DAMPING FACTOR CONSTRAINTS AND METABOLITE PROFILE SELECTION INFLUENCE MAGNETIC RESONANCE SPECTROSCOPY DATA QUANTIFICATION

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Abstract: Magnetic Resonance Spectroscopy (MRS) is a technique used for the diagnostics of tumour and metabolic diseases by estimating the metabolite concentrations of the tissue under investigation. Unreliable metabolite estimation may mislead the diagnosis and therefore quantification of MRS *in vivo* signals must be performed carefully. In this work, we quantify 1.5 Tesla (T) and 9.4 T MRS *in vivo* signals and study the influence of the damping factor constraint and the metabolite profile selection used in the quantification method. The damping factor bounds the linewidth of the metabolite profiles and may yield bad fits if wrongly selected. Furthermore, MRS data quantification leads to overestimation of some metabolite concentrations when the selected metabolite basis set is incomplete suggesting that metabolites are fitting the region of their neighboring components. Here, we evaluate the normality of the residual which in cases of good fitting contains no metabolites and only white Gaussian noise. Furthermore, we propose to estimate the damping bound adaptively by taking into account information from the linewidth of the signal and the metabolite basis set.

1 INTRODUCTION

Magnetic Resonance Spectroscopy (MRS) is a non-invasive technique used to estimate the metabolite concentration of living tissue. MRS is used in the diagnosis of cancer, epilepsy, metabolic and other diseases because it provides information about the biochemical condition of a tissue. Acquisition is performed in the time domain, resulting in Free Induction Decay (FID) signals, and the conversion into the frequency domain using the Fourier transform is called the MR spectrum. A variety of quantification methods exist for estimating the metabolite concentrations using either the time or the frequency domain data (Ratiney et al., 2004; Provencher, 2001; Poullet et al., 2007). For quantifying MRS signals we make use of the time domain method presented in (Poullet et al., 2007), where a basis set of reference metabolites is employed for estimating the metabolite concentrations with the model in Eq.(1). In the ideal case when the metabolite basis set completely describes the signal under investigation and the noise on the signal is white, the method in (Poullet et al., 2007) is a maximum likelihood approach. A thorough investigation of the MRS noise and the conditions for this noise being white complex Gaussian are presented in (Grage and Akke, 2003). The model that describes the MRS signals under investigation is:

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

where K is the number of metabolites, $j = \sqrt{-1}$, $v_k(t)$ the given metabolite profile k in the basis set, a_k the unknown amplitude, ϕ_k the unknown phase shift correction, d_k the unknown damping, f_k the unknown frequency shift and $B(t)$ is the baseline. In this case we also measured *in vivo* the macromolecular contribution which is included in the basis set and decreases the contribution of $B(t)$. Among these parameters, the most essential are the amplitudes a_k, since they are proportional to the concentration. The quantification method described by (Poullet et al., 2007) estimates the unknown parameters a_k, d_k, f_k and ϕ_k using

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a nonlinear least squares problem for fitting model (1) to the MRS signal. To encourage a reliable and meaningful fit, extra constraints, such as equal phases and some bounds on the frequencies and dampings are imposed on these parameters. Quantification is commonly evaluated visually by checking the residual and numerically by checking the Cramér-Rao bounds of the fitted metabolites. A fit can be considered unsuccessful when metabolites are not well-estimated (large Cramér-Rao bounds) or the residual contains metabolite contributions. Graphical statistical measures for residual analysis are useful together with numerical measures because they are directly related to visual inspection of the entire data set at once and can easily point out a range of relationships between the model and the data. On the other hand, numerical measures are more focused on a particular property of the data and often try to compress that information into a single number. Depending on the data and analysis requirements, one might need to use both types of measures to evaluate the quality of the fit. A well-fitted signal contains no metabolites in its residual and therefore the residual should contain only white complex Gaussian noise.

In this paper, we focus on two aspects that have strong influence on the quantification method's performance. First, we show that mis-specification of the damping factor constraint in the quantification method of (Poullet et al., 2007) is systematically reflected in the residual of the fit. Second, we examine the influence of the number and importance of the reference metabolites used in the basis set and how residual analysis can help in identifying incomplete metabolite basis sets. To evaluate the goodness of the fit we compute a quality factor proposed by (Slotboom et al., 2009) and we extend it to estimate problematic frequency regions in the residual by using a moving window. Furthermore, we employ the normal probability plot, the cumulative probability and the Rayleigh distribution to study the behavior of the complex residual. In particular we assess whether it contains only Gaussian noise or whether systematic patterns from the metabolites are still present.

