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Optimized angle selection for radial sampled NMR experiments

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ABSTRACT

Sparse sampling offers tremendous potential for overcoming the time limitations imposed by traditional Cartesian sampling of indirectly detected dimensions of multidimensional NMR data. Unfortunately, several otherwise appealing implementations are accompanied by spectral artifacts that have the potential to contaminate the spectrum with false peak intensity. In radial sampling of linked time evolution periods, the artifacts are easily identified and removed from the spectrum if a sufficient set of radial sampling angles is employed. Robust implementation of the radial sampling approach therefore requires optimization of the set of radial sampling angles collected. Here we describe several methods for such optimization. The approaches described take advantage of various aspects of the general simultaneous multidimensional Fourier transform in the analysis of multidimensional NMR data. Radially sampled data are primarily contaminated by ridges extending from authentic peaks. Numerical methods are described that definitively identify artifactual intensity and the optimal set of sampling angles necessary to eliminate it under a variety of scenarios. The algorithms are tested with both simulated and experimentally obtained triple resonance data.

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1. Introduction

With the advent of cold probe technology, time rather than sensitivity is often a limiting factor in multidimensional NMR experiments of macromolecules such as proteins. This is particularly true in the case of experiments of high dimensionality. For example, the collection of a traditional four-dimensional experiment with high resolution, because of the strict requirement of Cartesian sampling, would generally require weeks if not months of measurement time. Multiple approaches have recently been introduced in an effort to overcome the measurement time requirements presented by sequential and equi-spaced sampling of time domain data. These include analysis of non-linearly sampled time domain data [1,2], filter diagonalization [3], the GFT-based approach [4], projection reconstruction [5] and the direct multidimensional Fourier transform [6–8]. Although all of the methods listed have proven utility, the basis for selecting one method over another has yet to be established. This uncertainty arises from the various sparse sampling schemes employed by each of the methods.

Of the sparse sampling methods radial sampling of the indirect evolution domain is perhaps most appealing under the appropriate conditions because of its suitability to processing with both deterministic and statistical methods [9–13]. Widely implemented in the context of projection reconstruction and the equivalent multidimensional Fourier transform, this sampling scheme is desirable in many cases because of the flat baseline outside of the ridges that extend from the peaks. Additionally, it has been shown that relatively few data points are needed to resolve specific spectral information [12]. In the context of (3,2) projection reconstruction and its related techniques, radial sampled data are first processed into two-dimensional tilt planes where the tilt angle is dependent upon the radial sampling angle selected during data collection. Subsequently, various methods can be used to either generate a final spectrum or peak list. In the context of direct multidimensional Fourier transform, the radial sampled data are processed either into single angle multidimensional spectra, with ridges extending from the peak chemical shifts at a vector dependent upon the radial sampling angle. Then the single angle spectra are compared to generate a final spectrum. Alternatively, multiple angle data sets can be combined and Fourier transformed simultaneously to produce a final multidimensional spectrum with ridges extending at all of the sampling angles included. Regardless of the processing method applied, the quality of the final data is directly dependent upon the radial sampling angles chosen during data collection. It is the issue of angle selection that is the focus here.

Two methods have been implemented for angle selection. The first, implemented in the context of HIFI-NMR, uses a probability distribution to determine subsequent angles from an initial data set [14]. The second, implemented in the context of projection reconstruction, selects subsequent angles by choosing the angle

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that resolves the most peaks from a provisional spectrum [15,16]. In brief, this approach first generates a provisional spectrum from data that has already been collected. Subsequent sampling angles are assessed by generating a skyline projection spectrum for each angle and scoring the skyline projections for the number of resolved peaks it contains. A skyline projection spectrum is generated for each potential sampling angle by taking the maximum value along a vector extending through the provisional spectrum perpendicular to the angle of interest. If two peaks in the provisional matrix are on the same vector only one response is shown in the skyline projection. The next angle is selected by comparing the number of resolved peaks in each skyline projection spectrum and avoiding angles that have relatively few resolved peaks in their skyline projections. As pointed out by the authors, this algorithm functions optimally when a spectrum is not too complex. When the complexity of the spectrum increases the algorithm could falter, primarily from limited resolution in the skyline spectra. Additionally, this method does not present the ability to determine when a sufficient number of radial sampled angle spectra have been collected. This inability arises from not treating the peaks in the provisional spectrum individually, but rather looking at the total number of resolved peaks in the skyline projection. Only in the case where the total number of peaks resolved in the skyline spectrum is equal to the number of peaks in the provisional spectrum is one able to assess that 'enough' data have been collected. In the absence of such a condition it is impossible to decipher an authentic peak from an artifact peak. In the absence of a deterministic angle selection algorithm, data collection becomes inefficient and time is potentially wasted by collecting too much data or by collecting data of poor quality (i.e. data with a large number of artifact peaks).

