Soliton mediated protein folding

S. Caspi and E. Ben-Jacob
School of Physics and Astronomy, Tel Aviv University, 69978 Tel Aviv, Israel.
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Abstract

A novel approach to protein folding dynamics is presented. We suggest that folding of protein may be mediated via interaction with solitons which propagate along the molecular chain. A simple toy model is presented in which a Sine-Gordon field interact with another field $\phi$ corresponding to the conformation angles of the protein. We demonstrate how a soliton carries this field over energy barriers and consequently enhances the rate of the folding process. The soliton compensate for its energy loss by pumping the energy gained by the folded field. This scenario does not change significantly even in the presence of dissipation and imposed disorder.

The possibility for existence of solitons in bio-molecules has been widely studied since the work by Davidov which described solitons in proteins as means to transfer energy and charge [1]. It is evident today that solitonic excitation should be included in order to describe properly the biophysics of proteins and DNA molecules (e.g. see [2], [3], [4]), though their importance to the biological activity is still controversial.

In this paper we suggest that solitons may take part in the process of protein folding. The way in which a protein, a linear chain of amino acids, folds into a well defined, three dimensional native structure, is still far from being understood, although considerable effort is devoted to the subject. Since many biological proteins fold correctly without assistance, it is clear that all the information about their native state exists already in the sequence of amino acids [5]. The folding dynamics may be viewed as navigation process in the energy landscape of the protein conformational space. It is believed that the native structure corresponds to a small region in that space located in the vicinity of the ground state. Identifying this ground state is highly non trivial, but this is not the entire story. The ground state should be accessible dynamically within time scales not larger than minutes. As pointed out by Levinthal, stochastic search for the ground state over a random landscape might take cosmological time. From this fact one may draw the conclusion that the landscape of natural proteins is not random, but, rather, directed towards the ground state [6]. Conventionally, overcoming the energetic barriers is ascribed to a stochastic and uncorrelated thermal activation. Here we shall explore another option. Surly, random thermal processes have
important role in folding dynamics, but it may be that other processes, correlated and deterministic, dictates the folding pathway. To illustrates what is meant by this, suppose that energy gained at a point where the molecule already reached the lower energy state, could propagate efficiently to another point along the molecule and induce consequent fold there. This may go on further, as more energy is now released. In this way, large sections of a protein can fold very fast, and moreover, the folding process can be orchestrated deterministically. Solitons provide a mechanism for such stable, non dispersive energy transfer. We shall refer to a folding process induced by the propagation of a solitonic wave along the molecular chain as a Soliton Mediated Folding (SMF).

In order to explore the possibilities of soliton interaction with local conformation angles of the molecular chain, we introduce a toy-model inspired by the essential properties of protein molecules. Proteins have two local angles per residue (usually denoted \( \phi \) and \( \psi \)), which are relatively free, and may be considered as the only relevant degrees of freedom. For almost all amino residues in a polypeptide chain there are two distinct minima of the local potential energy in the \((\phi, \psi)\) plane, corresponding to the \( \alpha \) and the \( \beta \) local conformation of the chain. The only exceptions are glycine which has four minima and proline which has only one. We shall use a scalar variable \( \phi \) to represent local conformation of the protein. The local potential energy will be simply modeled by an asymmetric \( \phi^4 \) double well potential, namely

\[
V(\phi) = \varepsilon(\phi + \delta)^2(\phi^2 - \frac{2}{3}\phi\delta + \frac{1}{3}\phi^2 - 2),
\]

where \( \delta \) is the asymmetry parameter, ranging from \(-1\) to \(1\). The two minima are positioned at \( \phi = \pm 1 \). The energy difference between the minima is

\[
\Delta E = \frac{16}{3}\varepsilon\delta.
\]

The maxima is positioned at \( \phi = -\delta \) and its energy is always zero. We shall denote by \( \theta(x) \) an additional field \( (x \text{ is the position along the protein}) \), for which solitonic excitations can be realized. Excluding the interaction with \( \phi \), we choose its dynamic to be governed by the Sine-Gordon equation. It is convenient to picture \( \theta \) as an integral over a charge density field. Indeed, it was suggested that the dynamic of a charge in an ordered linear media is governed by the SG equation \[7\], \[4\]. Nevertheless, many nonlinear phenomena can be described using equations which allow solitonic excitation, and the SG dynamics was chosen mainly for practical reasons.

In order that solitons propagating through the protein backbone could mediate changes in its conformation, an interaction of an appropriate form should be introduced. Consider the following interaction potential:

\[
u(\theta, \phi) = \frac{\Lambda}{\Lambda + 1}(1 - \cos \theta)\phi^2,
\]

where \( \Lambda \) is a positive parameter. This is a natural way to introduce an interaction with the SG model (for example, interaction with an impurity in a long Josephson
transmission line \[8\]). Note that when \(\theta = 0 \mod 2\pi\) there is no interaction. If \(\theta\) is non zero \((\mod 2\pi)\), then, at the minima, the energy of the combined \(V\) plus \(u\) potential increases, which effectively lowers the barrier. We therefore expect that a sufficiently energetic soliton may enable transition from a meta-stable to a stable conformation (even without thermal noise).

