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Achievable Accuracy of Parameter Estimation for Multidimensional NMR Experiments

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A fundamental issue in NMR spectroscopy is the estimation of parameters such as the Larmor frequencies of nuclei, *J* coupling constants, and relaxation rates. The Cramer–Rao lower bound provides a method to assess the best achievable accuracy of parameter estimates resulting from an unbiased estimation procedure. We show how the Cramer–Rao lower bound can be calculated for data obtained from multidimensional NMR experiments. The Cramer–Rao lower bound is compared to the variance of parameter estimates for simulated data using a least-squares estimation procedure. It is also shown how our results on the Cramer–Rao lower bound can be used to analyze whether an experimental design can be improved to provide experimental data which can result in parameter estimates with higher accuracy. The concept of nonuniform averaging in the indirect dimension is introduced and studied in connection with nonuniform sampling of the data.

Key Words: **nuclear magnetic resonance (NMR) spectroscopy; Cramer–Rao lower bound (CRLB); Fisher information matrix; nonlinear least-squares estimation; nonuniform sampling; nonuniform averaging; experimental design.**

1. INTRODUCTION

Many, if not most, NMR spectroscopy exeriments involve parameter estimation problems, for example for the determination of Larmor frequencies, *J* coupling constants, and relaxation parameters. The accuracy of the estimates of the spectral parameters which are obtained by NMR spectroscopy is becoming an increasingly important issue, in particular in the determination of high resolution protein structures. In many recently developed techniques the success of the experiment depends on being able to obtain highly accurate parameter estimates (see, e.g., (*1–3*)).

A fundamental result in statistics and signal processing, typically known as the *Cramer–Rao lower bound (CRLB)*, gives an explicit bound on the achievable accuracy of parameter estimation. The important aspect is that this result is independent of the particular estimation method that is being used, provided that this method is *unbiased*, i.e., that on average it will produce the correct value. This means for example that the bound is independent of whether time-domain or frequency-domain methods are applied. What does influence this bound is the underlying quality of the data, such as the type of noise, the noise level, the number of data points, and the sampling method.

The availability of such a bound has a number of important applications. For example, parameter estimation algorithms can be evaluated and compared based on how closely they approach this bound. Moreover, experimental designs can be compared to determine which design produces a data set with lower Cramer–Rao lower bound and will therefore allow the parameters to be

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estimated more accurately. These considerations have of course been central to endeavours of all experimentalists. The Cramer–Rao lower bound adds an analytical tool that can be used to evaluate the various approaches.

This paper is not the first to discuss the use of the Cramer–Rao lower bound in the context of NMR spectroscopy. In (*4*) and (*5*) it has been used for the investigation of one-dimensional experiments. However, to the best of our knowledge, this is the first paper that derives the Cramer–Rao lower bound for multidimensional experiments, and in particular two-dimensional (2D) experiments. Since multidimensional NMR experiments are notoriously time-consuming it is especially important that those experiments are planned in such a way as to produce data that allow the parameters to be estimated most accurately.

In the main result of the paper (Section 2 and the Appendix) the Fisher information matrix, i.e., the inverse of the Cramer–Rao lower bound, is calculated for a general data model of a two-dimensional NMR data set that allows for an arbitrary number of resonances. The data are assumed to be corrupted by additive Gaussian noise. Aside from the presentation of this main result our objective is to illustrate how this result can be used in the context of two-dimensional NMR spectroscopy. To this end we carefully investigate the Cramer–Rao lower bound for simple example systems. Considering the significant role that the Fisher information matrix and Cramer–Rao lower bound have played in other areas we are confident that the potential uses of the Cramer–Rao lower bound go well beyond the few applications that we have space to discuss here.

In Section 3 we discuss the relation between a nonlinear least squares estimation problem and the Cramer–Rao lower bound. In particular we show that in the case of an example data set a nonlinear least squares estimatation procedure can produce or come very close to producing parameter estimates whose covariance matrix equals the Cramer–Rao lower bound. This implies that the performance of a parameter estimation algorithm can be evaluated using the Cramer–Rao lower bound. First, the quality of an alternative algorithm can be compared to the existing one by investigating how close the alternative algorithm comes to achieving the same (low) covariance matrix of the parameter estimates, knowing for theoretical reasons that none can be found that improves on the Cramer–Rao lower bound. Second, it can serve to detect convergence problems of an algorithm. A notorious problem in the use of nonlinear estimation routines for parameter estimation in NMR applications is that the estimates may not converge fully to the correct estimates or that the estimates may converge to an incorrect value due to local minima of the criterion function. If the estimation procedure is initialized with different initial conditions the estimate of the covariance matrix of the parameter estimates can be determined. If this covariance estimate is significantly different from the Cramer–Rao lower bound, it is an indication that either the algorithm is far from optimal or that serious convergence problems exist, e.g., due to local minima.

A second and possibly even more important use of the Cramer–Rao lower bound in NMR spectroscopy lies in its use as an analytical tool for experiment design (Section 4). The Cramer–Rao lower bound promises to be a particularly powerful tool for the analysis of experimental designs for multidimensional NMR experiments. The extensive experimental time that is required makes careful design of the experiment an important consideration. Since in many cases the purpose of an NMR experiment is to obtain estimates of certain parameters, it is the accuracy of these parameters that is a prime concern in the design of an experiment. The Cramer–Rao lower bound and therefore the best achievable covariance properties of the estimates depend crucially on the experimental situation. The parameters that are given by the sample and the available equipment, e.g., frequencies of the resonances and interconnectivity patterns, typically have to be assumed to be fixed. On the other hand, many other experimental parameters such as the number of data points that are acquired and the sampling scheme can be adjusted. Even the signal-to-noise ratio is adjustable by either changing the concentration of the sample or by averaging a number of identical scans. Limitations on material and experimental time put serious constraints on the experimental design. The problem therefore arises to find and evaluate various experimental designs. The Cramer–Rao lower bound provides a powerful tool for this purpose.

We should point out that it is not the intention of this paper to advocate one experimental design over another. The Cramer–Rao lower bound allows the spectroscopist to quantitatively evaluate the tradeoffs of the various designs from the point of view of the expected variance of the parameter estimates. In a concrete situation it is easily conceivable that the spectroscopist will take other criteria into consideration that are not reflected in the Cramer–Rao lower bound. An experienced spectroscopist may have a good understanding of the qualitative benefits of one experimental design over another. We believe, however, that the availability of a powerful quantitative tool will be of value in many practical circumstances.

As part of the discussion on experimental design we also investigate what we believe to be the novel notion of nonuniform averaging.

2. ANALYTICAL EXPRESSION FOR THE FISHER INFORMATION MATRIX

In this section the Cramer–Rao lower bound is derived for 2D NMR data sets. First, a very general data model is introduced for two-dimensional NMR experiments. For this data model the Fisher information matrix, i.e., the inverse of the Cramer–Rao lower bound, is derived (see Appendix A.1 for the derivation and Appendix A.2 for a complete listing of the result). As an illustration, in a subsequent example these results are specialized for a small example data set. We now specify the assumptions on the data sets that we are considering. The data of a 2D NMR experiment is described as (*6–8*)

$$\begin{aligned} s(n,m) &= \sum_{k=1}^{K}\sum_{l=1}^{L} c_{kl} e^{i\phi_{kl}} e^{(i\omega_{1k}+r_{1k})t_n+(i\omega_{2l}+r_{2l})s_m} + \epsilon(n,m) \\ &= \sum_{k=1}^{K}\sum_{l=1}^{L} c_{kl} e^{r_{1k}t_n+r_{2l}s_m} e^{i(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})} + \epsilon(n,m) \\ &= \sum_{k=1}^{K}\sum_{l=1}^{L} c_{kl} e^{r_{1k}t_n+r_{2l}s_m} \cos(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl}) \\ &\quad + \mathrm{Re}(\epsilon(n,m)) + i\left(\sum_{k=1}^{K}\sum_{l=1}^{L} c_{kl} e^{r_{1k}t_n+r_{2l}s_m}\right. \\ &\quad \left.\times \sin(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl}) + \mathrm{Im}(\epsilon(n,m))\right), \end{aligned}$$

