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2. NUMERICAL SIMULATIONS OF THE DYNAMICS OF POLYPEPTIDE CHAINS AND PROTEINS

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ABSTRACT

The study of energy transport and storage in proteins was revolutionized over ten years ago when Davydov proposed a new nonlinear theory of interacting amide-I vibrations and localized sound waves on the protein α-helix, giving stable pulse-like waves called solitons. Further studies were carried out by Scott and and his group at Los Alamos. More recently, attention has shifted to the study of solitons in crystalline acetanilide (ACN), a material with polypeptide chains similar to those on the protein α-helix. The work on ACN has now been extended to a general theory of self-trapped pulses on regular and irregular lattices. In general, stationary and travelling solitons on regular lattices are now reasonably well understood, but much work remains to study the energetics of irregular lattices such as globular proteins.

1. INTRODUCTION

The fundamental mechanism which we seek to model here is the transport and storage of energy on biologically important macro-molecules. We assume energy is released in a concentrated form at or near a site A on the molecule, usually in units of 0.49eV by hydrolysis of adenosine triphosphate (ATP) to ADP. This energy is stored at site A or travels to site B, arriving in a localised packet. On arrival at B the energy packet may be used to initiate some reaction, or it may be trapped and stored to bring about some conformational change. Alternatively, the energy may initially arrive at the molecule in a diffuse form, spread out over many atomic sites, and become focused at a few sites.

The presence of moving or stationary packets of energy may affect the transport of other energy pulses. It is possible that different sites on a molecule can be switched from one state to another by these pulses in a rough analogy with the working of an electronic or optical computer or a dendrite tree on a nerve axon.

I shall leave more detailed speculation on these topics to other authors in this volume. The main concern in this paper is the study of the formation and transport of such localized energy packets. Here the key word is "localized". Until recently, it was assumed by biologists that the energy in any initially concentrated packet would become dispersed on a time scale of 10^{-12} sec., too quickly on the biological time scale for this energy to be transported from one site to another or to be put to productive use. This will occur whenever the molecule is modelled well by a linear system, such as a chain of linear springs (harmonic oscillators). Davydov was the first to point out in 1973 [1,2] that a nonlinear model might be more appropriate in many cases, and such systems would support a mobile concentrated pulse of energy that did not disperse in time. Such an entity had been observed in other physical systems, and was known as a **solitary wave or soliton.** (The first sighting was in 1834 in the form of a solitary wave on a canal near the present site of Heriot-Watt University, by John Scott Russell, a Scottish mathematician and engineer).

Some readers of this paper may not be familiar with the terms soliton or solitary wave, so a short description may be appropriate. The two terms are not quite synonymous, but for our purpose we can regard them as essentially the same. Basically a solitary wave or soliton is a wave with a single "hump" which travels along at

constant shape and speed in the absence of perturbations, and which is extremely stable to interactions with other pulses. It usually has a bell-shaped outline as shown in the Fig. 1 below

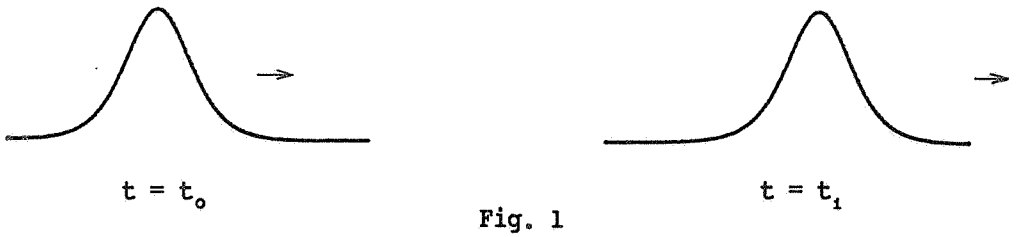


Fig. 1

Mathematicians often reserve the word "soliton" for pulses which maintain their exact shape after collision, but physicists adopt a weaker condition of approximate stability, which we will follow here. Generally the soliton occurs in systems where there is nonlinearity and dispersion: it maintains a dynamical balance between the nonlinearity tending to sharpen the pulse and the dispersion causing the pulse to spread out. A more detailed description of the soliton will be found in one of the many books on the subject (c.f. [3]); a survey of the role of solitons in chemistry has been given by Collins [4].

