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Communication

The single basis filter diagonalization method: A rapid multidimensional data processing scheme

Geoffrey S. Armstrong*, Brad Bendiak

Department of Cell and Developmental Biology and Biomolecular Structure Program, University of Colorado Health Sciences Center, Mail Stop 8108, P.O. Box 6511, Aurora, CO 80045, USA

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Abstract

A new way to apply the filter diagonalization method (FDM) that results in a large increase in the speed of calculation of multidimensional NMR spectra is presented. The speed increase is accompanied by slight differences in spectral lineshapes, although frequency estimates remain essentially identical. For contoured spectra, the method does not result in appreciable differences from the full FDM calculation. Optimal parameter sets for an FDM calculation can be estimated far more rapidly, which makes the FDM more straightforward to employ in practice. The performance of the method versus the full FDM was investigated for both model and experimental signals. The effect of noise on the method was also studied.

Keywords: Filter diagonalization method; Multidimensional NMR; Single basis

1. Introduction

A flurry of fast multidimensional techniques have emerged recently [1], fueled by the need, with many molecules, for high-dimensional NMR spectroscopy. Often, however, these methods require that the pulse sequence be altered in such a way as to preclude standard processing techniques. This can make it difficult to directly evaluate the performance of the method as compared to conventional methods such as the Fourier transform (FT) or mirror-image linear prediction (MI-LP). The filter diagonalization method (FDM) [2–5] is a generally applicable data processing scheme that requires no adaptation of NMR pulse sequences to achieve high-resolution spectral estimates from short multidimensional data sets. The computational time required for the FDM, however, can be rather cumbersome, especially when the calculation needs to be performed several times to optimize the parameters of the method. This can make its application somewhat time consuming, especially for an inexperienced user.

The FDM is a powerful method for the generation of high-resolution spectral estimates from data sets having far fewer increments in the indirect dimensions [6–9]. For multidimensional NMR, this is particularly important as experimental time constraints limit the number of points that can be collected. For methods that process the data orthogonally (by orthogonal we mean that each dimension is processed independently and sequentially from each other, as is the case for FT or MI-LP) this places an upper limit on the resolution that can be achieved in the indirectly observed dimensions. For the FDM, which uses all the data points from all FIDs collectively, the resolving power is limited by the total product of data points in all dimensions, as long as at

* Corresponding author. Fax: +1 303 724 3420.
E-mail address: Geoffrey.Armstrong@UCHSC.edu (G.S. Armstrong).

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least two points are available in each dimension. Hence, for multidimensional cases, while the number of points in each indirect dimension may be small, their product is very large. This improves the resolving capabilities of the FDM relative to orthogonal processing methods. It also leads to a rather intensive calculation, which may take several hours to complete for large data sets. This, combined with the fact that the FDM calculation usually needs to be applied several times [4,5] to arrive at an optimal parameter set, can make using the FDM a little laborious for the uninitiated. In this communication a new way to apply the FDM is presented. This technique, called the single basis FDM, affords a huge increase in the speed of the calculation (from hours to seconds) with only a small sacrifice in the quality of the resulting spectral estimate. This allows the optimal parameter set for the FDM to be achieved very quickly, setting the stage for the large basis calculation to be done confidently. The performance of the new method on noiseless and noisy model signals, as well as on a challenging experimental case, has been investigated in comparison with the "traditional" large basis FDM.

2. Theory

The derivation of the single basis FDM is presented in 2D, but it can easily be generalized to multiple dimensions [3]. The method is based on the assumption that a uniformly sampled signal ($c(n_1,n_2) := c(n_1\tau_1, n_2\tau_2)$, ($n_1 = 0,\ldots, N_1-1$, $n_2 = 0,\ldots, N_2-1$)) is composed of a finite number of sinusoids with frequencies ω_{1k} and ω_{2k}, and amplitudes d_k. This signal can be described completely by the commutative evolution operators $\hat{U}_1$ and $\hat{U}_2$, acting upon an initial state $|\Phi\rangle$.

$$\begin{aligned} c(n_1,n_2) &= \sum_{k=1}^{K} d_k \mathrm{e}^{-\mathrm{i}n_1\tau_1\omega_{1k}}\mathrm{e}^{-\mathrm{i}n_2\tau_2\omega_{2k}} \\ &= (\Phi|\hat{U}_1^{n_1}\hat{U}_2^{n_2}|\Phi) := (\Phi_{00}|\Phi_{n_1n_2}). \end{aligned} \tag{1}$$

