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Computation of Cramér-Rao Lower Bounds (CRLB) for spectral baseline shapes

Kelley M. Swanberg[1], Martin Gajdošík[1], Karl Landheer[1], and Christoph Juchem[1,2]
[1]Biomedical Engineering, Columbia University School of Engineering and Applied Science, New York, NY, United States, [2]Radiology, Columbia University Medical Center, New York, NY, United States

Synopsis

Cramér-Rao Lower Bounds (CRLB) are widely applied to characterize the minimum possible variance of metabolite amplitude parameters estimated by linear combination modeling. It has been argued that calculating the CRLB in the absence of baseline terms cannot adequately capture error but that the distribution of spectral baseline modeling parameters themselves cannot be sufficiently represented by this index. In this work we test the practical implications of these principles by treating baselines as linear combinations of polynomials to show that CRLB can under some circumstances offer precision estimates on spectral baseline shapes, notably to the improvement of metabolite CRLB accuracy.

Introduction

Since the rise of spectral quantification by linear combination models built upon prior knowledge functions[1] the Cramér-Rao Lower Bound (CRLB)[2,3] has been historically used to estimate the precision of these procedures. To correctly represent the lowest bound of standard deviation on metabolite amplitudes estimated by linear combination modeling (LCM), CRLBs must be calculated from an information matrix that represents a complete fit model[3]; in line with this, previous results suggest that metabolite amplitude CRLBs are significantly affected by accommodations for the spectral baselines often necessary for reliable quantification[4-7].

Given some measure of uncertainty surrounding the simulated or measured lineshapes used for metabolite bases, as well as the routine use of constraints in the fit procedures of not only baselines but also metabolites for which CRLBs are nonetheless routinely employed, the difference in both the integrity and flexibility of models underpinning metabolite and baseline shapes, and therefore CRLB estimates for fit parameters thereof, is a matter of degree and not a binary state. It is therefore important to empirically address the extent to which CRLBs may be used to inform precision estimates surrounding baseline models themselves both because some manner of including baseline terms in CRLB calculations may improve estimates of metabolite CRLBs as previously suggested and because understanding the validity of a baseline modeling approach can itself influence metabolite quantification precision and accuracy[8,9].

In this work we treat baselines as overlapping piecewise polynomial shapes akin to metabolite basis functions in order to include them in the Fisher information matrix for calculation of CRLBs on their amplitudes. We thereby assess the degree to which these and metabolite amplitude CRLBs represent the standard deviations of corresponding parameter estimates in fully determined spectral fits including heavily overlapping polynomial or spline baselines.

Methods

CRLBs for linear combination model parameters were calculated in time domain by inverting the fit Fisher information matrix[2,] wherein model partial derivatives w.r.t. baseline shape were expressed as inverse Fourier transforms of either full or piecewise polynomials, split by order and domain. Piecewise splines were smoothed for CRLB calculation to mitigate jump discontinuities from zero within the spectral fit range (Fig. 1). Validation analyses employed a MARSS[10]-simulated sLASER (T_E 20.1 ms) metabolite spectrum line-broadened 6 Hz, frequency-shifted, and scaled including a cubic polynomial baseline to an analogous prefrontal cortex (PFC) acquisition[11] (T_R 2 s, N_R 128) acquired on a 3 T MAGNETOM Prisma (Siemens Healthineers, Erlangen, Germany) (Fig. 2).

Simulated complex cubic polynomial or complex smoothed[1] cubic spline baselines were derived from LCM fits to the in vivo alignment reference following measured macromolecule subtraction; spline knot interval and smoothing λ were optimized for minimum between-subjects tNAA/tCr coefficient of variation across LCM fits to PFC spectra from 10 healthy adults (5 female, 23 ± S.D. 5 y.o., $\leq$27 cm^3 cubic voxels) similar to and including the alignment reference[11] (Fig. 3).

This preprocessed simulated brain spectrum was summed with either the polynomial (Analysis I) or spline (Analysis II) baseline and then scaled to ten linearly spaced SNR from 18 to 180 (signal from 3.03-ppm creatine). The same 50 complex Gaussian noise patterns were then added to each SNR group, with noiseless references retained for relative error calculation, for 510 simulated spectra per analysis. Spectral quantification by LCM, including baseline modeling and CRLB calculations, was then performed on these simulated spectra by scripting in INSPECTOR[12]. Group statistics and Bonferroni (N=10)-corrected Shapiro-Wilk analyses for normality of observed fit parameter distributions were performed in R (v. 3.4.4; R Foundation for Statistical Computing, Vienna, Austria).

