The free energy of globular protein chain is considered to be a functional defined on smooth curves in three dimensional Euclidean space. From the requirement of geometrical invariance, together with basic facts on conformation of helical proteins and dynamical characteristics of the protein chains, we are able to determine, in a unique way, the exact form of the free energy functional. Namely, the free energy density should be a linear function of the curvature of curves on which the free energy functional is defined. This model can be used, for example, in Monte Carlo simulations of exhaustive searching the native stable state of the protein chain.

1. Introduction

A fascinating and open question challenging physics, biochemistry and even geometry is the presence of highly regular motifs such as $\alpha$ – helices and $\beta$ – sheets in the folded state of biopolymers and proteins. A wide range

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of approaches have been proposed to rationalize the existence of such secondary structures (see, for example, reviews\textsuperscript{1,2} and references therein).

We propose a pure geometrical approach\textsuperscript{3,4,5} to describe the free energy of proteins, proceeding from the most general invariance requirements and basic experimental facts concerning the protein conformation. Taking into account the one-dimensional nature of the protein chains, the relevant macroscopic free energy $F$ should be considered as a functional defined on smooth curves $x(s)$ (or paths) in the three dimensional Euclidean space

$$F = \int f[x(s)] ds,$$

where $s$ is the length of a protein molecule. The reparametrization invariance of the functional $F$ demands the free energy density $f$ to be a scalar function depending on the geometrical invariants of the position vector $x(s)$, which describes the spatial shape of the protein chain. In three dimensional ambient space a smooth curve has two local invariants: curvature $k(s)$ and torsion $\kappa(s)$. In the general case of $D$ dimensional Euclidean embedding space there are $D - 1$ principal curvatures $k_\alpha(s), \alpha = 1, 2, ..., D - 1$ of a curve, where $k_1(s) = k(s)$ and $k_2(s) = \kappa(s)$.

The first principal curvature, or simply the curvature, $k_1(s) = k(s)$ of a curve characterizes the local bending of the curve at the point $s$. Hence, the dependence of free energy density $f$ on $k(s)$ specifies the resistance of a protein chain to be bent. The second curvature or torsion $\kappa(s)$ is determined by the relative rotation, around the tangent $dx(s)/ds$ at the point $s$, of two neighbor infinitely short elements of the protein chain. It is well known\textsuperscript{1,2} that, in the case of protein molecules, such a rotation is quite easy, as it requires little effort. In other words, this rotation results in small energy differences, allowing many overall conformations of a protein chain to arise. Thus the dependence of the free energy density $f$ on torsion $\kappa(s)$ can be neglected at least as a first approximation. Finally one can consider the free energy density $f$ to be a function only of the curvature $k(s)$, i.e., $f = f(k(s))$. In what follows we shall try to specify this dependence explicitly keeping in mind the description of globular protein conformation.

A peculiarity of conformation of globular proteins is that they can be ordered assemblies either of helices or of sheets as well as a mixture of helices and sheets\textsuperscript{1,2}. In the phenomenological macroscopic approach, which is developed here, the presence of sheets in the spatial structure of globular proteins implies the necessity to introduce, in addition to space curves $x(s)$, new dynamical variables $y(s, s')$ describing surfaces in ambient space. Obviously such an extension of the problem setting would complicate consid-
erably our consideration. Therefore we confine ourselves to helical proteins and try to answer the question: Is it possible to specify the function \( f(k(s)) \) in such a way that the extremals of the functional \( F = \int f \, ds \) would be only helices? The answer to this question turns out to be positive and unique, namely, the density of the free energy \( f(k(s)) \) should be a linear function of the curvature \( k(s) \). We sketch here the proof of this assertion (for details see Ref. 6,7,8).

2. Euler-Lagrange equations in terms of principal curvatures and their exact integrability

For an arbitrary functional \( F \) defined on curves \( x^i(s) \) in \( D \)-dimensional space the Euler-Lagrange equations are a set of exactly \( D \) equations

\[
\frac{\delta F}{\delta x^i} = 0, \quad i = 1, 2, \ldots, D. \tag{2}
\]

However, if the functional \( F \) depends only on the curvature

\[
F = \int f(k(s)) \, ds, \tag{3}
\]

then \( D \) equations (2.3) for \( D \) variables \( x^i(s), \quad i = 1, 2, \ldots, D \) give \( D - 1 \) equations for the principal curvatures \( k_\alpha(s), \quad \alpha = 1, 2, \ldots, D - 1 \)

\[
\frac{d^2}{ds^2} \left( f'(k_1) \right) = -\left( k_1^2 - k_2^2 \right) f'(k_1) + k_1 f(k_1), \tag{4}
\]

\[
2 \frac{d}{ds} \left( f'(k_1) k_2 \right) = k_2' f'(k_1), \tag{5}
\]

\[
k_3(s) = k_4(s) = \ldots = k_{D-1}(s) = 0. \tag{6}
\]

Thus, in the problem under consideration there are two nontrivial equations (4) and (5) for the curvatures \( k_1(s) \) and \( k_2(s) \). Equation (5) can be integrated with arbitrary free energy density \( f(k_1) \)

\[
(f'(k_1))^2 k_2 = C, \tag{7}
\]

where \( C \) is an integration constant.

Relation (7) enables one to eliminate the torsion \( k_2(s) \) from Eq. (4). As a result we are left with one nonlinear differential equation of the second order for the curvature \( k_1(s) \)

\[
\frac{d^2}{ds^2} \left( f'(k_1) \right) + \left( k_1^2 - \frac{C^2}{f'(k_1)^4} \right) f'(k_1) - k_1 f(k_1) = 0. \tag{8}
\]

Having resolved this equation for \( k_1(s) \), one can determine the rest of curvatures by making use of Eqs. (7) and (6). Integration of the respective
Frenet equations with principal curvatures found enables one to recover the curve $x(s)$ itself.

