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Application of Linear Prediction and Rapid Acquisition to Nuclear Magnetic Resonance

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A method for the acquisition of 1-dimensional nuclear magnetic resonance (NMR) data, which obtains signals more rapidly than the conventional method is presented. However, because the data are truncated, data processing by Fourier transformation is overcome by alternative spectral estimation methods. Linear prediction (LP) is used to reconstruct the spectrum from the incomplete time-domain magnetic resonance data. A pulse sequence modified from the driven-equilibrium Fourier transform (DEFT) implements truncated acquisition with forced return to equilibrium. This combination of truncated acquisition and LP processing is a novel way of acquiring and processing NMR data. The technique is demonstrated using a ^{31}P NMR acquisition where the conventional procedure required 17 h whereas the proposed method took only 45 min.

Keywords: NMR; linear prediction; driven-equilibrium Fourier transform; singular value decomposition

INTRODUCTION

In NMR spectroscopy, a perturbation (a pulse of RF energy) is applied to a chemical sample in a strong magnetic field, causing the nuclei in the sample to tip out of the equilibrium position. Under first order dynamics, the nuclei return to equilibrium.

It is during this time, when the magnetization is returning to equilibrium, that the decay can be detected in a suitably positioned pickup (receiver) coil. The voltage induced in the coil is recorded as the free induction decay or FID. Because of slight differences in local magnetic fields in molecules, each nucleus will precess with its own characteristic Larmor frequency on its way back to equilibrium. The resulting FID, once subjected to Fourier transformation, yields the NMR spectrum, which is a set of resonance lines which have Lorentzian-shaped peaks. The information contained herein yields the structure of the molecule whose atomic nuclei gave rise to the NMR spectrum. As a standard procedure, pulse NMR utilizes the discrete Fourier transform (DFT) to obtain the spectrum from the free induction decay. DFT is an estimate of the frequency response of a molecular system [1]. In the case of the pulse RF approach, the impulse response, $x(t)$ (i.e., the free induction decay or FID), is recorded as a function of time t, and the frequency response function $X(f)$ is calculated by applying the Fourier transform. However, since $x(t)$ is sampled for a finite period of time, only the discrete Fourier transform can be calculated.

If the relaxation process by which the perturbed nuclear magnetization returns to equilibrium is a first-order process, the theoretical impulse response will be a sum of decaying sinusoids:

$$x(t) = \sum_{k=1}^{K} A_k e^{-\alpha_k t} e^{j(2\pi f_k t + \varphi_k)} \qquad (1)$$

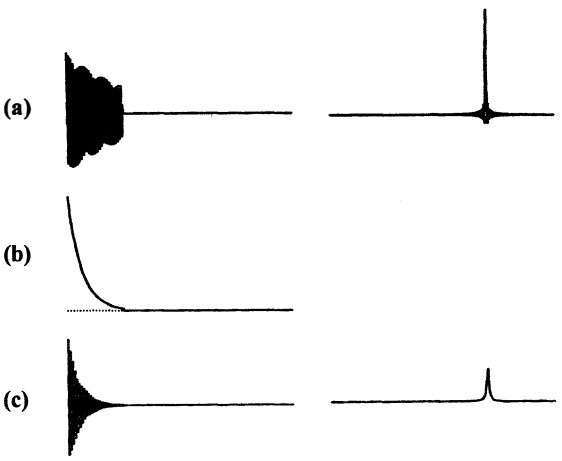

Fig. 1. Truncation and its amelioration by a window function. (a) *truncated FID and its Fourier spectrum with "sinc wiggles";* (b) *exponential apodiazation function;* and, (c) *apodized FID and its Fourier spectrum. Note the loss of intensity from a to c* [5].

where A_k, α_k, f_k, φ_k, j are the real-valued amplitude, damping factor, frequency, phase of the k*th* sinusoid and the square root of (-1), respectively. The assumed model of exponentially decaying sinusoids is known to be an accurate one [2].

In the case where the FID is "truncated" (*i.e.,* when the data are acquired only up to a point where the nucleus has not yet fully relaxed) "sinc wiggles" in the spectrum baseline result (Fig. 1). Such baseline distortions prevent the accurate integration of the spectrum. An alternative processing method, called linear prediction, can be used to generate the spectrum from truncated data. Barkhuijsen and co-workers [3] first applied linear prediction to NMR data in 1985, and since then various authors have proposed a number of alternative approaches. Koehl has written a comprehensive review of the application of LP to NMR data [4].