The full Lagrangian density reads:

\[
\mathcal{L} = \frac{1}{2} \dot{\theta}^2 - \frac{1}{2} \theta_x^2 - \frac{(1 - \cos \theta)}{\Lambda + 1} + \frac{1}{2} m \dot{\phi}^2 - V(\phi) - u(\theta, \phi). \tag{4}
\]

Note that we used a continues limit for \(\phi\). This may be a reasonable approximation if the \(\theta\) field changes slowly in space compared with the length of a peptide unit. To make this model more realistic one may vary the parameters from point to point along the molecular chain since they depend on the nature of the local residue. Interaction between different points along the protein, due to electrostatic and Van der Waals forces, hydrogen bonding etc, can be introduced by letting the parameters depend on the overall conformation \(\text{i.e. they should be functionals of } \phi\). Nevertheless, to test our proposal for SMF, the simple model will suffice.

From Lagrangian (4) we get the equations of motion

\[
\ddot{\theta} = \theta_{xx} - \frac{1 + \Lambda \phi^2}{1 + \Lambda} \sin \theta - \Gamma \dot{\theta}, \tag{5}
\]

\[
m \ddot{\phi} = -4 \varepsilon (\phi + \delta)(\phi^2 - 1) - \frac{2 \Lambda}{1 + \Lambda} \phi(1 - \cos \theta) - \Gamma \phi \dot{\phi}, \tag{6}
\]

which also include dissipation terms. The scale was chosen in a way so that when \(\phi\) is at a minima, the coefficient of the \(\sin \theta\) term is exactly 1.

First, let us consider the small interaction limit (we ignore dissipation at this stage). We choose

\[
\theta(x, t) = f(\gamma(x - vt)) + \Delta \theta(x, t) \\
\phi(x, t) = 1 + \Delta \phi(x, t), \tag{7}
\]

where \(f(z) = 4 \tan^{-1} e^{-z}\) is the usual SG kink soliton moving with velocity \(v\) (\(\gamma\) is the relativistic factor). Assuming \(\Lambda\) is small and expanding to first order one finds:

\[
\Delta \ddot{\phi} + \omega^2 \Delta \phi = -\frac{4 \Lambda}{m \cosh^2 \gamma(x - vt)}, \tag{8}
\]

with \(\omega^2 = 8 \varepsilon (1 + \delta)/m\). The solution is

\[
\Delta \phi = -\frac{4 \Lambda}{\gamma v m \omega} \int_z^\infty dz' \frac{\sin \frac{\omega (z' - z)}{\gamma m}}{\cosh^2 z'}, \tag{9}
\]

where \(z \equiv \gamma(x - vt)\). Asymptotically, for large \(z\)
\[ \Delta \phi \simeq -\frac{4\Lambda}{m} \frac{e^{-2z}}{(\gamma v)^2 + (\omega/2)^2}. \]  

(10)

For \( v = 0 \) we can write an explicit solution

\[ \Delta \phi = -\frac{4\Lambda}{m\omega^2 \cosh^2 x}. \]  

(11)

We may compare this to the asymptotic result (10). Interpolation yields the following approximate solitary wave solution:

\[ \Delta \phi \simeq -\frac{4\Lambda/m}{(\gamma v)^2 + (\omega/2)^2} \frac{1}{\cosh^2 \gamma(x - vt)}. \]  

(12)

As we can see, near the center of the \( \theta \) kink, \( \phi \) is pushed away from its local minima \( \phi = 1 \) towards the other local minima so we expect that for strong enough interaction this would allow \( \phi \) to cross the energy barrier.

In order to get further insight into the behavior of this model when interaction is strong, we set all time derivative terms in (5) to zero, looking for a static solution. The equations can be solved exactly in the symmetric (\( \delta = 0 \)) case. we get (note that \( \phi = 0 \) is not a stable solution)

\[ \phi^2 = 1 - \frac{\Lambda}{2\varepsilon(1 + \Lambda)}(1 - \cos \theta). \]  

(13)

Inserting this to the equation for \( \theta \) we have

\[ \theta_{xx} = (1 - a) \sin \theta + a \sin \theta \cos \theta, \]  

(14)

with

\[ a \equiv \frac{\Lambda^2}{2\varepsilon(1 + \Lambda)^2}. \]  

(15)

A localized solution is

\[ \theta = 4 \tan^{-1} \frac{1}{q + \sqrt{1 + q^2}}, \quad \phi^2 = 1 - \frac{\Lambda}{\varepsilon(1 + \Lambda)} \frac{1}{1 + q^2}, \]  

(16)

with \( q \equiv \sqrt{1 - a} \sinh(x - x_0) \). We note that no localized solution exist for \( a > 1 \). This is the strong interaction - low energy barrier regime, where the solitonic behavior is totally destroyed. For small asymmetry, we may try to calculate first order correction to the above result. Generally, introducing a perturbation \( \Delta V \) in the static symmetric \( \phi \) equation, it can be shown that the first order correction is given by

\[ \Delta \theta(x) = -\frac{\Lambda}{4\varepsilon(1 + \Lambda)} \int_{-\infty}^{x} dx' G(x - x') \frac{\sin \theta_0(x')}{\phi_0(x')} \Delta V(x'). \]  

