Supplementary Materials

Importance of time-ordered non-uniform sampling of multi-dimensional NMR spectra of $A\beta^{1-42}$ peptide under aggregating conditions

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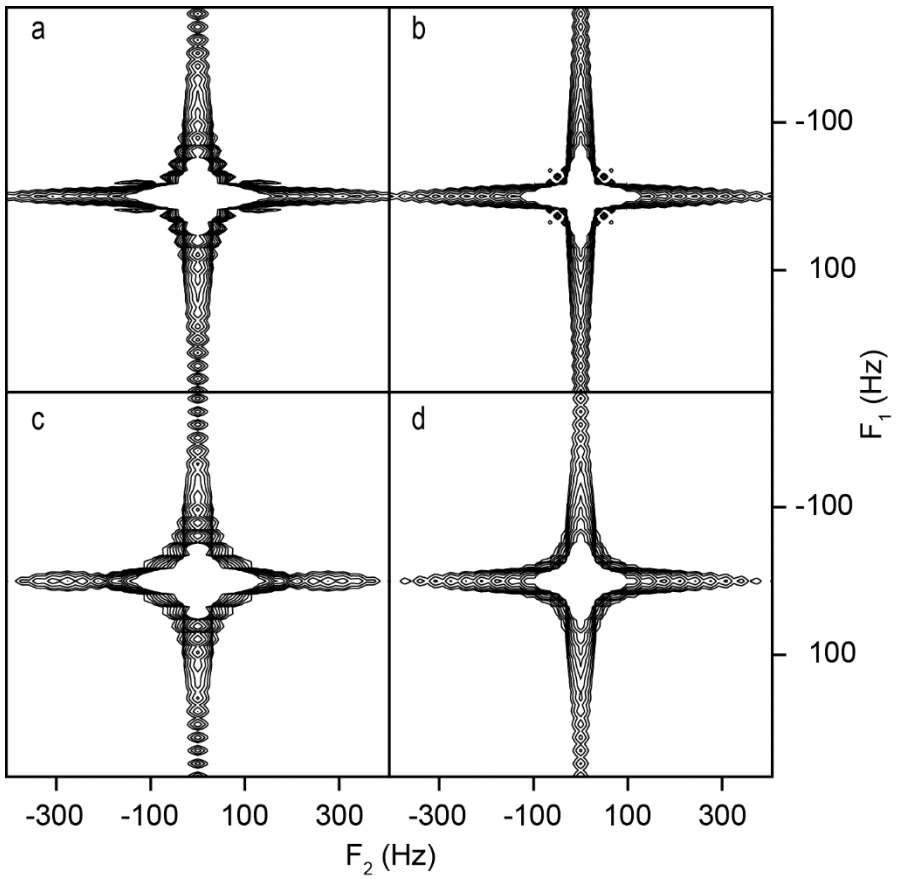

Fig. S1 The same 2D (F_1, F_2) cross sections as presented in Fig. 2**b**,**c**,**e**,**f** of the main text, but plotted at a 4 times lower contour level (*i.e.* 0.05% of the peak height). Ordering schemes used: (**a**) sum: $\sum_{i=1,2} k_i$; (**b**) normalized sum: $\sum_{i=1,2}(k_i/N_i)$; (**c**) radial length: $\sqrt{\sum_{i=1,2}(k_i)^2}$; and (**d**) the normalized radial length: $\sqrt{\sum_{i=1,2}(k_i/N_i)^2}$.

