Collective excitations in alpha-helical protein structures interacting with the environment

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Abstract

Low-frequency vibrational excitations of protein macromolecules in the terahertz frequency region are suggested to contribute to many biological processes such as enzymatic activity, energy/charge transport, protein folding, and others. Two possible mechanisms of the long-lived excitation in the form of vibrational modes and solitary waves in proteins were earlier proposed by H. Fröhlich and A.S. Davydov, respectively, to explain high effectiveness of energy storage and transport in proteins. In this paper, we developed a quantum dynamic model of vibrational excitation in alpha-helical proteins interacting with the environment formed by water molecules. In the model, we distinguished three coupled subsystems in alpha-helix, i.e. (i) a chain of hydrogen-bonded peptide groups (PGs), interacting with (ii) the subsystem of side residuals which in turn interacts with (iii) the environment (surrounding water) responsible for dissipation and fluctuation processes in the system. It was shown that under reasonable approximations the equation of motion for phonon variables of the PG chain can be transformed to nonlinear Schrodinger equation for order parameter which admits bifurcation into the solution corresponding to weak damped vibrational modes (Fröhlich-type regime). A bifurcation parameter in the model is derived through the strength of interaction between alpha-helical protein and the environment. As shown, in the bifurcation region, a solution corresponding to Davydov soliton can exist. The suggested mechanism underlying emergence of the macroscopic dissipative structures in the form of collective vibrational modes in alpha-helical proteins is discussed in connection with the recent experimental data on the long-lived collective protein excitations in the terahertz frequency region.

Keywords: alpha-helical protein, collective excitation, phonons, solitons, Fröhlich condensation

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1. Introduction

A concept of protein molecules as dynamic systems is backed by the numerous experimental and theoretical investigations of the correlation between protein dynamics, structure and functions. Currently, intense efforts are undertaken to elucidate contribution of the dynamic modes of internal protein motion and excitations to protein functions such as enzyme activity, charge/energy transport, structural, sensor, signal transduction, and others [1], [2], [3]. Protein excitations related to their functions include either localised oscillation of atom groups and bonds or the large-scale vibrations of subdomains of the proteins. High-frequency vibrations of atom groups and intrapeptide bonds (e.g. C=O stretching) lie within the IR optical spectrum, while low-frequency collective vibrational modes are ranged at the lowest end of the far IR spectrum and in the terahertz frequency range [4] [5].

Large-scale collective excitations such as normal vibration modes [6], [7], sound waves (phonons) [8], and coherent vibrational states [9], [10] are reported to be excited in protein molecules on a timescale from picosecond to nanosecond. A role of these collective modes and their interaction with the localised excitations in protein functions are the subject of intensive experimental and theoretical works [6], [7], [11]–[13].

The physical mechanism of collective coherent excitations far from thermal equilibrium and their possible protein functions in biosystems were proposed and investigated by H. Fröhlich [14], [15]. He has developed a phenomenological non-linear model of collective longitudinal vibrational-polar modes (phonons) excited in the 0.1 GHz - 1 THz frequency range and suggested their role in biological processes such as enzymatic catalysis, biomembrane function and protein-protein interaction [12].

The general idea underlying this mechanism of long-lived coherent vibrations in biological systems is in an assumption that when the energy is supplied to the system at a rate greater than that of energy loss, vibrational modes can condense into the lowest-frequency vibrational mode like the phenomenon of Bose-Einstein condensation. In contrast to Bose-Einstein condensation occurring in thermal equilibrium, Fröhlich condensation takes place in non-equilibrium condition at the energy supply and dissipation in non-linear molecular structures [16]. Thus, excitation of the Fröhlich mode, in the form of the coherent quantum dynamic structure, can be considered as the emergence of a space-temporal dissipative structure in according to Prigogine's theory [17] which is governed by the self-organization principals of Haken's synergetics in non-linear systems [18]. At present, further development of the Fröhlich model in quantum dynamics and quasi-classical approaches are undertaking in

order to determine physical conditions of phonon condensation in proteins far from thermal equilibrium [19], [20] [21],[22],[23].

Another type of coherent excitation in the form of solitary waves was proposed theoretically by A.S. Davydov in order to unravel one of the central problems in bioenergetics i.e. a highly effective long-distance transport of energy/charge within macromolecules [24]. As a result of a series of his works, the theory of soliton transport of energy/charge in the alpha-helical proteins has been developed [24], [25]. Additionally, it was concluded that alpha-helical peptide structure plays a significant role in the formation of the soliton, travelling a long distance with weak decay.

The soliton model was applied to describe transport of energy, released in the hydrolysis of ATP and localised in the amide-I vibration (C=O bond), along the chain of peptide groups at room temperature [24]. Mechanisms of localisation, storage, and transport of energy is defined in the model as non-linear interactions of the high-frequency amide-I excitation (1667 cm^{-1}) and low-frequency acoustic modes in the 1D protein structure.

An alternative to the quantum Davydov model [25], a classical vibrational model of the interpeptide excitation dynamics was suggested by Takeno, who studied soliton stability at room temperature [26]. Many theoretical aspects of soliton dynamics in protein macromolecules including soliton stability, thermalization, solitons' interaction and others were investigated in various approximations [27]. The unified approaches to the description of both Davydov soliton mode and Fröhlich condensation mode excitations in proteins at the conditions far away from thermal equilibrium were developed [9], [16], [28], [29].

Searching for the experimental observation both of these types of coherent excitations in proteins remains an area of intense experimental research and source of lively debate [20]–[22], [23], [30]. Experimental evidence of the coherent vibrational state emergence in protein macromolecules was obtained by the IR, Raman, terahertz spectroscopy and their combinations [23], [31], [32].

In this work, we develop further the molecular models of the collective excitations in alpha-helical peptide macromolecules [27], [33], [34] and extend quantum dynamics approach to take into account the dynamics of protein side chains responsible for proteins interacting within the environment. Following the Fröhlich approach [35] we distinguished three subsystems in the protein molecule interacting with its environment: (i) a chain of hydrogen-bonded peptide groups (PGs) interacting with (ii) the subsystem of side residuals of the protein which in turn interact with (iii) surrounding water. Here we used the quantum mechanics approach which was developed earlier to model autolocalized states (polaron) of quantum

quasiparticle (valent electron) of intramolecular excitation in the PG chain [27], [33], [34]. The developed model is used in part in the investigation of the conditions in which molecular interaction between the PGs, side residual chain and protein's environment causes excitations of vibrational and soliton types in alpha-helical protein structures.

