Solitons in Protein Folding - A Unified Model

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Abstract:

In the context of protein folding mediated by solitons propagating through the backbone of a protein a unified model is proposed. A fourth order nonlinear Schrödinger (NLS) field interact with another field ϕ corresponding to the conformational angles of the protein. Adopting numerical computation the solutions are developed for a system of coupled nonlinear partial differential equation and the momentum calculations are carried out. The dynamics is qualitatively analysed by plotting the trajectories in the two dimensional phase plane. An infinitesimal effect of folding dynamics by the addition of spring tension is also studied.

Keywords : Soliton, protein folding, nonlinear Schrödinger equation.

1 Introduction

Certain class of nonlinear dispersive system exhibits an exciting type of wave solutions of finite energy having remarkable stability properties, called soliton. Polymers are real dynamic systems that exhibit both dispersion and nonlinearity [1-2]. The earlier suggestion for a "'Polymer Soliton" was made by Davydov [3-8] in an attempt to solve an outstanding riddle of Biochemistry. A protein is a polymer built from twenty different aminoacids ordered in sequence. This sequence is called the primary structure of that protein. Under normal conditions it folds to a predetermined and rather static structure such as α helices and β-sheets called as native state. Tertiary structure refers to the spatial relationships among all aminoacids in a polypeptide.

Since protein folding is a spontaneous process it is clear that the aminoacid sequence of each protein contains the information that specifies both the native structure and the pathway to attain that state [9-12]. Temperatures above or below the range that cells tend to live in will cause proteins to unfold or denature. Incorrectly folded (misfolded) proteins are responsible for the cause of several diseases and some cancers [13]. However, the main mechanisms responsible for a structured folding pathway have not yet been identified.

Davydov's nonlinear dynamic model for the α-helix protein confirm the prediction of soliton formation. These solitons are robust localized dynamic entities that couple molecular (amide-I) vibrations to longitudinal sound waves. They may provide an efficient mechanism for

energy transport in biological systems [14-15]. Recently caspi et. al. [16] suggested that Davydov's solitons propagating through the backbone of a protein can mediate conformational transition referred as Soliton Mediated Conformational Transition (SMCT) and folding of a protein to its native state termed as Soliton Mediated Folding (SMF) [17-21]. A simple toy model was presented in which a NLS field interacts with another field ϕ corresponding to the conformational angles of the protein. The interaction provided the conformation field with the energy needed in order to overcome energy barriers for folding, thus avoiding the need for thermal activation. The soliton compensates for its energy loss by absorption of the energy gained in the folding process.

Later Natalia [22] proposed a simple phenomenological model by adding the spring tension and demonstrated that the transition from the primary to the secondary conformation in a protein could, in principle, result from an interplay between the energy supplied by a solitary wave moving through the protein backbone and the potential energy of the chain tension. The described folding pathway follows the scenario of that for known proteins [23].

Davydov's α - helix protein was further extended by Daniel and Latha [24,25] by considering the discrete and continuum models with different orders of molecular excitations and interactions. In the above cases integrable models were identified for specific choice of parameters. As many higher order NLS and coupled NLS equations are available in the literature of NLS family of equations, our interest lie on taking a completely integrable Fourth Order NLS (FONLS) equation for our study of protein folding [24] which is not reported in the literature. The present work is the collective work of the authors [16-17,22,24].

In this paper we suggest a unified model that describes the folding pathway mediated by the FONLS soliton that travels along the backbone of a protein and is given in section 2. The numerical solution is developed in section 3 and the interaction effect on folding dynamics is also analysed. The momentum calculation and the outcome of the numerical result is discussed in section 4. The folding dynamics is further extended by incorporating the spring tension and is described in Section 5. The results are concluded in section 6.