Results

Amplitude CRLBs for complex polynomial baseline shapes demonstrated identity relationships with the standard deviations of their parameter estimations (Fig. 4). CRLBs for complex piecewise polynomials within splines (optimized knot interval 0.25 ppm, lambda 5; Fig. 3) also demonstrated linear relationships with the standard deviations of their parameter estimates, though some deviations from identity were observed (Fig. 4). Including either polynomial or spline baseline shapes in the Fisher information matrix improved correspondence between calculated CRLBs and observed standard deviations of metabolite fit amplitudes (Fig. 5).

Conclusions

Here we have shown the following:

- Cramér-Rao Lower Bounds calculated on baseline shapes analogously to metabolite bases can estimate fit amplitude standard deviations on polynomials and inform those for piecewise smoothed splines, despite the fact that for the latter the standard deviation of observed fit amplitudes is expected to be constrained by smoothing and neighboring pieces in a manner not represented in the straightforward calculation of CRLBs from the Fisher information matrix.

- Incorporating either polynomial or spline baseline shape information directly into the Fisher information matrix can improve the correspondence between calculated CRLBs and observed standard deviations of metabolite fit amplitudes.

Our implementation of this foundation for characterizing the precision of spectral baseline parameter estimates via Cramér-Rao Lower Bounds enables further systematic elaboration thereof. These include modifications accounting for expected disruptions to parameter estimate normality by model constraints, i.e., on the knots of piecewise splines by neighboring pieces, as well as investigations into the degree to which baseline CRLBs calculated in this manner can further improve CRLB estimates for metabolite amplitudes in cases of greater uncertainty regarding baseline models for the spectral data sets at hand, i.e., in vivo.

Acknowledgements

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Figures

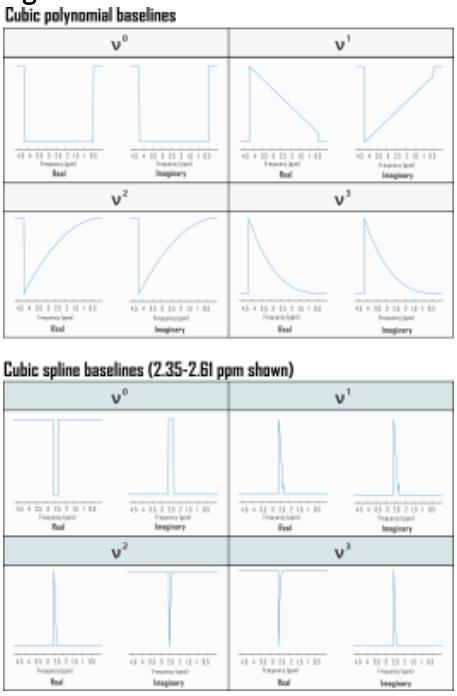

Fig. 1. Partial derivatives of linear combination model with respect to complex baseline shapes for Fisher information matrix calculation. Shown here are the Fourier transforms of example real and imaginary polynomial and spline baseline components incorporated into the Fisher information matrix used to estimate Cramér-Rao Lower Bounds (CRLB) for linear combination model fits to simulated in vivo sLASER (T_E 20.1 ms) metabolite proton spectra. Each shape is scaled by its corresponding polynomial coefficient for direct calculation of relative CRLBs. ppm: parts per million.

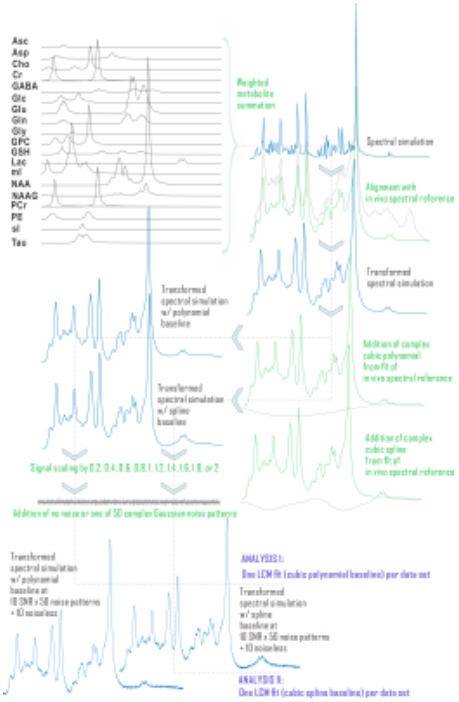

Fig. 2. Numerical pipeline for validating metabolite and baseline amplitude Cramér-Rao Lower Bounds against observed distributions of estimated fit parameters. Noisy (500 per analysis) simulated metabolite spectra with known polynomial or spline baselines were generated to compare calculated baseline CRLBs with standard deviations of baseline parameters obtained by linear combination model fitting. Noiseless fits (10 per analysis) were used as standards for estimates of fit parameter error. LCM: linear combination model.

