Complex movements of motor protein relay helices during the power stroke

Miljko V. Satarić
Faculty of Technical Sciences, University of Novi Sad, 21 000 Novi Sad, Serbia and Montenegro

Leif Matsson
Department of Applied Physics, Chalmers University of Technology SE-412 96 Göteborg, Sweden

Jack A. Tuszyński*
Division of Experimental Oncology, Cross Cancer Institute, 11560 University Avenue, Edmonton, Alberta, Canada T6G 1Z2
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We use the Toda soliton formalism to propose a possible complex movement of α helices with a very important role in energy transduction during the power stroke of motor proteins. We find that this approach has advantages in comparison with the Davydov soliton model and its variants. We estimated the model's parameters and calculated corresponding properties of the predicted solitary waves including propagation velocities and energies. The energies are found to be within the expected range.

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I. INTRODUCTION

When three-dimensional structures of protein molecules are compared, although overall protein conformations differ, two internal patterns are particularly common because they result from regular hydrogen bond interactions between the amide links joining the amino acids. These regular patterns are known as α helices and β sheets. In an α helix, a common structural element in protein structures, the backbone of the amino-acid chain winds about a central axis in a roughly helical shape as shown in Fig. 1, while the various side chains project outward.

In contrast, β sheets consist of several relatively straight sections of backbone parallel or antiparallel to each other in a common plane. The side chains project outward from this plane in both directions.

An example protein might be a compact structure with a core of β sheets and/or α helices. These features are connected by loops, sequences with more varied backbone conformations. These loops typically comprise a large fraction of the surface, and so binding sites for other molecules are often formed in part of these loops; examples are the binding sites for ATP in the kinesin and myosin families [1,2], and for GTP in tubulin, the constitutive protein of microtubule polymers [3].

Two loops, known as switch I and switch II, are almost identical in both kinesin and myosin, and homologous to structures throughout the G protein superfamily [2]. These "sensor" loops detect the presence or absence of the γ phosphate in ATP and ADP and switch between conformational states depending on whether ATP or ADP is bound.

Analysis of the myosin and kinesin structures reveals that movements of this γ-phosphate sensor are transmitted to distant regions of the protein using an α helix that is connected to the switch-II loop at its NH_2 terminus (see Fig. 2). This highly conserved helix is called the relay helix (RH) [1] or switch II helix. For simplicity, this paper uses only the former terminology.

In both kinesin and myosin, the RH is a key structural and functional element in the communication pathway linking the catalytic (ATP hydrolysis) site, the polymer binding site, and the mechanical element. A RH undergoes a nucleotide-dependent conformational change that approximates the motion of a nanopiston [2]. We recently predicted a similar me-

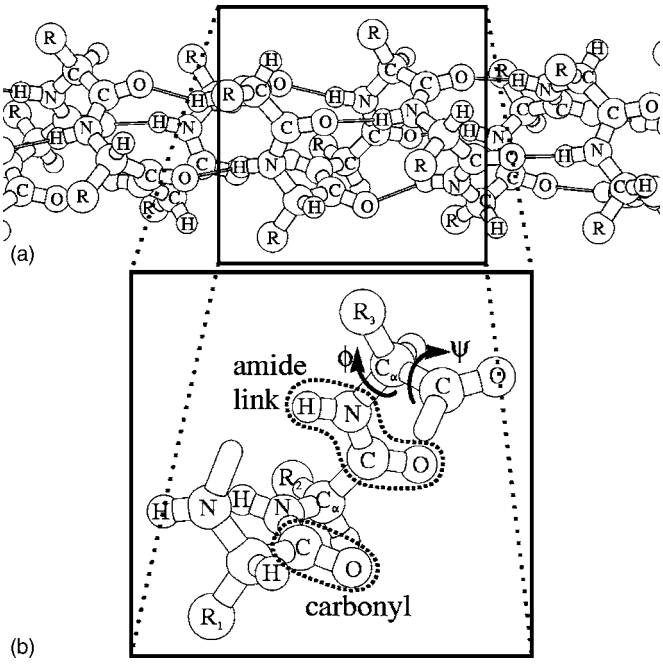

FIG. 1. α-helix backbone geometry. (a) Hydrogen bond network shown as thin cylinders. (b) A close-up of three amino acids; in one an amide linkage has been marked, as has the carbonyl bond of another. Also marked are the bonds about which the ϕ and ψ torsions occur. The atoms of the side chain have been trucated to a single R atom for clarity.

