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Parametric Spectrum Analysis of 2D NMR Signals. Application to *in Vivo J* Spectroscopy

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Parametric modeling techniques for spectrum analysis, based on the linear prediction principle, have previously been proposed to process NMR data. In this paper, they are tested on different practical NMR signals, and especially on *in vivo* 2D NMR spectroscopy data. The linear prediction version of the maximum entropy method, using AR modeling, and the Prony method are outlined with some considerations about the choice of the AR algorithm. Then simulation and experimental results obtained with the Prony method are presented and compared with those obtained with classical 2D Fourier transform processing. The data processed here result from homonuclear 2D *J*-resolved spectroscopy experiments performed to measure the spin–spin coupling constants between the three phosphorus nuclei of ATP in the rat brain. The parametric techniques (especially the Prony method) applied in both dimensions yield increased resolution and sensitivity and their ability to process limited data allows the total acquisition time to be reduced without loss of resolution. Although the noise may damage the performances, the results obtained here, on *in vivo* 2D data, are quite encouraging.

In 1D NMR spectroscopy, because of complex structures and resolution limitations, the spin–spin coupling constants can be difficult to measure. Fortunately, two-dimensional NMR spectroscopy has proved to be of great value for unraveling spectra that are complicated by extensive and multiple overlapping of spin-multiplet structure. In *J* spectroscopy, spin echoes are modulated by spin–spin coupling and information about spin coupling constants J is obtained in the second dimension (corresponding to the time interval t_1 characterizing the pulse sequence) while the first dimension (corresponding to the acquisition time t_2) exhibits the chemical shifts $\delta(1)$.

However, the development of the application of 2D spectroscopy to the field of *in vivo* NMR has been slow, probably due to the low concentration of the species to be detected, which implies a very low sensitivity, and to the bad resolution achievable in the second dimension when T_2 is short. In addition, in order to obtain a reasonable resolution when FT processing is used, *in vivo* 2D NMR experiments require quite a

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large number of acquisitions in the second dimension, leading to prohibitively long data acquisition times.

These difficulties encountered in 2D *in vivo* NMR make very desirable the implementation of alternative data processing methods which would yield the same kind of information as the Fourier transform method but which would do so with a smaller data set (hence requiring fewer acquisitions in the second dimension) and better resolution.

Recently several different methods based on the maximum entropy principle and linear prediction (*2–19*) have been proposed to analyze NMR free induction decays leading to an improvement in resolution and noise level on the spectra. In this work, the Prony method is tested and compared with the FFT method for processing various data resulting from simulations, from a phantom experiment, and from practical *in vivo* 2D NMR spectroscopy.

As noted by Vitti *et al.* (*2*), there are two fundamentally different approaches of the maximum entropy method (MEM). One, which could be called the linear prediction version of MEM (LPMEM) and was first proposed by Burg, is based on an extrapolation of the autocorrelation function of a time series in such a way that the entropy of the resulting time series is maximum. This method involves only a set of linear equations. The second approach is concerned with a constraint optimization of the entropy over a set of trial spectra obtained with the usual FFT. Among all the feasible spectra (i.e., spectra for which the corresponding trial FID is in agreement with the observed data), the FFT spectrum chosen is that having the greatest entropy. This second method, developed by many authors (*20–31*), is intrinsically nonlinear in its implementation and requires an iterative algorithm using a χ^2 test (*22*).

Here we want to emphasize that we deal with the LP version of the MEM because we are concerned with a fast processing technique involving only linear equations and no iterative algorithm. As will be shown below, this method is related to autoregressive modeling. But it should be noted that although the LPMEM involves only the solution of a set of linear equations, the spectral estimate obtained with LPMEM is not linear, especially in its behavior with respect to additive noise.