2. Phonons in a one-dimensional chain of hydrogen-bonded peptide groups interacting with side radicals

The secondary protein structure, alpha-helix is formed as a result of folding up of polypeptide chain in a helix due to the interaction of amino acid residues (Fig. 1a). This interaction determines space periodicity of the secondary structure in proteins, and in turn, its stability is ensured by hydrogen bonds between NH- and CO-groups of the backbone (Fig. 1b). The alpha-helix has a form of a coil, and its inner part consists of a tightly twisted backbone with amino acid radicals directed outwards (Fig. 1c). Electrical charge distribution in the peptide group forms its electrical dipole moment equal to 3.5 D and directed along H-bond [25].

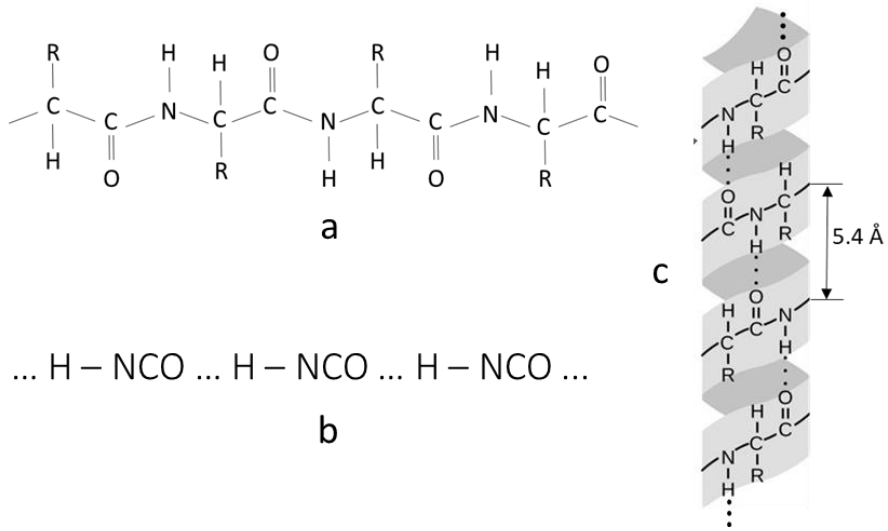

Fig. 1. (a) The polypeptide chain. (b) The chain of hydrogen-bonded peptide groups. (c) Structure of alpha-helical protein, where one of the three hydrogen-bonded PG chains with side radicals (R) is shown. Hydrogen-bonds are depicted by dots.

Consider a one-dimensional chain of hydrogen-bonded peptide groups with hydrogen bonds between (NH)- and CO-groups (Fig. 1b). Assume intrinsic motion of proton and the rest of the PGs (NCO) and define equilibrium positions of the PGs in the l-site $z=la$ (l=0, 1, 2, …) along the alpha-helix (the z-axis), where a= 5.4 Å is chain spacing. Denote displacement of

the atoms from equilibrium positions of the PG in the l-site by $\xi_{l,1}$ for hydrogen and $\xi_{l,2}$ for the rest of the PG atoms. In harmonic approximation, potential energy of interaction between atoms of the nearest PGs and nearest radicals R is expressed by a quadratic form:

$$U = \frac{1}{2}\sum_{l}\left[\chi_{1,2}\left(\zeta_{l+1,1} - \zeta_{l,1}\right)^2 + \chi_{2,1}\left(\zeta_{l,1} - \zeta_{l,2}\right)^2 + \chi_{0,1}\xi_{l,1}^2 + \chi_{0,2}\xi_{l,2}^2\right], \quad (1)$$

where $\chi_{1,2}$ and $\chi_{2,1}$ are elastic coefficients of hydrogen and valence bonds respectively; $\chi_{0,1}$ and $\chi_{0,2}$ are elastic coefficients of the interaction of protons and NCO group with the side chain radicals, respectively. Choose the following cyclic boundary condition for the PG chain

$$\zeta_{l,\alpha} = \zeta_{l+N,\alpha} \text{ for } \alpha\text{=1 and 2}, \quad (2)$$

where N is a number of GPs in the chain.

To write the Hamiltonian of the PG chain, express the operators of atom displacement from equilibrium positions through the operators of the creation $b_{-k,s}^{+}$ and annihilation $b_{k,s}$ of phonons as

$$\xi_{l,1}^{(s)} = \sum_{k}\left[\frac{\hbar}{2m_\alpha N\Omega_s(k)}\right]^{1/2} e^{ikx}\left(b_{k,s} + b_{-k,s}^{+}\right), \quad (3)$$

where the operators of the creation and annihilation satisfy the commutative relationships

$$[b_{k,s}, b_{k',s'}^{+}] = \delta_{kk'}\delta_{ss'} \text{ and } [b_{k,s}, b_{k',s'}] = 0. \quad (4)$$

Here δ is the Kronecker symbol, k is the wave number taking N values in the first Brillouin zone

$$k = \frac{2\pi\eta}{Na}, \text{where } \eta = 0, \pm 1, \cdots, \pm\frac{N}{2}, \quad (5)$$

and index s points to either acoustic (s=1) or optic (s=2) phonons.

The Hamiltonian of phonons in the PG chain can be written in the harmonic approximation as

$$H_p = \sum_{k,s}\hbar\,\Omega_s(k)\left(b_{k,s}^{+}b_{k,s} + \frac{1}{2}\right), \quad (6)$$

where two functions $\Omega_s(k)$ define dispersion relationship for frequencies of acoustic and optic branches of the vibration in the PG chain with s = 1 and 2 respectively. We used harmonic approximation to derive eqs. (1) and (6) that is a typical procedure in the theoretical investigation in nonlinear dynamics of molecular chains [17]–[19], [28].

