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Journal of Magnetic Resonance 170 (2004) 15–21
JMR Journal of Magnetic Resonance
www.elsevier.com/locate/jmr

Accelerated acquisition of high resolution triple-resonance spectra using non-uniform sampling and maximum entropy reconstruction

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Received 18 February 2004; revised 11 May 2004
Available online 19 June 2004

Abstract

Non-uniform sampling is shown to provide significant time savings in the acquisition of a suite of three-dimensional NMR experiments utilized for obtaining backbone assignments of H, N, C′, CA, and CB nuclei in proteins : HNCO, HN(CA)CO, HNCA, HN(CO)CA, HNCACB, and HN(CO)CACB. Non-uniform sampling means that data were collected for only a subset of all incremented evolution periods, according to a user-specified sampling schedule. When the suite of six 3D experiments was acquired in a uniform fashion for an 11 kDa cytoplasmic domain of a membrane protein at 1.5 mM concentration, a total of 146 h was consumed. With non-uniform sampling, the same experiments were acquired in 32 h and, through subsequent maximum entropy reconstruction, yielded spectra of similar quality to those obtained by conventional Fourier transform of the uniformly acquired data. The experimental time saved with this methodology can significantly accelerate protein structure determination by NMR, particularly when combined with the use of automated assignment software, and enable the study of samples with poor stability at room temperature. Since it is also possible to use the time savings to acquire a greater numbers of scans to increase sensitivity while maintaining high resolution, this methodology will help extend the size limit of proteins accessible to NMR studies, and open the way to studies of samples that suffer from solubility problems.

Keywords: Non-uniform sampling; Protein backbone chemical shift assignments; Maximum entropy reconstruction; Reduced time multidimensional NMR spectroscopy

1. Introduction

The progress of biomolecular NMR studies can be substantially hindered by the extensive experimental time required to establish unambiguous spectroscopic evidence for chemical shift assignments. For proteins, many weeks or even several months of experimental time may be devoted to obtaining all multidimensional NMR experiments needed to complete a structural study, particularly for unstable or partially unfolded proteins. It is clearly a high priority to significantly reduce the time needed to carry out multidimensional NMR experiments on proteins.

Protein chemical shift assignments are generally determined first for nuclei composing the protein backbone and then for amino acid side chain carbon and proton nuclei. Backbone shift assignments are determined by contrasting coherence transfer pathways among sequential amino acids in pairs of three-dimensional (3D) experiments, such as HNCA/HN(CO)CA, HN(CA)CO/HNCO, and HNCACB/HN(CO)CACB

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doi:10.1016/j.jmr.2004.05.016

[1–4], which are ideal for deuterated proteins. The HN(CA)HA/HN(COCA)HA pair [5,6] can be added for non-deuterated proteins. Complete sequential assignments can be obtained in principle from just one pair of experiments, but it is usually necessary and generally desirable to acquire all three pairs of 3D spectra to obtain complete assignments of backbone and C^{β} carbons and to eliminate ambiguities that may arise from analysis of just one pair.

The time needed to carry out these experiments depends upon achieving two goals for the quality of the data: a sufficient sensitivity and well resolved resonances. First, for a protein of a given size, factors affecting sensitivity include protein concentration and stability, and salt conditions [7]. Second, pulse sequences vary in the number and type of coherence transfer steps in each experiment, which further affects the sensitivity. For example, the HNCO experiment generally achieves ten times the sensitivity that is observed in the companion HN(CA)CO experiment. Third, the ability to resolve peaks will depend upon the degree of isotopic enrichment, the size of the protein, and its folded conformation. This will also largely determine the magnitude of the relaxation rates that govern the line widths of the detected signals. Fourth, it is well known that experimental variables influencing both sensitivity and spectral resolution include the static field strength, digital resolution, and maximum evolution times in the indirect evolution periods [8]. The complex array of sample-specific factors and experimental variables affecting sensitivity and resolution require that a highly general method be found to accelerate multidimensional NMR experiments.