Many authors have already dealt with the LP version of MEM. Vitti, Barone, and colleagues (*2–5*) have tested AR modeling and the Prony method on 1D data. Barkhuijsen, Delsuc, and colleagues (*6–10*) have also used linear prediction with singular value decomposition (LPSVD) for 1D data. Noorbehesht *et al.* (*11*) have processed *in vivo* 1D NMR data using Prony's model with a priori information about frequencies and damping constants. Other authors like Tang and Norris (*12, 13*) and Sibisi (*20*) propose a two-dimensional representation of 1D NMR data. Ni and Scheraga (*14*) are interested in a phase-sensitive spectral reconstruction using the Burg MEM algorithm.

Although it has been demonstrated that the nonlinear iterative version of the maximum entropy method can be more successful than the FT method in processing 2D data (*23, 27, 28*), only little work has been done concerning the LP version of MEM applied to 2D spectroscopy. Hoch (*15*) and Schussheim and Cowburn (*16*) have processed 2D NMR data using the LPMEM only in the second dimension, while a Fourier transform was performed in the first dimension. Very recently, Gesmar and Led (*17*) also presented some simulation results concerning the application of LP in

where the first difficulty encountered is low sensitivity. Now, one of the most important features of spectroscopy systems is the resolution, which is limited by noise. The choice of modern spectrum analysis methods for processing NMR data should partially overcome this dilemma.

It is the few points available in the second dimension that first led us to test the parametric methods on *in vivo* 2D NMR spectroscopy data. Indeed, those few points available in the t_1 dimension (due to experimental time limitations) induce truncation artifacts and produce side lobes (not with ATP for which T_2 is short but with phosphocreatine) on the spectra when performing Fourier transform in the second dimension. With modern spectrum analysis, good resolution without truncation artifacts can be achieved even with very limited data while with FFT, resolution is proportional to $1/T$, where T is the duration of the signal. Thus, parametric methods may allow the number of acquisitions (following time t_1) to be reduced hence reducing the total experiment time.

The poor resolution of the multiplets achievable with FFT in the second dimension (due to noise and above all to short T_2 values) is one more reason to try new processing techniques.

OUTLINE OF THE LP VERSION OF MEM

In this section and the next, we outline the two parametric processing methods we have applied, namely the LPMEM and Prony method. Thereafter, the results from the Prony method will be presented.

The basis of the LPMEM is the following. For a Gaussian random process, the entropy H can be written

$$H = \int_{-F_e/2}^{+F_e/2} \mathrm{Log}(S(f))\,df, \qquad [1]$$

where $S(f)$ is the power spectral density of the signal and F_e is the sampling frequency. This entropy is maximized, subject to the constraint of the Wiener-Khinchine theorem,

$$S(f) = \mathrm{FT}\{R(t)\}, \qquad [2]$$

where $R(t)$ is the autocorrelation function and FT means Fourier transformation.

The solution obtained with the technique of Lagrange multipliers yields the expression for the spectrum (*33*)

$$S(f) = \frac{\sigma^2 \Delta t}{\left|1 + \sum_{k=1}^{p} a_k \exp(-j2\pi f k \Delta t)\right|^2}, \qquad [3]$$

where the a_k's are the coefficients of a prediction filter of order p and σ^2 is the noise power.

where the a_k's are the coefficients of a polynomial $\psi(z)$, the roots of which are precisely the complex exponentials z_m of the model

$$\psi(z) = \prod_{m=1}^{p} (z - z_m) = \sum_{k=0}^{p} a_k z^{p-k} \qquad \text{with} \qquad a_0 = 1. \qquad [10]$$

Equation [9] shows that Prony's model (consisting of a sum of damped exponentials in additive white noise) is equivalent to a particular ARMA process with identical MA and AR coefficients.