(17)

where \( \theta_0 \) and \( \phi_0 \) are the solutions (10) with \( x_0 = 0 \), and the Green function is
\[ G(x) = \frac{1}{2} \left( (1 - a) \sinh x + \frac{(3a - 1)a \sinh x + (3a + 1)(1 - a)x \cosh x}{1 + (1 - a) \sinh^2 x} \right). \]  

Unfortunately, for most of the interesting perturbations, including the asymmetric barrier perturbation

\[ \Delta V = 4\varepsilon \delta(\phi_0^2 - 1), \]  

the integral (17) can not be calculated analytically.

We shall turn now to discuss results of numerical simulations for the model. When a topological constraint was enforced upon the \( \theta \) field (a difference of \( 2\pi \) between the boundaries) and the system was allowed to relax via dissipation to a static conformation, a result similar to that of equation (11) was observed. Next we considered initial conditions of a moving \( \theta \) kink, with \( \phi = 1 \) (local minima) for all \( x \). Though it seems reasonable, based on the form of the interaction potential, that a traveling soliton might transfer enough energy to the \( \phi \) field to lift it over the energy barrier, it is certainly not obvious a priori whether this energy would be returned to the soliton. Note that interacting solitons also radiate plasmons, so it loses energy through this channel too (even without dissipation). It is useful to defines collective coordinate and momentum for a soliton

\[ Q = -\frac{1}{2\pi} \int_{-\infty}^{\infty} dx \, x \theta_x \quad P = -\int_{-\infty}^{\infty} dx \, \theta_x \dot{\theta}. \]  

These are in fact canonical variables which represent the soliton’s ‘center of mass’ and its conjugate momentum. The relation \( \dot{Q} \simeq P/E \) holds, with \( E \) being the total energy of the soliton (deviations from the exact formula are due to deformation of the interacting soliton shape). We used \( P \) as an indicator for the soliton’s kinetic energy. Simulations reveal that when \( \delta = 0 \) (i.e. symmetric barrier) the kink slows down and stops after a short period of time. Next, \( \delta \) is decreased so that the \( \phi = -1 \) conformation becomes lower in energy. When interaction is strong enough, the kink transfers enough energy to the conformation angles, allowing them to cross the potential barrier and reach the ground state (\( \phi = -1 \)), in practically every point it passes. However, the soliton extract back some of the conformation energy. After short period of time it reaches a steady state finite velocity (up to some periodic fluctuations), when the energy gained balances the energy lost. When dissipation is introduces, it lowers the steady state velocity, but the overall picture remains the same. Results of simulation are shown in fig. 1. We conclude that within this model, a soliton is able to mediate folding (i.e. carry conformational degrees of freedom over energy barriers) and in the process compensate for energy losses by pumping it back from the folded field.

In actual unfolded state local folding angles are supposed to be distributed somehow between \( \alpha \) and \( \beta \) conformation. We have checked the behavior of a traveling kink in a disordered initial conditions, namely, when the \( \phi \) field is randomly distributed between the two minima. Still, a steady state velocity is reached, though lower compared with the ordered case (see fig. 2). This can be easily explained since less compensating energy is available to the soliton when already
half the conformational degrees of freedom are at their ground state. Nevertheless, the folding mediated is not less effective. For sufficient asymmetry all the angles reach the lower energy. The soliton did not only lowered the energy but also the entropy.

We have demonstrated, using a simple toy model, how soliton, propagating along a protein backbone provides an effective mechanism for fast and deterministic folding of the protein. By mediating correlated fold of large sections of the polypeptide chain, it reduces significantly the number of effective degrees of freedom, since large structures may be created by a single soliton. Moreover, these structures are created in a controlled process. It is possible that the amino acids sequence dictates whether soliton propagation would be allowed or suppressed in a specific location at a specific time. therefore the folding pathway may not be stochastic but, rather, predetermined. The limiting rate of the folding process would be the rate in which solitons are produced. Soliton creation is probably induced spontaneously by thermal excitation. There might exist other mechanisms for creation of solitons, such as interaction with ‘chaperones’, enzymes that catalyze protein folding. It is our belief that the concept of SMF will improve scientific understanding of such phenomena.

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FIGURES

FIG. 1. The collective momentum and the energy of a soliton moving through a protein which is initially in a metastable (unfolded) state. The momentum is indicated by the dashed line. Continues line indicates soliton energy. The energy of the conformation field is shown in the small box. The parameters have the following values: $\varepsilon = 1, m = 10, \Lambda = 100, \delta = -0.5, \gamma_\phi = 0.1, \Gamma_\theta = 0.1$. Note that, although dissipation is introduced, the soliton momentum has a constant positive average value.

FIG. 2. The collective momentum and the energy in a disordered initial conditions. Dissipation parameter $\Gamma_\theta$ was set to zero. All other parameters have the same value as in Fig. 1. The protein conformation energy is shown is the small box.