Quantification of *in vivo* Magnetic Resonance Spectroscopy signals with baseline and lineshape corrections

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***Abstract*—Quantification of Magnetic Resonance Spectroscopy (MRS) signals is a method to estimate metabolite concentrations of the tissue under investigation. Estimation of these concentrations provides information about the biochemical characteristics of the tissue and are finally used as a complementary information in the diagnosis of cancer, epilepsy and metabolic diseases. Obtaining reliable metabolite concentrations is still a challenge due to the experimental conditions affecting the spectral quality. The decay of MRS signals (lineshape of MR spectra), for instance, is affected by inhomogeneities in the magnetic field caused by shimming problems and tissue heterogeneities. To handle this type of distortions, we study a method where the unsuppressed water is used to correct lineshape distortions, an inversion recovery signal is used to account for macromolecules and lipids present in the tissue and splines are used to correct additional baseline distortions. In this study, we consider rat brain *in vivo* signals and quantify them taking into account both lineshape distortions and the background signal.**

I. Introduction

Magnetic Resonance Spectroscopy (MRS) signals provide the metabolite information of tissues used for the diagnosis of cancer, epilepsy and metabolic diseases. This information is estimated using quantification methods that provide the concentration of metabolites present in the tissue under investigation. Numerous methods have been developed to estimate metabolite concentrations, based on e.g. using time or frequency domain techniques to fit a model based on known metabolites to the signals under analysis [1]–[3]. MRS signals Fourier transformed to the frequency domain are called MR spectra. In this domain, the lineshape of each spectral component is commonly represented by a Lorentzian, Gaussian or Voigt function. In *in vivo* studies, the natural lineshape of MR spectra is highly affected by field inhomogeneities, tissue heterogeneities and movements of the patients causing unsystematic distortions, and not even higher-order shimming procedures are able to completely correct such alterations. Therefore, several signal processing methods have been proposed to correct for field inhomogeneities, eddy currents and other unwanted distortions [4]–[6]. The method used here to correct for lineshape distortions is inspired by [4], [7], where the unsuppressed water is used as a reference and a common distortion is assumed to be affecting all spectral components.

Another factor affecting *in vivo* signals comes from macromolecular and lipid contamination present in the tissues. In the frequency domain it is observed as an underlying profile (see Fig. 1 bottom), which overlaps with the metabolite peaks and makes quantification more complicated. This macromolecular signal can be either measured *in vivo* using an inversion recovery pulse or modeled using mathematical functions such as splines or Lorentzians [8].

In this study, we compare quantification results on healthy *in vivo* rat brain signals with and without lineshape distortions. Quantification is performed taking into account the presence of macromolecules and the effect of using the unsuppressed water for lineshape correction is evaluated.

II. Materials and Methods

1) Materials: MRS data were acquired on a 9.4 Tesla (T) Bruker Biospec small animal MR scanner (Bruker BioSpin MRI, Ettlingen, Germany) with a magnet bore of 20 cm using a 7 cm linear body resonator as transmitter combined with a circular polarized ^{1}H rat brain surface coil for signal reception. *In vitro* metabolites and *in vivo* Single Voxel Spectroscopy (SVS) signals were obtained using the PRESS pulse sequence [9] with implemented pre-delay Outer Volume Suppression (OVS) as well as the water suppression method, VAPOR [10]. MRS parameters are: repetition time of TR=8s, echo time of TE=20ms, bandwidth of SW=4KHz and 128 averages. Spectra were corrected for B_0 eddy currents as well as B_0 drift using the Bruker built-in routines. Shimming was performed using FASTMAP [11]. SVS and FASTMAP Volumes of Interest (VOI) were 4x4x4 mm^3.

We measured rat brain spectra from a voxel in the right hemisphere of the thalamus. Besides a well-shimmed signal, a distorted signal was acquired by mis-setting the shimming parameters producing in this way a lineshape distortion (See Fig.1). For studying one of the ways of facing the background problem, we measured the *in vivo* signal of macromolecules using an inversion recovery sequence with a 1ms Hermitian inversion pulse. The inversion time and repetition time were TI=800ms and TR=3s respectively and 1024 averages were acquired.

