

Semi-Parametric Estimation in *In Vivo* MR Spectroscopy

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Abstract—Semi-parametric disentanglement of parametric parts from non-parametric parts of a signal is a universal problem. This study concerns estimation of metabolite concentrations from *in vivo* Magnetic Resonance Spectroscopy (MRS) signals. Due to *in vivo* conditions, so-called macromolecules contribute non-parametric components to the signals. Disentanglement is achieved by exploiting prior knowledge about the parametric and non-parametric parts directly in the measurement domain (as opposed to the Fourier domain). Cramér-Rao bounds and bias depend on the degree of modelling the non-parametric part.

Keywords—Metabolomics, MR Spectroscopy, semi-parametric iterative model, disentanglement, Cramér-Rao bounds

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 and a number of unidentified metabolites of lesser concentration poses problems. Three procedures for alleviating the problem exist: 1) Tuning of the scanner to a metabolite of interest – ‘spectral editing’ – can clean up the MRS signal significantly. 2) Separate (but approximate) measurement of the macromolecule signal and then masquerading it as metabolite signal. 3) *Semi*-parametric estimation of the model parameters of interest from the MRS signal. See Refs. [1–11] on page 8.

In ProRISC 2004, we contributed to the spectral editing approach [12]; see Ref. [13] for the most recent example. This time, we contribute to semi-parametric estimation of simulated signals, building on our contributions to ProRISC 2002 and 2003. Emphasis will be on the semi-parametric estimation method ‘Subtract’, which is part of the MRS signal processing program QUEST [2–4]. QUEST, in turn, is part of the freely available MRS software package jMRUI; see <http://www.mrui.uab.es/mrui/>. We will tackle the problem of systematic and

statistical errors which is crucial in semi-parametric estimation.

This paper is arranged as follows. Sec. II treats the parametric and non-parametric *in vivo* MRS signals and estimation methods. Sec. III gives results and discusses their implications. Finally, Sec. IV summarizes the situation and draws conclusions.

II. MATERIALS AND METHODS

A. The Metabolite Signal

The *parametric* part of an *in vivo* MRS signal – *i.e.*, that pertaining to a number of M metabolites – is modelled as

$$s(t) = e^{i\varphi_0} \sum_{m=1}^M \left(a(m) e^{(\alpha(m)+2\pi i\nu(m))t} \times \sum_{k=1}^{K_m} a_m(k) e^{(\alpha_m(k)+2\pi i\nu_m(k))t+i\varphi_m(k)} \right), \quad (1)$$

where $t = n\Delta t + t_0$ is the real time; in t , t_0 is a (often unknown) scanner ‘dead time’, Δt is the sampling interval, and $n = 0, 1, \dots, N - 1$ are the sample numbers. $i = \sqrt{-1}$. Unknown parameters – hence to be estimated – have been coloured **red**. Note that the ‘dead time’ t_0 occurs in both lines of Eq. 1, through time t .

The parameters in the first line of Eq. 1 are the (usually unknown) overall phase φ_0 , the metabolite concentrations (also called amplitudes) $a(m)$, the metabolite damping corrections $\alpha(m)$, and the metabolite frequency corrections $\nu(m)$. Ideally, the $\alpha(m)$ and $\nu(m)$ ¹ are zero, but conditions in living tissue require estimation of these parameters. Most often the metabolite concentrations $a(m)$ are the only parameters of medical interest.

Summarizing line 1 of Eq. 1, we estimate a minimum of $3M + 2$ parameters, indicated by $p(j)$, $j = 1, 2, \dots, 3M + 2$, when convenient. (In some cases, it is necessary to replace φ_0 by a set of phases $\varphi(m)$, but this is ignored in the present study.) From this point, the colouring of parameters to be estimated is discontinued.

¹Indicated by $\Delta\alpha(m)$ and $\Delta\nu(m)$ in Refs. [2–4].

The second line in Eq. 1 represents the so-called ‘metabolite database’. Each metabolite $m = 1, 2, \dots, M$, contributes a number of K_m damped sinusoids with *known* amplitudes, damping factors, frequencies, phases, $a_m(k), \alpha_m(k), \nu_m(k), \varphi_m(k), k = 1, 2, \dots, K_m$, respectively. In this study, we simulate three metabolites – *i.e.*, $M = 3$ – with concentrations set to $a(1) = 0.50$, $a(2) = 1.0$, $a(3) = 2.0$. The related database parameters are listed in Table I. Some remarks about our choice of pa-

TABLE I
THE PARAMETERS OF THE METABOLITE DATABASE
FEATURING IN LINE 2 OF EQ. 1.

m	k	$a_m(k)$	$\alpha_m(k)^\dagger$	$\nu_m(k)^\dagger$	$\varphi_m(k)^\ddagger$
1	1	0.50	-0.030	0.150	0.0
	2	1.50	-0.030	0.160	60.0
	3	1.50	-0.030	0.170	120.0
	4	0.50	-0.030	0.180	180.0
2	1	0.30	-0.030	0.130	0.0
	2	0.60	-0.030	0.150	30.0
	3	0.90	-0.030	0.170	60.0
	4	1.20	-0.030	0.190	90.0
3	1	1.00	-0.030	-0.160	0.0

[†] $\alpha_m(k)$ and $\nu_m(k)$ are in units of $1/2\Delta t$.

[‡] In units of degrees.

parameter values in Table I are in order.

