Proceedings of the 28th IEEE
EMBS Annual International Conference
New York City, USA, Aug 30-Sept 3, 2006

Frequency-selective quantification of short-echo time Magnetic Resonance spectra

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Abstract— **Short-echo time magnetic resonance (MR) spectra contain large nuisance components which should be removed in order to improve quantification of the underlying metabolite concentrations. This paper shows that powerful filtering techniques such as the maximum-phase FIR filter or HLSVD-PRO proposed by Sundin *et al.* and Laudadio *et al.*, respectively, as used in long-echo time MR spectral quantification, can be applied to their more complex short-echo time spectral counterparts. Both filters are extensively studied in the presence of various unwanted components. In most of the cases the maximum-phase FIR filter outperforms HLSVD-PRO. The potential and limitations of both filters are reported.**

I. Introduction

Efficient and accurate quantification of metabolites from short-echo time in vivo MR spectroscopy (MRS) may be a very important aid in the correct noninvasive diagnosis of pathology. Quantification of short-echo (SE) time MR spectra provides more metabolite information than long-echo (LE) time spectra. Typically, LE time MR signals are modeled as sums of complex damped exponentials (lorentzian line-shapes in the Fourier domain), while SE time MR signals, although they share the same model, are modeled using a database of metabolite signals. Quantification of SE time MR spectra is complicated by broad baseline signal contributions, resonance line-shape distortions and the complexity of the spectra due to overlap in the frequency domain (see, *e.g.*, [1]). The water resonance may overlap with the metabolites of interest and the noise may be large in short-echo time MR spectra. The attention paid in the literature to denoising schemes for MRS data points out the importance of taking the noise into account in the quantification process [2]. Therefore, a quantification method of SE time MR spectra such as AQSES (described in [3]) needs an efficient and accurate filter implementation to remove the unwanted components. This paper considers three types of unwanted or nuisance components: the baseline, the water resonance and the noise. The quantification problem in AQSES is formulated as a separable nonlinear least squares fitting problem in the time domain, solved numerically using a variable projection procedure. A macromolecular baseline is incorporated into the fit via nonparametric modeling, efficiently implemented using penalized splines.

In order to validate the preprocessing methods in AQSES for SE time MR spectral quantification, this paper compares HLSVD-PRO [4] and the maximum-phase finite impulse response (MP-FIR) filtering [5], both implemented in AQSES. HLSVD-PRO is a subspace-based method for modeling a sum of damped exponentials, which can be used as a frequency-selective filter. In AQSES, HLSVD-PRO is applied, before entering the iterative quantification procedure, to the MRS signal and to each metabolite profile that forms the database. In contrast, MP-FIR is applied inside the iterative quantification procedure to the signal and to each **corrected** metabolite profile. However, the coefficients of MP-FIR are calculated only once since they do not depend on the corrections made on the metabolite profiles. Both methods have been successfully used for LE time spectral quantification, in particular for solvent suppression (see, *e.g.*, [6] and [7]). The choice of these methods results from their characteristics. HLSVD-PRO represents a good trade-off between efficiency (computation time) and accuracy compared to other subspace-based methods [8]. Applying MP-FIR boils down to matrix multiplication, resulting in a very efficient technique. For LE time MR spectra, it has been shown in [5] that MP-FIR outperforms subspace-based methods such as HLR or HLSVD in terms of accuracy and efficiency.

In this paper, we compare the performances of both filters in terms of robustness against the nuisance components and with respect to the choice of the filter parameters. Both filtering techniques are compared in a similar way as described in [5]. In order to estimate the metabolite amplitudes from the filtered spectra, we applied AQSES instead of AMARES [9] which is the most popular method for LE time MRS data quantification. Although AMARES has been applied to SE time spectra as described in [10], quantification algorithms based on the use of metabolite profile data sets such as LCModel, QUEST and AQSES (see, *e.g.*, [11], [12] or [13]) are preferred. Furthermore, the goal of the paper is to validate the filter preprocessing methods used in AQSES. The impact of the choice of the filter parameters, such as the bounds of the frequency region of interest or the model order, on the amplitude estimates has been investigated. The other filter parameters are automatically tuned [6].

