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AUTHOR(S) Peter S. Lomdahl

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Los Alamos **MASTER**
Los Alamos National Laboratory
Los Alamos, New Mexico 87545

NONLINEAR DYNAMICS OF GLOBULAR PROTEINS

Peter S. Lomdahl

Center for Nonlinear Studies
Los Alamos National Laboratory
Los Alamos, NM 87545

1. INTRODUCTION

The general opinion and knowledge about nonlinear phenomena in the physical sciences has grown quite remarkably within the last 20 years. The prevalence of nonlinear processes in nature has been recognized for a long time - but until recently - also often neglected when dealing with specific problems. This approach was necessary in order to get tractable models which could be handled with the well proven linear mathematical tools, such as Fourier analysis and superposition principles. The fruitful collaboration over the last two decades between applied mathematicians, physicists, and engineers - has however brought about new mathematical tools which makes it possible to deal with certain nonlinear problems in a more systematic way. In particular, there are systems in which nonlinear and dispersive effects coexist and compete - this competition is often relieved by formation of a stable pulslike object - it is in such systems that the concept of the soliton plays a useful role. Especially when viewed as a paradigm for a new nonlinear "normal" mode. This approach has already been applied with success in a number of areas of physics where dispersive and nonlinear effects are important, i.e. condensed matter, plasmas, and optics.¹ So it is with some optimism that we are now facing the similar but much more complicated problems in biological systems.

DAVYDOV has as a first step in this direction considered a regular chain of hydrogen-bonded peptide groups. I shall not outline the details of the theory here - it is well described in the references^{2,3} and also in A. C. SCOTT's contribution to these proceedings. Also, the mathematical formalism is in certain cases

identical to that of the molecular crystal model developed by HOLSTEIN.⁴ However, I would like to emphasize the following basic rationals behind the theory: i) All peptide groups have a particularly characteristic intramolecular vibration called amide-I, consisting mainly of C = O valence vibrations with a frequency of 1650 cm^{-1} ($\sim 0.21 \text{ eV}$). It is tempting to view the amide-I mode as a possible "basket" for storage of energy (released during ATP hydrolysis ($0.43 \text{ eV} \sim 2 \times 0.21 \text{ eV}$) e.g.). ii) One mechanism which tends to act against localization of amide-I energy is due to resonant transfer of energy between the identical peptide groups in the molecular chain. This dispersion mechanism can be approximated as an electrostatic dipole-dipole interaction and is particularly important because the transition dipole moment of the amide-I vibration is relatively large ($d \sim 0.3D$). iii) Counteracting this mechanism, is the coupling between the amide-I vibration and other intra- and intermolecular excitations. In DAVYDOV's original work, emphasis was put on the displacement of the peptide group as a whole. When a particular peptide group is excited with amide-I energy its interaction with neighboring peptide groups changes, resulting in a change in the equilibrium distance between groups. The actual energy of a peptide group thus depends on its displacement, making the system nonlinear. In the recent work by CARERI et al.⁵ the displacement of the proton intrinsic to the peptide group was considered as an intramolecular excitation coupled to the amide-I vibration. Here, the result is essentially the same - the coupling leads to focusing of amide-I bond energy.

The above mentioned competition between dispersion and focusing of amide-I energy, will in a regular system of hydrogen-bonded peptide groups - like α -helix proteins or acetanilide crystals - lead to the formation of a soliton like object which can travel along the chain without changing their shape. This is essentially a manifestation of the fact that the system has perfect translational symmetry. A natural question to ask is: "How is this competition relieved in a real globular protein?" Such a system will in general not have translational invariance between the different peptide groups, and soliton formation is not to be expected. However, the mechanisms for dispersion and focusing of amide-I energy will still be present.

In this paper I will describe some ongoing work which is aimed at generalizing DAVYDOV's ideas to a real globular protein. So far, a computer code, "GLOP", which calculates amide-I bond energy evolution on a globular protein has been developed and tested. The code is quite versatile and takes as input the coordinates of a protein. The full geometry of the molecule is then taken into account when the dipole-dipole interaction between peptide groups is calculated. The amide-I energy is coupled to one intramolecular excitation, but can without difficulty be extended to more or to include intermolecular excitations. The outline of the paper is as follows: In

section 2, I describe the model Hamiltonian, in section 3 preliminary results for two structures are given, the first - acetanilide - is a test case for a regular chain structure of peptide groups, the second is for the globular protein - lysozyme. Finally in section 4, I comment on future work and relations to similar work in other fields.