1. In accordance with reality, the frequencies of the ‘quartets’ $m = 1, 2$, overlap severely. In fact, the values 0.150 and 0.170 are shared. This causes strong correlations in the covariance matrix and concomitant increases of the related Cramér-Rao Bounds (CRBs) [3].
2. The phases $\varphi_m(k)$ of the quartets have been chosen such that corresponding spectral peaks are partly negative. In MRS-practice, negative peaks are not uncommon, a notorious case being lactate. Figs. 3–6 show such negative peaks. When disentangling metabolites from macromolecules in the frequency domain, this negativity can pose problems. In the time domain, any value of a phase is as good as another.
3. The frequency of the singlet $m = 3$ does not overlap with those of the quartets $m = 1, 2$. As a result, the CRBs of this component are lower than those of the quartets.

B. The Macromolecule Signal

The *non*-parametric part of an *in vivo* MRS signal comprises contributions from macromolecules, water, lipids. Here we consider only the macromolecules. Simulation of the corresponding time-domain signal was treated in detail in a previous contribution to ProRISC [14].

In the present study, the macromolecule signal is mimicked by six sinusoids with Gaussian decay and a combination of sinc-type signals with Lorentzian decay. A total of 30 real-valued model parameters was used to describe the shape. This implies that at least 15 noiseless complex-valued data-points would be needed to estimate all macromolecule model parameters. In actual practice, the macromolecule model function is unknown. Consequently, an accurate approximation by some mathematical ‘surrogate’ would need many more data-points.

Fig. 1 shows the FFT of the macromolecule signal and the constituent components, in absence of noise. Fig. 2 shows the real part of 60 initial (of $N = 1024$) data-points of the time-domain version. The horizontal magenta lines indicate \pm twice the standard deviation of the noise. Apparently, the macromolecule signal ‘decays into the noise’ at around $n = 10$.

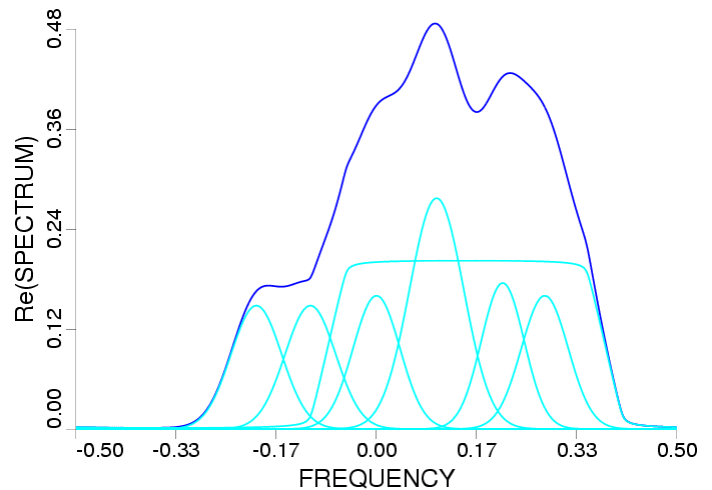


Fig. 1

FFT of the macromolecule signal (blue) and its seven constituent components (cyan); noise omitted.

C. Parametric estimation of metabolite model parameters

In absence of a macromolecule signal, it is relatively easy to estimate the metabolite model parameters $p(j)$ in Eq. 1. To this end, we adopted the fast nonlinear least-squares fit method described in Sec. 3.3 of Ref. [15]. Briefly, it amounts to deriving a first-order Taylor expansion of Eq. 1 with respect to the $p(j)$ and iteratively solving for the unknown increments of the $p(j)$ by invoking the LAPACK subroutine DGELSS. Usually, convergence is reached in 5 to 10 iterations. Monte Carlo simulations with 1000 different noise realizations showed the bias $p(j)_{\text{mean}} - p(j)_{\text{true}}$ of each estimated parameter to be negligible with respect to the standard deviation $\sigma_{p(j)}$. In addition, the $\sigma_{p(j)}$ agreed well with the related Cramér-Rao Bounds, $\text{CRB}_{p(j)}$.

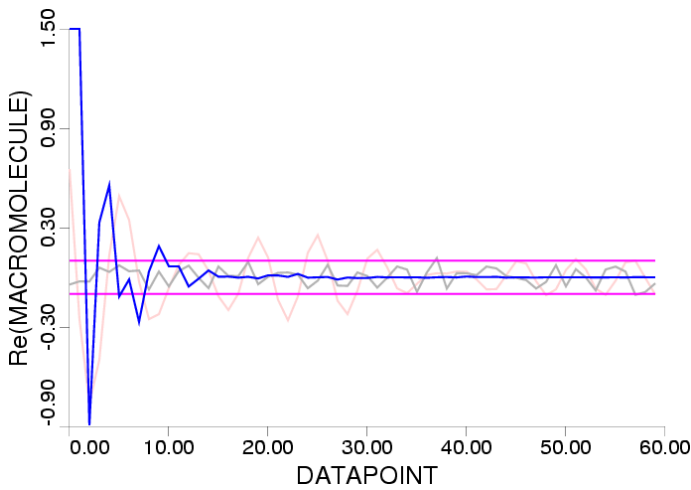


Fig. 2

Real part of sixty initial data-points of the simulated macromolecule signal (blue); added noise (grey); $2 \times$ the noise standard deviation (magenta). The maximum value – of data-point(0), clipped in the Figure – is 13. For reference, the real part of the simulated metabolite signal, divided by 5, is shown too (light orange).

