Obtaining Proton Chemical Shifts and Multiplets from Several 1D NMR Signals

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A broad-band proton-decoupled proton NMR spectrum, in which all of the proton multiplets collapse to sharp singlets, has been pursued since the early days of NMR. Two-dimensional (2D) methods, like a skew 45° projection of an absolute-value (AV) *J*-spectrum[1] or a constant-time (CT) experiment[2,3] are hampered by poor resolution because of phase-twist line shapes. Furthermore, high resolution is required in the F_1 dimension, lengthening experiment time and reducing sensitivity.[4] The *J*-spectrum has thus fallen into disuse; the 45° projection is unimpressive, and the 2D spectrum is of only marginal help for assignment. Heavy digital filtering by a "pseudo-echo"[5] improves AV line shapes but introduces intensity distortions and sensitivity loss. Frequency-domain fitting routines[6] require a high-resolution data matrix of lines with similar widths and do not necessarily converge.

We present a promising new way to compute 1D projections directly from a 2D time-domain signal using a new numerical procedure, a 2D extension[7] of the filter diagonalization method (FDM).[8,9] The result is a decoupled-proton spectrum and, for each decoupled signal, an estimate of the corresponding multiplet. Remarkably, no 2D spectrum is ever constructed: problems with 2D line shapes and the time-frequency uncertainty principle are thereby avoided. Good results can be obtained with a few as four t_1 increments, Figure 1.

FDM, in the 2D case, amounts to fitting a discrete uniformly sampled 2D time signal $c(n_1,n_2)$ with $0 < n_1 < N_1 - 1$ and $0 < n_2 < N_2 - 1$ to the form

$$c(n_1,n_2) = \sum_k d_k \exp(-in_1\tau_1\omega_{1k}) \exp(-in_2\tau_2\omega_{2k}) \quad (1)$$

where d_k ω_{1k}, ω_{2k}, are a set of unknown complex-valued spectral parameters characterizing amplitude, phase, position, and width. Using these parameters, an "ersatz" absorption-mode $\vec{p}$-projection is given by

$$A_{\vec{p}}(\omega) = -\sum_k \mathrm{Im}\left\{\frac{d_k}{\omega - \omega_{\vec{p}k} + i\gamma}\right\} \quad (2)$$

where $\vec{p} = (p_1,p_2)$ and $\omega_{\vec{p}k} = \dfrac{\tau_1}{\tau_2}p_1\omega_{1k} + p_2\omega_{2k}$. The 45°

projection of a 2D *J*-spectrum is obtained with $\vec{p} = (-\dfrac{\tau_2}{\tau_1}, 1)$

and $\omega_{\vec{p}k} = \omega_{2k} - \omega_{1k}$; the (0,1) projection is the conventional

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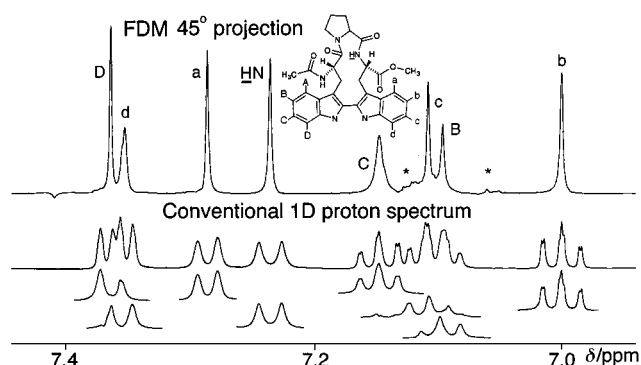(9) Mandelshtam, V. A.; Taylor, H. S. *J. Chem. Phys.* **1997**, *107*, 6756.

Figure 1. The absorption-mode FDM 45° projection (upper trace), the conventional 1D proton spectrum (second trace), and estimates of all eight proton multiplets from the aromatic region of a ditryptophan tripeptide, Ac-Trp-Pro-Trp-OMe. The two tryptophans have been cross-linked, enforcing an inverse γ turn conformation.[10] About 10 mg of material was dissolved in 1 mL of DMSO-d_6. The spectral widths for the 2D *J*-spectrum were $SW_1 = 80$ Hz and $SW_2 = 8$ kHz. The purely phase-modulated 2D time signal with four FIDs each of 12000 complex points, $N_1 \times N_2 = 4 \times 12000$ was processed with 2D FDM. Small strong coupling artifacts are noticeable midway between protons B and C and b and c. Proton A, $\delta = 7.75$ ppm, is outside the window shown.

1D proton spectrum. The smoothing parameter $\gamma > 0$ is used to broaden the lines as *both* frequency *and* width are subtracted in $\omega_{\vec{p}k}$ leading, as in the CT experiment, to narrow spikes that are inconvenient for presentation to the eye.