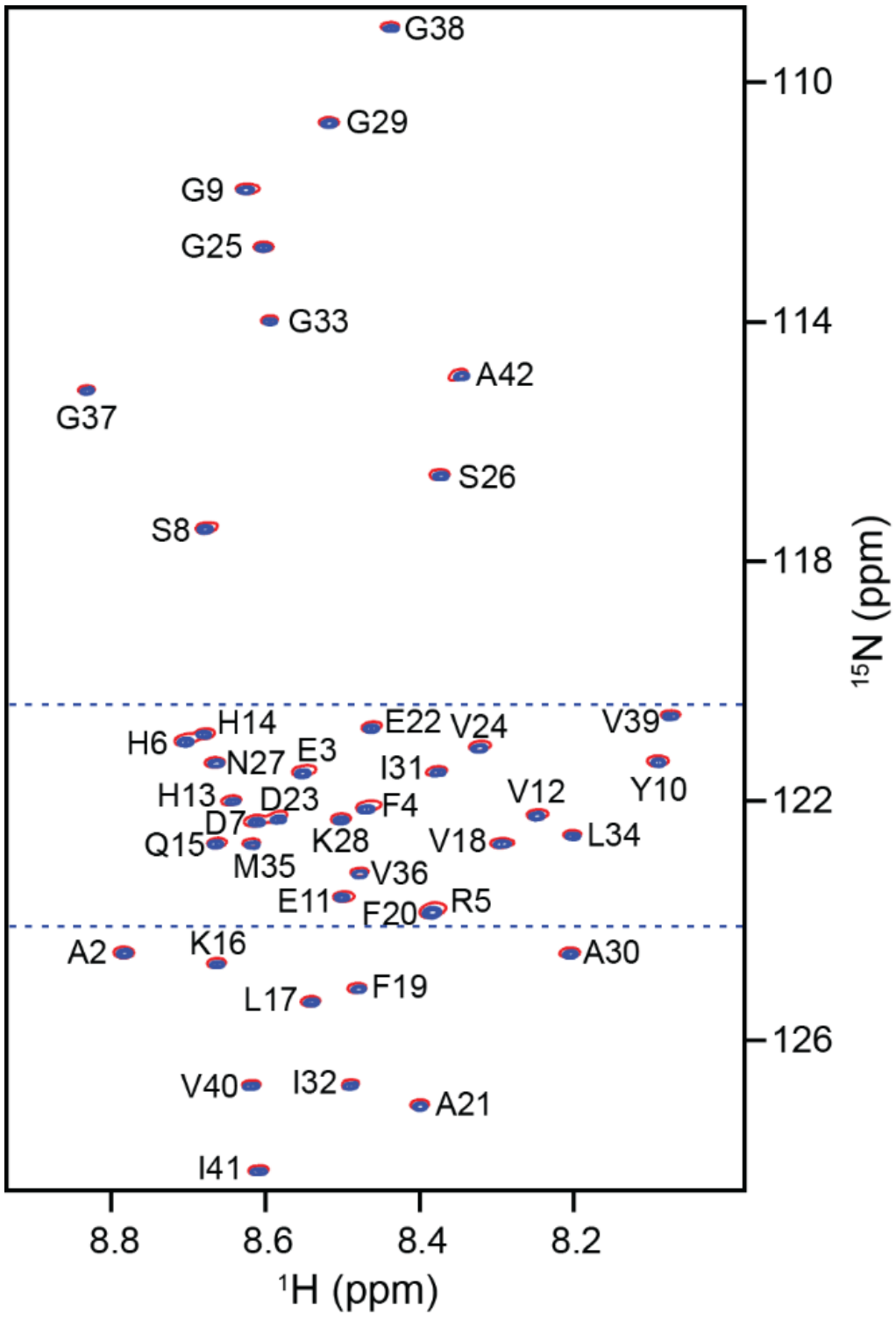

Fig. S2 Overlay of the 2D $^{1}H^{N}$-^{15}N HSQC spectra for the 1.2 mM (red single contour) and 20 µM (blue contours) samples, each recorded at 3.0 kbar, 280 K, 900 MHz ^{1}H frequency. Residue assignments are labeled near individual peaks. The region between the two broken lines was projected to generate the 2D ^{1}H-^{1}H plane presented in Fig. 4 of the main text.