Expressing $\hat{U}_1$ and $\hat{U}_2$ in terms of their eigenvalues (u_{1k}, u_{2k}) and eigenvectors ($|\Upsilon_k\rangle$)

$$\sum_{k=1}^{K}(\Phi|\Upsilon_k)u_{1k}^{n_1}u_{2k}^{n_2}(\Upsilon_k|\Phi) = \sum_{k=1}^{K} d_k \mathrm{e}^{-\mathrm{i}n_1\tau_1\omega_{1k}}\mathrm{e}^{-\mathrm{i}n_2\tau_2\omega_{2k}}, \tag{2}$$

it becomes evident that the frequencies and amplitudes may be obtained:

$$\begin{aligned} \omega_{1k} &= \mathrm{i}\ln(u_{1k})/\tau_1, \\ \omega_{2k} &= \mathrm{i}\ln(u_{2k})/\tau_2, \\ d_k &= \sqrt{(\Phi|\Upsilon_k)}. \end{aligned} \tag{3}$$

Following Eq. (1), the matrices that describe the operators $\hat{U}_1$ and $\hat{U}_2$ can be established in terms of the signal:

$$\begin{aligned} [\mathbf{U}_0]_{l_1l_2,m_1m_2} &:= (\Phi_{l_1l_2}|\Phi_{m_1m_2}) = c(l_1+m_1, l_2+m_2), \\ [\mathbf{U}_1]_{l_1l_2,m_1m_2} &:= (\Phi_{l_1l_2}|\hat{U}_1|\Phi_{m_1m_2}) = c(l_1+m_1+1, l_2+m_2), \\ [\mathbf{U}_2]_{l_1l_2,m_1m_2} &:= (\Phi_{l_1l_2}|\hat{U}_2|\Phi_{m_1m_2}) = c(l_1+m_1, l_2+m_2+1), \end{aligned} \tag{4}$$

where l_1, $m_1 = 1,\ldots,N_1/2-1$ and l_2, $m_2 = 1,\ldots, N_2/2-1$. These matrices can then be diagonalized using a generalized eigenvalue algorithm to obtain the corresponding eigenvalues and eigenvectors:

$$\begin{aligned} \mathbf{U}_1\mathbf{B}_k &= u_{1k}\mathbf{U}_0\mathbf{B}_k, \\ \mathbf{U}_2\mathbf{B}_k &= u_{2k}\mathbf{U}_0\mathbf{B}_k. \end{aligned} \tag{5}$$

In practice, however, the result of such a calculation is ill-conditioned, resulting in spectral artifacts that are highly dependent on the parameters of the calculation. This requires the solution of a modified eigenvalue problem [4]:

$$\begin{aligned} \mathbf{U}_0^{\dagger}\mathbf{U}_1\mathbf{B}_k &= u_{1k}(\mathbf{U}_0^{\dagger}\mathbf{U}_0 + q^2)\mathbf{B}_k, \\ \mathbf{U}_0^{\dagger}\mathbf{U}_2\mathbf{B}_k &= u_{2k}(\mathbf{U}_0^{\dagger}\mathbf{U}_0 + q^2)\mathbf{B}_k. \end{aligned} \tag{6}$$

This leads to one of the chief adjustable parameters of the FDM (q^2, the regularization parameter). Note that these matrices have dimensions $N_1N_2/4 \times N_1N_2/4$, and may therefore require solution of a very large eigenvalue problem. This can be numerically very expensive, so it is useful to apply a "filter" to the matrix before diagonalization. This is done by casting the problem into the Fourier basis:

$$\begin{aligned} [\mathbf{U}_0]_{IJ} &= \sum_{l_1,m_1=0}^{N_1/2-1}\sum_{l_2,m_2=0}^{N_2/2-1} \mathrm{e}^{-\mathrm{i}\tau_1(l_1\varphi_{i_1}+m_1\varphi_{j_1})}\mathrm{e}^{-\mathrm{i}\tau_2(l_2\varphi_{i_2}+m_2\varphi_{j_2})} \\ &\quad\times c(l_1+m_1, l_2+m_2), \\ [\mathbf{U}_1]_{IJ} &= \sum_{l_1,m_1=0}^{N_1/2-1}\sum_{l_2,m_2=0}^{N_2/2-1} \mathrm{e}^{-\mathrm{i}\tau_1(l_1\varphi_{i_1}+m_1\varphi_{j_1})}\mathrm{e}^{-\mathrm{i}\tau_2(l_2\varphi_{i_2}+m_2\varphi_{j_2})} \\ &\quad\times c(l_1+m_1+1, l_2+m_2), \\ [\mathbf{U}_2]_{IJ} &= \sum_{l_1,m_1=0}^{N_1/2-1}\sum_{l_2,m_2=0}^{N_2/2-1} \mathrm{e}^{-\mathrm{i}\tau_1(l_1\varphi_{i_1}+m_1\varphi_{j_1})}\mathrm{e}^{-\mathrm{i}\tau_2(l_2\varphi_{i_2}+m_2\varphi_{j_2})} \\ &\quad\times c(l_1+m_1, l_2+m_2+1). \end{aligned} \tag{7}$$

