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Analytical Modeling of Globular Protein-Ferritin in α-Helical Conformation: A White Noise Functional Approach

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Abstract**—**This study presents a conformational model of the helical structures of globular protein particularly ferritin in the framework of white noise path integral formulation by using Associated Legendre functions, Bessel and convolution of Bessel and trigonometric functions as modulating functions. The model incorporates chirality features of proteins and their helix-turn-helix sequence structural motif.

Keywords**—**Globular protein, modulating function, white noise, winding probability.

I. Introduction

UNDERSTANDING the dynamics, simulation and prediction of protein structure is of great interest in various fields ranging from bioinformatics to thermal chemistry for proteins are able to perform their functions by coiling their amino acid sequences into specific three-dimensional structure known as protein folding [1], [2]. Also, functional properties of proteins depend upon their folded conformations. Driven by experimental results that protein molecules demonstrate Brownian motion, the overwinding of DNA strands when stretched by forces as well as the chirality features of proteins and their helix-turn-helix structure, an analytical stochastic model of biopolymer conformations was developed and investigated successfully through the context of white noise analysis [3]-[6]. An interesting feature of this model is the modulating function $f(s)$, also known as the drift coefficient, where $0 \le s \le L$ (L being the length of the polymer), which contains information in the linear sequence of monomers in the biopolymer being considered. In this report, we used the Bessel and associated Legendre functions as modulating functions $f(s)$ which best describes Ferritin molecule in terms of chirality and helical structures.

II. Brownian Motion Model for Biopolymers

One of the features of biopolymers is its specific three-dimensional shapes or tertiary structure. For the case of protein molecule, the sequence of amino acids which make up its linear structure dictates the manner in which a polypeptide folds. To guide us in constructing an analytical model of biopolymers, it is important to consider previous experiments involving biopolymer's behavior in random-walk path representing polymer conformations.

In this section, we shall briefly review the work of C. C. Bernido et al. [3], [9]-[11] on particle entanglement. Consider a biomolecular chain of monomers of length L, winding around a second straight molecular chain taken to be oriented along the z-axis. Here L is taken to be the length of the winding molecule composed of N number of monomers, each of length l, such that $L = Nl$. Each monomer is allowed to rotate like a freely hinged rod and in discussing helical structures, it is convenient to employ circular cylindrical coordinates, that is $\mathbf{r} = (r, \vartheta, z)$. Taking the intersection of the straight polymer with the plane at the origin, we can now view the entangled polymer on the plane as a two-dimensional random walk consisting of N steps each of length l. By this, we can examine the various configurations of the random walk on the plane having endpoints $\mathbf{r}_0$ and $\mathbf{r}_1$. The radius r being fixed, $r=R$, since the interest is on the number of polymer's windings around the origin, where ϑ is taken to track the number of turns. By this, we can take the solutions of the Fokker-Planck equation, whose probability function is given by;

$$P(\vartheta_1, \vartheta_2) = \int \exp\left[-\frac{l}{L} \int_0^L \left[R\left(\frac{d\vartheta}{ds}\right) - \frac{l}{2D} A(s) \right]^2 ds \right] D[Rd\vartheta] \qquad (1)$$

where D is a constant diffusion coefficient and $A(s)$ is a length-dependent drift coefficient that is, $A(s) = f(s)$ where $0 \le s \le L$.

III. Winding Probabilities

Note that for a very long polymer chain on the $x-y$, that is $L = Nl$ that winds $n-$times around the $z-$axis, forming a helical configuration, the winding probability is given by [3]-[6].

$$W(n, L) = \sqrt{\frac{4\pi R^2}{lL}} \times \exp\left\{ -\frac{R^2}{lL} \left[2n\pi + \frac{l}{2DR} \int_0^L f(s) ds \right]^2 \right\} \qquad (2)$$

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where R is the radius of the helix and $L = Nl$. The function $f(s)$ is the drift coefficient that simulates the biochemical information encoded in the amino acids that make the polypeptide chain and D is a diffusion coefficient. Designating conventions for the handedness or chirality features for biopolymers [3], [6] and [12], a biopolymer that winds counterclockwise $(n > 0)$ is a left-handed polymer and right-handed for biopolymer which winds clockwise $(n < 0)$. Handedness or chirality of the biopolymers has a significant effect in obtaining the winding probability, $W(n, L)$. This winding probability function is used to model features of biopolymers not only the chirality, but also the overwinding when stretched and the helix-turn-helix motif. When the modulating function is zero, the winding probability is independent of the biopolymer's chirality or handedness.