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The following metabolites were measured *in vitro* to be used as basis set: 50mM solutions of Alanine (Ala), Aspartate (Asp), Creatine (Cre), Gamma-Aminoburytic acid (GABA), Glucose (Glc), Glutamine (Gln), Glutamate (Glu), Glycerolphosphorylcholine (GPC), Glutathione (GSH), Lactate (Lac), Myo-Inositol (m-Ins), N-Acetyl Aspartate (NAA), Phosphorylcholine (PCh), Phospocreatine (PCr), Phosphoryl Ethanolamine (PE) and Taurine (Tau). Metabolites were dissolved in Phosphate Buffer Solution (PBS) and 5mM DSS was added as a chemical shift reference. GPC and PCh were dissolved in 100mM NaCl containing 5mM DSS. See Fig.2.

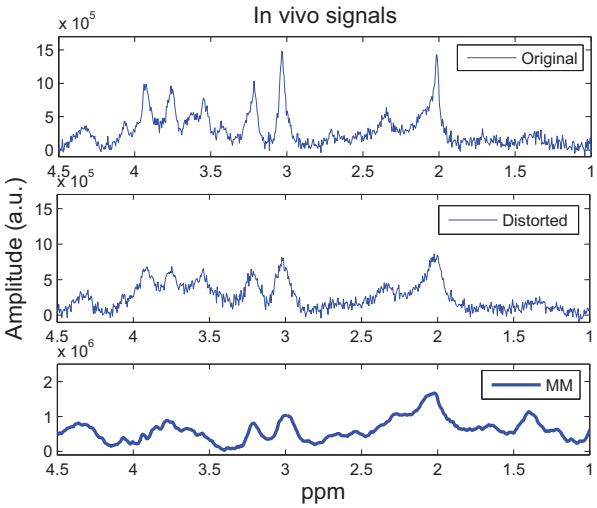

Fig. 1. Real part of the spectra with lineshape distortions and macromolecules-lipids background signal (MM). Top: Signal with good shimming. Middle: 'Distorted signal', acquired by mis-setting the shimming parameters of the second order shim coil Z^2. Bottom: macromolecules-lipids signal acquired with an inversion recovery sequence.

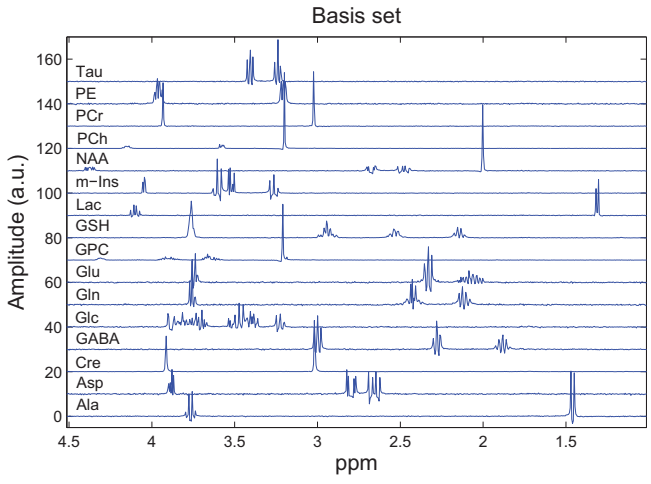

Fig. 2. Real part of the spectra of the *in vitro* basis set of metabolites acquired at 9.4T used for quantification of the signals.

2) Methods: The quantification method modified here is AQSES [3], a time-domain method that uses metabolite profiles to fit the signal under analysis and includes the modeling of the baseline using splines. The model used in AQSES to describe the MRS signal under investigation in the time domain is:

$$y(t) = \sum_{k=1}^{K} a_k e^{(j\phi_k)} e^{(-d_k t + 2\pi j f_k t)} v_k(t) + b(t) \qquad (1)$$

where $y(t)$ is the experimental signal, K is the number of metabolites, $v_k(t)$ the metabolite k in the basis set, a_k the amplitude, ϕ_k the phase shift correction, d_k the damping correction, f_k the frequency shift and $b(t)$ stands for the time domain baseline.

