DON'T USE RELATIVE CRAMER RAO LOWER BOUNDS FOR ELIMINATION OF LOW QUALITY DATA!

Roland Kreis[1] and Sreenath Pruthviraj Kyathanahally[1]
[1]*Depts. Radiology and Clinical Research, University Bern, Bern, Switzerland*

PURPOSE

To evaluate the effect of automatic quality filtering of MRS data based on relative Cramér Rao error bounds.

INTRODUCTION

Cramér Rao estimation of the lower bounds of fitting errors [1] has become the standard way of estimating the minimum error associated with a MRS measurement from a single spectrum. It reflects the maximum trust that can be associated with an area (and thus concentration) estimated in model fitting. Cramér Rao lower bounds (CRLB) include limitations due to the specific fitting model and the interdependence of fitting variables (thus including the effect of linewidth/shim), and are proportional to the noise in the spectrum. CRLB are also very popular as a means for unsupervised quality filtering. In particular, relative CRLB, expressed as percentage (CRLB%) of estimated metabolite content, are used for this purpose [2-3]. The notion is that if a measured value has a high relative uncertainty, its reliability and thus usability must be low. Unfortunately, this is a wrong concept, given that the CRLB do not depend on the size of the estimated area parameter itself, but rather on the values of the other parameters, but that CRLB% obviously inversely scale with the size of the estimated parameter. This contribution demonstrates this ill-suitability of CRLB% for quality filtering.

METHODS

For the first two cases, distributions of metabolite values were constructed where the data was assumed to be Gaussian distributed with a specific mean value for each group and with the width of the distribution determined by the (absolute) CRLB, hence assuming homogeneous groups with the size of the error determined by fitting of the data and not any other influences. In addition, it was assumed that the model parameters (aside from areas) estimated from the spectrum would be sufficiently similar as not to grossly change the calculated CRLVB (e.g. similar shim). The third case is illustrated with simulated spectra, normal spectra and a single spectrum where the contribution from creatines is missing, but which is equal in all other aspects. (PRESS TE 136 ms, SNR for NAA of ~40, normal T_2s, 3 Hz Gaussian broadening, evaluation with QUECC in jmrui.

RESULTS

Case 1: A patient and a control cohort with the question whether brain Gln levels are altered in disease. Straightforward data analysis yields 3.41±0.96 mM Gln (mean±SD, n=150) in controls and 2.92±0.92 mM Gln (n=150) in patients with p<0.0001 in a t-test (CRLB of 1.0 mM) confirming pathologically low Gln. However, if a CRLB% threshold of 30% is used to eliminate "unreliable" data, the results change strongly: 4.10±0.57 mM (n=83) for controls vs. 3.95±0.44 mM (n=52) for patients (p=0.1). The distorted data distribution with biased selection of the upper arm of the data is shown in Fig. 1. Quality filtering by CRLB% leads to overestimation of both cohort means and loss of significance for the group difference.

Case 2: A patient and a control cohort with the question whether in subjects with large brain atrophy a reduced NAA signal (3.8±0.9 vs. 7.7±0.9 mM; p<0.001) is due to atrophy alone (partial volume effect) or also a result of low NAA in the remaining brain tissue. After CSF correction, straightforward analysis gives 8.5±2.1 vs. 8.5±1.0 mM; p>0.1. With selection of "high quality" data with CRLB<30%, we get 9.2±1.7 vs. 8.5±1.0 mM; p<0.001; hence an erroneous conclusion of NAA accumulation in remaining brain tissue.

Case 3: The simplest illustration that CRLB% are not suited for blind quality filtering comes from its clinical use, i.e. the comparison of a single patient spectrum to a database of normal spectra. In this case study, illustrated by Fig. 2, the question is not about a pathological increase of a small signal above the noise, but rather the inverse, a suspected reduction of a metabolite peak to near noise level. In this constructed case of creatine deficiency, MRS could never provide data that is qualitatively good enough to demonstrate the complete absence of creatine, if the measured creatine peak is required to be associated with a CRLB% of < 30%. Even in the marvelous long TE spectrum in Fig. 2, the CRLB% of Cr is 70% - just because the determined level of Cr is near the noise (0.08±0.05 mM). To note, the absolute error of Cr in this example is actually lower than the errors of NAA 0.1 mM (1% CRLB%), or myo inositol 0.3 mM (15%).

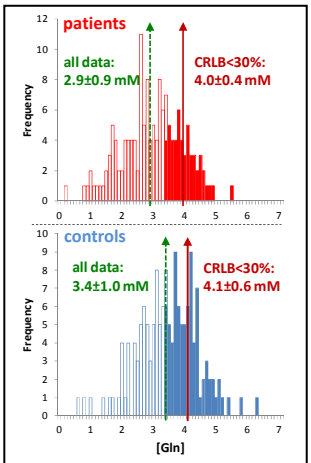

Fig. 1*. Distribution of Gln values obtained in synthetic cohorts. Filled columns represent the part of the data selected by CRLB< 30%, an ill-representation of the true means and variance, hiding the difference in cohort means.*

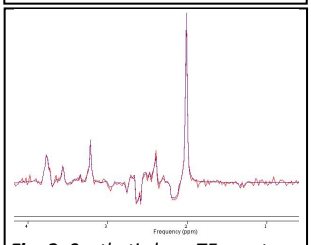

Fig. 2. *Synthetic long TE spectrum for a case of creatine deficiency, i.e. a normal brain spectrum without creatine (fit overlaid) which could not be used to prove the pathology, because CRLB% are bigger than 50%.*

DISCUSSION and CONCLUSIONS

It has been demonstrated that the usage of relative CRLB can easily lead to wrong conclusions - either to believe in metabolic alterations where there are none or to miss significant effects. In addition, consequent application of rejection of data with high CRLB% prevents the clinical use of MRS to diagnose any disease leading to very low metabolite levels.

CRLB are a valuable tool to judge the maximum trust one can have in a MRS based measurement, but it has to be judged either as an absolute value or relative to the normal/control metabolite levels. Relative CRLB may still be useful to rate in a control cohort, which metabolites can reliably be determined with a certain measurement condition (e.g. those that on average have a CRLB% below a specific threshold).

REFERENCES: 1. Cavassila et al. NMR Biomed 2001;14:278; 2. Kreis NMR Biomed 2004;17:361. 3. Oz et al. Radiology 2014;270:658.

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