2 The model

A new unified model is proposed where the soliton propagating through the backbone of the protein can be approximated by the Fourth Order Nonlinear Schrodinger equation [24]

$$iq_t + q_{xx} + 2|q|^2 q + \gamma[q_{xxxx} + 8|q|^2 q_{xx} + 6q^* q_x^2 + 4|q_x|^2 q + 2q^2 q_{xx}^* + 6|q|^4 q] = 0. \quad (1)$$

It was already proved to be an integrable equation possessing soliton solution. Since recently more attention has been given on numerical simulation, the above equation is attempted to solve numerically and the one soliton solution obtained is depicted in fig(1).

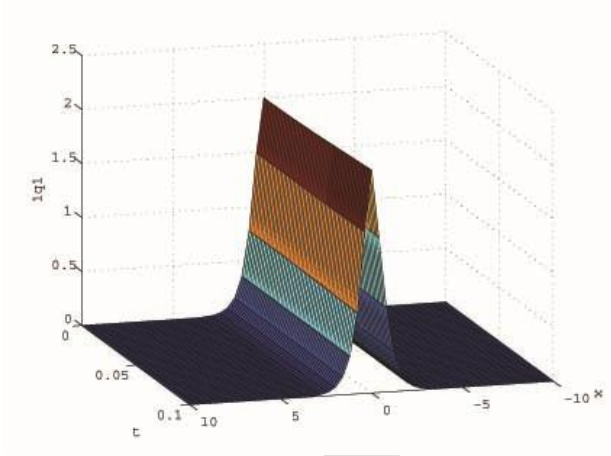

Figure 1: One soliton solution of FONLS equation .

As the peptide bond(C-N) in protein is essentially rigid, the polypeptide chain has only two degrees of rotational freedom, about $N-C_\alpha(\phi)$ and $C_\alpha-C(\Psi)$ per aminoacid residue. Let us use a scalar variable ϕ to represent the local conformation of the protein. The local potential energy will be simply modeled by an asymmetric ϕ^4 double well potential as suggested by caspi et. al. [17] namely

$$V(\phi)=\varepsilon(\phi+\delta)^2\left(\phi^2-\frac{2}{3}\phi\delta+\frac{1}{3}\delta^2-2\right) \tag{2}$$

where δ is the asymmetry parameter ranging from -1 to +1. The two minima are positioned at $\phi=\pm1$. The energy difference between the minima is

$$\Delta E=\frac{16}{3}\varepsilon\delta. \tag{3}$$

The maxima is positioned at $\phi=-\delta$ and its energy is always zero. The plotted potential well for ε=2.0 and δ=-0.5 taken for our study is depicted in fig.2.

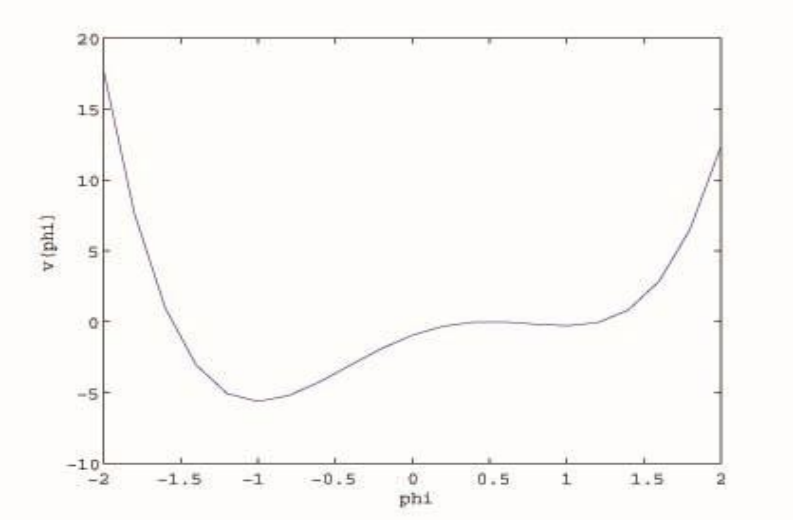

Figure 2: Double well potential .

