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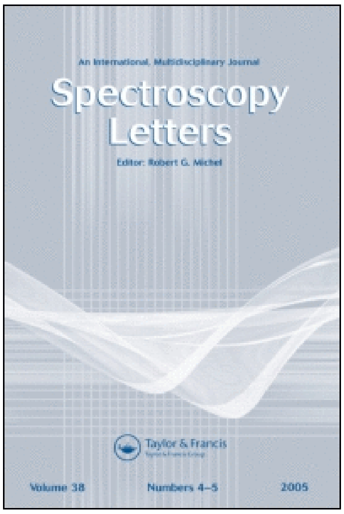

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Solvent Peak Removal in NMR Spectra Using Bayesian Analysis

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SOLVENT PEAK REMOVAL IN NMR SPECTRA USING BAYESIAN ANALYSIS

Key words: Solvent peak, Bayesian

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Abstract

In this paper we demonstrate the use of Bayesian analysis methods for the removal or suppression of solvent peaks from NMR spectra. Typically solvent peaks are the dominant feature in the NMR spectrum and often mask or seriously overlap smaller resonance from which important information of the molecule under study may be obtained. Although applied to NMR spectra, the method is general and may be applied to large peak suppression in most spectroscopic techniques.

INTRODUCTION

Large peak suppression is a desireable data analysis technique in many forms of spectroscopy. In NMR spectroscopy the solvent peak often obscures much smaller resonances nearby which are due to the molecule under study. A common example is the large water peak obtained from protein NMR in aqueous solvents. In Fourier-transform NMR spectroscopy, the signal is acquired in the time-domain and the final spectrum is presented by Fourier transformation of the acquired signal into the frequency-domain. The large solvent peak obtained in the frequency-domain spectrum often makes peak assignment difficult, particularly in the amide region of the spectrum. Although several experiment pulse methods have been

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utilized for solvent peak suppresionn [1], it is possible that modern data analysis methods combined with A/D converters with a large dynamic range may provide superior large peak suppression. In this paper we present the use of Bayesian analysis methods for the suppression of large resonances or peaks in an experimentally acquired spectrum.

THEORY

Bayes' theorem is

$$P(A|B,I)=\frac{P(A|I)\times P(B|A,I)}{P(B|I)} \qquad (1)$$

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where the proposition that A is true given B and any prior information, I, denoted by the probability P(A|B,I) is related to the proposition A is true given only the prior information, P(A|I), the proposition B is true given A and the prior information, denoted by P(B|A,I), divided by the probability B is true given the prior information, P(B|I). To clarify the use of Bayes' theorem, particularly in application to spectroscopy, let's take A to be a hypothesis, H, that a given equation can be used to describe a given set of data, D. The probability P(A|B,I), now expressed as P(H|D,I) is the best measure of how well the equations "fits" the data. In a more conventional approach the equation would be fit to the data, usually using a non-linear least-squares algorithm. This is related to the probability P(D|H,I). Bayes's theorem demonstrates, as we will see below, how fitting the equation to the data can be used to determine how appropriate the equation (or model function) is in describing the data. For example, we can "fit" a decaying time data set to a decaying exponential and to a gaussian function and obtain two different R values, or goodness of fits. Bayes' theorem can be used to determine which model is the correct choice. Note that the goodness of fit is not a sufficient criterion. Bayes' theorem, as applied below, also may be used to determine an optimum set of parameters in an equation being used to fit a given data set. Such a set of parameters would optimize P(D|H,I) and, therefore, P(H|D,I). In applying Bayes' theorem in this manner the method begins to approach non-linear least-squares fitting of the data. The adjustable parameters in the model function, the equation used to describe the data, are optimized until the maximal value in P(H|D,I) is located. These values are taken to be the "correct" values. There are two distinct advantages of Bayesian analysis over conventional non-linear least-squares; prior information, I, such as ranges of allowed values of parameters may be incorporated into the model in a more natural way and some of the parameters, called nuisance parameters, may be removed from the probability before the fitting procedure is applied. To date, no one has investigated spectroscopic application of Bayes theorem employing prior information and it is not included in this work. The removal of nuisance parameters will be discussed below. To summarize, Bayes theorem may be viewed as a method of "fitting" an equation to a data set in which several of the parameters may be eliminated from the equation before it is fit to the data.