2 MRS SIGNALS

We analyze two types of signals:

- An ^{1}H MRS signal from human brain acquired at 1.5 Tesla (T) on a Philips NT Gyroscan scanner. This signal was obtained using the PRESS pulse sequence (Bottomley, 1984). MRS parameters were: repetition time of 6s, TE = 23 ms, SW = 1 KHz and 64 averages. B0 eddy current correction (Klose, 1990) was performed using the water reference before quantification. See Fig.1 (a).
- An ^{1}H MRS signal from rat brain acquired at 9.4 T on a Bruker Biospec small animal MR scanner (Bruker BioSpin MRI, Ettlingen, Germany). This signal was acquired using the PRESS pulse sequence (Bottomley, 1984) with implemented pre-delay Outer Volume Suppression (OVS) and making use of the water suppression method VAPOR (Tkáč et al., 1999). MRS parameters were: repetition time of 8s, TE = 20 ms, SW = 4 KHz and 128 averages. B0 eddy current correction as well as B0 drift removal were performed using the Bruker built-in routines and shimming was performed using FASTMAP (Gruetter, 1993). See Fig.1 (b).

Additionally, an unsuppressed water signal is always measured, which is commonly used as a reference for phase and lineshape corrections.

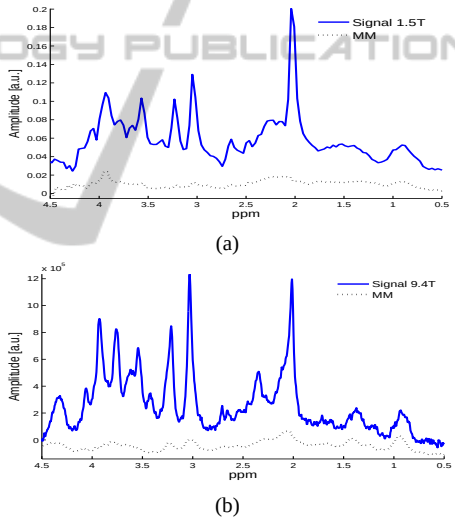

Figure 1: Real part of the *in vivo* spectra. The dotted curve is the nulled metabolite signal corresponding to the measured macromolecules and lipids. (a) Human brain signal acquired at 1.5T. (b) Rat brain signal acquired at 9.4T.

On both scanners, an *in vitro* basis set of reference metabolites was measured. The following metabolites were used: Alanine (Ala), Aspartate (Asp), Creatine (Cre), Gamma-Aminobutyric 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). A typical problem for *in vivo* MRS quantification is the presence of a macromolecular signal affecting the baseline of the spectra. For this

study, we measured the *in vivo* spectrum of macromolecules (MM) using an inversion recovery sequence. The inversion time was fine-tuned experimentally for metabolite nulling and this MM signal was added to the basis set of reference metabolites.

3 QUANTIFICATION

3.1 Preprocessing

In *in vivo* ^{1}H MRS signals, the concentration of water in the brain is several orders of magnitude higher than the concentration of the metabolites. This signal is suppressed during acquisition in order to increase the resolution of the metabolites of interest. Nevertheless, there is always some residual water around 4.7 ppm that must be removed to reduce the complexity of the signal analysis and improve the quantification accuracy. The signals presented here were filtered using a method called Hankel Singular Value Decomposition (Pijnappel et al., 1992), which decomposes the FID in a sum of exponentials and eliminates the components found in the specific frequency region of the water. In particular, the more efficient HLSVD-PRO implementation (Laudadio et al., 2002) is used. Other preprocessing steps for these signals include phase correction for better visualization of the spectra, and time circular shift for the Bruker signals, which were performed using the jMRUI software package (Stefan et al., 2009).