The frequencies φ_{i_1} and φ_{i_2} correspond to the frequency points of the discrete Fourier transform, and are spread uniformly over the Nyquist range ($\omega_{1\min} < \varphi_{i_1} < \omega_{1\max}$). There are half as many frequencies as there are time-domain points in each dimension ($I = 1,\ldots,i_1 + (i_2-1)K_1,\ldots, K_1K_2$, where $K_1K_2 = N_1N_2/4$), which preserves the overall dimensionality of the matrices. But, the form of the Fourier basis localizes the large matrix elements along the diagonal, allowing the generalized eigenvalue problem to be solved in block diagonal fashion, with each block corresponding to a small frequency region of the 2D spectrum. In practice, values for $K_{1\mathrm{win}}$ and $K_{2\mathrm{win}}$ are often chosen such that $K_{\mathrm{win}} := K_{1\mathrm{win}}K_{2\mathrm{win}}$

is in the range of 100–1000. Once K_{win} is defined, the calculation is split into frequency windows, each encompassing K_{win} basis functions and overlapping the previous window by half. This results in a list of frequencies and amplitudes for each window in the calculation. The presence of noise and other factors that affect the Lorentzian behavior of the time-domain data, lead to numerous entries in the frequency list for each peak. Therefore, the list of frequencies does not correspond one-to-one to the list of true spectral peaks. For this reason, it is more effective to generate the spectrum from the list of FDM frequencies than to analyze the list directly. The spectrum is calculated using a Gaussian lineshape [6], with a smoothing parameter (Γ, chosen to be on the order of the natural linewidths of the spectral features) applied to the linewidths. The results from each spectral window are then progressively added to the results from previous windows, weighted according to the extent of overlap of the spectral windows. In our case a sine-bell weighting function is used.

The form of the Fourier basis has interesting implications in certain circumstances. The above derivation was conducted without considering the relative number of points available in each dimension. Suppose that one has a signal in which one of the dimensions has many more points than the other ($N_2 \gg N_1$). In this case, it is possible that no resolution enhancement is necessary in the dimension having many points and the time cost of evaluating the FDM in large windows may be prohibitive. A scheme where the large number of points in the 1D is used more efficiently may be desirable. It would be useful to have this type of algorithm to generate a "rough" spectral estimate quickly, and still be able to compute the full 2D FDM calculation once the parameters have been optimized and key regions identified.

Consider the case where the size of the window in which the FDM is calculated is reduced to include only one frequency basis function in the dimension having a large number of points. In effect the problem has been reduced from diagonalizing a $K_{1win}K_{2win} \times K_{1win}K_{2win}$ matrix to performing the same task with a $K_{1win} \times K_{1win}$ one. The calculation of the matrix elements in Eq. (7) is also simplified, as one of the double Fourier sums may now be evaluated as a single sum:

$$\sum_{l_1,m_1=0}^{N_1/2-1}\sum_{l_2,m_2=0}^{N_2/2-1} e^{-i\tau_1(l_1\varphi_{i_1}+m_1\varphi_{j_1})}e^{-i\tau_2\varphi_2(l_2+m_2)}c(l_1+m_1,l_2+m_2) = \sum_{l_1,m_1=0}^{N_1/2-1}\sum_{l_2=0}^{N_2-2} e^{-i\tau_1(l_1\varphi_{i_1}+m_1\varphi_{j_1})}e^{-i\tau_2\varphi_2 l_2}G_{l_2}c(l_1+m_1,l_2). \quad (8)$$

This sum is related to the FT in the dimension having many points with a triangular weighting function given by $(G_{l_2} = N_2/2 - |N_2/2 - 1 - l_2|)$ applied at the frequency φ_2. If this small calculation is performed at many different frequencies (i.e., many small windows), the effect is similar to applying the FT in the dimension with many points, with FDM estimation in the dimension having only a few increments. However, the FT followed by FDM is not the same as applying the 2D FDM. The fact that the single basis FDM solves two eigenvalue problems, whereas the FT-FDM scheme solves only a single eigenvalue problem, is the essential difference between the two schemes. In the former case, each calculation is performed as a narrow 2D strip, and each window overlaps the previous window, introducing a redundancy into the calculation that can improve the results in certain circumstances. The regularization (q^2) also enables a reproducible spectral estimate. However, the triangular weighting function may introduce some artifacts in the shape of the resulting lines. In principle these may be removed by applying an additional function during the calculation of the matrix elements, but in practice it is easier to apply Gaussian convolution once the spectral estimate has been generated.