The exact least-squares parameter estimation that minimizes the sum of the errors e_n over the entire range $n = p, \ldots, N-1$ leads to a set of nonlinear equations difficult to solve. A suboptimal solution, called the extended Prony method, avoids this nonlinear solution by approximating the ARMA process of Eq. [9] by an AR process,

$$x_n = -\sum_{k=1}^{p} a_k x_{n-k} + \epsilon_n \qquad \text{for} \qquad n = p, \ldots, N-1, \qquad [11]$$

where ϵ_n is a correlated error defined from the error samples e_{n-k}. One then minimizes $\sum_{n=p}^{N-1} |\epsilon_n|^2$ instead of $\sum_{n=p}^{N-1} |e_n|^2$. Hence the extended Prony method reduces to the estimation of an AR process defined by Eq. [11]. For this AR parameter estimation, the same algorithms as used in the LPMEM can be adopted (Levinson, Burg, SVD, etc.). The number of exponentials p can be selected via an automatic order selection criterion (like FPE) or via an eigenvalue analysis (SVD).

Once the a_k are determined, the exponential parameters z_m (frequencies and damping factors) are found as the roots of polynomial $\psi(z)$. When the z_m's are computed, Eq. [5] reduces to a set of linear equations with unknown b_m. A least-squares procedure for solving this equation gives an estimate of the b_m's.

So the extended Prony method consists in solving two sets of linear equations via a least-squares technique plus an intermediate polynomial rooting that concentrates all the nonlinearity of the problem. Once all the parameters are known, the Prony spectrum is evaluated, based on the Fourier transform of the model.

ALGORITHMS

Our 2D spectrum analysis routine, written in Fortran 77, is implemented on a VAX computer. It offers a choice among three methods, namely FFT, LPMEM, and the Prony method. It works in single precision on complex data. Note that 2D processing does not require a two-dimensional algorithm; indeed, the 2D transform may be implemented via two 1D transforms.

Among the subroutines for AR parameter estimation which may be chosen are Levinson algorithm, forward linear prediction; Burg algorithm, combination of forward and backward linear prediction; Marple algorithm, combination of forward and backward linear predicition (*35*); Morf algorithm, separate forward and backward prediction (*36*); or an algorithm based on SVD of the data matrix with the choice among forward, backward, or forward and backward linear prediction (*37–39*).

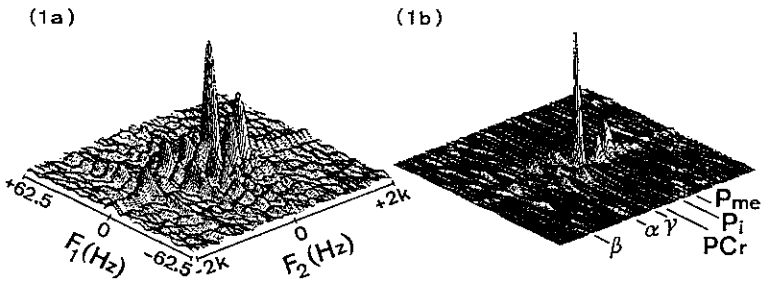

FIG. 1. Simulated 2D spectra. The simulated data consist of 16 acquisitions of 1K data points each. (a) Classical FFT processing with LB (40 Hz); 1K data points processed. (b) Parametric processing without LB. The Prony method is used in both dimensions; only the first 256 data points of each acquisition are processed.

EXPERIMENTAL RESULTS

Classical FFT processing of in vivo 2D NMR data. The signal is from an *in vivo* 2D NMR surface coil experiment performed on rat brain. The spectrometer used is a 200 MHz Bruker. The pulse sequence has been modified to take into account the RF field inhomogeneity by using composite pulses and depth pulse techniques (*40*). Data consist of 16 acquisitions of 1024 complex points each. Sampling frequencies are $F_e = 4$ kHz in the first dimension and $F_e = 125$ Hz $= 1/\Delta t$ (where $\Delta t = 8$ ms) in the second dimension.

The FFT processing in the first dimension yields 16 spectra represented in Fig. 3a where peaks can be identified as shown on the figure. Obviously, the multiplet structure corresponding to ATP lines is indistinguishable on such 1D spectra.

Fourier transform in the second dimension allows the doublet structure of α-ATP and γ-ATP to be resolved but the triplet structure of β-ATP remains unresolved (Fig. 3c). In addition, on the 2D spectrum (Fig. 3b), the side lobes due to truncation in the second dimension are important, especially for phosphocreatine. The measured coupling constants J are about 20 Hz. The bad resolution achieved with FFT and the truncation artifacts in the second dimension justify the use of other spectrum analysis methods based on parametric modeling.

