

Lineshape Accommodation in Quantitation of Magnetic Resonance Spectroscopy Signals

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Abstract—¹H Magnetic Resonance Spectroscopy (MRS) signals obtained *in vivo* contain many overlapping spectral components from many metabolites and a background signal originating mainly from macromolecules and lipids. Moreover, lineshape distortion due to residual eddy currents and magnetic field inhomogeneities are often present. Recent quantitation methods such as the *semi-parametric* algorithm QUEST are based on prior knowledge of a metabolite basis-set. Through Monte-Carlo studies, the influence of two lineshape accommodation strategies on QUEST quantitation results for signals mimicking ¹H *in vivo* spectra of rat brain at 9.4 Tesla, are investigated. Analytical formulae of the Cramér-Rao lower bounds on model function parameters of a Lorentzian and a Gaussian singlet are also derived and compared.

Keywords—Magnetic Resonance Spectroscopy, Signal Processing, Quantitation, Metabolites, Lineshape, Basis-set.

I. INTRODUCTION

Magnetic *In vivo* Resonance Spectroscopy (MRS) signals are obtained in the time-domain. When the echo-time is short, ¹H signals contain many overlapping spectral components from many metabolites and a background signal originating mainly from macromolecules and lipids. Moreover, lineshape distortion due to residual eddy currents and magnetic field inhomogeneities are often present in short echo-time ¹H spectroscopic data. If left uncorrected, these lineshape distortions lead to errors in metabolite concentration estimates when using quantification methods that incorporate model functions with specific lineshapes (i.e., Lorentzian or Gaussian) [1]. Recent quantitation methods such as the *semi-parametric* algorithm QUEST are based on prior knowledge of a metabolite basis-set [2, 3]. Several methods have been proposed for lineshape correction, 1) The distorted *in vivo* signal can be given an ideal Lorentzian lineshape by using lineshape correction methods such as QUALITY deconvolution [4] and eddy current correction (ECC) [5] or the hybrid method QUECC [6]. These methods use a separate reference spectrum for lineshape correction (for

instance unsuppressed tissue water [7]), 2) The lineshape distortions with respect to the basis-set spectra are corrected in the quantitation procedure [2, 3]. In this paper, we propose and investigate a new approach, the lineshape of the metabolite *basis-set* is given the unknown lineshape of a reference spectrum. The influence of different lineshape accommodation strategies on QUEST quantitation results for signals mimicking ¹H *in vivo* spectra at 9.4 Tesla are investigated through Monte-Carlo studies. Moreover, analytical formulae for the Cramér-Rao lower bounds (CRBs) on model function parameters of a Lorentzian [8] and Gaussian singlet are derived and provide insights in the lineshape accommodation strategy to be used.

This paper is set up as follows. In Sec. II, we first treat the QUEST quantitation method, then CRBs on model parameters of a singlet with both Lorentzian and Gaussian lineshapes are derived. Finally, in Sec. III Monte-Carlo studies are described enabling conclusions in terms of bias-variance trade-off on QUEST quantitation results.

Note that MRS signals are traditionally displayed in the frequency-domain, after estimation of the spectra by FFT. We quantitate directly in the measurement-domain, which is the time-domain.

II. METHOD

A. Metabolite Quantitation

The time-domain algorithm Subtract-QUEST, for optimal fitting of metabolite basis-set signals to (contaminated) data is based on a *semi-parametric* approach. Subtract-QUEST sequentially uses 1) untangling of the background from the metabolite signal, 2) separate modelling, and 3) a parametric nonlinear least-squares fitting of the untangled metabolite signal knowing the background [2, 9]. In absence of – or after removal of – the nonparametric part, a Levenberg-Marquardt algorithm is used to minimize the distance between the raw signal x and the model function \hat{x} . The complex-valued time-

domain model samples, $\hat{x}_n, n = 1, 2, \dots, N$ where N is the number of data-points, is written as a linear combination of the M – either quantum-mechanically simulated or *in vitro* measured – weighted metabolite basis-set samples $\hat{x}_n^m, m = 1, 2, \dots, M, n = 1, 2, \dots, N$ of the basis set