IV. Modulating Functions for Helical Conformations

The drift coefficient $f(s)$ accounts for the constant interaction between the monomers in the polypeptide chain with its aqueous environment. It can also be noted from that for different forms of $f(s)$ as modulating function leads to different forms of winding probability $W(n, L)$ which in turns out to describe a specific winding conformation. In this report, we expand the work of Aringa, H. P. et al., [6], [13] to include the convolution of Bessel and trigonometric functions as drift coefficients.

A. Convolution of the Bessel and Trigonometric Functions

Consider a convolution of the Bessel and trigonometric function of the form

$$f(s) = k\begin{Bmatrix}\left[J_1(vs) + J_3(vs) + J_5(vs) + J_7(vs)\right] \\ -J_{-\frac{1}{2}} - \sin(vs)\cos(vs)\end{Bmatrix} \quad (3)$$

After thorough manipulation of this modulating function, the corresponding winding probability equation is given by

$$W(n,L) = \sqrt{\frac{4\pi R^2}{lL}} \times \exp\left\{-\frac{R^2}{lL}\left(2n\pi + \frac{lk}{2DRv}\begin{bmatrix} J[0] + \\ J[1] + J[2] + J[3] \\ -2C\left(\sqrt{vL}\right) + \dfrac{\cos(2vL) - 1}{4}\end{bmatrix}\right)^2\right\} \quad (4)$$

where

$$\begin{aligned} J[0] &= 1 - J_0(vL) \\ J[1] &= 1 - J_0(vL) - 2J_2(vL) \\ J[2] &= 1 - J_0(vL) - 2\{J_2(vL) - J_4(vL)\} \\ J[3] &= 1 - J_0(vL) - 2\{J_2(vL) - J_4(vL) - J_6(vL)\}, \end{aligned} \quad (5)$$

and $2C\left(\sqrt{vL}\right)$ is the Fresnel cosine integral.

As an application, consider ferritin [16], a globular protein complex consisting of protein subunits and is the primary intracellular iron-storage protein in both prokaryotes and eukaryotes keeping iron in a soluble and non-toxic form. Ferritin is consists of 183 residues in which 68% is helical forming 6 helices, which would be about 35 turns.

Using the data for proteins [14] where the radius of the helix $R = 0.25nm,\ l = 0.15nm,\ n = -35\ turns,$ the corresponding $W(n, L)$ versus L graph is shown in Fig. 1. The result shows 6 major peaks which conforms to the 6 helices of the ferritin's helix-turn-helix motif. It could be noticed that initially, there is a zero winding probability which signifies a non-helix structure followed by a winding shown in the curve that signifies a helix structure. In between the peaks are flat regions corresponding to zero winding probability, $W(n, L) = 0,$ regions in which windings or helical formations are inhibited. When one obtains the $W(n,L)$ versus L graph for left-handed polymer, that is, for $n > 0,$ a graph of $W(n,L) = 0$ yields for the same range of L which is interpreted as chiral symmetry is broken.

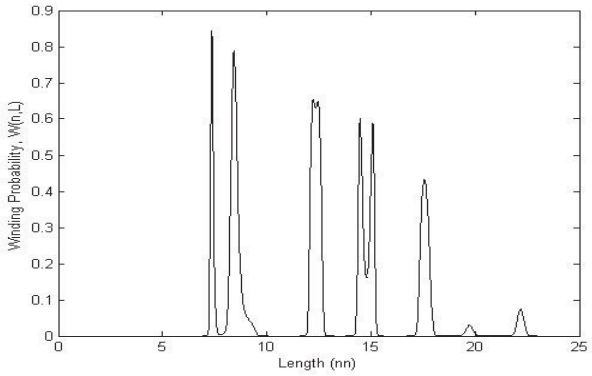

Fig. 1 $W(n, L)$ versus L for v=1.27 nm^{-1} and k/D =303.5 nm^{-1}

B. Associated Legendre Functions

Consider the drift coefficient of the form $f(s) = kP_l^m \cos(vs),$ where $P_l^m \cos(vs)$ is the Associated Legendre polynomials. The recurrence relations are generated using the relation given by [15]:

$$P_l^m(x) = (1 - x^2)^{m/2} \frac{d^m}{dx^m} P_l(x) \quad (6)$$

with $m \geq 0$ and $P_l(x)$ are the Legendre functions.

