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Periodicity, planarity, residual dipolar coupling, and structures

Joseph D. Walsh, Yun-Xing Wang *

Protein Nucleic Acid Interaction Section, Structural Biophysics Laboratory, NCI-Frederick, NIH, Frederick, MD 21702, USA

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Abstract

The periodic behavior of residual dipolar couplings (RDCs) arising from nucleic acid and protein secondary structures is shown to be more complex and information-rich than previously believed. We have developed a theoretical framework which allows the bond vector orientation of nucleic acids and the peptide plane orientations of protein secondary structures to be extracted from their Dipolar waves. In this article, we focus on utilizing ''Dipolar waves'' of peptides to extract structure information, and describe in more detail the fundamental principles of the relationship between the periodicities in structure and RDCs, the practical procedure to extract peptide plane orientation information from RDC data, and assessment of errors using Monte-Carlo simulations. We demonstrate the utility of our method for two model α-helices, one kinked and one curved, and as well as an irregular β-strand. Published by Elsevier Inc.

Keywords: RDC; Periodicity; Planarity; Secondary structure

1. Introduction

The vast majority of protein and nucleic acid structures consist of highly regular secondary structures, such as α-helices, β-strands, and duplexes. These regular secondary structures are the building blocks that are arranged in three-dimensional space to form the scaffolds of protein and nucleic acid structures. These building blocks are highly repetitive and periodical in nature, a property which is reflected in any type of geometric physical measurements, such as residual dipolar couplings (RDCs) [1–3].

When a protein or nucleic acid sample is dissolved in an alignment medium (pf1 phage, DMPC/DHPC, purple membrane, etc.), dipolar interactions between spins are no longer averaged to zero. In a weakly aligned solution, this interaction is called the residual dipolar coupling because it is only a factor of 10^{-3} compared to its static value [4]. The amplitude and sign of the RDC depends on the orientation of the vector connecting the pair of spins relative to the alignment axis system in a magnetic field. For this reason, the RDC is said to contain orientation information about how a pair of spins (atoms) are aligned in relation to a common reference system, i.e., the alignment tensor axis system, and have been used for structure determination in various ways since the late 1990s [5–8].

Since the RDC reflects the orientations of a spin pair, it is rather intuitive and obvious in retrospect that the repetitiveness and periodicity in regular protein and nucleic acid secondary structures are closely correlated to the amplitude and sign of the RDC. When they are plotted vs. the residue number of a regular secondary structure, the RDCs show a periodical pattern (Fig. 1) [1–3]. The significance of this Dipolar wave should not be underestimated. First, it provides a direct link between regular secondary structure and RDC measurements, as illustrated in Fig. 1. What is shown in Fig. 1 is not only the periodic pattern of the Dipolar wave but also a certain resemblance of the Dipolar wave to the structure itself if the molecule is aligned at particular angles relative to the alignment tensor axis system. In other words, the wave itself is indicative of the type of second-

* Corresponding author. Fax: +1 301 846 6231.
E-mail address: wangyu@ncifcrf.gov (Y.-X. Wang).

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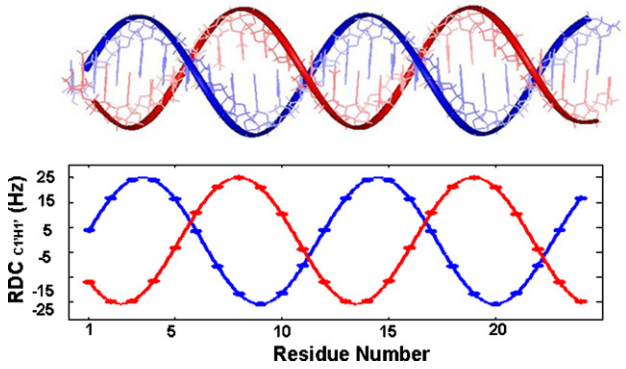

Fig. 1. The periodicity inherent in a duplex structure is strikingly mirrored in the Dipolar Waves when a duplex is orientated at a particular angle. In this case, the Dipolar wave from the ribose C1′H1′ for a B-form DNA duplex oriented at $(\Theta, \Phi) = (40°, 90°)$ is shown.

ary structure element. Second, the shape and amplitude of the Dipolar waves depend on the orientation of the structure elements in relation to the alignment axis system [2]. When the RDC is explicitly written in terms of the spin pair orientation in a molecular frame in relationship to the alignment tensor system, one can extract the orientation information of spin pairs as well as that of the secondary structure elements [2].