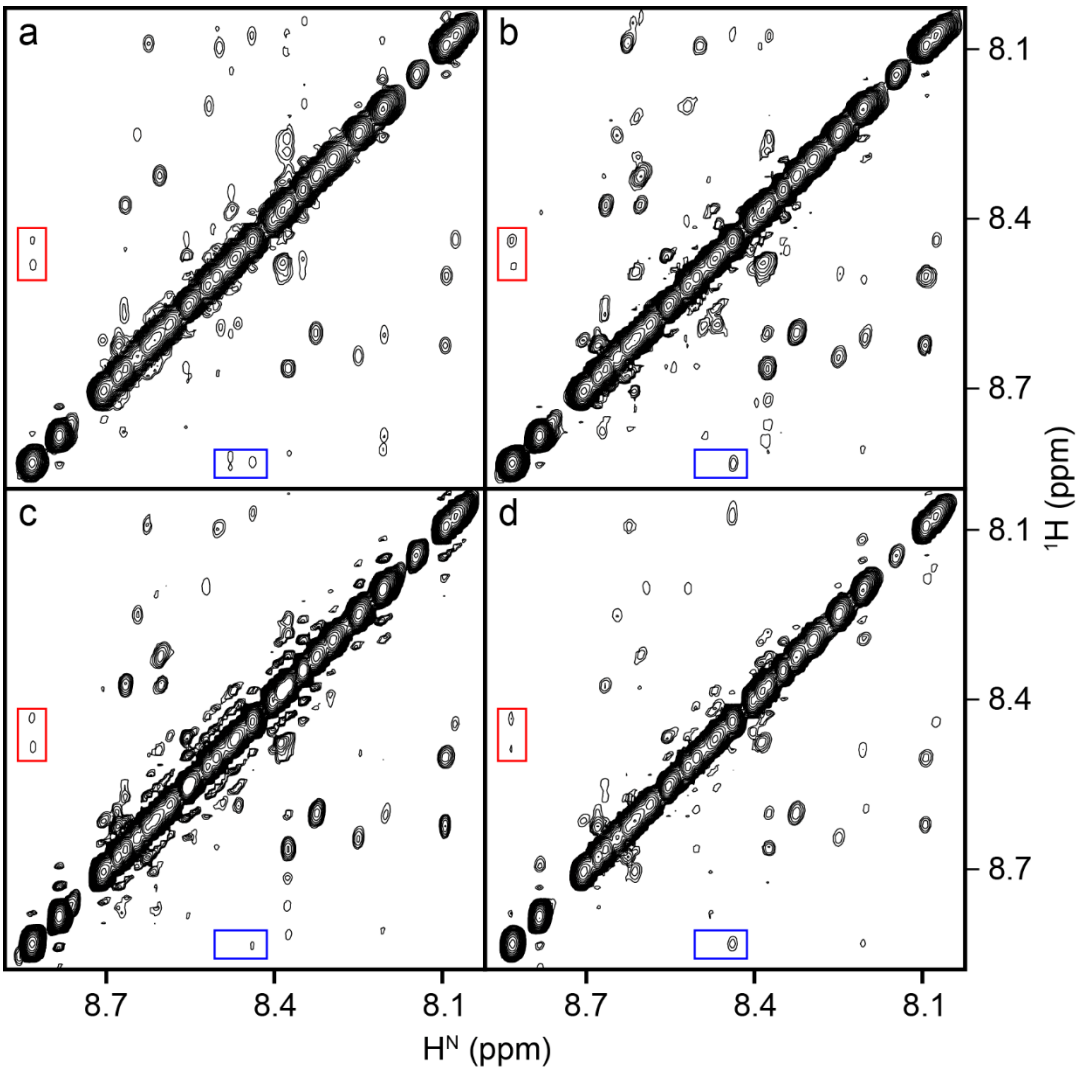

Fig. S3 2D ^{1}H-^{1}H plane projected from the entire ^{15}N dimension of the 3D randomly ordered NOESY-HSQC spectra, reconstructed using a number of different algorithms: (**a**) SMILE with the reconstructed signals not being downscaled, (**b**) IST by hmsIST, (**c**) IRLS by MDDNMR, and (**d**) MDD by MDDNMR, indicating that all reconstruction methods are strongly impacted by the amplitude noise obtained for a randomly ordered NUS data set on a decaying sample. The first contour level for each panel is set to be slightly below the weakest cross peaks in the red boxes. The mirror images of these NOE cross peaks are marked in the blue boxes. For clarity, only positive contours are plotted.