D. Non-parametric estimation of the MacroMolecule (MM) contribution

Signals from MMs are most often considered as nuisance, to be removed (disentangled) from the rest. Given this current appreciation, it would suffice to directly estimate the MM signal *itself* [6], rather than the parameters of some mathematical model that represents it. On the other hand, such modelling – with, *e.g.*, sinusoids, wavelets, splines – enables one to reduce the degrees of freedom, leading to ‘sparse modelling’. We opt for the latter approach, using the State Space (SS) formalism which models with exponentially damped sinusoids, as vehicle [2, 3, 16]. The choice relates to the fact that an MR signal is by nature a sum of damped sinusoids. The SS algorithm used here is called HSVD in the MR community [15]; its input parameters are the number of data-points to be used N_{SS} and the number of exponentially damped sinusoids $K_{SS} (< N_{SS}/2)$ to model with. A similar approach is advocated in Ref. [17].

Important non-parametric modelling choices to be made are:

1. How *few* initial data-points, N_{SS} , to use?

The choice of N_{SS} depends on the decay of the MM signal relative to the level of the noise. In the present simulation, see Fig. 2, about 10 data-points suffice.

2. How *few* components, K_{SS} , to estimate (sparseness)?

By choosing K_{SS} low, HSVD is constrained to model only the strongest part of the MM signal, *i.e.*, that accounting for the overall width shown in Fig. 1 (blue line). In

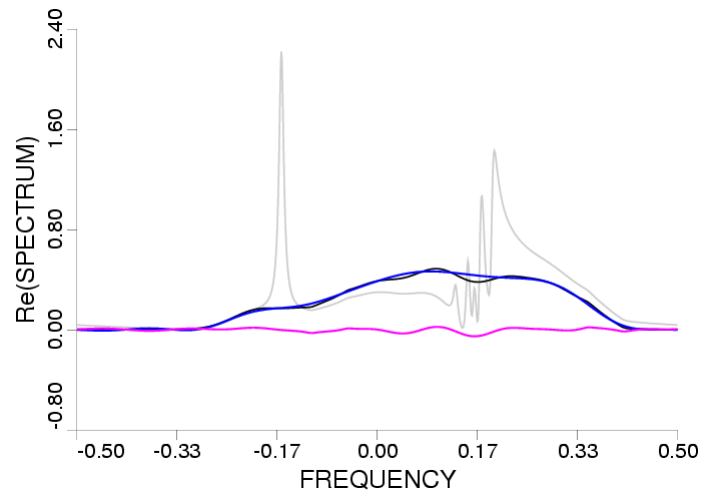


Fig. 3

FFT of sparse state-space modelling, with $N_{SS} = 8$ and $K_{SS} = 3$, of the *true* macromolecule (MM) signal. Black is the FFT of the true MM signal, blue its modelled version, magenta the modelling residue. The grey line represents the signal. This example is noiseless so as not to bury modelling details in noise. See Sec. III-B.1.

other words, a small K_{SS} yields a smoothed version of the MM spectrum, see Fig. 3. Recall from the above that MR data-points are complex-valued and that an exponentially damped sinusoid needs four parameters – amplitude, frequency, damping factor, phase.

Should an MM signal contain strong less-rapidly decaying components, one can treat them as metabolite signals. However, the distinction between macromolecular components and metabolite signals with broad spectral patterns is not always easy. This is a major problem area.

For comparison, results obtained via direct MM signal estimation (full parametrization), mentioned above, will be shown too. Our implementation of this approach is described in the Appendix, page 9. The parameters in question are estimated simultaneously with those of the metabolites. We shall address whether or not the information content of the metabolite part in the initial data-points is rendered inaccessible.

E. Semi-parametric estimation of metabolite model parameters

In semiparametric estimation, one seeks to disentangle the parametric and non-parametric parts of a signal [9]. Although this is a very difficult task, conditioned by both the geometric properties of the processes underlying the model to be implemented, but also by the chosen model itself, various solution pathways have been suggested; see, *e.g.*, Refs. [1–8, 10, 11] on page 8, among many others.

E.1 The method ‘Subtract’

As described in the Introduction, the present study is based on the method ‘Subtract-QUEST’, hereafter, abbreviated as ‘Subtract’, devised by Ratiney *et al* [2–4]. Briefly, ‘Subtract’ amounts to the following steps.

1. Truncate the initial data-points in which the macromolecule signal decays to below or near the noise level. Perusing Fig. 2, this is the case at about $n = 10$. The metabolite part of the signal decaying much slower, much of it is still available at $n \geq 10$.

2. Estimate the metabolite parameters $p(j)$ in Eq. 1 with a nonlinear least-squares (NLLS) fit. Thanks to the truncation, the estimate is not perturbed by the macromolecules [18]. However the truncation causes some loss of metabolite information too, resulting in reduced precision of the estimate.

3. From the estimated $p(j)$, compute the metabolite signal for $n = 0, 1, \dots, N - 1$, and *subtract* the result from the measured (simulated) MRS signal. The remainder is a ‘metabolite-free’ estimate of the macromolecule signal including the measurement noise. However, due to the reduced precision in the previous point, the property ‘metabolite-free’ is only approximate.