3. Results

3.1. Model signal

The single basis FDM was compared with the large basis ("traditional") FDM for several representative cases. It was useful to evaluate the performance of the method on model signals for which the correct results were already known. This illustrates the advantages of the method as well as possible artifacts. The model signal used in these calculations was designed to represent a TOCSY-type experiment where magnetization has been transferred from "nuclei" in the indirect dimension through a correlated spin system. The signal is therefore degenerate in both the direct and indirect dimensions and represents a challenging case for the FDM. The model signal is composed of 1024×16 points, and has spectral widths of 1000 and 200 Hz in the direct and indirect dimensions, respectively. All calculations were performed on an Apple PowerMac G5 desktop computer, with two 2.0 GHz CPUs.

Fig. 1 compares the 2D spectrum and 1D projection obtained via the single basis method and the "traditional" large basis method. The large basis method is usually performed in as few windows as possible, generally employing K_{win} values of up to 1500. With the single basis method, K_{win} values rarely exceed 100, making for a much faster calculation even though there are many windows. In the indirect dimensions, the full basis available for the given signal size was employed for both methods. In Fig. 1, the accuracy of the large basis method (B) is evident, as the exact lineshape of the model signal is reproduced in both the 2D spectrum and the 1D projection, but the computational time is substantial

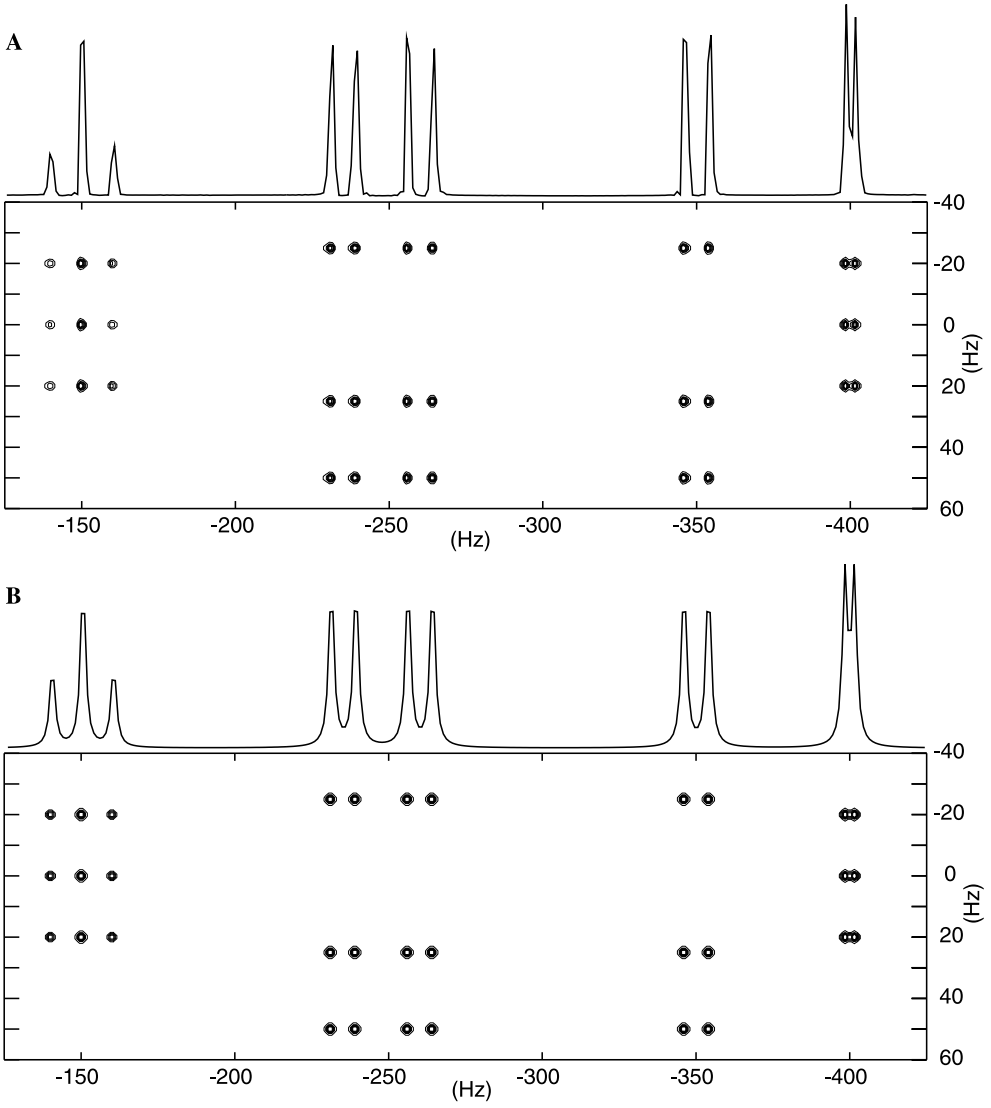

Fig. 1. Performance of the single basis FDM (A) versus the large basis FDM (B) on a representative model signal. While the differences in the 2D spectra are minor, the 1D projections demonstrate the limitation of the single basis method (A) in reproducing the correct lineshapes (B). Note that frequency estimates, however, are essentially identical in both dimensions. The main advantage to the single basis is the relative speed. The large ($K_{win} = 1344$) calculation took 36 min to complete, while the single basis calculation ($K_{win} = 8$) took less than a second. The model signal consisted of 1024×16 points, with spectral widths of 1000 and 200 Hz in the direct and indirect dimensions, respectively.