*Also at: Department of Physics, University of Alberta, Edmonton, Alberta, Canada T6G 2J1. Electronic address: jtus@phys.ualberta.ca

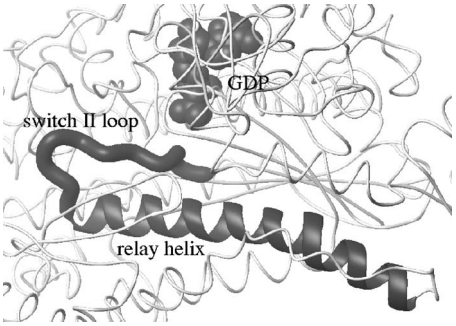

FIG. 2. Secondary structure in myosin showing locations of the switch-II loop, the relay helix, and the adenosine phosphate. Figure prepared using MOLMOL [4] and Protein Data Bank entry 1BR2 [5].

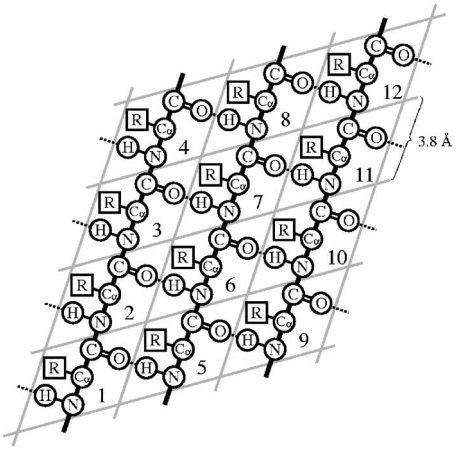

FIG. 3. α-helix geometry showing the hydrogen-bond network. The cylindrical structure has been flattened, splitting the backbone (thick line), with the cylindrical axis running horizontally across the page. The 3.8 Å distance is the C_α to C_α distance in sequential amino acids.

chanical movement within β-tubulin monomers in a microtubule during the GTP catalytic cycle [6].

Over 30 years ago, being aware of the importance of α helices in actin-myosin complexes, Davydov introduced a solitonic model to explain muscle contraction [7–10], attempting to understand how the chemical energy of ATP hydrolysis, released in discrete units of about 0.5 eV, is utilized by molecules in a cell. His idea was that this energy should be converted into a resonant vibronic excitation about the carbonyl (double carbon-oxygen) bond on the amino-acid backbone [see Fig. 1(b)]. He introduced nonlinear vibron-phonon coupling, leading to a nonlinear Schrödinger equation with localized bell-shaped solitons, Davydov solitons (DSs).

II. WEAKNESS OF THE DS MODEL AND ALTERNATIVE MODELS

The main problem with Davydov's concept is that the linewidth of the absorption peak due to the dipole-dipole interactions between carbonyl vibrations imposes a lifetime on the order of 10^{-12} s. This is too short to excite an accompanying deformation of the lattice and the subsequent generation of the predicted DS. Another weakness arises from the value of the coupling strength parameter between vibrational excitations and lattice deformations. An estimate was made for a very narrow "window" of parameter values, imposing highly restrictive conditions for DS formation. A final inconsistency is that, for the most part, the energy released in ATP hydrolysis is utilized in the pistonlike motion of the α helix, so there is not enough energy left to excite the bonds.

On the basis of the above arguments, it is very likely that the DS model is not an appropriate mechanism to describe the energy transfer from ATP (GTP) hydrolysis to distant regions of proteins. In this paper we propose a nonlinear mechanism based on an exponential (Toda) interatomic potential as a basis for a mechanism of energy transfer via relay helices.

It is widely accepted that exponential potentials adequately describe hydrogen-bond interactions in biological structures. For example, the Morse potential was adopted for DNA base-pair interactions in several relevant papers [11–13]. Further, Yomosa adopted the Toda potential [14] more than 20 years ago, as an alternative to the DS model, to try to model the process of muscle contraction.

Two of the present authors have previously examined possible roles of Toda solitons (TSs) in biological structures and proposed Mössbauer spectroscopy as a promising tool for the detection of TSs [15]. We have also considered a possible catalytic behavior of TSs propagating in two-dimensional substrates [16].