4. Model the macromolecule signal by a sum of K exponentially damped sinusoids with the State Space method. Keep the number of sinusoids small, *e.g.*, $K_{SS} = 3, 4, 5, 6$, so as to restrict degrees of freedom.

5. *Subtract* the State Space modelling result from the measured (simulated) MRS signal. Subject to the success of the State Space modelling, the remainder is a ‘macromolecule-free’ estimate of the metabolite signal including the measurement noise, for *all* n . Thus, the loss of metabolite information incurred in step 1, has now been reduced.

6. Estimate the metabolite parameters $p(j)$ in Eq. 1 from the signal resulting in the previous step with an NLLS fit. Because all initial data-points are again available, the precision is now better than in step 2.

With this algorithm, the global initial uncertainty is encompassed in a reduced model where the statistical accuracy loss in estimating the parameters of interest is straightforwardly measured after accounting for the nuisance components.

E.2 Iterating ‘Subtract’

The above six steps constitute the semi-parametric method ‘Subtract’, originally introduced as a single-pass approach [2–4]. Among other things, the present study investigates whether iteration of Subtract can be beneficial. Usually, iterative models are more accurate than single-pass ones thanks to the possibility of further extracting

structural features in the residuals vector, or correspondingly de-noising it. Iterations should of course be subject to careful analysis, for instance through ad hoc selection of stopping criteria to avoid over-fitting.

Relating this generic idea to Subtract, note that success of the latter hinges on the quality of metabolite model function resulting from step 2. Therefore, if the metabolite model function resulting from the final step 6 has improved, a restart at step 3 may improve the result further, etc. At the same time, the smoothing of the model function of the MM signal (see Sec. III-B.1) subtracted in step 5, introduces a systematic error. A trade-off between statistical and systematic errors is sought.

Finally, these iterations are not be confused with those mentioned in Sec. II-C.

F. Noiseless and noisy simulations

A valid critique of simulations is that mimicking realistic clinical cases is difficult. A counter argument from the signal processing community is that tuning a method to only a few real-world cases – too many variations to accommodate – has limited application. In addition, a clinical session often allows only a single MRS measurement. Under this condition, it is difficult to provide confidence intervals for the parameters of interest. Simulations, on the other hand, enable one to undertake all sorts of experiments.

One advantage of simulations is that one can omit noise, thus enabling separation of statistical errors due to noise from systematic errors due to model deficiencies. This per-

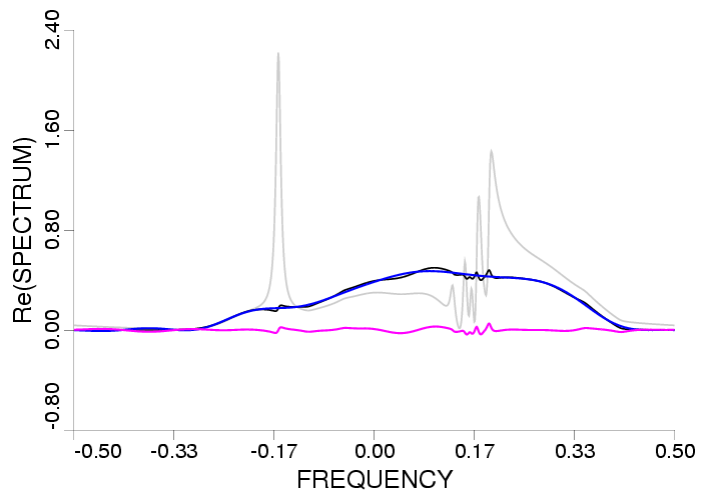


Fig. 4

FFT of sparse state-space modelling, with $N_{SS} = 8$ and $K_{SS} = 3$, of an *estimated* version of the MM signal. Black is estimated MM signal, blue its modelled version, magenta the modelling residue. The grey line represents the signal. This example is noiseless, so as not to bury modelling details in noise. See Sec. III-B.

tains not only to parameter estimates but also to modelling residues (shown below). In the case of a measured signal, statistical and systematic errors are inextricably mixed.

In this study, we investigate the systematic error incurred with a noiseless signal. In addition, we compute the Cramér-Rao Bounds (CRBs) from the true simulation parameters. We compare these quantities to the bias and standard deviations obtained from Monte Carlo simulations with many noise realizations.

Examples of model deficiencies, alluded to above are 1) Estimating metabolite parameters with Eq. 1 while contributions from other molecules are not negligible, 2) *Sparse* State Space modelling.

III. RESULTS AND DISCUSSION

A. Introduction

A crucial aspect of semi-parametric estimation is the modelling of the non-parametric part. As said above, important choices have to be made. This paper focuses mainly on the number of initial data-points N_{SS} used for modelling the macromolecule – henceforth abbreviated as MM – signal, and on the number of exponentially damped sinusoids K_{SS} used to sparsely model it with the State Space method. Comparison with full parametrization of initial data-points of the MM signal is reported too.

Before proceeding, recall from Sec. II-E that one iteration of ‘Subtract’ actually subtracts twice: Invoking the graphical presentation in Fig. 6, which is to be discussed later, one sees that subtraction of the metabolite signal (red) from the MRS signal (black + grey) yields an estimate of the disentangled macromolecule signal including noise. State space modelling (parametrization) of the latter yields the blue signal. Finally, subtraction of the blue signal from the MRS signal, in turn yields an estimate of the disentangled metabolite signal including noise. This terminates ‘Subtract’ (iteration 0). Subsequent rounds of ‘Subtract’ are indicated by iteration 1, iteration 2 . . .