It has been previously shown that if poor sensitivity requires collecting a number of transients per free induction decay (FID) that exceeds the phase cycle length, then cryocooled probes, which enhance the sensitivity by factors of about 3–4, can improve the acquisition times of multidimensional experiments [9]. Yet this sensitivity enhancement will be attenuated in high conductivity buffers [7], or may be expended to make large proteins or dilute samples more amenable to study. Further, even if a high sensitivity permits using a number of scans per FID that matches the phase cycle length, long experimental times are needed to construct the complete (i.e., uniform) three-dimensional matrix of FIDs with maximal carbon and nitrogen evolution times that provide sufficient resolution. Thus, cryogenic probes have their limits in accelerating the acquisition of multidimensional NMR experiments. Sample deuteration and transverse relaxation optimized spectroscopy improve both resolution and sensitivity for large proteins [10,11], but still require long experimental times [12]. Typical experimental times for the six 3D experiments considered in this report can range from 12 to 72 h per experiment, resulting in 1–3 weeks of continuous measuring time to acquire the full suite, depending on whether cryogenic probes are available or not. Unstable proteins may need to be prepared multiple times in order to acquire all such experiments, entailing high costs for isotopic enrichment and further delaying the progress of a study.

A general solution for obtaining rapid multidimensional NMR experiments is to couple non-uniform sampling in indirect evolution periods with maximum entropy (MaxEnt) reconstruction. Non-uniform sampling of multidimensional NMR data to improve resolution or reduce instrument time was first explored by Barna and Laue [13] but has not been widely used, in part because of the steep computational requirements imposed by methods capable of handling non-uniformly sampled data. Other approaches for reducing experiment time include reduced-dimensionality experiments [14,15] and back-projection reconstruction [16,17]. MaxEnt reconstruction is more general than either of these approaches in several respects. Non-uniform sampling does not produce overlap of multiplexed resonances, as can occur in reduced-dimensionality experiments, and MaxEnt spectra can be analyzed using conventional approaches. The data sampling employed in back-projection reconstruction is a special case of non-uniform sampling, and the data can be processed by MaxEnt reconstruction. An advantage of MaxEnt reconstruction over back-projection is that the spectra maintain the projection–cross-section relationship of conventional Fourier spectra that is lost by minimum back-projection. These advantages, rapid improvements in computational power (including clusters of inexpensive computers), and the development of efficient algorithms for MaxEnt reconstruction of multidimensional spectra [18,19], make non-uniform sampling and MaxEnt reconstruction an attractive approach for improving sensitivity, resolution, and reducing experiment time in multidimensional NMR.

Previously, an HNCO triple-resonance experiment was modified to perform non-uniform sampling in one indirect dimension, the constant-time ^{15}N evolution period, which resulted in a moderate but significant saving in measurement time [20]. Here we report the use of non-uniform sampling in the two indirect dimensions of the commonly used triple-resonance experiments resulting in a dramatic speed up of data acquisition. This approach requires only modest modifications to data collection schemes, and is phase sensitive in all dimensions via the States-TPPI method. This strategy yields high quality spectra suitable for manual or automated backbone chemical shift assignments. We show that experimental times are reduced up to fivefold in comparison to uniformly acquired experiments while maintaining high resolution and sufficient sensitivity. This allows acquisition of the three pairs of triple-resonance experiments commonly recorded for sequential assignments in less than one and a half days. An application of

non-uniform sampling to accelerate the acquisition of side chain assignment experiments is described in a separate publication [21].

2. Materials and methods

Spectra were acquired on an 11 kDa cytoplasmic domain of a membrane protein with a concentration of 1.5 mM in 90%H_2O/10%D_2O at a pH of 6.8, and a temperature of 25 °C. Uniformly sampled data were acquired for the HNCO, HN(CA)CO, HNCA, HN(CO)CA, HNCACB, and HN(CO)CACB experiments [22], and using States-TPPI quadrature detection in all cases. Water suppression was obtained by using the WATERGATE method [23] in conjunction with water flip back pulses. The spectra were measured with 512 complex points in the proton dimension, 32 complex points in the nitrogen dimension, and 64 complex points in the carbon dimension, as illustrated in Fig. 1A, except for the HN(CO)CA for which 51 complex points were measured in the carbon dimension. Spectral widths were 7507 and 1520 Hz for proton and nitrogen evolution, respectively. The carbon spectral widths were 2516 Hz for HNCO/HN(CA)CO, 3773 Hz for HNCA/HN(CO)-CA, and 7546 Hz for HNCACB/HN(CO)CACB. A recycle delay of 1 s was used. Acquisition times were 21 h and 15 min (8 scans per FID) for HNCA, HNCACB, and HNCO, 17 h and 10 min (8 scans) for HN(CO)CA, 21 h and 30 min (8 scans) for HN(CO)CACB, and 43 h and 15 min (16 scans) for HN(CA)CO, amounting to a total acquisition time of 6 days 1 h and 40 min.