(36 min). If one were trying to optimize the FDM parameters using this method, each change would take 36 min to complete, which is not efficient. Comparing this to the single basis method (Fig. 1A), the advantages of the new processing scheme become evident. For the 2D spectra, the differences between the two methods are very subtle but the frequency estimates are essentially the same. With a computational time of less than a second for the single basis method, changes to the parameter set can be evaluated very rapidly. Practically, this is much more effective than the long calculation. There are some drawbacks, however. The single basis calculation produces slightly distorted lineshapes in the 1D projection (Fig. 1A). As discussed above, this can be alleviated somewhat by applying Gaussian convolution to the spectrum. If lineshapes that are representative of the signal are required, it would simply be more effective to rapidly find the optimal parameter set using the single basis method and, once a reasonable spectrum is produced, repeat the calculation using large windows (the optimal parameter set does not change appreciably between the single basis and large basis calculation). Therefore, the single basis calculation is well suited to provide a "rough" estimate of the multidimensional spectrum, which may be optimized very quickly.

It is also useful to examine the effect of noise on the performance of the single basis method. A model signal was constructed with similar properties to that already presented, with the addition of random noise to the model FIDs. This results in a data set with fairly low

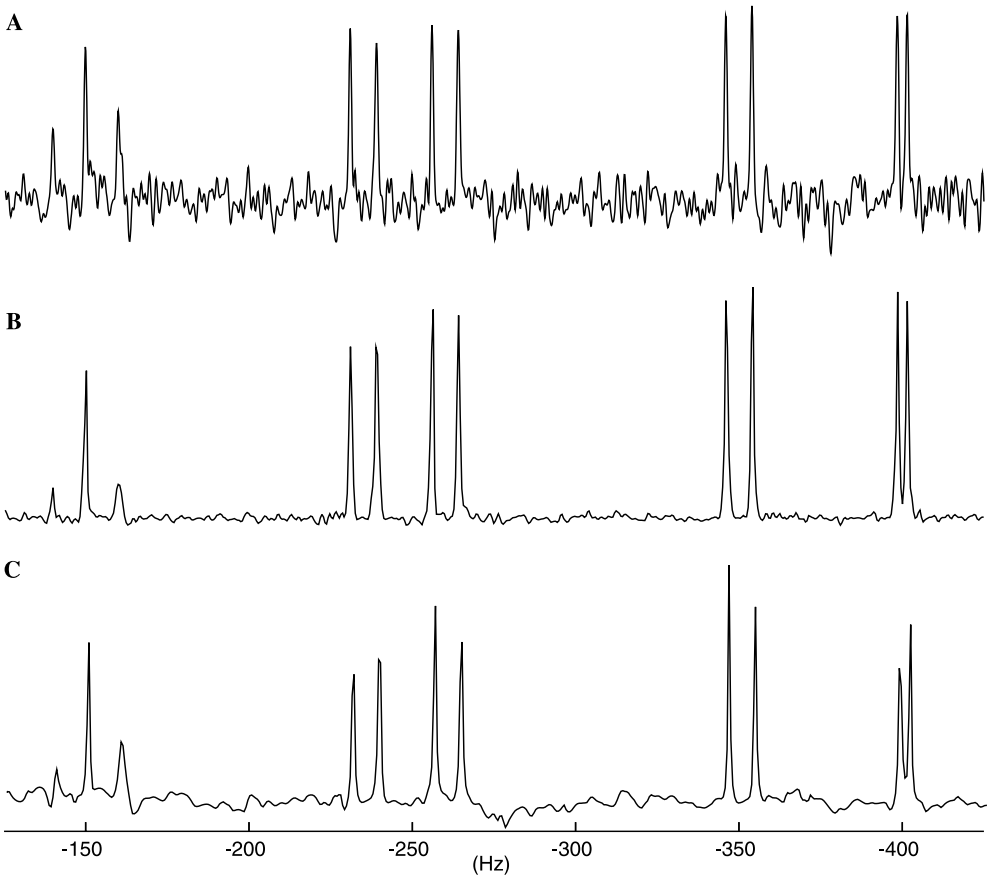

Fig. 2. Effect of noise on the single basis result versus the large basis result. The 1D FT of the first increment of the 2D data (A) is presented to show the level of noise in the signal. The 1D projections produced from the 2D model signal using both a single basis calculation (B) and a large basis calculation (C) are compared. Both the large and single basis methods provide essentially identical frequency estimates, but the single basis method appears to be somewhat more effective in discerning peaks from baseline noise. Any comparison between (A) and (B) would be invalid given that (A) represents a 1D transform of a single FID, whereas (B) represents the projection from a 2D calculation. The 2D model signal consisted of 1024×16 points, with spectral widths of 1000 and 200 Hz in the direct and indirect dimensions respectively. Random noise was added to the model FIDs to produce the data for this calculation.

signal-to-noise, as can be seen from the 1D FT of the first increment of the 2D data (Fig. 2A). The single basis FDM and large basis FDM were then applied to the data. The 1D projections of the 2D data from these calculations are shown in Fig. 2. From these projections it is evident that the single basis FDM (B) is able to distinguish signals quite well with respect to noise, giving a good estimate of the spectral frequencies despite the perturbation.

3.2. Experimental signal