In this study, we include in the algorithm the case when the lineshape is distorted and has a profile differing from the known Lorentzian shapes. Due to the fact that the same spectral lineshape distortion is assumed for all components, corresponding to a common decay, the exponential dampings $e^{(-d_k t)}$ in Eq.(1) are replaced by a common factor *g(t)*, resulting in:

$$y(t) = g(t) \sum_{k=1}^{K} a_k e^{(j\phi_k)} e^{(2\pi j f_k t)} v_k(t) + b(t) \qquad (2)$$

In this study, we set $g(t)$ as a normalized version of the unsuppressed water signal, which is then multiplied to the metabolite basis set used for the quantification. After this procedure, the macromolecular signal obtained by inversion recovery is added to the basis set of metabolites used during the fitting procedure, but it is not corrected by the water signal.
The suppressed water in the *in vivo* signals was filtered using HLSVD-PRO [12]. Since the baseline is not flat in the water region, we estimate also a smooth baseline modeled with splines.

We compare the quantification between this modified AQSES including lineshape correction from the water signal with the original AQSES which does not include lineshape corrections.

III. Results and Discussion

Fig.3 shows the quantification fits for the *in vivo* undistorted MRS signal. It compares the fitting for the undistorted signal with and without lineshape distortions taken into account. In both cases, the measured baseline is included in the basis set and any additional baseline problems are tackled using splines.
Fig.4 shows the Amplitudes relative to Cr+PCr for the undistorted signal: the first bar corresponds to the standard AQSES results, the second bar to AQSES modified with the water reference and the last two correspond to values from

literature [13], [14].[1] Fig.4 confirms that for the undistorted signal, lineshape correction is basically not necessary. In general, there are insignificant differences between relative amplitudes. On the other hand, for strongly overlapping metabolites (Glc, Asp and Tau) relative amplitudes show small differences.

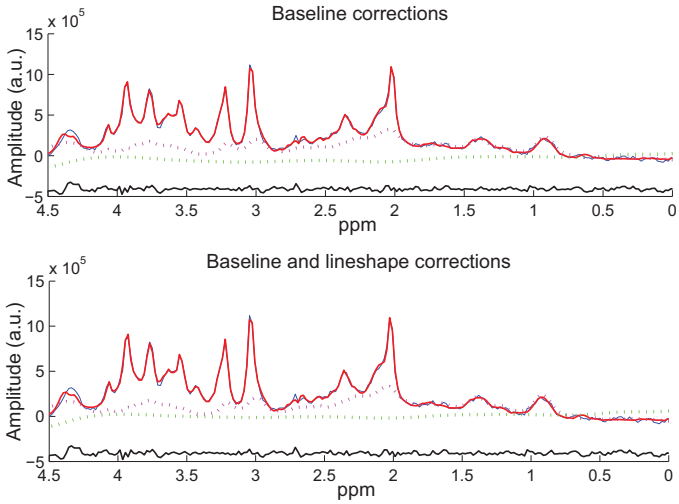

Fig. 3. Real part of the spectra of the fit for the undistorted *in vivo* signal. These quantifications are made including the measured macromolecules signal in the basis set. Top: results obtained with the standard method AQSES, bottom: results obtained with the modified AQSES with lineshape correction.

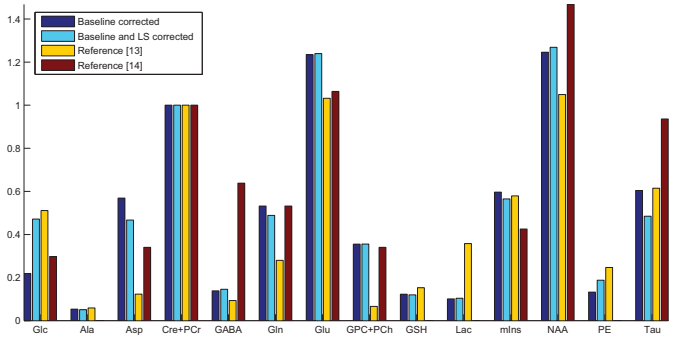

Fig. 4. Relative amplitude estimations of the original *in vivo* signal and literature. First bar corresponds to the standard method AQSES, the second one to the modified AQSES with lineshape corrections and the last two to the literature [13], [14].

In Fig.5 we show the results for the distorted signal and in this case the lineshape distortions are more significant. We obtain good fits using both approaches, however, a detailed observation of the NAA fit shows that the individual peaks are not correctly fitted when ignoring the lineshape problem. Fig.6 shows the amplitude estimations with the Cramér-Rao lower bounds (CRB) for the undistorted and the distorted signal when the lineshape correction is considered in the model. Estimations are similar and the CRB show a higher uncertainty for those metabolites in the regions with high overlap such as Ala, Glu, Gln, Lac and Tau. In particular, we observe an important influence in the region around 1.5 ppm where Ala and Lac are highly overlapping with lipids. Therefore, it is important to consider that the measured macromolecules may also contain some metabolites causing an underestimation of concentrations.