The dispersion relationship $\Omega_s(k)$ for the PG chain with interaction defined by eq. (1) can be obtained in the form

$$\Omega_s^2(k) = A + (-1)^s\sqrt{A^2 - B(k)}, \tag{8}$$

where

$$A = \frac{1}{m_1 m_2}\left[m_1\chi_{0,2} + m_2\chi_{0,1} + (m_1{+}m_2)(\chi_{1,2} + \chi_{2,1})\right]$$

and

$$B = \frac{1}{m_1 m_2}\left[(\chi_{0,1} + \chi_{0,2})(\chi_{1,2} + \chi_{2,1}) + \chi_{0,1}\chi_{0,2} + 4\chi_{1,2}\chi_{2,1}sin^2\left(\frac{ka}{2}\right)\right].$$

Here $m_1{=}m_p$ and m_2 = 41.7m_p are mass of proton and the PG group respectively. Dispersion curves calculated at the values of elastic constants of the PG chain [27] are shown in Fig. 2. As seen, according to dispersion equation (8), the PG chain with interaction (1) obeys a narrow band of the normal modes of the vibrations $\Omega_s(k)$ in the terahertz frequency range.

Similarly introduce the phonon Hamiltonian for the radical system of the PG chain which can be represented as a system of *N* oscillators of mass *M* having own frequencies of oscillation $\Omega_t(q)$

$$H_C = \sum_{q,t} \hbar\,\Omega_t(q)\left(c_{q,t}^{+}c_{q,t} + \frac{1}{2}\right), \tag{9}$$

where $c_{q,t}^{+}$ and $c_{q,t}$ are the operators of the creation and annihilation of phonons in the radical chain which correspond to the displacement of the radicals from their equilibrium positions ς_l. $\Omega_t(q)$ are the phonon frequency of type *t* in the radical chain and q is the wave number. The representation of the side chain system as a set of oscillators in the model is based on the experimental data on the protein side-chain dynamics obtained by the X-ray diffraction, NMR methods and spin labelling EPR spectroscopy which provide detailed data on the side chain order parameter and mobility on the picosecond to microsecond timescale [36], [37],[38]. Moreover, molecular dynamic and normal mode calculations of protein internal dynamics showed that harmonic approximation for the modelling of the side chain dynamics is the satisfactory approximation that gives the consistent description of the normal low-frequency modes with frequencies in the range of 120-200 cm^{-1} localised on the side chain [36]. Anharmonic contributions in the molecular chain dynamics beyond harmonic approximation is taken account below.

Consider interaction of the phonons in the PG and radical chains in the alpha-helical protein structure by adding the following anharmonic operator of interaction to the Hamiltonian of non-interacted chains

$$W = \sum_{l} V(l) \varsigma_l^{(t)} \xi_{l,1} \xi_{l,2} \,, \tag{10}$$

where

$$\varsigma_l^{(t)} = \sum_{q} \left[\frac{\hbar}{2MN\Omega_t(q)} \right]^{1/2} e^{ikx} \left(c_{q,t} + c_{-q,t}^{+} \right). \tag{11}$$

Substitution of eqs. (3) and (10) into eq. (9) gives the operator of anharmonic perturbation in the form

$$W = \sum_{k,k'} \left(V_{k,k'} c_{k-k'}^{+} b_k^{+} b_{k'} + H.c. \right) , \tag{12}$$

where

$$V_{k,k'} = \left(\frac{\hbar^3}{8N^3 m_1 m_2 M \Omega_s(k) \Omega_{s'}(k') \Omega_t(k-k')} \right)^{1/2} . \tag{13}$$

The matrix elements (13), which are different from zero on the functions of occupation numbers, corresponds to the processes occurring with energy and momentum conservation without consideration of umklapp process:

$$\Omega_t(k-k') + \Omega_s(k) = \Omega_{s'}(k').$$

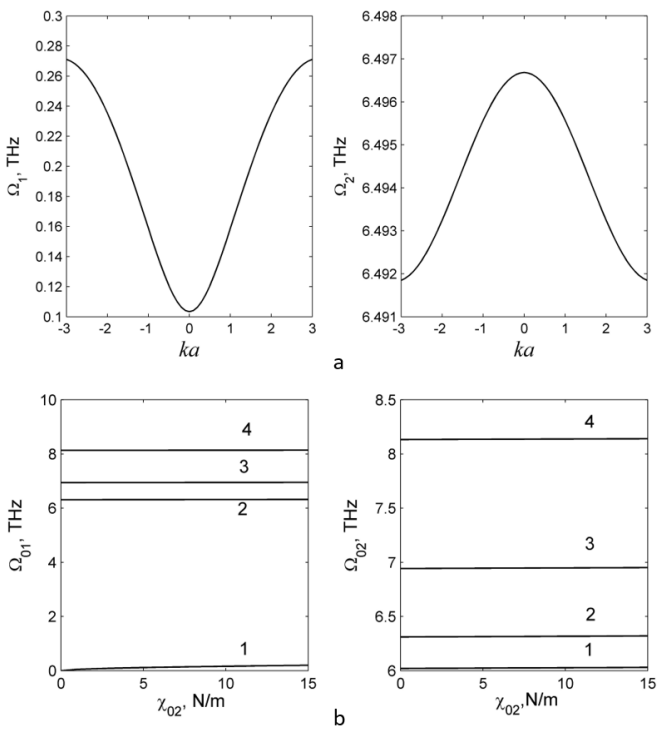

Fig. 2. Dispersion curves for the chain of hydrogen-bounded PGs calculated at the following elastic constants [27]. (a) s=1, $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$, $\chi_{0,1} = 5.0\ \mathrm{N}m^{-1}$, $\chi_{0,2} = 0\ \mathrm{N}m^{-1}$. (B) s=2, $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$, $\chi_{0,1} =$

5.0 Nm^{-1}, $\chi_{0,2} = 0$ Nm^{-1}. (b) Dependence of the frequency Ω_{01} (C) and Ω_{02} (D) (k=0) on constant χ_{02} at the fixed values of elastic constants $\chi_{1,2} = 13.0$ Nm^{-1}, $\chi_{2,1} = 17.0$ Nm^{-1} and different constant $\chi_{0,1}$: line 1 - $\chi_{0,1} = 0.0$ Nm^{-1}, line 2 - $\chi_{0,1} = 3.0$ Nm^{-1} , and line 3 - $\chi_{0,1} = 25.0$ Nm^{-1}. Dispersion curves were calculated in MATLAB package (MathWork Inc).