Goichuk *et al.* [17] published a model of nonlinear rotational oscillations of amides in an α helix. Although the C-N bond within an amide is largely rigid, the connecting C_α-C and N-C_α bonds rotate, with respective dihedral angles ψ and ϕ (see Fig. 1). These authors modeled rotations characterized by the angle $\zeta=\phi-\psi$, and assumed a quartic form for the corresponding torsional potential. Since amides have permanent dipoles, they incorporated dipole-dipole interactions along both the peptide chain and the hydrogen bonds (see Fig. 3). Performing Hirota's method [18] they obtained a bell-shaped solitonic rotary excitation, formally analogous to a DS. As in the DS case, prospects for this model are fairly pessimistic since the energy for the dipole-dipole excitations is not available as it is mostly consumed by translation of the RH. While the use of a one-dimensional approximation in these models is of concern, it has been routinely applied to both DNA [19] and protein dynamics [20]. It is expected that the principal direction of motion is maintained while the remaining degrees of freedom of the molecular complex mainly amount to stochastic fluctuations that average out over each cycle. An alternative approach to the problem requires computationally challenging molecular dynamics simulations.

III. THE RELAY HELIX AS A PISTON WITH TODA SOLITONS

Although the relay helix translates along its axis during the power stroke [2], its motion is more complex because there are also tilt and rotational components. Collectively, in myosin these drive the lever arm, the bulk motion of which

has been studied experimentally [21]. In this paper we develop a dynamic approach emphasising a hydrogen-bond role in the polypeptide chain of the RH. These soft bonds suggest that nonlinear dynamics of the switch loop motion in ATP hydrolysis may be important. Sharply localized compression at the RH end is here envisaged to produce a TS pulse.

It is well known that global motions of proteins in aqueous solutions are overdamped due to their low Reynolds numbers (approximately 0.05) [22]. However, local motions within a given protein, such as conformational changes involving helices or other structural elements, are much less studied and, while frictional damping is expected to be present due to interactions with neighboring residues, a typical relaxation time scale of these motions or the magnitude of the corresponding Reynolds number is largely an open topic of investigations. In this paper we will ignore frictional damping of the motion of relay helices focusing on Newtonian aspects of their motion.

Influenced by some recent experimental observations regarding the the role of the RH in motor proteins we believe that a better understanding of its impact on unidirectional motion will result from a reexamination of the role of internal nonlinear dynamics.

In the commonly accepted lever-arm model for myosin motion during the ATP chemical cycle it is expected that the main contribution is due to a pistonlike translation of the 8.5-nm-long RH. We estimate the force required to rigidly rotate the lever arm by modeling it as a flexible beam and displacing one end perpendicular to the beam length a (small) distance x from its relaxed position while holding the other end fixed. Thus, we have the textbook equation

$$F = \left(\frac{3E_f}{L^3}\right)x = \kappa x, \tag{1}$$

where E_f is the flexural rigidity and L the length of the lever arm. Interestingly, in proposing that the lever arm acts as an elastic element Howard and Spudich [23] use this same model.

Alternatively, the stiffness parameter κ can be expressed in terms of thermal energy (k_BT),

$$\kappa = \frac{3E_f}{L^3} = k_BT\left(\frac{L_P}{L^3}\right), \tag{2}$$

where L_P is the persistence length, and for the RH is

$$\frac{3E_f}{k_BT} = L_P = 100 \text{ nm} \tag{3}$$

from Howard and Spudich [23]. Taking as representative $L=8.5$ nm and $k_BT=4$ pN nm one gets

$$\kappa = 2.15\frac{\text{pN}}{\text{nm}} = 2.15 \times 10^{-3} \text{ N/m}. \tag{4}$$

We now neglect the requirement of Eq. (1) that $x \ll L$ and equate the beam and lever-arm tip displacements. For example, displacing the lever-arm tip by $x=4$ nm, which is within the range of reported values, gives the mechanical energy

$$E = \frac{1}{2}\kappa x^2 = 1.7 \times 10^{-20} \text{ J}. \tag{5}$$

Variation in x would change this energy, and reported values vary; 3.6 nm [21] and 12 nm [5] have both been reported. Since the energy of ATP hydrolysis is about 0.5 eV $\approx 8.0 \times 10^{-20}$ J, it is clear that much of this energy could be imparted into RH movement. This energy is, in our model, consumed to form TSs, which ultimately rotate the myosin lever arm. Note that choosing x at the upper range of reported values, i.e., 12 nm, gives an energy requirement that is nine times that of Eq. (5), almost twice the ATP energy. This suggests that such a large displacement is unlikely.