2. MODEL HAMILTONIAN

In this section, I will derive the equations of motion for amide-I bond energy evolution on a protein structure which does not necessarily have a regular symmetry. This set of equations form the basis for the construction of the numerical code. The analysis is with a few exceptions, quite in the spirit of DAVYDOV^{2,3}.

The amide-I vibrational excitation will be treated as a one-excited state in terms of quantum mechanics. It will be coupled to an intramolecular excitation which will be treated as a classical variable from the beginning. Here I specifically consider the out-of-plane vibration of the proton of each peptide group⁵ and assume that this motion can be described quasiclassically as an Einstein oscillator. I should stress that this simplified approach does not put limitations on the final code - the coupling to other intra- or intermolecular excitation can easily be included.

If $b_j^\dagger$ and b_j are boson creation and annihilation operators for an amide-I excitation on the j -th peptide group, then the Hamiltonian for the pure amide-I system is given by

$$H_A = \sum_j \epsilon_j b_j^\dagger b_j + \sum_{j \neq k} \sum_k \frac{V_{jk}}{2} (b_k^\dagger b_j + b_j b_k^\dagger) . \quad (1)$$

The summation is carried out over all N peptide groups in the system. The first term in Eq. (1) defines the amide-I excitation energy without considering the resonance dipole-dipole interaction. Here ϵ_j is the energy of the amide-I vibration on the j -th peptide group. This energy varies slightly from group to group - depending upon the actual configuration in which the peptide group is located (α -helix, β -sheet, random coil, etc.). For a regular chain structure it is of course a constant. The operators in the last term in Eq. (1) represent transfer of amide-I energy from group j to k (and vice versa) due to dipole-dipole interaction. The quantity V_{jk} is the dipole-dipole interaction energy between groups j and k .

This energy is calculated in the usual electrostatic approximation. Following CHIRGADZE and NEVSKAYA⁶ the location of the center of the transition dipole ($\vec{d}_j \approx d\vec{r}_j$) is placed about 0.4 Å from the oxygen atom in the oxygen-nitrogen direction (see Fig. 1).

Fig. 1. Dipole-dipole interaction between peptide groups. A unit vector in the $\vec{R}$ direction is $\vec{n} = \vec{R}/|\vec{R}|$.

The direction of the transition dipole moment is taken as lying in the amide group plane and making an angle of 20° between the $C=O$ bond, being inclined towards the direction of the CN bond. This approach is what was used by MOORE and KRIMM in their analysis of polyglycine.⁷ Knowing the location - the interaction energy is easily calculated. Dipole k sees the potential: $U(\vec{R}) = d\vec{r}_j \cdot \vec{R} / (4\pi\epsilon R^3)$. The field is: $\vec{E} = -\nabla U(\vec{R})$ or

$$\begin{aligned}\vec{E} &= -\frac{d}{4\pi\epsilon} \left[\frac{\vec{r}_j}{R^3} - \frac{3(\vec{r}_j \cdot \vec{R})}{R^4} \vec{n} \right] \\ &= -\frac{d}{4\pi\epsilon R^3} [\vec{r}_j - 3(\vec{r}_j \cdot \vec{n})\vec{n}] .\end{aligned}$$

The interaction energy is thus: $V_{jk} = -\vec{E} \cdot d\vec{r}_k = V_{kj}$ or

$$V_{jk} = \frac{d^2}{4\pi\epsilon R^3} [\vec{r}_j \cdot \vec{r}_k - 3(\vec{r}_j \cdot \vec{n})(\vec{r}_k \cdot \vec{n})] . \quad (2)$$

The dielectric constant, ϵ , is taken as the screened value: $\epsilon(R) = \epsilon$ for $R < R_0$ and $\epsilon(R) = n\epsilon$ for $R > R_0$. This reflects the fact that as $R \rightarrow 0$ there is no intervening matter between atoms to increase ϵ . Thus $\epsilon = \epsilon$ for R sufficiently small. In the code R_0 and n are adjustable parameters. For the results reported in section 3, R_0 and n were taken as 15 Å and 1.6, respectively.

