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Are Cramér-Rao Lower Bounds an Accurate Estimate for Standard Deviations in Magnetic Resonance Spectroscopy?

Karl Landheer[1] and Christoph Juchem[1,2]
[1]Biomedical Engineering, Columbia University, New York City, NY, United States, [2]Radiology, Columbia University, New York City, NY, United States

Synopsis

Cramér-Rao Lower Bounds (CRLBs) have become the routine method to approximate standard deviations for magnetic resonance spectroscopy. CRLBs are theoretically a lower bound on the standard deviation. Realistic synthetic 3 Tesla spectra were used to investigate the relationship between estimated CRLBs, true CRLBs and standard deviations. It was demonstrated that although the CRLBs are theoretically truly a lower bound on the standard deviation this approximation is valid only as long as the model properly characterizes the data. In the case when the basis set deviates from the measured data it was shown that the CRLBs deviate substantially from standard deviations.

Introduction

As magnetic resonance spectroscopy (MRS) is a time-limited modality it is typically not feasible to perform multiple repetitions of the same experiment to calculate the standard errors. As such the field has adopted the Cramér-Rao Lower Bound[1] (CRLB) to circumvent this problem. Here a simulation study is presented which investigates the relationship between CRLBs and standard deviations (SDs) for two related but distinct cases: 1) the signal is well characterized by the model (i.e., the basis set of metabolites accurately reflects the experimental reality and the macromolecule signal has been measured a priori and is included in the linear combination modeling fit); and 2) the signal is approximately characterized by the model (i.e., the macromolecules have been measured a priori, however its exact shape has been modulated by T_1 effects, as the double inversion preparation typically used to measure MM highly sensitizes these resonances to T_1 variations[2]).

Methods

Synthesis of Spectra

Spectra were synthesized similar to what has previously been performed[3,4]. Spectra were Gaussian broadened[3] with a linewidth of 3, 8 or 20 Hz[2] (NAA full width at half maximum of 4.6 Hz, 6.2 Hz and 8.9 Hz), which reflected good, adequate and poor quality shims, respectively, at 3T[5]. Five different noise factors (NF) were chosen to span the range of typically encountered signal-to-noise ratios (SNR). These noise scaling factors were 1, 2, 4, 8 and 16, where NF = 1 corresponds to an SNR of 773, 640, 523, for Gb = 3, 8 and 20 Hz[2], respectively. The macromolecule signal was approximated as the sum of 10 individual Lorentzian resonances with measured concentration and T_2 values[2]. The case when the macromolecule signal was approximately known (corresponding to the case where the macromolecules were measured but their amplitudes were modulated by T_1 effects) was also investigated here. To approximate this effect the amplitude of the 10 macromolecule resonances varied by ±20%.

Calculation of SDs and CRLBs

5000 Monte Carlo simulations differing in additive white Gaussian noise for each noise factor and shim quality were performed. At each trial the parameters (amplitude, frequency shift, Lorentzian linewidth, Gaussian linewidth and phase) were estimated via the interior trust region approach[6] in INSPECTOR[7,8]. The estimated CRLB, $\widehat{CRLB}$, and true CRLB were calculated by inverting the Fisher information matrix[9]. $\widehat{CRLB}$ was calculated using the extracted fit parameters and noise power from the Monte Carlo simulations, while the true CRLB used the a priori parameter values and noise power.

Results and Discussion

The simulated spectra appear visually very similar to those obtained experimentally with the same sequence[4] (Figure 1). Excellent fits were obtained in the case where the perfect model and small but noticeable discrepancies were observed for the imperfect model (Figure 2). The number of chosen was sufficient to provide convergence for both SD and CRLB (Figure 3).

In the case of a perfect model the CRLB/SD for the amplitude parameters are given in Figure 4. The true CRLB and estimated CRLB, $\widehat{CRLB}$, for all major metabolites (i.e., NAA, Cr, Glu, Gln, Cho, GPC, mI) are within 20% of the SD of amplitude when the SNR is above the breakdown threshold. Consistent with previous work[10] when the SNR is below the breakdown threshold the CRLB can vary substantially from the SD.

In the case when the basis macromolecule signal deviates from the macromolecule signal in the spectrum the CRLB/SD for the amplitude parameters is given in Figure 5. The CRLB becomes a much poorer approximation for SD across virtually all metabolites. Major metabolites such as NAA and creatine can have CRLBs approximately 50% of the SD even in the cases of a high quality shim and high SNR. The appropriate parameterization of the macromolecule signals is a topic of ongoing research[2,13–15], and the results here demonstrate that if the macromolecules were able to be measured accurately then CRLBs would be a reasonable approximate SDs. In other words, the CRLB is adequate at estimating the *aleatoric* uncertainty, while it does not incorporate the *epistemic* uncertainty.

In the case of an accurate model the result that CRLB/SD ≈ 1 indicates that the estimators are nearly efficient[16]. Thus the only substantial improvement novel methods such as denoising[17,18], deep learning[19,20] and non-Fourier methods[21] will be able to yield is in relation to being able to extract values in the presence of an imperfect knowledge or in dealing with data with artefacts. These would be important improvements, however it is critical that this fundamental bound is acknowledged, which effectively eliminates the search for the holy grail of MRS algorithms: obtaining orders of magnitude more information from the same signal.