These experiments were then modified to enable non-uniform sampling in the ^{15}N and ^{13}C indirect dimensions. Pulse programs are available upon request to the corresponding author and are also made available at the url, http://gwagner.med.harvard.edu/. Following the scheme depicted in Fig. 1B, 500 complex points were selected from a matrix of 40×62 points for the ^{15}N and ^{13}C dimensions, respectively, representing a fivefold reduction of the sampled data versus a uniform sampling of the same space. Both dimensions are phase sensitive by using the States-TPPI method. The spectra were recorded with the same sample on the same Bruker Avance spectrometer operating at 500 MHz for protons, albeit with different cryogenic probes for the uniform and non-uniform data. Uniform data were acquired with a 5 mm ^{1}H–^{15}N–^{13}C TXI CryoProbe with a recycling delay of 1 s, whereas the non-uniform experiments were acquired on a 5 mm TCI CryoProbe in which both ^{1}H and ^{13}C coil circuits are cryogenically cooled and a longer recycling delay of 1.5 s was used to address a temporary lock instability. The acquisition times were 2 h and 34 min for HNCO (4 scans per FID), 7 h and 27 min for HN(CA)CO (8 scans), 3 h and 44 min for HNCA (4 scans) and HN(CO)CA (4 scans), 7 h and 23 min for HNCACB (8 scans), and 7 h and 27 min for HN(CO)CACB (8 scans). The total acquisition time for the complete set of non-uniformly sampled experiments was 32 h and 30 min. Using the same probe and recycling delay as those of the conventional experiment, it is feasible to record the non-uniformly sampled data in one day. The higher experimental time due to the use of more scans/FID in some of the uniformly acquired

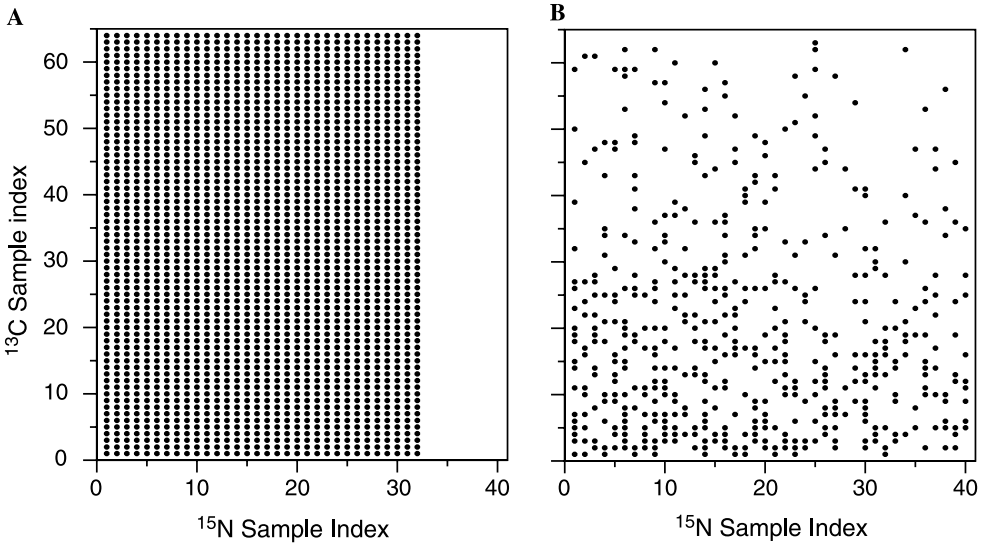

Fig. 1. The (A) uniform and (B) non-uniform sampling schedules employed for all spectra in this report are represented as a pattern of dots that fall on the two-dimensional grid of all evolution times in the carbon and nitrogen evolution periods regularly spaced by the fixed intervals (dwell times) appropriate for each dimension. To obtain quadrature detection, each dot in this figure represents four spectra corresponding to the real and imaginary sense of signal evolution for each dimension. The schedule in (A) has 2048 samples and completely covers all possible values for signal evolution while the schedule in (B) has 500 samples distributed over a space spanned by 62×40 samples, and was used for every 3D data set collected non-uniformly in this study.

experiments is matched by the higher recycling delay used in the non-uniformly acquired experiments, which justifies the direct comparison in measuring time.

