [P_{I2} - \ldots$,

where P_{I1} and P_{I2} represent the inversion pulses, Loc includes the STEAM localization $[P_1 - TE/2 - P_2 - TM - P_3]$, and the proposed interpulse delays, d_{SR}, d_{IR1}, and d_{IR2} are defined in Table 2. In all sequences, inversion by 20-ms hyperbolic secant pulses and $TE = 10$ ms, $TM = 40$ ms were supposed; the delays exclude inversion pulses but include slice selection pulses to their respective focus points.

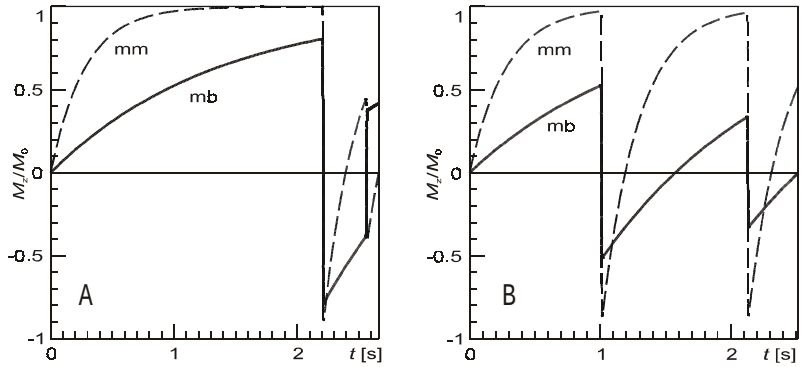
Table 1: Average T_1 and T_2 relaxation times [ms] of cellular metabolites and macromolecules

MB / MM	ppm	B_0 [T]									
		2.1 *(Ref. 11)*		3.0 *(Ref. 13)*		4.0 *(Ref. 15)*		4.7 *(Ref. 14)*		9.4 *(Ref. 7)*	
		T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2	T_1	T_2
NAA	2.01	--	--	1470	247	1630	185	1650	273	1410	144
tCr/PCr	3.03	--	--	1460	125	1720	140	1460	162	1340	104
Cho	3.22	--	--	1320	207	1290	142	1300	277	1370	147
tCr/PCr	3.93	--	--	970	116	--	--	1030	119	880	91
MM (average)		250	44	--	--	--	--	--	--	300	26

Experimental verification was performed on the human brain in a 3 T magnetic field, utilizing a 10-cm-diameter single-loop transmit/receive surface coil, and localizing a $2\times2\times2$ cm^3 volume centered 3 cm below the skull in the occipital lobe of a healthy volunteer. Water suppression was performed by a downfield-offset 3+1-pulse WASHCODE sequence in order to avoid problems with acoustic modulation sidebands. Because of software limitations, no OVS was performed. In STEAM with $TM = 50$ ms and $TE = 7$ ms, 2.15-ms asymmetric 90° RF pulses with optimized frequency profiles have been used for slice selection. Attention was paid to reducing all kinds of motion to make phase cycling as efficient as possible.

Table 2: Pulse sequence timings [ms]

Sequence	t_{SR}	t_{IR2}	t_{IR1}	TR
S_{mb1}	2460	-	170	2700
S_{mb2}	2355	220	35	2700
S_{mb3}	2187	335	88	2700
S_{mm1}	1700	-	730	2500
S_{mm2}	999	1100	371	2560
S_{std1}	2650	-	-	2700
S_{std2}	3950	-	-	4000
S_{std3}	5950	-	-	6000



MM and MB magnetizations M_z during double-inversion sequences for (A) MM- (B) MB-nulling.

Results

For these sequences, the dependences of detection or suppression efficiencies of MB and MM resonances on their relaxation times have been investigated. The data in Table 3 were computed for $T_{1(MB)} = (1.35 \pm 0.1)$ s, $T_{1(MM)} = (0.28 \pm 0.03)$ s, $TE = 10$ ms, $TM = 40$ ms. For MM detection schemes a MB intensity reduction factor of 0.7 due to the truncation and/or apodization was taken into account. The values of line intensity per unit time ($S/\sqrt{TR}$) are normalized with respect to the standard sequence S_{std1}, providing, for instance, the MB/MM ratio of NAA (2.02 ppm) and the macromolecule M1 (0.9 ppm) signals of ~4.

Table 3: Detection efficiencies and suppression factors

MB detection					MM detection				
Seq.	*TR* [s]	MB/$\sqrt{TR}$	MM/$\sqrt{TR}$	MB/MM factor	Seq.	*TR* [s]	MB/$\sqrt{TR}$	MM/$\sqrt{TR}$	MM/MB factor
S_{std1}	2.7	1.0	1.0	1.0	S_{std1}	2.7	0.70	1.0	1.4
S_{std2}	4.0	0.895	0.82	1.09	S_{std2}	4.0	0.63	0.82	1.3
S_{std3}	6.0	0.753	0.672	1.12	S_{std3}	6.0	0.53	0.67	1.3
S_{mb1}	2.7	0.670	0.074	9.1	S_{mm1}	2.5	0.018	0.90	50
S_{mb2}	2.7	0.592	0.042	14	S_{mm2}	2.56	0.0035	0.52	150
S_{mb3}	2.7	0.470	0.010	47					

