

Signal Disentanglement in *In Vivo* MR Spectroscopy: By Semi-Parametric Processing or by Measurement?

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Abstract—In practice, a signal often comprises a parametric part and a non-parametric part. Disentangling the two parts from each other is a universal problem. This study concerns two methods of disentangling in the field of *in vivo* Magnetic Resonance Spectroscopy (MRS) where metabolites contribute the parametric part and so-called macromolecules the non-parametric part. One method is based on semi-parametric estimation using *a priori* knowledge and was treated at length by us in Proc. ProRISC 2005. This year, automation of the semi-parametric method is treated. The other method is based on separate, additional measurement of the macromolecules-only contribution, at the cost of doubling the total measurement time. Ideally, the macromolecule contribution can then be simply subtracted, thus yielding the metabolite-only contribution. We analyse advantages and disadvantages of the two methods by way of Monte-Carlo simulations and Cramér-Rao theory.

Keywords—MR-Spectroscopy, automation, semi-parametric, metabolite-nulling, Monte-Carlo simulations

I. INTRODUCTION

Magnetic Resonance Spectroscopy (MRS) is a unique tool for *non-invasive in vivo* detection and quantitation of metabolites. This makes MRS an indispensable tool for combating major diseases.

Although modern MRS-methods are increasingly capable of detecting metabolites and quantifying their concentrations, perturbation by signals from so-called macromolecules poses problems. These problems have to do with the unavailability of a physical model function for the macromolecule signal, which classifies it as non-parametric. The model functions of the metabolite signals are available, classifying them as parametric. The task is to *disentangle* the parametric and non-parametric parts of a signal from each other. This includes error estimation that enables reliable experimental design; till today, this is a challenge in many fields of measurement science.

In MRS, at least three disentanglement procedures can be distinguished:

1. Tuning the scanner to a single metabolite of interest – ‘*spectral editing*’. This simplifies the MRS signal significantly. At present, it is applicable to only a few of the many *in vivo* MRS-visible metabolites.
2. Separate measurement of the macromolecules-only signal and then subtracting it from the MRS (= metabolite + macromolecule) signal. This requires additional measurement time. In the sequel, both ‘separate’ and ‘additional’ allude to this fact.
3. *Semi-parametric* estimation of the model parameters of interest from the mixed parametric/non-parametric MRS signal.

In Proc. ProRISC 2004, we contributed to signal disentanglement by the spectral editing approach [1]. This time, we contribute to disentanglement by

- *Automation* of the semi-parametric estimation method ‘Subtract’, developed in our contributions to Proc. ProRISC 2002, 2003, 2005 [2–4], and in Refs. [5, 6]. Note that we deem universal automation of processing of all diverse, present-day MRS-signals to be elusive. In this work, only the noise realisation and its standard deviation were subject to change.

- Subtraction of the separately measured macromolecules-only signal.

All results presented in this paper have been obtained by simulations. The organisation of the paper is shown at the end through a list of Contents and Figures (relative page numbers).

II. MATERIALS AND METHODS

A. *The Metabolite signal*

The model function of the simulated signal – typically comprising $n = 1024$ complex-valued data-points in the time domain – has been described extensively in our Proc. ProRISC 2005 paper [4]. The ultimate signal-processing task in *in vivo* MRS is to estimate concentrations of metabolites in patients, and this including realistic

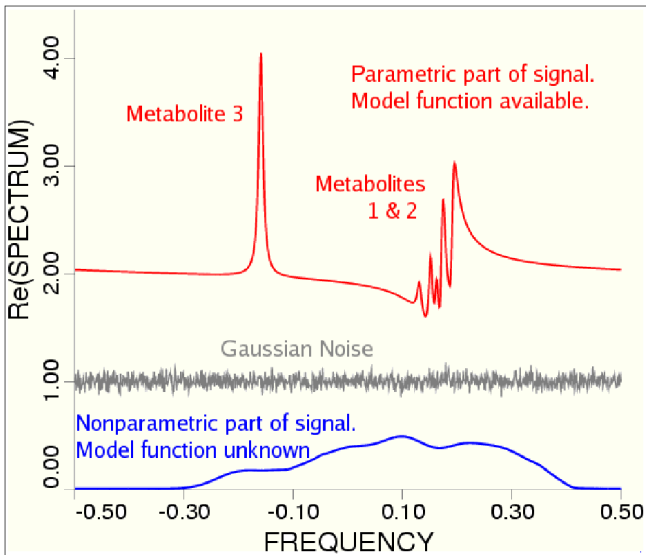


Fig. 1

Real parts of the spectra of the contributions to the simulated MRS signal. Metabolites 1 and 2 each contribute a quartet. Due to heavy spectral overlap, the sum resembles a quintet rather than an octet. The non-parametric part originates from macromolecules. Contributions from water and lipids were excluded.

error bars. In this Section, we recall briefly the spectral content and decay times of our simulated *in vivo* MRS signal.