Uniformly sampled data sets were processed using NMRPipe [24]. The ^{15}N dimension was extended to 64 complex points with linear prediction. Both ^{15}N and ^{13}C dimensions were apodized with a shifted squared sine-bell apodization function and zero filled to 256 complex points prior to Fourier transformation. Non-uniformly sampled data sets were processed using the maximum entropy reconstruction algorithm implemented in the RNMRTK processing environment [25] and were processed to a final size of 256 complex points in the ^{15}N and ^{13}C dimensions. All data were analyzed within the program XEASY [26] and assignments were obtained with the help of the program IBIS [27] (Sastry, Subbarao, Stehle, Wagner, unpublished). Previously, MaxEnt reconstruction was applied to data that were non-uniformly sampled in only one dimension, and a row-wise constant-lambda algorithm was developed to handle these cases [18]. However for reconstructing planes of data that result from non-uniform sampling in two dimensions it is necessary to carry out full plane-wise reconstructions. While this increases the computational demands of carrying out the spectral estimation, the RNMRTK implementation includes multi-threading capabilities and each data set could be processed in 15–20 min on a dual processor (Xeon-3.2 GHz) computer.

A computer program was written in the Tcl/Tk scripting language to assist in choosing and configuring sampling schedules and processing scripts for the six backbone assignment experiments. It is named COAST (Configuring Acquisition Sampling Tables) (Rovnyak, unpublished, available at URL http://gwagner.med.harvard.edu/) and was used to create properly formatted sampling tables and processing scripts for all non-uniformly sampled experiments in this report. Features include a graphical interface, a relaxation rate calculator, a choice of several preconstructed schedules, and the ability to save a master parameter file that can be reviewed at a later time. Processing scripts generated by COAST suggest conservative initial values of two adjustable parameters that are used by the MaxEnt algorithm, *def*, and *lambda*, whose optimal values depend in principle on the noise level of the time domain data. *def* is a scaling factor applied to a modified Shannon entropy expression [28] which influences the magnitude of the smallest amplitude signal that will be detected with the MaxEnt algorithm. *lambda* weights the experimental data and influences the degree of non-linear scaling of resonances in the spectral estimations. Presently it is more efficient to optimize *def* and *lambda* manually and we find that the quality of MaxEnt reconstructions is very tolerant to variations in their values. The initial values suggested by COAST are chosen such that, for most data sets, a user should gradually decrease *def* to maximize sensitivity, and increase *lambda* to minimize non-linearity. This process may require up to 2–4 trial values in some cases, and is efficient since the software allows for performing MaxEnt reconstruction on a single plane before running a full reconstruction. More detailed discussions on *def, lambda*, and the MaxEnt algorithm employed here have been described previously [18,25,28]. RNMRTK is available from J. Hoch upon request (hoch@uchc.edu).

3. Results and discussion

We define non-uniform sampling in this report as acquiring data using a different number of transients for different evolution times. We do not consider acquiring data at non-integer multiples of the incremented time interval (dwell time) in a given indirect evolution period since the MaxEnt reconstruction algorithm depends upon an inverse Fourier transform and therefore requires all time domain data to occur on an evenly spaced grid of sample times [25]. Previous reports of non-uniform sampling with MaxEnt reconstruction to obtain multidimensional spectra in both solution [18,20,29] and solid phase [30] have operated in the special case of acquiring either zero or a fixed number of transients for every point on the regular grid of evolution times that would otherwise be sampled uniformly. We follow this practice here also, but note that gradient coherence selection techniques can significantly shorten the lengths of phase cycles and enable more general implementations of non-uniform sampling.

Whereas previous implementations used non-uniform sampling in three-dimensional experiments in only one indirect dimension [20], in the current study we employed non-uniform sampling in both indirect dimensions. This is achieved by collecting data for a subset of samples selected from the full two-dimensional grid of uniformly distributed samples, as shown in Fig. 1B. An important motivation for performing non-uniform sampling stems from the ability to match the density of acquired data to the expected signal envelopes. Thus the average density of samples is constant across the constant-time nitrogen evolution period, and exponentially decaying across the carbon period. For observing Lorentzian signals, an exponentially decaying density of samples ensures that the majority of experimental time is devoted to the region where the signal, and hence the signal-to-noise ratio (SNR), is strongest, while collecting data sparsely at long evolution times, where the SNR is low, ensures that high resolution is obtained [31]. This explains why the overall sensitivity remains high, even though non-uniform sampling involves acquiring many fewer transients than uniform sampling (see Fig. 3) [12].