3.2 AQSES

The quantification method used here for analyzing the spectra is AQSES (Poullet et al., 2007). This is a time-domain method that combines metabolite profiles in the best way as expressed in Eq.(1) to fit the signal under analysis. The most important output parameters of this method are the amplitudes of each metabolite, because these are proportional to the concentration of metabolites in the tissue. However, the quantification method also requires the tunning of other model parameters such as small frequency shifts f_k, damping corrections d_k and a common phase term ϕ_k=ϕ for each metabolite. In particular, the damping parameters allow the metabolite profiles to be narrower or wider for better fitting the signal. An essential model parameter is the *upper bound* for the damping parameters used as a constraint in the quantification method AQSES. This is needed in order to avoid metabolite profiles to become too broad and fit the baseline. However, a too low upper bound is not desired, as metabolites are then badly fitted. Until now this damping bound was chosen as a fix value independent on the signal information. In this study, we propose to estimate this bound as an adaptive method that takes into account information from the signal and the metabolite basis set. To this end, we make use of the fact that the damping of a complex damped exponential is equal to the linewidth (*i.e.* the Full Width at Half Maximum (FWHM)) of the corresponding Lorentzian peak. Thus, we approximate the upper bound for the damping factor constraint as the difference between the FWHM of the unsuppressed water signal of the *in vivo* and a singlet from the *in vitro* metabolites (*i.e.* NAA). As can be seen in Fig.1, there is a macromolecular background signal underlying the *in vivo* signal. Baseline correction in AQSES is accounted for by simultaneously using the MM signal in the basis set as well as a smooth spline model for additional baseline correction.

3.3 Statistical Residual Analysis

The residual is the difference between the measured signal and the fit of this signal as obtained by AQSES. We use the residual in the frequency domain either for graphical assessment of the goodness-of-fit, or as an indication of possible fitting problems. If the fit is correct, the residual should not contain metabolites and should be white noise. To assess the goodness of the fit, we use a quality factor proposed by (Slotboom et al., 2009): $Q_{fit}(N) = \frac{R^2}{N.\sigma^2}$, where σ^2 is the variance of the signal noise calculated from the metabolite-free region, R is the norm of the residual and N is the number of points of the least-squares fit. This value of Q_{fit} is close to 1 when the fit is perfect, bigger than 1 when the model is probably incomplete (lack of metabolites) and smaller than 1 when parts of the noise are fitted (overfitting) which means that the model has too many degrees of freedom.

4 RESULTS AND DISCUSSION

4.1 Effect of Damping Factor Constraint

We study the effect of the damping factor constraint, which allows each metabolite in the basis set to be as narrow or wide as the *in vivo* signal. Figure 2 shows the results of quantification for 3 different damping factor constraint values. Quantification can be first of all evaluated by visual inspection of the residual, which already provides information about the regions that are not well-fitted. Setting the upper bound on the

damping factors too low is clearly reflected in the pattern of the residual, where peaks with similar shape are observed in the region of the metabolites. Subsequently, when a bigger damping is allowed, improvements in the fitting are reflected in the residual (see Fig.2, *e.g.* around 2 ppm, 3 ppm and 3.9 ppm). Although large increases of the damping with regards to the good bound do not improve or worsen the residual, a more detailed look into the results illustrate that when a too large damping factor is allowed, some metabolites may wrongly take over other metabolites or baseline contribution (see especially the bottom profile of Glc in Fig.3). Moreover, this effect is not obvious from the fitting results and it may affect the stability of the method, leading to wrong estimations.

Correlation is also used to evaluate the goodness of the fit by correlating the original signal with the fitting. Values close to 1 reflect a good correlation and thus a good fit. However, a good correlation does not mean good estimates and therefore we must carefully interpret this parameter. The correlations of the original and the fitted signal for the three damping values at 1.5 T were 0.9234, 0.9770 and 0.9786 respectively; and the correlations for the 9.4 T signal were 0.9241, 0.9808 and 0.9861 respectively. For testing the assumption that the residual estimated after a good fit is random noise (*i.e.* white Gaussian noise), we evaluated and tested the real and imaginary parts of the residuals. A zero mean bivariate normal variable $Z = (X,Y)$ with X and Y uncorrelated with equal variances, $\sigma_X^2 = \sigma_Y^2 = \sigma$ can be expressed in polar coordinates as $Z = (R\cos(\theta), R\sin(\theta))$ where the radius R has a Rayleigh distribution with scale parameter σ and the angle θ is uniformly distributed on the interval $[-\pi,\pi]$ (Grage and Akke, 2003). This assumption has been used to assess whether the real and imaginary parts of the residual are independent and identically distributed (results not shown here).