In order to study the soliton(q) interaction with local conformation(ϕ) of molecular chain, an interaction of an appropriate form

$$U(q,\phi) = \Lambda |q|^2 \phi^2 \tag{4}$$

should be introduced, where Λ is a positive parameter. If q is nonzero, then at the minima, the energy of the combined V and U increases, which effectively lowers the barrier for a folding transition. The full Lagrangian density then reads

$$\begin{aligned} L &= iq^*q_t - |q_x|^2 + |q|^4 - \gamma[-|q_{xx}|^2 \\ &+ 8|q|^2|q_x|^2 + (q^*)^2 q_x^2 + q^2(q_x^*)^2 - 2|q|^6] \\ &+ \frac{1}{2}m\phi^2 - V(\phi) - U(q,\phi). \end{aligned} \tag{5}$$

The terms upto the square bracket in equation (5) represent a Lagrangian of FONLS, which describes the soliton energy. The next two terms correspond to the conformational field energy. The last term describes the interaction between the two fields. The Euler - Lagrange equations written for the Lagrangian (5) have the form

$$\begin{aligned} iq_t &= -q_{xx} - 2|q|^2 q - \gamma[q_{xxxx} + 8|q|^2 q_{xx} + 6q^*(q_x)^2 + 4|q_x|^2 q \\ &+ 2q^2(q_{xx})^* + 6|q|^4 q] + \Lambda\phi^2 q \end{aligned} \tag{6}$$

and

$$m\phi \ddot{=} -4\varepsilon(\phi+\delta)(\phi^2-1) - 2\Lambda|q|^2\phi - \Gamma\phi \tag{7}$$

where the last term in equation (7) represents dissipation. The inclusion of dissipation lowers the steady state velocity without altering the overall picture. Equation (6) and (7) represent the coupled system of time dependent, nonlinear partial differential equations.

3 Numerical Solution

Our next focus is to solve the coupled equation to get fascinating result. In recent times there are numerous mathematical ideas and techniques to study such nonlinear systems. An efficient method best suited for our problem is the numerical method. Thus finite difference method [26-28] is used to discretize the coupled system of nonlinear partial differential equations. As q is a complex quantity and by substituting $q = u + iv$ and implementing forward difference formula for $u_t, u_x, u_{xx}, u_{xxxx}, v_t$ and v_{xx} in equation (6) one can obtain $|q_{i,j}|$. Similarly applying forward difference formula to equation (7) and adopting the same procedure we get

$$\phi_{i,j} = \phi_{i,j-1} + \frac{k^2}{2m+\Gamma k}[-4\varepsilon(\phi_{i,j-1}+\delta)(\phi_{i,j-1}^2-1) - 2\Lambda|q_{i,j-1}|^2\phi_{i,j-1}]. \tag{8}$$

Using proper initial and boundary condition the remaining grid points are obtained by writing a program in MATLAB [29,30] and the solution graph for q and ϕ are developed.

Initially when the interaction between the soliton and the conformation field is taken to be zero (ie $\Lambda = 0$) the one soliton solution (same as fig(1)) is obtained for equations (6) and (7). Now Λ is slightly increased and the shape and the size of the soliton after interaction is noticed and plotted as a surface plot. We conclude that if Λ is too large ($\Lambda > 5$) the solitary wave will loose its energy very quickly and stop. If the coupling constant Λ, is too small the soliton will not be able to transfer enough energy to take ϕ from one state to another over the energy barrier. The better choice of the parameter Λ for our model is 5. The surface plot for some interaction parameter Λ is given in fig.3.