The paper is laid out as follows. In Section 2 we survey briefly some work on Davydov solitons on α-helix proteins and in Section 3 we describe some calculations on stationary solitons on a "model protein", crystalline acetanilide (ACN). A generalization of this study leads to a generic equation, the Discrete Self-Trapping equation, outlined in Section 4. Finally in Section 5 we describe some recent work on the dynamics of solitons on folded chains, and suggest a model, based on the discrete Nonlinear Schrödinger (NLS) equation, which leads to a qualitative understanding of solitons on the α-helix and ACN, and points the way to a theory of soliton dynamics on globular proteins.

2. DAVYDOV SOLITONS ON THE α-HELIX

In a short section we can only hope to capture the flavour of this line of research, referring the reader to the original literature for details. The theory of solitons on the protein α-helix was originally proposed by Davydov and co-workers [1,2]. A more recent survey of the work of the Kiev school will be found in [5]. The theory was taken up by Scott and co-workers in the USA: some references are [6-12]. An excellent introductory article to this topic has been published by Lomdahl et al. [13]. This latter paper in particular contains many informative figures which lack of space precludes including in this article.

The basic ideas behind Davydov's theory are as follows. As suggested in Section 1, energy arrives in packets of about 0.49eV by the hydrolysis of ATP to ADP. This energy is stored and transported as localized packets based on the amide-I (C=0) resonance, which has a quantum energy of 0.205eV. Linear theory suggests that this energy would be dispersed due to dipole-dipole coupling between the bonds in the order of 10^{-12}sec. Davydov suggested that dispersion could be avoided by the following mechanism:

(a) introduction of localized amide-I bond energy induces longitudinal sound waves on the helix;

(b) longitudinal sound acts as a potential well to trap the bond energy and prevent its dispersion.

The coupling between the longitudinal sound waves and the amide-I bond energy is, as we shall see below, a nonlinear term in the equations: schematically this mechanism

can be represented the a feedback loop shown in Fig. 2

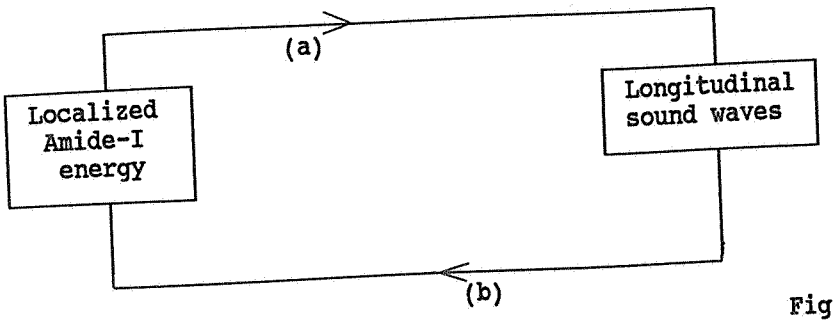


Fig. 2

The structure of the α-helix is such [7] that there are, to a first approximation, three "spines" of linear chains of hydrogen-bonded peptide groups along the helix.

$$C{=}O \cdots H{-}N{-}C{=}O \cdots H{-}N{-}C{=}O \cdots H{-}N{-}C{=}O \cdots H{-}N{-}C{=}O \cdots$$

(Here we use "linear" in its geometrical sense: the chain forms a rough straight line, but the interactions within the chain are nonlinear functions of amide-I bond energy and longitudinal sound energy).

Space does not allow us here to discuss the details of the Davydov model: we go directly to the resulting equations

$$i\hbar\,\dot{a}_{n\alpha} = \Big[E_o + W + \chi_1\Big(\beta_{n+1,\alpha} - \beta_{n-1,\alpha}\Big)\Big]a_{n\alpha} - J\Big(a_{n+1,\alpha} + a_{n-1,\alpha}\Big) + L\Big(a_{n,\alpha+1} + a_{n,\alpha-1}\Big) + \chi_2\Big[\Big(\beta_{n+1,\alpha} - \beta_{n\alpha}\Big)a_{n+1,\alpha} + \Big(\beta_{n\alpha} - \beta_{n-1,\alpha}\Big)a_{n-1,\alpha}\Big] \tag{2.1a}$$

$$M\ddot{\beta}_{n\alpha} - W\Big(\beta_{n+1,\alpha} - 2\beta_{n\alpha} + \beta_{n-1,\alpha}\Big) = \chi_1\Big(|a_{n+1,\alpha}|^2 - |a_{n-1,\alpha}|^2\Big) + \chi_2\Big[a^*_{n\alpha}\Big(a_{n+1,\alpha} - a_{n-1,\alpha}\Big) + \Big(a^*_{n+1,\alpha} - a^*_{n-1,\alpha}\Big)a_{n\alpha}\Big] \tag{2.1b}$$

$$W \equiv \frac{1}{2}\sum_{n,\alpha}\Big[M\dot{\beta}^2_{n\alpha} + W\Big(\beta_{n\alpha} - \beta_{n-1,\alpha}\Big)^2\Big]. \tag{2.1c}$$