An important benefit of the non-uniform sampling strategy described here is that the spectra produced by

MaxEnt reconstruction are in the same format as multidimensional spectra produced through conventional Fourier processing of uniformly sampled data and can be analyzed in an identical manner. This is in contrast to reduced dimensionality experiments in which the chemical shift information must be obtained with additional analysis of the frequency-domain spectra [14,15,32,33]. However, the approach described here can be used to generate a basis set of 3D experiments from which information equivalent to 4D data can be extracted, following the strategies of reduced-dimensionality [32] and/or projection–reconstruction methods [17] as described in [21]. Herein we use a conventional method of determining assignments which entails comparing narrow spectral regions in the ^{1}H–^{13}C planes of the 3D backbone assignment experiments, called strip plots, to determine the topologies of spin systems. Strip plots of the spectra obtained by maximum entropy reconstruction of non-uniformly acquired data are shown in Figs. 2D–F and plots from the identical spectral regions from conventionally processed uniformly acquired data are shown in Figs. 2A–C. In spite of the much shorter acquisition time, the spectra in Figs. 2D–F display similar resolution in both the nitrogen and carbon dimensions as the spectra shown in Figs. 2A–C, which have been acquired with the use of uniform sampling. Importantly, the spectra of Figs. 2A–C and D–F show very similar sensitivity (Fig. 3) indicating that elimination of three-quarters of the sampling points in the non-uniform sampling approach does not critically compromise sensitivity (see Fig. 3B, where both spectra have the same number of scans). Since MaxEnt reconstruction is insensitive to incompletely sampled data, there is no need to apply a weighting function to the data before processing. In this respect, it is possible to obtain higher resolution spectra from truncated, uni-