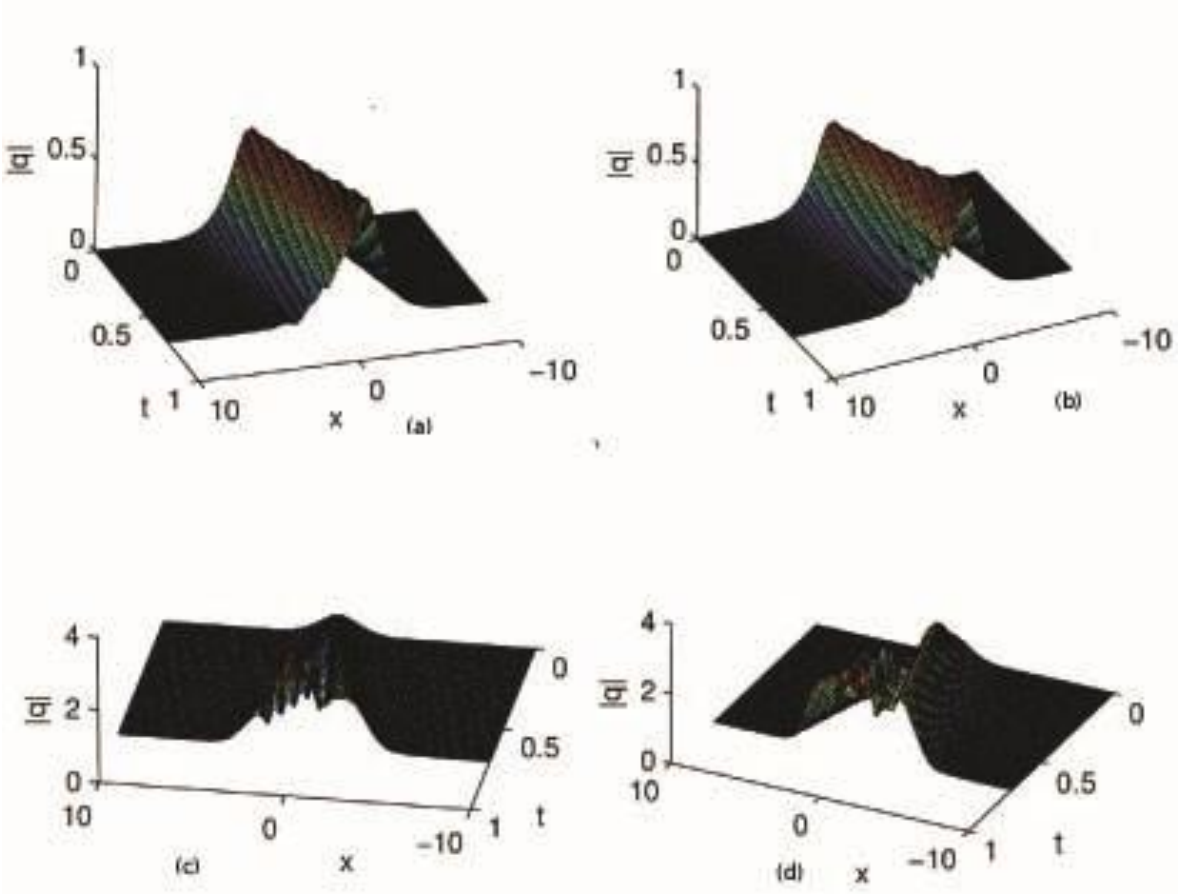

Figure 3: soliton solution for various interaction parameter Λ .

(a) Λ= 5 (b) Λ = 10 (c) Λ = 50 (d) Λ = 100

The phase portrait (|q|,d|q|/dt) of the system (equation 6) can also be developed for few Λ values in order to study the dynamics of the system qualitatively (fig.4.). For some parameter ranges (Λ lies between 0 and 5) soliton are stable. For other parametric choices (ie.Λ = 10 and Λ=30), some structural changes occur: An exchange of energy between soliton and conformation field takes place, as aresult two solitons are merged to form a new bound state [31]. The above two analysis make us to fix the value of Λ as 5 for further investigation.