IV. TODA MODEL FOR RELAY HELIX

Toda [24] found exact soliton solutions in a lattice model where the interaction between neighbouring sites is essentially exponential. A TS is a compressional supersonic pulse with an infinite lifetime. It is stable against perturbations and it does not transfer energy or momentum during collisions with other TSs.

The presence of hydrogen bonds in the RH (Fig. 3), is the key departure point in our model of chain oscillations using a nonlinear Toda potential. We use a Newtonian approach to the dynamics of the biomolecular system and discuss its limitations in Sec. V.

α helices composed of amino acids with near identical masses are especially favorable for sustaining TSs. We begin the development of our model by considering RHs as helical chains of amino acids with hydrogen bonds between appropriate nearby positions as a Toda lattice of equal masses M located along an axis with equilibrium distances $R_0=4.5$ Å between neighboring sites (see Fig. 3).

The nearest-neighbor interaction Toda potential U_T is expressed by

$$U_T = \sum_n \frac{k}{b}\left[(u_n - u_{n-1}) + \frac{1}{b}(e^{-b(u_n-u_{n-1})} - 1)\right] \tag{6}$$

where u_n denotes the displacement of the nth amino acid in the chain from its equilibrium position. The parameter k represents the transverse elastic coefficient of small amplitude oscillations (in the harmonic approximation) while b, is characteristic of the Toda potential well width (see Fig. 4).

The force on the nth site due to the hydrogen bonds is

$$F_n = -\frac{\partial U_T}{\partial u_n}, \tag{7}$$

or more explicitly, using Newton's second law and Eq. (6),

$$F_n = M\frac{d^2u_n}{dt^2} = \frac{k}{b}(e^{-b(u_n-u_{n-1})} - e^{-b(u_{n+1}-u_n)}). \tag{8}$$

Introducing the relative displacement $\rho_n = u_{n-1} - u_n$ and using Eq. (8) gives

$$M\frac{d^2\rho_n}{dt^2} = \frac{k}{b}(e^{b\rho_{n+1}} - 2e^{b\rho_n} + e^{b\rho_{n-1}}). \tag{9}$$

A single TS solution of Eq. (9) is given by

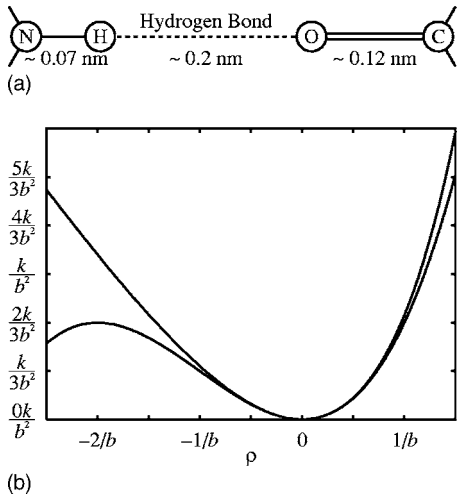

FIG. 4. Dimensions of the hydrogen bond. (a) Distances between atomic centers with the hydrogen bonds. (b) The single-site Toda potential well U_{Tn} (upper curve) and an approximation to it, U'_{Tn}; see Eq. (23) (lower curve).

$$\rho_n = \frac{1}{b}\ln\left(1 + \frac{\sinh^2\mu}{\cosh^2[\mu(nR_0 - vt)/R_0]}\right), \tag{10}$$

describing a compression pulse traveling along the chain with the lattice spacing R_0 and the velocity v, where

$$v = \frac{v_0}{\mu}\sinh(\mu), \quad v_0 = R_0\sqrt{\frac{k}{M}}, \tag{11}$$

and v_0 represents the speed of sound from a corresponding linear approximation of the Toda potential, Eq. (6).