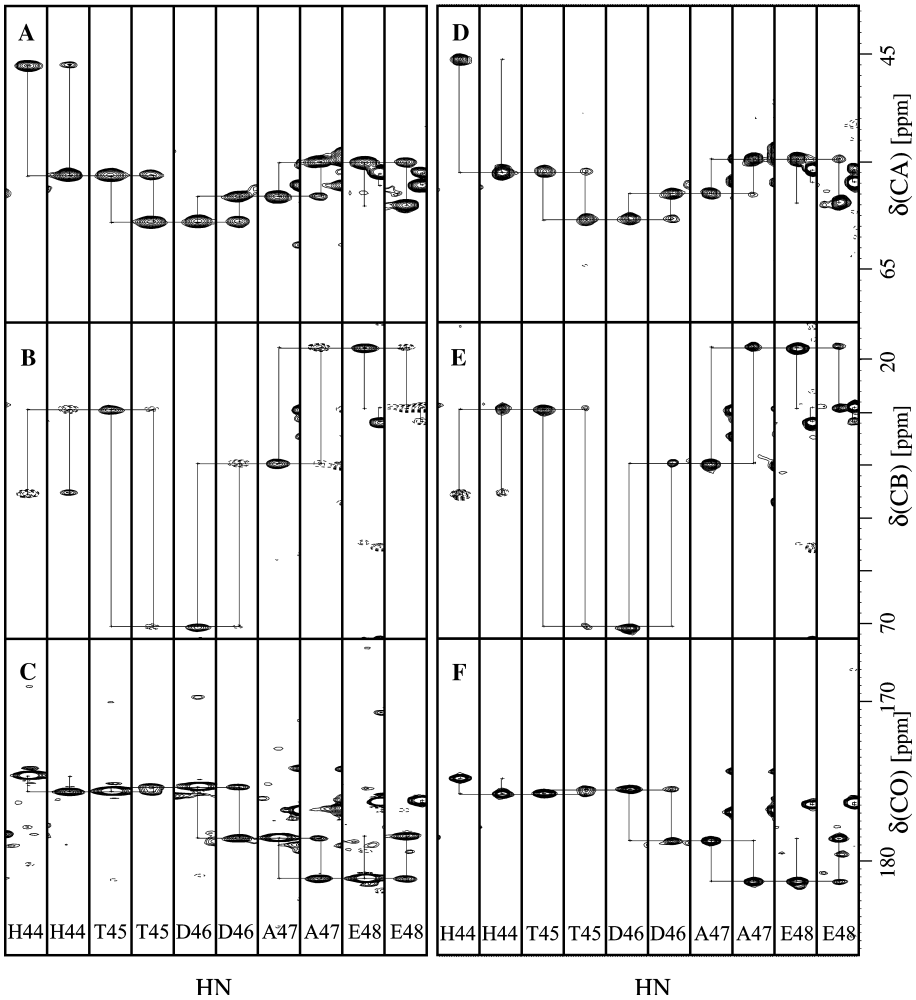

Fig. 2. Selected strips of spectra obtained with (D–F) the non-uniform sampling scheme described in the text and in Fig. 1 and conventional experiments (A–C). Alternating strips of (A, D) HN(CO)CA and HNCA spectra, starting from left with the HN(CO)CA, (B, E) HN(CO)CACB and HNCACB, and (C, F) HNCO and HN(CA)CO. It is instructive to use strip positions based upon ^{1}H–^{15}N peak lists generated from the uniformly sampled spectra for both sets of spectra to highlight the conservation of the peak positions between the two types of spectra. Note that the interresidue peak that seems to be missing in the HNCA strip of H44 can be observed at a lower contour level.

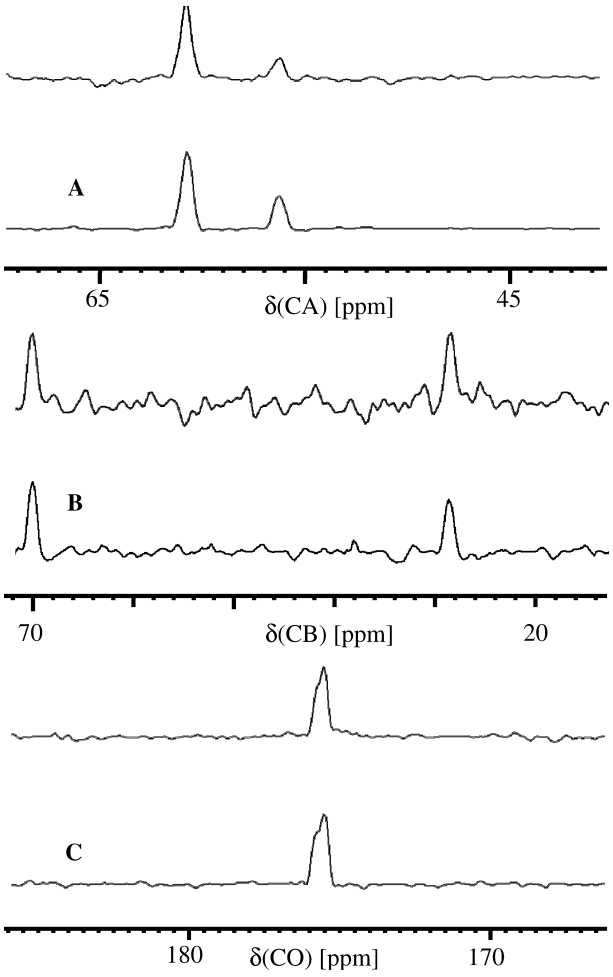

Fig. 3. Cross-sections taken along the carbon dimensions of (A) HNCA, (B) HNCACB and (C) HN(CA)CO spectra. For each spectrum, a trace of the strip of residue T45 (see Fig. 2) is displayed for the non-uniformly (top) and conventionally (bottom) acquired data. The comparison clearly emphasizes the conservation of good signal to noise and resolution in the spectra obtained non-uniformly.

form data by MaxEnt reconstruction than by Fourier transform methods, which would rely upon apodization functions to suppress truncation artifacts at the expense of introducing additional line broadening.

The sequential strip connections and peak assignments shown here, which are currently under investigation, were obtained with the help of the automated assignment program IBIS [27]. Most importantly, non-uniform sampling and MaxEnt reconstruction provide the opportunity to collect data with higher resolution [20,34]. Improving the accuracy and resolution of spectra by using non-uniform sampling and MaxEnt reconstruction means that these spectra are more amenable to determining assignments, and should lead to enhanced performance of automated assignment software [27].

Spectra obtained by MaxEnt reconstruction show high accuracy and sensitivity [34]. However, unlike the discrete Fourier transform (DFT), spectral estimates via maximum entropy reconstruction are non-linear functions of the initial experimental data. We observe that MaxEnt reconstruction enhances strong peaks but slightly attenuates weak peaks (compare Figs. 2A–C and D–F and see Fig. 3). This side effect can be minimized by adjusting the parameters in the MaxEnt reconstruction, which was, however, not necessary in the current work. Besides, this is not a serious concern for the experiments described here as all sequential connections are established via the major cross peaks within each pair of experiments.