The criterion for success of iteration is whether the L1-norm – sum of absolute values – of the residue decreases. See the magenta line in Figs. 5 and 6 for examples of the residue.

B. Systematic errors with noiseless simulations

B.1 Can iterations yield the correct estimate?

Suppose one is at the end of some iteration that yielded the correct estimate of the metabolite parameters. Consider now what happens when one iterates yet once more. Correct metabolite parameters yield a correct estimate of the metabolite signal. Subtraction of the latter from the MRS-signal in turn provides a correct estimate of the MM

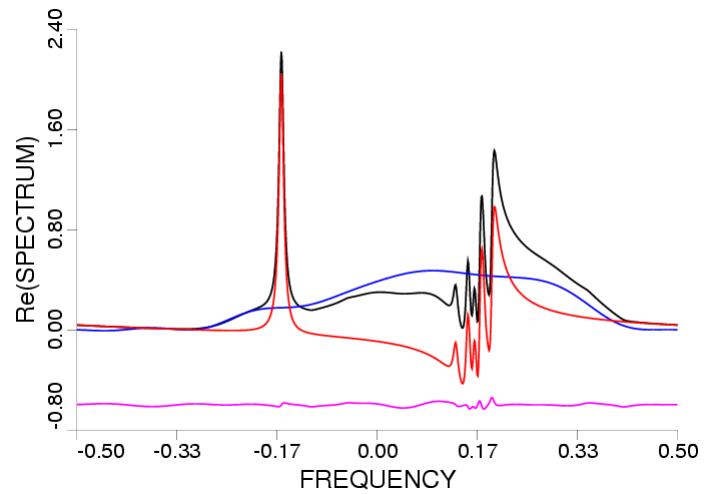


Fig. 5

FFT of semi-parametric estimation of a noiseless simulated MRS signal. Black: Simulated metabolites plus macromolecules. Red: Estimated metabolite contribution. Blue: Estimated macromolecule contribution. Magenta: black – (red + blue), shifted downward to avoid crowding. See Sec. III-B

signal. The (FFT of the) latter is indicated in Fig. 3 by the black line. (Normally, a simulation/measurement contains noise, and then the black line does so too.) Next, step 4 of Subtract models the MM signal by the State Space method, with *e.g.* $N_{SS}, K_{SS} = 8, 3$, resulting in the smoothed blue version in Fig. 3. The residue, depicted by the magenta line, is clearly not zero in the frequency region of metabolites 1 and 2 around $\nu = 0.17$, which forebodes errors in the estimates of the related parameters. This is confirmed in Table II, row 2, columns 3,4. *The conclusion is that a smoothing operation inescapably causes systematic errors in the subsequent metabolite estimates. This in turn implies that convergence to the correct metabolite parameters is not possible.*

Making the State Space modelling less smooth, *e.g.* $N_{SS}, K_{SS} = 14, 6$, yields a flat residue (not shown) and correspondingly smaller errors, as listed in Table II, row 3, columns 3,4. However, when noise is present, estimating more parameters causes an increase of statistical errors.

B.2 Iterations reduce systematic errors

Sec. III-B.1 considered the fate of presumed error-free metabolite parameter estimates in the next iteration. It turned out that errors of some magnitude always exist. Therefore the ensuing metabolite signal estimate has errors too. As a consequence, the MM signal estimate always contains ‘traces’ of the metabolite signal, shown in Fig. 4. The Figure shows too that the broad negative feature – clearly visible at $\nu = 0.17$ in Fig. 3 – has diminished significantly. The combined effect of the ‘metabo-

TABLE II
SYSTEMATIC ESTIMATION ERRORS $\Delta a(m)$ WITH
'SUBTRACT' IN ABSENCE OF NOISE.[▼]

MM [†] version	Iter ¶	$\Delta a(1)$	$\Delta a(2)$	$\Delta a(3)$	SS [‡] mod.
True ^b	NA	0.0000	0.0000	0.0000	NA
True*	NA	0.0358	0.0403	0.0138	8,3
True*	NA	0.0082	0.0086	0.0016	14,6
Est.♦	0	-0.0091	0.0323	0.0034	8,3
Est.♦	2	0.0057	0.0144	-0.0043	8,3
Est.▲	0	-0.0243	0.0376	0.0001	14,6
Est.▲	8	-0.0011	0.0193	0.0021	14,6
Est.♣	NA	0.0731	0.0347	-0.0032	NA
Est.♠	NA	-0.0032	-0.0005	-0.0074	NA

[▼]NA = Not Applicable. [†]MM stands for macromolecule signal, either the true or an estimated version. [‡]SS-mod.: StateSpace-modelling with parameters N_{SS}, K_{SS} . [¶]'Subtract' procedure iterated 'Iter' times. ^bTrue MM signal, and **not** modelled. *True MM signal, but modelled. ^{♦▲}Estimated MM signal, then modelled. [♣]10 (row 8) or [♠]15 (row 9) initial data-points of the MM signal directly estimated (full parametrization) simultaneously with the metabolite parameters. See also Fig. 5.

lite trace' and the remainder of the broad feature can be gleaned from rows 4–7 of Table II. With $N_{SS}, K_{SS} = 8,3$, the systematic errors are below those pertaining to the correct MM signal, for both iteration 0 and 2 (and for 1, not shown). With $N_{SS}, K_{SS} = 14,6$, iteration is beneficial up to # 8. The corresponding systematic errors pertaining to the correct MM signal are smaller though. We emphasize that the improvements pertain to the heavily overlapping metabolites $m = 1, 2$, but less so or not for $m = 3$.