To perform a complete evaluation of the single basis method on experimental data, a challenging case for the FDM was chosen. An experiment was designed to transfer magnetization from a ^{13}C-labeled carbonyl group in a small ^{13}C-acetylated oligosaccharide (α-D-Glc-[1 → 3]-α-D-Glc-[1 → 4]-α-D-Glc-[1 → 3]-α-D-Glc-ol, Sigma N7263 reduced with $NaBH_4$ [9]), through a HEHAHA transfer [9–11] to a correlated proton, and through HOHAHA to all correlated protons in the sugar ring spin-system. Because the heteronuclear TOCSY-type experiment is degenerate in both dimensions (although it is far more degenerate in the proton dimension due to proton coupling) it has traditionally been avoided for FDM processing. Instead non-degenerate HSQC type spectra were preferred. Here, we demonstrate that the FDM may be used for processing heteronuclear TOCSY-type experiments using both the single basis and large basis methods, but the latter, due to the size of signal required in the proton dimension, is inefficient. This 2D data set is constant-time [12] in the indirect dimension, which affords an advantage to the FDM [6–9], but it is not a requirement of the method. The data set is composed of 1024×38 complex points with spectral widths of 1200 and 300 Hz in the proton and carbonyl dimensions, respectively. It was collected using 16 transients on a 500 MHz Varian Unity INOVA spectrometer equipped with a standard triple resonance gradient probe. Phase sensitive data was obtained using TPPI

[13] in the indirect dimension. For the FDM calculations, the smoothing parameter (Γ) was set to 1 Hz in each dimension (the approximate natural linewidths of the peaks). For the single basis method, K_{win} was set to 27 (1 in the proton dimension, and 27 in the carbon dimension, the maximum available over the spectral range processed). For the large basis calculation, K_{win} was set to 702 (26 in the proton dimension, and 27 in the carbon dimension). For both calculations the regularization (q^2) was optimized manually to 1×10^{-3} using an iterative procedure.

The resulting spectral estimates from the two FDM calculations are shown in Fig. 3. As in Fig. 1 the 2D spectra are quite similar for both methods. There are some subtle differences between the single basis method (Fig. 3A) and the large basis method (Fig. 3B), mostly in the crowded regions of the spectrum. The single basis method seems to reveal more structure in these regions than the large basis method, but due to the density of peaks there is more uncertainty to these peaks. It should be noted that to resolve these spectra, the entire data set was used in both FDM calculations. This is a departure from the traditional application of the FDM where the signal is usually truncated in the direct dimension to achieve the best results. The reason that the full signal is required here is the large degeneracy of the signal. Unfortunately, for the large basis calculation, the large number of data points in the proton dimension (1024) results in a very long calculation (1 h 20 min). The single basis calculation, however, generates a reasonable spec-

