Abstract

Using Magnetic Resonance Spectroscopic Imaging (MRSI), the spatial distribution of metabolites can be investigated in the human body. To be able to use the diagnostic information present in the MRSI data, accurate quantitation is needed. In this paper AMARES, a time domain method which provides maximum likelihood parameter estimates is extended to multivoxel processing using a FIR filter for solvent suppression. The advantage of this multivoxel approach is that relations between parameters of different voxels can be used by the algorithm. This new algorithm will be applied to simulated MRS data as well as to in-vivo data. We show that depending on the prior knowledge imposed, the multivoxel approach improves the accuracy of parameter estimates. We also demonstrate that the model order has an influence on the parameter estimates.

1 Introduction

To assist the clinician in diagnosing different cancers in-vivo Magnetic Resonance Spectroscopic Imaging (MRSI) can be used. MRSI can reveal information on the spatial distribution of chemical markers in-vivo. Different approaches exist for determination of the spatial metabolic distribution from the raw MRSI data. In our approach, the data are estimated by using a time domain model [1] to reveal the relevant information. Because of the intrinsic low signal/noise ratio of MRSI signals, prior knowledge is often used [2, 3]. Processing MRSI datasets demands more complex algorithms than those needed for single voxel spectroscopy, because many more spectra have to be quantified and the processing of all spectra should preferably be done automatically. For MRSI to become a clinical useful tool, it has to be accurate, robust and automated.

A new combination of filtering and quantitation in the time domain is used to improve the processing of MRSI datasets in terms of accuracy. We show that the quantitation of voxels from an MRSI experiment becomes more accurate when prior knowledge on the parameters of different voxels is exploited in the quantitation phase. This is done by processing different voxels simultaneously, called multivoxel processing. The type of prior knowledge determines which parameter estimates become more accurate using this multivoxel processing. It is shown in our Monte Carlo simulations that over-modeling a signal does not influence the accuracy of the amplitude estimates.

2 Methods

The spectra acquired in a MRS experiment can be modeled in the time domain as a sum of $K$ exponentially damped sinusoids:

$$y(n) = \bar{y}(n) + e(n)$$

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

$$n = 0, 1, \ldots, N - 1$$

where $a_k$ is the amplitude, $f_k$ the frequency, $d_k$ the damping and $\phi_k$ the phase of the $k^{th}$ resonance.
(k = 1, . . . , K); t(n) = nΔt + t0 with Δt the sampling interval, t0 the time between the effective time origin and the first data point to be included in the analysis and e(n) complex white Gaussian noise. The bar on the y indicates that this is a model for the signal, not the actual measurements. In all the simulations in this paper t0 was set to 0. The amplitudes of the different resonances are proportional to the concentrations of the metabolite and the purpose is to estimate these as accurately as possible.

The algorithm which will be used is AMARESfts which is based on AMARES [3]. The principle of AMARES is to minimize the absolute difference of the model function and the measured data (the cost function) which results in maximum likelihood estimates of the parameters of the signals. AMARESfts combines AMARES with a multivoxel approach and a FIR filter for water suppression. The multivoxel approach allows quantitation of several voxels simultaneously by minimising one cost function which includes signals of different voxels.

Because the variables of different spectra are present in the same minimization problem, it is possible to express relations between the parameters of these spectra. They are imposed in the same way as relations between variables within a spectrum. This is the first time that prior knowledge between spectra of an MRSI experiment is imposed.

To remove the remaining water signal and/or other disturbing components in the spectrum, a FIR filter is used as was described in [4]. A FIR filter is defined by the convolution:

\[ y_f(n) = \sum_{m=0}^{M-1} h_m y(n-m) \]

\[ n = 0, 1, \ldots, N - 1 \quad (2) \]

where \( h_m \) are the constant filter coefficients. Because the signal is sampled from \( t = 0 \), the samples for \( n < 0 \) are not available. The solution to this problem, assuming that the signal is cyclic or that the signal is zero outside the time window, distorts the first \( M-1 \) samples. Therefore those \( M-1 \) samples should be discarded when calculating the filtered signal. A FIR filter is combined with the AMARES algorithm, which allows us to take filter effects into account in the quantitation phase.

For a mathematical description of both the FIR filter and multivoxel quantitation, the reader is referred to [4] and [5].

In the generated simulation signals (Sections 3 and 4) the frequencies, and in one case the phases, are kept constant so that the prior knowledge imposed on those signals is exact.

