

Supporting Information

GFT NMR, a New Approach to Rapidly Obtain Precise High Dimensional NMR Spectral Information

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I. Editing chemical shift multiplets in the frequency domain and relation to time domain editing

When designing a GFT NMR experiment (Figure 1), one first identifies a ‘target’ dimensionality, N_t , at which the majority of the peaks are resolved. The dimensionality N of a given FT NMR spectrum is then adapted to N_t by jointly sampling $K + 1$ chemical shifts ($K = N - N_t$) in a hypercomplex manner, while $N_t - 1$ dimensions are sampled in a conventional fashion. As outlined, this yields $2^K N_t$ D spectra. As an example, we describe here the case of $K = 3$ in the frequency domain (Figures 2,5,6). The indirect evolution time shall be t , and Ω_0 shall be the chemical shift detected in quadrature in each of the N_t D spectra. Ω_1 , Ω_2 and Ω_3 are the three jointly sampled shifts. The phases of the 90° pulses generating transverse magnetization for frequency labeling are chosen so that the transfer amplitudes of the real parts of the $2^K = 8$ spectra, S_{jr} ($j = 1 \dots 8$) are proportional to:

$$\begin{aligned}
 S1r &\propto \cos(\Omega_0 t) \cos(\Omega_1 t) \cos(\Omega_2 t) \cos(\Omega_3 t) \\
 S2r &\propto \cos(\Omega_0 t) \sin(\Omega_1 t) \cos(\Omega_2 t) \cos(\Omega_3 t) \\
 S3r &\propto \cos(\Omega_0 t) \cos(\Omega_1 t) \sin(\Omega_2 t) \cos(\Omega_3 t) \\
 S4r &\propto \cos(\Omega_0 t) \sin(\Omega_1 t) \sin(\Omega_2 t) \cos(\Omega_3 t) \\
 S5r &\propto \cos(\Omega_0 t) \cos(\Omega_1 t) \cos(\Omega_2 t) \sin(\Omega_3 t) \\
 S6r &\propto \cos(\Omega_0 t) \sin(\Omega_1 t) \cos(\Omega_2 t) \sin(\Omega_3 t) \\
 S7r &\propto \cos(\Omega_0 t) \cos(\Omega_1 t) \sin(\Omega_2 t) \sin(\Omega_3 t) \\
 S8r &\propto \cos(\Omega_0 t) \sin(\Omega_1 t) \sin(\Omega_2 t) \sin(\Omega_3 t).
 \end{aligned}$$

FT and, depending on the number n of chemical shift sine modulations the application of a zero-order phase correction of $n \cdot 90^\circ$ yields the frequency domain spectra A1...A8. These spectra encode Ω_1 , Ω_2 and Ω_3 in signal splittings of ‘chemical shift multiplets’ each comprising $2^K = 8$ components. Cosine and sine modulations give rise² to in-phase and anti-phase splittings,

respectively and linear combinations of spectra A1...A8 provide spectra B1...B8 with peaks only at the frequencies of the individual multiplet components. Spectrum B1: $\Omega_0 + \Omega_1 + \Omega_2 + \Omega_3$, B2: $\Omega_0 - \Omega_1 + \Omega_2 + \Omega_3$, B3: $\Omega_0 + \Omega_1 - \Omega_2 + \Omega_3$, B4: $\Omega_0 - \Omega_1 - \Omega_2 + \Omega_3$, B5: $\Omega_0 + \Omega_1 + \Omega_2 - \Omega_3$, B6: $\Omega_0 - \Omega_1 + \Omega_2 - \Omega_3$, B7: $\Omega_0 + \Omega_1 - \Omega_2 - \Omega_3$, and B8: $\Omega_0 - \Omega_1 - \Omega_2 - \Omega_3$ (Figure 2). Spectra B1 to B8 are the ‘basic spectra’, and the selection of chemical shift multiplet components represents the phase-sensitive ‘editing of chemical shift multiplets’.

As described in the manuscript, acquisition of peaks defining the centers of the chemical shift splittings (“central peaks”) is required for unambiguous assignment if two chemical shift quartets, $(\Omega_0, \Omega_1, \Omega_2, \Omega_3)$ and $(\Omega'_0, \Omega'_1, \Omega'_2, \Omega'_3)$, are correlated with degenerate chemical shifts in the other $N_t - 1$ dimensions. Furthermore, degeneracy may occur between two or more shifts of the quartet itself, e.g., one may have that $\Omega_1 = \Omega'_1$. The information of the MD experiment resolving degeneracy in up to $N - 1$ dimensions, is made available if central peaks are detected. First, spectra with transfer amplitudes of the real parts of $2^{K-1} = 4$ spectra, Sjr ($j = 9... 12$), encode Ω_1 and Ω_2 , but no Ω_3 signal splittings,

$$S9r \propto \cos(\Omega_0 t) \cos(\Omega_1 t) \cos(\Omega_2 t)$$

$$S10r \propto \cos(\Omega_0 t) \sin(\Omega_1 t) \cos(\Omega_2 t)$$

$$S11r \propto \cos(\Omega_0 t) \cos(\Omega_1 t) \sin(\Omega_2 t)$$

$$S12r \propto \cos(\Omega_0 t) \sin(\Omega_1 t) \sin(\Omega_2 t)$$

and provide the centers of the Ω_3 -splittings. S9... S12 yield, as described, spectra B9... B12 with peaks at: B9: $\Omega_0 + \Omega_1 + \Omega_2$, B10: $\Omega_0 - \Omega_1 + \Omega_2$, B11: $\Omega_0 + \Omega_1 - \Omega_2$, B12: $\Omega_0 - \Omega_1 - \Omega_2$. Second, spectra with transfer amplitudes for the real parts $2^{K-2} = 2$ spectra, Sjr ($j = 13., 14$), encode only Ω_1 -signal splittings,

$$S13r \propto \cos(\Omega_0 t) \cos(\Omega_1 t)$$

$$S14r \propto \cos(\Omega_0 t) \sin(\Omega_1 t)$$

and provide the centers of the Ω_2 -splittings. $S13$ and $S14$ yield $B13$ and $B14$ comprising peaks at: $B13: \Omega_0 + \Omega_1$, $B14: \Omega_0 - \Omega_1$. Third, $2^{K-3} = 1$ spectrum, $S15$ with a transfer amplitude for the real part encoding no signal splittings,

$$S15r \propto \cos(\Omega_0 t)$$

provides the centers of the Ω_1 -splittings.