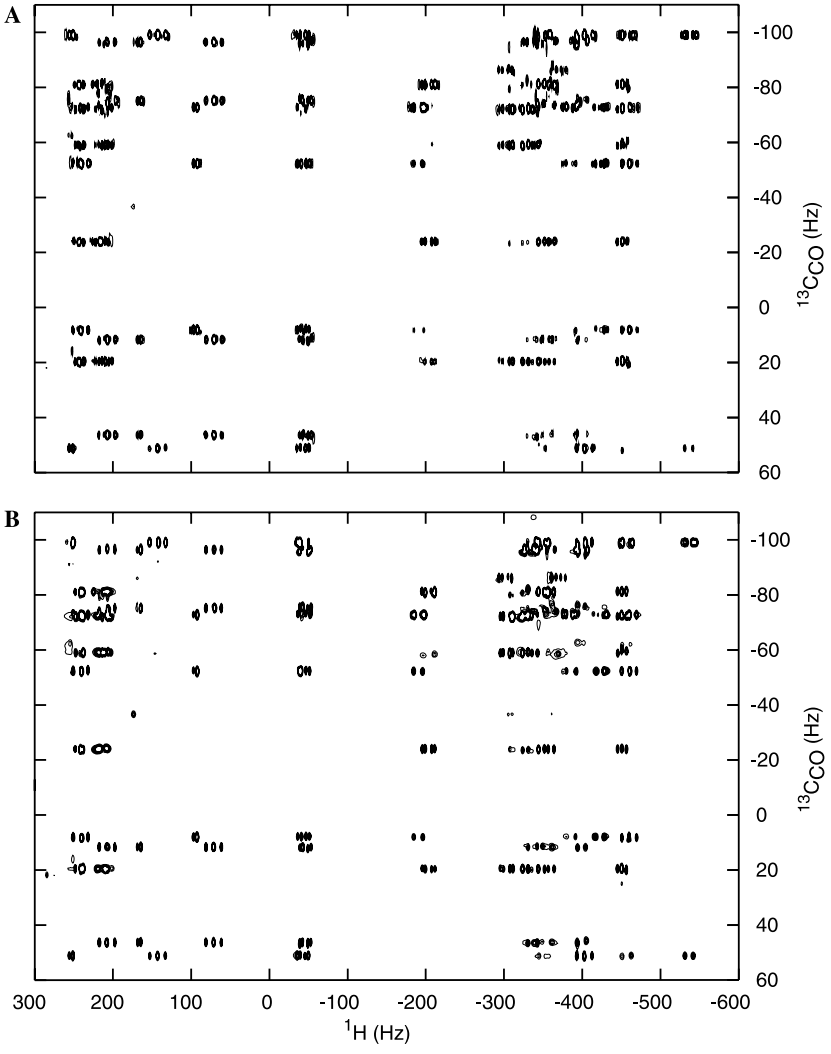

Fig. 3. A comparison of the 2D FDM performed on an experimental data set using the single basis method (A) and the large basis method (B). There are very minor differences between the spectra produced by the two methods, mostly in the crowded regions. The difference in time for the two calculations, however, was substantial: the large basis ($K_{\text{win}} = 702$) calculation took 1 h 20 min to complete, while the single basis calculation ($K_{\text{win}} = 27$) took just 8 s. The same parameter set was used for both calculations. The signal was from a constant-time 2D heteronuclear TOCSY-type experiment, correlating the [^{13}C]carbonyl frequencies to sugar ring proton frequencies in a small ^{13}C-acetylated oligosaccharide (α-D-Glc-[1 → 3]-α-D-Glc-[1 → 4]-α-D-Glc-[1 → 3]-α-D-Glc-ol) [9]. The experiment was carried out with acquisition of 1024 × 38 points and spectral widths of 1200 and 300 Hz in the proton and carbonyl dimensions, respectively.

tral estimate with a short computational time (8 s). This allows the optimization of the FDM parameters (q^2, Γ, K_{win}, see Section 2) to be completed very rapidly and vastly improves the efficiency of the FDM.

Mathematically, the single basis FDM is related to applying a Fourier transform in the large dimension, followed by 1D FDM in the short dimension. However, the two schemes are fundamentally different. Even though the windows are narrow in the large dimension, the single basis FDM still involves the solution of two eigenvalue problems. With an FT-FDM type scheme, however, the FT estimate is solely 1D and the FDM is then applied as a single eigenvalue problem. Fig. 4 illustrates this difference clearly. Because the single basis FDM result is comprised of a large number of narrow 2D windows that overlap each other, it provides a better estimate of frequencies in the indirect dimension than the FT-FDM, which is merely a series of 1D slices. This is especially apparent in crowded regions. There is no advantage to using the FT followed by the FDM. The 2D single basis FDM uses information from all points to estimate frequencies in both dimensions simultaneously, and provides the parameters necessary for a larger basis calculation. FT followed by FDM, however, is incapable of establishing parameters for the full FDM calculation, for any number of dimensions.