The spectral content – shown in Fig. 1 – comprises contributions from three metabolites (1, 2, 3), macromolecules, and Gaussian noise. Metabolites 1 and 2 each contribute four components (quartet), metabolite 3 only one component (singlet). The semi-parametric estimation of model parameters was intentionally made difficult for metabolites 1 and 2 by making their quartets overlap strongly with each other and with the spectrum of the macromolecules, the latter possessing some structure in the overlap region too. Metabolite 3, on the other hand, is less difficult to handle because its singlet spectrum overlaps only with the macromolecule spectrum, and this in a flat region of the latter.

The decay times – or rather the differences between them, see Fig. 2 – constitute a crucial property for semi-parametric disentanglement. The decay time of the macromolecule signal, $t_{\text{decay}}^{\text{MM}}$, is much shorter than that of the metabolite signal, t_{decay} . Thus, for $t > t_{\text{decay}}^{\text{MM}}$, the main contributors to the MRS-signal are metabolites and noise.

B. Automated Pre-Processing for Subtract

This Section describes automated processing to be run prior to Subtract. It provides estimates of the decay time

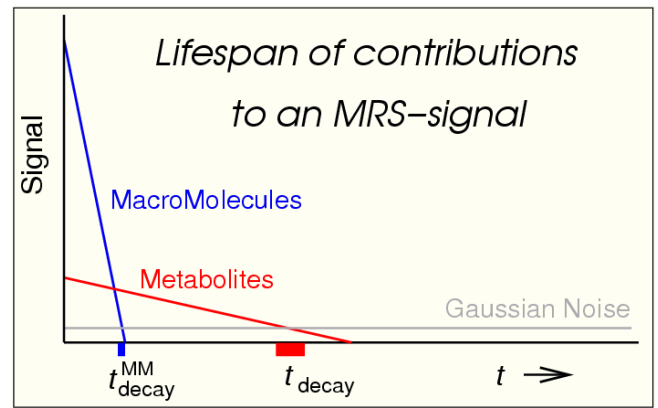


Fig. 2

Schematic display of contributions to an *in vivo* MRS signal. t_{decay} and $t_{\text{decay}}^{\text{MM}}$ are the points of time where the metabolite contribution and the macromolecule contribution respectively have decayed to about the noise level. The total number of data-points is 1024.

$t_{\text{decay}}^{\text{MM}}$ defined above and of the number of sinusoids $K_{\text{SS}}^{\text{MM}}$ used for modelling the macromolecule contribution with the State Space (SS) method.

The following 9 steps constitute the essence of our automation procedure.

1. Estimation of the noise level.
 2. Estimation of time t_{decay} , where the MRS-signal has decayed to the noise level; see Fig. 2. In practice, this time coincides with that where the metabolite signal has decayed to the noise level.
 3. SS-modelling of the MRS signal with K_{SS} sinusoids, over a time span of $0 \leq t \leq f \times t_{\text{decay}}$, where $1.0 \leq f \leq 2.0$. Step 5, below, provides info about the value of K_{SS} .
 4. Separation of the SS-model obtained in step 3 into a metabolite model s_{Met} and a macromolecule model s_{MM} , by the criterion that s_{MM} be strongly damped and avoids the known frequency regions of metabolite signals. $K_{\text{SS}}^{\text{MM}}$ equals the number of sinusoids assigned to s_{MM} .
 5. Repetition of steps 3 and 4 for many values of the hyper-parameters K_{SS} and f , namely
 - $K_{\text{SS}} = \text{nint}(t_{\text{decay}}/8\Delta t) + 0, 1, 2, 3, 4$, nint standing for nearest integer. In our simulations, $\Delta t = 1$.
 - f ranges from 1 to 2, in $\text{nint}(t_{\text{decay}}/10\Delta t)$ steps.
- The number of different pairs of (K_{SS}, f) can be, e.g., 5×13 . For each pair (K_{SS}, f) , the resulting $K_{\text{SS}}^{\text{MM}}$ and s_{MM} are stored for use the next step.
6. Taking the median [7, 8] – rather than the average – of the many $K_{\text{SS}}^{\text{MM}}$'s and s_{MM} 's obtained in the previous step 5. This procedure – *i.e.*, varying values of hyper-parameters and taking the median of the results – crucially improves the outcome.
 7. Smoothing of $|s_{\text{MM}}(t)|$ by averaging over five adjacent

points of time. Smoothing is necessary because $|s_{\text{MM}}(t)|$ is an oscillating function; see Fig. 3.