4. Conclusions

Non-uniform sampling of both indirect evolution periods of a suite of 3D triple-resonance NMR experiments coupled with MaxEnt reconstruction is shown to be a general solution for significantly reducing the experimental time needed to obtain these experiments. Six 3D experiments were acquired in 32 h and 30 min, compared to 146 h that are needed with uniform sampling. In this report, the number of scans per evolution time was 0 or a fixed integer multiple of the length of the phase cycle. This methodology can be further extended by allowing the number of scans per evolution time to be any integer multiple of the phase cycle, which would produce more finely grained non-uniform sampling.

Acknowledgments

We acknowledge support from the National Institute of Health (Grants GM47467 and RR 00995 to G.W., CA89940 to D.R.) and the Rowland Institute at Harvard. We thank Drs. Thilo Stehle and Gowtham Subbarao for providing the protein sample. We thank Dr. Sven Hyberts for help with the program IBIS and Gregory Heffron for assistance with the NMR instrument. DF was partially supported by the Swiss National Science Foundation (81EL-068377).

References

[1] L.E. Kay, M. Ikura, R. Tschudin, A. Bax, Three-dimensional triple-resonance NMR spectroscopy of isotopically enriched proteins, J. Magn. Reson. 89 (1990) 496–514.

[2] M. Ikura, L.E. Kay, A. Bax, A novel approach for sequential assignment of ^{1}H, ^{13}C, and ^{15}N spectra of proteins: heteronuclear triple-resonance three-dimensional NMR spectroscopy. Application to calmodulin, Biochemistry 29 (1990) 4659–4667.

[3] R.T. Clubb, V. Thanabal, G. Wagner, A constant-time three-dimensional triple-resonance pulse scheme to correlate intraresidue $^{1}H^{N}$, ^{15}N, and $^{13}C'$ chemical shifts in ^{15}N–^{13}C-labeled proteins, J. Magn. Reson. 97 (1992) 213–217.