Here μ denotes the characteristic parameter of a TS, and is strongly determined by initial conditions. This parameter and the soliton velocity together define the localization domain of the TS. Also related is the number of amino acids in the soliton, Δn, as

$$\mu\Delta n = 2\pi. \tag{12}$$

It is evident from Eq. (11) that the solitonic velocity always exceeds the speed of sound, so a TS may be called a "supersonic soliton." Moreover, it follows that a narrower TS, with larger μ, propagates faster.

In the continuum approximation, the gap between sites is small, $\Delta n \gg 1$ or equivalently $\mu \ll 2\pi$. Then Eq. (10) may be simplified as

$$\rho(x,t) = \frac{1}{b}\left(\frac{\sinh^2\mu}{\cosh^2(\mu\zeta/R_0)}\right), \tag{13}$$

where $\zeta = x - x_0 - vt$ represents a moving coordinate variable with x_0 as the TS's center (see Fig. 5). Here $\rho(x,t)$ replaces the discrete variable ρ_n and, in the continuum limit, is given by

$$\rho(x,t) = -R_0\frac{\partial}{\partial x}u(x,t). \tag{14}$$

We then integrate this for $u(x,t)$ using the boundary condition $u(\infty)=0$, so that we obtain

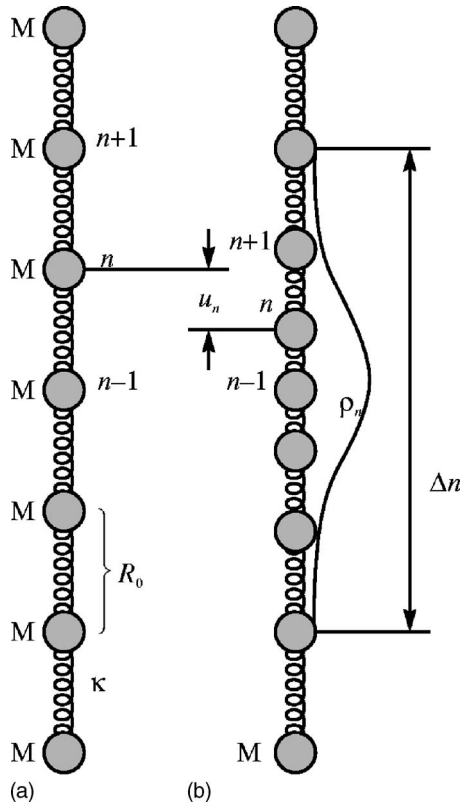

FIG. 5. Toda soliton chain dynamics: (a) relaxed chain (no soliton); (b) local contraction caused by a TS and displacement of sites $\rho_n(x)$.

$$u(\zeta) = \frac{2}{3b\mu^2}\frac{1 - \tanh(\mu\zeta/R_0)\sinh^2(\mu)}{1 + 2\cosh^2(\mu\zeta/R_0)}. \tag{15}$$

The momentum P associated with TS propagation is

$$P = \frac{M}{R_0}\int_{-\infty}^{+\infty}\left(\frac{\partial u}{\partial t}\right)\left(\frac{\partial u}{\partial \zeta}\right)d\zeta = M^* v \tag{16}$$

where the effective mass M^* of a TS is determined by the local lattice mass density change from lattice displacements in the TS. Combining the last two equations and integrating yields

$$M^* = \frac{M\sinh^4(\mu)}{3\mu R_0^2 b^2}. \tag{17}$$

A TS carries both kinetic and potential energy. These are, respectively,

$$E_k = \frac{M}{2R_0}\int_{-\infty}^{+\infty}\left(\frac{\partial u(\zeta)}{\partial x}\right)^2 dx = \frac{2M\sinh^4(\mu)}{3\mu R_0^2 b^2}v^2 \tag{18}$$

and

$$E_p = \frac{1}{b}\int_{-\infty}^{+\infty} U_T(\rho(\zeta))d\zeta \tag{19}$$

or

$$E_p = \frac{2k \sinh^2(\mu)}{3\mu b^2}\left(1 + \frac{4}{15}\sinh^2(\mu)\right). \tag{20}$$

The decrease in distances between neighbors is a local contraction. The total linear contraction $\langle \rho_0 \rangle$ is obtained by integrating the relative displacements of all sites in the chain,

$$\langle \rho_0 \rangle = \frac{1}{R_0}\int_{-\infty}^{+\infty} \rho(x,t)dx, \tag{21}$$

$$\langle \rho_0 \rangle = \frac{2\mu}{bv_0^2}\left(\frac{v_0 \sinh(\mu)}{\mu}\right)^2 = \frac{2\mu}{b}\left(\frac{v}{v_0}\right)^2 \cdots . \tag{22}$$

It clearly scales with the square of the relative TS propagation velocity v/v_0.