8. Fitting of a straight line to $\log(\text{smoothed } |s_{\text{MM}}(t)|)$.

9. Finally, the intersection of the straight line of step 8 and the grey line in Fig. 2 provides an estimate of $t_{\text{decay}}^{\text{MM}}$.

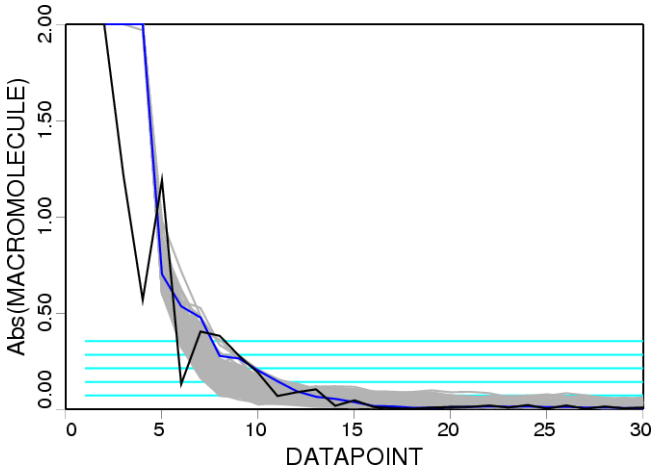


Fig. 3

Decay of $|s_{\text{MM}}(t)|$, $t = (n - 1)\Delta t$ for data-point $n = 1, 2, \dots, 30$. Black: True, noiseless version. $s_{\text{MM}}(0) = 13.0$. Blue: Smoothed, true, noiseless version. Grey: Smoothed, estimated versions, for 1000 realisations of added noise. For $n \geq 5$, the (grey) estimates are biased, causing $t_{\text{decay}}^{\text{MM}}$ to be on the small side. Cyan: 1 through $5 \times$ the standard deviation of the noise.

C. Semi-Parametric Estimation of Metabolite Model Parameters using Subtract

The automated pre-processing described in the previous Section, served to obtain estimates of the decay time $t_{\text{decay}}^{\text{MM}}$ and the hyper-parameter $K_{\text{SS}}^{\text{MM}}$. The basic steps of Subtract are as follows [4–6].

1. Estimation of the metabolite model parameters from the MRS signal for $t > t_{\text{decay}}^{\text{MM}}$ by Non-Linear Least Squares fitting (NLLS), invoking optimal prior knowledge in the form of a metabolite basis set.
2. Reconstruction of the metabolite signal from the suboptimal model parameters estimated in step 1. This constitutes a preliminary disentanglement.
3. Subtraction of the reconstructed metabolite signal from the MRS-signal, providing a suboptimal estimate of the macromolecule signal including noise.
4. SS-modelling of the macromolecule signal obtained in step 3. As in Sec. II-B, we vary the values of some hyper-parameters of the modelling. Thus, the number of sinusoids used is $k = \max(6, K_{\text{SS}}^{\text{MM}}) + 0, 1, 2$, while the number of data-points is $n = 2(k + 6) + 0, 1, \dots, 16$. Subsequently, the median [7, 8] of the corresponding 3×17 results is taken.

5. Subtraction of the SS-modelled macromolecule signal from the MRS signal for $0 \leq t \leq t_{\text{decay}}^{\text{MM}}$. This yields an improvement of the disentangled metabolite signal.

6. NLLS estimation of the metabolite model parameters from the disentangled metabolite signal obtained in the previous step, again invoking optimal prior knowledge in the form of a metabolite basis set.

A flowchart of Subtract is given in the Appendix.

D. Signal Disentanglement by Additional Measurement

Till today, measuring many metabolites in a single scan, without incurring contamination from macromolecules, is impossible. However, direct measurement of only the macromolecules – by so-called ‘metabolite-nulling’ – is possible. Subtracting this macromolecules-only signal from the previously measured metabolite-plus-macromolecule signal, yields the wanted metabolites-only signal [9, 10]. A powerful advantage of this strategy is that semi-parametric estimation and concomitant uncertainty is obviated. Disadvantages are *doubling* of the measurement time, plus a *decrease* of the resulting metabolite signal-to-noise ratio (SNR) by a factor of $\sqrt{2}$. To the best of our knowledge, this paper recognises and analyses the consequences of disentanglement by separate measurement in MRS for the first time.