Given with the coefficient for the Associated Legendre polynomials, $l = 1$ and $m = 0,$ the drift coefficient now is of the form $f(s) = kP_1^0 = k\cos(vs)$ and after evaluation of this function and inserting to (2) and supplying the data for proteins where, $R = 0.25nm, l = 0.15nm, n = -35\ turns$ gives the resulting graph as shown in Fig. 2 where 6 helices are exhibited.

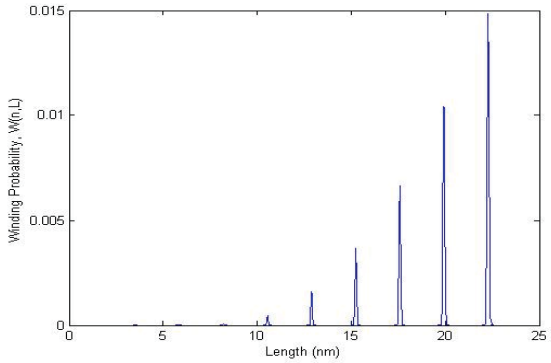

Fig. 2 $W(n,L)$ versus L for v=1.34 nm^{-1} and k/D =1843 nm^{-1}

If we consider $l=2$and $m=2$, the modulating function is of the form $f(s)=kP_2^2=3k\sin(vs)\cos(vs)$, and manipulation by inserting this to the winding probability equation given in (2), the corresponding graph is shown in Fig. 3 which conforms to some features of the globular protein-ferritin since 6 peaks were generated.

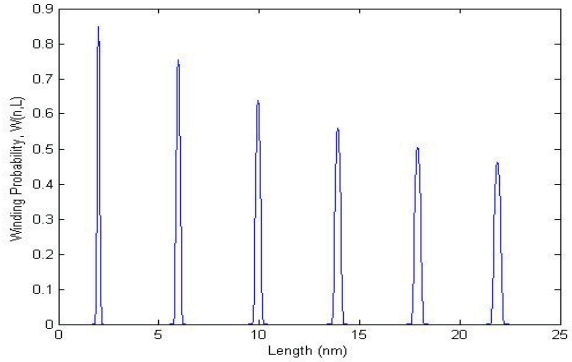

Fig. 3 $W(n,L)$ versus L for v=0.79 nm^{-1} and k/D =383 nm^{-1}

The above application of modulating functions namely: Associated Legendre functions and convolution of Bessel and trigonometric functions to the Winding Probability function mimics some of the features of the globular protein-ferritin molecule, its helix-turn-helix sequence as well as its chirality or handedness. In addition, an appropriate choice of drift coefficient could reproduce secondary structures of proteins which mainly consist of α -helices. It is further noted that the choice of drift coefficient or modulating function which resembles the studied functions is the non-periodic oscillatory behavior of the aforementioned functions applied in this study. However, the present mathematical formulation and representation of a polymer is based on a probabilistic theory and its results should be viewed in this context. Physically, for instance, the maximum number of winding is constrained by the total length L of the biopolymer [7]. Two proteins can have an identical three-dimensional structure even if only around 30% of their amino acid residues are identical [8].

As shown, in the application of the modulating functions to ferritin, it is interesting to note that if one graphs the winding probability $W(n,L)$ versus L, one obtains for $n>0, W(n,L)=0$, everywhere in the region for the same number of windings, values of the constants and range of L, which implies broken chiral symmetry. In these cases, right-handed biopolymers with α -helical secondary structures are favored.

V. Conclusion

In this paper, we have reported another way of handling the length-dependent drift coefficient $f(s)$, which serves as a modulating function of the model in the context of the white noise path integral formulation. We have expressed in particular, $f(s)$ in terms of the Associated Legendre functions and convolution of Bessel and trigonometric functions. The resulting winding probability $W(n,L)$ can be used to model globular proteins in an α -helical conformation. The specific protein, the ferritin is studied where some of the interesting features like its helix-turn-helix motif and chirality are employed. An extension of this work would be a more systematic use of available and existing data which could employ the form of the drift coefficient that encodes amino acid-solvent interactions for the many proteins whose main chains have α -helical secondary structures. The choice of the drift coefficient could also assess the physical features of the proteins in an α -helical conformation.

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