This research work was carried out at the ESAT laboratory in the framework of EU funded projects BIOPATTERN (EU network of excellence, contract no. 508803), eTumour (FP6 integrated project, contract no. 503094) and Health-Agents (contract no. FP6-2002-IST 027213), the Concerted Action Project AMBIORICS and CoE EF/05/006 Optimization in Engineering of the Flemish Community, and Belgian Federal Science Policy Office IUAP P5/22 ('Dynamical Systems and Control: Computation, Identification and Modeling').

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II. Mathematical formulation

The short-echo time MRS signal y is modeled in AQSES in the time domain as

$$y(n)=\sum_{k=1}^{K} \alpha_k \, \zeta_k^n \, v_k(n)+b(n)+w(n)+\varepsilon_n,\, n=0,\ldots,N-1, \tag{1}$$

where $\{v_k,\ \text{for}\ k = 1,\ldots,K\}$ denotes the metabolite database, $\alpha_k\zeta_k^n$ the correction applied to each profile k in this database, $b(n)$ the baseline, $w(n)$ the water component (as well as other nuisance components), ε_n the unknown noise of zero mean and N the number of points. The complex amplitudes α_k and the complex signal poles ζ_k can be written as (with $j=\sqrt{-1}$):

$$\alpha_k = a_k \exp(j\phi_k), \qquad \zeta_k = \exp(-d_k + j2\pi f_k)\Delta t, \tag{2}$$

where a_k are the real amplitudes, ϕ_k are the phase shifts, d_k are damping corrections, f_k are frequency shifts and Δt is the sampling time. The whole signal is modeled as a sum of complex damped exponentials (or sum of lorentzians). Let

$$\hat{y}_k(n) = \alpha_k \, \zeta_k^n \, v_k(n), \tag{3}$$

where $\hat{y}_k$ is the kth individually corrected metabolite profile. The main goal of both filters is to filter out the water component w which is located at a known frequency region. The baseline b overlaps with the frequency region of the metabolites.

A. HLSVD-PRO in AQSES

The lorentzians located in the frequency region of no interest are subtracted from the initial metabolite profiles v_k such that

$$\hat{y}_{fil}(n) = \sum_{k=1}^{K} \alpha_k \zeta_k^n \left(v_k(n) - \sum_{w_k=1}^{W_k} \alpha_{w_k} \zeta_{w_k}^n \right), \tag{4}$$

where α_{w_k} and $\zeta_{w_k}^n$ denote the complex amplitude and complex pole (respectively) of the w_kth lorentzian of central frequency f_{w_k} of the metabolite profile k located in the frequency region of no interest, W_k being the total number of modeled lorentzians in that region. α_{w_k} and $\zeta_{w_k}^n$ are defined similarly as in Eq. (2) and $\hat{y}_{fil}$ denotes the estimate of the filtered MRS signal. This filtered model is used to fit a given signal y, which is filtered similarly.

B. Analytical validation of MP-FIR for short-echo time MRS quantification

MP-FIR was initially designed for long-echo time MRS quantification. This section shows that this filter can be applied to short-echo time MR spectra as well.

The effect of a FIR filter is defined by the convolution

$$y_{fil}(n) = \sum_{m=0}^{M-1} h(m) y(n-m), \tag{5}$$

where $h(m)_{m=0,\ldots,M-1}$ are the constant (possibly complex) filter coefficients and M is the filter order. By truncating the distorted first $M-1$ data points of this filtered signal, with $n=0,...,N-M$, $\hat{y}_{fil}(n)$ can be expressed as

$$\begin{aligned} & \sum_{m=0}^{M-1} h(m)\hat{y}(n-m+M-1) \\ = & \sum_{m=0}^{M-1} h(m) \sum_{k=1}^{K-1} \hat{y}_k(n-m+M-1) \\ = & \sum_{k=1}^{K-1} \hat{y}_k(n) \sum_{m=0}^{M-1} \sum_{p=1}^{P_k} h(m)\zeta_k^{-m+M-1}\zeta_{k,p}^{-m+M-1}, \end{aligned} \tag{6}$$

