Short timescale energy transfer in proteins [1]

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Abstract

It is emphasized that the initial step after the hydrolysis of ATP is a quantum mechanical state of the protein which catalyses the reaction. The Davdydov/Scott model proposes a very specific state for this step, namely, a well-known vibrational excited state of the peptide group called amide I. According to equations (6,7) in section 2, which satisfy both the quantum statistics of the amide I excitation and the classical statistics of lattice, the amide I excitation follows a stochastic path from the active site to other regions of the protein. This is a robust way of transferring energy without loss and may constitute the first step in the many cellular processes which are powered by the hydrolysis of ATP.

1 Introduction

Many proteins function by changing conformation. Such conformational changes are triggered by many types of actions, including chemical reactions (e.g the hydrolysis of Adenosinetriphosphate - ATP) and ligand binding (either ions or small molecules). How is it that these relatively low energy actions, in small regions of the proteins, manage to induce the large scale domain motions that characterize conformational changes [1] ? While the concerted motion of a group of atoms is a classical phenomenon, *the underlying hypothesis in this work is that the initial result of the triggers of protein action is a quantum vibrational excited state of a local group in the protein.*

At first sight, the possibility that proteins, which are systems with hundreds to tens of thousands of atoms, have a quantum stage may seem very speculative. In fact, at least in some cases, it is trivial. E.g., the hydrolysis of ATP is a chemical reaction and a chemical reaction is a quantum process. It is thus straightforward to assume that the initial outcome of the hydrolysis of ATP is a quantum state of the protein. Although perhaps not so intuitive, quantum excitations can also be created by ligand binding [2]. Therefore, the question is not *whether* proteins have a quantum stage but what form this stage assumes, how long it lasts and which role it takes. In the Davydov/Scott model studied here [3, 4], it is assumed that the initial quantum state is a well-known vibrational mode of the peptide groups called amide I, consisting essentially of the stretching of the C=O bond. This article deals with the dynamics of this quantum state as a function of temperature.

In section 2 the Davydov/Scott model is introduced and in section 3 the states predicted by the Davydov/Scott model are presented as a function of temperature. The article ends with a discussion of the biological significance of the Davydov model and its integration within the protein work cycle.

2 The Davydov/Scott model

Davydov's Hamiltonian is formally similar to the Fröhlich/Holstein Hamiltonian for the interaction of electrons with a polarisable lattice. Thus, the Hamiltonian, $\hat{H}$, is:

$$\hat{H} = \hat{H}_{qp} + \hat{H}_{ph} + \hat{H}_{int} \tag{1}$$

where $\hat{H}_{qp}$ is the quasiparticle Hamiltonian, which describes the motion of the amide I excitations between adjacent sites, $\hat{H}_{ph}$ is the phonon Hamiltonian, which describes the vibrations of the lattice, and $\hat{H}_{int}$ is the interaction Hamiltonian, which describes the interaction of the amide I excitation with the lattice. The quasiparticle Hamiltonian $\hat{H}_{qp}$ is:

$$\hat{H}_{qp} = \epsilon \sum_{n=1}^{N} \hat{A}_n^\dagger \hat{A}_n - V \sum_{n=1}^{N} [(\hat{A}_n^\dagger \hat{A}_{n-1} + \hat{A}_n^\dagger \hat{A}_{n+1})] \tag{2}$$

where ϵ is the energy of the amide I vibration, $-V$ is the dipole-dipole interaction energy of the amide I excitations in neighbouring sites, $\hat{A}_n^\dagger(\hat{A}_n)$ is the boson creation(annihilation) operator for a quasiparticle at site n and N is the number of peptide groups in the lattice.

The phonon Hamiltonian $\hat{H}_{ph}$ is:

$$\hat{H}_{ph} = \frac{1}{2}\sum_{n=1}^{N}[\kappa\,(\hat{U}_n - \hat{U}_{n-1})^2 + \frac{\hat{P}_n^2}{M}] \tag{3}$$

where $\hat{U}_n$ is the displacement operator from the equilibrium position of site n, $\hat{P}_n$ is the momentum operator of site n, M is the mass of each peptide group and κ is the elasticity constant of the lattice.
Finally, the interaction Hamiltonian $\hat{H}_{int}$ is

$$\hat{H}_{int} = \chi\,\sum_{n=1}^{N}[(\hat{U}_{n+1} - \hat{U}_{n-1})\,\hat{A}_n^{\dagger}\hat{A}_n] \tag{4}$$

where χ is an anharmonic parameter arising from the coupling between the quasiparticle and the lattice displacements.