3 Monte Carlo Simulations

3.1 Monte Carlo simulations on a CSI from a brain tumour

3.1.1 Simulation signal with variable phase

A Monte Carlo study is performed on 30 simulated signals, derived from a brain CSI region containing tumour tissue. The 16×16 CSI was acquired at 63.61 MHz (1.5T Sonata Siemens), using an echo time of 135 ms. The field of view was 160 mm × 160 mm and the slice thickness 12.5 mm, this yields a voxel resolution of 10 × 10 × 12.5 mm³ or 1.25 cc. Using PRESS, a brain region with 30 voxels was selected. In this region 10 voxels contained tumor tissue. After water filtering with the HSVD method, the in-vivo spectra were quantified using a model containing choline, creatine, NAA, lactate and fat. Fat was modeled using one peak, but with a damping which was independent of the dampings of the other resonances. The simulated fat resonance amplitude is on average smaller than that of the metabolites, as can be seen in Figure 1 which shows the metabolite region of the simulated CSI.

To simulate the remaining water residue in each spectrum, the spectrum was quantified using 15 exponentially damped sinusoids. The exponentials lying between -20 Hz to 40 Hz were used to reconstruct the water region around 0 Hz. For each voxel this model for the water region was then added to the simulation signal of that voxel. On the simulated signals the following constraints were imposed: the dampings of all the resonances but fat are equal within a voxel, all resonances have a fixed frequency over all the voxels, the lactate doublet is 180 out of phase and has equal amplitudes. Each signal consists of 512 complex data points, the sampling interval is 1 ms, \( t_0 = 0 \) for each spectrum. On this simulated CSI dataset, noise from a Gaussian distribution with different noise standard deviations \( \sigma \) was added. Four different noise levels
were used: $\sigma = 0.7, 2, 3$ and $4.2$. This corresponds with a mean SNR for the NAA resonance of 20.3 to 4.8 dB. For these simulations an extra peak is added to model the fat resonance in the simulation signal.

The quantitation is done using two different models. The first is a 6-peak model which models all peaks present in the simulation signal (choline, creatine, NAA, lactate doublet and fat). A second model does not model the lactate doublet, resulting in a 4-peak model (choline, creatine, NAA and fat). The CSI was processed using different methods: single voxel processing, multivoxel processing with 5 voxels simultaneously and multivoxel processing with 10 voxels simultaneously.

In the 6-peak model the following prior knowledge within a voxel was used: dampings for all resonances but fat are equal, amplitudes for the lactate doublet are equal. Phases are all set to 0 relative to the overall phase, except for the lactate doublet, which is 180 degrees out of phase. The 5-peak model uses the same prior knowledge but the resonances of the lactate doublet are left out. For multivoxel processing, prior knowledge between voxels was imposed: frequencies of the different resonances are kept constant in the different voxels.

### 3.1.2 Simulation signal with constant phase

To investigate whether the imposition of additional prior knowledge could result in a more pronounced difference in accuracy for amplitude estimates between single and multivoxel processing, the simulation signal described in the previous section was slightly modified. The phases of the spectra from all the voxels in the simulation signal were kept constant (-36 degrees). This extra prior knowledge was imposed to the quantitation algorithm AMARESfts.

### 4 Results

For each voxel, absolute or relative root mean square errors (ARMSE and RRMSE) of the different peaks and parameters are calculated from the Monte Carlo simulation results. Those results are then averaged over all voxels. Absolute RMSE is used to display errors on the frequency and Relative RMSE is used for errors on the amplitude. Those errors are also compared with the theoretical Cramér-Rao (CR) bounds. The results of all the Monte Carlo simulations are described under two main headings: influence of multivoxel processing and the influence of the model order.

#### 4.1 Multivoxel processing

In Figure 2 the results are shown for the mean ARMSE for the frequency estimate of NAA. The multivoxel processing approach results in more accurate estimates of the frequency and this for both the 4-peak and 6-peak model. The difference between the two model orders will be discussed in the next subsection.

![Figure 2: Tumor brain CSI with varying phase.](image)

For the same Monte Carlo simulations no difference in accuracy of amplitude estimates could be detected between single voxel processing and multivoxel processing. This can be seen in Figure 3. In this figure also the CR bounds for each method are plotted. They confirm the results from the Monte Carlo simulations: no difference in accuracy of the amplitude estimates can be detected between the different methods.
Figure 3: TUMOR BRAIN CSI WITH VARYING PHASE: The mean RRMSE for the amplitude of creatine is shown here for the 4-peak model, and this for the three methods: single voxel processing (x marks), multivoxel processing with 5 voxels (circle marks) and 10 voxels (triangle marks). The theoretical Cramér-Rao lower bounds are shown in dashed lines for all methods. No difference in accuracy can be noticed between the different methods.