We simulated signal disentanglement by separate measurement with the following assumptions. 1) The measurement times of the MRS signal (macromolecules + metabolites) and macromolecules-only signal are equal. 2) The macromolecule contributions in both signals are equally strong, implying that mere subtraction of the signals suffices – *i.e.*, no pre-processing or model fitting required – to arrive at the metabolites-only signal.

E. Monte-Carlo Tests and Cramér-Rao Bounds

Both disentanglement approaches mentioned above were tested with the Monte-Carlo method: Thousand different realisations of white Gaussian noise were consecutively added to the simulated signal. All parameter estimates were carried out for each noise realization, and mean values, standard deviations, bias, root-mean-square errors (RMSE’s) were determined.

We judged the results by comparison to Cramér-Rao bounds (CRB’s) pertaining to *absence* of a macromolecule contribution to the signal, or, in other words, to metabolites only. The corresponding CRB’s are given the subscript Met .

In order to be independent of the actual values of CRB_{Met} – see Ref. [4] – we display the quantity ‘NDRMSE’, de-

fined as

$$\text{NDRMSE} = \frac{\text{RMSE} - \text{CRB}_{\text{Met}}}{\text{CRB}_{\text{Met}}} \times 100\% , \quad (1)$$

for each of the three metabolites. This implies that instead of RMSE itself, we display the Normalised Difference with its related metabolite-only CRB, the latter pertaining to the time needed for measuring only the macromolecule-plus-metabolite signal. For example, an RMSE of $\sqrt{2}$ times its related CRB_{Met} , results in $\text{NDRMSE} = (\sqrt{2} - 1) \times 100\% = 41.4\%$. For the sequel, the content of the grey box below must be kept in mind.

In all NDRMSE-displaying Figures, each CRB_{Met} refers to the SNR and measurement time associated with the *original* macromolecule-plus-metabolite signal. For example, 0% means $\text{RMSE} = \text{CRB}_{\text{Met}}$, pertaining to the original – not doubled – measurement time. $\text{RMSE} = \text{CRB}_{\text{Met}} \times \sqrt{2}$ is indicated by a red line, which is the same for each metabolite thanks to the normalisation. This serves to focus on the matter of how to spend a doubling of the measurement time. Note that, given such a doubling of the measurement time, an NDRMSE can well become negative. In that case, the doubling could be justified. Whether this actually happens remains to be seen (below).

III. RESULTS AND DISCUSSION

This Section gives results of metabolite quantitation after disentanglement of metabolite and macromolecule contributions to a simulated *in vivo* MRS signal.

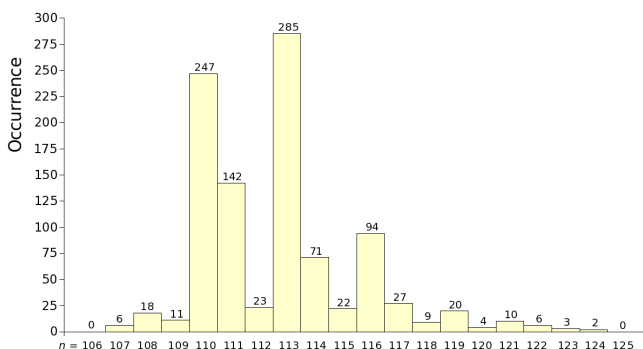


Fig. 4

Automatic estimation of $t_{\text{decay}} = n_{\text{decay}} \Delta t$ where the MRS signal $s(t)$ has decayed to the noise level, mentioned in step 2 of Sec. II-B. The heights of the yellow vertical bars indicate the occurrence of the n_{decay} -values, found for 1000 noise realisations. The values were contained in the horizontally plotted range $n = 107, \dots, 125$; the sum of occurrences equals 1000. The total number of data-points is $n = 1024$.

Disentanglement was done by 1) automated semi-parametric estimation and 2) separate measurement and subsequent subtraction of the macromolecule signal. The Monte-Carlo method was used with thousand noise realisations [4].