The next term we consider in our description of the peptide group system is the energy associated with the interaction of the amide-I excitation and the vibrations of the hydrogen-bonded proton in the out-of-plane NH bending direction. If y_j is a coordinate

denoting the displacement away from equilibrium of the proton on the j -th peptide group, then the interaction energy is

$$H_I = \chi \sum_j y_j b_j^\dagger b_j . \quad (3)$$

It reflects the fact that the amide-I energy depends on the distortion of the adjacent proton. The coupling constant, χ , is in fact the change in amide-I energy per unit extension of the NH bond.

The motion of the proton itself is governed by the classical Hamiltonian:

$$H_p = T + U = \frac{m_p}{2} \sum_j \dot{y}_j^2 + \frac{m_p \omega_p^2}{2} \sum_j y_j^2 . \quad (4)$$

The mass of the proton is m_p , while ω_p denotes the frequency of out-of-plane NH bending ($\sim 700 \text{ cm}^{-1}$).^{8,5} The first term is the kinetic energy and the second the potential energy.

The total Hamiltonian $H = H_A + H_p + H_I$ of the system must satisfy the time dependent Schrödinger equation:

$$i\hbar \frac{\partial}{\partial t} |\psi\rangle = H |\psi\rangle = (H_A + H_p + H_I) |\psi\rangle . \quad (5)$$

The state of the system is described by the wavefunction, $|\psi\rangle$, which is taken to have the form

$$|\psi\rangle = \sum_j \tilde{a}_j(t) b_j^\dagger |0\rangle , \quad (6)$$

where the $\tilde{a}_j(t)$ are complex numbers whose values at some initial time are arbitrary (apart from normalization), and where the ket, $|0\rangle$, denotes the "vacuum" state of the amide-I excitation, also defined as the state for which $b_j |0\rangle = 0$. For simplicity the normalization is chosen as:

$$\langle \psi | \psi \rangle = \sum_j |\tilde{a}_j(t)|^2 = 1 . \quad (7)$$

Inserting Eqs. (1), (3), and (4) in Eq. (5) and using Eqs. (6) and (7) the following equations are obtained:

$$i\hbar \dot{\tilde{a}}_j = [\epsilon_j + T + U] \tilde{a}_j + \chi y_j \tilde{a}_j + \sum_{k \neq j} v_{jk} \tilde{a}_k . \quad (8)$$

In this set of equations j is running from 1 to N (= number of peptide groups). As a closure, a set of equations for y_j is needed, this is readily obtained from H by applying Hamilton's equations

($\dot{q} = \frac{\partial H}{\partial p}$, $\dot{p} = -\frac{\partial H}{\partial q}$, here $q = y_j$, and $p = m_p \dot{y}_j$), combined with Eqs. (6)-(7):

$$\ddot{y}_j + \omega_p^2 y_j = -\frac{\chi}{m_p} |\tilde{a}_j|^2. \quad (9)$$

The Eqs. (8)-(9) are the main result of the analysis and form the basis for the code GLOP. They describe the time evolution of amide-I bond energy coupled to vibrations of the proton in the peptide group. The quantity $|\tilde{a}_j(t)|^2$ characterizes the distribution of amide-I energy over the individual peptide groups of the protein.

To get a better understanding for the behavior of Eqs. (8)-(9), it is instructive to look at time scales which are slow compared to ω_p . In this range $\ddot{y}_j \approx 0$ and Eqs. (8) and (9) can be combined to:

$$i\hbar \dot{\tilde{a}}_j = [\epsilon_j + U] \tilde{a}_j - \frac{\chi^2}{m_p \omega_p^2} |\tilde{a}_j|^2 \tilde{a}_j + \sum_{k \neq j} V_{jk} \tilde{a}_k. \quad (10)$$