Conclusions

CRLBs and SDs were calculated via Monte Carlo simulations for 18 different metabolites and a macromolecule signal. When the model accurately represents the spectrum there is relatively little deviation between the CRLBs and SDs, provided the SNR is above the breakdown threshold, indicating that these parameter estimators are almost efficient. This finding of near-efficiency has important implications for the development of novel quantification methods such as deep learning[19,20]. In the case where the model does not accurately represent the data there is substantial deviations of both the estimated and true CRLB from SDs.

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Figures

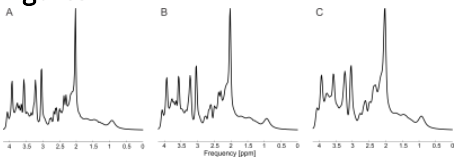

Figure 1: The synthesized spectra for the three different shim conditions: good, A, adequate, B, and poor, C. These spectra appear very similar to those obtained with the same pulse sequence experimentally (see Landheer et al.[4]).

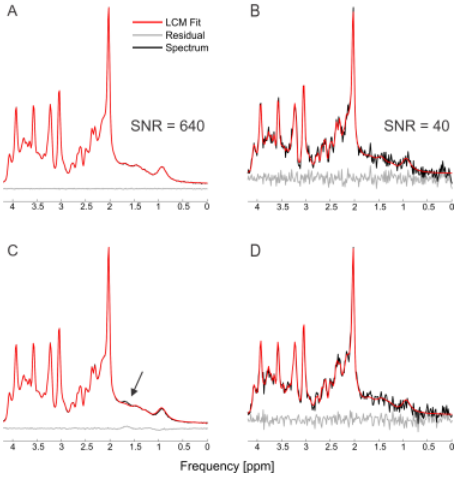

Figure 2: Plot of synthesized spectra (red), fits (black) and residual (grey) for the highest SNR spectra, A/C, and lowest SNR spectrum, B/D for the adequate shim case. Spectra shown in A/B depict the model perfectly representing the data, whereas spectra in C/D depicts the imperfect model. The deviation due to the imperfect model is most apparent in the region with little overlapping metabolites (arrow), whereas in the region with heavy overlap (i.e., 2.0 to 4.2 ppm) the metabolites 'compensate', i.e. variations in macromolecules result in changes in metabolite concentrations.

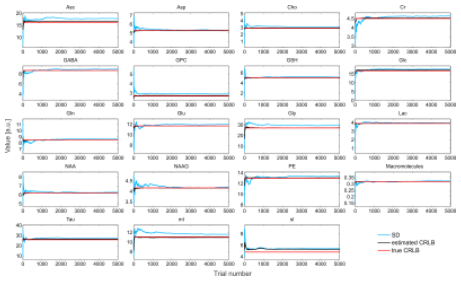

Figure 3: The three estimated values (SD, blue, estimated CRLB, black and true CRLB, red) vs the number of trials of the MC simulation NMC for the estimated amplitude for a representative case (NF = 1, Gb = 8 Hz^2, model perfectly characterizes data). Similar results were obtained for the other four estimated parameters and other four noise factors.

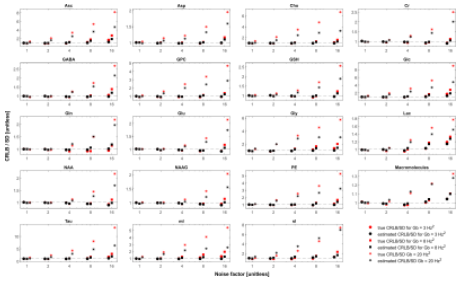

Figure 4: The true CRLBs (red) and estimated CRLBs (black) divided by the standard deviations calculated through MC simulations for the estimated amplitudes for the 18 metabolites and the macromolecules signal across 5 different noise factors (NF = 1 to 16) in the case where the model properly characterizes the data. The circles, squares and stars represent Gb = 3 Hz^2, 8 Hz^2, and 20 Hz^2, respectively. The breakdown SNR is reached when the true CRLB divided by standard deviation (red) is greater than 1. Similar results were obtained for the other four estimated parameters.

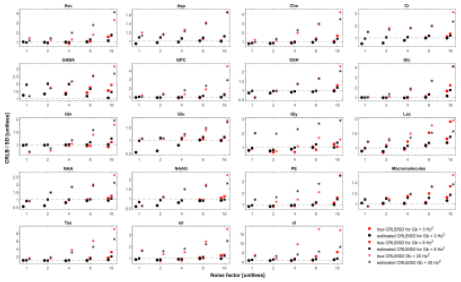

Figure 5: The true CRLBs (red) and estimated CRLBs (black) divided by the standard deviations calculated through MC simulations for the estimated amplitudes for the 18 metabolites and the macromolecules signal across 5 different noise factors (NF 1 to 16) in the case where the model does not properly characterize the data. The circles, squares and stars represent Gb = 3 Hz^2, 8 Hz^2, and 20 Hz^2, respectively. The breakdown SNR is reached when the true CRLB/SD (red) is consistently greater than 1. Similar results were obtained for the other four estimated parameters.

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