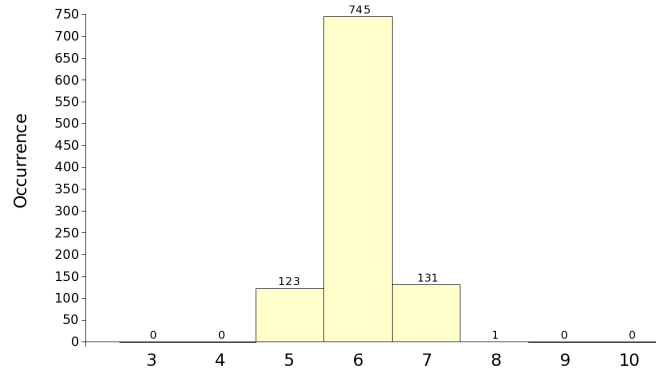


Fig. 5

Automatic estimation of the number of sinusoids K_{SS} used for SS-modelling of the macromolecule contribution to the MRS signal, in step 6 of Sec. II-B. K_{SS} is plotted horizontally. The occurrences of K_{SS} found with 1000 noise realisations are indicated by the heights of the yellow vertical bars; the sum of all occurrences equals 1000. 75% of the noise realisations yield $K_{\text{SS}} = 6$.

A. Automated Semi-Parametric Disentanglement and Estimation

With each noise realization, disentanglement by automated semi-parametric estimation ended successfully. This was established by perusing the plots of all SS-modelling residues, and by monitoring the number of iterations of the non-linear least-squares parametric model fits after the automated semi-parametric disentanglement. Figures 4, 5, 6, 7, and their captions show the main results.

A.1 Discussion of Figs. 4, 5, 6

Fig. 4 shows that 90% of the noise realisations yield a value of n_{decay} in the range of 110, \dots , 117 data-points. The decay time of the MRS signal is related to this through $t_{\text{decay}} = n_{\text{decay}} \Delta t$. The spread in the estimates is due to the fact that the metabolite signal does not decay smoothly. The latter in turn is caused by destructive and constructive interference of the contributing sinusoids with each other. **Fig. 5** reveals a strong preference for $K_{\text{SS}} = 6$ sinusoids be used for automatic SS-modelling of the macromolecule contribution to the MRS signal. We point out that in the automatic SS-modelling of the disentangled macromolecule signal, we do not allow that K_{SS} be below 6. The latter measure is based on ‘expert’ experience.

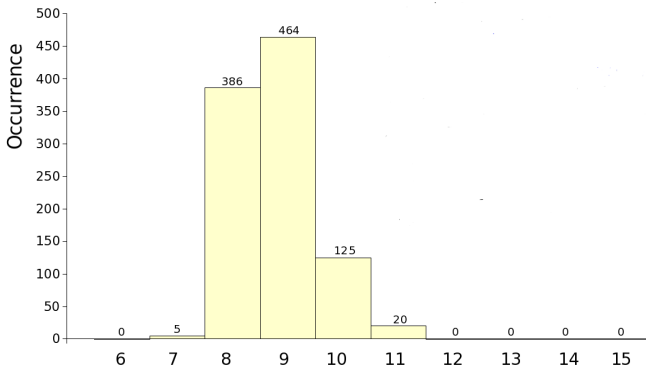


Fig. 6

Automatic estimation of $t_{\text{decay}}^{\text{MM}} = n_{\text{decay}}^{\text{MM}} \Delta t$, where the macromolecule contribution to the MRS signal has decayed to the noise level, mentioned in step 9 of Sec. II-B. $n_{\text{decay}}^{\text{MM}}$ is plotted horizontally. The occurrences of $n_{\text{decay}}^{\text{MM}}$ found with 1000 noise realisations are indicated by the heights of the yellow vertical bars. 97.5% of the $n_{\text{decay}}^{\text{MM}}$ -values were contained in the range $n = 8, 9, 10$; the sum of all occurrences equals 1000.

Fig. 6 is related to Fig. 3: Fig. 3 shows that the estimated smoothed version $\text{abs}(s_{\text{MM}})$ – see grey ‘cloud’ – is biased; for $5 \leq n \leq 12$, all grey lines are below the blue line. As a consequence, the estimate of $t_{\text{decay}}^{\text{MM}}$ is biased too, 97.5% of its related values $n_{\text{decay}}^{\text{MM}}$ lying in the range of 8, 9, 10, whereas Fig. 3 indicates that the ‘true’ value is around 12 or 13. Definition of a true value is difficult though, even for a simulation. In view of this underestimation, we have investigated the RMSE of the metabolite quantitation as a function of $t_{\text{decay}}^{\text{MM}}$; see below.

A.2 Discussion of Fig. 7

Fig. 7 summarises the essence of our automated semi-parametric estimation results. NDRMSE’s are shown for ten values of $n_{\text{decay}}^{\text{MM}}$, namely the value found automatically (‘auto’) augmented with a correction equalling -1, 0, +1, ... +7, and +10. Viewing the Figure, the NDRMSE’s of metabolites 1 (blue) and 2 (light-blue) appear to depend on the value of $n_{\text{decay}}^{\text{MM}}$. For metabolite 1, NDRMSE is minimal at correction equals +4, for metabolite 2 at correction equals +2.