Further, introducing $a_j(t) = \tilde{a}_j(t) e^{-iU t/\hbar}$ - together with the scaled time variable $\tau = t/T_0$, where $T_0 = \hbar \omega_p^2 / \chi^2$ - we get:

$$i \frac{da_j}{d\tau} = \delta_j a_j - |a_j|^2 a_j + \sum_{k \neq j} \gamma_{jk} a_k, \quad (11)$$

here $\delta_j = T_0 \epsilon_j / \hbar$ and $\gamma_{jk} = T_0 V_{jk} / \hbar$. Eq. (11) can also be written in matrix form:

$$i \frac{d\bar{A}}{d\tau} = \bar{H} \bar{A}, \quad (12)$$

where $\bar{A} \equiv \text{col}\{a_1, a_2, \dots, a_N\}$ and

$$\bar{H} \equiv \begin{pmatrix} \delta_1 - |a_1|^2 & \gamma_{12} & \gamma_{13} & \cdot & \cdot & \gamma_{1N} \\ \gamma_{12} & \delta_2 - |a_2|^2 & \gamma_{23} & \cdot & \cdot & \gamma_{2N} \\ \gamma_{13} & \gamma_{23} & \delta_3 - |a_3|^2 & \cdot & \cdot & \gamma_{3N} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \gamma_{1N} & \gamma_{2N} & \cdot & \cdot & \cdot & \delta_N - |a_N|^2 \end{pmatrix}_{N \times N} \quad (13)$$

In the form of Eqs. (12)-(13), it is readily seen that diagonal terms in $\bar{M}$ tend to focus amide-I energy while the off-diagonal terms are responsible for dispersion of energy. For numerical purposes it is useful to note the following conservation law for Eq. (12).

Multiplying Eq. (12) by $i\bar{A}^*$ one gets: $\dot{\bar{A}} \cdot \bar{A}^* = -i\bar{M}|\bar{A}|^2$, but since $\bar{M}$

is real we also have: $\dot{\bar{A}}^* \bar{A} = i\bar{M}|\bar{A}|^2$, from which it follows that

$\dot{\bar{A}}\bar{A}^* + \dot{\bar{A}}^*\bar{A} = 0$ or $\bar{A}\bar{A}^* = \text{constant}$. Considering Eq. (7) this is of course not surprising, but it is useful in monitoring the numerical integration of Eq. (12).

The code GLOP has been set up to integrate either Eqs. (8)-(9) or Eq. (11) with a given initial configuration of amide-I bond energy, $a_j(t=0)$, - and for Eqs. (8)-(9) initial proton displacement, $y_j(t=0)$. As a start the coordinates for the desired protein structure are input and the dipole-dipole interaction energies, V_{jk} , are calculated from Eq. (2). The equations of motion are then integrated using a versatile leap-frog predictor-corrector method⁹. The accuracy of the integration is monitored at each time-step via the conserved quantity. In addition to instantaneous pictures of $|a_j(t)|^2$ during the time evolution, quantities measuring total "bending" - like $|\sum_j |a_j| a_j|$ - are recorded as a function of time.

Various diagnostics - including Fourier analysis - can then be applied to such time series.

3. EXAMPLES

In this section, I will present two cases of what can be obtained from actual numerical integration of Eq. (11). These are only examples of preliminary results with the code GLOP - a detailed study of both systems will be published elsewhere.

In order to test the code I have first studied a regular lattice system - acetanilide (or ACN) which has recently been investigated quite extensively, both theoretically and experimentally⁶. The system basically consists of two close chains of hydrogen-bonded peptide groups. Attached to each group is a benzene ring and a methyl group¹⁰. In Fig. 2, two "unit cells" are shown. The dark atoms belong to one chain, while the white ones belong to the other. Some atoms in the dark chain are partly covered by those of the white chain. The actual system considered consisted of 50 "unit cells". The dipole-dipole interaction in this system will be quite regular because of the translational invariance of the lattice. In Fig. 3 the number of peptide groups with a particular interaction energy is shown as a function of energy. It is seen that only a few distinct values play an important role. In fact, if

Fig. 2. Acetanilide (or ACN) consisting of two close chains of peptide groups. Two "unit cells" are shown.

only nearest neighbor interaction between groups is taken into account, the system can be described by two coupled nonlinear Schrodinger equations⁵, and is thus expected to support soliton-like excitations.