Figure 4: TUMOR BRAIN CSI WITH CONSTANT PHASE: The mean RRMSE for the amplitude of creatine is shown here for the 4-peak model using the simulation signal with constant phase, and this for the three methods: single voxel processing (x marks), multivoxel processing with 5 voxels (circle marks) and 10 voxels (triangle marks). The theoretical Cramér-Rao lower bounds are shown in dashed lines for all methods. Contrary to figure 3, the creatine amplitude accuracy improves by multivoxel processing.

The results of the Monte Carlo simulations for creatine in which the phase over the CSI set was kept constant are shown in Figure 4. There is a difference now in accuracy of amplitude estimates. Processing 10 voxels simultaneously is the most accurate method for estimating the amplitude of creatine. The single voxel processing method produced the least accurate amplitude estimates. This difference is present for all peaks as well as in the CR bounds.

4.2 Model Order

The Monte Carlo simulations show the following results: the ARMSE on the frequency estimates is lower for the 6-peak model for each method, as can be seen in Figure 2. The same holds for the other metabolites present in the 4-peak model.

The influence of the model order on the amplitude estimates cannot be seen if the results are averaged over the whole data set. The reason for this is that the spectral content of the spectra changes throughout the CSI which means that another model order of the model function is needed to model the spectra exactly. Voxels containing tumor tissue will contain higher lactate levels than voxels with healthy tissue. Due to this inhomogeneity of the CSI the effect of the model order cannot be deduced from the averaged RRMSE on the amplitudes for the 4-peak and 6-peak model.

To address the issue of how the model order influences the accuracy of amplitude estimates, 2 selections of 8 voxels were made in the 30 MRSI simulation signals. The spectra of the first selection (voxels 1, 2, 3, 7, 8, 9, 13 and 14) contain no lactate as can be seen in Figure 1. Those spectra can be modeled by a 4-peak model. Selection 2 contains voxels with a high amplitude for the lactate doublet (voxels 10, 11, 19, 20, 22, 23 and 24). The exact model function for selection 2 spectra has a higher model order, i.e. a 6-peak model. The results of the errors on the quantitation of creatine for the 2 selections were then averaged over each selection. Figure 5 shows that in selection 2, containing spectra with high lactate amplitudes, there is a difference in accuracy between the 4-peak and 6-peak model. Remark that this difference is un-
observable in selection 1. The 6-peak model, in this case an 'exact' model, is more accurate than the 4-peak model which in selection 2 undermodels the signal. In contrast to selection 2, selection 1 does not include tumor region, hence the 4-peak model is 'exact' because lactate levels are negligible in this region and the 6-peak model is overmodeling the signal. In this case there is no difference in accuracy. Similar results were found for the other metabolites choline and NAA. No CR bounds are shown on Figure 5, because no CR bounds could be derived for the 6-peak model. This is due to the fact that the amplitude of fat is zero in some voxels, leading to singularities in the calculation of the CR lower bound.

5 Discussion and Conclusion

The results show that multivoxel processing allows to increase the accuracy of the estimates of the parameters of an MRSI data set. This is due to the possibility to include prior knowledge between different voxels in the multivoxel processing. However, which parameters benefit from the multivoxel approach depends on the kind of prior knowledge imposed. This was predicted by the calculated theoretical Cramér-Rao lower bounds on parameter estimates and confirmed by the different Monte Carlo simulations. Imposing prior knowledge on the frequencies between voxels results in more accurate estimates of the frequencies. Only when prior knowledge on the phases is added, also amplitudes benefit from multivoxel quantitation.

The choice of the model function is often not straightforward in MRSI datasets. Not every voxel contains the same metabolites, and therefore different model orders are needed to correctly model the spectra. Because MRSI processing needs to be automated, one model order is chosen for all spectra. Our simulations show that undermodeling the spectrum has a negative influence on the accuracy of the parameter estimates. On the other hand, slight overmodeling the spectra has no negative influence on the accuracy of amplitude estimates. This indicates that for limited overmodeling, a complete model function for all voxels can be chosen when processing MRSI datasets.

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References


Figure 1: Tumor brain CSI with varying phase: The metabolite region of the spectra of the simulated CSI based on a CSI containing a brain tumor. Creatine, choline and NAA, lactate and fat are visible on the spectra. Voxels from within the box contain only tumor tissue, voxels marked with an X contain both healthy and tumor tissue. All spectra were plotted with phase zero for presentation, actual phases differ from voxel to voxel. Voxels are arranged from left to right, top to bottom.
Figure 5: Tumor brain CSI with varying phase: The figures show the mean RRMSE for the amplitude of creatine using the single voxel method averaged over the ten signals in selection 1 (no lactate)(above) and selection 2 (lactate doublet)(below). For selection 1 no differences can be observed between the 4-peak and the 6-peak model. In the lower figure, it can be clearly seen that the 6-peak model performs better in estimating the amplitudes of creatine.