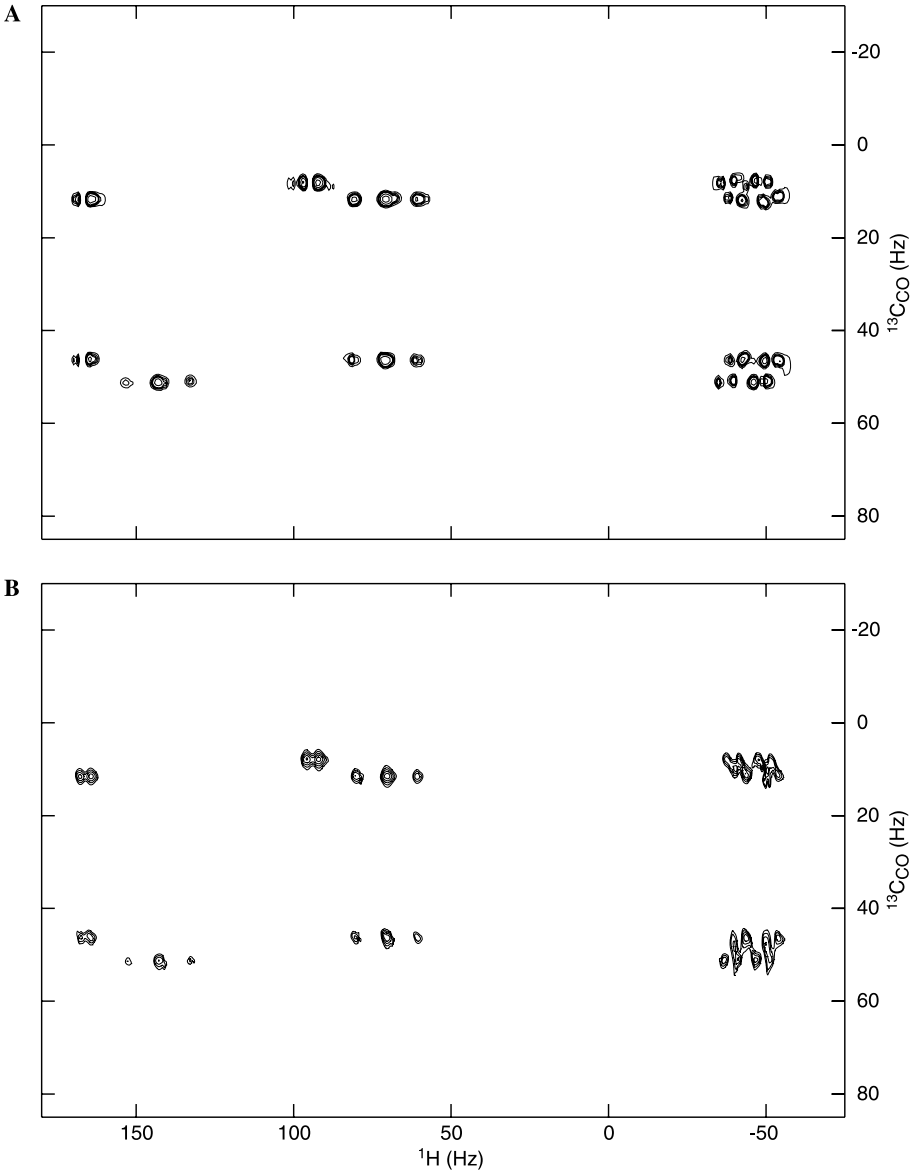

Fig. 4. A comparison of the FDM performed on a zoomed region of the experimental data set presented in Fig. 3, using the single basis method (A) and using a Fourier transform in the ^{1}H dimension followed by a 1D FDM calculation in the [^{13}C]carbonyl dimension (B). Because the single basis FDM is applied as a series of narrow 2D windows that overlap each other, it is able to provide a more precise estimate in the indirect dimension in crowded areas. The peaks generated by FT followed by 1D FDM, are generated from a series of 1D slices and are subject to the same limitations as other sequential 1D methods (FT and LP).

The single basis FDM is an effective method for rapidly (usually several orders of magnitude faster than the large basis method) optimizing the FDM parameter set, and obtaining a reasonable spectral estimate more efficiently than with the "traditional" large basis FDM. It can be accomplished without any modification of the FDM algorithm, merely by specifying that only one basis function be used in each window in the direct dimension. The lineshapes produced by this method may not be as good as those produced by a large basis calculation, but once a parameter set has been established using the single basis method, a large basis calculation can be performed easily to verify the results. The method also appears to be fairly robust with respect to noise. For simplicity, the method has been demonstrated on 2D cases (which will not differ significantly from orthogonal methods such as LP), but the real advantages to the method are realized with multidimensional (3D and higher) applications[9]. In these cases, the larger signal "area" improves the accuracy and resolving power of the FDM in every dimension. It should also be noted that this application of the FDM to a highly degenerate signal demonstrates the flexibility of the FDM in NMR data processing. Where the single basis FDM should prove most useful is in processing of ongoing experimental data sets during acquisition, to make informed decisions as to whether further acquisition of indirect increments is really necessary. The single basis FDM is a powerful adaptation of the "traditional" FDM processing scheme, which improves the efficiency and overall ease of use of the method.

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