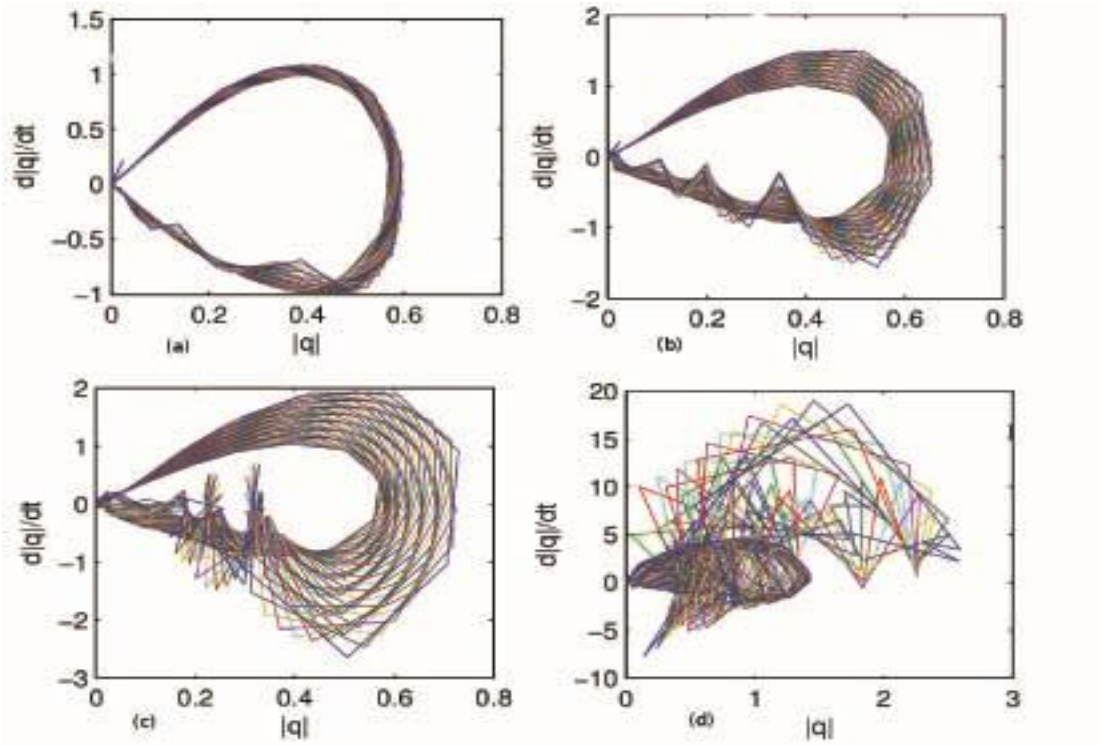

Figure 4: Phase portrait for various Λ values.

(a) Λ= 0 (b) Λ = 5 (c) Λ = 10 (d) Λ = 50

4 Momentum Calculation

From the Lagrangian density (equation 5) the soliton momentum and the conformation field momentum are defined by

$$P_{soliton} = -i\int_{-\infty}^{\infty}\left(q^{*}q_{x} - q_{x}^{*}q\right)dx \tag{9}$$

and

$$P_{conf} = -\int_{-\infty}^{\infty}\phi\dot{\phi}_{x}dx. \tag{10}$$

Using numerical integration by Simpson's (1/3) rule the momentum of the soliton and the conformation field momentum are evaluated and the graph plotted before and after interaction for various Λ values are depicted in fig(5).

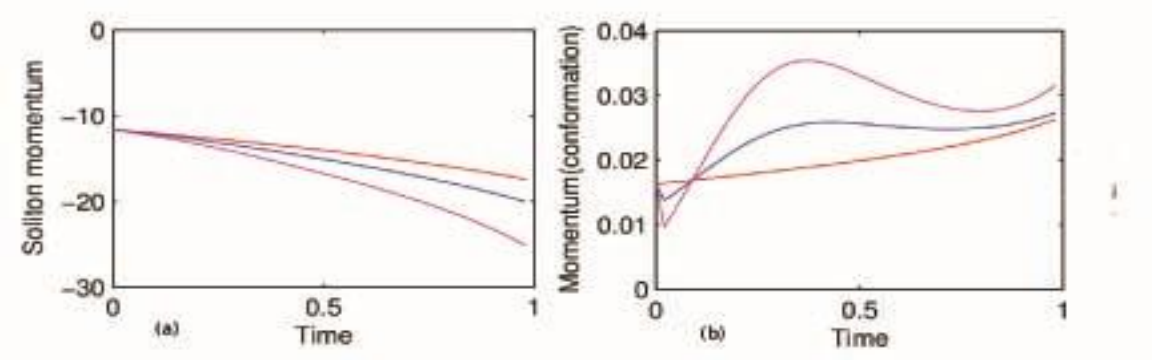

Figure 5: soliton and conformation field momentum before and after interaction.