A general solution for the one quantum state of the mixed quantum/classical Davydov/Scott system in which the motion of the lattice sites is treated classically is [5]:

$$|\psi> = \sum_{j=1}^{N}\varphi_j(\{u_n\},\{p_n\},t)\,\hat{A}_j^{\dagger}\,|0> \tag{5}$$

where φ_j is the probability amplitude for an excitation in site j and the dependence of φ_j on the classical displacements $\{u_n\}$ and momenta $\{p_n\}$ of the lattice is not specified *a priori*. Inserting (5) in the Schrödinger equation, and using the Hamilton equations for the lattice variables, it is possible to derive the following equations of motion [6-8]:

$$E\varphi_n = \epsilon\varphi_n - V\,(\varphi_{n-1} + \varphi_{n+1}) + \chi\,(u_{n+1} - u_{n-1})\,\varphi_n \tag{6}$$

$$M\frac{d^2u_n}{dt^2} = \chi\,(\mid\varphi_{n+1}\mid^2 - \mid\varphi_{n-1}\mid^2) + \kappa\,(u_{n+1} + u_{n-1} - 2\,u_n) + F_n(t) - ,\,\frac{du_n}{dt} \tag{7}$$

where the stochastic forces $F_n(t)$ and the friction terms $-,\,\frac{du_n}{dt}$ obey the fluctuation-dissipation relation $< F_n(t)\,F_m(t') >= 2M,\,k_BT\delta_{nm}\delta(t-t')$. These equations are valid when the quantum excitation is much faster than the lattice, as was discussed in [8]. The equations of motion (6,7) are integrated by solving the eigenvalue problem (6) at each time step and applying the Metropolis scheme [9] to choose which energy state E will drive the lattice equations (7), at that time step. As was shown in [8] eqs. (6,7) satisfy both the classical statistics of the lattice and the quantum statistics of the amide I excitation. In the next section the motion of the amide I as a function of temperature, as predicted by eqs. (6,7), is presented.

3 Results

In figures 1-3 the evolution, at three temperatures, of the exact minimum energy one quantum state is displayed. The coupling to the thermal bath involves stochastic and

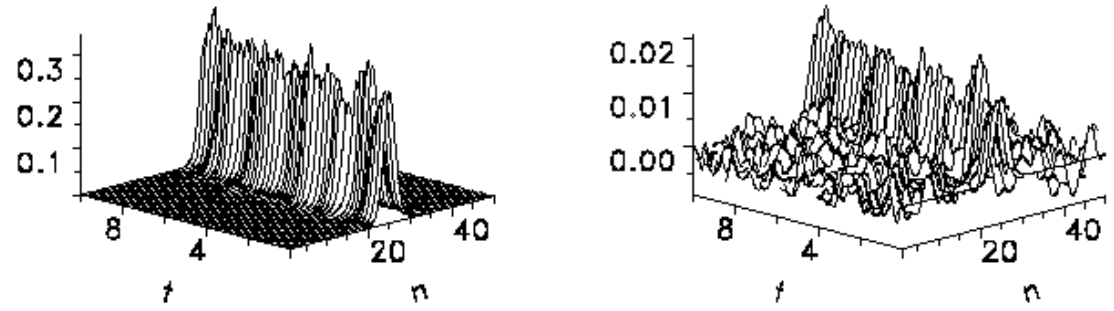

Figure 1: Time dependence of the probability for an excitation in site n, $|\varphi_n|^2$, and of its correlated lattice distortion $-(u^c_{n+1} - u^c_{n-1})$, in Å, calculated by integration of equations (6,7). The initial condition is the exact minimum energy one quantum state of the mixed quantum/classical Davydov/Scott model. The temperature is $T = 0.1$ K. Other parameters are: $V = 1.55\ 10^{-22}$ J, $\kappa = 39$ N/m, $\chi = 62$pN, and $M = 5.7\ 10^{-25}$ Kg. Stochastic forces and damping terms are applied every 0.05 ps.

damping forces applied to all sites every 0.05 picoseconds. This allows for a clear view of the mechanism of decay of the initial soliton state.

In the absence of the bath, the excitation and the associated lattice distortion would not move, because the initial condition is an exact stationary state of the system. At finite temperature, however, the phonons induced by the presence of the excitation, which are responsible for the lattice distortion, are scattered by thermal phonons. The lattice configuration thus starts to change. According to eq. (6), for each lattice configuration defined by a set of displacements $\{u_n\}$, there are N possible states for the amide I excitation. As the lattice configuration changes, this band of N states also changes. At low temperature, thermal phonons merely scatter the initial lattice distortion without distroying it. The lattice distortion moves along the chain and the amide I excitation follows it. This is observed in figure 1 and, apart from the lattice disorder visible even at such a low temperature, it is very similar to the coherent propagation of a soliton.