To relate this more directly to spectroscopy, consider a general time-domain function, f(t), define as

$$f(t)=\sum_{j=1}^{m} B_j G_j(t,\{\omega\}) \tag{2}$$

where G_j is some function of time which depends parametrically on a set of frequencies. Perhaps it is a set of decaying sine or cosine functions each of which is composed of several frequencies. Each of these cosine functions has an amplitude, B_j. f(t) is thus a set of model functions which may described the experimental data, D. Bayes theorem can then be used to determine the probability that the model functions, which may contain adjustable parameters, correctly describe the experimental data

$$P(B,\{\omega\}|D,I)=\frac{P(B,\{\omega\}|I)\times P(D|B,\{\omega\},I)}{P(D|I)} \tag{3}$$

One advantage of the Bayesian formulation is that linear parameters in the probability may be removed by marginalization, that is, the parameter-dependence may be integrated out of the probability. This marginalization is the approach used to remove unecessary parameters as discussed above. In the model functions typically used in NMR analysis, decaying cosine functions, the amplitude may be marginalized so that only the frequency of each resonance and its associated decay rate remain. These two parameters, unlike the amplitude, are not strongly correlated so that non-linear least-squares adjustment of the parameters to optimize the probability now become feasible, even for complicated spectra.

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It has previously been shown that marginalization of the amplitude leads to the following expression for the probability [2]

$$P(\omega,\alpha|D) \equiv \left\{1-\frac{m\overline{h}^2}{N\overline{d}^2}\right\}^{\frac{m-N}{m}} \tag{4}$$

where m is the number of model functions, N is the number of data points, w and a are the frequency and decay rate of each peak in the NMR spectrum, $\overline{h}^2$ is the sufficient statistic, defined by

$$\overline{h}^2 = \frac{1}{m}\sum_{j=1}^{m} h_{ij} \tag{5}$$

where h_{ij} is the projection of the orthogonalized model function onto the data and $\overline{d}^2$ is given by

$$\overline{d}^2 = \frac{1}{N}\sum_{i=1}^{N} d_i^2 \tag{6}$$

where the orthogonalized model functions are obtained by forming the matrix, g_{ij}, of all possible products $G_i * G_j$ of the model functions given in eq. 2 and obtaining the eigenvectors of this matrix.

To make these points clearer we now describe the method of applying these equations. The Bayesian method is a non-linear least-squares optimization of the probability, given by eq. 4, where the frequency and decay rate of each model function, i.e. peak in the spectrum, is adjusted. For a given set of frequency and decay rates the current estimate of the model function is obtained from eq. 2. The model function is then "projected" onto the experimental data to compute the sufficient statistic, h2, using eq. 5. This projection is accomplished as one would project two vectors to produce a scalar quantity. For each point in the data a sum of the product of the orthogonal model function times the data point is computed. The more closley the orthogonal model function "fits" the data the larger this projection becomes resulting in a larger sufficient statistic. The sum-square of the data points is computed via eq. 6 and, finally, the probability is computed using eq. 4. The frequency and decay rates are adjusted by a suitable algorithm until the probability is maximized. The values of the parameters that maximize the probability are then assumed to be the "correct" or best values.

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Note that the amplitudes are not included in the orthogonal model functions. They are nuisance parameters and have been marginalized out. The marginalized parameters, in this case the amplitude of each resonance, may be obtained from the final finals of the estimated parameters. We have previously shown that the Bayesian method provides reliable estimates of frequencies, decay rates and amplitudes of peaks within complicated NMR spectra [3].

With these estimations of the parameters of the model functions which describe the experimental data, we can expect to remove or suppress large peaks in the data as they make the major contribution to the experimental FID. That is, we can assume as our model a single model function, i.e. one resonance, which would then provide estimates of the contribution of the largest peak to the experimental spectrum. We than subtract this decaying sinusoid from the experimental FID and anticipate that the FFT of the residual FID reasonably approximates the frequency-domain spectrum with the largest peak removed. Below we provide an application to synthetic data and then to experimental data and discuss current limitations of the procedure.

