Feasibility of Computer-Intensive Methods for Estimating the Variance of Spectral Fitting Parameters

P. J. Bolan[1], W. F. Auffermann[1], P-G. Henry[1], M. Garwood[1]

[1]Radiology, Center for Magnetic Resonance Research, Minneapolis, MN, United States

Introduction

The goal of quantitative *in vivo* spectroscopy is to generate estimates of one or more model parameters, such as peak amplitude, from an acquired spectrum. For each estimated parameter, some measure of the estimation precision should also be calculated and presented. Variance estimates are particularly important when interpreting fits of low signal-to-noise (SNR) resonances, as the variance is often used for establishing a detection threshold. Repeatability studies are the most reliable way to determine measurement variance, but such measurements are not practical in many research and clinical applications. It is common practice to calculate the Cramer-Rao minimum variance bounds and use the bound itself as an estimate for the measurement variance (*1*). In theory, the Cramer-Rao (CR) method gives a lower limit on the variance of the parameter estimate. In practical situations, particularly in cases with low SNR and when the data is imperfectly described by the model, the CR method may not give an accurate estimate of the measurement variance.

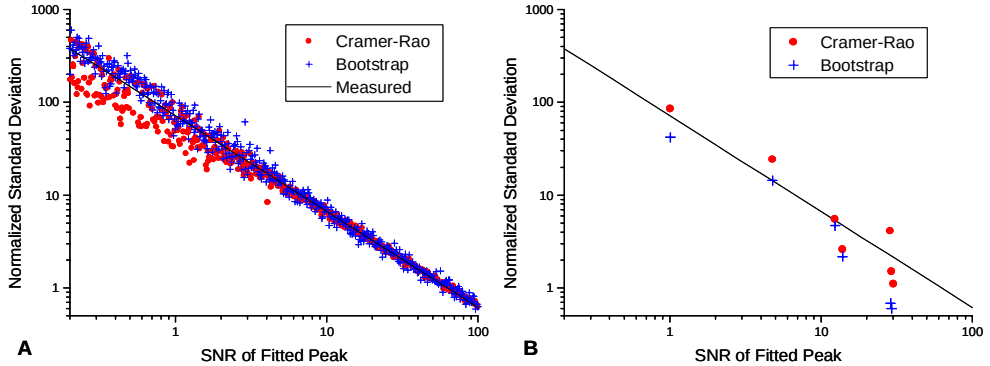
Computer-intensive methods provide an alternate means of calculating parameter variances. The most common approach, termed the bootstrap, generates new data sets by randomly sampling from the acquired data. Variances are determined by measuring the repeatability of estimating parameters from the resampled data sets. This and other resampling methods require that individual data are saved prior to averaging so that it can be resampled. In high-field NMR experiments, it is becoming common practice to individually save each FID acquired in order to correct phase and frequency variations prior to averaging. In these situations, resampling methods such as the bootstrap can be used to extract statistical information which is lost in the averaging process. The parameter variances produced by these methods could be used to validate conventional CR-based calculations, and in some situations may produce more accurate variance estimates. Although well-known in fMRI applications, we are not aware of any reports of computer-intensive methods used in fitting NMR spectra. The goal of this work is to 1) demonstrate the feasibility of using a computer-intensive method for estimating parameter variances in spectral fitting, and 2) evaluate its performance on simulated and *in vivo* data.

Methods

Spectroscopic fitting and variance estimation using both Cramer-Rao (CR) and bootstrap methods were performed on simulated Monte Carlo data sets and on *in vivo* spectra. All simulation and processing was performed in Matlab (The Mathworks, Natick MA). For the computational experiment, free-induction decays (FIDs) consisting of a single Lorentzian resonance (FWHM=10Hz, 256 pts, SW=200Hz) plus complex Gaussian noise were simulated. For each target signal-to-noise (SNR) value *s*, a series of N=100 spectra were simulated, each with SNR = $s\sqrt{N}$. This is designed to emulate the experimental practice of saving individual FIDs prior to averaging. Five-hundred of these spectral series were generated such that their total SNR *s* after averaging varied from 0.2 to 100. Each averaged spectral series was fit with a time-domain/frequency-domain (TDFD) method, using a time-domain model of a single Lorentzian line and minimizing residuals in the frequency domain (*3*), to estimate the peak amplitude *A*. The Cramer-Rao minimum variance bounds for the parameter *A*, denoted $\sigma^2_{A,CRB}$, was calculated using the covariance matrix provided by the Matlab fitting function (lsqnonlin). The bootstrap method was also used to estimate the variance of *A*, denoted $\sigma^2_{A,boot}$. For each spectral series, a resampled series was created by randomly selecting *N* FIDs, with replacement, from the original series. The resampled series was averaged and fit as before to produce a new estimate of the peak amplitude, A'_i . One thousand such resamples were generated for each spectral series. The bootstrap estimate for the variance of the *A* is equal to the variance of the resampled amplitudes $\sigma^2_{A,boot} = \mathrm{var}(A'_1, A'_2, ..., A'_{1000})$. The true variance as a function of SNR was determined by simulating and fitting 100 spectral series at each SNR value and measuring the variance of the estimated peak amplitude *A*. Six *in vivo* breast spectral series containing a detectable *total choline* resonance (tCho) were also evaluated. In each series, *N*=64 FIDs were acquired and individually saved. Each series was phase- and frequency- corrected, averaged, and fit using a similar TDFD method adapted specifically for breast spectra (*4*). The variance of the tCho peak amplitude was calculated using both the CR method and bootstrap method with 256 resamples. Calculation time was ~10 min/per series on a Pentium 4 Linux workstation.

Results & Discussion

The results of the Monte Carlo simulation are shown in Figure 1. This plot demonstrates the feasibility of the bootstrap method for estimating parameter variance and compares its performance to the CR method. At high SNR (>10), the CR method gives a better estimate of the true variance. At low SNR (<4), CR gives more biased and variable estimates. The performance of the bootstrap method is generally less dependent on the peak SNR. The variances estimates for the six *in vivo* data sets are shown in Figure 2. If it can be assumed that the relationship between variance and SNR is the same as in the simulated case, then it appears that the CR method gives a more consistent variance estimate than the bootstrap. This relationship may be different in the *in vivo* case due to small differences in the fitting procedures, spectral baseline effects, or physiological noise. Repeatability studies should be conducted to determine the true i*n vivo* measurement variance and determine which method performs best. Computer-intensive methods such as the bootstrap provide an alternative to the CR method, and may help improve variance estimates. These methods can be used with any fitting and quantification method such as LC Model or VARPRO, provided that FIDs are individually saved before averaging.



References

1. Cavasilla S, *et al.*, NMR Biomed 14(4) 2001.
2. Zoubir AM, *et al.*, IEEE Signal Proc. Mag. 1998; 15(1) 56-76.
3. Slotboom J, *et al.*, Magn Reson Med 1998; 39:899-911.
4. Bolan PJ, *et al.*, Magn Reson Med 2003; in press.

Acknowledgements

NIH grants R01 CA92004 and P41 RR08079; University of Minnesota Doctoral Dissertation Fellowship.

Figure 1. A) Monte Carlo simulation comparing the SNR dependence of the measured normalized standard deviation (NSD) with the NSD calculated using the Cramer-Rao and bootstrap methods. B) Estimates of the NSD of the tCho peak amplitude *A* obtained from fitting *in vivo* ^{1}H breast spectra. The solid line indicating the measured variance from the Monte Carlo simulation is shown for reference.