This is exactly what is depicted in Fig. 4. It shows the time evolution of $|a_j(t)|^2$ resulting from the numerical integration of Eq. (11). The results are displayed for 50 different times in the interval $0 < t \leq 60$ ps. The peptide groups are numbered from 1 to 100, where 1-50 correspond to groups on one chain and 51-100 to groups on the other chain. The initial condition was one quantum of amide-I energy placed on group number one. A non-dispersive soliton-like object is seen to form, and propagate down the chain system. In addition, it is seen that the energy is oscillating between the two chains. When $|a_j(t)|^2$ is large on one chain it is

Fig. 3. Dipole-dipole interaction energy distribution for acetanilide.

Fig. 4. Result of numerical solution of Eq. (11) with one quantum of amide-I energy placed at peptide group no. 1 in the acetanilide system. Groups with no. 1-50 are on one chain and groups with no. 51-100 on the other chain. The time evolution is shown for the first 60 ps approx. The coupling constant, χ , was $1.0 \cdot 10^{-10}$ N (see Ref. 5).

low on the other. This behavior is to be expected from an analysis based on two coupled nonlinear Schrödinger equations⁵. The result of Fig. 4 is confirming that this is actually a good approximation - even when the full dipole-dipole interaction is taken into account the nearest neighbor interaction tells the main story.

To test the code on a real globular protein - preliminary runs with the enzyme lysozyme (from chicken egg-white) have been done. The structure is well known¹¹ and consists of 129 peptide groups. The carbon atoms in the peptide groups are shown connected as a "backbone" in Fig. 5. The overall non-regular structure is quite clear. Part of the structure is however in the α -helix configuration, those groups (5-15, 24-34, 88-96) are indicated by black carbon atoms in Fig. 5. The number of groups with a particular dipole-dipole interaction energy is shown in Fig. 6. The disordered structure is clear when compared with Fig. 3 for ACN. In Fig. 7 we show the result of the solution of Eq. (11) with initially two quanta placed on peptide groups 33 and 34 which is the end of the longest α -helix part. It is interesting to note that the energy basically stays localized on the α -helix part - it oscillates between the two ends for approximately 225 ps (as far as the integration was performed). Additional runs where the energy was initiated on other peptide groups (non α -helical), showed that dispersion of energy easily can occur too.

Fig. 5. Chicken egg-white lysozyme. The carbon atoms (from the $C=O$ group, not α -carbon) in each peptide group are shown. The black atoms indicate α -helix regions (peptide groups 5-15, 24-34, 88-96).

Fig. 6. Dipole-dipole interaction energy distribution for lysozyme.

Fig. 7. Results of numerical solution of Eq. (11) with two quanta of amide-I energy placed at peptide groups no. 33 and 34 (α -helix). The time evolution is shown for approx. 225 ps₂. The coupling constant, χ , was chosen to $0.4 \cdot 10^{-11}$ N and $m_{pp} \omega_p^2$ was equal to 13 N/m.

4. CONCLUDING REMARKS

The examples given above are of course not exhaustive and more work is needed before conclusive statements can be made. In addition to the study of the specific systems mentioned above, work is in progress to improve the code. In particular the following areas are considered.

1) Finding localized stationary states. The possible initial conditions used for the dynamics calculations with Eq. (11) are not ideal at the present time. Stationary states - i.e. solutions to Eq. (12) of the form $\bar{A} = \bar{A} e^{-i\omega t}$, where ω is a constant - would form a better starting point. Note that the superposition of such states is in general not a new stationary state. The nonlinear dynamics of Eq. (11) would govern the evolution. Inserting $\bar{A} = \bar{A} e^{-i\omega t}$ in Eq. (13) leads to a nonlinear eigenvalue problem, where Eq. (7) is a constraint equation. The solution of this problem is the main difficulty in finding the stationary states. Of particular interest are those states which are localized and have low energy (small ω). Such states could be expected to have soliton-like character if they were localized in places where the protein structure was fairly regular.

In connection with this problem it is interesting to note that related work has been going on for some years in the area of amorphous semiconductors. Here equations similar to Eq. (11) arise naturally too. We refer the interested reader to the review by THOULESS¹¹.

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2) More realistic coupling to other intra- and intermolecular modes. The simple system represented by Eq. (9) should be extended to include more intra- and intermolecular excitations. More conventional molecular dynamics codes¹² are already considering such systems and should be incorporated in GLOP. In this respect it is also important to consider dissipative effects (energy transfer from the protein into water e.g.). As a starter this could be done by including phenomenological damping terms in Eq. (11).

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