Parametric processing of in vivo 2D NMR data. We have tested both AR modeling (or LPMEM) and Prony modeling. However, in this paper, we present only results concerning the Prony method, which seems to be more efficient. Results concerning MEM can be found in (*41*). Our preference for the Prony method was motivated by the fact that it keeps the phase information of the signal, thus allowing this method to be applied even in the first dimension. Moreover, this model is well suited for NMR signals and gives explicitly all the parameters of interest: frequencies, amplitudes, damping factors, and phases.

When viewing the 16 1D spectra (Fig. 3a), it can be seen that the last four contain frequency information only about phosphocreatine. Hence, we have processed only 12 acquisitions instead of 16. Reducing the number of acquisitions is very important in *in vivo* NMR experiments in order to also reduce the total acquisition time (this is not possible with FFT because of truncation and resolution considerations).

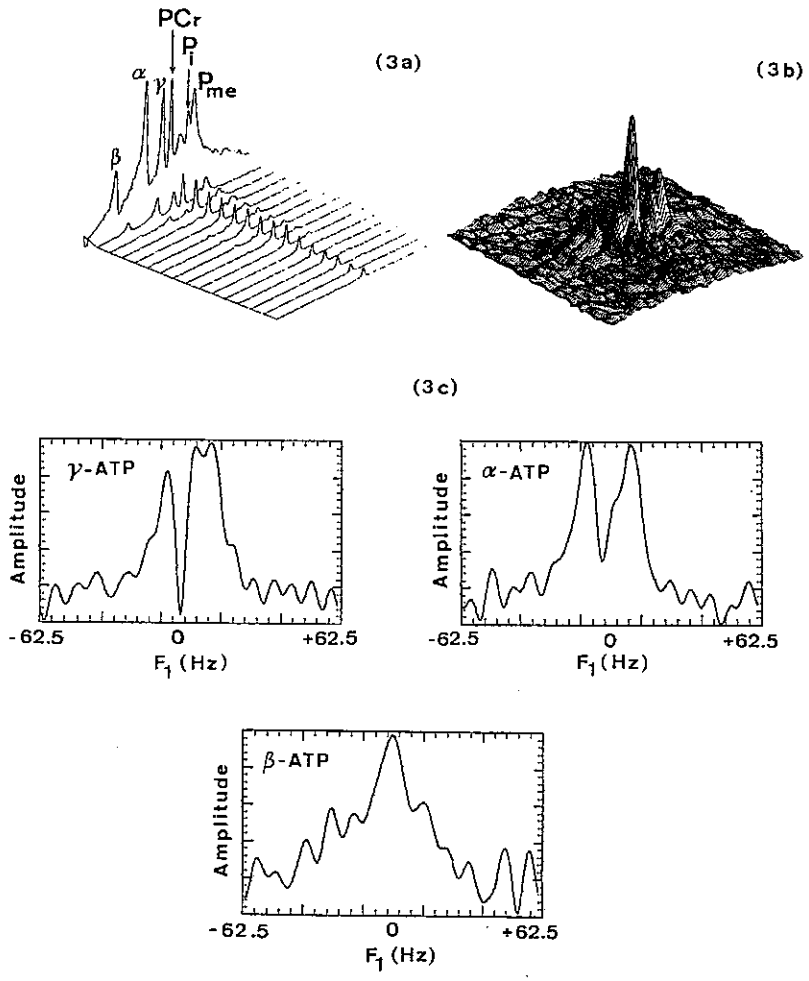

FIG. 3. Experimental results from *in vivo* ^{31}P *J* spectroscopy performed on a rat brain—classical FFT processing. Data consist of 16 acquisitions (1K data points each). Sampling frequencies are 4 kHz in the first dimension and 125 Hz in the second. LB = 40 Hz; FFT in both dimensions with zero-filling in the second dimension. (a) Fourier transform of the 16 acquisitions; the peaks are identified on the spectra. (b) 2D spectrum: (c) Cross sections corresponding to α, β, and γ peaks of ATP.

algorithm is used in the first dimension; the model order is 32 and the rank of the data matrix is fixed as 12 (although it could be automatically chosen). The Prony method with the Levinson algorithm is used in the second dimension (with model order 6).