In order to increase the utility of the radial sampling approach we present methods to optimize the set of sampling angles employed. The approaches can be classified into two general situations. The first is when the peak resonance frequencies are known and need to be resolved from artifact and the second is when the peak resonance frequencies are not known and need to resolved and assigned. The former case corresponds to a need to measure variation in intensity such as in a hydrogen exchange or classical relaxation experiment. For this two algorithms have been developed. One determines the *minimum* set of angles necessary to distinguish authentic peak intensity from artifactual intensity introduced by the Fourier analysis of radially sampled data (i.e. the ridges). The second algorithm determines the fewest angles needed to produce an artifact free spectrum when a lower value comparison is performed. Alternatively, for situation where the peak resonance frequencies are not known, an algorithm is developed to provide for iterative post-acquisition determination of the optimal sampling angles to collect and to provide a definitive conclusion regarding the separation of authentic peak intensity from ridge artifacts. This type of algorithm is essential for the optimized application of radial sampling of data to be employed for de novo resonance assignment. Both algorithms are tested in the context of a radial sampled HNCO processed with the direct multidimensional Fourier transform combined with lower value comparison but are applicable, with minor modifications to the selection criteria, to more sophisticated artifact removal schemes.

2. Theory

In a three-dimensional spectrum, radial sampling is accomplished by linking the evolution of the two indirect dimensions by setting $t_1 = \tau\cos(\alpha)$ and $t_2 = \tau\sin(\alpha)$, where τ is the incremented time domain and α is the sampling angle, while continuing to collect the traditional quadrature pairs for both indirect dimensions [15]. To generate a frequency domain spectrum the data can be processed with a direct single step, 2D Fourier transform [11]

$$S(\omega_1,\omega_2) = \sum_{t_1=0}^{t_1^{max}} \sum_{t_2=0}^{t_2^{max}} \exp(-i\omega_1 t_1)\exp(-j\omega_2 t_2) f(t_1,t_2) w(t_1,t_2)$$

where i and j are quarternion numbers; t_1, t_2 are the incremented times, ω_1 and ω_2 comprise the frequency pair being determined, $f(t_1,t_2) = \exp(-i\Omega_1 t_1)\exp(-j\Omega_2 t_2)$ is the data being transformed, Ω_1 and Ω_2 are the chemical shifts for time domains 1 and 2, respectively, and $w(t_1,t_2)$ is a weighting factor to account for the non-equispaced sampling of the time domain.

When t_1 and t_2 are incremented independently, in traditional Cartesian fashion, the direct 2D Fourier transform produces the same results as the traditional sequential one-dimensional Fourier transforms. In the case of radial sampling the Fourier transform is effectively underdetermined and produces ridges that extend through the spectrum where Eq. (2) is satisfied

$$\frac{\omega_1 - \Omega_1}{\omega_2 - \Omega_2} = \tan(\alpha) \tag{2}$$

This relationship is true when α is either positive or negative, leading to two ridges extending from the each peak in the spectrum, one with a positive slope and the other with a negative slope.

We define an ordered triple with the directly detected dimension, ω_3, in the first position and the two linked indirect dimensions, ω_1 and ω_2, in the second and third positions, respectively. The following linear equation describes the ridge extending from a peak located at point P_1 in the so-called (3,2) radially sampled experiment, where we employ the nomenclature of Szyperski and Atreya [17]

$$P = P_1 + n(0, \cos(\pm(90-\alpha)), \sin(\pm(90-\alpha))) \tag{3}$$

where P represents a point on the ridge, α is the sampling angle and n is a scalar. As before, the ± sign is included because two ridges extend, one with a positive slope and another with a negative slope. In the case of a (4,2) radially sampled experiment four ridges would extend from each peak. In this case, Eq. (3) is expanded to account for two sampling angles, α and β, as described by the following equation:

$$P = P_1 + n(0, \cos(\pm(90-\alpha))\cos(\pm(90-\beta)), \sin(\pm(90-\alpha)) \times \cos(\pm(90-\beta)), \sin(\pm(90-\beta))) \tag{4}$$

These basic descriptions allow the determination of whether two peaks are resolved at a given sampling angle and where all of the potential artifact positions are located. Further, this description allows all peaks to be analyzed simultaneously, regardless whether they are resolved in the directly detected dimension.

2.1. Peak–peak resolution

Two peaks in a radially sampled experiment are not resolved if the ridge from one of the peaks intersects the second. To determine if two peaks are resolved the distance from one of the peaks to the closest points on the positive and negative ridge components of the other peak is determined. If both distances are greater than a specified cutoff (chosen to reflect a finite line width), the peak is considered resolved. The distance measurement is illustrated in Fig. 1A, where the peaks are represented by points P_1 and P_2. For clarity only one of the ridge components is shown in the figure. The distance between P_2 and the ridge from P_1 is determined by applying the point to line distance algorithm commonly encountered in computer graphics [18]. Here we generalize this approach. The first step is to define an equation in order to solve for point P_{min}, the closest point on the ridge to the peak located at P_2

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