Expressed mathematically, the basic LP equation states:

$$\hat{x}_n = \sum_{m=1}^{M} a_m x_{n-m} \qquad (2)$$
$$n = M, \ldots, N\text{-}1$$

The values a_m, $m=1,\ldots,M$ are called the LP, or prediction, coefficients. The value of the number M is called the prediction order or filter order. Given a time series of N points, we can extrapolate the series beyond N by applying Equation 2 if we know the LP coefficients. Linear prediction is especially important in spectral analysis because the classes of time series that obey the LP equation are the sums of exponentially decaying (or growing) sinusoids, and the method provides a way of linearly fitting an exponential to such a time series [5]. While the original procedure by Prony exactly fits an exponential curve having M exponential terms, the extended Prony method gives an approximate fit with M exponentials to a data set of N samples using a least-squares estimation procedure. The model assumed in the extended Prony method is a set of M exponentials of arbitrary amplitude, phase, and frequency and damping factor:

$$\hat{x}_n = \sum_{m=1}^{M} \beta_m z_m^n \qquad (3)$$
$$n = 0, \ldots, N\text{-}1$$

For generality, β_m and z_m are assumed to be complex and

$$\beta_m = A_m \exp(j\varphi_m) \qquad (4)$$
$$z_m = \exp(-\alpha_m + j2\pi f_m)\Delta t \qquad (5)$$

where A_m is the amplitude, φ_m is the phase in radians, α_m is the damping factor and f_m is the oscillation frequency in hertz, while Δt represents the sample interval in seconds. For a discussion of the relationship of Equation 3 to Equation 1, the reader is referred to the literature [6, 7].

Finding these four parameters that minimize the squared error between the actual time series data and each estimate is a difficult nonlinear least-squares problem, the solution for which involves an iterative process in which an initial value of the unknown parameters is successively improved.

The extended Prony method provides a way of linearly fitting the model of Equation 3 to such a time series. The method consists of solving two sequential sets of linear equations with an intermediate polynomial rooting step that concentrates the nonlinearity of the problem in the rooting step [6]. This avoids an iterative procedure and the need for an initial guess of the unknown parameters.

First, the N data points are used to generate an overdetermined set of N-M equations of type Equation 1, and the coefficients a_m are determined by a linear least-squares fitting procedure. After the prediction coefficients are found, the frequencies and damping factors of the M signal components are determined from the M roots of the polynomial

$$z^M - a_1 z^{M-1} - \ldots - a_M = 0 \qquad (6)$$

by computing

$$f_m = \tan^{-1}[\mathrm{Im}(z_m)/\mathrm{Re}(z_m)]/2\pi\Delta t \qquad (7)$$

$$\alpha_m = \ln|z_m|/\Delta t \qquad (8)$$

for each root z_m.

The time domain signal is now modeled using the M roots by Equation 3 above. This generates yet another set of linear equations with M unknown β parameters (the z's are known coefficients) that are found using a second linear least-squares fit. Finally, the amplitudes and phases of the signal components are computed from the β values by

$$A_m = |\beta_m| \tag{9}$$

$$\theta_m = \tan^{-1}[\mathrm{Im}(\beta_m)/\mathrm{Re}(\beta_m)] \tag{10}$$

Equation 2 is called the forward LP equation because it gives a way to extrapolate a time series in the forward direction. The linear prediction can also be applied in a backward sense, predicting values from the immediately subsequent ones in a time series:

$$\hat{x}_n = -\sum_{m=1}^{M} b_m x_{n+m} \tag{11}$$

$$n = 0,\ldots,N\text{-}M\text{-}1$$

In the same manner as was used for Equation 2, the backward coefficients b_m can be obtained by using the procedure above. Rooting of the new polynomial will then yield signal-related backward roots that, after root reflection around the unit circle and complex conjugation are identical (or nearly identical, in the presence of noise) to the signal related roots of Equation 6. Complex conjugation is necessary because the time reversal inherent in backward linear prediction results in apparent frequencies that are opposite in sign to those in the forward direction.

