^{1}H MR DATA QUANTITATION: REPRODUCIBILITY EVALUATION BY SIMULATION

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Abstract: Magnetic Resonance Spectroscopy is a useful method for metabolism studies in vivo, in a non-invasive and non-ionizing manner. However, absolute quantitation is still not fully applicable. In the present paper we propose a method, based on simulation results, for evaluating the reproducibility of Magnetic Resonance Spectroscopy data quantitation, as function of the signal-to-noise-ratio and the number of signals acquisition.

Introduction

Magnetic Resonance is widely used as a non invasive means of obtaining clinically useful information; in particular, Magnetic Resonance Spectroscopy (MRS) offers a multi-metabolic approach for biochemical studies in vivo.

The application of a static field B_0 induces electronic currents in atoms and molecules, and these produce a further small field at the nucleus which is proportional to B_0. Therefore, the total effective field, B_{eff}, at the nucleus becomes[1]:

$$B_{eff} = B_0(1-\delta) \qquad (1)$$

where δ is the contribute of the small secondary field generated by the electrons. Then, the resonance frequency ν_0 becomes:

$$\nu_0 = \frac{\gamma}{2\pi} B_0(1-\delta) \qquad (2)$$

where γ is the gyromagnetic ratio. The δ value is dependent upon the electronic environment of the nucleus, and therefore nuclei in different chemical environments give rise to signals at different frequencies. So that: MRS signals are generated by applying a radio-frequency pulse to the sample; the signal from the sample is measured and Fourier transformed, in order to visualize and, possibly, to analyse the spectral shifts due to the chemical composition of the sample.

An accurate and efficient quantitation of MRS signals is the essential step prior to the conversion of the estimated signal parameters into biochemical quantities, although much effort is still needed to establish rigorous means for accurate analysis. In fact, MRS signals are characterized by low Signal-to-Noise-Ratio (SNR) and simple signal processing techniques are in general not adequate, [2]. Moreover, in proton MR spectroscopy (^{1}H-MRS) large solvent water resonance may cause problems on accurate quantitative analysis when not properly suppressed [3].

Furthermore, accurate quantitation is complicated by the presence of noise-induced errors. In literature, great effort has been directed towards minimizing noise levels in order to optimise the signal but in some instances, and particularly in vivo, where a lot of data should be acquired in a short time, the noise levels are higher than acceptable, leading to a reduced signal-to-noise ratio (SNR) and, consequently, to an increasing error on metabolites concentration estimation. One solution is to repeat signal acquisition and to perform signal averages in order to obtain less noisy signals; however, such solution is time consuming and not practicable when dynamic information is necessary: this is the case of functional spectroscopy or spectroscopic imaging, where a lot of spectra, covering a huge anatomic area, must be acquired. So that, fixing a high number of signal averages (NSA) is not always a good solution. It is therefore critical to know the limitations of such measurements and to determine how quantitation depends on SNR.

In this paper we present a method, based on simulation results, for evaluating the reproducibility of MRS data quantitation, as function of NSA and of SNR.

Methods

The proposed method is obtained through the following simulation and analysis steps.

MRS signals modeling: the function used to model the N points MRS signal is the sum of exponentially dumped complex sinusoids, as follows:

$$x(n) = \hat{x}(n) + \varepsilon(n) = \sum_{k=1}^{K} a_k e^{j\phi_k} e^{-(d_k + j2\pi f_k)n\Delta t} + \varepsilon(n)$$
$$n=0, \ldots, N-1 \qquad (3)$$

where K is the model order, $j=\sqrt{-1}$, a_k is the amplitude, ϕ_k is the phase angle, d_k is the dumping factor, f_k is the frequency of the k-th sinusoid (for k=1, ..., K), Δt is the

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MRS signal sampling interval and ε(n) is the complex white Gaussian noise; the ' ^ ' symbol on x indicates that this quantity represents the model function rather than the actual measurements.