Equation (2.1a) describes the propagation of amide-I vibrations via dipole-dipole interactions, and (2.1b) describes the propagation of longitudinal sound. The total longitudinal sound energy is defined in (2.1c). The notation used in equations (2.1) is as follows. The dots represent differentiation with respect to time, i.e. $\dot{a} = da/dt$, $\ddot{\beta} = d^2\beta/dt^2$. The double subscript refers to the numbering (n) of each amide group along the spine labelled by α. Here α = 1,2 or 3 and $n = 0,1,2,\ldots n_{max}$. The complex quantity $a_{n\alpha}$ is the bond occupation amplitude, i.e. $|a_{n\alpha}|^2 \equiv a_{n\alpha}a^*_{n\alpha}$ is the probability of finding a quantum of bond energy E_o at group n on spine α. The real quantity $\beta_{n\alpha}$ is the displacement of the amide group n on spine α from its equilibrium position. M is the mass of the unit cell and w is the linear restoring force per unit of hydrogen bond stretching. The terms with coefficients J

and L represent the effects of dipole-dipole couplings between the amide-I bonds, with the J term representing interactions along the spine and the L term representing interactions between different spines. The nonlinear coefficients χ_1 and χ_2 represent anharmonicity in the longitudinal hydrogen bonds.

In the study of Hyman et al. [6], equations (2.1) were numerically integrated with $n_{max} = 200$ and other constants fixed as described in the reference. The numerical method used was a third order Adams-Bashford-Moulton predictor-corrector method operating in PECE mode [14]. The only coefficients that were varied were the nonlinear coefficients χ_1 and χ_2 which were set equal $\chi_1 = \chi_2 = \chi$ and varied in the range $0 \leq \chi \leq 10$ ($\times 10^{-11}$ newtons).

A convenient graphical summary of some of the results is given by the computer film "Davydov solitons on the alpha-helix" [15], shown with the oral presentation of this talk. In the film, initial conditions ($t = 0$) were one quantum of amide-I energy on each of the three spines at $n = 0$ (symmetric excitation) and the quantities graphed are the bond energy U_n and the sound energy V_n

$$U_n = \sum_\alpha |a_{n\alpha}|^2, \quad V_n = \sum_\alpha \left[\dot{\beta}_{n\alpha}^2 + \left(\beta_{n+1,\alpha} - \beta_{n\alpha} \right)^2 \right] \tag{2.2}$$

in normalized units. Fig.3 shows two frames redrawn from the film, with two different values of χ, $\chi = 2$ and $\chi = 6$, at $t = 350$.

The sound energy forms two distinct components: a "fast" component travelling at the limiting sound speed $\sqrt{(w/M)}$, essentially independent of the bond energy, and a "slow" pulse coupled to the bond energy and moving at the same speed. In Fig. 3a, the bond energy is clearly dispersing over a large number of sites, whereas in Fig. 3b, the pulse has stayed localized and is propagating along the helix with a fixed shape and speed. Further studies show that there is a clear threshold at about $\chi = 3 (\times 10^{-11}$ newtons) below which no soliton forms and the initial energy disperses. The estimated actual value of χ is ≈ 3.5, so it is reasonable to expect Davydov solitons on real α-helix protein.

The initial calculations of Hyman et al. have been refined by later work by Scott and co-workers by adding to the model extra terms, proper inclusion of the spiral nature of the helix, etc., and these studies further support the hypothesis that the true value of $\chi_1 = \chi$ is compatible with soliton formation. However these later studies have shown that $\chi_2 << \chi_1$ and that the χ_2 terms are not significant in the calculation.

One other feature of the refined model is that if χ is too high, a stationary soliton is formed near $n = 0$ which does not propagate down the chain. We shall return to this point in Section 5.