As described in ‘‘Theory’’, GFT NMR data acquisition (Figure 1) requires recording of a total of $p = \sum_{k=0}^K 2^k = 2^{K+1} - 1$ N_t D spectra (e.g., $S1\dots S15$ for $K = 3$) with 2^K basic spectra and a total of 2^{K-1} central peak spectra. This set of p data sets is designated an ‘ (N, N_t) D GFT NMR experiment’, and central peaks due to omission of m chemical shifts are denoted to be of m -th order (e.g., $B9\dots B12$, $B13$ and $B14$, and $B15$ represent first, second and third order central peaks, respectively).

For frequency domain editing, the data sets $S1\dots S15$ are Fourier transformed to yield spectra $A1\dots A15$ (Figure 2), and, depending on the number n of chemical shift sine modulations, a zero-order phase correction of $n \cdot 90^\circ$ is applied. Subsequent linear combination yields the edited spectra $B1\dots B15$ (Figures 5,6) according to

$$\hat{B}(K) = \hat{F}(K) \cdot \hat{A}(K) \quad (\text{S1}),$$

where $\hat{F}(K)$ can be readily obtained from $\hat{F}(K-1)$ by tensor product formation:

$$\hat{F}(K) = \hat{F}(K-1) \otimes \hat{F}(1) \quad \text{with} \quad \hat{F}(1) = \begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix} \quad (\text{S2}).$$

One thus obtains for $K = 2$

$$\begin{bmatrix} B9 \\ B10 \\ B11 \\ B12 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \end{bmatrix} \cdot \begin{bmatrix} A9 \\ A10 \\ A11 \\ A12 \end{bmatrix} \quad (\text{S3}),$$

and for $K = 3$

$$\begin{bmatrix} B1 \\ B2 \\ B3 \\ B4 \\ B5 \\ B6 \\ B7 \\ B8 \end{bmatrix} = \begin{bmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 & 1 & -1 & 1 & -1 \\ 1 & 1 & -1 & -1 & 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 & 1 & -1 & -1 & 1 \\ 1 & 1 & 1 & 1 & -1 & -1 & -1 & -1 \\ 1 & -1 & 1 & -1 & -1 & 1 & -1 & 1 \\ 1 & 1 & -1 & -1 & -1 & -1 & 1 & 1 \\ 1 & -1 & -1 & 1 & -1 & 1 & 1 & -1 \end{bmatrix} \cdot \begin{bmatrix} A1 \\ A2 \\ A3 \\ A4 \\ A5 \\ A6 \\ A7 \\ A8 \end{bmatrix} \quad (\text{S4}).$$

For the sake of completeness, the equations for $K = 1$

$$\begin{bmatrix} B13 \\ B14 \end{bmatrix} = \begin{bmatrix} 1 & 1 \\ 1 & -1 \end{bmatrix} \cdot \begin{bmatrix} A13 \\ A14 \end{bmatrix} \quad (\text{S5}),$$

and for $K = 0$

$$B15 = A15 \quad (\text{S6}),$$

are likewise given here.

In this paragraph we provide the relation of the matrices $\hat{G}(K)$ and $\hat{F}(K)$ for time and frequency domain editing of chemical shift multiplets. The matrices $\hat{G}(K)$ and $\hat{F}(K)$ for time and frequency domain editing of chemical shift multiplets (Figures 1,2) are related to each other according to $\hat{G}(K) = \hat{H}(K) \cdot \hat{P}(K)$ with $\hat{H}(K) = \hat{F}(K) \otimes \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$. $\hat{H}(K)$ applies the addition scheme of $\hat{F}(K)$ (eq S2) to both real and imaginary parts. To derive $\hat{P}(K)$, we first define $\hat{P}(1) = \begin{bmatrix} \hat{E} & 0 \\ 0 & \hat{P} \end{bmatrix}$ with $\hat{E} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix}$ and $\hat{P} = \begin{bmatrix} 0 & -1 \\ 1 & 0 \end{bmatrix}$. The matrix \hat{P} maps the real onto the imaginary, and the imaginary onto the negative real part. This corresponds to a zero-order 90° phase correction in the frequency domain. Accordingly, application of \hat{P}^n corresponds to applying the $n \cdot 90^\circ$ zero-order phase correction alluded to above.

$\hat{P}^{(K+1)}$ can be constructed from the $\hat{P}^{(K)}$ according to

$\hat{P}^{(K+1)} = \hat{P}^{(K)} \otimes \begin{bmatrix} \hat{E} & 0 \\ 0 & \hat{P} \end{bmatrix}$. Expansion of the products of \hat{E} and \hat{P} resulting *after* (multiple) tensor product formation yields $\hat{P}^{(K)}$, a matrix with a 2×2 block diagonal form.

For $K = 3, 2,$ and 1 , we thus obtain for $\hat{H}(K)$ and $\hat{P}(K)$

$$\hat{H}(3) = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 \\ 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 \\ 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 \\ 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 \\ 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 \\ 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 & -1 \\ 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 \\ 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 \\ 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & 1 \\ 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 & 1 & 0 & 1 & 0 & -1 \end{bmatrix}, \hat{H}(2) = \begin{bmatrix} 1 & 0 & 1 & 0 & 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 1 & 0 & -1 & 0 & 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 & 0 & 1 & 0 & -1 \\ 1 & 0 & 1 & 0 & -1 & 0 & -1 & 0 \\ 0 & 1 & 0 & 1 & 0 & -1 & 0 & -1 \\ 1 & 0 & -1 & 0 & -1 & 0 & 1 & 0 \\ 0 & 1 & 0 & -1 & 0 & -1 & 0 & 1 \end{bmatrix}, \hat{H}(1) = \begin{bmatrix} 1 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 1 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 \end{bmatrix}$$

and

$$\hat{P}(3) = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \end{bmatrix}, \hat{P}(2) = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \end{bmatrix}, \hat{P}(1) = \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & -1 \\ 0 & 0 & 1 & 0 \end{bmatrix}.$$

II. Options to implement central peak acquisition in GFT NMR

The successive identification of peak pairs belonging to central peaks of *decreasing* order ensures the unambiguous assignment of chemical shift multiplet components (Figures 2,3). Such central peak acquisition can be achieved in three different ways.