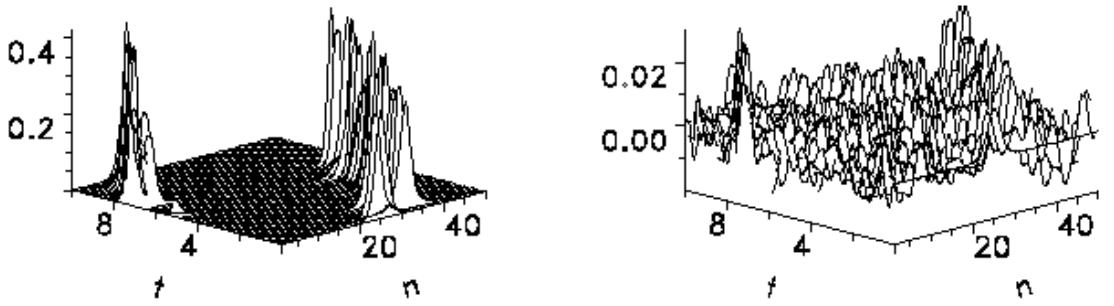

Figure 2: Same plot as figure 1 but for $T = 0.5$ K.

As temperature increases, the impacts of thermal phonons are stronger leading both to a faster movement of the lattice distortion and to a greater degree of disorder, as seen in figure 2. Following the lattice distortion, however, is only one of the causes of the movement of the amide I excitation at finite temperature. A second cause is quantum transitions. When the temperature is sufficiently low so that, for each lattice configuration, kT is much smaller than the energy gap between the lowest energy level and the next level, only the lowest level is populated and quantum transitions between the N levels in the band do not occur. Above a threshold temperature, it becomes possible for higher levels to be occupied. In a disordered lattice, the higher levels are also localised states, but located around lattice sites which may not overlap with that of the main lattice distortion. At low temperature, if such a quantum transition occurs, the amide I excitation is still able to induce a distortion in the new site which is larger than the average disorder in the lattice. Examples of such quantum transitions are displayed in figure 2, for instance, approximately 0.2 ps into the dynamical simulation.

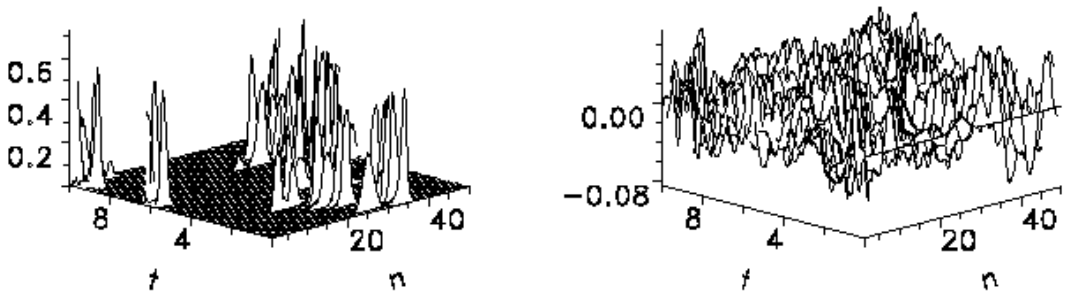

Figure 3: Same plot as figure 1 but for $T = 10$ K.

At higher temperatures, both causes of motion are important and the lattice distortions due to thermal motion are much larger than the lattice distortions induced by the presence of the excitation. Thus, the lattice distortion correlated with the excitation disappears in the thermal noise in the subpicosecond timescale. The motion of the amide I excitation is that of a Brownian particle in a disordered lattice as is illustrated in figure 3.

4 Discussion

Equations (5 - 7) are valid in the mixed quantum/classical regime in which the amide I excitation is treated quantum mechanically and the motion of the latttice sites is treated classically. The assumption that the lattice can be treated as a classical entity has been made by many other authors [3, 4, 10, 11]. The validity of this approximation was assessed by comparing the results of a Monte Carlo simulation for the full quantum system with the corresponding results for the mixed quantum /classical system [12]. Since the difference between the two approaches lies in the treatment of the lattice, the lattice distortion correlated with the position of the excitation was the variable chosen for the

comparison. It was found that while at very low temperature (i.e., below 11 K) quantum effects led to a 23 % *stronger* correlation for the full quantum system, above 11 K, the lattice distortion of the mixed quantum/classical system was indistinguishable from that of the full quantum system. Thus, the results of the mixed quantum/classical system at low temperatures, such as presented in figures 1-3, *underestimate* the lattice distortion due to the excitation. On the other hand, at biological temperatures the mixed quantum/classical system provides a good description of the motion of the amide I excitation.