where we assume that each metabolite profile $v_k(n)$ can be modeled by a sum of lorentzians, i.e. $v_k(n) = \sum_{p=1}^{P_k} \alpha_{k,p}\zeta_{k,p}^n$, P_k being the number of lorentzians used to model the metabolite profile k. Note that the linear part, $\alpha_{k,p}$, and the nonlinear part, $\zeta_{k,p}$ are defined similarly as in Eq. (2). In order to keep the magnitude of the corrected metabolite profile k undistorted, *i.e.* $|\hat{y}_{fil,k}(n)| = |\hat{y}_k(n)|$, $|\sum_{m=0}^{M-1}\sum_{p=1}^{P_k} h(m)\zeta_k^{-m+M-1}\zeta_{k,p}^{-m+M-1}|$ should be equal to 1 ($\hat{y}_{fil}(n) = \sum_{k=1}^{K} \hat{y}_{fil,k}(n)$). If we assume the corrections on the metabolite profiles to be small enough, i.e. $\zeta_k^{-m+M-1} \simeq 1$, the condition for no distortion becomes $|\sum_{m=0}^{M-1}\sum_{p=1}^{P_k} h(m)\zeta_{k,p}^{-m+M-1}| \simeq 1$. This condition then leads to the formulation as used in [5] for the case of LE time MRS quantification, except that each metabolite profile is assumed to be a sum of lorentzians and not a unique lorentzian. Consequently, the remarks made in [5] are still valid for SE time MR spectra if the above assumptions are correct. The condition for no distortion of metabolite k can be rewritten as

$$|\sum_{p=1}^{P_k} \bar{h}\bar{\zeta}_{k,p}| = 1 \tag{7}$$

where

$$\bar{h} = (h_{M-1} \ \ldots \ h_0) \tag{8}$$

and

$$\bar{\zeta}_{k,p}=(1 \ \ e^{(-d_{k,p}+j2\pi f_{k,p})\Delta t} \ \ldots \ e^{(M-1)(-d_{k,p}+j2\pi f_{k,p})\Delta t})^T. \tag{9}$$

Selesnick *et al.* [14] provided tools for calculating the coefficients $h(m)$. Roughly speaking, the magnitude response of $\bar{h}$ is approximately equal to 1 in the frequency region of interest and equal to zero elsewhere. If we use the linear FIR by Selesnick, the components with higher damping factors $d_{k,p}$ will undergo a smaller gain than the other ones resulting in signal distortion as described in [5]. In order to reduce the effect of this distortion vector, Sundin *et al.* [5] proposed to transform the Selesnick's FIR filter into a maximum-phase FIR filter, moving most of the energy towards the first coefficients of $\bar{h}$ (i.e., $h_{M-1}, h_{M-2}, ...$).

III. Methods

In this section, we detail how the database, the simulated signals and the experiment are built up. The robustness of HLSVD-PRO and MP-FIR are compared with respect to the

choice of a variety of nuisance components and filtering regions.

A. Database and simulated signals

The database used in AQSES is identical to the one used in [3] with 8 metabolites: Myo-inositol (Myo), Phosphorylcholine (PCh), Creatine (Cr), Glutamate (Glu), N-acetylaspartate (NAA), Lactate (Lac), Lipid at 1.3 ppm (Lip1), Lipid at 0.9 ppm (Lip2). Simulated data were generated to compare both filtering methods, HLSVD-PRO and MP-FIR. One signal free from nuisance components (except for the reference peak at 8.44 ppm) has been chosen from set 1 in [3]. This signal, displayed in Fig. 1, was quantified perfectly (*i.e.*, no error in amplitude estimation) with AQSES. This guarantees that all estimation errors are due to nuisance components. For sake of clarity and space, only one signal (*i.e.*, one set of parameters a_k, ϕ_k, d_k and f_k) has been analyzed. Although different signal parameter values will lead to other results, one can expect that the general trends (*i.e.*, limitations and potential of each filtering technique) are preserved. The nuisance components have been added to this signal to generate 4 different sets of signals (2 baseline levels and 2 noise levels) as follows:

- set 1 = signal + low noise
- set 2 = signal + low noise + high baseline + water
- set 3 = signal + high noise
- set 4 = signal + high noise + high baseline + water