The latter phenomenon is due to a combination of spectral overlaps: The spectra of metabolites 1 and 2 overlap strongly with each other *and* with that of the macromolecules. The model function of the macromolecule signal being *a priori* unknown there is no way to detect and prevent intermixing of signals (spectra) in the overlap region [4].

The extent of intermixing is influenced by the size of the

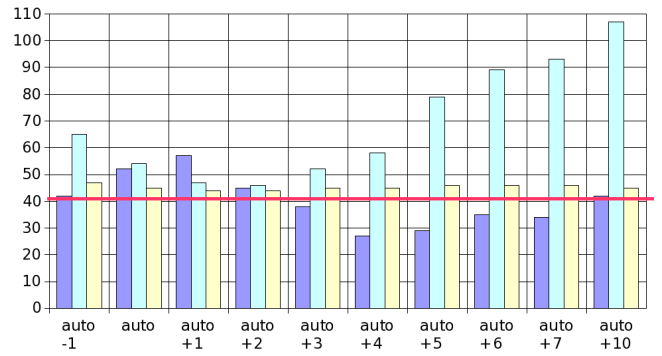


Fig. 7

Errors in units of $\text{NDRMSE} = [(\text{RMSE} - \text{CRB}_{\text{Met}}) / \text{CRB}_{\text{Met}}] \times 100\%$ (vertical), obtained with automated semi-parametric estimation of metabolite concentrations. Plotted horizontally is ‘auto’+ integer number, where ‘auto’ equals $n_{\text{decay}}^{\text{MM}}$, discussed in Sec. III-A.1. Blue: Metabolite1. Light-blue: Metabolite2. Yellow: Metabolite3. The horizontal red line indicates $\text{CRB}_{\text{Met}} \times \sqrt{2}$.

residual macromolecule signal after applying ‘Subtract’ in the time slot $0 \leq t \leq t_{\text{decay}}^{\text{MM}} = n_{\text{decay}}^{\text{MM}} \Delta t$. According to the Figure, a best correction of the automatically estimated $n_{\text{decay}}^{\text{MM}}$ is about +2. This is a reasonable value given the bias of the ‘grey cloud’ shown in Fig. 3. However, for a *real-world in vivo* MRS measurement, there is no method for estimating a best correction; one has to rely on experience.

The NDRMSE of metabolite 3 (yellow), whose spectrum overlaps only with that of the macromolecules and not with that of other metabolites – see Fig. 1 – turns out to be largely independent of $n_{\text{decay}}^{\text{MM}}$.

Finally, recall that the horizontal red line indicates $\text{RMSE} = \text{CRB}_{\text{Met}} \times \sqrt{2}$ – see grey box on page 4. Its significance stems from the following: Should one decide to spend an additional, equal time on measuring also the macromolecules-only signal, and subtract this from the metabolite + macromolecule signal, the ensuing metabolite-only CRB’s will all rise to the red line. This is explained below, in Sec. III-B. Already, one can observe that in the region of $n_{\text{decay}}^{\text{MM}} = \text{auto} + 2$, the semi-parametric NDRMSE’s are around the level of the red line. This result is remarkable given the fact that doubling of the measurement time is avoided in the semi-parametric case.

B. Disentanglement by Additional Measurement

B.1 Subtracting All Macromolecule Data-Points

As mentioned in Sec. II-D, semi-parametric estimation and its related complexities can be obviated by *measuring* rather than *estimating* the macromolecule signal. As-

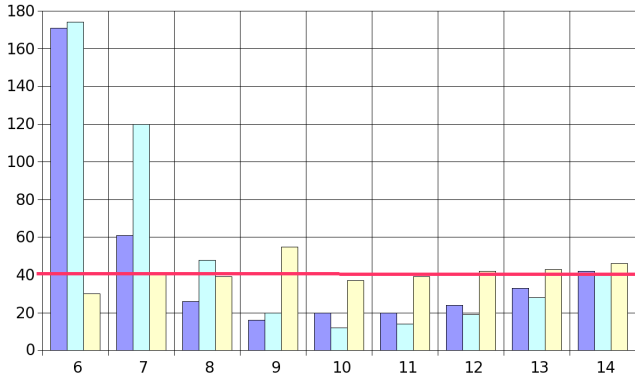


Fig. 8

Errors in units of $\text{NDRMSE} = [(\text{RMSE} - \text{CRB}_{\text{Met}}) / \text{CRB}_{\text{Met}}] \times 100\%$ (vertical), obtained with parametric estimation of metabolite concentrations, after subtraction of the measured macromolecules-only signal, only up to and including initial data-point $n_{\text{init}} = 6, 7, \dots, 14$ (horizontal). Blue: Metabolite1. Light-blue: Metabolite2. Yellow: Metabolite3. The horizontal red line indicates $\text{CRB}_{\text{Met}} \times \sqrt{2}$.