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RESULTS AND DISCUSSION

To test and to display the potential of the method we have generated a synthetic data set similar to one that would be acquired on a conventional FFT-NMR instrument. The data set is generated in the time-domain, Fig 1B with three resonances or peaks. The frequencies of the three resonances are 10, 20 and 30Hz in a 1:100000:1 ratio of amplitudes. In other words, the amplitude of the middle peak is 100000 times that of the two peaks on either side. White noise with a relative amplitude of 1% (relative to the smaller resonances) is added to the data set. The FID appears to be a single decaying sinusoid, while the FFT displays what appears to be a single peak at 20Hz, Fig 1A. Using the method outlined above a single model function is estimated from the data set and subtracted from the time-domain signal. The residual FID is shown in Fig. 1D. The FFT of the residual FID is shown in Fig. 1C clearly showing the two smaller resonances.

With this demonstation of the technique we now apply the method to experimentally acquired data. It is important to demonstrate such data analysis and extraction methods on experimental data as methods such a Bayesian analysis rely on model functions to describe the experimental data. Synthetic data which is generated

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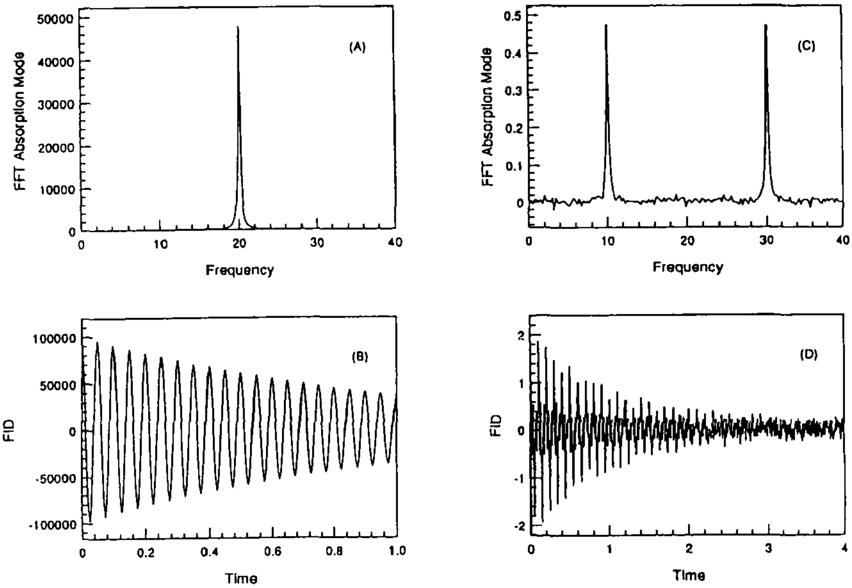

Fig. 1. Example of large peak suppression from a synthetic data set.

using these model functions always leads to remarkable demonstrations of the applicability of the method. An experimental NMR spectrum of a derivatized cyclodextran compound is shown below. The spectrum was acquired on a Varian 400 Unity FT-NMR spectrometer. In Fig. 2 we show the FFT of the resulting time-domain data (not referenced). The region near the solvent peak is shown on an expanded scale while the insert displays the full spectrum acquired over the experimental spectral range.

Following the procedure described above we performed a full Bayesian analysis on the above time-domain data with a single model function The analysis took 20s on a 5K data set on a SUN Model 2 workstation. Using the final optimized values of the parameters the large resonance is subtracted from the experimental FID. The resulting FFT spectrum is shown below. The region near the solvent peak is shown on an expanded scale.

