Experimental Errors as Alternative to the Theoretical Cramér-Rao Minimum Variance Bounds in MRS: ER-ARSOS - Error Estimation by Multiple Quantification of Recombined ARSOS-filtered Output Signals

J. Slotboom[1], D. van Ormondt[2], O. Scheidegger[1], C. Brekenfeld[1], R. Wiest[1], G. Schroth[1], and D. Graveron-Demilly[3]
[1]DRNN-DIN/SCAN, University Hospital Berne, Berne, Switzerland, [2]Applied Physics, Delft University of Technology, Delft, Netherlands, [3]Laboratoire Creatis-LRMN, Université Claude Bernard LYON 1, Lyon, France

Introduction

The Cramér-Rao minimum variance bound (CR-MVB) is widely used to estimate the theoretical minimal variances (errors) of estimated spectral parameters in localized *s*ingle *v*oxel magnetic resonance *s*pectroscopy (SVS). The estimation of the CR-MVB requires only the spectral model function, the obtained set of optimal estimated spectrum model parameters, and the variance of the Gaussian noise. Further, the CR-MVB is valid under the condition that the assumed parametric model is *complete*. Due to the macromolecular baseline, unknown line-shapes, and other artefacts resulting from non-stationary signal acquisition conditions (e.g. patient motion, scanner-instabilities, etc.) or RF-pulse imperfections the parametric model is normally *incomplete*, and, strictly taken, the CR-MVBs estimates become invalid. Mistakenly, it is frequently believed that the CR-MVB accounts also for error sources like patient motion etc. mentioned above. In general the CR-MVB *underestimates* the variances in the estimated spectral parameters. This work presents a novel method to estimate the experimental errors of the parameters, as an alternative to the CR-MVBs for the case of single voxel spectroscopy (SVS). The only extra requirement for the proposed method is separate storage of the multiple signal acquisitions.

Method

Let $S_m[n]$ $(1 \le m \le M;\ 0 \le n \le N\text{-}1)$ be the *m*-th acquired single voxel time-domain signal during signal averaging having Gaussian noise and possibly contaminated by heavily tailed noise (e.g. outlier signals). Filtering the *M low* SNR signals $S_m[n]$ by means of all rank selected order statistic filtering technique ARSOS [1] results in *M high* SNR output signals $O_m[n]$ $(1 \le m \le M;\ 0 \le n \le N\text{-}1)$, which is a unique feature of ARSOS. Due to the fact that the noise of the output signals $O_m[n]$ have an *asymmetric* probability density function (pdf), straightforward non linear least squares NLLS-fitting of the *M*-output signals would result in biased parameter estimates. Fortunately, the *M*-output signals with asymmetric pdf can be recombined to ½*M* output signals with symmetric pdf (see ref.[1]). These ½*M* output signals can be fitted with one of the available fitting routines resulting in a ½*M* parameter vectors $\boldsymbol{p}_m = (p_{m,1}, p_{m,2}, .., p_{m,K})^T$. Separate statistical analysis of the set of ½*M* parameter vector elements $\{p_{1,k}, p_{2,k}.., , p_{½M,k}\}$ of the *k*-th fitted parameter enables the computation of the mean $\langle p_k \rangle$ and variance var(p_k) of each estimated model function parameter p_k. The standard deviation stdev(p_k) is defined as the √var(p_k) and is regarded as *experimental* error estimate and can be used as alternative to the CR-MVB.

Results

For a SVS voxel localized in the parietal human white matter (PRESS/ TE=135/TR=1.5sec/N=2048/M=24/15x15x15mm^3, @3T) the signal amplitudes obtained with conventional processing with QUEST/CR-MVB (see ref. [2]) were compared to those obtained with ER-ARSOS-QUEST and ER-ARSOS errors. The MRS-signals were subjected to reliability testing and passed the tests (see ref. [1]). The peak areas obtained with both methods do *not* significantly differ statistically (TTEST; p>0.99). However, the *errors* obtained by conventional CR-MVB are on average a factor of 2.55 smaller than the average ER-ARSOS-errors (TTEST; p<0.03).

Table 1: Comparison of conventional QUEST without and with ER-ARSOS-filtering preprocessing.

Metabolite	Conventional Peak Area (QUEST)	ER-ARSOS Peak Area (QUEST)	Parameter Differences (QUEST)	CR-MVB Error (St. dev)	ER-ARSOS Error (St. dev)	Error factor
CHOLINE (CHO)	0.662	0.649	-0.0133	0.012	0.066	5.49
CREATINE (CR)	2.792	2.787	-0.0046	0.048	0.107	2.21
GLUTAMATE (GLU)	0.645	0.681	0.0360	0.039	0.082	2.12
GLUTAMINE (GLN)	0.184	0.164	-0.0204	0.020	0.076	3.75
MYO-INOSITOL (M-INS)	0.507	0.508	0.0005	0.031	0.040	1.3
N-ACETYL ASPARTATE (NAA)	2.130	2.130	0.0001	0.026	0.051	1.95
TAURINE (TAU)	0.272	0.307	0.0354	0.046	0.046	1.02

Discussion

In our method, (QUEST-) fitting is performed on M/2 high-SNR ARSOS output signals with different noise realisations, resulting in M/2 optimal parameter values. This can be compared with the bootstrap method (see, e.g., ref. [3]), with the difference that our method does not need generation of synthetic data, but rather works exclusively on measured data.

The reasons for ER-ARSOS-errors being systematically larger than the corresponding CR-MVBs, for all metabolites, are:

(**1.**) The SNR of ARSOS output signals is slightly lower than that of the averaged signal. (**2.**) Outliers in a signal increase the variance of parameters estimated from such signals. A CR-MVB calculation, applying to a mean over many noise realisations, can not account for outliers in individual signals. Depending on the degree of robustness of the model function used, non-optimal starting values and modest variations in input signal may cause appreciable variations of ensuing parameter estimates.

Conclusion

Application of ARSOS filtering to *M* low SNR separately stored single voxel spectroscopy input signals results in ½*M* high SNR output signals which *all* can be quantified separately, resulting in ½*M* parameter vectors $\boldsymbol{p}_m = (p_{m,1}, p_{m,2}, .., p_{m,K})^T$ The standard deviations of the parameters $p_{m,K}$ estimated from the ½*M* high SNR output signals can be regarded as the experimental error in the parameters. In case the measured data contains outlier signals, the experimental errors of the estimated parameters will increase. This novel ER-ARSOS method has been implemented as a jMRUI 4.1. plug-in

References

1. Slotboom, J.; Nirkko, A.; Brekenfeld, C. & van Ormondt, D., " *Reliability testing of in vivo magnetic resonance spectroscopy (MRS) signals and signal artifact reduction by order statistic filtering*", Measurement Science and Technology, 2009, 20, 104030 (14pp)
2. D. Stefan, F. Di Cesare, A. Andrasecu, E. Popa, A. Lazariev, E. Vescovo, O. Strbak, S. Williams, Z. Starcuk, M. Cabanas, D. van Ormondt and D. Graveron-Demilly, Meas. Sci. Technol. **20** (2009) 104035 (9pp)
3. B. Effron, R.J. Tibishrani: 'Bootstrap Methods for Standard Errors, Confidence Intervals, and Other Measures of Statistical Accuracy' Stat. Sci. (1986) 1 54-77.