MRS simulation: we simulated MRS signals according to Montecarlo method by using simulation parameters values similar to experimental ^{1}H-MRS signals. In particular: MRS signal data set is the sum of three components: residual water, five metabolites, and noise; according to the previous formula, residual water and metabolites peaks are simulated as exponentially dumped sinusoids. The central frequencies of the metabolites spectral peaks range from 60Hz to 210Hz; in particular: $f_1,...f_6$= [60, 90, 120, 150, 180, 210] Hz. The peaks amplitudes a_k, k=1,...,6, values are: [1, 1.1, 1.2, 1.3, 1.4, 1.5] (in arbitrary units) respectively. The dumping value d_k, k=1,..,6 is simulated with value 7 for all the peaks. The amplitude ratios between residual water and metabolites peaks are between 10 and 100, as it happens on experimental spectra, acquired using some water suppression technique. Water resonances have been simulated as a sum of seven peaks, according to [4], with peaks amplitudes a_w (w=1,...7), from 15 to 1150 (in arbitrary units), central frequencies f_w from – 8.40 Hz to 6.31 Hz, dumping factors d_w from 4.25 to 12.45.

Montecarlo simulation included the realization of a total of 5600 signals, grouped by series of 200 averaged MRS spectra; each series includes different NSA values and different Gaussian noise variance σ^2.

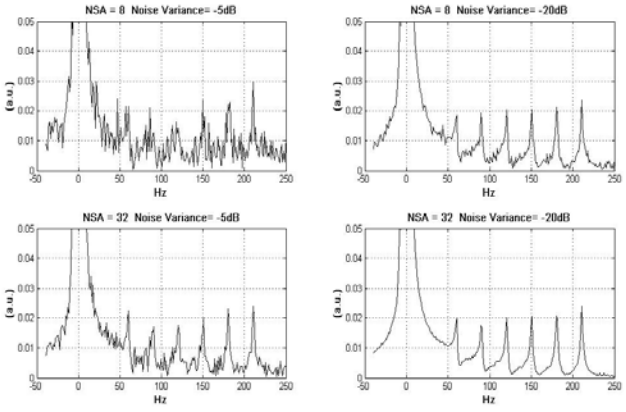

Figure: 1 Examples of simulated MRS spectra

Some examples of simulated MRS spectra are shown in figure 1. In particular, left spectra are relevant to signals generated for σ^2 = -5dB, while curves on the right are obtained for σ^2 = -20dB. Spectra on the higher part of the figure are relevant to NSA=8, that is a typical value in in-vivo experiments, and curves on the bottom are obtained for NSA = 32. From figure it is evident the presence of the residual water, with an amplitude sensibly higher than the peaks relevant to the simulated metabolites. On the spectra on the left of the figure 1, the presence of noise is also evident.

Model parameters estimation: such operation has been performed by using Maximum Likelihood estimates of the model parameters, by minimizing a so-called variable projection functional [2] after splitting the model function into a linear and nonlinear part. In more detail, in order to derive such functional, the model function (3) is modified as

$$\hat{x}(n) = \sum_{k=1}^{K} c_k \eta_k(\nu_k, n), \qquad n = 0,...,N-1 \qquad (4)$$

where c_k are the complex amplitudes i.e. $a_k e^{jfk}$, ν_k = $[f_k, d_k, \Delta t]$ and $\eta_k(\nu_k,n)$= $\exp(-d_k+j\pi f_k)n\Delta t$. Using matrix notation, (4) becomes:

$$\hat{\mathbf{x}} = \mathbf{N}\mathbf{c} \qquad (5)$$

So that, Maximum Likelihood estimation problem becomes to minimize the following cost function:

$$\left\|\mathbf{x} - \hat{\mathbf{x}}\right\|^2 \Rightarrow \left\|\mathbf{x} - \mathbf{N}\mathbf{N}^{+}\mathbf{x}\right\|^2 \qquad (6)$$

([2]), where $\mathbf{N}^+$ is the pseudo-inverse of $\mathbf{N}$, i.e. $\mathbf{N}^+$ = $(\mathbf{N}^H\mathbf{N})^{-1}\mathbf{N}^H$ and 'H' symbol is for denoting complex conjugate.

Then, the solution of (6) is found as a nonlinear least-squares problem, by searching for a local minimum.

Water suppression is obtained by discharging the estimated water coefficients on simulated MRS signals. In the simulation, SNR values are evaluated considering as signal the spectral peaks of the MRS, and as noise the variance of the Gaussian noise σ^2 that we used as input in the simulation.