with $0 \le t_1 < t_2 < \cdots < t_n < \cdots < t_N$, $1 \le n \le N$, and $0 \le s_1 < s_2 < \cdots < s_m < \cdots < s_M$, $1 \le m \le M$. Here $c_{kl}, \omega_{1k}, \omega_{2l}, r_{1k}, r_{2l}$, and ϕ_{kl} are real constants. They are respectively the amplitudes, the angular frequencies, the damping factors, and the phases. The noise component $\epsilon(n,m)$ is assumed to be complex Gaussian, with zero mean. The real and imaginary parts are assumed to have variance σ_m^2 and to be independent and uncorrelated; i.e., $\mathrm{var}(\mathrm{Re}(\epsilon(n,m))) = \mathrm{var}(\mathrm{Im}(\epsilon(n,m))) = \sigma_m^2$ and $E(\mathrm{Re}(\epsilon(n,m))\mathrm{Im}(\epsilon(n,m))) = 0$. The noise-free signal is denoted by

$$\begin{aligned} g(n,m) :&= \sum_{k=1}^{K}\sum_{l=1}^{L} c_{kl} e^{r_{1k}t_n+r_{2l}s_m} e^{i(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})} \\ &= s(n,m) - \epsilon(n,m). \end{aligned}$$

Note that we have not assumed that the variance of the noise in the indirect dimension is identical for each increment. This will be analyzed further in Section 4. We also allow for nonuniform sampling in our setup in both the direct and the indirect dimensions.

Using the well-known description of the probability distribution function of Gaussian noise we can write down the probability distribution function $p(x,\Theta)$ (Θ is the parameter vector) of an acquired sample $(x(n,m))_{1\le n\le N; 1\le m\le M}$ of the data as

$$\begin{aligned} p(x,\Theta) &= \prod_{n=1}^{N}\prod_{m=1}^{M} \frac{1}{\sqrt{2\pi\sigma_m^2}} e^{-\frac{1}{2\sigma_m^2}(\mathrm{Re}(x(n,m))-\mathrm{Re}(g(n,m)))^2} \\ &\quad \times \frac{1}{\sqrt{2\pi\sigma_m^2}} e^{-\frac{1}{2\sigma_m^2}(\mathrm{Im}(x(n,m))-\mathrm{Im}(g(n,m)))^2}. \end{aligned}$$

The log-likelihood function is therefore

$$\begin{aligned} \ln(p(x,\Theta)) = \sum_{n=1}^{N}\sum_{m=1}^{M}\Bigg[&-\ln(2\pi) - 2\ln(\sigma_m) \\ &- \frac{1}{2\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))^2 \\ &- \frac{1}{2\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))^2\Bigg]. \end{aligned}$$

The *Fisher information matrix* is defined as

$$F(\Theta) = \left[-E\frac{\partial^2 \ln p(x,\Theta)}{\partial\Theta_i\partial\Theta_j}\right]_{1\le i,j\le P},$$

where E stands for taking the expectation and the parameter vector Θ is given by

$$\Theta = (\theta_1\theta_2\cdots\theta_P).$$

For any unbiased estimator $\hat{\Theta} = (\hat{\theta}_1\hat{\theta}_2\cdots\hat{\theta}_P)$ of the parameter vector Θ we then have that the *Cramer–Rao lower bound* is given by (see, e.g., (*9*))

$$\mathrm{var}(\hat{\theta}_i) \ge [F^{-1}(\Theta)]_{ii}.$$

An important result of the paper is that the entries of the Fisher information matrix can be computed analytically for the 2D NMR data given above. This result is presented in the Appendix.

In Section A.1 we also show how to derive several of the entries of the Fisher information matrix. The results presented in the Appendix address the relatively general case for two-dimensional NMR experiments that was introduced above. Specific practical situations may require a somewhat different setting. Expressions for the higher dimensional NMR experiments can be derived analogously. Similarly, for example, if certain parameters are known, this information can be included in a relatively straightforward fashion. Another situation that may present itself is when the parameters that are discussed here are not the ones that are being sought but a transformation of these parameters is the actual interest of the experiment. For example, it may be a frequency shift that is to be estimated rather than the actual frequency. In this case a standard transformation result is of use (see, e.g., (*9*)).

2.1. Example

The above derived expressions of the Fisher information matrix for the general data model are rather lengthy. To illustrate the results we therefore specialize the expressions for a relatively simple situation. For the special case of one (not necessarily identical) resonance in the direct and indirect dimensions, i.e., the case $K = L = 1$, the data are given by

$$\begin{aligned} s(n,m) &= c_{11}e^{i\phi_{11}}e^{(i\omega_{11}+r_{11})t_n+(i\omega_{21}+r_{21})s_m} + \epsilon(n,m) \\ &= c_{11}e^{r_{11}t_n+r_{21}s_m}e^{i(\omega_{11}t_n+\omega_{21}s_m+\phi_{11})} + \epsilon(n,m) \\ &= c_{11}e^{r_{11}t_n+r_{21}s_m}\cos(\omega_{11}t_n+\omega_{21}s_m+\phi_{11}) \\ &\quad + \mathrm{Re}(\epsilon(n,m)) \\ &\quad + i(c_{11}e^{r_{11}t_n+r_{21}s_m}\sin(\omega_{11}t_n+\omega_{21}s_m+\phi_{11}) \\ &\quad + \mathrm{Im}(\epsilon(n,m))). \end{aligned}$$

We assume that all six parameters $c_{11}, r_{11}, r_{21}, \omega_{11}, \omega_{21}$, and ϕ_{11} are unknown.

Specializing the formulae in Appendix A.2 we can obtain the entries of the 6×6 Fisher information matrix $F(\Theta)$. If the parameter vector Θ is given by

$$\Theta = (c_{11}, r_{11}, r_{21}, \omega_{11}, \omega_{21}, \phi_{11})$$

then the entries of the symmetric Fisher information matrix are

$$F(1,1) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}e^{2(r_{11}t_n+r_{21}s_m)},$$

$$F(2,2) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{11}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}t_n^2,$$

$$F(3,3) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{21}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}s_m^2,$$

$$F(4,4) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{11}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}t_n^2,$$

$$F(5,5) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{21}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}s_m^2,$$

$$F(6,6) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \phi_{11}^2} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)},$$

$$\begin{aligned} F(1,2) = F(2,1) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}\partial r_{11}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}e^{2(r_{11}t_n+r_{21}s_m)}t_n, \end{aligned}$$

$$\begin{aligned} F(1,3) = F(3,1) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}\partial r_{21}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}e^{2(r_{11}t_n+r_{21}s_m)}s_m, \end{aligned}$$

$$F(1,4) = F(4,1) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}\partial \omega_{11}} = 0,$$

$$F(1,5) = F(5,1) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}\partial \omega_{21}} = 0,$$

$$F(1,6) = F(6,1) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial c_{11}\partial \phi_{11}} = 0,$$

$$\begin{aligned} F(2,3) = F(3,2) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{11}\partial r_{21}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}t_ns_m, \end{aligned}$$

$$F(2,4) = F(4,2) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{11}\partial \omega_{11}} = 0,$$

$$F(2,5) = F(5,2) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{11}\partial \omega_{21}} = 0,$$

$$F(2,6) = F(6,2) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{11}\partial \phi_{11}} = 0,$$

$$F(3,4) = F(4,3) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{21}\partial \omega_{11}} = 0,$$

$$F(3,5) = F(5,3) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{21}\partial \omega_{21}} = 0,$$

$$F(3,6) = F(6,3) = -E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{21}\partial \phi_{11}} = 0,$$

$$\begin{aligned} F(4,5) = F(5,4) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{11}\partial \omega_{21}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}t_ns_m, \end{aligned}$$

$$\begin{aligned} F(4,6) = F(6,4) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{11}\partial \phi_{11}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}t_n, \end{aligned}$$

$$\begin{aligned} F(5,6) = F(6,5) &= -E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{21}\partial \phi_{11}} \\ &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}c_{11}^2e^{2(r_{11}t_n+r_{21}s_m)}s_m. \end{aligned}$$