Note that iterations have been continued till a minimum of the L1-norm of the residue (the magenta line in Fig 5) was reached. Additional iterations made the L1-norm of the residue rise again. At the last iteration, the L1-norm of the residue (not shown in the Table) was lowest for the less sparse modelling case of $N_{SS}, K_{SS} = 14,6$. However, preference for these parameter values is premature, since noise may well alter the outcome. This is the subject of Sec.III-C.

Finally, the last two rows of Table II list errors incurred when *directly* estimating 10 or 15 initial data-points of the complex-valued MM signal, represented by 20 or 30 real-valued parameters respectively – 'full parameterization'. Considering the last row of Table II, it is now tempting to choose this method, with 15 initial data-points. But the influence of noise should be considered too; see next Section.

TABLE III
CRAMÉR-RAO BOUNDS (CRB) OF THE METABOLITE
CONCENTRATION ERRORS FOR VARIOUS SEMI-PARAMETRIC
APPROACHES[▼]. $\sigma_{\text{noise}} = 0.05$.

Case	CRB a(1)	CRB a(2)	CRB a(3)	K_{MM} *
No MM [†]	0.0182	0.0204	0.0169	NA
No MM [‡]	0.0828	0.0452	0.0403	NA
SS 8,3♦	0.0229	0.0300	0.0268	12
SS 14,6▲	0.0710	0.0422	0.0365	24
Full 10♣	0.0420	0.0361	0.0305	20
Full 15♠	0.0828	0.0452	0.0403	30

[▼]NA = Not Applicable. [†]No macromolecule (MM) signal. [‡]No macromolecule (MM) signal *and truncation of 15 initial data-points*. * K_{MM} parameters used for modelling the MM signal. ^{♦▲}SS-modelling of the MM signal with $N_{SS}, K_{SS} = 8,3$, or 14,6. [♣]10 or [♠]15 initial data-points of the MM signal directly estimated (full parametrization) simultaneously with the metabolite parameters.

C. Cramér-Rao Bounds (CRBs)

This Section concerns the influence of noise on the precision of the estimated parameters with the aid of the Cramér-Rao Bounds. In parametric estimation, CRBs are independent of the estimator, enabling 'universal' applicability, including MRS [19]. However, in semi-parametric estimation this useful property lacks. This is because the non-parametric part of a signal can be modelled in infinite ways. In order to yet attain practical results, we assume a chosen model to be physically correct, enabling incorporation in the calculation of 'parametric' CRBs. In this context, recall from Sec. II-B that the MM signal was generated from known complex-valued functions with a total of 30 real-valued parameters. Use of this knowledge for calculating correct parametric CRBs was not undertaken. Inclusion of the effect of MMs on the CRBs with the method of Refs. [3,4] was not undertaken either, pending study of Refs. [10,11].

Table III shows the results for six cases. It becomes immediately clear that one can not choose a case on the basis of the systematic error alone. If the latter is low, the statistical error can be high, and vice versa. Both need consideration and a trade-off must be sought.

As was to be expected, the CRBs are lowest when the MM signal is absent (row 1). When present, the simplest way of dealing with it is to simply omit some 15 initial data-points; but the penalty for this is severe (row 2) [18]. We emphasize that the penalty is strongly metabolite-dependent, as was the case in Table II. Note that the values in row 2 equal those in row 6, pertaining to fully parameterized 15 initial MM signal data-points. See the Appendix

on page 9 for a general analytic proof of this fact.

The increase of the CRBs with respect to row 1 is lowest when the MM signal is sparsely modelled, *i.e.*, 12 parameters estimated from 8 initial data-points (row 3). Comparing row 3 to row 4, one sees that the low systematic error attendant on MM signal-modelling with 24 parameters (Table II) is spoiled by a high statistical error.

Combining Tables II and III, the method ‘Subtract’ seems now favourite. However, the effect of iteration is not accounted for in the CRBs. This aspect requires a Monte Carlo simulation, which is the subject of the next Section.

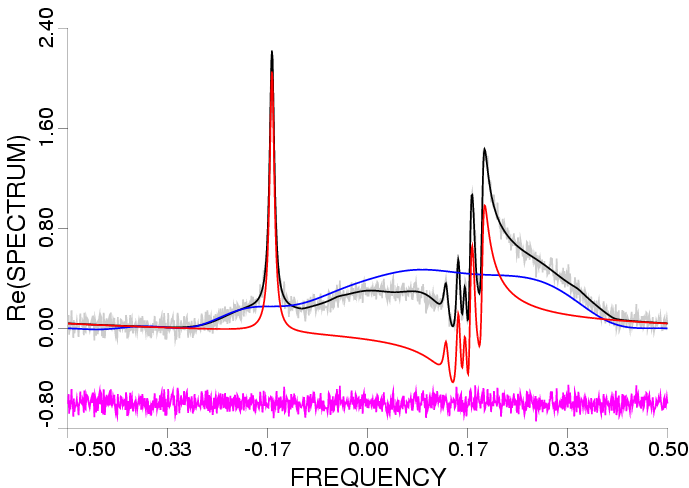


Fig. 6

FFT of semi-parametric estimation of a the noisy version of the case in Fig. 5, corresponding to column 2 of Table IV. Black: Simulated metabolites plus macromolecules; grey: added noise. Red: Estimated metabolite contribution. Blue: Estimated macromolecule contribution. Magenta: (black + grey) – (red + blue), shifted downward to avoid crowding.