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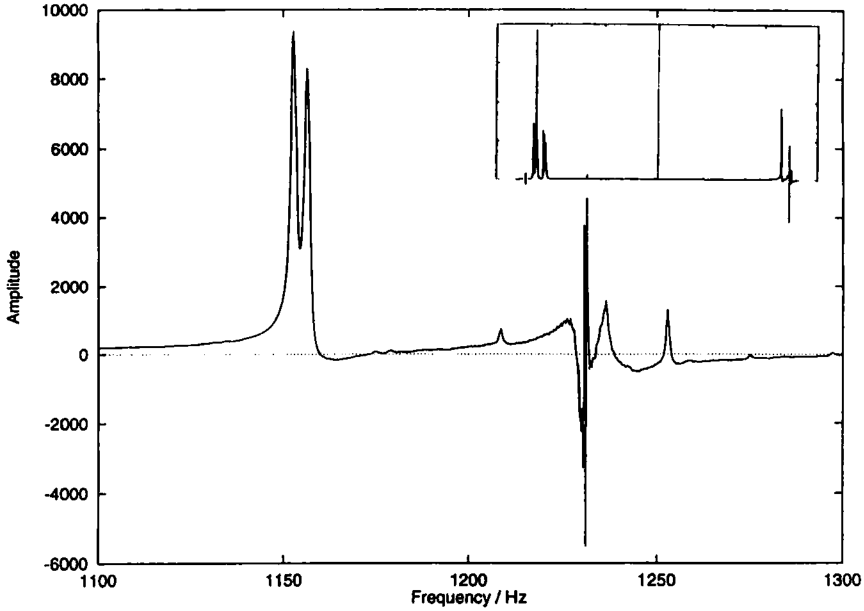

Fig. 2. Experimental FFT spectrum of a derivatized cyclodextran compound.

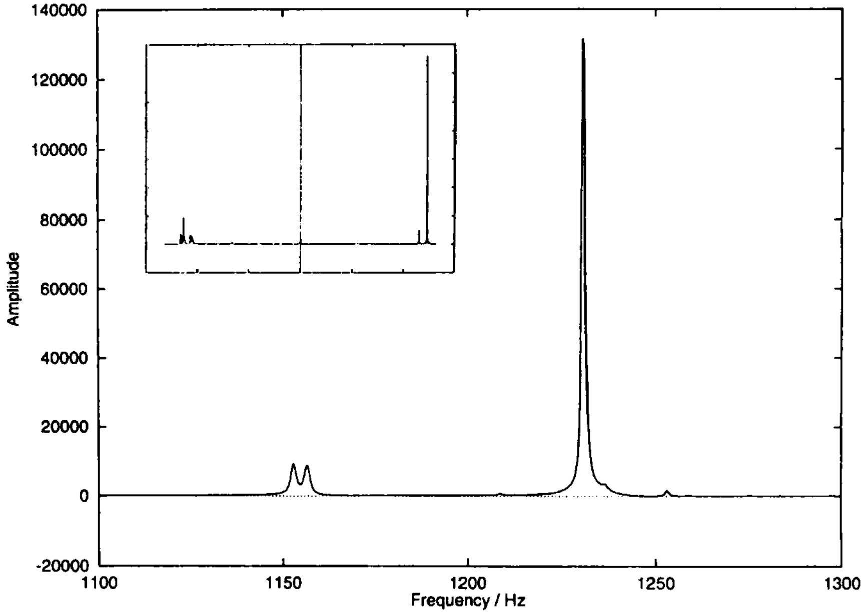

Fig. 3. Experimental FFT spectrum of the above spectrum with suppression of the solvent peak.

Looking first at the FFT spectrum prior to solvent suppression we notice two small features in the spectum near the solvent peak at approximately 1210 Hz and 1260 Hz, plus a shoulder on the high-frequency side of the solvent peak. Now looking at Fig 3., with the solvent peak removed. We note that the two peaks at 1210 and 1260 Hz, respectively are clearly visible in the residual spectrum and that the shoulder peak has been baseline resolved from the solvent peak. The current limitation of the method is evident in the rapid oscillations in the residual spectrum centered at the solvent peak frequency. These oscillations result from the fact that imperfect shimming of the NMR magnetic field has led to non-lorentzian lineshapes and therefore non-exponential decay of the experimental FID. Our simple model functions, therefore, do not correctly described the experimental FID. A much "cleaner" removal of the solvent peak may be accomplished once a more realistic model function incorporating imperfect shimming is used. The above synthetic and experimental applications of the method demonstrate both the potential of the method in addition to deficiences that should be addressed in future research in this area.

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