suming that the two conditions quoted at the end of sub-Sec. II-D are satisfied, it yields the metabolite-only signal by simple subtraction. However, the cost is a doubling the total measurement time. The results of this alternative approach can be simply represented by the horizontal red line in Fig. 7. To understand this, note first that adding (or subtracting) two noise realisations of equal standard deviation σ yields a new noise realisation with a standard deviation $\sigma \times \sqrt{2}$. Since the macromolecule contributions to the macromolecules + metabolites signal and macromolecules-only signal are equal, subtraction of *all* data-points of the two signals yields a metabolites-only signal with standard deviation of $\sigma \times \sqrt{2}$. This will give rise to an increase of the parametric estimation errors by $\sqrt{2}$. Bias having been eliminated, the estimation is rendered parametric (maximum-likelihood), and therefore testing this approach with the Monte-Carlo method is not necessary.

B.2 Subtracting Only *Initial* Macromolecule Data-points

Although the simplicity of the approach of the previous Sec. III-B.1 is advantageous, the concomitant loss of precision by a factor of $\sqrt{2}$ is disappointing. Possibly, the loss can be alleviated, at the cost of reduced simplicity. This is based on the idea that subtraction should be necessary only so long as the macromolecule signal is above the noise, *i.e.* for $t \leq t_{\text{decay}}^{\text{MM}}$. Thus, leaving the MRS signal untouched beyond this point of time seems recommendable. We investigated this possibility by subtracting the

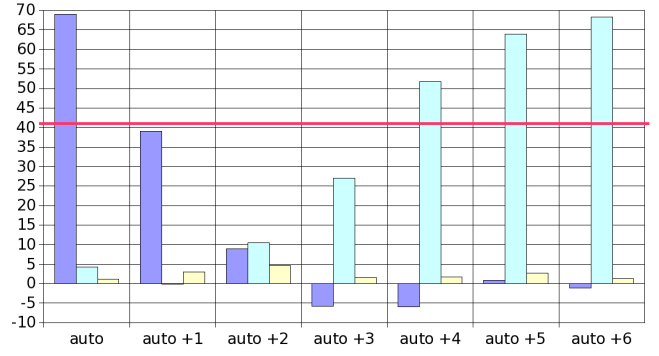


Fig. 9

Errors in units of $\text{NDRMSE} = [(\text{RMSE} - \text{CRB}_{\text{Met}}) / \text{CRB}_{\text{Met}}] \times 100\%$ (vertical), obtained with automated semi-parametric estimation of metabolite concentrations, after *doubling* of the measurement time. Plotted horizontally is 'auto' + integer number, where 'auto' equals $n_{\text{decay}}^{\text{MM}}$, discussed in Sec. III-A.1. Blue: Metabolite1. Light-blue: Metabolite2. Yellow: Metabolite3. The horizontal red line indicates $\text{CRB}_{\text{Met}} \times \sqrt{2}$.

measured macromolecules-only signal for a varying number n_{init} of initial data-points up to about the value $n_{\text{decay}}^{\text{MM}}$. SS-modelling was omitted. Invocation of the Monte-Carlo method was necessary because bias-variance trade-off is involved.

Fig. 8 summarises the results, in units of $\text{NDRMSE} = [(\text{RMSE} - \text{CRB}_{\text{Met}}) / \text{CRB}_{\text{Met}}] \times 100\%$.

First of all, recall that NDRMSE should reach the red line when *all* macromolecules-only data-points are subtracted. It seems this outcome is already approached for $n_{\text{init}} = 14$.

Clearly, the results for the heavily overlapping metabolites 1 and 2 depend much stronger on n_{init} than do the results for the 'isolated' metabolite 3. The optimum number of initial macromolecule data-points to be subtracted is around 11. These results were to be expected.

Less expected is the phenomenon that the results for metabolites 1 and 2 reach well below the red line – as hoped – whereas the results for metabolite 3 remain relatively close to the red line – not hoped. To be investigated further.

Overall, subtraction of only about $n_{\text{init}} \approx n_{\text{decay}}^{\text{MM}}$ measured initial macromolecule data-points is recommendable. If it does not help, it does not hurt either.