D. Monte-Carlo Simulations

For the Monte-Carlo simulation, we generated thousand different realizations of the random noise shown in Fig. 6 (grey line). Each realization was added to the signal (black line) and the sum subjected to the semi-parametric estimation methods already described in Sec. III-B. Of each metabolite parameter $p(j)$, its mean $p(j)_{\text{mean}}$ and standard deviation $\sigma_{p(j)}$ were calculated. From this followed the Root Mean Square Errors (RMSE), defined as

$$\text{RMSE} = \sqrt{(p(j)_{\text{mean}} - p(j)_{\text{true}})^2 + (\sigma_{p(j)})^2} \quad (2)$$

and listed in Table IV for cases deemed relevant in view of results above. The numbers indicate that for this simulation, Subtract and its iteration improve the semi-parametric estimates of the metabolite concentrations (amplitudes).

Also listed are the bias, defined as $p(j)_{\text{mean}} - p(j)_{\text{true}}$, and the $\sigma_{p(j)}$ (stdev). Interestingly, the trends in the systematic errors in Table II agree with those in the biases in Table IV. The same goes for the CRBs in Table III and the standard deviations in Table IV, apart from the case $N_{\text{SS}}, K_{\text{SS}} = 14, 6, a(1)$.

The number of iterations at which the L1-norm of the residue is minimal, appeared to depend on the realization of the noise (not shown in the Table). This was to be expected. However, for sparse modelling, case $N_{\text{SS}}, K_{\text{SS}} = 8, 3$, the dependence was found to be much less pronounced than for more elaborate modelling, case $N_{\text{SS}}, K_{\text{SS}} = 14, 6$. This has to do with the size of the systematic error: the sparser the modelling, the larger the systematic error, and the more it reduces the influence of the noise-related error. In general, one should keep the modelling sparse and iterate once or twice with the aim to reduce the bias. The effect of iterations on $\sigma_{p(j)}$ seems modest.

TABLE IV
SEMI-PARAMETRIC ESTIMATION ERRORS OF THE METABOLITE CONCENTRATIONS. MONTE-CARLO SIMULATION WITH 1000 NOISE REALIZATIONS.
 $\sigma_{\text{noise}} = 0.05$.

Case	RMSE, Bias, Standard Deviation of		
	$a(1)$	$a(2)$	$a(3)$
No MM [†]	0.0186	0.0204	0.0178
Iter =0 \blacklozenge	0.0236	0.0431	0.0239
SS 8,3	-0.0073	0.0334	0.0047
	0.0224	0.0272	0.0234
Iter =2 \blacklozenge	0.0280	0.0322	0.0263
SS 8,3	0.0100	0.0161	-0.0013
	0.0261	0.0279	0.0263
Iter =0 \blacktriangle	0.0330	0.0539	0.0240
SS 14,6	-0.0220	0.0441	0.0043
	0.0245	0.0309	0.0236
Iter =2 \blacktriangle	0.0281	0.0405	0.0290
SS 14,6	-0.0046	0.0215	0.0016
	0.0277	0.0343	0.0290
Full 10 \clubsuit	0.0868	0.0551	0.0303
	0.0739	0.0374	-0.0032
	0.0455	0.0404	0.0301
Full 15 \spadesuit	0.0833	0.0464	0.0403
	-0.0018	0.0032	-0.0066
	0.0833	0.0463	0.0398

[†]No macromolecule (MM) signal. \blacklozenge 0 or 2 Subtract iterations using StateSpace modelling of the MM signal with $N_{\text{SS}}, K_{\text{SS}} = 8, 3$ or $14, 6$. \clubsuit 10 or \spadesuit 15 initial data-points of the MM signal directly estimated (full parametrization), simultaneously with the metabolite parameters.

IV. CONCLUDING REMARKS

In vivo MRS signals comprise a parametric and a non-parametric part, originating from metabolites and macromolecules respectively. The parameters of clinical interest are the concentrations of the metabolites. Estimation of the latter calls for a semi-parametric approach. We investigated iteration of our recently devised [2–4] single-pass semi-parametric method ‘Subtract’ which can easily handle strongly overlapping metabolite signals with arbitrary phases. We distinguish three main goals. 1) Reduction of errors in semi-parametrically estimated metabolite parameters. 2) Estimation of reliable semi-parametric estimation errors. 3) Prediction of realistic error bounds on metabolite parameters for various MRS measurement protocols. The latter is to enable clinics to estimate the measurement time required to obtain metabolite concentrations within a specified confidence interval – Experimental Design. The current results are itemized below.