Note that in fact the Fisher information matrix has a number of repeated entries. If we set

$$\begin{aligned} a &:= F(1,1), & b &:= F(2,1), & c &:= F(1,3), \\ d &:= F(2,2), & e &:= F(2,3), & f &:= F(3,3), \\ g &:= F(4,6), & h &:= F(5,6), & z &:= F(6,6), \end{aligned}$$

we have that the Fisher information matrix $F(\Theta)$ is given by

$$F(\Theta) = \begin{bmatrix} a & b & c & 0 & 0 & 0 \\ b & d & e & 0 & 0 & 0 \\ c & e & f & 0 & 0 & 0 \\ 0 & 0 & 0 & d & e & g \\ 0 & 0 & 0 & e & f & h \\ 0 & 0 & 0 & g & h & z \end{bmatrix}.$$

Note that this matrix is block diagonal, which has interesting consequences for the Cramer–Rao lower bound. The Cramer–Rao lower bound is given by the diagonal elements of the inverse of $F(\Theta)$,

$$\mathrm{CRLB}_i = [F(\Theta)^{-1}]_{ii} = \begin{bmatrix} R & 0 \\ 0 & Q \end{bmatrix}_{ii},$$

where

$$R = \frac{1}{-ae^2 + 2bce - b^2 f - c^2 d + afd} \cdot \begin{bmatrix} -e^2 + fd & ce - bf & -cd + eb \\ ce - bf & -c^2 + af & bc - ae \\ -cd + eb & bc - ae & -b^2 + ad \end{bmatrix}$$

$$Q = \frac{1}{dfz - dh^2 - e^2 z + 2geh - g^2 h} \cdot \begin{bmatrix} fz - h^2 & -ez + gh & eh - gf \\ -ez + gh & dz - g^2 & ge - dh \\ eh - gf & ge - dh & df - e^2 \end{bmatrix}.$$

3. CRAMER–RAO LOWER BOUND AND PARAMETER ESTIMATION

As was discussed in Section 2 the Cramer–Rao lower bound provides a lower bound for the variance of any parameter estimate given by an unbiased estimation procedure. One of the ways in which this bound can be used is to evaluate the performance of an estimation algorithm. Clearly, by the fundamental result the variance of an unbiased estimator cannot be lower than the Cramer–Rao lower bound. However, it is not a priori obvious that there are algorithms that attain this bound. We will illustrate this with an example that a least square estimation procedure attains or at least comes close to attaining the bound.

Consider the case of two (not necessarily identical) resonances in the direct and indirect dimensions, respectively; i.e., the case $K = L = 2$, for which the data are given by

$$\begin{aligned} s(n,m) &= \sum_{k=1}^{2}\sum_{l=1}^{2} c_{kl} e^{r_{1k}t_n + r_{2l}s_m} \cos(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl}) \\ &\quad + \mathrm{Re}(\epsilon(n,m)) + i\left(\sum_{k=1}^{2}\sum_{l=1}^{2} c_{kl} e^{r_{1k}t_n + r_{2l}s_m}\right. \\ &\quad \left.\times\ \sin(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl}) + \mathrm{Im}(\epsilon(n,m))\right). \end{aligned}$$

For this example, we assume that all 16 parameters are ordered into the following parameter vector

$$\Theta = (c_{11},\ c_{12},\ c_{21},\ c_{22},\ r_{11},\ r_{12},\ r_{21},\ r_{22},\ \omega_{11},\ \omega_{12},\ \omega_{21},\ \omega_{22},\ \phi_{11},\ \phi_{12},\ \phi_{21},\ \phi_{22}).$$

For the purpose of illustration, we fix the values of the parameter vector as

$$\Theta_0 = (.15,\ .22,\ .12,\ .13,\ -.1,\ -.35,\ -.15,\ -.45,\ 1.445,\ 2.136,\ 2.702,\ .88,\ .683,\ 1.366,\ 2.4167,\ .982).$$

Gaussian noise is then added to the signal. The noisy signal is uniformly sampled with 1024 samples in the direct and 32 samples in the indirect dimension (see Fig. 1 for a plot of a trace of the noisy 2D data set with a −20-dB noise level). To demonstrate the validity of the Cramer–Rao lower bound, we choose five different noise levels (−10, −20, −30, −40, −50 dB, respectively). The noise level is defined as follows. If the simulated Gaussian white noise has zero mean and variance σ^2 then the noise level in dB is defined by $10\log_{10}(\sigma^2) = 20\log_{10}(\sigma)$.

For each noise level, we estimate the parameters from the simulated data using a nonlinear least-squares estimation procedure,

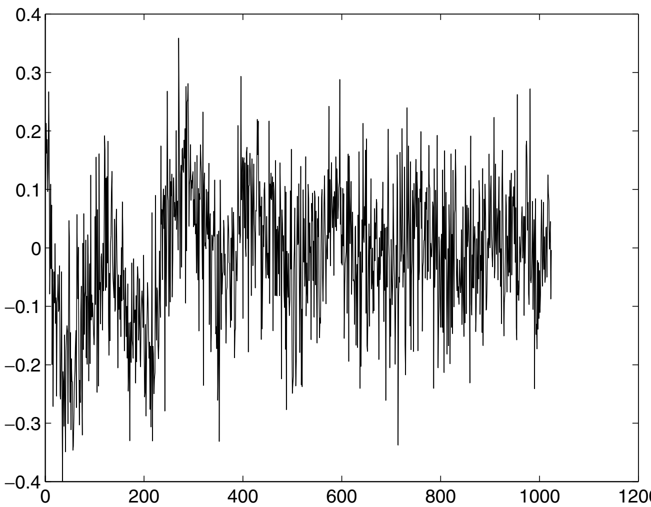

FIG. 1. The real part of the first trace of a 1024 × 32 2D data set with noise level at −20 dB.

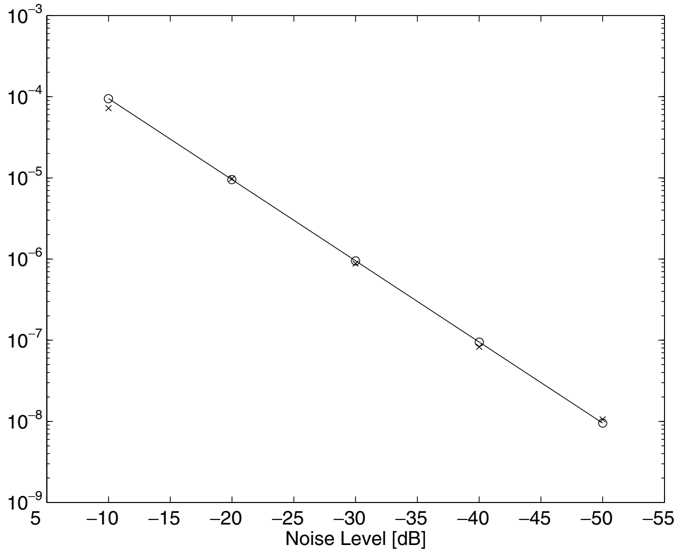

FIG. 2. Comparison of lower bound obtained for CRLB for the variance estimate of ω_{11} (solid line -○-) with estimated variance based on nonlinear least-squares parameter estimate ($\times$) for five noise levels (-10, -20, -30, -40, -50 dB).

and the number of Monte Carlo runs is set to 50. When running the nonlinear least-squares optimization algorithm, we start with a random initial estimate vector in the neighborhood of the real parameter vector. The least-squares optimization routine was coded in Matlab (*10*) using the optimization toolbox in a straightforward way.

In Fig. 2 we show a comparison of the bound for the variance obtained from the Cramer–Rao lower bound for the parameter ω_{11} and the estimated parameter based on the least-squares estimates. The comparison is shown for the five noise levels -10, -20, -30, -40, -50 dB, respectively. The plot shows a high level of agreement. Full agreement cannot be expected since finite sample effects are unavoidable for the estimated variances. These finite sample effects could also result in the estimated variance being even lower than the CRLB. The plots also show that the variance of the estimates decreases with decreasing noise level of the data.