The main advantage of using backward LP is that it is able to distinguish signal-related roots from "extraneous" roots (those that do not correspond to actual signal components). Kumaresan [8] has shown that when the least-squares method is used to find the coefficients of an LP filter of order M for a time series consisting of fewer than M sinusoids in the absence of noise, any extra zeros will be located inside the unit circle in the complex plane and hence separable from the signal zeros, in which the latter are located outside the unit circle for the case of backward prediction. The extraneous roots will also be roughly evenly dispersed around the unit circle. There is no such distinction in forward prediction—both sets of zeros will be inside the unit circle. In the case of noisy data, the extraneous zeros tend to fall closer to or outside the unit circle. Kumaresan also used singular value decomposition (SVD) as the numerical algorithm of choice in solving the LP Equations 3 and 11.

Normally, the number of signal components is not known beforehand. Thus the filter order M cannot be known, but some reasonable limit can be assumed. With noise in the data, it is better that the coefficients are overdetermined. It can be seen from Equations 1 and 10 that if N is the total number of data points and M is the filter order, then the number of equations that the LP coefficients must satisfy is $(N\text{-}M)$. For the coefficients to be uniquely determined M must be no larger than $N/2$. However, it has been shown in the previous case that the solution to the underdetermined case is possible: Kumaresan and Tufts [9] found a good choice of M is equal to $3N/4$. The least square solutions to the underdetermined case are discussed by Cline and Plemmons [10].

Cadzow [11] proposed a signal enhancement technique that corrects the noise in the singular values and "cleans up" the data matrix. It is based on averaging the signal matrix to maintain Hankel symmetry. Chen *et al.* [12] proposed an improved signal-enhancement technique called the minimum variance (MV) estimation method and found their method to be superior to Cadzow's method, being more efficient and having better resolution when overlapping peaks are quantified. They also found that one or two iterations of the procedure were sufficient to improve the estimates.

The single-pulse experiment is the simplest of all NMR experiments: flip the magnetization vector into the x-y plane, and then record the nuclear signal (FID) as it returns to equilibrium (Fig. 2). For good signal-to-noise, many repetitions of the pulse sequence are carried out, and the results of the individual acquisitions are added together—a form of signal averaging. A 90-degree pulse value for PW gives the largest

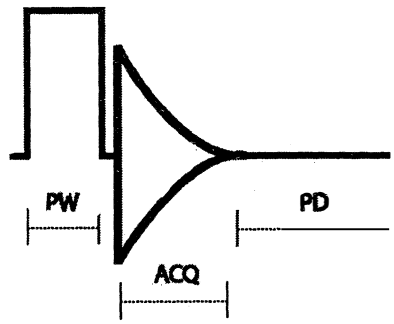

Fig. 2. Basic single pulse sequence. PW denotes the pulse-width duration, ACQ is acquisition time interval, and PD is pulse delay interval.

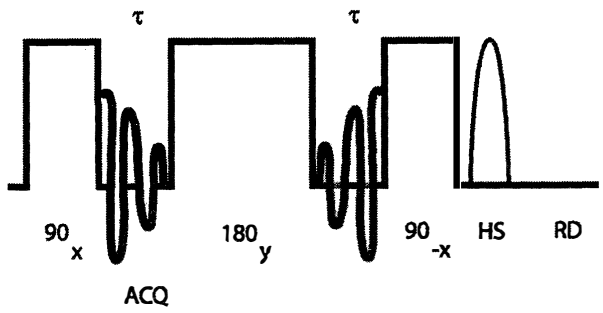

Fig. 3. The modified DEFT pulse sequence. 90_x, 180_y and 90_{-x} denote pulse angles and phases. ACQ is the acquisition time interval, while RD is relaxation delay. HS is an optional homospoil pulse.

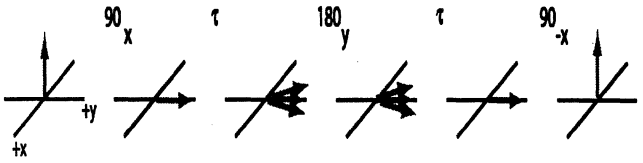

Fig. 4. Evolution of spins in the modified DEFT sequence.

x-y magnetization, and would be ideal to use, except for the requirement that the subsequent pulse delay, PD (normally five times the longitudinal relaxation time T_1 to allow the magnetization to relax back to equilibrium), is too long. Complete relaxation of nuclei is particularly important for NMR experiments in which quantitative information is important.

A pulse sequence modified from the driven-equilibrium Fourier transform or DEFT [1] implements truncated acquisition with forced return to equilibrium (Fig. 3) The original DEFT experiment had a full acquisition interval ACQ (for instance, hundreds of milliseconds for ^{13}C). This modified DEFT sequence has a very short τ time delay (at most 100 microseconds for ^{13}C) such that the data acquired are truncated.