Before Interaction (Λ=0) Λ = 2 Λ = 5

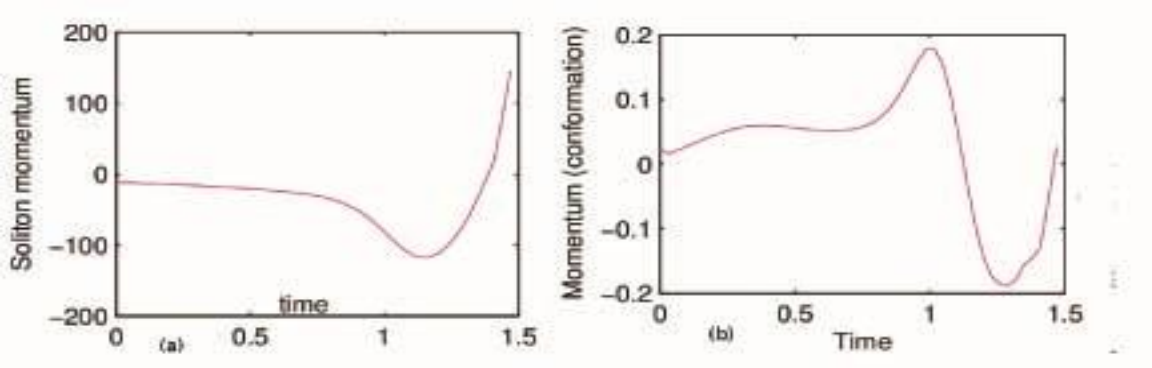

Figure 6: soliton and conformation field momentum for a single SMCT event (Λ=5).

The outcome of the numerical results may be summarized as follows. The conformational field momentum is nearly zero and the soliton momentum is almost constant before interaction. Hence no conformation transition takes place initially. When the interaction (Λ) is turned on, the soliton slows down due to the transfer of momentum and hence energy to the conformation field. The interaction may be in such a way that the conformation field gets enough energy from the soliton to cross the potential barrier. Depending upon the magnitude of interaction the conformation field is raised to a particular higher energy state (metastable state). Fig.5 clearly visualize the above fact.

A single SMCT event occured in protein folding is given in Fig.6. According to our toy model soliton interact with the conformation field and transfer its momentum. The conformation field crosses the potential barrier and causing the transition from metastable to stable state. Since the conformational transition process are exothermic, the soliton gets back some of the energy and hence the momentum of the soliton increases. Thus the soliton extract the energy in a single event of local conformational transition and transfering it to distant location. There it may be used to activate another transition and the energy released in that process could be extracted again.This picture is very different from the usual assumption that the energy released in each folding dissipates to the environment. Similar transition takes place continuously and hence large sections of a protein can fold very fast. Within a short duration folding process is completed and thereafter soliton reaches a steady state finite velocity as discussed by the author [16]. Note that a small change in momentum of the conformation field induces a large change in soliton momentum. Hence enough momentum (Energy) is always available in the backbone of the protein for further

folding. Thus we confirm that the conformational transition or folding process is mediated by solitons that travel along the backbone of the protein.

It is always custumary in nonlinear dynamics to identify solitons in every natural process. The muscle contraction had already been explained by means of Davydov solitons. In a similar way this simple toy model explains the soliton mediated protein folding.