In Fig. 3 the full 16×16 matrix for the CRLB is shown for a noise level of -20 dB. The diagonal terms provide a lower bound for the variances of the corresponding parameter. For example $9.5 \cdot 10^{-6}$ which is the (9, 9) entry of the CRLB matrix provides a lower bound for the variance of any unbiased estimate of the 9th parameter in the parameter vector, i.e., for $\theta_9 = \omega_{11}$. The off-diagonal terms provide information on the covariance between the parameter estimates for two different parameters. For example, the fact that the (1, 13) entry is very small indicates that the parameter estimates for θ_{11} and c_{11} are essentially uncorrelated, i.e., independent of one another. In Fig. 4 the estimated variance matrix is presented based on the simulations and estimation procedure discussed above. The agreement between

$$\left(\begin{array}{rrrrrrrrrrrrrrrr}
3.17e-05 & -4.43e-06 & 1.86e-05 & -5.04e-06 & -8.86e-06 & 1.24e-05 & -2.29e-05 & 2.29e-05 & 1.24e-06 & -5.83e-05 & -1.79e-07 & 2.82e-06 & -6.76e-18 & -4.23e-05 & 1.42e-04 & 7.76e-05 \\
-4.43e-06 & 6.51e-05 & -1.32e-05 & -3.05e-05 & -1.18e-05 & 5.81e-05 & 1.56e-05 & -7.13e-05 & -8.19e-07 & -6.82e-07 & -4.98e-06 & 3.63e-06 & 6.20e-05 & -2.68e-19 & 9.39e-05 & 9.49e-05 \\
1.86e-05 & -1.32e-05 & 5.86e-05 & 3.48e-05 & -1.83e-06 & -1.29e-04 & -1.72e-05 & 6.73e-06 & 8.15e-06 & -4.16e-05 & -7.37e-07 & 6.53e-06 & -1.13e-04 & -5.12e-05 & -1.49e-17 & 1.67e-05 \\
-5.04e-06 & -3.05e-05 & 3.48e-05 & 1.18e-04 & 1.09e-05 & -1.55e-04 & -2.58e-06 & -3.55e-05 & 4.91e-06 & -1.28e-05 & -5.37e-06 & 4.59e-06 & -6.73e-05 & -5.61e-05 & -1.81e-05 & -1.44e-17 \\
-8.86e-06 & -1.18e-05 & -1.83e-06 & 1.09e-05 & 9.50e-06 & -1.65e-05 & -5.73e-19 & 1.72e-18 & 3.61e-20 & 1.88e-05 & -1.43e-19 & 2.38e-19 & -8.28e-06 & 3.72e-06 & -6.79e-05 & -3.78e-05 \\
1.24e-05 & 5.81e-05 & -1.29e-04 & -1.55e-04 & -1.65e-05 & 8.12e-04 & 3.77e-18 & -1.20e-17 & -1.88e-05 & 1.05e-17 & -2.88e-19 & 1.60e-18 & 3.88e-04 & 3.10e-06 & 3.46e-04 & 9.82e-05 \\
-2.29e-05 & 1.56e-05 & -1.72e-05 & -2.58e-06 & -5.71e-19 & 3.76e-18 & 4.27e-05 & -2.50e-05 & 1.05e-19 & -4.42e-18 & -7.19e-19 & -3.73e-06 & 1.19e-06 & 2.26e-05 & 6.14e-06 & 4.13e-05 \\
2.29e-05 & -7.13e-05 & 6.73e-06 & -3.55e-05 & 1.72e-18 & -1.20e-17 & -2.50e-05 & 2.53e-04 & 3.08e-19 & 3.00e-18 & 3.73e-06 & -1.75e-18 & -1.88e-05 & -1.65e-05 & -5.44e-05 & -3.53e-05 \\
1.24e-06 & -8.19e-07 & 8.15e-06 & 4.91e-06 & 3.66e-20 & -1.88e-05 & 1.04e-19 & 3.09e-19 & 9.50e-06 & -1.65e-05 & 5.76e-19 & -2.59e-18 & -5.91e-05 & -5.39e-05 & -1.52e-05 & 8.39e-05 \\
-5.83e-05 & -6.82e-07 & -4.16e-05 & -1.28e-05 & 1.88e-05 & 1.06e-17 & -4.43e-18 & 3.02e-18 & -1.65e-05 & 8.12e-04 & -5.28e-18 & 1.19e-17 & 8.29e-05 & 2.64e-04 & -1.08e-03 & -1.19e-03 \\
-1.79e-07 & -4.98e-06 & -7.37e-07 & -5.37e-06 & -1.45e-19 & -2.43e-19 & -7.20e-19 & 3.73e-06 & 5.67e-19 & -5.28e-18 & 4.27e-05 & -2.50e-05 & -1.52e-04 & 7.09e-05 & -1.43e-04 & -1.98e-05 \\
2.82e-06 & 3.63e-06 & 6.53e-06 & 4.59e-06 & 2.50e-19 & 1.53e-18 & -3.73e-06 & -1.74e-18 & -2.59e-18 & 1.20e-17 & -2.50e-05 & 2.53e-04 & 1.53e-04 & -3.24e-04 & 5.60e-05 & -2.73e-04 \\
-6.76e-18 & 6.20e-05 & -1.13e-04 & -6.73e-05 & -8.28e-06 & 3.88e-04 & 1.19e-06 & -1.88e-05 & -5.91e-05 & 8.29e-05 & -1.52e-04 & 1.53e-04 & 1.41e-03 & -1.34e-04 & 1.03e-03 & -2.58e-04 \\
-4.23e-05 & -2.29e-19 & -5.12e-05 & -5.61e-05 & 3.72e-06 & 3.10e-06 & 2.26e-05 & -1.65e-05 & -5.39e-05 & 2.64e-04 & 7.09e-05 & -3.24e-04 & -1.34e-04 & 1.35e-03 & -5.00e-04 & -1.07e-03 \\
1.42e-04 & 9.39e-05 & -1.49e-17 & -1.81e-05 & -6.79e-05 & 3.46e-04 & 6.14e-06 & -5.44e-05 & -1.52e-05 & -1.08e-03 & -1.43e-04 & 5.60e-05 & 1.03e-03 & -5.00e-04 & 4.07e-03 & 2.23e-03 \\
7.76e-05 & 9.49e-05 & 1.67e-05 & -1.44e-17 & -3.78e-05 & 9.82e-05 & 4.13e-05 & -3.53e-05 & 8.39e-05 & -1.19e-03 & -1.98e-05 & -2.73e-04 & -2.58e-04 & -1.07e-03 & 2.23e-03 & 7.00e-03
\end{array}\right)$$

FIG. 3. Cramer–Rao lower bound matrix for 2D NMR data set in Section 3 with noise level -20 dB.