Figure 4 shows the evolution of the vectors as the pulse sequence is applied. The first 90-degree pulse (along *x*) places the spins on the +*y* axis. Once on the *y*-axis, the individual vectors begin to precess according to their own resonance frequencies, which may be higher or lower than the Larmor frequency. A short time delay τ follows. It is during this time that a partial FID is obtained. Before the vectors completely relax to equilibrium, a 180-degree pulse is applied along the *y*-axis, causing the fast and slow vectors to flip around. Their sense of precession is now reversed, and they combine once more along the *y*-axis after another time delay τ. Once recombined, they are flipped to the upright *z*-axis by a –90 degree x-pulse, where they are now back to the equilibrium position. (An optional homospoil pulse may be used at this point to remove any remaining magnetization on the *x-y* plane.) Thus the two requirements of truncated acquisition and return to equilibrium are met.

Table 1. Parameters of the test FID used in the simulations.

Signal No.	*Frequency* (Hz)	*Line Width* (Hz)	*Amplitude* (Arbitrary Units)	*Phase* (Degrees)
1	–3200	120	1	20
2	–1200	70	1.5	0
3	–1000	65	1.8	0
4	–100	60	1.6	–5
5	300	80	4.3	–10
6	1100	85	4.3	–10
7	2500	100	4.2	–15

Table 2. Percent errors of the estimates with one minimum variance iteration.

Peak No.	*Frequency* (Hz)	*Line Width* (Hz)	*Amplitude* (Arbitrary Units)	*Phase* (Degrees)
1	0.00	6.17	3.41	2.84
2	0.01	3.29	0.98	#
3	0.05	3.83	2.41	#
4	0.58	2.82	0.33	14.49
5	0.05	0.57	0.17	1.43
6	0.00	1.28	0.52	2.38
7	0.01	0.59	0.41	1.21

Since the true value is zero, the percent error cannot be computed due to division by zero.

EXPERIMENTAL

All NMR experiments were carried out using a JEOL 400 MHz Lambda spectrometer (9.4 tesla B_0 field).

The sample used in testing the linear prediction calculations contained 3.8 mg of glucose-1-phosphate (G1P) and 47.8 mg of adenosine tri-phosphate (ATP), dissolved in 10 mL of solvent, which contained water and 1 mL of deuterated water (D_2O) for field/frequency lock.

The linear prediction calculations were performed under Matlab [14] version 5.3 running on a 400 MHz Pentium II PC with 256 MB RAM.

RESULTS AND DISCUSSION

Simulations with noise-free FID. To test the accuracy of the backward SVD algorithms, these were applied to simulated FID data. A set of seven signals (adapted from those used by Uike *et al.* [15] with various frequencies, line widths, amplitudes and phases were added together to form a noise-free FID (corresponding to the noiseless case). To this FID, normally distributed (gaussian) noise sequences with variance 0.1 were added and three different noisy FIDs were made, being careful to set the seed value for each random number noise sequence uniquely to avoid any correlation between the noise sequences. The following formula was used to compute the signal to noise ratio:

$$SNR = 10 \log \frac{A^2}{\sigma^2} \qquad (12)$$

The data, composed of 1024 points sampled at a rate of 10240 Hz, were truncated to 128 points. It was then subjected to 0, 1, 3, 20, and 100 iterations of the minimum-variance regularization method, followed by the backward LP algorithm and a subsequent matrix inversion. The results for the four parameters for each of the three sequences were tabulated, and statistics were generated from the three sequences (mean,

standard deviation, and residuals or differences from the actual value). The results show that the noiseless FID, truncated to N = 128 points, gave estimates that were essentially perfect. It should be noted that there were only seven non-zero singular values for the noiseless case, and thus it is trivial to know how many singular values ought to be retained in the matrix inversion procedure. When noise is introduced, all the singular values will be non-zero, and an educated guess as to how many singular values to retain has to be made. SVD-based LP relies on the fact that the signal-related singular values can be distinguished from those only related to noise [4]. By plotting the singular values versus their index, one can estimate the number of signal components. Usually, this is equal to the number of the singular values before a plateau in the graph.