In the case of protein, the peptide backbone consists of consecutive peptide planes. Within a peptide plane, there are a number of spin pairs whose RDCs are experimentally measurable. The orientation of inter-nuclear vectors connecting these spin pairs within the plane is dictated by the constraints of planarity of the peptide backbone and its chemical bond angles. When the orientations of inter-nuclear vectors within the plane are considered collectively, the RDC can be expressed explicitly in terms of the plane orientation (Eq. (4)). The plane orientation is defined by its normal vector, plus a rotation around the normal (Fig. 3) in spherical coordinates. The significance of the interpretation of the RDC in terms of the planarity as the intrinsic peptide backbone structural feature is twofold. First, it eliminates numerous possible bond vector orientations that would otherwise satisfy RDC values when RDCs are considered individually but significantly deviate either from planarity or the chemical bond angles of the peptide plane. Second, when considering the peptide plane normal vectors these normals also exhibit periodicity in regular secondary structure. Therefore, when the RDC is expressed in terms of both planarity and periodicity in an explicit analytical equation (Eq. (4)), RDCs can be interpreted more directly in a "structural" way.

Using Eq. (4) one can extract orientation information pertinent to both individual bond vectors and secondary structure elements because the structure is determined directly in the alignment tensor axis system using the intrinsic constraints of periodicity and planarity (unpublished result). This report gives a more detailed account of the intricate relation between the RDC and periodicity and planarity, and how this can be used to derive local structural information of individual peptide plane orientations in a global reference system. This approach is distinct from the existing singular value decomposition (SVD) method [7] that relates the alignment tensor to a known molecular structure (solving for the Saupe matrix elements) without yielding new local structure information. We should point out that relating bond vectors within a peptide plane to solid state NMR measurements has been considered previously [9–11]. In this report we present a detailed account for a rigorous theoretical treatment of the correlation between the periodicity, planarity, and RDC measurement.

2. Theory

2.1. Periodicity in the RDC

For structural elements of a known type, such as the duplex in nucleic acids, or a protein α-helix or β-strand, the RDC between nuclei A and B, D_{AB}, can be expressed in terms of the coordinate system most natural to the structure. In this coordinate system, the orientation of the secondary structure mean axis is defined by the spherical angles (Θ, Φ) with respect to the alignment frame, and an individual inter-nuclear vector is referenced to this axis by use of spherical angles (δ_i, ρ_i). The slant angle, δ_i is the angle the inter-nuclear vector AB makes with the structure axis, with ρ_i the phase of the inter-nuclear vector about this axis. For a structural element with axis oriented along the principle alignment axis Z, the inter-nuclear vector AB is hence given in the usual spherical coordinate notation as

$$\hat{r}^{\mathrm{AB,sec.str.}} = (\sin\delta^{\mathrm{AB}}\cos\rho^{\mathrm{AB}}, \sin\delta^{\mathrm{AB}}\sin\rho^{\mathrm{AB}}, \cos\delta^{\mathrm{AB}}) \quad (1)$$

with the inter-nuclear vector orientation for an arbitrary alignment (Θ, Φ) given by $\hat{r}^{\mathrm{AB}} = R_z(\Phi)R_y(\Theta)\hat{r}^{\mathrm{AB,sec.str.}}$.

By expressing the RDC equation using this coordinate system, RDCs are seen to possess periodicity in the azimuthal angle, ρ_i whose amplitude is modulated by coefficients dependent on Θ, Φ, and δ_i [2]

$$\begin{aligned} D_{\mathrm{AB},i} = {} & C_1(\Theta,\Phi,\delta_i)\cos 2\rho_i + C_2(\Theta,\Phi,\delta_i)\sin 2\rho_i \\ & + C_3(\Theta,\Phi,\delta_i)\cos\rho_i + C_4(\Theta,\Phi,\delta_i)\sin\rho_i \\ & + C_5(\Theta,\Phi,\delta_i). \end{aligned} \quad (2)$$

This equation is universally applicable to any periodical structural element. In it, $\rho_i = \rho_1 + 2\pi(i-1)/T$ is the phase of the inter-nuclear vector AB in the ith residue, which is related to the phase of the inter-nuclear vector of the first residue, ρ_1, and to the period, T ($T \approx 11$ residues/turn for A-form $T \approx 10$ residues/turn for B-form nucleic acids, and $T \approx 3.6$ residues/turn for an α-helix and $T \approx 2$ residues/turn for a β-strand in a protein). The coefficients $C_k = C_k(\Theta, \Phi, \delta_i)$ are given in Table 1.

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