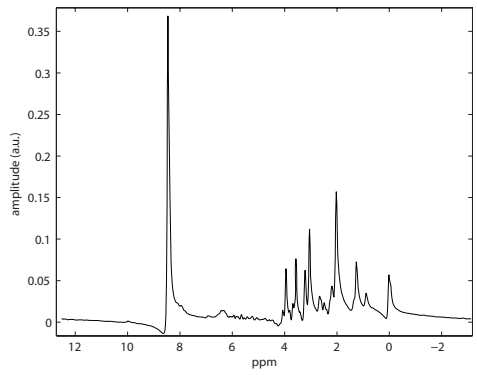

Fig. 1. Signal chosen from set 1 in [3].

The baseline distortion was based on information from Table 1 in [15]; the baseline is the sum of gaussians referred to as lip3, lip4, lip5, mm2, mm3 and mm4 in that paper. The water profile has been extracted from an in vivo spectrum by means of HLSVD-PRO. The SNR is defined as the ratio of the reference peak height at 8.44 ppm and the standard deviation of the circular white gaussian noise, both in the frequency domain. Low and high noise levels correspond to SNR=300 and SNR=75, respectively. Each set contains 256 simulated spectra. As illustration, one signal from set 4 is plotted in Fig. 2.

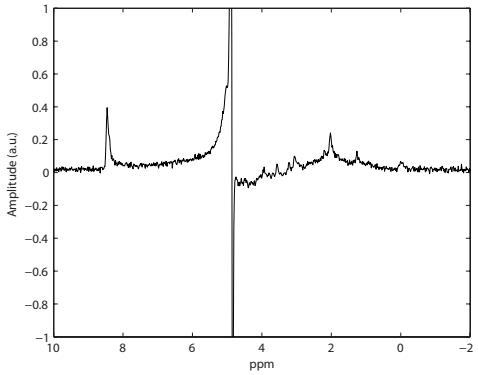

Fig. 2. Signal from set 4.

B. Methodology

In order to test the sensitivity of each method with respect to the frequency bounds of the nuisance region, we defined two filtering regions: [0.25,4.2], [0.25,4.5] in ppm. The frequency region close to the water resonance at 4.7 ppm is more sensitive than the other one. Therefore, we limited our study to the variations of the bounds for that region.

The effect of the nuisance components are tested with 6 experimental settings, which differ from each other regarding three options: choice between HLSVD-PRO or MP-FIR, the use of a baseline in the model or not, and the bounds of the region to be filtered. Note that these options can be easily defined in AQSES-GUI, the graphical user interface of AQSES [3]. The choice of the regularization parameter λ has been defined manually. This parameter is used only when the baseline is included in the model (as a linear combination of spline basis functions). For each set, the best value of λ (*i.e.*, providing the amplitude estimates closest to the true amplitudes) was chosen for each filtering technique, resulting in 2*4=8 values of λ for all sets.

The 6 settings were defined as follows:

- Experiment 1: Use of the **baseline** in the model and **MP-FIR** filtering in [0.25,**4.2**] ppm
- Experiment 2: Use of the **baseline** in the model and **MP-FIR** filtering in [0.25,**4.5**] ppm
- Experiment 3: **No** use of **baseline** in the model and **MP-FIR** filtering in [0.25,**4.2**] ppm
- Experiment 4: Use of the **baseline** in the model and **HLSVD-PRO** filtering in [0.25,**4.2**] ppm
- Experiment 5: Use of the **baseline** in the model and **HLSVD-PRO** filtering in [0.25,**4.5**] ppm
- Experiment 6: **No** use of **baseline** in the model and **HLSVD-PRO** filtering in [0.25,**4.2**] ppm

Each experiment was performed on each set defined in Section III-A. In order to compare the results of the different experiments, we use the relative root mean square error (RRMSE), defined as

$$RRMSE_k = 100\sqrt{\frac{1}{L}\sum_{l=1}^{L}\frac{(a_k-\tilde{a}_{k,l})^2}{a_k^2}}, \qquad (10)$$

where a_k (resp. $\tilde{a}_{k,l}$) is the true (resp. estimated) simulated

amplitude for metabolite profile k, l refers to the lth simulation and L is the total number of simulations within each set, i.e. 256. The model order used in HLSVD-PRO was fixed at 25 as recommended in [16].