Signal enhancement of simulated noisy data. The MV signal enhancement technique was applied to the simulated noisy data above to see if indeed an improvement of the estimated parameters could be made. The effect of the number of iterations was also studied. Backward linear prediction based on SVD was followed by an n-number of minimum variance iterations before final extraction of parameters, where n was 0, 1, 3, 20, and 100.

It was found that using only one to three iterations can improve the estimated parameters; in this case, the smallest error is found for that of a single iteration. In fact, using a large number of iterations harms the accuracy of the estimates—but this is fortunate since fewer iterations means less computation time. The explanation for this behavior is that the iterated Cadzow (and thus also the minimum variance) procedure does not converge to the correct value: it yields a Hankel matrix of rank p, but not necessarily the one closest to the original noisy input [5]. The percent error and standard deviation, respectively, of the estimates for the case of a single iteration of minimum variance are tabulated in Table 2 and Table 3.

Looking at the percent error of the line width estimates, it can be seen that the largest error is a little over 6% for the signal component with the lowest signal to noise ratio (SNR). For the signal component with the highest SNR, the percent error is only about 0.6%. The standard deviations represent the precision of the estimates and show similar behavior with SNR, ranging from 0.62 to 3.77 for the estimates of the line widths. Phase estimates show a possibility for a large error such as the estimate for peak number 4 showing 14.5% error, but with reasonable precision. The remaining parameter estimates—frequency and amplitude—show excellent agreement with the actual values. Frequency estimates show excellent accuracy and reasonable precision, while the reverse is true for amplitude estimates. This result is important since the latter two parameters are the ones sought by the NMR spectroscopist.

In summary, it can be said that SVD-based linear prediction yields reasonable estimates of the true value of parameters, even under conditions of noise. If the same results were to apply to real data, such as in typical NMR applications, LP should yield good estimates of the true value.

Actual sample. To test the effectiveness of the estimation procedure on an actual sample, a sample containing 3.8 mg of α-D-glucose-1-phosphate (G1P) and 47.8 mg of adenosine 5'-triphosphate (ATP), dissolved in 10 mL of 10% D_2O in water. ^{31}P data were obtained using the modified DEFT pulse sequence with the following parameters: pulse angle=90°, 2K points, 1024 scans, acquisition time=102.4 ms, PD = 1 s. The standard single pulse ^{31}P data were obtained using the following parameters: pulse angle = 73°, 16K points, zero filled to 32K, 1000 scans, acquisition time=814.28 ms, PD = 60 s. The pulse delay was set based on a previously determined T_1 of 12 s for the ^{31}P nuclei in the sample. The DEFT experiment took only 45 min. In comparison, the standard ^{31}P NMR experiment took 17 h.

The DEFT data were subjected to the backward LP algorithm with M=N/5 (backsvd2) and inverted using 12 retained singular values (there were ten significant singular values found). The total number of flops was 20 gigaflops. There were ten

Table 3. Standard deviations of the estimates with one minimum variance iteration.

Peak No.	*Frequency* (Hz)	*Line Width* (Hz)	*Amplitude* (Arbitrary Units)	*Phase* (Degrees)
1	1.86	3.77	0.04	0.74
2	1.36	1.83	0.02	0.65
3	1.50	1.36	0.03	1.32
4	0.70	3.51	0.07	0.38
5	0.78	1.84	0.08	0.88
6	0.71	1.26	0.06	0.36
7	0.47	0.62	0.04	0.04

Table 4. Results of estimation, no minimum variance iteration.

Signal No.	*Frequency* (Hz)	*Line Width* (Hz)	*Amplitude* (Arbitrary Units)	*Phase* (Degrees)
1	−1935.03	14.5959	1382709	51.7819
2	−1913.82	3.8416	1005766	86.8037
3	−1894.69	19.4978	2175517	93.464
4	−22.145	10.3638	2353005	63.0537
5	−0.96207	9.9944	2289850	76.0832
6	70.5352	7.2645	1506915	67.6806
7	91.3563	11.0616	2204153	83.0636
8*	153.8425	5.8533	76944.43	169.7414
9*	189.0076	3.0749	40547.15	-169.535
10	1623.518	0.42619	101308.9	63.826