Relative root mean squared error evaluation: the reproducibility of the quantitation is evaluated as the relative root mean squared error (RRMSE) in percent, between reference coefficients and estimated ones: the generic parameter p_k (i.e. a_k, f_k, ϕ_k,or d_k) relevant to the peak k is evaluated as

$$\mathbf{RRMSE}_{p_k} = 100\sqrt{\frac{1}{S}\sum_{s=1}^{S}\frac{\left(p_k - \hat{p}_k^s\right)^2}{p_k^2}} \qquad (7)$$

where S is the number of simulation runs and $\hat{p}_k^s$ is the estimate of p_k obtained in simulation run s.

Estimation accuracy evaluation by comparison with Cramer-Rao relative lower bound: in order to evaluate the estimate goodness, the RRMSEs are compared with the relative Cramer-Rao lower bounds (CRlb). CRlb is an index giving the best possible accuracy of an estimate for any unbiased estimator. The algorithm we implemented is described in [5].

Results

The figure 2 shows simulation results obtained for evaluating the RRMSE, as function of SNR and NSA.

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Data are relevant to the spectral peak amplitude of the peak at frequency 60 Hz (i.e. the parameter a_1 in (3)). The CRlb is also shown, in order to evaluate the accuracy of the estimation algorithm implemented.

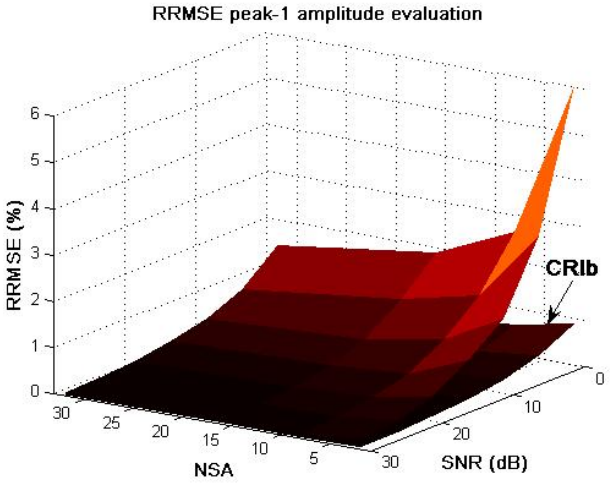

Figure 2: peak-1 amplitude RRMSE (in percent) values as function of NSA and SNR. The relevant CRlb is also shown.

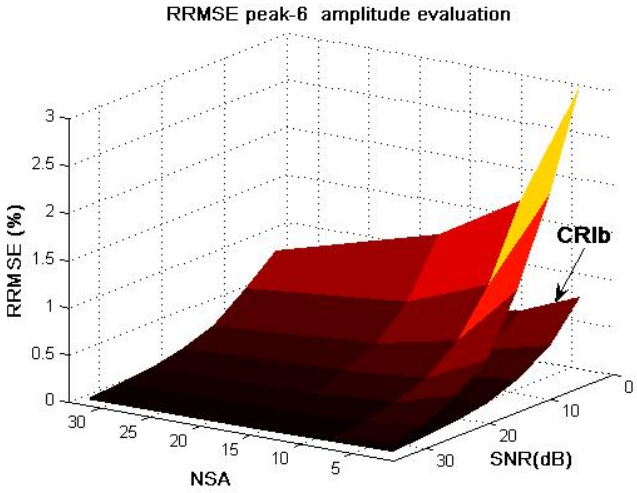

Figure 3: peak-6 amplitude RRMSE (in percent) values as function of NSA and SNR. The black curve is the relevant CRlb.

In figure 3 results relevant to peak-6 amplitude (i.e. parameter a_6 of (3)) estimation, together with the relevant CRlb, are shown.

From figures 2 and 3, it can be seen that the RRMSE values arise when NSA decreases or/and SNR decreases. The highest RRMSE value is present for minimum NSA and SNR. Such trend is maintained for all the estimated peaks parameters. We have also to note that RRMSE values from figure 2 are higher than the ones in figure 3: it seems that estimate of peak-1 amplitude (a_1 of formula (3)) parameter is less reproducible than a_6.