- The semi-parametric method ‘Subtract’ accommodates severe spectral overlap of metabolite signals.
- ‘Subtract’ accommodates arbitrary phases of signal components notwithstanding concomitant negativity of related spectral intensities.
- Iteration of ‘Subtract’ can reduce estimation errors of the parametric part. Yet, more study of the mechanism of the reduction is needed.
- Reduction of estimation errors pertains mainly to strongly overlapping (correlated) metabolite signals.
- Systematic errors incurred in a noiseless simulation provide insight in the bias incurred with noisy versions of the simulation (Monte Carlo).
- Cramér-Rao bounds that include a modelled version of the non-parametric part provide insight in the standard deviations incurred with Monte Carlo simulations.
- Unavoidably, *lower* bounds on errors in metabolite estimates depend on the way of accounting for macromolecules. This complicates experimental design of clinical applications of MRS.
- Spectral editing alleviates the semi-parametric estimation task. If only one metabolite is of interest, it is the method of choice.

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APPENDIX

Effect of ‘Full MM-parametrization’ on the Metabolite CRBs

‘Full parametrization’ of the MM-signal contribution to N_{init} initial data-points is accomplished by adding the complex-valued signal $s_{\text{MM}}(t)$ to Eq. 1, and including the parameters $\text{Re}[s_{\text{MM}}(n)]$, $\text{Im}[s_{\text{MM}}(n)]$, $n = 1, 2, \dots, N_{\text{init}}$, in the parametric estimation procedure. This contributes an extra $2N_{\text{init}} \times 2N_{\text{init}}$ unit matrix \mathbf{I}_{MM} and a $(N - 2N_{\text{init}}) \times 2N_{\text{init}}$ zero matrix $\mathbf{0}$ to the Jacobian matrix \mathbf{J} of the derivatives of the MRS-signal w.r.t. the parameters to be estimated, as indicated below.

$$\mathbf{J} = \begin{array}{|c|c|} \hline \mathbf{J}_1 & \mathbf{I}_{\text{MM}} \\ \hline \mathbf{J}_2 & \mathbf{0} \\ \hline \end{array},$$

in which \mathbf{J}_1 and \mathbf{J}_2 together form the Jacobian matrix of the metabolite part (all N data-points). With this, the Fisher matrix becomes

$$\mathbf{F} = \mathbf{J}^T \mathbf{J} = \begin{array}{|c|c|} \hline \mathbf{F}_m & \mathbf{J}_1^T \\ \hline \mathbf{J}_1 & \mathbf{I}_{\text{MM}} \\ \hline \end{array},$$

in which $\mathbf{F}_m = \mathbf{J}_1^T \mathbf{J}_1 + \mathbf{J}_2^T \mathbf{J}_2$ is the Fisher matrix of the metabolite part (all N data-points). Working out the product of \mathbf{F} given above and \mathbf{F}^{-1} given below,

$$\mathbf{F}^{-1} = (\mathbf{J}^T \mathbf{J})^{-1} = \begin{array}{|c|c|} \hline \mathbf{X} & \mathbf{Y}^T \\ \hline \mathbf{Y} & \mathbf{Z} \\ \hline \end{array},$$

in which $\mathbf{X} = (\mathbf{J}_2^T \mathbf{J}_2)^{-1}$, $\mathbf{Y} = -\mathbf{J}_1 (\mathbf{J}_2^T \mathbf{J}_2)^{-1}$, $\mathbf{Z} = \mathbf{I}_{\text{MM}} + \mathbf{J}_1 (\mathbf{J}_2^T \mathbf{J}_2)^{-1} \mathbf{J}_1^T$, one arrives at a unit matrix. This establishes correctness of the formula of \mathbf{X} . Thus, the CRBs on the metabolite estimates are the square roots of the diagonal elements of $(\mathbf{J}_2^T \mathbf{J}_2)^{-1}$. The latter originate from the Jacobian matrix \mathbf{J}_2 , which in turn corresponds to the $N - N_{\text{init}}$ data-points that remain after truncating N_{init} initial data-points. This formally proves the observation made in Sec. III-C. See also page 11 of Ref. [20].

In summary, the information content of the metabolite part in the initial data-points is rendered inaccessible by the simultaneous estimation of the MM-signal without some form of regularization (smoothing).

CONTENTS

I	Introduction	1
II	Materials and Methods	1
II-A	The Metabolite Signal	1
II-B	The Macromolecule Signal	2
II-C	Parametric estimation of metabolite model parameters	2
II-D	Non-parametric estimation of the Macromolecule (MM) contribution	3
II-E	Semi-parametric estimation of metabolite model parameters	3
II-E.1	The method ‘Subtract’	4
II-E.2	Iterating ‘Subtract’	4
II-F	Noiseless and noisy simulations	4
III	Results and Discussion	5
III-A	Introduction	5
III-B	Systematic errors with noiseless simulations	5
III-B.1	Can iterations yield the correct estimate?	5
III-B.2	Iterations reduce systematic errors	5
III-C	Cramér-Rao Bounds (CRBs)	6
III-D	Monte-Carlo Simulations	7
IV	Concluding Remarks	8

LIST OF TABLES

I	The parameters of the metabolite database	2
II	Systematic errors, noiseless	6
III	CRBs	6
IV	Root Mean Square Errors (RMSE)	7

LIST OF FIGURES

1	FFT of the macromolecule (MM) signal . . .	2
2	The first 60 data-points of the MM signal . . .	3
3	FFT of sparse state-space modelling of the true MM signal	3
4	FFT of sparse state-space modelling of the estimated MM signal	4
5	FFT of semi-parametric estimation of simulated noiseless MRS signal	5
6	FFT of semi-parametric estimation of simulated noisy MRS signal	7