3. STATIONARY SOLITONS IN ACN

Experimental evidence for solitons on the α-helix is sparse and open to alternative interpretations. The best evidence for the existence of solitons in proteins comes from the study of the spectrum of a "model protein", the cystalline polymer acetanilide ($(CH_3CONHC_6H_5)_X$), or ACN. As first noted by Carieri (c.f.[16]), ACN possesses a chain of hydrogen-bonded peptide groups whose bond length and angles are very close to those in natural proteins. The resulting experimental study is described by Gratton elsewhere in this volume. A theoretical study [17] of this system along the lines of the Davydov model for the α-helix leads to a set of equations with similar features to (2.1). The main physical differences are that the detailed molecular structure is somewhat different in ACN, and in the latter theory the coupling of the amide-I bond is to optical rather than acoustic phonons.

The numerical study of soliton dynamics on ACN can be carried out in much the same way as for the α-helix. A new observation, shown both theoretically and numerically for

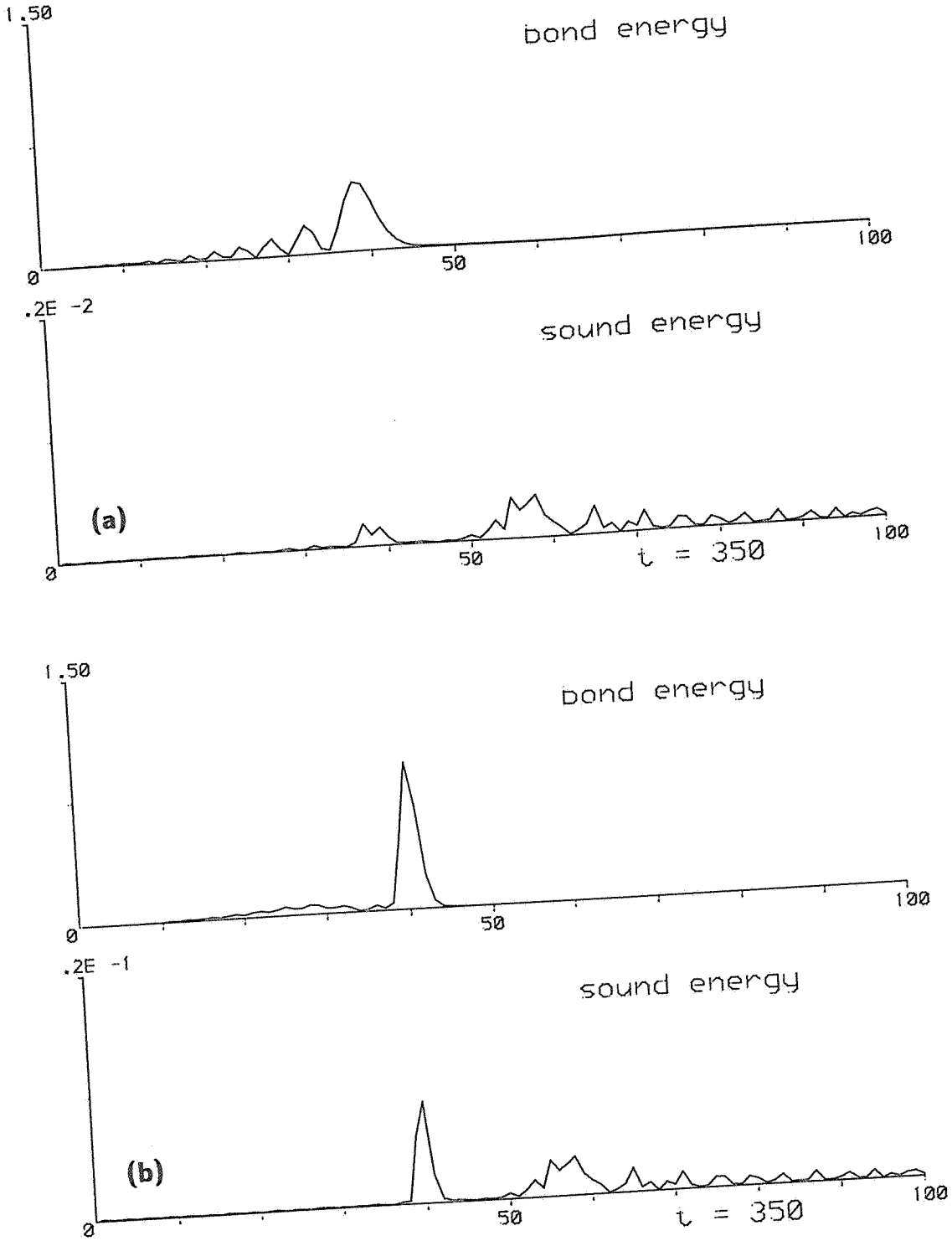


Fig. 3 Davydov Solitons on the α-helix: (a) $\chi = 0.2$; (b) $\chi = 0.6$

ACN, is that energy initially spread out over a large number of sites is focused or self-trapped into a concentrated pulse or soliton. However the main thrust of this study of ACN was an investigation of the detailed spectrum of stationary soliton states as a function of the nonlinear parameter γ in the problem. This was carried out by the investigation of "stationary states" with the form $a_n(t) = \Phi_n \exp\{i\omega t\}$: here $a_n(t)$ is, as before, the probability of finding a quantum of energy on the nth amide-I bond. Numerically, this involves use of path-following techniques of the sort developed by Keller et al. [18]. This study reveals the possibility of soliton formation which gives a plausible explanation for an otherwise anomalous line in the infrared absorption spectrum of ACN.