4.2 Lack of Metabolites in the Basis Set

Additionally, we study the effect of the number of metabolites used for quantification as this may also cause over- or underestimation. Fig.4 shows the results of amplitude estimation for the 1.5 T and 9.4 T signals when using a complete and incomplete basis set of metabolites. For the 1.5 T signal we considered 3 groups of metabolite profiles: (a) all 13 metabolites (Ala, Asp, Cho, Cre, GABA, Glc, Gln, Glu, Lac, Myo, NAA, Tau), (b) the 6 most relevant metabolites having a high concentration in normal brain (Cho, Cre, Gln, Glu, Myo, NAA), (c) the 4 most relevant metabolites having the highest concentration (Cho, Cre, Glu, NAA). For the 9.4 T signal we also considered 3 groups of metabolite profiles: (a) all 16 metabolites (Ala, Asp, Cre, GABA, GPC, GSH, Glc, Gln, Glu, Lac, Myo, NAA, PCh, PCr, PE, Tau), (b) the 8 more relevant metabolites having a high concentration (Cre, GPC, GSH, Gln, Glu, Myo, NAA, PE),

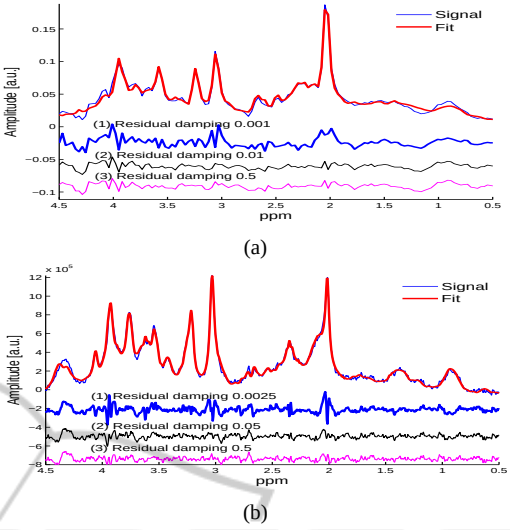

Figure 2: Quantification results using different damping factor constraints which reflect the over- or underestimation of amplitude estimates and the importance of its careful selection. The best fitted signal is the overlapped thick line and the residuals are the curves beneath. (a) 1.5 T signal and (b) 9.4 T signal. (1) Residual with damping factor constraint 0.001 (small bound). (2) Residual with damping 0.01 factor constraint (good bound). (3) Residual with damping 0.5 factor constraint (big bound).

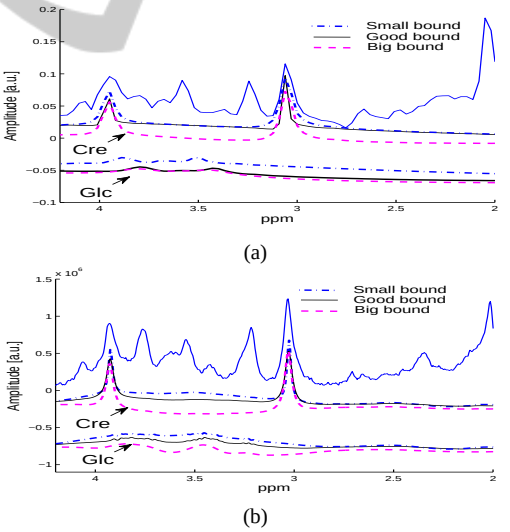

Figure 3: Effect of damping factor constraint in metabolites shows a higher impact in small metabolites. The curves beneath the signal correspond to metabolite estimates of Creatine and Glucose using small, good and big damping factor constraints. (a) 1.5 T signal and (b) 9.4 T signal.

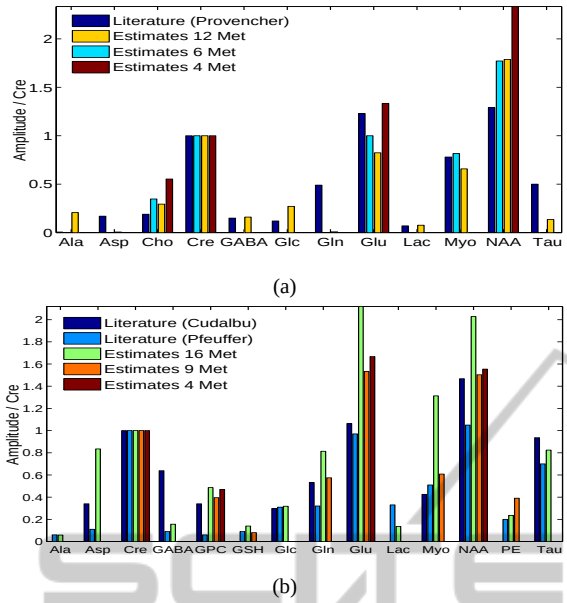

Figure 4: Amplitude estimates and comparison using a complete and incomplete basis set. (a) Amplitude estimation of metabolites relative to Cre compared to literature (Provencher, 2001). (b) Amplitude estimation of metabolites relative to Cre compared to literature (Cudalbu et al., 2006; Pfeuffer et al., 1999).