4.43e−05	−2.90e−05	2.71e−05	−3.28e−06	−7.23e−06	−2.27e−05	−3.60e−05	5.23e−05	−8.81e−07	−7.37e−05	−1.43e−05	2.88e−05	5.52e−05	−1.09e−04	2.89e−04	6.39e−05
−2.90e−05	7.71e−05	−3.12e−05	−3.21e−05	−4.19e−06	9.08e−05	3.49e−05	−9.74e−05	−2.02e−06	1.35e−05	8.73e−06	3.82e−06	7.37e−05	4.64e−05	−4.82e−05	2.64e−05
2.71e−05	−3.12e−05	7.27e−05	4.37e−05	−1.81e−06	−1.82e−04	−2.59e−05	2.33e−05	1.02e−05	−5.87e−05	−4.19e−06	2.06e−05	−1.55e−04	−6.21e−05	5.27e−05	−1.36e−04
−3.28e−06	−3.21e−05	4.37e−05	1.18e−04	1.43e−05	−1.73e−04	−8.93e−06	−2.74e−05	8.57e−06	4.00e−05	5.74e−07	−5.54e−05	−1.69e−04	3.50e−05	−9.20e−05	5.11e−05
−7.23e−06	−4.19e−06	−1.81e−06	1.43e−05	6.84e−06	−1.41e−05	2.37e−07	−7.25e−06	7.50e−07	1.95e−05	5.77e−07	−1.47e−05	−1.66e−05	1.33e−05	−6.58e−05	8.68e−06
−2.27e−05	9.08e−05	−1.82e−04	−1.73e−04	−1.41e−05	8.73e−04	6.42e−05	−1.64e−05	−4.79e−05	3.68e−06	−6.62e−07	5.10e−05	6.88e−04	4.73e−05	5.42e−04	6.12e−05
−3.60e−05	3.49e−05	−2.59e−05	−8.93e−06	2.37e−07	6.42e−05	5.42e−05	−3.78e−05	−1.26e−06	1.45e−05	1.85e−05	−2.97e−05	−3.93e−05	1.01e−04	−1.32e−04	3.76e−05
5.23e−05	−9.74e−05	2.33e−05	−2.74e−05	−7.25e−06	−1.64e−05	−3.78e−05	3.07e−04	−8.33e−08	−1.91e−05	−4.07e−05	1.19e−04	1.07e−04	−2.31e−04	2.86e−04	−6.87e−05
−8.81e−07	−2.02e−06	1.02e−05	8.57e−06	7.50e−07	−4.79e−05	−1.26e−06	−8.33e−08	8.57e−06	−3.66e−06	1.23e−06	−1.08e−05	−7.20e−05	−6.41e−06	−3.85e−05	4.91e−05
−7.37e−05	1.35e−05	−5.87e−05	4.00e−05	1.95e−05	3.68e−06	1.45e−05	−1.91e−05	−3.66e−06	1.04e−03	−1.02e−05	7.15e−05	1.22e−05	5.04e−05	−1.41e−03	−9.22e−04
−1.43e−05	8.73e−06	−4.19e−06	5.74e−07	5.77e−07	−6.62e−07	1.85e−05	−4.07e−05	1.23e−06	−1.02e−05	4.75e−05	−3.55e−05	−1.80e−04	7.62e−05	−2.26e−04	−4.28e−05
2.88e−05	3.82e−06	2.06e−05	−5.54e−05	−1.47e−05	5.10e−05	−2.97e−05	1.19e−04	−1.08e−05	7.15e−05	−3.55e−05	2.90e−04	2.28e−04	−3.40e−04	5.08e−06	−5.96e−04
5.52e−05	7.37e−05	−1.55e−04	−1.69e−04	−1.66e−05	6.88e−04	−3.93e−05	1.07e−04	−7.20e−05	1.22e−05	−1.80e−04	2.28e−04	1.93e−03	−3.72e−04	1.74e−03	2.99e−04
−1.09e−04	4.64e−05	−6.21e−05	3.50e−05	1.33e−05	4.73e−05	1.01e−04	−2.31e−04	−6.41e−06	5.04e−05	7.62e−05	−3.40e−04	−3.72e−04	9.98e−04	−7.23e−04	−4.82e−04
2.89e−04	−4.82e−05	5.27e−05	−9.20e−05	−6.58e−05	5.42e−04	−1.32e−04	2.86e−04	−3.85e−05	−1.41e−03	−2.26e−04	5.08e−06	1.74e−03	−7.23e−04	5.85e−03	2.80e−03
6.39e−05	2.64e−05	−1.36e−04	5.11e−05	8.68e−06	6.12e−05	3.76e−05	−6.87e−05	4.91e−05	−9.22e−04	−4.28e−05	−5.96e−04	2.99e−04	−4.82e−04	2.80e−03	7.33e−03

FIG. 4. Variance matrix for parameter estimates based on simulations of 2D NMR data set in Section 3 with noise level −20 dB.

the two matrices is good, also taking into consideration the finite sample effects that were discussed above.

4. EXPERIMENT DESIGN USING THE CRAMER–RAO LOWER BOUND

In the previous section we have seen that the Cramer–Rao lower bound is essentially attained by a least-squares parameter estimation method. In this section we investigate how the Cramer–Rao lower bound can be used to give insights into how the experimental design influences the accuracy with which the parameters can be estimated. We follow the approach discussed earlier that a reduced variance of an unbiased parameter estimate is interpreted as a more accurate estimate. An experimental design can then be analyzed by computing the Cramer–Rao lower bound for the data set that will result from the implementation of the experimental design. A decreased Cramer–Rao lower bound would then lead to a parameter estimate that has increased accuracy assuming that a parameter estimation method is available that attains the bound, as was shown to exist for the example discussed in Section 3.

In the following two sections we will be looking at two examples of such considerations. The first shows how the CRLB could be used to evaluate whether nonuniform sampling might improve the accuracy of the estimates. The second shows how to evaluate averaging schemes of traces in 2D experiments. It should be pointed out that our main concern is not to advocate certain experimental designs, such as nonuniform sampling over uniform sampling. Our interest is to provide a tool to the experimentalist that allows the experimentalist to decide in quantitative terms which experimental design is superior from the point of view of minimizing the Cramer–Rao lower bound.

These two applications are only a small number of the potential uses of the Cramer–Rao lower bound to evaluate experimental designs. They should, however, give a good indication for the type of analysis that is possible. For ease of presentation we again use a relatively simple data model. The same approach could be used to investigate more general data models.

4.1. Nonuniform Sampling

The question as to whether nonuniform sampling is to be preferred over uniform sampling has been addressed by various authors (see, e.g., (*11*) for a textbook treatment). Here we do not wish to advocate a new sampling scheme. However, we would like to show how our results on the CRLB can be used to evaluate various schemes.

We again consider the 2D example of Section 3. For this example we are going to consider uniform and nonuniform sampling in the direct and indirect dimensions. We first consider the sampling process in the indirect dimension. For the uniform sampling scheme the following 16 sampling points are chosen with sampling interval $\Delta t = 1.54$ as (0.00 1.54 3.07 4.61 6.14 7.68 9.21 10.75 12.28 13.82 15.35 16.89 18.42 19.96 21.49

TABLE 1
CRLB for Different Sampling Methods

	$u\|u$	$n\|u$	$n\|n$
c_{11}	5.923e-05	4.534e-05	2.655e-05
c_{12}	1.220e-04	8.709e-05	4.619e-05
c_{21}	8.925e-05	7.332e-05	4.244e-05
c_{22}	1.852e-04	1.417e-04	7.341e-05
r_{11}	1.842e-05	2.355e-05	1.147e-05
r_{12}	1.459e-03	1.167e-03	6.827e-04
r_{21}	7.548e-05	5.347e-05	6.197e-05
r_{22}	4.580e-04	2.715e-04	1.834e-04
ω_{11}	1.842e-05	2.355e-05	1.147e-05
ω_{12}	1.459e-03	1.167e-03	6.827e-04
ω_{21}	7.548e-05	5.347e-05	6.197e-05
ω_{22}	4.580e-04	2.715e-04	1.834e-04
θ_{11}	2.632e-03	2.015e-03	1.180e-03
θ_{12}	2.521e-03	1.799e-03	9.543e-04
θ_{21}	6.198e-03	5.092e-03	2.947e-03
θ_{22}	1.096e-02	8.385e-03	4.344e-03

Note. $u|u$ ($n|n$) stands for (non)uniform sampling in both dimensions; $n|u$ stands for nonuniform sampling in the indirect dimension and nonuniform sampling in the direct dimension. The precise sampling scheme is explained in the text.

23.03). The nonuniform sampling points have been determined following an exponential scheme discussed in (*11*) with

$$t_{j+1} = -\frac{e^{-Lt_j} - \frac{1-e^{-LT}}{M-1}}{L}, \qquad j = 1, 2, \ldots, M-1,$$

where $t_1 = 0$, $L = 0.1$, $T = 23.03$, and $M = 16$ for getting the nonuniform sample points in the indirect dimension in this example. These samples are given by (0.00 0.62 1.28 1.98 2.74 3.57 4.46 5.45 6.54 7.77 9.16 10.79 12.73 15.14 18.33 23.03).

In the direct dimension the 1024 sampling points were sampled in the uniform case at a sampling interval of $\Delta s = 0.015$. For the nonuniform sampling scheme the data points were generated using an exponential scheme given by a formula similar to the above one for t_{j+1} except that now $L = 1.15$, $T = 15.35$, and $M = 1024$.

