AUTOMATIC QUANTIFICATION OF MAGNETIC RESONANCE SPECTROSCOPIC SIGNALS: EVALUATION AND COMPARISON OF AQSES AND QUEST

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1 Introduction

Magnetic Resonance (MR) is an extensively used technique to obtain clinical images and to study metabolic processes non-invasively. An important application is Magnetic Resonance Spectroscopy (MRS), which can be used to study signals of chemical substances, named metabolites. The metabolic information makes it possible to determine the tissue type and, in presence of a tumor, the grade of malignancy. In order to obtain this information, an accurate quantification of the *in vivo* measured MRS signals, followed by a correct classification based on these quantified values, is required.

The most common *in vivo* MRS technique in medical applications is proton MRS (^{1}H MRS), not only because a proton is the most sensitive nucleus but also because it is more abundant in nature.
An important parameter is the echo time (TE), the time between the emission of an exciting pulse and the acquisition of the measured signal, mostly called the *'free induction decay'* (FID) signal. A shorter TE leads to more information (more peaks) present in the signal, but on the other hand it causes more overlap between the spectra of the different metabolites, augmenting the difficulty to distinguish each metabolite.

The purpose of quantification is to determine the concentrations of every metabolite contained in the analyzed tissue, what could be done by estimating the measured sum of resonances. The concentrations give information about the tissue. Therefore, techniques in time domain as well as in frequency domain – like the commercial LCModel [3] – exist. In time domain, one distinguishes between the interactive and the blackbox methods. Since interactive methods are based on nonlinear least squares optimization and can take prior knowledge into account [6], they are preferred for MRS quantification.

In this paper, two automatic quantification methods for short echo time ^{1}H MRS, AQSES [2] and QUEST [4], are validated and compared in an extensive simulation study. Both methods belong to the group of interactive methods, based on the principle of optimization.

Because the MRS signals can contain several nuisance components like noise, a residual water component and a baseline signal that accounts for the presence of unknown macromolecules, an extra difficulty arises. The way these unwanted components are removed, constitutes a major difference between AQSES and QUEST.

2 Quantification

2.1 FID signal

A measured FID signal is the sum of different metabolite contributions, each with its own characteristic frequency. Theoretically, an FID signal can be modeled in general as a sum of K complex damped exponentials:

$$y(t_n) = \sum_{k=1}^{K} a_k e^{j\phi_k} e^{(-d_k + j2\pi f_k)t_n} \qquad (1)$$

with a_k the amplitude, f_k the frequency shift, d_k the damping correction and ϕ_k the phase shift of the k^{th} spectral component. t_n is the time vector: $t_n = t_0 + n\Delta t, n = 0,...,N-1$, with t_0 the start point of the measurement and Δt the sampling interval. In this model, the weight factors or amplitudes in the linear combination are most relevant because they are representative for the unknown metabolite concentrations. However, also corrections in frequency, damping and phase have to be estimated because they can differ between different acquisitions [4].

2.2 AQSES

Mathematical modeling

In AQSES, a database is composed of *in vitro* measured metabolite signals v_k for *k* = 1,…,*K*. Each metabolite is a complex time signal of length *m*. An *in vivo* NMR signal y – also of the same length *m* – can be written as:

$$y(t) = \hat{y}(t) + \varepsilon_t = \sum_{k=1}^{K} \alpha_k (\zeta_k)^t v_k(t) + b(t) + w(t) + \varepsilon_t \quad (2)$$

for $t = t_0, \ldots, t_{m-1}$. The complex amplitudes α_k en the complex signal poles ζ_k can be written as:

$$\alpha_k = a_k \exp(j\phi_k)$$
$$\zeta_k = \exp(-d_k + j2\pi f_k) \quad (3)$$

with a_k, f_k, d_k and ϕ_k the same parameters as in section 2.1. In (2), $b(t)$ is the chemical part which will not be modeled in the first term and represents the response of some unknown macromolecules, missing in the database. Mathematically, $b(t)$ is a smooth function in the Fourier domain. The term $w(t)$ corresponds to the remaining water component, but can also represent the influence of other nuisance components. Finally, ε_t indicates an unknown white Gaussian noise perturbation.