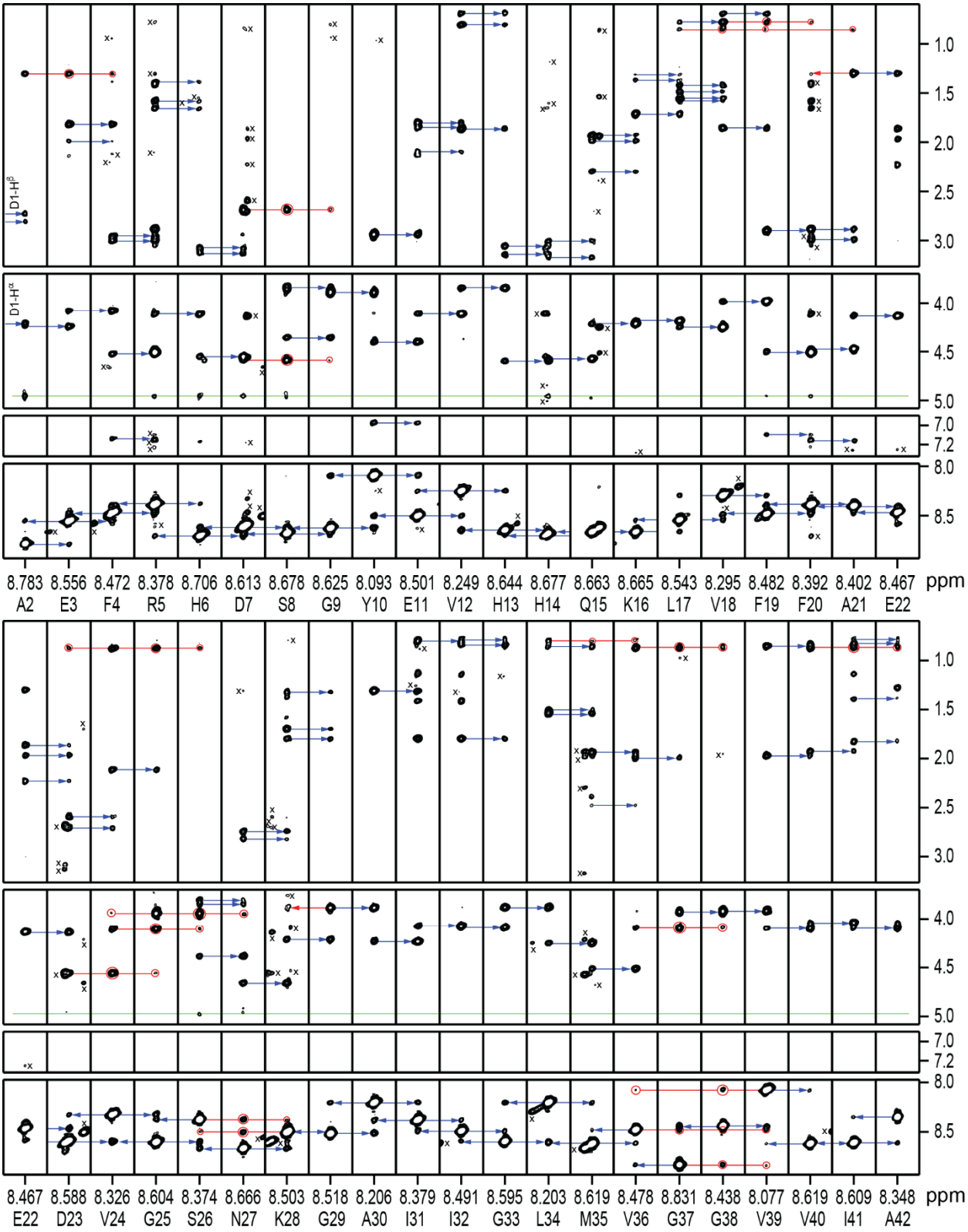

Fig. S4 Strip plot of the 900-MHz 3D time-ordered NOESY-HSQC spectrum for residues A2 through A42 of $A\beta^{1-42}$. The sequential H^N-H^N and H^{C}_{i}-H^{N}_{i+1} NOEs are connected by blue arrows,

unless there is a longer-range NOE passing through the sequential one. Red lines represent less commonly observed sequential and medium-range connectivities, with inter-residue peaks circled in red. Sequential NOEs between H^{N}_{i} and H^{C}_{i+1} are marked by red arrows. Hydrogen exchange cross peaks