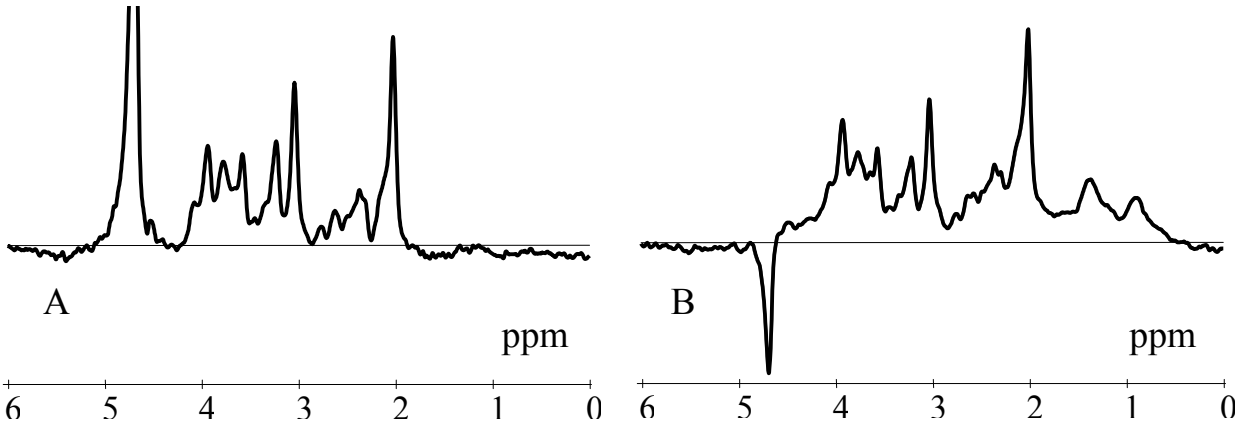
Discussion

For the combined MB and MM detection by a standard nondiscriminating sequence, the minimum repetition time $TR > 1.75$ s such that the SAR is safely within the allowed limits should be chosen. As shown in Table 3, extending *TR* reduces the SNR per unit time (SNRT). Compared with the standard sequence S_{std1}, the MM nulling sequences reduce the MB detection efficiency. A strong correlation between the improvement of MB/MM discrimination and the MB detection efficiency decrease has been found.

For instance, the MM-nulling double-inversion sequence S_{mb3} with a 47-fold improvement of the MB/MM ratio (achieving MB/MM ~ 190) has a detection efficiency of only 47%.

In the comparison between the direct and indirect strategies for obtaining pure MB spectra, the signal truncation effect has to be considered as well. With an α-fold acquisition time reduction (α~1/4 may be assumed), the noise is reduced from N to $N\sqrt{\alpha}$. In subtracting the MM spectrum from a standard spectrum, the MM intensity must be identical, and it is reasonable to require that both spectra have the same level of noise. This is achieved by a proper choice of the number of acquisitions of the two types of signals and by adjusting the scaling factor of the MM spectrum subtracted. The final MB detection efficiency is then related to the component efficiencies $\sigma_{mb\_std} = MB/\sqrt{TR}$, $\sigma_{mm\_std} = MM/\sqrt{TR}$ in the standard sequence, and $\sigma_{mb\_mm} = MB/\sqrt{TR}$ in the MB-nulling sequence by a formula $\sigma_{mb\_std}\,[2\,(1+\alpha(\sigma_{mm\_std}/\sigma_{mm\_mm})^2)]^{-1/2}$. For a combination of S_{std1} and S_{mm2}, the values of Table 3 yield a MB detection efficiency of 51%.

This shows that from this point of view, both strategies are well comparable. The advantage of the former is avoiding data manipulation, while the latter has the advantage of providing separate information on MM in the subtracted spectrum.



In vivo ^1H MR spectra measured (A) with a double-inversion MM-nulling sequence S_{mb2} and (B) with a standard sequence. The spectra were normalized according to the NAA peak at 2.02 ppm. Details in text.

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References

1. Kreis, R.: Prog. NMR Spectrosc.31 (1997) 155-193.
2. Young, K. et al.: Magn.Reson.Med. 40 (1998) 816-821.
3. Young, K. et al.: Magn Reson. Med. 40 (1998) 822-831.
4. Gasparovic, C. and Berghmans, K.: Magn. Reson. Med. 41(1999) 293-298.
5. Saunders, D. E. et al.: J. Magn. Reson. Imaging 7 (1997) 1116-1121.
6. Tkáč, I. et al.: Magn. Reson. Med. 41 (1999) 649-656.
7. Pfeuffer, J.: J. Magn. Reson. 141 (1999) 104-120.
8. Seeger, U. et al.: Magn. Reson. Imaging 17 (1999) 1219-1226.
9. Starčuk, Z. et al.: Proc. ISMRM (1999) 1852.
10. Starčuk, Z. et al.: MAG-MA (2000) 180.
11. Behar, K. L. et al.: Magn. Reson. Med. 32 (1994) 294.
12. Starčuk, Z. et al.: Proc. ISMRM (2001) 1670.
13. Mlynárik V. et al.: MAG-MA (2000) 187-188.
14. Graaf R. A. et al.: Magn. Reson. Med. 41 (1999) 1136-1144.
15. Posse S. et al.: Magn. Reson. Med. 33 (1995) 246-252.