Option 1: The p spectra constituting the (N, N_f) D GFT NMR experiment are acquired by successive omission of shift evolution periods from the ND FT NMR radiofrequency pulse scheme affording the basic spectra.

Option 2: Central peaks can be obtained from incomplete polarization transfer.^{6e} The exclusive use of this approach corresponds to their simultaneous acquisition in the 2^K basic spectra.

Option 3: Heteronuclear steady state magnetization can be recruited.^{6g,i} For each order of central peaks obtained in such a way a recording of two subspectra is required so that the number of data sets increases twofold. The exclusive use of this approach would require recording of 4^K different N_t D data sets. These yield after data processing the desired $p = 2^{K+1} - 1$ spectra.

Depending on the particular magnetization transfer pathway and practical constraints one can combine the three options for central peak detection. The second and third option offer that (i) magnetization yielding unwanted “axial peaks” in the conventional experiment is used,^{6g} and that (ii) central peaks are registered even if the resonances in the higher-order spectra are broadened. Overall, $2^K < p < 4^K$ data sets thus need to be recorded to obtain the (N, N_t) D GFT NMR experiment: the resulting ‘sampling demand’ is equivalent to recording an ND FT NMR experiment with only *one* (2^K data sets) to *two* (4^K data sets) complex points in each of the K dimensions.

III. Reductions in minimal measurement times for different options for central peak detection

Option 1: If the p data sets defining the (N, N_t) D experiment are separately recorded, the ratio ε_1 is as defined in eq 2:

$$\varepsilon_1 = \frac{T_m(FT)}{T_m(GFT)} = (2^K / (2^{K+1} - 1)) \cdot \left(\prod_{j=0}^K n_j \right) / \left(\sum_{j=0}^K n_j \right), \quad (3), (S7)$$

Option 2: If the basic spectra are recorded with simultaneous acquisition of central peaks from incomplete INEPT one obtains ε_2 :

$$\varepsilon_2 = \frac{T_m(FT)}{T_m(GFT)} = \left(2^{K+1} \cdot \prod_{j=0}^K n_j \right) / \left(2^K \cdot 2 \cdot \sum_{j=0}^K n_j \right) = \left(\prod_{j=0}^K n_j \right) / \left(\sum_{j=0}^K n_j \right), \quad (S8),$$

i.e., the ratio becomes simply the product of the number of points over the corresponding sum.

Option 3: If heteronuclear magnetization is exclusively used for central peak detection one obtains

ϵ_3 :

$$\epsilon_3 = \frac{T_m(FT)}{T_m(GFT)} = (1/2^K) \cdot \left(\prod_{j=0}^K n_j \right) / \left(\sum_{j=0}^K n_j \right). \quad (\text{S9}).$$

For representative calculations see Table S1.

For the present implementation of (5,2)D HACACONHN, $^{13}\text{C}^\alpha$ steady state magnetization was used to detect the first order central peaks defining the $\Omega_1(^1\text{H}^\alpha)$ splittings (see ‘NMR spectroscopy’ and ‘data processing’), which yields a second set of 8 data sets. Second and third order central peaks defining, respectively, the $\Omega_2(^{13}\text{C}^\alpha)$ and $\Omega_1(^{13}\text{C}')$ splittings were obtained from separate recording of somewhat higher resolved Reduced-dimensionality^{4,6} 2D HNNCO, an experiment derived from the HNNCO scheme³ (two data sets), and 2D [^{15}N , ^1H]-HSQC,² respectively (Figure 5). The use of $^{13}\text{C}^\alpha$ steady-state magnetization for first order central peak detection yields $\epsilon = 250$ (see text) being intermediate between ϵ_1 (eq 3) and ϵ_3 (eq S9).

IV. Data processing of (5,2)D HACACONHN

First order central peaks were derived from ^{13}C steady state magnetization.^{6g,i} This requires a “pre-processing” prior to G -matrix transformation. The data sets $R1\dots R16$ are combined to yield the basic data sets, $S1\dots S8$, and first order central peak data sets, $S9\dots S12$, respectively, according to:

$$\begin{bmatrix} S1 \\ S2 \\ S3 \\ S4 \\ S5 \\ S6 \\ S7 \\ S8 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & -1 \end{bmatrix} \cdot [R1 \dots R8 \ R9 \dots R16]^T \quad (\text{S10}).$$

and

$$\begin{bmatrix} S9 \\ S10 \\ S11 \\ S12 \end{bmatrix} = \begin{bmatrix} 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \end{bmatrix} \cdot [R1 \dots R8 \ R9 \dots R16]^T \quad (\text{S11}).$$

This corresponds to the difference and sum formation for central peak acquisition using $^{13}\text{C}^\alpha$ steady state magnetization.^{6g,i} Transverse ^{13}C magnetization originating from ^{13}C longitudinal steady state magnetization is 90° out of phase relative to transverse ^{13}C magnetization originating from ^1H magnetization.^{6g,i} Hence, $\sin[\Omega(^{13}\text{C}^\alpha)t]$ and $\cos[\Omega(^{13}\text{C}^\alpha)t]$ modulation are ‘swapped’ for central peak acquisition and rows 1 and 2, and 3 and 4 in eq S11 are exchanged compared to eq S10. With $S13$ and $S14$ from 2D HNNCO, and $S15$ from 2D [$^{15}\text{N},^1\text{H}$]-HSQC, the $p = 2^{K+1} - 1 = 15$ data sets constituting the (5,2)D HACACONHN experiment become available. The required phase sensitive editing of the chemical shift multiplet components can be achieved either in the frequency (see Supporting Information) or the time domain (eq 1).