Automation of estimating $t_{\text{decay}}^{\text{MM}} = n_{\text{decay}}^{\text{MM}} \times \Delta t$ is still to be done. This should be relatively easy.

C. Semi-Parametric Approach With Doubled Measurement Time

In this Section, we investigate whether the additional time, allotted to measuring a macromolecules-only signal in the previous Section, could possibly be spent in a better

way. For this purpose, note that pursuing a measurement till time elapsed has doubled, improves the SNR by a factor of $\sqrt{2}$. The question can then be posed whether the errors incurred in Sec. III-A might decrease by the same order of magnitude. The answer seems not trivial because semi-parametric estimation involves bias-variance trade-off. Therefore, we repeated the Monte-Carlo simulations of Sec. III-A, but then with the standard deviation of the measurement noise decreased by a factor of $\sqrt{2}$. The results are displayed in Fig. 9.

Recall that, as everywhere else in this paper, the red line in Fig. 9 pertains to a rise of $\text{NDRMSE} = [(\text{RMSE} - \text{CRB}_{\text{Met}})/\text{CRB}_{\text{Met}}] \times 100\%$ by $(\sqrt{2} - 1) \times 100\% = 41.4\%$ with respect to the CRB_{Met} 's. The latter pertain to the original (not the doubled) measurement time and therefore to the original SNR.

As before, the results for metabolites 1 and 2 depend clearly on the value of $t_{\text{decay}}^{\text{MM}}$ (auto + . . .), whereas the results for metabolite 3 seem relatively constant.

The optimal values of (auto + . . .) in Figs. 7 and 9 are approximately equal. The improvement for metabolites 1 and 2 at the optimal value is beyond doubt.

Comparing Figs. 8 and 9 reveals that in the present simulated case, doubling of the measurement time might be better spent on simply continuing the measurement of the metabolite + macromolecule signal, rather than spending the extra time for measuring a macromolecule-only signal.

IV. CONCLUDING REMARKS

This paper is summarised with the following remarks.

- Our attention concentrated on the semiparametric case of simulated *in vivo* MRS data with contributions from metabolites (parametric) and macromolecules (non-parametric). Contributions from water and lipids (both non-parametric) were not considered.
- Automation of semi-parametric estimation of metabolite concentrations from *in vivo* MRS data is feasible. However, the attendant setting of hyper-parameters may need adaptation to the type of measurement at hand. This applies especially to the case where metabolite spectra overlap strongly with each other and with the macromolecule spectrum.
- By measuring an additional 'macromolecule-only' signal, one can avoid application of semi-parametric estimation and its attendant automation problems. However, this requires a doubling of the measurement time and need not result in improved metabolite concentration estimates perse.

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APPENDIX

The ‘Subtract’-variant of the semi-parametric QUEST algorithm for quantitative analysis of *in vivo* MRS data is shown in Fig. 10. QUEST is freely available for Academia on <http://www.mrui.uab.es/mrui/>

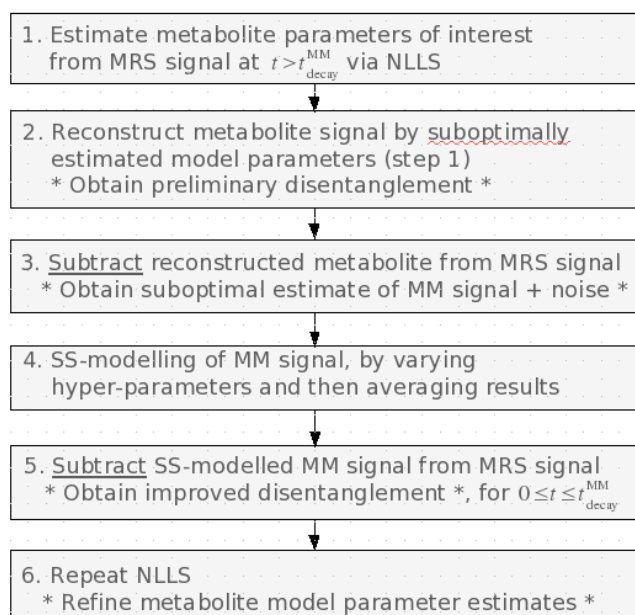


Fig. 10

Flowchart of the Subtract algorithm, one of the various alternative realisations of the semi-parametric QUEST algorithm [2–6]. MM stands for MacroMolecules, SS for State Space. Other perturbing contributors to *in vivo* MRS data, such as water and lipids, have not been considered in the present work.

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