Approximations (Eqs (10)-(12)), which we used at the description of the coupled PG chain and side chain dynamics, are based on the experimental data obtained by site-directed spin labelling NMR and EPR spectroscopy on side chain mobility and the backbone order parameter [2], [37]. This data showed, in part for alpha-helical structures, the tight coupling between backbone and side chain dynamics, but at the same time reviled the liquid-like dynamics of side chains that significantly contributes in the folded protein structures and functions.

3. Interaction of alpha-helical protein with environment (heat reservoir)

Consider the interaction of the alpha-helical protein with its environment, surrounding water molecules which form a heat reservoir with a non-zero temperature T. This protein-water interaction defines dissipation processes in the system and contributes to the structure and functions of proteins. In the model, we represent surrounding water by a large set of harmonic oscillators interacting with the protein molecule and suggest that this system possesses collective excitation modes with dynamics similar to that of an oscillators' ensemble. This approximation can be backed by the observation of the collective vibrational subpicosecond dynamics (phonons) of the hydrogen bond network which was observed in hydration shells of protein molecules in terahertz and IR spectra [39].

Then the energy operator of the heat reservoir (surrounding water) can be written as a sum of energy operators for the independent oscillators through the operators of the creation $B^{+}_{p,t}$ and annihilation $B_{p,t}$ of phonons with the wave number p and frequencies dispersion relation $\omega_t(p)$

$$H_B = \sum_{p,t} \hbar\omega_t(p)\left(B^{+}_{p,t}B_{p,t} + \frac{1}{2}\right). \tag{14}$$

To calculate energy W_B of joint action of heat reservoir's oscillators on the protein macromolecule, we assumed that each oscillator contributes linearly to the energy W_B and interacts only with the radical chain of the alpha-helical protein. So, following [26], we

suggested that the PG chain interacts with the environment through radicals R (Fig. 1). Then, interaction operator W_B can be written as

$$W_B = \hbar \sum_{p,gt,t\prime} \left\{ \sigma_{tt\prime}(g,p) c_{g,t}^{+} B_{p,t\prime} + H.c. \right\}. \tag{15}$$

Parameter $\sigma_{tt\prime}(g,p)$ defines a strength of interaction between heat reservoir's oscillators of types t' and the side chain oscillators of type *t*. Note that operator (15) describes a wide class of relaxation mechanisms related to collective excitation [27]. The representation of the heat reservoir by a set of harmonic oscillators (Eq. 14) and protein interaction with the thermal reservoir in the form of eq. (15) are commonly used in the modelling molecular chain dynamics in part in the Wu-Austin Hamiltonian approximation [37], [19],[40].

For simplicity, let drop indexes which define phonon type, and indexes *s*, *t*, and *t'* of variables will below mean that the specific variable belongs either to the PG chain or the radical chains or heat reservoir respectively.

4. Equation of motion

One of the features of a self-organisation behaviour of complex systems is the occurrence of the system instability with respect to either one or several variables (dynamic modes) at some critical conditions [18]. If the rest of the modes damp the different exclusion procedures of the stable variables can be applied at the modelling. It follows that the system behaviour as a whole is defined by the behaviour of a few unstable variables which govern all the damped modes. In real systems, a hierarchy of relaxation times takes place that allows applying adiabatic approximation for the exclusion of the fast-relaxing variables. In the case of protein molecules, the fast-relaxing variables c_g^{+} and c_g relate to the radical subsystem which directly interacts with the environment (structured water) surrounding a native protein and supporting stability of its structure. This approximation is based on the experimental data on NMR relaxation order parameter and analysis of the time scale in backbone and side chain dynamics [37], [40]. The experimental results reviled that the side chains exhibit faster sub-nanosecond dynamics than microsecond motions of the backbone.

To exclude fast-relaxing variables c_g^{+} and c_g, we use Heisenberg equation for these operators

$$i\hbar \frac{dA}{dt} = [A, H], \tag{16}$$

where $\mathrm{A} = \{c_g^{+}, c_q\}$ and *H* is the energy operator of the macromolecule-heat reservoir system

$$H = H_P + H_C + H_B + W_P + W_B. \tag{17}$$

Substitution of H_P, H_C, H_B, W_P, and W_B in to eq. (17) and then to eq. (16) gives the equation of motion for the operator c_g

$$i\hbar \frac{dc_g}{dt} = \hbar\Omega_t(g)c_g + N\sum_k V_{k,g} b_{k-g}^+ b_k + \hbar\sum_p \sigma(p,q)B_p, \tag{18}$$

and the identical equation for the operator c_g^+. Then let require

$$\frac{dc_g}{dt} = \frac{dc_g^+}{dt} = 0. \tag{19}$$

The following relationship can be obtained for c_g^+ and c_g from eqs. (18) and (19)

$$c_g = -\frac{N}{\hbar\Omega_t(g)}\sum_k V_{k,g} b_{k-g}^+ b_k - \sum_p \frac{\sigma(p,q)}{\Omega_t(g)} B_p. \tag{20}$$

Using eqs. (20) and commutation relations (4) for the Bose-operators, we get the energy operator in the form

$$H_S = H_P + H_B + H_{PB}, \tag{21}$$

where the energy operator of protein macromolecule is expressed only through the variables related to the PG chain

$$H_P = \sum_k \varepsilon_k b_k^+ b_k - \frac{N^2}{\hbar}\sum_{g,k,k'} \frac{V_{k,k'}V_{k',g}^*}{\Omega_t(g)} b_k^+ b_{k'-g}^+ b_{k-g} b_{k'}. \tag{22}$$

Here

$$\varepsilon_k = \hbar\Omega_t(k) - \frac{2N^3|V|^2}{\hbar\Omega_t(k)}. \tag{23}$$

Hamiltonian operator of the heat reservoir H_B is written in the form

$$H_B = \sum_p \varepsilon_p B_p^+ B_p\ , \tag{24}$$

where

$$\varepsilon_p = \hbar\omega(p) - \frac{\hbar N|\sigma|^2}{\Omega_t(p)}. \tag{25}$$