4. THE DISCRETE SELF-TRAPPING EQUATION

Numerical and theoretical analysis of the Davydov equations (2.1) suggest that the solitons travel slowly with respect to the speed of longitudinal sound waves. This suggests neglecting the kinetic energy of the sound waves by assuming $\dot{\beta}_n = 0$ [13], whereupon $\beta_n - \beta_{n-1} = -\chi_1 |a_n|^2/W$. Assuming also that $\chi_2 = 0$ as discussed in Section 2, and assuming for the moment that $L = 0$, we get the nonlinear differential-difference equation for one spine.

$$\left[i\hbar\frac{d}{dt} - E_o\right]a_n + J\left[a_{n+1} + a_{n-1}\right] + \gamma|a_n|^2 a_n = 0 \qquad (4.1)$$

where $\gamma = \chi^2/W$. The term E_o can be transformed out by the phase change $a_n \to a_n \exp(-iE_o t/\hbar)$, and hereafter we will choose units in which $\hbar = 0$, so that (4.1) becomes in vector form

$$i\dot{A} + \gamma \mathrm{diag}[|a_1|^2, |a_2|^2, \ldots]A + \epsilon M A = 0 \qquad (4.2)$$

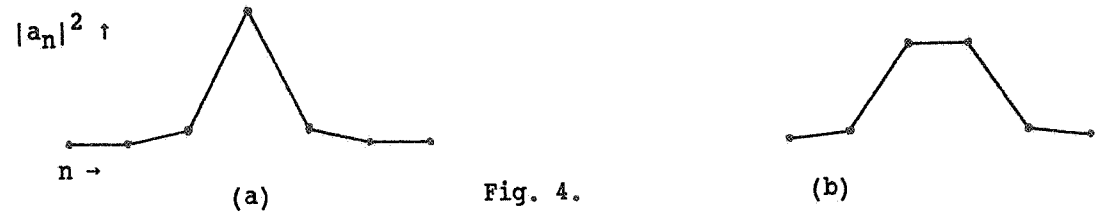
where $A(t)$ is a complex n-vector with components $(a_1, a_2, \ldots, a_n)$; the matrix diag[..] is a diagonal matrix with diagonal elements $(|a_1|^2, \ldots, |a_n|^2)$; $\epsilon \equiv J$, and the $n \times n$ matrix M has elements

$$m_{ij} = 1 \quad \text{if} \quad |i - j| = 1, \quad m_{ij} = 0 \quad \text{otherwise.} \qquad (4.3)$$

If $L \neq 0$ in (2.1) then (4.2) can still be used if the excitation is symmetrical on each spine by absorbing the L term into the E_o term: if this is not the case then (4.2) is still obtained but with a more complicated matrix M and A enumerated over each amide-I bond on each spline.

The soliton equation for ACN can also be transformed into (4.2) with a different choice for M (block tridiagonal in this case). This suggests that (4.2) has more general applications and deserves further study. It turns out that (4.2), which has been named the Discrete Self-Trapping (DST) equation, is also useful, in the case of small n, as a model for the nonlinear vibrations of small molecules [19].