$$\hat{x}_n = \exp(i\phi_0) \times \sum_{m=1}^M a_m \hat{x}_n^m \exp[(\Delta\alpha_m + i\Delta\omega_m)t_n + i\Delta\phi_m], \quad (1)$$

where

- \hat{x}^m, m being a superscript represents the basis-set signals. The damping factors of \hat{x}^m should be set close and preferably not greater than the *in vivo* values. Note that the basis-set signals can have *arbitrary* damping forms (lineshapes in the frequency domain).
- a_m are M amplitudes to be estimated. Note that these amplitudes represent the relative proportions of the M metabolites signals \hat{x}^m in the signal x rather than the amplitudes of individual spectral components.
- $\Delta\alpha_m, \Delta\omega_m, \Delta\phi_m$ represent small changes of the damping factors (*Lorentzian correction*), angular frequencies, and phase shifts respectively. These changes – relative to the initial values in the metabolite basis set – are included in the estimation procedure to automatically compensate for the effect of magnetic field inhomogeneities. In most of cases $\Delta\phi_m = 0$. Soft constraints on $\Delta\alpha_m$ and $\Delta\omega_m$ have been used in the minimization procedure,
- $t_n = nt_s + t_0, n = 1, 2, \dots, N$, are the sampling times, in which t_0 is the dead-time of the receiver – included in the estimation – and t_s the sampling interval,
- ϕ_0 is an overall phase, included in the estimation,
- $i^2 = -1$.

The vector p of the metabolite parameters to be estimated is then $p = ((a_m, \Delta\alpha_m, \Delta\omega_m, \Delta\phi_m), m = 1, 2, \dots, M; \phi_0, t_0)^T$ where the superscript T denotes transposition. Note that the number of parameters is only $4M + 2$.

B. Metabolite Basis-set

The basis-set signals were simulated with NMR-SCOPE [10] using spin parameters given in [11]. Eleven metabolites – aspartate (Asp), choline (Cho), creatine (Cr), γ -amino-butyric acid (GABA), glucose (Glc), glutamate (Glu), glutamine (Gln), lactate (Lac), myo-Inositol (mI), N-acetylaspartate (NAA and NAAG), taurine (Tau) – were included in the basis-set. Signals modelling the lipids (Lip) at 0.9 and 1.3 ppm were included too. The metabolite basis-set at 9.4 Tesla used in QUEST is shown

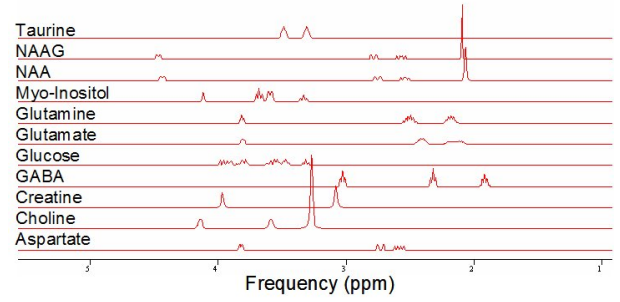


Fig. 1. Fourier transform of a metabolite basis-set at 9.4 Tesla, simulated by Quantum Mechanics with NMR-SCOPE. Lorentzian lineshapes are used.

in Fig. 1. The basis-set signals were given Lorentzian and Voigt damping factors (lineshapes) respectively.

C. Analytical Formulae for the Cramér-Rao Bounds on Model Parameters of a Singlet

Quantitation errors of metabolites are caused by measurement noise and inadequate modelling of the signal. The noise related errors are calculated by estimating the CRBs [8, 12, 13]. The latter method is valid only if the model function is known.

For the metabolites – model functions assumed known – the CRBs are usually computed from the Fisher information matrix [12]. When the model function is correct, the correlation matrix reveals the nature of quantitation problems. If the model function is incorrect, the estimates of the metabolite parameters will become biased. To help in finding the best lineshape accommodation strategy for quantitation, we derived (with Maple) analytical formulae for the CRBs on parameters of a singlet having a Lorentzian and a Gaussian lineshape respectively. The CRB on the amplitude of a Gaussian singlet is equal to

$$\sqrt[4]{18/\pi\sigma} \sqrt{t_s} \sqrt[4]{\beta} \quad (2)$$

where β is the damping factor of the Gaussian singlet. σ is the noise standard deviation.