The energy of interaction of the alpha-helical protein with the heat reservoir H_{PB} after exclusion of the variables related to the side chain is defined by

$$H_{PB} = -\sum_{k,p}\{G(k,p) b_k^+ b_{k-p}^+ B_p + H.c.\}, \tag{26}$$

where

$$G(k,p) = \frac{\sigma(k,p)VN}{\Omega_t}. \tag{27}$$

Equation of motion for dynamic variables of the PG chain and reservoir can be derived using Heisenberg equation (16) for the operators $b_k, b_k^+, B_p,$ and b_p^+, the Hamiltonian operator (21), and eqs. (22)-(27)

$$i\hbar\frac{db_k}{dt} = \varepsilon_k b_k - \frac{N^2}{\hbar}\sum_{g,k\prime}\frac{V_{k,k\prime}V_{k\prime,g}^*}{\Omega_t(g)}b_{k\prime-g}^+ b_{k-g}b_{k\prime} - \sum_p G(k,p)b_{k-p}^+ B_p \tag{28}$$

and

$$i\hbar\frac{dB_p}{dt} = \varepsilon_p B_p - \sum_k G^*(k,p)b_{k-p}b_k^+. \tag{29}$$

At the next step, we use the obtained eqs. (28) and (29) to derive the motion equation for the growing modes and define system dynamics near unstable stationary points. Moreover, we describe dissipation in the system and express fluctuating forces which are coursed by the interaction of the protein macromolecule with the environment.

5. The Langevin equation for generalized coordinates of the macromolecule

As known, all basic (microscopic) equations of motion are invariant with respect to time reversal, that is the motion is entirely reversal. Although dissipative forces, violating this invariance, cannot be expressed in the original equations, under certain assumptions the Langevin equations can be derived from the Heisenberg equation for a system interacting with a heat reservoir represented by a set of harmonic oscillators [41].

So far, we considered the model of alpha-helical protein molecule interacting with the heat reservoir as the systems of quantum oscillators. However, this molecular system can be considered as the classical ones. This approximation can be justified by that a number of phonons in strongly exciting modes defining protein dynamics, and a number of oscillators in the heat reservoir are significantly larger than unit. This allows us to represent phonon amplitudes by c-numbers and substitute operators b_k, b_k^+, B_k , and B_k^+ in eqs. (28) and (29) for c-numbers $\beta_k, \beta_k^*, B_k,$ and B_k^* respectively. Amplitude $\beta_k(t)$ can be considered as the generalized coordinates with corresponding generalized momentum $i\hbar\beta_k^*$. Moreover, coefficients, defining intensity of phonon interaction of the different subsystems in the model, are assumed to weakly depend on the phonon momentum. Then, eqs. (28) and (29) can be integrated as the classical ones that gives the solution of eq. (29) in the form:

$$B_p(t) = B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t} + i\int_{-\infty}^{t}\sum_k \frac{G^*(k,p)}{\hbar}\beta_{k-p}(\tau)\beta_k^*(\tau)e^{-i\frac{\varepsilon_p}{\hbar}(t-\tau)}d\tau\,, \tag{30}$$

where $B_p(0)$ is the initial value of amplitude $B_p(t)$ at t=0.

Introduce a new variable $\widetilde{\beta_k}(t)$

$$\beta_k(t) = \widetilde{\beta_k}(t) e^{-i\Omega_k t} \tag{31}$$

and use after that the previous notation $\beta_k(t)$. Then apply adiabatic approximation commonly used in the modelling of cooperative systems, i.e. the relaxation times of the strong exciting phonon modes become longer in comparison with the typical relaxation times for the heat reservoir variables. This allows factoring out the preexponential term in eq. (30) and obtain it in the form

$$B_p(t) = B_p(0) e^{-i\frac{\varepsilon_p}{\hbar}t} + \\ +i\sum_k \frac{G^*(k,p)}{\hbar}\beta_{k-p}(t)\beta_k^*(t)\int_{-\infty}^{t} exp\left\{-i\left[\frac{\varepsilon_p}{\hbar} - \Omega_{k-p} + \Omega_k\right](t-\tau)\right\} d\tau\,. \tag{32}$$

Integrals in eq. (32) gives

$$\int_{-\infty}^{t} exp\left\{-i\left[\frac{\varepsilon_p}{\hbar} - \Omega_{k-p} + \Omega_k\right](t-\tau)\right\} d\tau = -\frac{i}{\frac{\varepsilon_p}{\hbar} - \Omega_{k-p} + \Omega_k} = -\frac{i}{\Lambda} = \\ = -i\left[P\left(\frac{1}{\Lambda}\right) + i\pi\delta(\Lambda)\right], \tag{33}$$

where P is a symbol of principal value. Finally, $B_p(t)$ is obtained in the form

$$B_p(t) = B_p(0) e^{-i\frac{\varepsilon_p}{\hbar}t} + i\sum_k \frac{G^*(k,p)}{\hbar\Lambda(k,p)}\beta_{k-p}(t)\beta_k^*(t). \tag{34}$$

Substitution of eq. (34) into eq. (28) gives us equation for $\beta_k(t)$

$$\frac{d\beta_k(t)}{dt} = -i\frac{\varepsilon_k}{\hbar}\beta_k(t) + iN^2\sum_{g,k'}\frac{V_{k,g}V_{k',g}^*}{\hbar^2\Omega_t}\beta_{k-g}(t)\beta_{k'-g}(t)\beta_{k'}^*(t) - \\ - i\sum_{g,k'}\frac{G(k,p)G^*(k',p)}{\hbar^2\Lambda}\beta_{k-p}(t)\beta_{k'-p}(t)\beta_{k'}^*(t) + \\ + i\sum_p \frac{G(k,p)}{\hbar}\beta_{k-p}(t)B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t}\,. \tag{35}$$

Eq. (35) is the Langevin equation for phonon amplitudes $\beta_k(t)$

$$\frac{d\beta_k(t)}{dt} = -\frac{i}{\hbar}(\varepsilon_k + e_k)\beta_k(t) + \frac{iN^2|V_k|^2}{\hbar^2\Omega_t}\sum_{g,k'}\beta_{k-g}(t)\beta_{k'-g}(t)\beta_{k'}^*(t) - \\ - \frac{1}{2}\gamma_k\beta_k(t) + iF_p(t)\,, \tag{36}$$

where the following variables are introduced

$$e_k = \frac{1}{\hbar}\sum_{p,k'} G(k,p)G^*(k',p)\beta_{k'-p}\beta_{k'}^* P\left(\frac{1}{\Lambda}\right), \tag{37}$$

$$\gamma_k = \frac{2\pi}{\hbar^2}\sum_{p,k\prime} G(k,p)G^*(k',p)\beta_{k\prime-p}\beta^*_{k\prime}\delta(\Lambda) \tag{38}$$

and

$$F_k(t) = \widetilde{F_k}(t)e^{-i\Omega_k t} = \frac{1}{\hbar}\sum_p G(k)\beta_{k-p}(t)B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t}. \tag{39}$$