IV. Results

The results are shown in Fig. 3. Each subfigure corresponds to one specific set. The RRMSE remains under 50% for all metabolites and all sets in the case of experiment 1, whereas it reaches values larger than 100% for some metabolites for HLSVD-PRO. HLSVD-PRO encounters more difficulties to estimate the parameters from the metabolites of lower concentration such as Lac, Lip1 and Lip2.

The smallest RRMSE are obtained when the baseline is modeled (*i.e.*, included in the model) and MP-FIR is used. Including the baseline into the model is especially interesting when the signal baseline is large. Nevertheless, we observe relatively large errors for set 2 and 4 even when the baseline is modeled. The differences between HLSVD-PRO and MP-FIR are larger when the signal contains a strong baseline. They show up for set 1 especially for Lac, Lip1 and Lip2, but they also appear for Cr and NAA in the presence of a high baseline. Moreover, these differences seem to be less pronounced in case of high noise at least for the metabolites Myo, PCh, Cr, Glu, NAA. Cr and Myo are less affected by the addition of the baseline than the other metabolites. Cr is known as not being correlated to the baseline [12]. The profile of Glu is relatively widely spread in the frequency domain. Therefore, in the presence of a strong baseline, Glu tends to fit a part of the baseline resulting in large errors for this metabolite. The fact that MP-FIR removes partially the baseline by truncation of the initial points while HLSVD-PRO does not, plays in favor of MP-FIR for this type of component.

The noise mainly affects the metabolites of lower concentration such as Lac, Lip1 and Lip2. HLSVD-PRO is less sensitive to the noise in the absence of a baseline (compare Fig. 3(a) with Fig. 3(c)). The water resonance does not have an important impact on the RRMSE as mentioned in [3].

HLSVD-PRO seems to be less sensitive than MP-FIR regarding the choice of the filtering region. We note that a filtering region too close to the water resonance can result in wrong amplitude estimates.

V. Discussion

In our experiments, we have investigated the sensitivity of MP-FIR and HLSVD-PRO used in AQSES with respect to the nuisance components and the filtering regions.

In general, MP-FIR exhibits much better results than HLSVD-PRO whatever the nuisance components are. This is particularly the case if the baseline is strong. Nevertheless, MP-FIR seems to be more sensitive to the noise which was expected since MP-FIR truncates the initial part of the signal resulting in a lower SNR.

The fact that the transition band is not specified beforehand [14] can be a problem when choosing a cutoff frequency too close to the water component. The MP-FIR finds the best transition bands for given ripple magnitudes in the frequency region of passband and stopband. Consequently, if the ripples are too severe, the transition will be enlarged such that the water component will be located in the transition band, resulting in worse amplitude estimates. However, we have noticed that in a reasonable range around 4.2 ppm ([4.0 4.3] ppm), the results were similar. Note that the typical attenuation of the FIR filter is -65 dB in the stopband which suffices for in vivo MR spectra with presaturated water resonance.

HLSVD-PRO is applied to each metabolite profile and to the signal with an identical model order. HLSVD-PRO increases the error of the final estimates because the number of peaks in each metabolite varies and certainly differs from the number of peaks in the signal to be processed. Indeed, HLSVD-PRO, being applied before correcting the metabolite profiles (and especially their frequency shifts), may remove partially, in the presence of noise, the metabolites of interest located in the frequency region where the metabolite profiles and the MRS signal do not match. In contrast, MP-FIR does not depend on the number of peaks. Since MP-FIR is applied at each iteration on the corrected metabolite profiles (see Eq. (6)), the transition band of this signal and the metabolite profiles of the basis set will match after a couple of iterations thereby avoiding border problems. Note that HLSVD-PRO could be applied after correcting the metabolite profiles. However, if numerous signals have to be processed (*e.g.* with MRS imaging data), HLSVD-PRO becomes computationally much more intensive since it involves an SVD decomposition of a large matrix [8] for each signal. The filter coefficients of MP-FIR are computed only once resulting in a fast method applicable in an iterative process. Adding the baseline in the model slows down the quantification procedure. However, it improves substantially the parameter estimates. For the simulated signals (1024 sample points), we noticed that less than 2s were needed per signal to obtain the parameter estimates when the baseline was modeled. Therefore, we recommend to model the baseline.