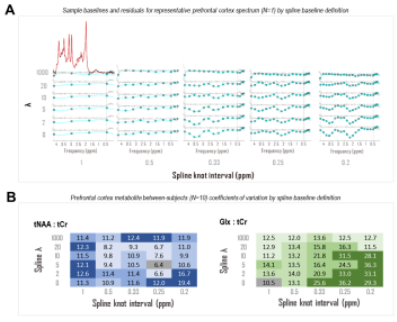

Fig. 3. Simulated spline baseline optimization. To create an in vivo-like simulated spline baseline, macromolecule-subtracted prefrontal cortex sLASER (T_E 20.1 ms, T_R 2 s, N_R 128, ≤27 cm^3 cubic voxels) spectra (N=10; 5 female, 23 ± S.D. 5 y.o.) were fit with metabolite bases and various splines (A), with splines yielding minimum between-subjects CoV boxed in grey (B). Note that multitudinous baseline definitions contribute to visually similar residuals despite divergent CoVs. tNAA: total N-acetyl aspartate; tCr: total creatine; Glx: glutamate + glutamine; ppm: parts per million.

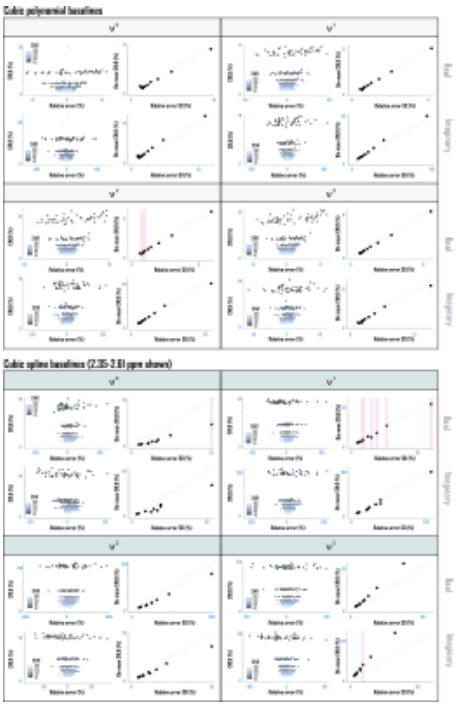

Fig. 4. Baseline amplitude Cramér-Rao Lower Bounds (CRLB) closely resemble standard deviations of fit amplitude estimates. Relative CRLB and amplitude estimate standard deviations (S.D.) by SNR are normalized to the same noiseless fit standards. For maximum correspondence with Fig. 5, spline results are for an interval near N-acetyl aspartate and glutamate. Non-normal distributions (pink), for which S.D. may not be an appropriate measure of parameter variability, were found more often for spline than polynomial baseline fit amplitudes. ppm: parts per million.

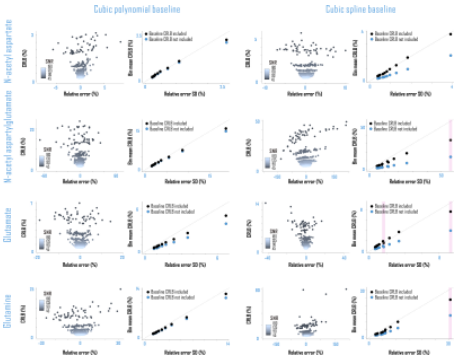

Fig. 5. Baseline Cramér-Rao Lower Bounds (CRLB) improved metabolite CRLB accuracy. Calculating amplitude CRLBs for polynomial or spline baselines directly from the Fisher information matrix improved correspondence between metabolite amplitude CRLBs and parameter estimate standard deviations (S.D.) by SNR (before=blue; after=black). Correspondent with Fig. 4, non-normal distributions (pink), for which S.D. may not be an appropriate measure of parameter variability, were observed more often for fits using spline than polynomial baselines. ppm: parts per million.

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