Filtering

To remove irrelevant information from the *in vivo* NMR signal, a *Finite Impulse Response* (FIR) filter is available which selects a frequency range while processing a time signal. This makes it possible to take only into account the interesting metabolites and not the water component which resonates at a different frequency. More specifically, AQSES uses a maximum-phase filter [5], automatically optimized to eliminate that water peak.

Baseline removal

A baseline is modeled in a non-parametric way by a set of splines, since each non-linear function can be approximated by a linear combination of splines. The algorithm uses a combined optimization problem for the model and the baseline.

2.3 QUEST

Mathematical modeling

In QUEST, a database can be generated as in AQSES, but initially, it was quantum mechanically simulated. An *in vivo* NMR signal is modeled in the same way as in AQSES (equation (2)).

Filtering

In QUEST, the removal of the water component is performed as a preprocessing step with a Hankel Lanczos singular value decomposition (HLSVD) filter [1].

Baseline removal

Baseline removal in QUEST is obtained by modeling a non-parametric baseline with heuristic methods, e.g. HLSVD. This baseline model can be subtracted from each measured signal or – as in AQSES – used as a part of the database for the quantification. The performance of these methods depends on the number of truncated data points, used to estimate the baseline, and the model order for the baseline fitting.

3 Simulation study

In order to validate and compare the performance of both quantification methods, different sets of simulated signals were developed. With these sets various aspects of the quantification algorithms were examined.

3.1 Nuisance components and their removal

The original set contains 100 signals created as a linear combination of the 6 most important metabolites and 2 simulated lipid signals. The metabolites are N-acetylaspartate (NAA), Myo-inositol (Myo), Creatine (Cr), Phosphorylcholine (Pch), Glutamate (Glu) and Lactate (Lac). Two additional sets were created by adding consecutively a water component and a baseline signal to the original set. In the last two sets a more realistic situation was simulated by combining all possible nuisance factors. These two sets only differ in their amount of noise and were created by adding circular Gaussian white noise (with an SNR of 25 and 15 respectively) to signals already disturbed by a water component and a baseline.

3.2 Prior knowledge

When quantifying MRS signals, it is possible to include prior knowledge by using a database with only those metabolites that are also present in the signals. To investigate the usefulness of this type of knowledge, various sets of 5 signals were created including only 4 metabolites (NAA, Pch, Glu and Lac). These signals were processed with a database of these same 4 metabolites, a database of 7 metabolites and a database of 11 metabolites.

3.3 Evaluation criterion

Every set of signals was processed both in AQSES and in QUEST and the results were evaluated with the following relative performance measure, namely the relative difference (in %) between the real and the estimated parameter values for each signal:

$$100 \cdot \left| \frac{a_{k,l} - \tilde{a}_{k,l}}{a_{k,l}} \right| \qquad (4)$$

with $a_{k,l}$ the real parameter value of metabolite *k* in signal *l* and $\tilde{a}_{k,l}$ the estimated value for the same situation.

4 Results and discussion

4.1 Nuisance components and their removal

In table 1 and 2 the results of processing the original set of 100 signals are illustrated with the percentage of accurately estimated amplitudes. The amplitude of a signal is considered as "accurately estimated" when its relative performance measure (equation (4)) is below a given threshold of 0.1% in table 1 and 1% in table 2.

Table 1: Percentage of correctly estimated amplitudes for an error threshold of 0.1 %

Method	NAA	Myo	Cr	Pch	Glu	Lac
AQSES	97%	97%	97%	96%	97%	97%
QUEST	60%	4%	54%	34%	61%	28%

Table 2: Percentage of correctly estimated amplitudes for an error threshold of 1 %

Method	NAA	Myo	Cr	Pch	Glu	Lac
AQSES	99%	98%	98%	97%	97%	97%
QUEST	93%	48%	93%	82%	94%	88%

These tables indicate that signals without any nuisance factor are more accurately estimated in AQSES than in QUEST, but both methods share the property that only the majority of the signals are well estimated while each time a small number of them (but each time different ones) are estimated very badly.