Function $F_k(t)$ (39) can be considered as a random force with the correlator:

$$< F^*_k(t)F_k(\tau) >=$$
$$= \frac{1}{\hbar^2}\sum_{p,p\prime}|G(k)|^2 < \beta^*_{k-p}(0)\beta_{k-p\prime}(0) >< B^*_p(0)B_p(0) > e^{-i(\Lambda(k,p)t-\Lambda(k,p\prime)\tau)}. \tag{40}$$

Assume that at the initial time, amplitudes $\beta(0)$ and $B(0)$ are not correlated, i.e.

$$< \beta^*_{k-p}(0)\beta_{k-p\prime}(0) >= n_p\delta_{pp\prime} \tag{41}$$

and

$$< B^*_p(0)B_{p\prime}(0) >= N_p\delta_{pp\prime}\,, \tag{42}$$

where

$$n_p = \left(e^{\theta\hbar\Omega_p} - 1\right)^{-1} \tag{43}$$

and

$$N_p = \left(e^{\theta\hbar\omega_p} - 1\right)^{-1}. \tag{44}$$

Here $\theta = 1/k_B T$, where T is envthe ironment (hear reservoir) temperature.

Substitute eqs. (41)-(44) into eq. (40) and take into consideration that the main contribution in a sum in eq. (40) is given by terms $\Lambda(k,p) = 0$ at not too small values of a difference $(t-\tau)$. Then finally obtain

$$< F^*_k(t)F_k(\tau) >= \frac{2\pi}{\hbar^2}|G(k)|^2 n_p N_p\delta(t-\tau) = D_k\delta(t-\tau). \tag{45}$$

It can be shown that after averaging in eq. (38) for γ_k with consideration of eq. (44) and substituting this result into eq. (45), the value D_k can be written in the form

$$D_k = \hbar^2\gamma_k N_p. \tag{46}$$

6. Vibrational dynamics of alpha-helical protein in a long wave approximation

Consider vibrational modes in the alpha-helical protein at the various parameters characterising its interaction with the environment. We applied a long-wave approximation to derive the equation for undamped modes which build up to macroscopic values and investigate system dynamics in the vicinity of an unstable point. In a long-wave approximation, for small values $ka \ll 1$ and according to eq. (8), phonon frequencies can be written in the form

$$\Omega_s(k) = \Omega_{0s} + I_s k^2 a^2, \tag{47}$$

where

$$I_s = (-1)^{s+1} \frac{\chi_{1,2}\chi_{2,1}}{4m_1 m_2 \Omega_{0s}\sqrt{A^2 - B(0)}}. \tag{48}$$

Here Ω_{0s} and $B(0)$ are defined by eq. (8) at k=0. Note, that the value

$$\sqrt{A^2 - B(0)} = \frac{1}{2}(\Omega_{02}^2 - \Omega_{01}^2) \tag{49}$$

can be found from the dependence of frequencies Ω_{0s} on the elastic constants shown in Fig. 2.

As in the long-wave approximation the value $\Lambda(k,p) = \Lambda(p)$ does not depend on k, we turn to continuum limit in eq. (36) after Fourie transformation by multiplication of all terms in eq. (36) by $N^{-1/2}e^{ikz}$ and summing up over k according to eq. (47). In continuum limit, eq. (36) for photon modes with the dispersion relation (47) takes the form

$$i\hbar\frac{\partial\beta_s(x,t)}{\partial t} + \hbar a^2 I_s \frac{\partial^2\beta_s(x,t)}{\partial z^2} - E_s\beta_s(x,t) + Q_s|\beta_s(x,t)|^2\beta_s(x,t) = F_s(x,t), \tag{50}$$

where

$$E_s = \varepsilon_{0s} - e_{0s} - \frac{i\hbar\gamma_s}{2} = E_{0s} - \frac{i\hbar\gamma_s}{2} \tag{51}$$

and

$$Q_s = \frac{N^2|V_s|^2}{\Omega_s}.$$

A solution of eq. (50) can be represented in the form

$$\beta_s(z,t) = \Phi_s(\rho)exp\left\{i(q_s z - \omega_s t) - \frac{\gamma_s}{2}t\right\}, \tag{52}$$

where $\rho = z - z_0 - V_s$, V_s is the velocity of excitation motion along the PG chain, and the real amplitude $\Phi_s(\rho)$ is satisfies the following normalization condition

$$\frac{1}{a}\int_{-\infty}^{+\infty} \Phi_s^2(\rho)\, d\rho = N_0\,. \tag{53}$$

Consider solutions of eq. (50) at weak damping, i.e. when $\gamma_s \approx 0$. The reasonable mechanism of the reduced relaxation of protein collective motion may be linked to the interaction of macromolecules with their environment, for example with ordered water clusters possessing slow dynamics [42], [43]. Another mechanism of slow relaxation of the collective modes was suggested to be based on the experimental observation of vibrational wave packets of a long lifetime over 500 picoseconds in bacteriorhodopsin exposed by picosecond far IR sources [43]. Authors discussed a possible mechanism of slow relaxation due to quantum

effects of restricted interaction of the low-frequency collective modes with solvent and suggested a link between undamped collective vibration and the conformational transitions in proteins enriched by alpha-helical structures.