$\hat{G}_c(K)$, as defined by eq 1, can be decomposed into real and imaginary part, $\hat{G}_c(K) = \hat{R}(K) + i \cdot \hat{I}(K)$. With $\hat{R}_j(K)$ and $\hat{I}_j(K)$ denoting the corresponding j -th row vectors one then obtains the real $2^{K+1} \times 2^{K+1}$ square G -matrix, $\hat{G}(K) = [\hat{R}_1 \ \hat{I}_1 \ \hat{R}_2 \ \hat{I}_2 \ \dots \ \hat{R}_{2^k} \ \hat{I}_{2^k}]^T$, which transforms $\hat{S}(K)$

into $\hat{T}(K) = [T_{1r} T_{1i} T_{2r} T_{2i} \dots T_{2^k r} T_{2^k i}]^T$ according to $\hat{T}(K) = \hat{G}(K) \cdot \hat{S}(K)$. For time domain editing of the (5,2)D HACACONHN experiment one thus obtains the following real G -matrices for $K = 3$

(basic spectra):

$$\begin{bmatrix} T_{1r} \\ T_{1i} \\ T_{2r} \\ T_{2i} \\ T_{3r} \\ T_{3i} \\ T_{4r} \\ T_{4i} \\ T_{5r} \\ T_{5i} \\ T_{6r} \\ T_{6i} \\ T_{7r} \\ T_{7i} \\ T_{8r} \\ T_{8i} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & -1 & 0 & -1 & -1 & 0 & 0 & -1 & -1 & 0 & -1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & 1 & 0 & 0 & -1 & 1 & 0 & 0 & -1 & 0 & -1 & -1 & 0 \\ 1 & 0 & 0 & 1 & 0 & -1 & 1 & 0 & 0 & -1 & 1 & 0 & -1 & 0 & 0 & -1 \\ 0 & 1 & -1 & 0 & 1 & 0 & 0 & 1 & 1 & 0 & 0 & 1 & 0 & -1 & 1 & 0 \\ 1 & 0 & 0 & -1 & 0 & 1 & 1 & 0 & 0 & -1 & -1 & 0 & 1 & 0 & 0 & -1 \\ 0 & 1 & 1 & 0 & -1 & 0 & 0 & 1 & 1 & 0 & 0 & -1 & 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 & 0 & 1 & -1 & 0 & 0 & -1 & 1 & 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 & -1 & 0 & 0 & -1 & 1 & 0 & 0 & 1 & 0 & 1 & -1 & 0 \\ 1 & 0 & 0 & -1 & 0 & -1 & -1 & 0 & 0 & 1 & 1 & 0 & 1 & 0 & 0 & -1 \\ 0 & 1 & 1 & 0 & 1 & 0 & 0 & -1 & -1 & 0 & 0 & 1 & 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 & 0 & -1 & 1 & 0 & 0 & 1 & -1 & 0 & 1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 & 1 & 0 & 0 & 1 & -1 & 0 & 0 & -1 & 0 & 1 & -1 & 0 \\ 1 & 0 & 0 & -1 & 0 & 1 & 1 & 0 & 0 & 1 & 1 & 0 & -1 & 0 & 0 & 1 \\ 0 & 1 & 1 & 0 & -1 & 0 & 0 & 1 & -1 & 0 & 0 & 1 & 0 & -1 & -1 & 0 \\ 1 & 0 & 0 & 1 & 0 & 1 & -1 & 0 & 0 & 1 & -1 & 0 & -1 & 0 & 0 & -1 \\ 0 & 1 & -1 & 0 & -1 & 0 & 0 & -1 & -1 & 0 & 0 & -1 & 0 & -1 & 1 & 0 \end{bmatrix} \cdot \begin{bmatrix} S_{1r} \\ S_{1i} \\ S_{2r} \\ S_{2i} \\ S_{3r} \\ S_{3i} \\ S_{4r} \\ S_{4i} \\ S_{5r} \\ S_{5i} \\ S_{6r} \\ S_{6i} \\ S_{7r} \\ S_{7i} \\ S_{8r} \\ S_{8i} \end{bmatrix} \quad (\text{S12}),$$

for $K = 2$ (first order central peaks):

$$\begin{bmatrix} T_{9r} \\ T_{9i} \\ T_{10r} \\ T_{10i} \\ T_{11r} \\ T_{11i} \\ T_{12r} \\ T_{12i} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & -1 & 0 & -1 & -1 & 0 \\ 0 & 1 & 1 & 0 & 1 & 0 & 0 & -1 \\ 1 & 0 & 0 & 1 & 0 & -1 & 1 & 0 \\ 0 & 1 & -1 & 0 & 1 & 0 & 0 & 1 \\ 1 & 0 & 0 & -1 & 0 & 1 & 1 & 0 \\ 0 & 1 & 1 & 0 & -1 & 0 & 0 & 1 \\ 1 & 0 & 0 & 1 & 0 & 1 & -1 & 0 \\ 0 & 1 & -1 & 0 & -1 & 0 & 0 & -1 \end{bmatrix} \cdot \begin{bmatrix} S_{9r} \\ S_{9i} \\ S_{10r} \\ S_{10i} \\ S_{11r} \\ S_{11i} \\ S_{12r} \\ S_{12i} \end{bmatrix} \quad (\text{S13}),$$

for $K = 1$ (second order central peaks):

$$\begin{bmatrix} T_{13r} \\ T_{13i} \\ T_{14r} \\ T_{14i} \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 & -1 \\ 0 & 1 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & -1 & 0 \end{bmatrix} \cdot \begin{bmatrix} S_{13r} \\ S_{13i} \\ S_{14r} \\ S_{14i} \end{bmatrix} \quad (\text{S14}),$$

and for $K = 0$ (third order central peaks):

$$\begin{bmatrix} T_{15r} \\ T_{15i} \end{bmatrix} = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} S_{15r} \\ S_{15i} \end{bmatrix} \quad (\text{S15}).$$

Since real and imaginary parts are recorded for all four chemical shifts Ω_0 , Ω_1 , Ω_2 , and Ω_3 in the basic spectra (eq S12), the particular choice of Ω_0 is, in principle, arbitrary. A suitable rearrangement of the FIDs would allow one to exchange Ω_0 with any of the other three chemical shifts after data acquisition. However, the order chosen for central peak detection defines Ω_0 . For the present (5,2)D HACACONHN experiment, 2D [^{15}N , ^1H]-HSQC is the most sensitive choice for third order central peak detection so that $\Omega_0 = \Omega(^{15}\text{N})$.