between water and H^{N} protons are marked by the light green line. Note that the amides of R5 and F20 partially overlap and the cross-peak with water for F20 is dominated by the contribution from R5. Noise, artifacts, and off-strip peaks above the threshold are marked ×.

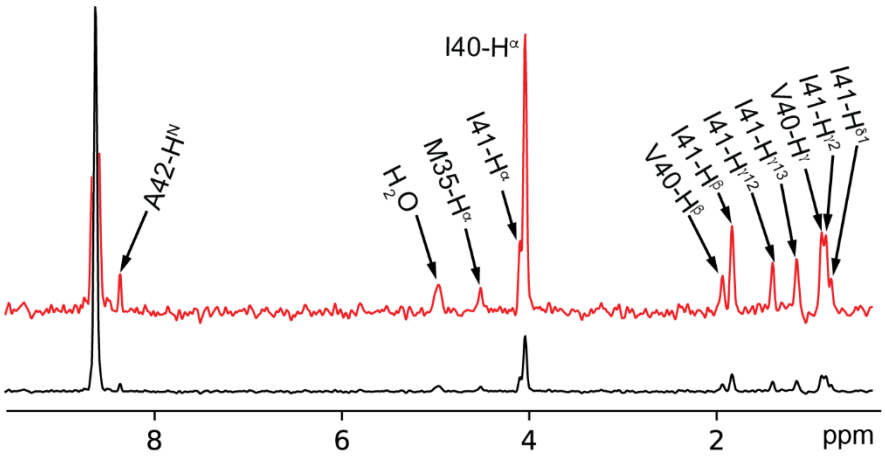

Fig. S5 1D cross section taken along the indirect ^{1}H dimension for I41 from the 3D NOESY-HSQC spectrum acquired at pH 8, 3 kbar, and 278 K using time-ordered sampling. The red trace is upscaled 10-fold. NOE cross peaks are labeled.