[1]Reference [13] reports absolute concentrations on spectra acquired with TE=20ms, TR=6s, at 9.T; reference [14] reports concentrations for TE=20ms, TR=5s, at 7T. Some of the metabolite amplitudes considered here are not available in these references.

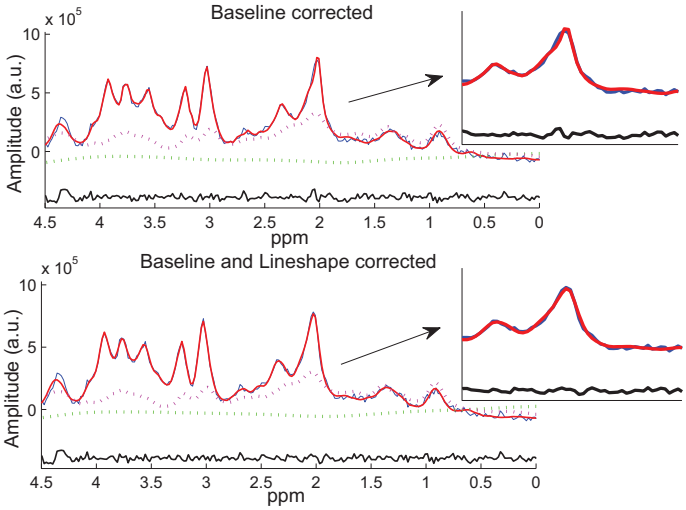

Fig. 5. Real part of the spectra of the fit for the distorted *in vivo* signal. These quantifications are made including the measured macromolecules signal in the basis set. Top: results obtained with the standard method AQSES, bottom: results obtained with the modified AQSES with lineshape correction.

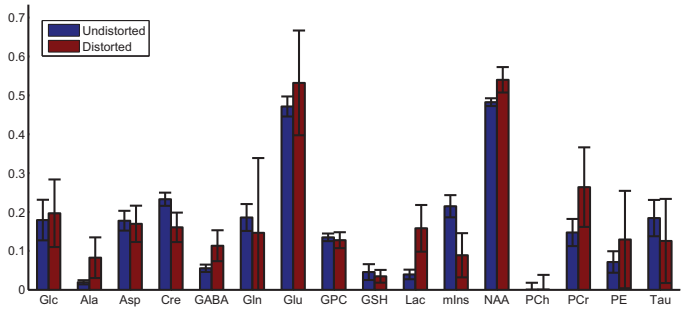

Fig. 6. Amplitude estimations of the undistorted and distorted *in vivo* signals with the corresponding Cramér-Rao lower bounds (CRBs).

IV. Conclusion

This study shows that unsystematic distortions affecting the typical lineshape of MRS signals, mostly seen as Lorentzian, must be corrected when doing quantification. Here the unsuppressed water signal together with the macromolecular background signal and a spline-based baseline are taken into consideration for the quantification. Results show a variability

that depends on tissue type, measurement and environmental conditions. Amplitude estimate are especially critical for those metabolites highly overlapping with the background signal, such as Tau, Lac and Ala. In this case the baseline estimation plays an important role and further studies are foreseen including more prior knowledge.

Although the MM signal is known to provide a well approximation of the macromolecular contamination, it is also true that it requires a long acquisition time and is not reproducible when the conditions of the region of interest is affected by diseases. Thus, MMs are different on healthy and tumor tissue. Therefore, it is important to rely on a method that handles this issue automatically. Furthermore, it is also crucial to correct for lineshape distortions in an automated way, specially when series of clinical data need to be analyzed. One important aspect to consider in both cases is the fact that metabolites might be under or overestimated, which is bound to the measurement conditions for the *in vivo* case and the constrain setting parameters for the modeling case. Therefore, baseline estimation must be carefully handled. In further studies we will compare lineshape and baseline corrections as a continuation of the work done in [6] and compare the performance in combination with the methods such as QUEST [1] and LCModel [2].

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