As far as the goodness of the implemented estimation algorithm, figures 2 and 3 show that the algorithm efficiency is enough sensitive to the SNR values; in fact, for lower SNR values, RRMSE values sensitively deviate from the relevant CRlb ones. The algorithm efficiency is almost insensitive to NSA changes. We also note that, extending the analysis to all metabolites parameters, differences between RRMSE values and CRlb are always less than 10%.

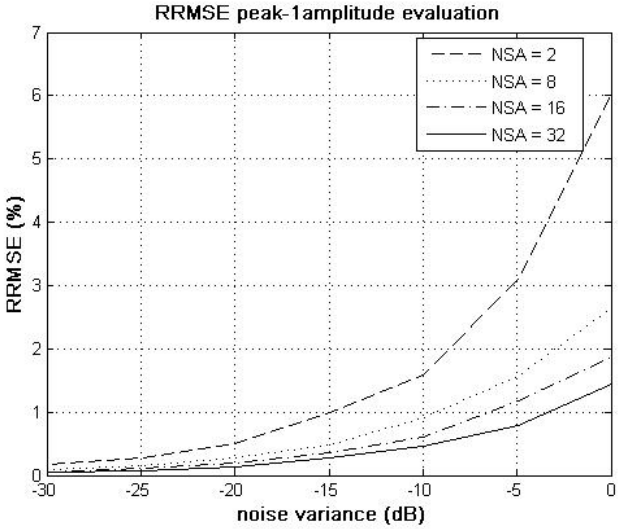

Figure 4: RRMSE relevant to peak-1 amplitude, as function of noise variance, in dB.

Figure 4 shows the RRMSE-peak1 amplitude as function of the Gaussian noise variance, σ^2, as used in the simulation, for different NSA values. As expected, RRMSE values arise with an exponential trend as σ^2 increases; moreover, for low NSA values, RRMSE increases, while it decreases for high NSA. Exponential trend shown in figure 4 is very similar for all simulated metabolites peaks.

Table 1:RRMSE (in %) values obtained by estimating peak-1 parameters

	NSA=8		**NSA= 32**	
σ^2	***-5 dB***	***-20 dB***	***-5 dB***	***-20 dB***
a_1	1.56	0.27	0.78	0.13
f_1	0.41	0.19	0.27	0.02
d_1	23.04	9.90	14.02	6.75

Table 1 shows the RRMSE (in %) values relevant to peak-1 parameters. In particular, the estimated parameters are the peak amplitude, a_1, the frequency, f_1 and the dumping factor d_1. Variations of RRMSE are shown for two σ^2 values, that are typical in experimental

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acquisitions: σ^2 = -5dB and –20 dB, and for two NSA values.

Table 2: RRMSE values obtained by estimating peak-1 parameters

	NSA=8		**NSA= 32**	
σ^2	***-5 dB***	***-20 dB***	***-5 dB***	***-20 dB***
a_1	1.03	0.18	0.53	0.079
f_1	0.05	0.017	0.05	0.008
d_1	12.72	3.94	8.15	1.36

Table 2 shows the same data as table 1, but they are relevant to peak-6.

Tables 1 and 2, show that for all estimated parameters, relevant to both metabolites 1 and 6, by increasing NSA, the estimation error (i.e. RRMSE value) decreases; by maintaining NSA value constant, for higher σ^2 values, RRMSE increases. Moreover, reproducibility of metabolites center frequencies f_k is the highest, while the dumping factor d_k is the worst, both for peak 1 (from table 1) and 6 (from table 2). All peak parameters estimation is better for metabolite peak 6 than for peak 1.

Conclusions

Simulation results suggest that the proposed MRS data quantitation algorithm allows a good reproducibility; we have demonstrated that, for acquisition parameters values typically used in experimental MRS exams, the estimation error remains quite low. The presence of residual water in the MRS signal is a problem that we partially solved by estimating its parameters and discarding them; however, from tables 1 and 2 we have seen that the error values obtained in estimating the first peak parameters is slightly higher than for the 6th peak ones, perhaps it is due to the presence of water components near the peak 1, as shown in figure 1.

Moreover, the proposed method allows determining the best NSA for a particular SNR and a prefixed relative RMS error, [6,7]. In fact, simulation results should be applied in experimental MRS as follows: 1) the SNR is estimated during acquisition phase as ratio between power spectral peaks and baseline variance in the time domain; 2) using simulated data, the best NSA is determined for a prefixed SNR.

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