With this processing, not only are the doublets resolved without ambiguity but also the triplet structure of β-ATP. The amplitudes of the multiplets are in agreement with those found with FFT processing although the two lines of the γ-ATP doublet are not strictly equal in amplitude. The noise seems to be responsible for this amplitude difference (see next section). The coupling constants measured from the spectrum

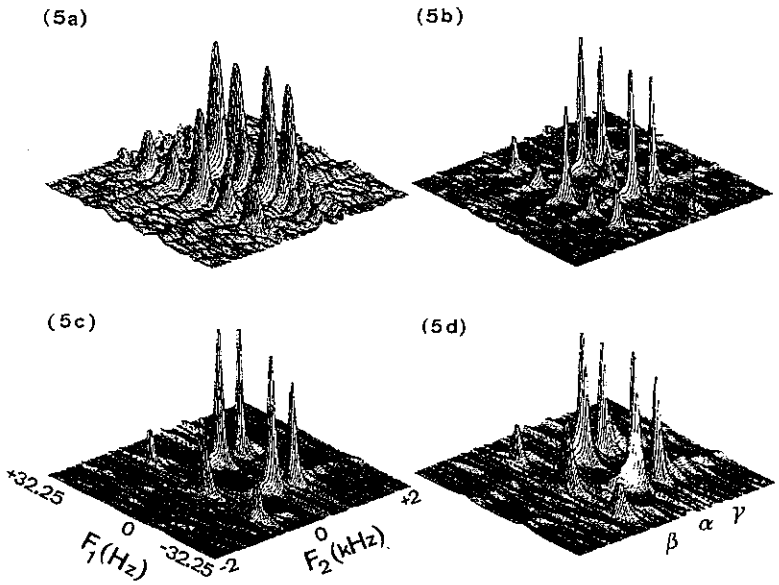

FIG. 5. High-resolution 2D J spectroscopy of a 0.1 M solution of ATP: the data consist of 16 acquisitions (256 points processed per acquisition). Sampling frequencies are 4 kHz in the first dimension and 62.5 Hz in the second. (a) Classical FFT processing with LB = 40 Hz; FFT applied in both dimensions with zero-filling in the second dimension. (b) Parametric processing with no LB; Prony/SVD in the first dimension; Prony/Levinson with order 8 in the second dimension. (c) Parametric processing with no LB; Prony/SVD in the first dimension; Prony/Levinson with order 4 in the second dimension. (d) Parametric processing with LB = 40 Hz; Prony/SVD in the first dimension; Prony/Levinson with order 4 in the second dimension.

ities. The FFT processing (after line broadening of all the FIDs) introduces side lobes in the 2D spectrum, some of which have an amplitude greater than that of the lateral lines of the triplet (Fig. 5a).

A parametric modeling, similar to that described above (the Prony method in both dimensions), leads to the spectra shown in Figs. 5b, 5c, and 5d. With a model order of four in the second dimension, all erroneous peaks are suppressed (Figs. 5c or 5d). However, without LB before parametric processing (Fig. 5c), the amplitudes of the γ-ATP doublet are not exactly equal. The noise is responsible for this problem. Indeed, when applying a LB before performing the same parametric processing, the amplitudes are well estimated (Fig. 5d). This illustrates the nonlinear behavior of such methods with respect to noise.

The well-known problem bound with parametric modeling is of course the model order selection. With model order 8, some extraneous peaks appear as shown in Fig. 5b. However, their amplitude remains smaller than those of the triplet lateral lines. So, even if the order is overestimated, an improvement over FFT processing is achieved. Note also the obvious improvement in the linewidths when no LB is performed.

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