For both methods the quantification of the signals became much more inaccurate when they contain one or more nuisance components.

The results for water removal by AQSES and QUEST are illustrated in figure 1. The relative differences between the real and estimated amplitudes for the metabolite NAA are plotted after sorting them according to their absolute value.

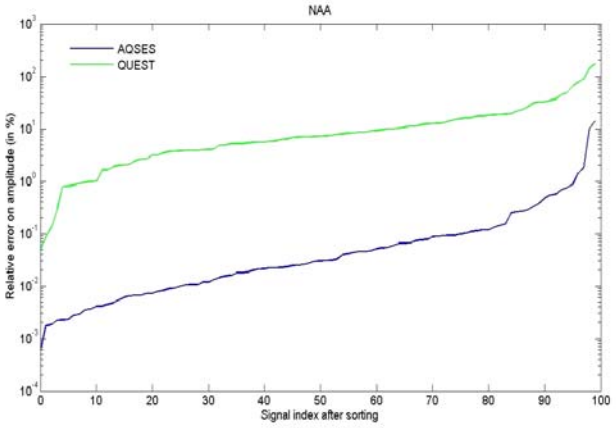


Figure 1: Sorted relative differences between real and estimated amplitudes of NAA for signals with water component processed by AQSES and QUEST

From this figure it is obvious that signals with a residual water component were better processed in AQSES than in QUEST. This is partly due to the better quantification in AQSES for signals without nuisance factors but also to the FIR filter in AQSES. This filter is part of the quantification algorithm, which makes it more efficient than the HLSVD filter in QUEST, applied as a preprocessing step.

With respect to baseline removal however, the results of AQSES, with a fixed level of smoothness for the baseline, could not compete with the quality of the results in QUEST. This is illustrated in figure 2 where the relative performance measure is plotted for the amplitude of NAA. For QUEST, it was also noted that more noise requests a lower optimal value for the number of truncated data points.

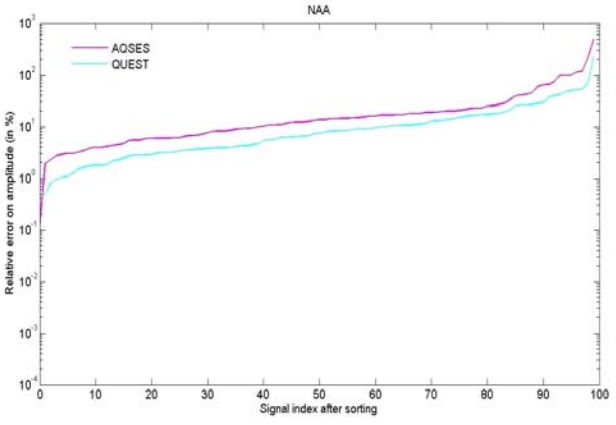


Figure 2: Sorted relative differences between real and estimated amplitudes of NAA for signals with baseline component processed by AQSES and QUEST

4.2 Prior knowledge

When processing the signals in both AQSES and QUEST with databases of 4, 7 and 11 metabolites, it was noted that there is hardly any difference between the various results. This observation indicates the interesting property that both methods do not require any prior knowledge about the contained metabolites, to estimate the concentration of the metabolites one is interested in.

4.3 Conclusion

Our simulations showed that the FIR filter of AQSES is better to take into account the water signal, while the baseline-fitting of QUEST is superior. An optimal quantification method would combine the FIR filter of AQSES and the baseline method of QUEST. In the future we will also compare these methods with LCModel in order to investigate differences in time and frequency fitting.

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