# Is spending extra scan time on measuring a `macromolecules-only' signal worthwhile?

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## INTRODUCTION

Quotation of reliable error bars on estimated metabolite concentrations is imperative in both research and clinical environments. Yet, estimation of errors is notoriously difficult, especially when derived from `once-only' measurements. Usually, one quotes Cramér-Rao Bounds (CRBs) as surrogates of the errors. These CRBs are necessarily based on estimated model parameters rather than on (*a priori* unknown) exact model parameters, and may therefore not be sufficiently reliable. The situation is aggravated when the metabolite signal is perturbed by a macromolecule signal. This situation is called *semi*-parametric, because the MRS signal contains a parametric part -- metabolites, model function supposedly known -- and a *non*-parametric part -- macromolecules, model function unknown. Whenever it occurs, the error bars of the metabolite concentrations become even less reliable [1-3].

Under the circumstances, one should consider whether it is worthwhile to measure the `macromolecules-only' signal too -- by inversion-recovery [4] -- and use the latter to render the signal parametric. This in turn could improve the reliability of the error bars of the estimated metabolite concentrations.

## METHODS

This work addresses the question just raised in a quantitative manner through a Monte Carlo simulation. The assumptions made are as follows. First, one measures the metabolites + macromolecules signal during a time $T_{scan}$. Next, another, equal time $T_{scan}$ is allotted which can be used in two alternative ways:

**Option A**

Pursue the measurement of the metabolites + macromolecules signal. This *increases* the signal-to-noise ratio (SNR) by a factor of $\sqrt{2}$, but the case remains semi-parametric.

**Option B**

Measure the `macromolecules-only' signal, with inversion recovery. Ideally, the macromolecules signal and noise standard deviation $\sigma_{noise}$ are supposed to be equal to those in Option A. Simple subtraction of this signal from the metabolites + macromolecules obtained in the first $T_{scan}$ renders estimation of metabolite parameters parametric, and thus improves error estimation. However, the SNR of the ensuing metabolites-only signal decreases by a factor of $\sqrt{2}$.

**RESULTS** are shown in Figs 2 and 3. Vertical: The relative root mean square errors (RMSE) of the estimated concentrations, (RMSE-CRB)/ CRB × 100%, for each metabolite. The CRB used here for each metabolite pertains to absence of macromolecules and measurement time = 1 × $T_{scan}$ ('Gold standard'). The total measurement time being 2 × $T_{scan}$, RMSE < CRB cannot be excluded. Therefore, negative values of (RMSE-CRB)/CRB × 100% can occur. Zero indicates RMSE = CRB. The red lines indicate RMSE = CRB × $\sqrt{2}$ (= +41.4 %). Dark-blue, light-blue, yellow indicate metabolites 1, 2, 3, respectively. Horizontal: The value of a hyper-parameter of the non parametric part of the model function. In Fig.2, its value was determined automatically (=auto) and subsequently varied. Fig.3 indicates that when one subtracts all data-points of the measured 'macromolecules-only' signal, the red line is reached. This is the true parametric situation. It is already approached at 14. This is the safest option but not necessarily the best. Subtracting fewer initial data-points (with their noise) can reduce errors to below the red line.

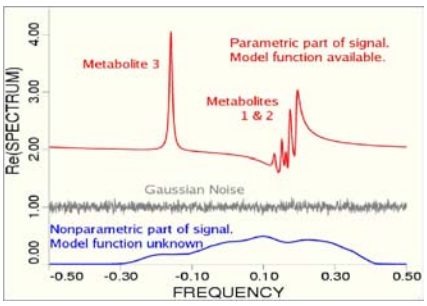


Figure 1. Real part of the FFT of the simulated signal. There are 3 metabolites, macromolecules, and white Gaussian noise (1000 realisations). Metabolites 1 and 2 overlap strongly.

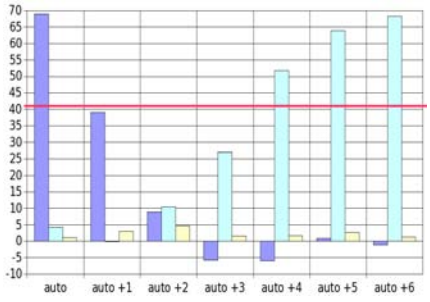


Figure 2. Result for **Option A**. Several values of the hyper-parameter yield lower errors than Option B does. Absence of macromolecules would yield -41.4 %. Skillful handling of hyper-parameters is required.

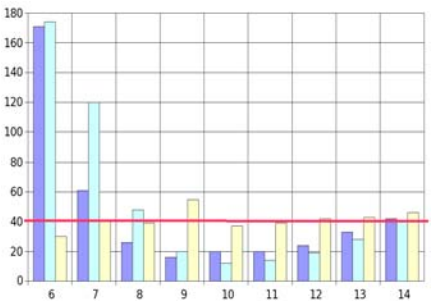

Figure 3. Result for **Option B**. Subtraction of all macromolecules-only data-points should yield the red line. This is the safest option. Furthermore, subtracting only a limited number of initial data-points can yield improvement.

**CONCLUSION** In this example, **option A** is best, but requires good semi-parametric hyper-parameters. **Option B** is safest.

**References**

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