In Table 1 the results of the corresponding Cramer–Rao lower bound calculations are summarized. It follows clearly that by introducing the above discussed non-uniform sampling the CRLB is generally decreased. Ignoring other possible considerations such as ease of parameter estimation, this shows that the experimental design based on using the given nonuniform sampling schemes for both dimensions will produce the best data amongst the three experimental designs that were analyzed. The term *best data set* is used here to indicate the data set that allows for the most precise estimation of the underlying parameters as assessed by the CRLB, amongst the data sets that are being considered. It might be intuitively clear that the presented nonuniform sampling scheme is superior to the uniform sampling scheme for the given data set. The value of using the Cramer–Rao lower bound to evaluate the different sampling strategies lies in the fact that a precise quantitative evaluation for the various strategies is possible. In practice the spectroscopist would have to weigh the established benefits of the nonuniform sampling scheme against other considerations that are not addressed by the Cramer–Rao lower bound such as the fact that nonuniformly sampled data cannot be processed by the standard Fourier transform-based methods to obtain a spectrum.

4.2. Averaging to Improve Parameter Estimation Accuracy

Experimental time is at a premium in NMR spectroscopy, in particular for multidimensional experiments. The experimental time is directly proportional to the number of scans that are acquired. The signal-to-noise ratio is often improved by averaging scans. This amounts to changing the variance σ_m^2 in the noise description. Note that if σ_m^2 is constant for all m, i.e., $\sigma^2 := \sigma_m^2$, for $m = 1, 2, \ldots$, it follows from the expressions for the Cramer–Rao lower bound in the Appendix that the Cramer–Rao lower bound is proportional to σ^2. This shows that uniformly lowering the noise level will lead to an improvement in the bound on the variance of the parameter estimates by an equal amount.

The question that will be addressed now to illustrate the potential use of the Cramer–Rao lower bound is whether it can, for example, be beneficial to average more scans for low increment numbers rather than averaging the same number of scans for each increment. In Table 2 the results of CRLB calculations are summarized for our standard 2D example system (see Section 3) with 16 being the size of the indirect dimension. Two averaging schemes were considered. The first is the traditional scheme in which for each increment in the indirect dimension a fixed number of repeated experiments (in our case 16) are acquired and then averaged. Since in our example the indirect dimension has 16 increments this amounts to a total of 256 acquired traces. In the second scheme we propose to acquire an unequal number of

TABLE 2
CRLB for Different Sampling and Weighting Methods

	$u\|u$ UA	$n\|u$ UA	$n\|u$ NA	$n\|n$ NA
c_{11}	3.702e-06	2.834e-06	2.569e-06	1.471e-06
c_{12}	7.627e-06	5.443e-06	4.680e-06	2.483e-06
c_{21}	5.578e-06	4.583e-06	3.677e-06	2.096e-06
c_{22}	1.158e-05	8.856e-06	6.894e-06	3.597e-06
r_{11}	1.151e-06	1.472e-06	2.184e-06	1.062e-06
r_{12}	9.118e-05	7.296e-05	6.683e-05	3.900e-05
r_{21}	4.718e-06	3.342e-06	2.440e-06	2.829e-06
r_{22}	2.863e-05	1.697e-05	1.113e-05	7.524e-06
ω_{11}	1.151e-06	1.472e-06	2.184e-06	1.062e-06
ω_{12}	9.118e-05	7.296e-05	6.683e-05	3.900e-05
ω_{21}	4.718e-06	3.342e-06	2.440e-06	2.829e-06
ω_{22}	2.863e-05	1.697e-05	1.113e-05	7.524e-06
θ_{11}	1.645e-04	1.259e-04	1.142e-04	6.540e-05
θ_{12}	1.576e-04	1.125e-04	9.670e-05	5.130e-05
θ_{21}	3.874e-04	3.182e-04	2.553e-04	1.456e-04
θ_{22}	6.850e-04	5.240e-04	4.079e-04	2.129e-04

Note. $u|u$ ($n|n$) stands for (non)uniform sampling in both dimensions; $n|u$ stands for nonuniform sampling in the indirect dimension and uniform sampling in the direct dimension. UA (NA) stands for (non)uniform averaging in the first dimension. The precise sampling and weighting scheme is explained in the text.

traces per increment. In this nonuniform averaging scheme we propose to again acquire 256 scans for the 2D experiment but we acquire and average 29 traces for the first increment, 27 traces for the second increment, 26 for the third, etc. The list of numbers of traces for all the increments is given by 29, 27, 26, 24, 22, 20, 19, 17, 15, 13, 12, 10, 8, 6, 5, 3. In the noise description for a two-dimensional data set we allowed each column $s(n, m)_{n\geq 1}$ to have a different variance σ_m^2, $m \geq 1$. This means that our proposed averaging scheme can be easily incorporated in the general data model. If an acquired trace has variance σ^2 then the average of k traces will have variance σ^2/k. This means, for example, that in our case the variance σ_1^2 for the first increment will be $\sigma_1^2 = \sigma^2/29$.

Four different experimental designs have been considered, in which uniform averaging and nonuniform averaging have been combined with uniform and nonuniform sampling. The results in Table 2 show that a combination of the above discussed nonuniform averaging scheme with the nonuniform sampling schemes introduced in Section 4.1 produces a reduction in the CRLB for the various parameters by a factor of about 3.

An issue that needs to be addressed in the context of experimental design is that in practice the parameters of a system are often not known and the purpose of the experiment is to estimate these unknown parameters. We believe that the presented results can nevertheless be of importence in practice. First, in many situations the experimentalist has a relatively good knowledge of the ranges within which the parameters can be expected to lie. An experimental design can then be evaluated using expected parameters. Such an approach would give the experimentalist a good indication about which parameters are difficult and which are less difficult to estimate. Moreover, a preliminary experiment could be carried out to obtain this initial information. Based on the preliminary results a careful experimental design could be developed for a full experiment that is aimed to very precisely estimate the required parameters.

5. CONCLUSIONS

Classical statistical results show that the Cramer–Rao lower bound provides a lower bound for the variance of a parameter estimation scheme, provided it is unbiased, i.e., provided that on average it produces the correct results. Here we have shown that the CRLB can be calculated explicitly for a parameter estimation problem for a general 2D NMR data set. Using Monte Carlo type simulations we have shown for a simulated example that the variance of estimates using a nonlinear least-squares parameter estimation algorithm in fact attain this bound. It was also shown how the developed results can be applied to study questions of experimental design. Using example systems we used our CRLB results to show that a certain nonuniform sampling scheme in fact produces superior results over the uniform sampling scheme that was considered. We also introduced (for the first time to the best of our knowledge) a nonuniform averaging scheme for traces. This was also investigated in conjunction with nonuniform sampling to show that an improved CRLB can be obtained for the examined system.

APPENDIX: THE ENTRIES OF THE FISHER INFORMATION MATRIX

A.1. Derivation of Entries of Fisher Information Matrix

We are here going to show how to derive the entries for a few cases. The other entries are derived similarly and the results are listed below.

To compute the entries of the Fisher information matrix the second order partial derivatives of ln $p(x, \Theta)$ have to be calculated. The first order partial derivatives are given by

$$
\begin{aligned}
\frac{\partial \ln(p(x,\Theta))}{\partial c_{kl}} &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))e^{r_{1k}t_n + r_{2l}s_m}\cos(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl}) \\
&\quad + \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))e^{r_{1k}t_n + r_{2l}s_m}\sin(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl}), \\
\frac{\partial \ln(p(x,\Theta))}{\partial r_{1k}} &= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))\sum_{v=1}^{L}c_{kv}e^{r_{1k}t_n + r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})t_n \\
&\quad + \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))\sum_{v=1}^{L}c_{kv}e^{r_{1k}t_n + r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})t_n \\
&= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv}) \\
&\quad + \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv}),
\end{aligned}
$$

$$\frac{\partial \ln(p(x,\Theta))}{\partial r_{2l}} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))s_m e^{r_{2l}s_m}\sum_{u=1}^{K} c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))s_m e^{r_{2l}s_m}\sum_{u=1}^{K} c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul}),$$

$$\frac{\partial \ln(p(x,\Theta))}{\partial \omega_{1k}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv}),$$

$$\frac{\partial \ln(p(x,\Theta))}{\partial \omega_{2l}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))s_m e^{r_{2l}s_m}\sum_{u=1}^{K} c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))s_m e^{r_{2l}s_m}\sum_{u=1}^{K} c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul}),$$

$$\frac{\partial \ln(p(x,\Theta))}{\partial \phi_{kl}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))c_{kl}e^{r_{1k}t_n + r_{2l}s_m}\sin(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))c_{kl}e^{r_{1k}t_n + r_{2l}s_m}\cos(\omega_{1k}t_n + \omega_{2l}s_m + \phi_{kl}),$$