Figure 1-3 should be contrasted with the early simulations of thermal effects on the motion of the amide I excitation in proteins by Lomdahl and Kerr [10]. The latter led to the dispersion of the quantum excitation in a few picoseconds. According to the simulations of Lomdahl and Kerr, for values of the parameters which lead to a soliton at zero temperature, the lattice distortion associated with the excitation should decrease as the temperature increases. This result was at odds with the quantum Monte Carlo simulations of Wang *et al.* [13], which are numerically exact simulations of the equilibrium regime of the full quantum system. It was shown that this difference was due to the fact that the coupling of a classical bath to a mixed quantum/classical system leads to a classical treatment of the quantum part [14]. Equations (6,7) satisfy both the quantum statistics of the amide I and the classical statistics of the lattice and show that, at finite temperature, the amide I excitation is represented by localised states, not very different from the soliton states which can arise at very low temperatures. The lattice, however, is in a dynamically disordered state and propagation of the amide I excitation is not coherent, as would happen for a soliton, but stochastic.

The thermal instability of the Davydov soliton does have consequences on the mechanisms by which proteins function. In the mechanism of muscle contraction proposed by Davydov [3], the sliding of the myosin with respect to actin should take place as the soliton propagates along the myosin. The idea was that the lattice distortion associated with the position of the excitation lead to the binding of myosin to actin and, as the soliton moved within myosin, myosin would be dragged along with it. As was emphasized in a previous paper [7], this mechanism presupposes that the position of the excitation is always associated with a local lattice contraction. In the stochastic solutions displayed in figure 3, however, although the excitation is localised, the position of the excitation is not always associated with a lattice compression and as the amide I excitation travels through the protein there is no instantaneous lattice compression travelling with it. The Davydov mechanism for muscle contraction therefore cannot be sustained by the stochastic motion predicted by eqs. (6,7).

Another main point to be emphasized is that the fact that a particular solution, and a particular mechanism related to that solution, are not applicable, does not invalidate all solutions of the Davydov/Scott model. In the past, the Davydov soliton has often been equated with the Davydov/Scott model. But the Davydov soliton is only one among an infinite number of states of the associated Hilbert space. The suggestion here is that the Davydov/Scott model is more fundamental than the particular solution which has so far constituted the focus of most studies in this field. As emphasized in the introduction, the state immediately after the hydrolysis of ATP *must* be a quantum state of the protein. From this point of view, *the greatest merit of the Davydov/Scott model is the specification*

of the nature of this initial quantum state. I.e., according to the Davydov/Scott model the initial quantum state is an amide I excitation in the peptide group. It is then important to have reliable equations to predict the nature of the propagation of the amide I excitation from the active site to other regions of the protein. According to eqs. (6,7) the states are localised and follow a stochastic path which can deliver the full energy released at the active site to other regions in a few picoseconds.

The hydrolysis of ATP acts as an energy donating reaction in many cellular processes. If the fundamental assumption is correct, the Davydov/Scott model constitutes the first step in these processes. The fact that energy propagation in the Davydov/Scott model takes place in the picosecond timescale, a much shorter time than protein work cycle of milisecond or more, may make it difficult to detect. But it does not make it any less important. Coming back to muscle contraction, it is proposed that, rather than explaining the full cycle of muscle contraction, as Davydov intended, the Davydov/Scott model explains only a part of this cycle, i.e., the transfer of energy from the active site at the myosin head to the hinge around which the conformational change takes place. Such a possibility has also been suggested by Scott [4]. The Davydov/Scott model cannot describe the transfer of the energy stored in the amide I excitation to the classical, conformational degrees of freedom of the protein because the amide I excitation is conserved. In order to describe this process, extra terms must be added, as in the Takeno vibron model [15].

A stochastic mechanism for energy transfer may not appear as interesting as the propagation of a soliton. But this is the physicist's way of looking at it. The biologist's eyes may instead focus on the robustness of a stochastic mechanism. Indeed, while a soliton follows one pathway only and is thus sensitive to any changes along this pathway, a stochastic solution can explore many pathways. If a mutation makes one pathway inaccessible, a stochastic solution can easily find other ways to get to the same spot. The stochastic mechanism is more resistant to environmental and evolutionary changes.

Two lines of investigation are very important for progress of this field. One is experimental and the other is theoretical. On the experimental side it is important to devise and perform experimental tests on the basic assumption of the Davydov/Scott model, namely, that the initial carrier of the energy released in the hydrolysis of ATP is the amide I vibration. Until now, the applicability of the Davydov/Scott Hamiltonian has only had indirect confirmation in acetanilide [4, 16], an organic crystal that has the same hydrogen bonded chains as α-helices. These studies must be extended in order to find out which quantum modes are populated after the hydrolysis of ATP. On the theoretical side, it is important to study Takeno's vibron to get insights into how the energy of the amide I excitation is delivered to the classical modes of the protein and thereby generates conformational changes. Such work in progress.

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