5 Effect of spring tension

The soliton energy is transferred to the conformation field causing the transition from metastable to globally stable state. For reversing this transition external interactions should be added. As suggested by author [22] we shall introduce tension potential between neighbouring regions

$$T(\phi) = \xi\left[(\phi(x) - \phi(x - l_i))^2 + (\phi(x) - \phi(x + l_i))^2\right] \tag{11}$$

if $x_{i-1} \le x < x_i$ where ξ is a positive constant. $T(\phi)$ represents the potential energy arising from two adjacent aminoacids being in two different conformational states. The full Lagrangian density then becomes

$$L = iq^*q_t - |q_x|^2 + |q|^4 - \gamma[-|q_{xx}|^2 + 8|q|^2|q_x|^2 + (q^*)^2 q_x^2$$
$$+ q^2(q_x^*)^2 - 2|q|^6] + \frac{1}{2}m\phi^2 - V(\phi) - U(q,\phi) - T(\phi) - \frac{1}{2}\phi_x^2 \tag{12}$$

where the last term of (12) represents tension of the protein. Lagrange equation of motion for q is same as equaion (6) and the equation of motion for ϕ takes the form

$$\phi_{tt} = \phi_{xx} - 2\Lambda|q|^2\phi - 4\varepsilon(\phi + \delta)(\phi^2 - 1) - 2\xi[\phi(x) - \phi(x - l_i)]$$
$$- 2\xi[\phi(x) - \phi(x + l_i)] - \Gamma\phi_t, \tag{13}$$

where the last term represents dissipation. The same procedure considered in section (3) is used to solve the coupled partial differential equation (6) and (13) and the solution curve is developed for $|q|$ and ϕ. The inclusion of spring tension in this model does not make much difference in the solution curve but the amplitude of the soliton slightly decreases. The momentum calculations are also carried out and plotted as fig.7 which reveals that the scenario does not change significantly in the presence of spring tension.

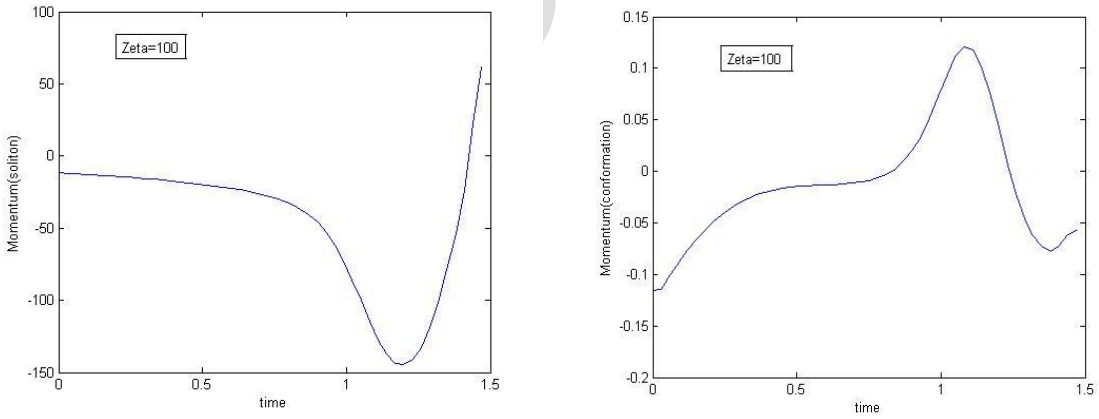

Figure 7: Soliton and conformation field momentum by including spring tension(ξ = 100)

6 Conclusion

Many biological processes in living organisms are associated with conformational changes and folding of proteins. Proteins fold correctly without assistance. Scientists suggested that they are usually as being thermally induced. But we have suggested that the soliton propagating through the backbone of a protein can mediate folding of a protein by introducing an unified model and an appropriate interaction. In order to study the dynamics of protein folding more accurately more information about aminoacids must be taken into account. The model we presented is too simplistic to describe the actual folding process of a complex biomolecule. However by means of systematic numerical simulation we study the folding dynamics and the conformational transition mediated by solitons. The interaction parameter (Λ) between soliton and the conformation field plays an important role in folding dynamics. But the inclusion of spring tension and dissipation in our model produces only an infinitesimal effect.

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