* Spurious peaks

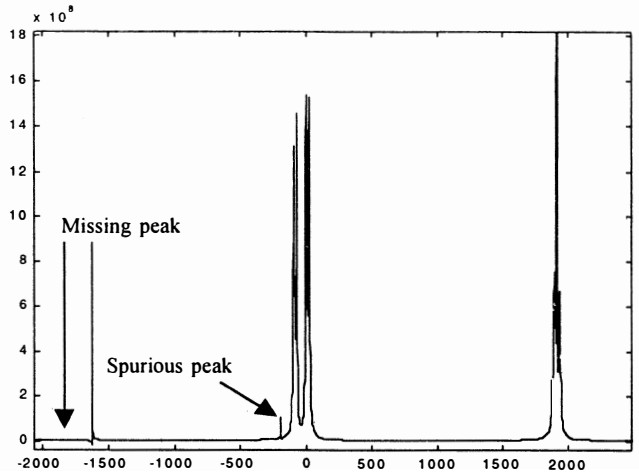

Fig. 5. The generated spectrum from modified DEFT truncated acquisition processed using 3 minimum variance iterations. The positions of missing and spurious peaks are indicated.

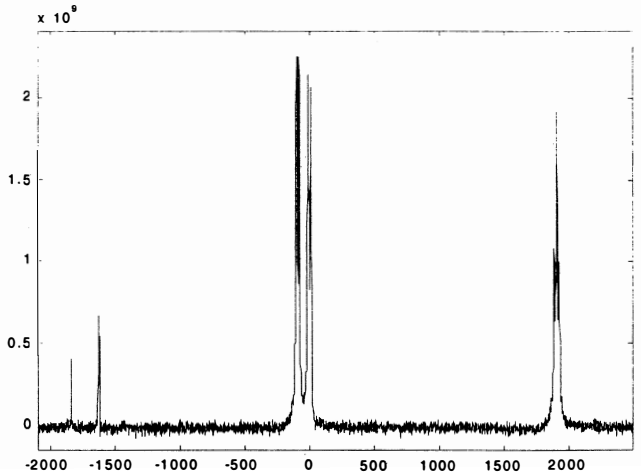

Fig. 6. ^{31}P spectrum obtained from conventional acquisition and Fourier transformation.

Table 5. Results of estimation of with three minimum variance iterations.

Signal No.	*Frequency* (Hz)	*Line Width* (Hz)	*Amplitude* (Arbitrary Units)	*Phase* (Degrees)
1	-1935.11	14.3651	1374321	51.5082
2	-1913.82	3.7755	1002212	86.9585
3	-1894.71	19.2601	2169303	93.4834
4	-22.2058	10.2835	2325619	62.6493
5	-0.86698	10.0972	2304687	77.1489
6	70.7288	6.9381	1467266	70.41
7	91.1667	11.6511	2319730	81.7949
8*	193.6096	0.60539	22913.36	-166.241
9	1623.714	0.46095	101698	65.5117

*. Spurious peak

peaks found, although comparison with the regular NMR experiment showed that two small peaks were spurious, or false, peaks. Thus only eight peaks of the expected 12 peaks were recorded. Table 4 summarizes the results.

Minimum variance iterations were also carried out. After three iterations, the spurious peaks were reduced to one. However, not all of the peaks were found. Table 5 summarizes the results. Figure 5 shows the generated spectrum from modified DEFT truncated acquisition while Fig. 6 shows the conventional FT spectrum.

Uike *et al.* [14] also reported failure to detect peaks using a similar LP-SVD method, but reported that another method (modified total least squares or TLS) retrieved all peaks when applied to the same data. The use of oversampling (increasing the number of points for the same acquisition time) to increase identification power of LP, as well as accuracy and precision of the estimates, has been reported [16]. Looking for a robust and accurate approach is an area for further investigation.

CONCLUSION

It was shown that is possible to obtain NMR spectroscopic data in a truncated fashion much quicker than the conventional pulse-and-acquire methods. The quicker method is a modification of the DEFT method. The study confirms the results of Carlotti *et al.* [17] which also recommended DEFT for such cases but did not use LP for data analysis. They found that a significant improvement in signal-to-noise can be achieved provided the ratio τ/T_2 is made as small as possible. This suggests that this technique would be most useful for nuclei with long relaxation times.

The LP method is a useful method for processing truncated data provided its limitations are taken into account. Unlike FT, truncation of data does not present a problem. All of the spectral parameters may be obtained directly in tabular form. The accuracy and precision of the estimates are representative of reasonably good analytical technique. This is especially true of frequency and line width, which are important parameters in NMR spectroscopy. Although spurious peaks may appear, these may be reduced by regularization methods such as the minimum variance method.

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