Editing of time instead of frequency domain data is advantageous, because the extension of the time domain data by linear prediction² (from 53 to 106 complex points for data sets $T1$ to $T12$ and from 128 to 192 for data sets $T13$ and $T14$) profits from both maximizing the signal-to-noise of the time domain data and reducing the number of chemical shifts (“oscillators”) to be predicted. After linear prediction, the data sets $T1\dots T15$ were multiplied by a sine function shifted by 70° and Fourier transformed to yield spectra $B1\dots B15$ (Figures 5,6). The digital resolution after zero-filling was 7.8 Hz/point along ω_1 and 6.9 Hz/point along ω_2 ,

V. Table with reductions in minimal measurement times in GFT NMR

Table S1. The reduction of minimal measurement times, ϵ , for $K = 1, 2, 3$ and different approaches for central peak detection assuming that each of the projected $K+1$ dimensions are sampled with 16 (32) complex points.

	2^K basic data sets ^a eq S8	$2^{K+1} - 1$ data sets ^b eq 3	4^K data sets ^c eq S9
$K = 1$	$\epsilon_2 = 8$ (16)	$\epsilon_1 = 5.3$ (10.7)	$\epsilon_3 = 4$ (8)
$K = 2$	$\epsilon_2 = 85$ (341)	$\epsilon_1 = 48.6$ (195)	$\epsilon_3 = 21$ (85)
$K = 3$	$\epsilon_2 = 1024$ (8192)	$\epsilon_1 = 546$ (4369)	$\epsilon_3 = 128$ (1024)

^a Central peaks obtained exclusively from incomplete polarization transfer.^{6e}

^b Central peaks obtained by successive omission of chemical shift evolution periods in the parent experiment.

^c Central peaks exclusively obtained from heteronuclear steady-state magnetization.^{6g}

VI. Table with chemical shifts

Table S2. Chemical shifts^a of ubiquitin measured in (5,2)D HACACONHN. The following standard deviations were obtained (Figures 5,6,7,8): $\sigma(^{15}\text{N}) = \pm 0.043$ ppm (2.4 Hz), $\sigma(^1\text{H}^{\text{N}})^{\text{b}} = \pm 0.006$ ppm (3.3 Hz), $\sigma(^{13}\text{C}^{\prime}) = \pm 0.017$ ppm (2.6 Hz), $\sigma(^{13}\text{C}^{\alpha}) = \pm 0.019$ ppm (2.9 Hz), $\sigma(^1\text{H}^{\alpha}) = \pm 0.006$ ppm (3.7 Hz).

Residue	$\delta(^{15}\text{N})$	$\delta(^1\text{H}^{\text{N}})^{\text{a}}$	$\delta(^{13}\text{C}^{\prime})$	$\delta(^{13}\text{C}^{\alpha})$	$\delta(^1\text{H}^{\alpha})$
M1			170.500	54.505	4.220
Q2	122.911	8.965	176.021	55.178	5.289
I3	115.095	8.328	172.351	59.678	4.161
F4	118.498	8.624	175.151	55.162	5.642
V5	121.256	9.317	174.775	60.430	4.815
K6	127.847	8.954	177.095	54.682	5.293
T7	115.413	8.762	176.890	60.564	4.932
L8	121.248	9.129	178.821	57.561	4.302
T9	105.850	7.656	175.494	61.463	4.423
G10	109.192	7.845	173.952	45.428	3.612/4.344
K11	121.890	7.286	175.722	56.318	4.359
T12	120.604	8.657	174.334	62.380	5.051
I13	127.688	9.562	175.149	60.029	4.522
T14	121.650	8.757	173.731	62.043	4.977
L15	125.150	8.751	174.525	52.827	4.754
E16	122.459	8.139	175.802	54.968	4.889
V17	117.511	8.956	174.039	58.479	4.694
E18	119.306	8.679			
P19			175.261	65.330	4.124
S20	103.394	7.048	174.592	57.431	4.360

D21	123.869	8.070	176.285	55.924	4.687
T22	108.971	7.895	176.760	59.658	4.905
I23	121.290	8.538			
E24 ^c			178.964	60.734	3.890
N25	121.406	7.942	178.288	56.068	4.558
V26	122.156	8.118	177.918	67.684	3.398
K27	118.967	8.580	180.483	59.222	4.592
A28	123.484	7.994	180.214	55.419	4.161
K29	120.211	7.875	180.257	59.793	4.202
I30	121.352	8.301	178.151	66.124	3.487
Q31	123.551	8.568	178.820	60.067	3.822
D32	119.733	8.036	177.278	57.454	4.333
K33	115.432	7.446	177.777	58.193	4.310
E34	114.269	8.742	177.909	55.395	4.570
G35	108.796	8.518	173.915	46.100	3.929/4.135
I36	120.298	6.174			
P38			178.246	66.138	4.116
D39	113.588	8.546	177.032	55.819	4.411
Q40	116.885	7.834	175.381	55.647	4.463
Q41	118.029	7.498	176.133	56.684	4.223
R42	123.033	8.524	173.854	55.186	4.483
L43	124.390	8.843	175.257	53.051	5.367
I44	122.295	9.119	175.795	58.972	4.943
F45	125.055	8.866	174.578	56.597	5.161
A46	132.938	8.993	177.317	52.598	3.697
G47	102.422	8.138	173.732	45.412	3.450/4.100
K48	121.961	7.999	174.627	54.640	4.598
Q49	123.000	8.664	175.566	55.922	4.540
L50	125.679	8.579	176.611	54.287	4.090
E51	123.110	8.407	175.475	55.979	4.511
D52	120.354	8.179			
G53 ^c			174.754	45.245	4.062