For signals well-represented by the plane-wave form of eq 1, resolution in the ersatz spectrum can be extremely high even with very few t_1 increments. This property of 2D FDM follows from informational considerations that are entirely different than the FT uncertainty principle. The utility of single−multiplet presentations is obvious; the steps required to obtain them will now be summarized. The signal $c(n_1,n_2)$ is written as the time autocorrelation function of a fictitious quantum dynamical system[8]

$$c(n_1,n_2) = \left(\Phi_0\middle|\exp(-in_1\tau_1\hat{\Omega}_1)\exp(-in_2\tau_2\hat{\Omega}_2)\Phi_0\right) \quad (3)$$

with two commuting complex symmetric "evolution operators" $\hat{U}_1 = \exp(-i\tau_1\hat{\Omega}_1)$ and $\hat{U}_2 = \exp(-i\tau_2\hat{\Omega}_2)$ defined implicitly by their eigenvalues $u_{1k} = \exp(-i\,t_1\omega_{1k})$, $u_{2k} = \exp(-i\,t_2\omega_{2k})$, and the overlap integrals $d_k = (\Phi_0\,|Y_k)\,(Y_k\,|\Phi_0)$ between the eigenfunctions Y_k and the "initial state" Φ_0 that belong to an abstract space. Diagonalizing $\hat{U}_1$, $\hat{U}_2$ is equivalent to inverting eq 1 and can be used to construct an entire 2D FDM spectrum.[7,10] FDM is the key advance that makes such diagonalizations feasible.

More efficient, if only the $\vec{p}$-projection is of interest, is to use FDM to diagonalize the operator

$$\hat{U}_{\vec{p}} = \exp[-i(p_1\tau_1\hat{\Omega}_1 + p_2\tau_2\hat{\Omega}_2)] \quad (4)$$

with the eigenvalues $u_{\vec{p}k} = \exp(-i\tau_2\omega_{\vec{p}k})$. The number of peaks for the "chemical shift operator" corresponding to the 45° projection is reduced compared to the conventional 1D spectrum, so fewer t_1 increments are needed to get a good fit and extract the shifts with high accuracy.

Computationally, for $\vec{p} = (-\dfrac{\tau_2}{\tau_1}, 1)$, (i) choose a basis Ψ_j over

a spectral range of interest and construct three small complex symmetric matrixes $\mathbf{U}_0$, $\mathbf{U}_1$, $\mathbf{U}_2$, corresponding to the matrix

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representations of, respectively, l, $\hat{U}_1$, $\hat{U}_2$ in the basis Ψ_j. The formulas for these matrix elements in terms only of $c(n_1,n_2)$ have been published.[7] (ii) Assuming that $\tau_1 > \tau_2$ ($SW_1 < SW_2$) as is the case in *J*-spectroscopy, solve the generalized eigenvalue problem (GEP)

$$\mathbf{U}_1\mathbf{B}_k = u_{1k}\mathbf{U}_0\mathbf{B}_k \qquad (5)$$

with $u_{1k} = \exp(-i\tau_1\omega_{1k})$. Normalize the column eigenvectors $\mathbf{B}_k$ by

$$\mathbf{B}_k^T\mathbf{U}_0\mathbf{B}_k = 1 \qquad (6)$$

(iii) Scale the $\mathbf{U}_1$ matrix using

$$\tilde{\mathbf{U}}_1 = \sum_k (u_{1k})^{(\tau_2/\tau_1)}\mathbf{U}_0\mathbf{B}_k^T\mathbf{U}_0 \qquad (7)$$

(iv) Solve another GEP

$$\mathbf{U}_2\tilde{\mathbf{B}}_k = u_{\bar{p}k}\tilde{\mathbf{U}}_1\tilde{\mathbf{B}}_k$$

normalizing the $\tilde{\mathbf{B}}_k$ with respect to $\mathbf{U}_0$ as in eq 6 and use these $u_{\bar{p}k}$ $= \exp(-i\tau_2\omega_{\bar{p}k})$ and $\tilde{\mathbf{B}}_k$ to obtain $\omega_{\bar{p}k}$ and d_k for input into eq 2. (v) Choose the next spectral range.

The outlined procedure is numerically stable and fast, since only small linear algebraic problems have to be solved. Steps (iii) and (iv) distinguish the present version of 2D-FDM as different from that in the literature.[7,10] An example of the calculation is shown in the upper trace of Figure 1. Proton shifts are resolved even with only *four* t_1 increments.

Clearly, by solving

$$\mathbf{U}_2\mathbf{B}_k = u_{2k}\mathbf{U}_0\mathbf{B}_k \qquad (9)$$

the conventional 1D spectrum (or the (0,1)-projection) is obtained, indistinguishable from the second trace of Figure 1. Some multiplets in this spectrum overlap, making it difficult to discern their structure. However, using FDM we can separate these multiplets, even when the peaks from different multiplets are quite broad and overlapping, and display them one at a time. Namely, each peak of the well resolved 45° projection is a superposition of several contributions corresponding to a particular single multiplet. The eigenvectors of these contributions form the single-multiplet subspace in which we can simply evaluate the conventional (0,1)-projection, thus obtaining estimates of each single multiplet, as displayed in Figure 1.

FDM projections are a powerful addition to the data processing arsenal for multidimensional NMR. Intrinsic limitations of *J*-spectroscopy, like strong coupling, are still in effect, and some spectra will not be resolved even in the 45° projection. However, the method outlined here is quite general and can also produce higher-dimensional decoupled spectra of stunning clarity. We will outline these developments soon.