It was shown [25] that, although the spike of a TS represents compression of the lattice, the corresponding trough gives a contribution to elongation, and as a whole a TS produces an elongation of the lattice.

In order to estimate key parameters in the TS model, we take the local Toda potential at position n, a single term from the sum of Eq. (6), and expand about the bottom of the potential curve [see Fig. 4(b)]

$$U_{Tn} \approx U'_{Tn} = \frac{k}{2}\rho^2 + \frac{kb}{6}\rho^3. \tag{23}$$

This resembles the effective potential between two (hydrogen-bonded) DNA base pairs when perturbed by an external force [13]. Differentiating this we get two local extrema $\rho_1 = 0$ and $\rho_2 = -2/b$. The value of U'_{Tn} at the second (a local maximum) is

$$U'_{Tn}(\rho_2) = \frac{2}{3}\frac{k}{b^2}. \tag{24}$$

We now take $|\rho_1 - \rho_2| \approx 1$ Å and chose $U'_{Tn}(\rho_2)$ as the depth of the potential well.

Since the energy of a single hydrogen bond is of the order of the physiological thermal energy (k_bT) [13] this implies the order of magnitude approximation

$$U'_{Tn}(\rho_2) \approx 2k_BT = 0.05 \text{ eV} = 8 \times 10^{-21} \text{ J}. \tag{25}$$

Combining Eqs. (24) and (25) and these choices one gets

$$b = 2 \times 10^{10} \text{ m}^{-1}, \quad k = 5 \text{ N/m} \tag{26}$$

as rough estimates of the important parameters of the TS model of the R. Let us now take $M = 115$ Da $= 1.9 \times 10^{-25}$ kg as the average amino-acid mass. Assuming that a TS is spread across $\Delta n \approx 6$ neighboring amino acids that form an interacting cluster, giving $\mu = 1$, we obtain the following set of values from Eqs. (11), (18), (20), and (22):

$$v = 3 \times 10^3 \text{ m/s},$$

$$E_p = 1.5 \times 10^{-20} \text{ J},$$

$$E_k = 2.1 \times 10^{-20} \text{ J},$$

$$\langle \rho_0 \rangle = 1 \text{ Å}. \tag{27}$$

It is gratifying to note that the total energy of such a TS is

$$E_{\text{tot}} = 3.6 \times 10^{-20} \text{ J} \tag{28}$$

which is smaller than the 8.0×10^{-20} J released in ATP hydrolysis that generated the TS and is still large enough to provide the estimated 1.7×10^{-20} J required for lever-arm motion given by Eq. (5). While the energy estimate in Eq. (28) is only an order of magnitude approximation, it indicates that our choice of parameters was reasonable.

No less important is that the maximum compressional forces produced by such a TS is

$$F_{\max} = \frac{k}{2b} = 1.3 \times 10^{-10} \text{ N} = 130 \text{ pN}. \tag{29}$$

This value is an order of magnitude smaller than the estimate by Yomosa [26] of 840–2000 pN which is much beyond the experimental values at which hydrogen bonds break [13].

V. CONCLUSION AND DISCUSSION

Directional biological motion requires that the cell be able to convert stored chemical energy into mechanical energy. Understanding how this mechano-chemical energy transduction occurs and how small biological forces, on the order of piconewtons, generated at the molecular level, are organized to produce (large) cellular-scale movement is fundamental to understanding cell motility.

Here we have examined the relay helices of these complex machines. The way in which protein motors can work and be precisely tuned to have so many different motile behaviours may well be due, in part, to RHs and their dynamics.

On the basis of experimental observations we theoretically examined the motion of a RH, paying special attention to internal degrees of freedom associated with hydrogen bonds within the α-helix backbone. We estimated energies and forces involved and critically compared this TS model with some other theoretical approaches.