R54	119.329	7.482	175.316	54.338	4.725
T55	108.815	8.847	176.490	59.700	5.237
L56	118.016	8.168	180.752	58.673	4.053
S57	113.484	8.499	178.282	61.149	4.242
D58	124.505	7.954	177.401	57.440	4.291
Y59	115.770	7.276	174.663	58.295	4.651
N60	115.940	8.174	174.256	54.179	4.351
I61	118.831	7.264	174.514	62.470	3.371
Q62	124.948	7.642	175.751	53.653	4.477
K63	120.514	8.505	175.694	57.905	3.979
E64	114.574	9.335	175.205	58.419	3.330
S65	114.914	7.683	172.008	60.931	4.632
T66	117.439	8.742	173.741	62.506	5.291
L67	127.691	9.432	175.314	53.866	5.085
H68	119.271	9.255	173.703	56.002	5.141
L69	123.921	8.311	175.356	53.848	5.184
V70	126.737	9.202	174.033	60.654	4.378
L71	123.087	8.125	177.806	54.030	5.021
R72	123.792	8.620	175.284	55.713	4.262
L73	124.533	8.372	177.388	54.846	4.396
R74	121.936	8.453	176.837	56.613	4.303
G75	111.089	8.505	173.633	45.331	3.966
G76	115.040	7.959			

^a Chemical shifts are in ppm and relative to 2,2-dimethyl-2-silapentane-5-sulfonate (DSS).

^b Directly measured chemical shift.

^c Glu 24 and Gly 53 show broadened ¹⁵N-¹H^N resonances.

VII. Figure S1 and additional statistical calculations based on the Gaussian law of error propagation

Figure S1 shows the results of Monte-Carlo simulations for the case that only four out of eight basic spectra of (5,2)D HACACONHN (Figure 6a) are selected to calculate the chemical shifts. The standard deviations for the chemical shift measurements are plotted *versus* the number assigned to a particular combination. (a) $\sigma(^{15}\text{N})$, (b) $\sigma(^{13}\text{C}')$, (c) $\sigma(^{13}\text{C}^\alpha)$ and (d) $\sigma(^1\text{H}^\alpha)$ represent the standard deviations for the measurement of the chemical shifts $\Omega_0(^{15}\text{N})$, $\Omega_1(^{13}\text{C}')$, $\Omega_2(^{13}\text{C}^\alpha)$ and $\Omega_3(^1\text{H}^\alpha)$, respectively. (e) Assignment of numbers to the selections of four out of the 64 possible combinations $\left\{ \binom{8}{4} - 6 = (8 \cdot 7 \cdot 6 \cdot 5) / (4 \cdot 3 \cdot 2 \cdot 1) - 6 = 64 \right\}$. The six combinations which are subtracted from the binomial coefficient $\binom{8}{4}$ correspond to the cases where one of the three chemical shifts Ω_1 , Ω_2 or Ω_3 is added to or subtracted from Ω_0 in all of the four selected spectra (i.e., no splitting is present among the four selected spectra which encodes the respective chemical shift). The spectra selected for a particular combination number are indicated as dots. The statistical model used for the Monte Carlo simulations is the same as described in the legend of Figure 8.