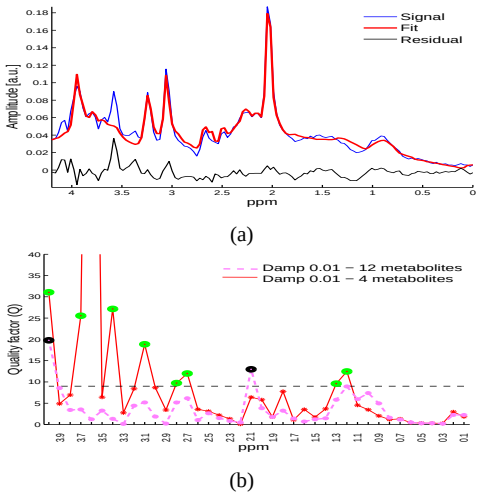

Figure 5: Quantification analysis via the Quality factor (Q) for the signal at 1.5 T using an incomplete basis set of metabolites. (a) Fit using a basis set with 4 metabolites. (b) Quality factor plot for the signal using a complete and incomplete basis set (12 and 4 metabolites). The quality factor computed for the signals was 2.1207 and 7.4472 respectively.

(c) the 4 most relevant metabolites having the highest concentration (Cre, GPC, Glu, NAA). Each basis set is extended with the corresponding MM signal. The lack of some metabolites in the basis set leads to a

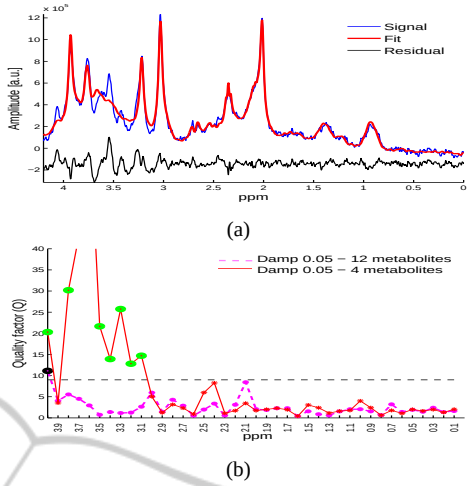

Figure 6: Quantification analysis via the Quality factor (Q) for the signal at 9.4 T using an incomplete basis set of metabolites. (a) Fit using a basis set with 4 metabolites. (b) Quality factor plot for the signal using a complete and incomplete basis set (16 and 4 metabolites). The quality factor computed for the signals was 1.4033 and 5.1740 respectively.

slight under- or overestimation of some other metabolites and this is also reflected in the residual. Amplitude estimates in Fig.4 are close to those presented in literature, however, it is important to mention that they are highly affected by individual conditions of the tissues, small differences in the measurement parameters, size of the voxel measured and therefore diverse concentration ranges are found in similar studies, leading to a high variability of the amplitude estimates. In Fig.5 (a) and 6 (a) we observe that the fits with an incomplete basis set are not good and the corresponding Q_{fit} of 7.4472 and 5.1740 also confirm the imperfect quantification. In order to further evaluate the quantification, we selected a span or window of 0.1 ppm to evaluate the quality factor in a moving window. In Fig.5 (b) and 6 (b) we present the results of this quality measure where the plotted curves represent the Q_{fit} values obtained for all the frequency intervals selected and the dashed line represents the confidence bound calculated as three times the standard deviation ($\frac{R^2}{N} > (3\sigma)^2$ or equivalently $Q_{fit} > 9$). A missing metabolite is considered when the Q_{fit} value is higher than the selected threshold.

5 CONCLUSIONS

Reliable metabolite estimation of *in vivo* MRS signals for determination of metabolite concentrations is of paramount importance for obtaining additional information in the diagnostics of cancer and metabolic

diseases. Therefore, quantification of MRS signals was performed evaluating the influence of the damping factor constraint and the number of components used in the metabolite basis set used for quantification. We observed in particular, that the damping factor in the quantification method AQSES plays an important role in amplitude estimation. From the quantification results, we examined the residual and analyzed the fit of the individual components which are sensible to quantification constraints. The selection of the metabolites for the basis set is important for quantification, thus an incomplete basis set will provide fits where one metabolite fits the region that corresponds to its neighbor. The residual is used to determine the goodness of the estimates. It is assumed that a good estimate will lead to residuals resembling pure white noise. A test of normality would also help to analyze the residual and determine how close it is to white noise.

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