We believe that a TS's local compression could catalyze the process of latching [2] translated RHs by repositioning termini nearer to their counterparts in the docking step in accordance with the "lock and key" model of biomolecular interactions.

Of course in myosin this strong compression would propagate into the converter regions driving the motions that result in the lever-arm movement, as it reached the far end of the RH.

One very appealing point of the theory is the compatability between the total mechanical energy of moving the RH, the energy that may be supplied by ATP hydrolysis, and our estimate of the energy the RH must provide to move the lever arm.

We mention here that Ginzburg-Landau- (GL-)type interactions also provide an interesting framework to examine energy transduction in biological systems. As has been demonstrated for microtubules [27] and DNA-protein systems [28], within GL-type models it is possible to relate chemical

energy per protein complex directly to the vibrational energy in the system, and to the energetic threshold required for dissociation of protein complexes. Given a dynamic model, this precise relation between chemical and mechanical energies could be tested experimentally. In principle it would be possible to discriminate between different types of nonlinear dynamic models.

For instance, a mechanical model [28,29] proposes how phosphorylation of the retinoblastoma (Rb) protein might lead to conformational changes and ultimately dissociation of Rb protein from histone deacetylase and the transcription factor E2F. Functionally, Rb protects against cancer by regulating progression of the cell cycle during the G1 phase. To understand and discriminate between normal function and various dysfunctions of Rb protein it would be particularly interesting to determine the dynamics transducing the chemical energy into movement. We believe α helices have an indispensable role in these subtle variations in protein dynamics.

It should be mentioned that the inclusion of internal friction between various domains of a protein is a real problem that has not been adequately addressed in our paper but, unfortunately, there is neither much experimental nor theoretical evaluation of its role that can be readily found in the literature. McCammon [30] states that proteins' atomic motions can be compared to those that occur in other dense materials. Small motions at short times are similar to what is observed within the molecules of liquids. Larger motions in proteins, such as slow conformational changes, are opposed by the forces that stabilise their native structures, resulting in solidlike features. Moreover, strong coupling has been observed between local and collective displacements resulting in nonlinear dynamical behavior. Importantly, this coupling governs the character of many ligand-binding processes and structural transformations, such as relay helix dynamics, that are essential to biological function. The absence of friction in the models of DNA dynamics, for example, is more a rule than an exception and it can be traced to the original paper by Peyrard and Bishop [31], its extension to statistical properties of DNA melting [32], and the account of base-pair sequences [33]. The internal dynamics of protein components is also often described using Newtonian approaches and Garcia [34] states that global motions of conformational changes in proteins are governed by nonlinear dynamics with some damping using molecular dynamics. The global nonlinear collective excitations are responsible for most of the atomic fluctuations of the molecule. This is consistent with the approach we adopted in our paper.

Nonetheless, it would be instructive to quantitatively assess the magnitude of viscous forces within the atoms of a protein. Following Howard's book ([22] p. 40) we estimate the viscosity coefficient as the product of the following factors: (a) the fraction of time spent by a molecule attached as a cross link (hydrogen bond), (b) the time spent attached to a link (typically 10^{-11} s), and (c) the stiffness of the bonds that are being broken in the process of moving (approximately 2 pN/nm in our case). Hence the force of friction is proportional to the number of broken bonds. The friction force is proportional to the above viscosity coefficient and the average velocity of the domain's motion, so using our value of the average velocity as 3×10^{3} m/s we obtain a friction force of 6 pN assuming only 10% of the time is spent attached. This is not a significant amount compared to the maximal compressional force of 130 pN found in our paper. However, it strongly depends on the proportion of the time spent attached. Thus, with 50% of the time spent by the domain being attached the friction force rises to 30 pN and at 100% the value is 60 pN, i.e., close to one-half of the total compressional force. It is, therefore, reasonable to expect that damping effects will slow the TS motion down over its course. It is not necessary for these nonlinear objects to be destroyed by internal viscosity. In this connection, we wish to refer the reader to our recent paper where viscosity was introduced as a perturbation leading to slight distortion and deceleration of breather solitons in biomolecular systems [35].

Since experimental evidence for α helix dynamics is still missing we would like to suggest that deuterium-labeled neutron scattering could be a possible tool for its determination.

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