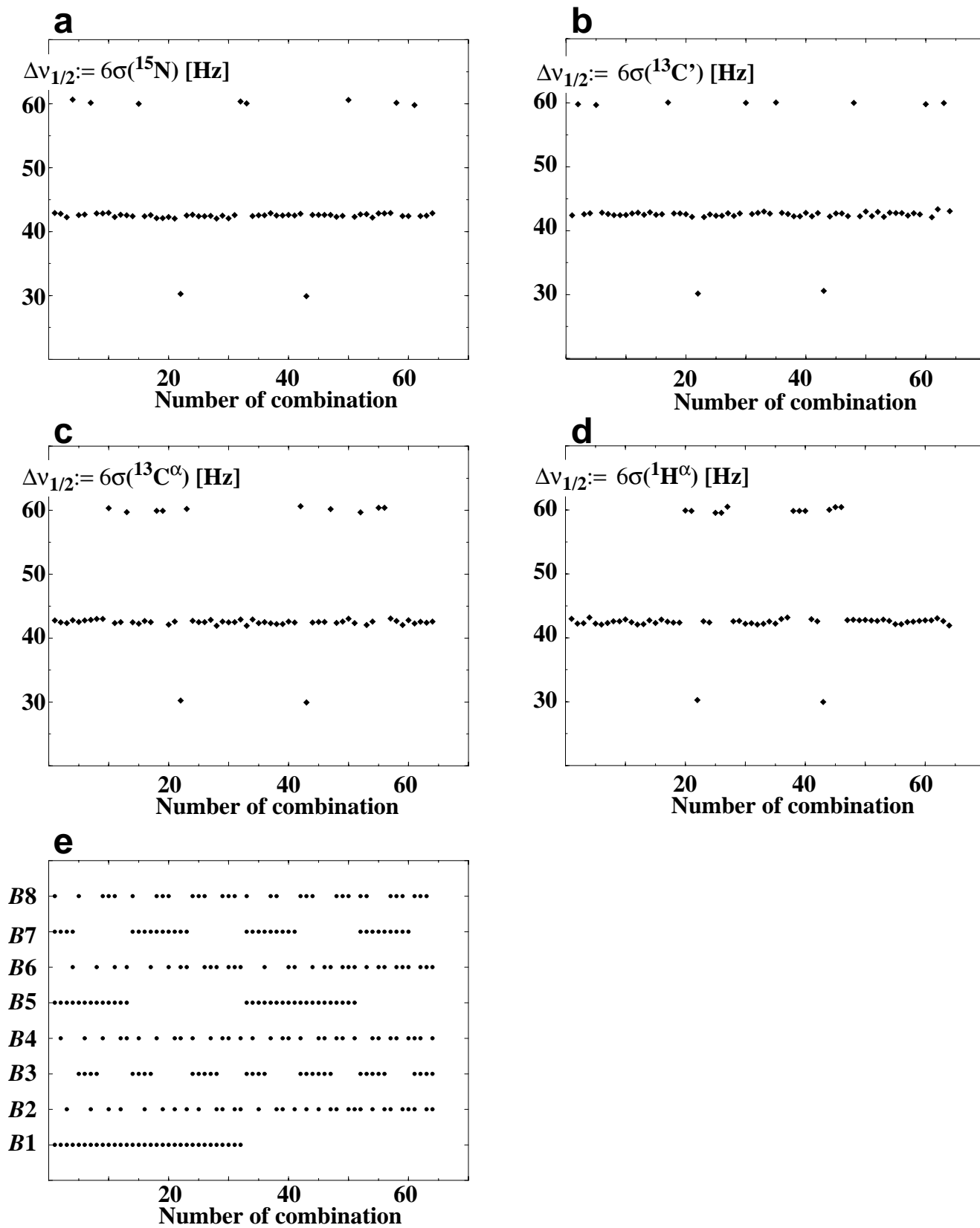


Figure S1

Three different classes of combinations are identified.

(I) 2 combinations provide high precision [$\sigma(X) = \frac{1}{2} \cdot \sigma(\text{basic})$; $X = {}^1\text{H}^\alpha, {}^{13}\text{C}^\alpha, {}^{13}\text{C}', {}^{15}\text{N}$] for all

four chemical shifts:

$$B1 [\Omega_0 + \Omega_1 + \Omega_2 + \Omega_3]; B4 [\Omega_0 - \Omega_1 - \Omega_2 + \Omega_3],$$

$$B6 [\Omega_0 - \Omega_1 + \Omega_2 - \Omega_3] \text{ and } B7 [\Omega_0 + \Omega_1 - \Omega_2 - \Omega_3], \text{ or}$$

$$B2 [\Omega_0 - \Omega_1 + \Omega_2 + \Omega_3]; B3 [\Omega_0 + \Omega_1 - \Omega_2 + \Omega_3];$$

$$B5 [\Omega_0 + \Omega_1 + \Omega_2 - \Omega_3]; \text{ and } B8 [\Omega_0 - \Omega_1 - \Omega_2 - \Omega_3].$$

(II) 26 combinations provide intermediate precision [$\sigma(X) = \frac{1}{\sqrt{2}} \cdot \sigma(\text{basic})$; $X = {}^1\text{H}^\alpha, {}^{13}\text{C}^\alpha, {}^{13}\text{C}',$

${}^{15}\text{N}$] for all four chemical shifts.

(III) 37 combinations provide intermediate precision [$\sigma = \frac{1}{\sqrt{2}} \cdot \sigma(\text{basic})$] for three of the shifts

and low precision [$\sigma = \sigma(\text{basic})$] for one of the four shifts.

The standard deviation depend on the number of equations that need to be linearly combined to calculate the shifts. This shall be discussed for three examples, one representing each of the cases.

(I) $B2 [\Omega_0 - \Omega_1 + \Omega_2 + \Omega_3]; B3 [\Omega_0 + \Omega_1 - \Omega_2 + \Omega_3]; B5 [\Omega_0 + \Omega_1 + \Omega_2 - \Omega_3];$ and $B8 [\Omega_0 - \Omega_1 - \Omega_2 - \Omega_3]$ shall be selected. We then obtain the individual chemical shifts from:

$$4 \Omega_0({}^{15}\text{N}) = B2 + B3 + B5 + B8$$

$$4 \Omega_1(^{13}\text{C}') = -B2 + B3 + B5 - B8$$

$$4 \Omega_2(^{13}\text{C}^\alpha) = B2 - B3 + B5 - B8$$

$$4 \Omega_3(^1\text{H}^\alpha) = B2 + B3 - B5 - B8$$

with 'BX' representing the shifts extracted from the spectrum BX (X = 2,3,5,8). Each shift from BX is associated with a standard deviation of $\sigma(\text{basic})$. Hence, the Gaussian law of error propagation⁹ yields:

$$\sigma[4 \Omega_0(^{15}\text{N})] = 4 \sigma[\Omega_0(^{15}\text{N})] = \sqrt{4} \sigma(\text{basic}) = 2 \cdot \sigma(\text{basic})$$

$$\sigma[4 \Omega_0(^{13}\text{C}')] = 4 \sigma[\Omega_0(^{13}\text{C}')] = \sqrt{4} \sigma(\text{basic}) = 2 \cdot \sigma(\text{basic})$$

$$\sigma[4 \Omega_0(^{13}\text{C}^\alpha)] = 4 \sigma[\Omega_0(^{13}\text{C}^\alpha)] = \sqrt{4} \sigma(\text{basic}) = 2 \cdot \sigma(\text{basic})$$

$$\sigma[4 \Omega_0(^1\text{H}^\alpha)] = 4 \sigma[\Omega_0(^1\text{H}^\alpha)] = \sqrt{4} \sigma(\text{basic}) = 2 \cdot \sigma(\text{basic}),$$

or equivalently,

$$\sigma[\Omega_0(X)] = \frac{1}{\sqrt{4}} \sigma(\text{basic}) = \frac{1}{2} \cdot \sigma(\text{basic}) \text{ for } X = ^1\text{H}^\alpha, ^{13}\text{C}^\alpha, ^{13}\text{C}', ^{15}\text{N}.$$

Thus, the resulting precision is equivalent to the one obtained from four statistically independent measurements.