Based on the above first order partial derivatives, we can continue to derive all the second order partial derivatives. However, since the derivation is long and tedious, we only give a few examples here. In particular, as to be illustrated in the following, we have to derive separately second order partial derivatives such as $(\partial \ln^2(p(x,\Theta)))/(\partial r_{1k}^2)$ and $(\partial \ln^2(p(x,\Theta)))/(\partial r_{1k}\partial r_{1p})$ $(k \neq p)$ since they are different from each other. However, after taking the expectation as required for the Fisher information matrix, it is often possible to use a general expression. For example, although we are unable to arrive at a unified expression $(\partial \ln^2(p(x,\Theta)))/(\partial r_{1k}\partial r_{1p})$ that would cover both cases $k = p$ and $k \neq p$, we are able to derive a unified expression $E((\partial \ln^2(p(x,\Theta)))/(\partial r_{1k}\partial r_{1p}))$ that does cover both cases $k = p$ and $k \neq p$.

$$\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}^2} = \frac{\partial}{\partial r_{1k}}\left\{\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right.$$
$$\left.+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right\}$$
$$= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n \frac{\partial}{\partial r_{1k}}\{e^{r_{1k}t_n}\}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial r_{1k}}\{(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))\}\, t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n \frac{\partial}{\partial r_{1k}}\{e^{r_{1k}t_n}\}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial r_{1k}}\{(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))\}\, t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$

$$= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n^2 e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{2r_{1k}t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)^2$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n^2 e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{2r_{1k}t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)^2.$$

On the other hand for $k \neq p$,

$$\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial r_{1p}} = \frac{\partial}{\partial r_{1p}}\left\{\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right.$$
$$\left.+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right\}$$
$$= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial r_{1p}}\{(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))\}\, t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial r_{1p}}\{(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))\}\, t_n e^{r_{1k}t_n}\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})$$
$$= -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)\cdot\left(\sum_{v=1}^{L} c_{pv}e^{r_{2v}s_m}\cos(\omega_{1p}t_n + \omega_{2v}s_m + \phi_{pv})\right)$$
$$- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)\cdot\left(\sum_{v=1}^{L} c_{pv}e^{r_{2v}s_m}\sin(\omega_{1p}t_n + \omega_{2v}s_m + \phi_{pv})\right).$$

It is not possible to consider $(\partial \ln^2(p(x,\Theta)))/(\partial r_{1k}\partial r_{1p})$ in a unified fashion for both cases $k = p$ and $k \neq p$. By taking the expectation, we have for the case $p = k$ that

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}^2} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{2r_{1k}t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)^2$$
$$- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{2r_{1k}t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)^2,$$

and for $k \neq p$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial r_{1p}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L} c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv})\right)$$
$$\cdot\left(\sum_{v=1}^{L} c_{pv}e^{r_{2v}s_m}\cos(\omega_{1p}t_n + \omega_{2v}s_m + \phi_{pv})\right)$$

$$
\begin{aligned}
&- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right)\\
&\cdot\left(\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\sin(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})\right).
\end{aligned}
$$

The above two expressions can be unified using a single expression:

$$
\begin{aligned}
E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial r_{1p}} = &- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right)\\
&\cdot\left(\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\cos(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})\right)\\
&- \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right)\\
&\cdot\left(\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\sin(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})\right),
\end{aligned}
$$

where k can be equal to p and also be different from p.

Two more second order partial derivatives are derived in the following.

$$
\begin{aligned}
\frac{\partial \ln^2(p(x,\theta))}{\partial c_{kl}^2} &= \frac{\partial}{\partial c_{kl}}\left\{\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))e^{r_{1k}t_n+r_{2l}s_m}\cos(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\right.\\
&\left. + \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))e^{r_{1k}t_n+r_{2l}s_m}\sin(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\right\}\\
&= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial c_{kl}}\{(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))\}\,e^{r_{1k}t_n+r_{2l}s_m}\cos(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\\
&+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial c_{kl}}\{(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))\}\,e^{r_{1k}t_n+r_{2l}s_m}\sin(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\\
&= -\sum_{n}\sum_{m}\frac{1}{\sigma_m^2}e^{2(r_{1k}n+r_{2l}m)}\cos^2(\omega_{1k}n+\omega_{2l}m+\phi_{kl}) - \sum_{n}\sum_{m}\frac{1}{\sigma_m^2}e^{2(r_{1k}n+r_{2l}m)}\sin^2(\omega_{1k}n+\omega_{2l}m+\phi_{kl})\\
&= -\sum_{n}\sum_{m}\frac{1}{\sigma_m^2}e^{2(r_{1k}n+r_{2l}m)}.
\end{aligned}
$$

$$
\begin{aligned}
\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial \omega_{2l}} &= \frac{\partial}{\partial \omega_{2l}}\left\{\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right.\\
&\left. + \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m)) - \mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right\}\\
&= \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))t_n e^{r_{1k}t_n}\frac{\partial}{\partial \omega_{2l}}\left\{\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right\}\\
&+ \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial \omega_{2l}}\{(\mathrm{Re}(x(n,m)) - \mathrm{Re}(g(n,m)))\}t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})
\end{aligned}
$$

$$
\begin{aligned}
&+\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m))-\mathrm{Im}(g(n,m)))t_n e^{r_{1k}t_n}\frac{\partial}{\partial\omega_{2l}}\left\{\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right\}\\
&+\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}\frac{\partial}{\partial\omega_{2l}}\{(\mathrm{Im}(x(n,m))-\mathrm{Im}(g(n,m)))\}\,t_n e^{r_{1k}t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\\
=&-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Re}(x(n,m))-\mathrm{Re}(g(n,m)))t_n s_m c_{kl}e^{r_{1k}t_n+r_{2l}s_m}\sin(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\\
&+\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\\
&+\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}(\mathrm{Im}(x(n,m))-\mathrm{Im}(g(n,m)))t_n s_m c_{kl}e^{r_{1k}t_n+r_{2l}s_m}\cos(\omega_{1k}t_n+\omega_{2l}s_m+\phi_{kl})\\
&-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv}).
\end{aligned}
$$

Other second order partial derivatives can be similarly derived, but are omitted here to save space.

A.2. List of Entries of Fisher Information Matrix

Using the notation of Section 2, and taking the expectation of the second order partial derivatives derived in the previous section of the Appendix, we here list the entries of the Fisher information matrix for the data analysis of 2D NMR data sets discussed in Section 2.

$$
\begin{aligned}
E\frac{\partial\ln^2(p(x,\Theta))}{\partial c_{kl}\partial c_{pq}} &= -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}e^{(r_{1k}+r_{1p})t_n+(r_{2l}+r_{2q})s_m}\cdot\cos((\omega_{1k}-\omega_{1p})t_n+(\omega_{2l}-\omega_{2q})s_m+(\phi_{kl}-\phi_{pq})),\\
E\frac{\partial\ln^2(p(x,\Theta))}{\partial r_{1k}\partial r_{1p}} &= -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right)\\
&\quad\cdot\left(\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\cos(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})\right)\\
&\quad-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\left(\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\right)\\
&\quad\cdot\left(\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\sin(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})\right).\\
E\frac{\partial\ln^2(p(x,\Theta))}{\partial r_{2l}\partial r_{2q}} &= -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}s_m^2 e^{(r_{2l}+r_{2q})s_m}\left(\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\right)\\
&\quad\cdot\left(\sum_{u=1}^{K}c_{uq}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2q}s_m+\phi_{uq})\right)
\end{aligned}
$$