[4] G.T. Montelione, G. Wagner, Triple resonance experiments for establishing conformation-independent sequential NMR assignments in isotope-enriched polypeptides, J. Magn. Reson. 87 (1990) 183–188.
[5] R.T. Clubb, V. Thanabal, G. Wagner, A new 3D HN(CA)HA experiment for obtaining fingerprint HN-Halpha peaks in ^{15}N- and ^{13}C-labeled proteins, J. Biomol. NMR 2 (1992) 203–210.
[6] R.T. Clubb, G. Wagner, A triple-resonance pulse scheme for selectively correlating amide ^{1}HN and ^{15}N nuclei with the ^{1}H alpha proton of the preceding residue, J. Biomol. NMR 2 (1992) 389–394.
[7] A.E. Kelley, H.D. Ou, R. Withers, V. Dötsch, Low-conductivity buffers for high-sensitivity NMR experiments, J. Am. Chem. Soc. 124 (2002) 12013–12019.
[8] R.R. Ernst, G. Bodenhausen, A. Wokaun, Principles of Nuclear Magnetic Resonance in One and Two Dimensions, Clarendon Press, Oxford, 1987.
[9] A. Medek, E.T. Olejniczak, R.P. Meadows, S.W. Fesik, An approach for high-throughput structure determination of proteins by NMR spectroscopy, J. Biomol. NMR 18 (2000) 229–238.
[10] K. Wüthrich, NMR of Proteins and Nucleic Acids, Wiley-Interscience, New York, 1986.
[11] R.A. Venters, R. Thompson, J. Cavanagh, Current approaches for the study of large proteins by NMR, J. Mol. Struct. 602–603 (2002) 275–292.
[12] D. Rovnyak, J.C. Hoch, A.S. Stern, G. Wagner, Resolution and sensitivity of high field nuclear magnetic resonance spectroscopy, J. Biomol. NMR (2004) (in press).
[13] J.C.J. Barna, E.D. Laue, Conventional and exponential sampling for 2D NMR experiments with application to a 2D NMR spectrum of a protein, J. Magn. Reson. 75 (1987) 384–389.
[14] S. Kim, T. Szyperski, GFT NMR, a new approach to rapidly obtain precise high-dimensional NMR spectral information, J. Am. Chem. Soc. 125 (2003) 1385–1393.
[15] K. Ding, A.M. Gronenborn, Simultaneous and accurate determination of one-bond (15)N–(13)C′ and two-bond (1)H(N)–(13)C′ dipolar couplings, J. Am. Chem. Soc. 125 (2003) 11504–11505.
[16] E. Kupce, R. Freeman, Fast multi-dimensional NMR of proteins, J. Biomol. NMR 25 (2003) 349–354.
[17] E. Kupce, R. Freeman, Fast reconstruction of four-dimensional NMR spectra from plane projections, J. Biomol. NMR 28 (2004) 391–395.
[18] P. Schmieder, A.S. Stern, G. Wagner, J.C. Hoch, Quantification of maximum-entropy spectrum reconstructions, J. Magn. Reson. 125 (1997) 332–339.
[19] K.-B. Li, A.S. Stern, J.C. Hoch, Distributed parallel processing for multidimensional maximum entropy reconstruction, J. Magn. Reson. 134 (1998) 161–163.
[20] P. Schmieder, A.S. Stern, G. Wagner, J.C. Hoch, Improved resolution in triple resonance spectra by nonlinear sampling in the constant-time domain, J. Biomol. NMR 4 (1994) 483–490.
[21] Z.J. Sun, S.G. Hyberts, D. Rovnyak, A.S. Stern, J.C. Hoch, G. Wagner, Rapid NMR side-chain assignments with reduced-dimensionality HC (CO)NH and non-uniform sampling (2004) (submitted).
[22] T. Yamazaki, W. Lee, C.H. Arrowsmith, D.R. Muhandiram, L.E. Kay, A suite of triple resonance NMR experiments for the backbone assignment of ^{15}N, ^{13}C, ^{2}H labeled proteins with high sensitivity, J. Am. Chem. Soc. 116 (1994) 11655–11666.
[23] V. Sklenár, M. Piotto, R. Leppik, V. Saudek, Gradient-tailored water suppression for ^{1}H–^{15}N HSQC experiments optimized to retain full sensitivity, J. Magn. Reson. A 102 (1993) 241–245.
[24] F. Delaglio, S. Grzesiek, G.W. Vuister, G. Zhu, J. Pfeifer, A. Bax, NMRPipe: a multidimensional spectral processing system based on UNIX pipes, J. Biomol. NMR 6 (1995) 277–293.
[25] J.C. Hoch, A.S. Stern, NMR Data Processing, Wiley-Liss, New York, 1996.
[26] C. Bartels, T. Xia, M. Billeter, P. Güntert, K. Wüthrich, The program XEASY for computer-supported NMR spectral analysis of biological molecules, J. Biomol. NMR. 5 (1995) 1–10.
[27] S. Hyberts, G. Wagner, IBIS — a tool for automated sequential assignment of protein spectra from triple-resonance experiments, J. Biomol. NMR 26 (2003) 335–344.
[28] J.C. Hoch, A.S. Stern, D.L. Donoho, I.M. Johnstone, Maximum entropy reconstruction of complex (phase-sensitive) spectra, J. Magn. Reson. 86 (1990) 236–246.
[29] P. Schmieder, A.S. Stern, G. Wagner, J.C. Hoch, Application of nonlinear sampling schemes to COSY-type spectra, J. Biomol. NMR 3 (1993) 569–576.
[30] D. Rovnyak, C. Filip, B. Itin, A.S. Stern, G. Wagner, R.G. Griffin, J.C. Hoch, Multiple-quantum magic-angle spinning spectroscopy using nonlinear sampling, J. Magn. Reson. 161 (2003) 43–55.
[31] J.C.J. Barna, E.D. Laue, M.R. Mayger, J. Skilling, S.J.P. Worrall, Exponential sampling, an alternative method for sampling in two-dimensional NMR experiments, J. Magn. Reson. 73 (1987) 69–77.
[32] T. Szyperski, G. Wider, J.H. Bushweller, K. Wuthrich, Reduced dimensionality in triple resonance experiments, J. Am. Chem. Soc. 115 (1993) 9307–9308.
[33] J.P. Simorre, B. Brutscher, M.S. Caffrey, D. Marion, Assignment of NMR spectra of proteins using triple-resonance two-dimensional experiments, J. Biomol. NMR 4 (1994) 325–333.
[34] A.S. Stern, K.-B. Li, J.C. Hoch, Modern spectrum analysis in multidimensional NMR spectroscopy: comparison of linear-prediction extrapolation and maximum-entropy reconstruction, J. Am. Chem. Soc. 124 (2002) 1982–1993.