Space precludes a detailed discussion of the properties of solutions of the DST equation here - the reader is referred to [20,21]. One particular result will be useful for the next section. For large γ, with M given by (4.3), the DST equation has stable stationary soliton solutions of the sort shown in Fig.4a, with most of the energy located on one site. There is also an unstable stationary soliton of the sort shown in Fig.4b, with the greater proportion of the energy split over two sites.



(a) Fig. 4. (b)

Such solutions have also been recorded for the ACN problem [17] and for other lattice models [22].

5. SOLITONS ON GLOBULAR PROTEINS

In comparison with the work on solitons on the α-helix and on ACN, little work has been carried out on the more difficult problem of the nonlinear dynamics of globular proteins. One of the few publications in this field is a description by Lomdahl [23] of a general purpose computer program "GLOP" which calculates the evolution of the energy of amide-I bonds on an arbitrary globular protein, requiring as input only the coordinates of the protein. In effect, this code calculates the appropriate elements of the matrix M in the DST equation (4.2) and integrates the equation in time. The most ambitious calculation reported is that on the enzyme lysozyme, consisting of 129 peptide groups. When two quanta of energy were placed on adjacent sites on that part of the protein which has α-helix structure, the energy stayed localized on the α-helix part. In some other runs, energy placed on a non α-helix part dispersed. However detailed analysis of results is difficult in such a complicated structure.

In order to draw out the salient features of such calculations, I have recently performed some trial calculations on a simplified protein model described by the discrete Nonlinear Schrödinger Equation. This system is basically (4.1), i.e. the DST equation (4.2), with M given by (4.3) plus some added terms and $n_{max} = 50$. If, for example, we also have $m_{ij} = 1$ if $|i - j| = n_{max} - 1$, then this represents a simple circular chain shown in Fig. 5a. (The closed chain has no physical significance, and is merely a mathematical convenience to save us from worrying about what happens at the end of the chain). If we add another pair of nonzero elements, say $m_{ij} = c$ if $i,j = 13,37$ and $37,13$ represents a twisted circular chain as shown in Fig. 5b.

Fig 5.

At the cross-over point, n = 13 and 37, the two halves of the chain are close enough to interact via the dipole-dipole coupling.

(If we make a continous approximation to the discrete NLS equation, we recover the normal Nonlinear Schrödinger equation, a partial differential equation with exact mathematical soliton solutions, cf. [3,4,7]).

Experiments on launching a soliton on the simple circular chain were conducted with a fixed input energy and the nonlinear parameter γ varying. For a range of γ values, a soliton-like pulse was seen to travel round the chain, one example being shown in Fig. 6a. If γ was too small, the energy dispersed and no soliton was seen. If γ was too large, the soliton was pinned by the discreteness of the lattice and did not move. This lattice pinning has a simple qualitative explanation. For the soliton to get from a configuration shown in Fig. 4a on one site to a similar configuration on the next site, it must go through a intermediate configuration of the sort shown in Fig. 4b. It is straightforward to show that the energy gap between these two states (the Peierls-Nabarro barrier, cf. [24]), is proportional to γ for large γ in the case of the DST equations. Thus with a fixed amount of energy input, if γ is large enough, the soliton has insufficient energy to penetrate this barrier.