In this condition ($\gamma_s \approx 0$), according to eq. (46) and fluctuation-dissipation theorem, fluctuations are small and can be neglected. Then eq. (50) takes the form:

$$\left[\Xi_s + \hbar a^2 I_s \frac{\partial^2}{\partial z^2} + Q_s |\Phi_s(\rho)|^2\right] \Phi_s(\rho) = 0, \tag{54}$$

where Ξ_s is a spectral parameter connected with phonon energy by the equation:

$$\hbar\omega_s = \Xi_s + E_s + \hbar q^2 a^2 I_s \,. \tag{55}$$

Eq. (54) has solution $\Phi_s(\rho) = const$:

$$\Phi_s(\rho) = 0 \quad \text{at } \lambda_s = \frac{\Xi_s}{Q_s} > 0 \tag{56}$$

and

$$\Phi_s(\rho) = 0 \text{ and } \Phi_s(\rho) = (-\lambda_s)^{1/2} \quad \text{at } \lambda_s < 0, \tag{57}$$

where parameter λ_s defines interaction of the PGs with its environment. At changing λ_s the oscillation modes become unstable and their amplitudes $\Phi_s(\rho)$ play a role of the order parameters. Solutions (56) and (57) obtained under conditions of the smallness of dissipation in the system and absence of fluctuations. Thus, living time τ_s of the dynamic modes of the PG chain corresponding to nontrivial solutions is less than the inverse-time of relaxation

$$\tau_s < \gamma_s^{-1} \,. \tag{58}$$

So, dynamics of this system is defined by weak damped (long-living) phonon modes. More detailed analysis of the dynamic equation of the type (50) is given in [44], where it was shown in part that the right-hand side of this equation can be obtained from the potential

$$U(|\Phi_s|) = \Xi_s |\Phi_s|^2 - \frac{1}{2} Q_s |\Phi_s|^4 \,. \tag{59}$$

This allows writing and solving the corresponding Fokker-Planck equation and then finding a distribution function for the phonons in a coherent excitation state

$$\Psi(\Phi_s) \sim exp\left\{-\frac{2U(|\Phi_s|)}{D_s}\right\}, \tag{60}$$

where parameter D_s defines an intensity of fluctuating force according to eqs. (45) and (46) at $k = 0$ for both phonon branches. From eq. (60) follows that fluctuations enable the system to switch to a new state. The role of fluctuations is much significant at the transition of the system

to an unstable mode at $\lambda_s \leq 0$ when, as known, fluctuations sharply increase [18]. At the sign change of parameter λ_s, solution $\Phi_s(\rho) = 0$ remains one of the solutions of eq. (54). Transition of the system to the new states, corresponding to nontrivial solutions $\Phi_s(\rho) \neq 0$, is possible as a result of an action of external factors including fluctuations.

Eq. (54), being nonlinear Schrodinger equation, besides the solutions considered above has a solution in the form of solitary wave (soliton) travelling along the z-axis and satisfying normalization condition (53). For any positive Q_s, eq. (54) has the normalized partial solution in the form

$$\Phi(\rho) = \left(\frac{a\Theta_0 N_0}{2}\right)^{1/2} \frac{1}{ch[\Theta_0(z - z_0 - V_{sol}t)]}, \tag{61}$$

where z_0 is the soliton centre, V_{sol} is soliton velocity, and

$$\Theta_0 = \frac{Q_s N_0}{4\hbar a I_s}. \tag{62}$$

In the presence of dissipation, when $\gamma_s \neq 0$, a solution of eq. (50) in view of eqs. (51) and (52) is written in the form:

$$\beta(x,t) = \left(\frac{a\Theta_0 N}{2}\right)^{1/2} \frac{e^{i(q_s z - \omega_s t)}}{ch[\Theta_0 e^{-\gamma_s t}(z - z_0 - V_{sol}t)]}, \tag{63}$$

where

$$N = N_0 e^{-\gamma_s t}.$$

The region occupied by soliton, soliton's width, is defined by equation

$$d(t) = \frac{\pi}{\Theta_0} e^{\gamma_s t}. \tag{64}$$

7. Discussion and Conclusions: Vibrational modes and self-organization in alpha-helical protein structures

In the present paper, we further developed the quantum dynamic model of the collective excitations in alpha-helical protein structures [25], [27], [33], [26] and extended this approach to taking into account the dynamics of the side chains responsible for protein interaction within the environment. The model development was based on a series of approximations which are either the typical ones in the theoretical modelling of molecular chains or based on experimental data on protein dynamics. Main parameters of the model were extracted from experimental data on the structure and strength of interpeptide bonds of the alpha-helical protein structure.

The investigation of the dynamics of the alpha-helical protein structures interacting with

the environment in the framework of the developed model showed that the equation for phonon dynamics of the PG chain can be considered as the equation for the order parameter that admits a bifurcation of its solutions. Thus, this molecular system can function in different dynamic modes, which are defined by the order parameter. Protein behaviour transition between different states occurs at a change in the bifurcation parameter λ_s which, according to eq. (37), determines the interaction of the macromolecule with its environment. The PG chain dynamics below and above of the switching threshold are significantly different. At the parameter $\lambda_s > 0$, the system is characterised by the absence of excited modes, and the PGs fluctuate that results in a zero-mean amplitude of the phonon modes.

At the parameter $\lambda_s < 0$, bethe haviour of the system changes so that either one or several vibrational modes become unstable and their amplitudes can grow to macroscopic values. This transition to a state, when the energy is condensated in a set of low-frequency vibrational modes, can lead to the excitation of coherent vibrations of alpha-helical proteins in the terahertz frequency range. Thus, the dynamic behaviour of the macromolecule in our model is defined by a) fluctuations governed by dissipation in the system and b) switching behaviours as a result of an order parameter change, controlled by the strength of protein interaction with the environment.

According to our model, the emergence of space-temporal structures in the form of solitary waves (Davydov regime) are possible in the PG chain, and the following features of solitons were obtained. First, soliton formation is governed by phonon-phonon interaction of the PGs with radical chains in alpha-helical proteins. Second, the Davydov regime realises at the bifurcation parameter value corresponding to the excitation of collective vibrational modes (Fröhlich-like regime). This result on the coexistence of the Frohlich vibration and Davydov soliton excitations in the same region of the control parameters of the PG chain agree with similar conclusion obtained by other research groups under different approaches such as kinetic approach of the Fröhlich rate equations and the Wu-Austin Hamiltonian approach [9], [16], [28], [29]. Some experimental data supporting Davidov soliton formation in proteins was obtained by IR and Raman spectroscopy as results of the observation of an anomalous line close to the amide I excitation in IR spectrum of the hydrogen-bonded chains in polymer macromolecules and alpha-helical protein structures [45], [46].