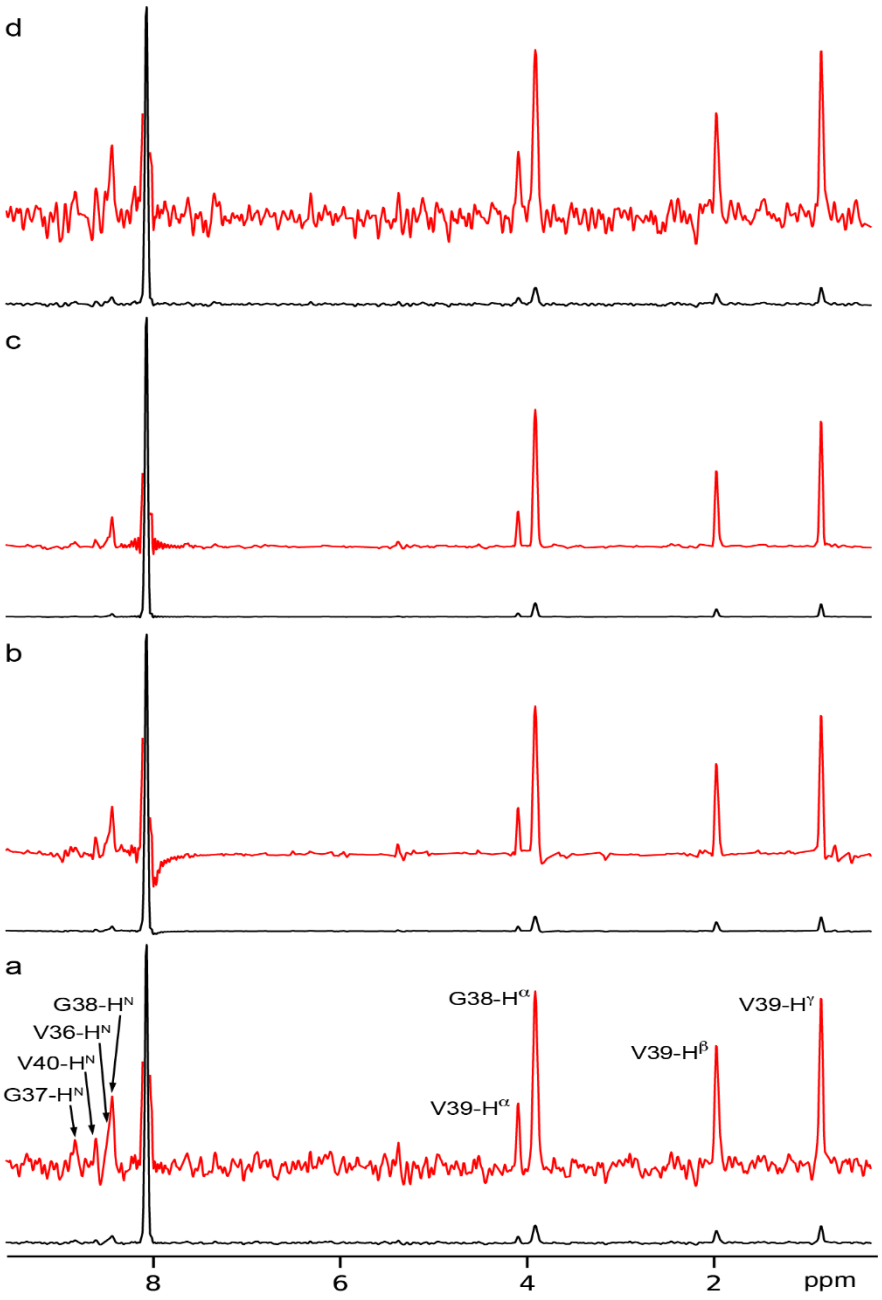

Fig. S6 The same cross section shown in Fig. 5**a** (Main Text), taken through the 3D time-ordered spectra, reconstructed using (**a**) SMILE, (**b**) hmsIST, (**c**) IRLS, and (d) MDD. In all panels, black traces are scaled to display the full amplitude of the diagonal resonance; red traces are upscaled 10-fold. Note that the apparent signal-to-noise ratio in hmsIST and IRLS cross sections does not directly reflect the true signal-to-noise ratio in the measured data because the reconstructed signals are not downscaled to account for the artificial enhancement of the peak intensity by roughly the reciprocal of the sampling sparsity. In contrast, SMILE essentially aims to remove the PSF noise while minimizing the impact on the thermal noise and the peak intensity encapsulated in the experimentally recorded data, thereby providing a more realistic representation for the uncertainty of the measured data.