For a Lorentzian singlet, the CRB on the amplitude [12] is

$$2\sigma \sqrt{t_s} \sqrt{\alpha} \quad (3)$$

These formulae show that the CRB on the amplitude depends on the noise, *not* on the amplitude and on the damping factors and is proportional to the square root of the sampling interval.

The damping factors of Lorentzian and Gaussian singlets having the same amplitude and the same line width at half height, are such that $\beta = \frac{\alpha^2}{4 \ln 2}$. The corresponding ratio of the CRBs on amplitudes, $\text{CRB}_{\text{Lorentz}}/\text{CRB}_{\text{Gauss}} = \frac{2}{\sqrt{3}} (2\pi \ln 2)^{1/4} \simeq 1.668$. The quantitation error is then

almost 40% lower for a singlet with a Gaussian lineshape. That enables one to infer that it may be advantageous quantitation-wise to give the basis-set signals the unknown damping factors of a reference peak rather than to give the distort *in vivo* signal an ideal Lorentzian lineshape by using a 'reference-deconvolution' algorithm.

D. Monte Carlo Simulations

To assess the performances – including bias – of QUEST for the different lineshape strategies, Monte-Carlo studies were performed. A ^1H signal (2048 data-points) mimicking an *in vivo* spectrum of rat brain at 9.4 Tesla was simulated. This signal comprises contributions from eleven metabolites and lipids whose amplitudes correspond to a healthy rat-brain. Voigt lineshapes were imposed (damping factor of the form $\exp(-\alpha t - \beta t^2)$). The line widths of the Lorentzian part range from 2Hz to 20Hz and that of the Gaussian part is 7.5 Hz. To this simulated noiseless signal, 200 different realisations of white Gaussian noise were added. The noise level was chosen as in *in vivo* conditions so that the SNR of the Cr singlet be 8.6:16.

III. RESULTS

The 200 Voigt noisy signals were quantitated with QUEST using a Lorentzian and an 'adapted' (the basis-set was given the Voigt lineshape of a reference singlet) metabolite basis-set respectively. An example of QUEST quantitation results from one of these signals mimicking a rat brain signal at 9.4 Tesla and used in the Monte Carlo study is shown in Fig. 2. These results were obtained with the jMRUI software package [14]. Figs. 3 shows the main Monte-Carlo results. The mean amplitudes of metabolites and two standard deviations estimated from the 200 signals for both the basis-set with Lorentzian and Voigt lineshapes respectively are displayed. Fig. 3 shows that only NAA and Cr have slightly biased amplitude estimates when the Lorentzian basis-set was used. The amplitudes are not significantly different though. The standard deviations for the two lineshape approaches are similar.

IV. CONCLUSIONS

We studied the influence of lineshape distortions on quantitation results when using a fitting algorithm based on a metabolite basis-set.

- Analytical formulae for the CRBs on model parameters of a Lorentzian and a Gaussian singlet provide insights in the lineshape accommodation strategy to be used. For a