Finally, we noticed that the choice of the model order used in HLSVD-PRO was not crucial as long as it remains around 25 and is kept sufficiently high.

VI. Conclusions

This paper shows that HLSVD-PRO and MP-FIR, two filtering techniques used in LE MRS data quantification, can be successfully applied to SE time spectra. MP-FIR outperforms pure frequency-selective filtering methods such as HLSVD-PRO. Furthermore, a strong benefit in terms of accuracy can be obtained in the presence of a baseline in the MRS signal by using MP-FIR and modeling the baseline.

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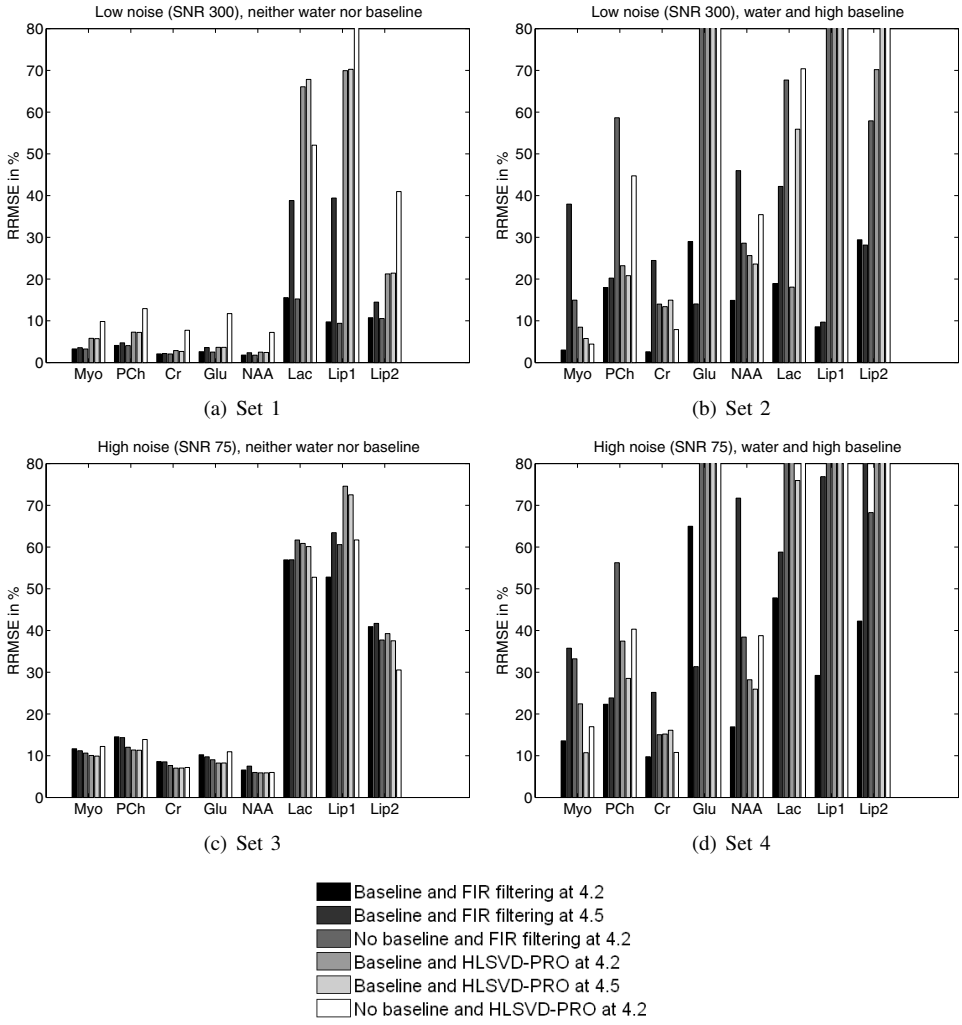

(a) Set 1 (b) Set 2

(c) Set 3 (d) Set 4

(e) Experimental settings

Fig. 3. Sensitivity of AQSES with respect to the filtering techniques, the nuisance components and the choice of the filtering region.

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