$$
\begin{aligned}
& - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} s_m^2 e^{(r_{2l}+r_{2q})s_m} \left(\sum_{u=1}^{K} c_{ul} e^{r_{1u}t_n} \sin(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul}) \right) \\
& \quad \cdot \left(\sum_{u=1}^{K} c_{uq} e^{r_{1u}t_n} \sin(\omega_{1u}t_n + \omega_{2q}s_m + \phi_{uq}) \right).
\end{aligned}
$$

$$
\begin{aligned}
E \frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{1k} \partial \omega_{1p}} = & - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} t_n^2 e^{(r_{1k}+r_{1p})t_n} \left(\sum_{v=1}^{L} c_{kv} e^{r_{2v}s_m} \sin(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv}) \right) \\
& \quad \cdot \left(\sum_{v=1}^{L} c_{pv} e^{r_{2v}s_m} \sin(\omega_{1p}t_n + \omega_{2v}s_m + \phi_{pv}) \right) \\
& - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} t_n^2 e^{(r_{1k}+r_{1p})t_n} \left(\sum_{v=1}^{L} c_{kv} e^{r_{2v}s_m} \cos(\omega_{1k}t_n + \omega_{2v}s_m + \phi_{kv}) \right) \\
& \quad \cdot \left(\sum_{v=1}^{L} c_{pv} e^{r_{2v}s_m} \cos(\omega_{1p}t_n + \omega_{2v}s_m + \phi_{pv}) \right).
\end{aligned}
$$

$$
\begin{aligned}
E \frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{2l} \partial \omega_{2q}} = & - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} s_m^2 e^{(r_{2l}+r_{2q})s_m} \left(\sum_{u=1}^{K} c_{ul} e^{r_{1u}t_n} \sin(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul}) \right) \\
& \quad \cdot \left(\sum_{u=1}^{K} c_{uq} e^{r_{1u}t_n} \sin(\omega_{1u}t_n + \omega_{2q}s_m + \phi_{uq}) \right) \\
& - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} s_m^2 e^{(r_{2l}+r_{2q})s_m} \left(\sum_{u=1}^{K} c_{ul} e^{r_{1u}t_n} \cos(\omega_{1u}t_n + \omega_{2l}s_m + \phi_{ul}) \right) \\
& \quad \cdot \left(\sum_{u=1}^{K} c_{uq} e^{r_{1u}t_n} \cos(\omega_{1u}t_n + \omega_{2q}s_m + \phi_{uq}) \right).
\end{aligned}
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial \phi_{kl} \partial \phi_{pq}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} c_{kl} c_{pq} e^{(r_{1k}+r_{1p})t_n + (r_{2l}+r_{2q})s_m} \cdot \cos((\omega_{1k} - \omega_{1p})t_n + (\omega_{2l} - \omega_{2q})s_m + (\phi_{kl} - \phi_{pq})).
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial c_{kl} \partial r_{1p}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \sum_{v=1}^{L} \frac{1}{\sigma_m^2} t_n c_{pv} e^{(r_{1k}+r_{1p})t_n + (r_{2l}+r_{2v})s_m} \cdot \cos((\omega_{1k} - \omega_{1p})t_n + (\omega_{2l} - \omega_{2v})s_m + (\phi_{kl} - \phi_{pv})).
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial c_{kl} \partial r_{2q}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \sum_{u=1}^{K} \frac{1}{\sigma_m^2} s_m c_{uq} e^{(r_{1k}+r_{1u})t_n + (r_{2l}+r_{2q})s_m} \cdot \cos((\omega_{1k} - \omega_{1u})t_n + (\omega_{2l} - \omega_{2q})s_m + (\phi_{kl} - \phi_{uq})).
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial c_{kl} \partial \omega_{1p}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \sum_{v=1}^{L} \frac{1}{\sigma_m^2} t_n c_{pv} e^{(r_{1k}+r_{1p})t_n + (r_{2l}+r_{2v})s_m} \cdot \sin((\omega_{1k} - \omega_{1p})t_n + (\omega_{2l} - \omega_{2v})s_m + (\phi_{kl} - \phi_{pv})).
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial c_{kl} \partial \omega_{2q}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \sum_{u=1}^{K} \frac{1}{\sigma_m^2} s_m c_{uq} e^{(r_{1k}+r_{1u})t_n + (r_{2l}+r_{2q})s_m} \cdot \sin((\omega_{1k} - \omega_{1u})t_n + (\omega_{2l} - \omega_{2q})s_m + (\phi_{kl} - \phi_{uq})).
$$

$$
E \frac{\partial \ln^2(p(x,\Theta))}{\partial\, c_{kl} \partial \phi_{pq}} = - \sum_{n=1}^{N} \sum_{m=1}^{M} \frac{1}{\sigma_m^2} c_{pq} e^{(r_{1k}+r_{1p})t_n + (r_{2l}+r_{2q})s_m} \cdot \sin((\omega_{1k} - \omega_{1p})t_n + (\omega_{2l} - \omega_{2q})s_m + (\phi_{kl} - \phi_{pq})).
$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial r_{2l}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul}).$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial \omega_{1p}} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\sin(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n^2 e^{(r_{1k}+r_{1p})t_n}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{v=1}^{L}c_{pv}e^{r_{2v}s_m}\cos(\omega_{1p}t_n+\omega_{2v}s_m+\phi_{pv}).$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial \omega_{2l}} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv}).$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{1k}\partial \phi_{pl}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\sum_{v=1}^{L}\frac{1}{\sigma_m^2}t_n c_{kv}c_{pl}e^{(r_{1k}+r_{1p})t_n+(r_{2l}+r_{2v})s_m}\cdot\sin((\omega_{1k}-\omega_{1p})t_n+(\omega_{2v}-\omega_{2l})s_m+(\phi_{kv}-\phi_{pl})).$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{2l}\partial \omega_{1k}} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv}),$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{2l}\partial \omega_{2q}} = \sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}s_m^2 e^{(r_{2l}+r_{2q})s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{u=1}^{K}c_{uq}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2q}s_m+\phi_{uq})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}s_m^2 e^{(r_{2l}+r_{2q})s_m}\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})\cdot\sum_{u=1}^{K}c_{uq}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2q}s_m+\phi_{uq}),$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial r_{2l}\partial \phi_{kq}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\sum_{u=1}^{K}\frac{1}{\sigma_m^2}s_m c_{kq}c_{ul}e^{(r_{1k}+r_{1u})t_n+(r_{2l}+r_{2q})s_m}\cdot\sin((\omega_{1u}-\omega_{1k})t_n+(\omega_{2l}-\omega_{2q})s_m+(\phi_{ul}-\phi_{kq})),$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{1k}\partial \omega_{2l}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\sin(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\sin(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul})$$
$$-\sum_{n=1}^{N}\sum_{m=1}^{M}\frac{1}{\sigma_m^2}t_n s_m e^{r_{1k}t_n+r_{2l}s_m}\sum_{v=1}^{L}c_{kv}e^{r_{2v}s_m}\cos(\omega_{1k}t_n+\omega_{2v}s_m+\phi_{kv})\cdot\sum_{u=1}^{K}c_{ul}e^{r_{1u}t_n}\cos(\omega_{1u}t_n+\omega_{2l}s_m+\phi_{ul}),$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{1k}\partial \phi_{pl}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\sum_{v=1}^{L}\frac{1}{\sigma_m^2}t_n c_{kv}c_{pl}e^{(r_{1k}+r_{1p})t_n+(r_{2l}+r_{2v})s_m}\cdot\cos((\omega_{1k}-\omega_{1p})t_n+(\omega_{2v}-\omega_{2l})s_m+(\phi_{kv}-\phi_{pl})),$$

$$E\frac{\partial \ln^2(p(x,\Theta))}{\partial \omega_{2l}\partial \phi_{kq}} = -\sum_{n=1}^{N}\sum_{m=1}^{M}\sum_{u=1}^{K}\frac{1}{\sigma_m^2}s_m c_{kq}c_{ul}e^{(r_{1k}+r_{1u})t_n+(r_{2l}+r_{2q})s_m}\cdot\cos((\omega_{1k}-\omega_{1u})t_n+(\omega_{2q}-\omega_{2l})s_m+(\phi_{kq}-\phi_{ul})),$$

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