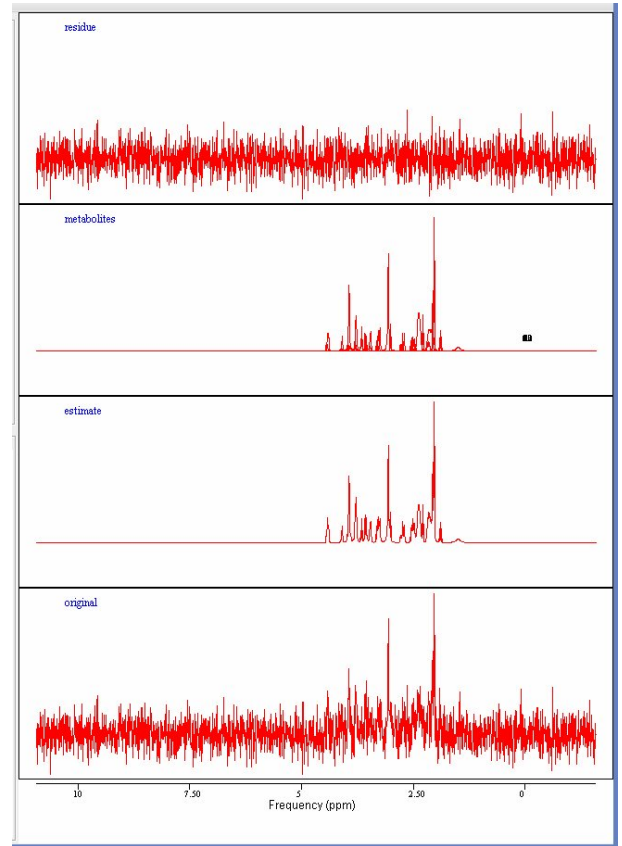


Fig. 2. QUEST quantitation results of a simulated spectrum mimicking a rat brain signal at 9.4 Tesla and used in the Monte Carlo study. From bottom to top, original and estimated spectra, individual metabolites and residue as obtained with the jMRUI software package [14].

singlet, they are in favour of adapting the lineshape of the basis-set.

- Giving the unknown lineshape of a reference peak to the metabolite basis-set lineshape seems preferable but no clear conclusions can be stated from our present Monte Carlo studies.
- Comparison with correcting the lineshape with a QUALITY-like algorithm prior to the quantitation step is in progress.

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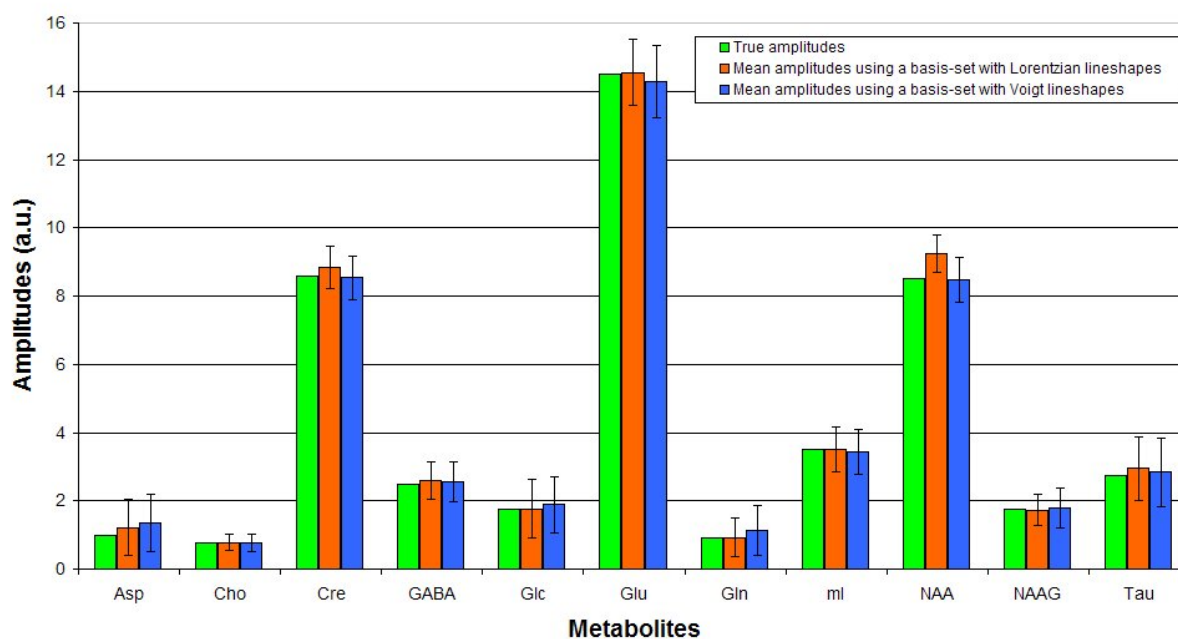


Fig. 3. Monte-Carlo studies. True amplitudes (green) and mean amplitudes of metabolites quantitated with Subtract-QUEST from the 200 signals. The lineshape of the metabolite basis-set was Lorentzian (orange) and Voigt (blue) respectively. The error bars correspond to one standard deviation.

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