$$\text{(II) } B1 [\Omega_0 + \Omega_1 + \Omega_2 + \Omega_3]; B5 [\Omega_0 + \Omega_1 + \Omega_2 - \Omega_3];$$

$$B7 [\Omega_0 + \Omega_1 - \Omega_2 - \Omega_3]; \text{ and } B8 [\Omega_0 - \Omega_1 - \Omega_2 - \Omega_3] \text{ shall be selected. We then obtain the}$$

individual chemical shifts from:

$$2 \Omega_0(^{15}\text{N}) = B1 + B8$$

$$2 \Omega_1(^{13}\text{C}') = B7 - B8$$

$$2 \Omega_2(^{13}\text{C}^\alpha) = B5 - B7$$

$$2 \Omega_3(^1\text{H}^\alpha) = B1 - B5$$

with 'BX' representing the shifts extracted from the spectrum BX (X = 1,5,7,8). Each shift from BX is associated with a standard deviation of $\sigma(\text{basic})$. Hence, the Gaussian law of error propagation yields:

$$\sigma[2 \Omega_0(^{15}\text{N})] = 2 \sigma[\Omega_0(^{15}\text{N})] = \sqrt{2} \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^{13}\text{C}')] = 2 \sigma[\Omega_0(^{13}\text{C}')] = \sqrt{2} \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^{13}\text{C}^\alpha)] = 2 \sigma[\Omega_0(^{13}\text{C}^\alpha)] = \sqrt{2} \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^1\text{H}^\alpha)] = 2 \sigma[\Omega_0(^1\text{H}^\alpha)] = \sqrt{2} \sigma(\text{basic}),$$

or equivalently,

$$\sigma[\Omega_0(X)] = \frac{1}{\sqrt{2}} \sigma(\text{basic}) \text{ for } X = ^1\text{H}^\alpha, ^{13}\text{C}^\alpha, ^{13}\text{C}', ^{15}\text{N}.$$

Thus, the resulting precision is equivalent to the one obtained from two statistically independent measurements.

(III) B1 [$\Omega_0 + \Omega_1 + \Omega_2 + \Omega_3$]; B4 [$\Omega_0 - \Omega_1 - \Omega_2 + \Omega_3$]; B5 [$\Omega_0 + \Omega_1 + \Omega_2 - \Omega_3$]; and B6 [$\Omega_0 - \Omega_1 + \Omega_2 - \Omega_3$] shall be selected. We then obtain the individual chemical shifts from:

$$2 \Omega_0(^{15}\text{N}) = B4 + B5$$

$$2 \Omega_1(^{13}\text{C}') = B5 - B6$$

$$2 \Omega_2(^{13}\text{C}^\alpha) = B1 - B4 - B5 + B6$$

$$2 \Omega_3(^1\text{H}^\alpha) = B1 - B5$$

with ‘BX’ representing the shifts extracted from the spectrum BX ($X = 1,4,5,6$). Each shift from BX is associated with a standard deviation of $\sigma(\text{basic})$. Hence, the Gaussian law of error propagation yields:

$$\sigma[2 \Omega_0(^{15}\text{N})] = 2 \sigma[\Omega_0(^{15}\text{N})] = \sqrt{2} \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^{13}\text{C}')] = 2 \sigma[\Omega_0(^{13}\text{C}')] = \sqrt{2} \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^{13}\text{C}^\alpha)] = 2 \sigma[\Omega_0(^{13}\text{C}^\alpha)] = \sqrt{4} \sigma(\text{basic}) = 2 \cdot \sigma(\text{basic})$$

$$\sigma[2 \Omega_0(^1\text{H}^\alpha)] = 2 \sigma[\Omega_0(^1\text{H}^\alpha)] = \sqrt{2} \sigma(\text{basic}),$$

or equivalently,

$$\sigma[\Omega_0(X)] = \frac{1}{\sqrt{2}} \sigma(\text{basic}) \text{ for } X = ^1\text{H}^\alpha, ^{13}\text{C}', ^{15}\text{N} \text{ and}$$

$$\sigma[\Omega_0(^{13}\text{C}^\alpha)] = \sigma(\text{basic})$$

Thus, the resulting precision is equivalent to the one obtained from two statistically independent measurements for three of the chemical shifts, while it is equivalent to a single measurement for one of the shifts.

In case all 15 spectra constituting the constant time (5,2)D GFT NMR experiment are selected, similar consideration show that the resulting standard deviations can be calculated⁹ according to following equations.

(a) Survey of constant time spectra, standard deviations and chemical shift measurements

Data	Number of Spectra	standard deviation	Chemical shift measurements
Basic	8	$\sigma(\text{basic})$	$\Omega_0(^{15}\text{N}) \pm \Omega_1(^{13}\text{C}') \pm \Omega_2(^{13}\text{C}^\alpha) \pm \Omega_3(^1\text{H}^\alpha)$
1st	4	$\sigma(\text{1st})$	$\Omega_0(^{15}\text{N}) \pm \Omega_1(^{13}\text{C}') \pm \Omega_2(^{13}\text{C}^\alpha)$
2nd	2	$\sigma(\text{2nd})$	$\Omega_0(^{15}\text{N}) \pm \Omega_1(^{13}\text{C}')$
3rd	1	$\sigma(\text{3rd})$	$\Omega_0(^{15}\text{N})$

(b) Calculation of error propagation

Chemical Shifts Standard Deviations

$$\Omega_0(^{15}\text{N}) \quad \sigma(^{15}\text{N}) = \frac{\sqrt{8 \cdot \sigma^2(\text{basic}) + 4 \cdot \sigma^2(1st) + 2 \cdot \sigma^2(2nd) + \sigma^2(3rd)}}{15}$$

$$\Omega_1(^{13}\text{C}') \quad \sigma(^{13}\text{C}') = \frac{\sqrt{8 \cdot \sigma^2(\text{basic}) + 4 \cdot \sigma^2(1st) + 2 \cdot \sigma^2(2nd)}}{14}$$

$$\Omega_2(^{13}\text{C}^\alpha) \quad \sigma(^{13}\text{C}^\alpha) = \frac{\sqrt{8 \cdot \sigma^2(\text{basic}) + 4 \cdot \sigma^2(1st)}}{12}$$

$$\Omega_3(^1\text{H}^\alpha) \quad \sigma(^1\text{H}^\alpha) = \frac{\sqrt{8 \cdot \sigma^2(\text{basic})}}{8}$$

The validity of these equations is neatly confirmed by the Monte Carlo simulation performed with input from all 15 spectra:

σ	6σ (simulated)	6σ (calculated)
$\sigma(^{15}\text{N})$	14.50	14.46
$\sigma(^{13}\text{C}')$	15.35	15.37
$\sigma(^{13}\text{C}^\alpha)$	17.41	17.36
$\sigma(^1\text{H}^\alpha)$	21.24	21.26