Notwithstanding its nonlinear character, Eq. (8) can be integrated in quadratures for arbitrary function $f(k_1)$. To show this, the first integral for this equation can be constructed proceeding from the symmetry properties of the variational problem under study

$$M^2 = \left(f'(k_1) - f(k_1)\right)^2 + \frac{C^2}{(f'(k_1))^2} + (k_1')^2(f''(k_1))^2.$$  

By direct differentiation of Eq. (9) with respect to $s$ one can be convinced that, for

$$f''(k_1) \neq 0,$$  

the relation (9) is an integral of the nonlinear differential equation (8), which determines the curvature of a stationary curve. From (9) we deduce

$$\frac{dk_1}{ds} = \pm \sqrt{g(k_1)},$$  

where

$$g(k_1) = \frac{1}{(f''(k_1))^2} \left[M^2 - \frac{C^2}{(f'(k_1))^2} - (k_1 f'(k_1) - f(k_1))^2\right].$$  

Integration of Eq. (11) gives

$$\int_{k_{10}}^{k_1(s)} \frac{dk}{\sqrt{g(k)}} = \pm (s - s_0)$$  

with $k_{10} = k_1(s_0)$.

Thus, if the free energy density $f(k_1)$ obeys the condition (10), then the curvature $k_1(s)$ and the torsion $k_2(s)$ of the stationary curve $x(s)$ are the functions of the parameter $s$ defined by Eqs. (13) and (7). The case when the condition (10) is not satisfied, i.e., when the free energy density $f(k_1)$ is a linear function of the curvature $k_1(s)$, will be considered below.

Now we are going to fix the function $f(k_1)$, requiring that all the solutions to the Euler-Lagrange equations are helices. From the differential geometry of curves it is known that the helices in three dimensional space have a constant curvature ($k_1$) and a constant torsion ($k_2$) which determine the radius $R$ and the step $d$ of a helix

$$R = \frac{k_1}{k_1^2 + k_2^2}, \quad d = \frac{2\pi|k_2|}{k_1^2 + k_2^2}. $$  

(14)
Under the condition (10) the curvature $k_1$ and the torsion $k_2$ of the stationary curve are not constant but they are the functions of the parameter $s$ which are defined in Eqs. (13) and (7). Hence, for the free energy density $f(k_1)$ we are looking for, we have to consider the case, when

$$f''(k_1) = 0,$$  \hspace{1cm} \text{(15)}

i.e., $f(k_1)$ is a linear function of the curvature $k_1(s)$

$$f(k_1) = \alpha + \beta k_1(s),$$  \hspace{1cm} \text{(16)}

where $\alpha$ and $\beta$ are constants. Indeed, substituting Eq. (16) into (7) and (8) we obtain the constant curvatures $k_1$ and $k_2$:

$$k_1 = -\frac{C^2}{\alpha\beta}, \quad k_2 = \frac{C}{\beta^2}. $$  \hspace{1cm} \text{(17)}

Since $k_1(s) = |x''(s)| > 0$, the constants $\alpha$ and $\beta$ should have opposite signs. It is natural to put $\alpha > 0$ and $\beta < 0$.

For the free energy density $f(k_1)$, linear in curvature, the integral (9) gives just the relation between the integration constants $M^2$ and $C^2$: $M^2(1 - (C/\beta M)^2) = \alpha^2$.

When $\alpha = 0$, Eq. (8) implies that the curvature $k_1(s)$ is an arbitrary function of $s$ and the integration constant $C$ vanishes. In this case Eq. (7) yields $k_2 = 0$. Hence, for $\alpha = 0$, the solutions to the Euler-Lagrange equations are arbitrary plane curves, which is evidently unacceptable for our purpose.

Finally, requiring that the stationary curves for the functional (3) are only helices, we uniquely determine the free energy density, namely it should be a linear function of the curvature

$$f(k_1) = \alpha - |\beta| k_1(s)$$  \hspace{1cm} \text{(18)}

with nonzero constants $\alpha$ and $\beta$, providing $\alpha > 0$ and $\beta < 0$. From the mathematical stand point, we have resolved in fact the inversion variational problem, i.e., proceeding from the specified solutions to the variational Euler-Lagrange equations (helical curves) we have uniquely recovered the respective functional.

Closing this section we would like to make the following note. It is well known, that in the protein physics the chirality property of these molecules is important. At the first glance we have ignored this point because from the very beginning we have eliminated the dependence of the free energy density $f$ on the curve torsion. But the fact is the integration constant $C$ in Eq. (7) is responsible for the chirality property of the helical curves under
consideration. Really, this constant is an analog of the Pauli-Lubanski pseudoscalar \(^6,12,13\) (in the three dimensional space-time the Pauli-Lubanski vector reduces to the pseudoscalar). The positive and negative values of this constant distinguish the left-hand and right-hand chirality of the helical curves.

3. Conclusion

Proceeding from rather general principles and making use of the basic facts concerning the conformation of globular proteins we have obtained, in a unique way, a geometrical model for phenomenological description of the free energy of helical proteins. It is worth noting that our functional (18) should be considered as an effective free energy of the helical protein which already takes into account the atomic interactions within the protein and with the solvent. Hence, there is no need to quantize it, as one proceeds in the random walk studies.\(^9,10\)

Certainly our simple model does not pretend to describe all the aspects of the protein physics. However, one can hope that it could be employed, for example, in Monte Carlo simulation to search for a stable native state of the protein. In this case the model can be used for the description of the free energy of individual parts (blocks) of a protein chain that have the helical form. Without any doubt, it should result in simplification and acceleration of the exhausting searching of the native stable state of the protein chain by a computer.\(^1,2\)

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