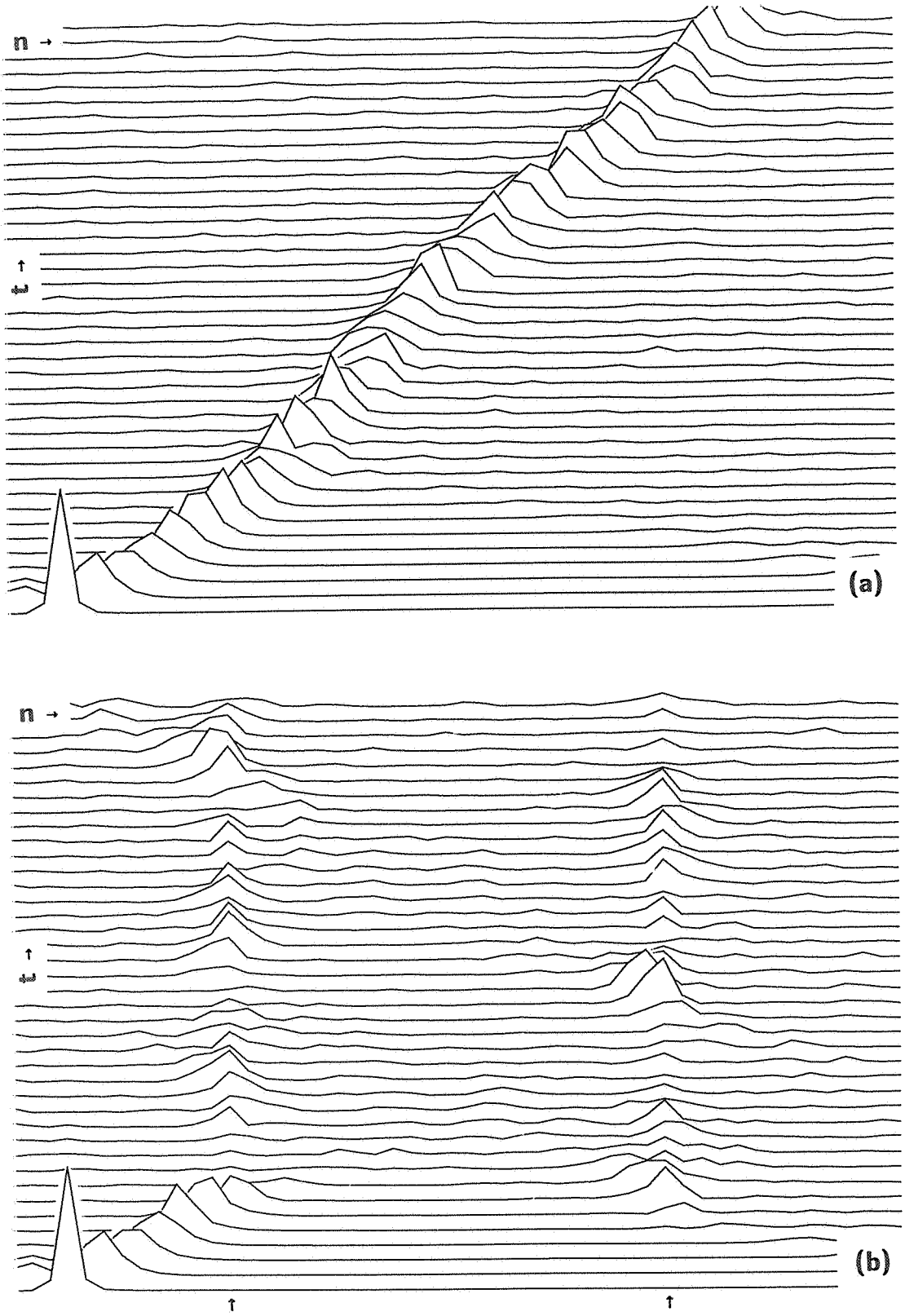


Fig. 6 Soliton propagation in a discrete NLS model, $\gamma = 3.4$, $\epsilon = 1$
(a) circular chain, (b) folded chain, $c = 0.75$, ↑ cross-over points

In the case of the twisted chain shown in Fig. 5b, energy from a soliton travelling round the chain can "leak across" at the cross-over point. If c, the cross-chain interaction is large, sufficient energy may disperse to destroy the integrity of the soliton altogether. If c is small, the soliton may travel round almost unchanged. For some intermediate values of c, the soliton may get trapped at the cross-over site. One example is shown graphically in Fig. 6b, where an initial pulse injected into the chain is trapped by the cross-over point at n = 13 and 37. (It is important to note that there are three separate trapping effects at work here: (a) the self-trapping (focusing) of the pulse due to nonlinear effects, (b) pinning due to the discreteness of the lattice, and (c) site trapping at cross-over points and other special sites in inhomogeneous lattices.)

These results on the simple discrete NLS model replicate results found on the more complicated α-helix and ACN lattices, and to some extent the results of Lomdahl's study of lysozyme. This suggest that the discreteness of the lattice, and the details of the interactions between different parts of the chain, are important factors in any model for solitons on proteins.

6. CONCLUSION

Much progress has been made on understanding stationary and travelling solitons on regular lattices such as the α-helix and ACN, and there is increasingly good experimental evidence for such modes. For the more difficult problem of the globular protein, some preliminary investigations have been carried out, but much remains to be done before a convincing theory can emerge.

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