Following the Fröhlich's hypothesis, cooperative behaviour of the PG chain may lead to the formation of a giant oscillating dipole [35] due to a large dipole moment of the PG. Its formation is suggested to be associated with protein functions such as selective forces, protein-

ligand interaction, molecular recognition, and catalytic enzyme activity. On the other hand, soliton formation (including acoustic solitons [24]) can lead to energy/charge transport along alpha-helical protein structures due to either exciton or electron-phonon interaction [34], [47]. A similar mechanism was explored in the theoretical description of collective vibrational mode excitation in microtubules [48], [49].

The obtained results on the dynamics of alpha-helical protein interacting with environment showed that vibrational mode instability, induced by a change in the parameter of protein-environment interaction, can cause a formation of new macroscopic space-temporal structures in the system. The joint action of random and deterministic forces can lead to the switching of the system to a dynamic state, characterised by cooperative behaviour of its subsystems (subunits), that making up protein macromolecule. One of the factors defining self-organisation process in the protein was shown to be the non-linear interaction of three subsystems in protein, i.e. the regular chains of hydrogen bonds, side chain radicals, and hydrogen bond networks of surrounding water molecules.

Note, that the developed model of the ideal alpha-helix interacting with the environment needs in the further development to build a more realistic model by considering in detail tertiary interactions of alpha-helical structures in native proteins. As the alpha-helical structure is not stable in solution and gets stable within the hydrophobic core of the folded proteins due to electrostatic interactions of the side chains with neighbouring structures. The developed model of vibration excitations in the ideal alpha-helix can be extended to the folded proteins enriched by alpha-helical structures buried in the hydrophobic core of proteins. In this case, the role of the alpha-helix environment responsible for dissipation and fluctuation processes is played by electrostatic interaction of the side chains with surrounding amino acids, which participate in the vibrational motion of the protein as a whole. Moreover, in folded proteins, alpha-helical structures form more complex structures such as the coiled-coil ones, supercoils (a superhelix) as well as alpha-helix barrel structures due to hydrophobic interaction of the non-polar side chains [50]. Thus, the extension of our model to these superhelix structures should include the interaction of water molecules with the polar side chains of the superhelix facing outward, toward surrounding water.

The amphipathic alpha-helical coiled-coil structures are stable in solution due to sequence repetition of hydrophobic and polar residues and play a significant role in molecular recognition and protein-protein interaction. For example, the leucine zipper (coiled coil) structures are responsible for recognition and binding of the transcription factors with the DNA promoter regions of about short ~20 nucleotide sequence [50]. Thus, excitation of the

vibrational modes in superhelices can be applied to explain the mechanism of molecular recognition that was suggested by Fröhlich in his hypothesis about dipole vibrational modes in proteins responsible for molecular recognition and protein-protein interaction [35].

The developed approach can also be extended to the modelling of vibrational excitation in other quasi-linear superhelix protein structures, such as amyloid-like fibres that are formed by the backbones of cross-beta-structures and exhibit most stable protein structures in solution under physiological conditions [51], [52]. Again, hydrogen bonds between neighbouring β-sheets and trapped water molecules play a similar role in vibrational energy dissipation as suggested in our model of the ideal alpha-helix. The quantum dynamic model of soliton dynamics in the alpha-helical structures discussed above can be extended to the modelling of intrapeptide excitation dynamics in β-sheet structures [27]. This development may help to describe the unique properties of self-assembled amyloid-like fibres such as intrinsic fluorescence and emergence of delocalized electron transport along the fibre backbone facilitated by long-range hydrogen bonding of the PGs as well as their cytotoxicity related to Alzheimer's and Parkinson's diseases [52].

Progress in terahertz spectroscopic techniques and their combination with other spectroscopic methods led to a revival of interest in the experimental observation of Fröhlich coherent excitation in biological structures [30], [32]. Recently, searching for experimental evidence of long-range quantum coherent states in the proteins was undertaken in experiments on the interaction of biomolecules with microwave and terahertz radiation [31]. Authors used X-ray crystallographic methods to visualise structural changes in the lysozyme protein crystal induced by 0.4 THz electromagnetic radiation [31]. They observed the excitation of longitudinal compression modes of microsecond lifetime in the protein alpha-helix that is significantly longer than femto- and nanosecond time scale of the intramolecular vibration decay due to protein interaction with the environment (thermalization). Authors attributed this underdamped low-frequency collective vibration modes to the Frohlich condensation mode, excited by terahertz radiation. The existence of these persisting motions indicates that damping and intermode coupling are weaker than previously assumed [7].

Experimental investigation of the coherent vibrational dynamics in proteins was intensified by the observation of long-lived coherent excitonic states in light-harvesting proteins in photosynthetic bacteria [12]. The results of 2D IR coherent spectroscopy suggests that the coherent vibrations in photosynthetic pigment–protein complexes contribute to the effective electron and energy transport due to the electron-vibrational couplings [10], [53]–[55]. It is notable that Fröhlich proposed the role of coherent longitudinal electric modes

(polarization waves) of lowest frequency (0.01 THz – 1 THz) in storage of light energy in photosynthesis in 1968 [14].

In recent intriguing work, the joint theoretical and experimental investigation of out-of-equilibrium collective oscillation of the Fröhlich type was carried out in the bovine serum albumin (BSA), the protein mainly composed of alpha-helical structures [23]. Authors recreated in their experimental setup the conditions close to the Fröhlich model i.e. they transferred energy to the protein and created far from the thermal equilibrium state in the macromolecule by optical pumping through the excitation of fluorochromes (at wavelength of 488 nm) bonded at the lysine residues to each BSA molecule. Using complementary THz spectroscopy, the strong resonance around 0.3 THz in absorption spectrum was observed, when optical pumping to the vibrational modes of the BSA took place through excitation of fluorochromes bound to the proteins. To theoretically analyse the experimental results, authors developed a classical version of the Fröhlich model and showed that phonon condensation is possible in nonequilibrium state of the protein, when energy flows from an external energy source to the protein and dissipates then through protein interaction with the environment. Authors treated a threshold like collective vibrational modes as non-equilibrium phase transition in open dynamic systems [18].

Note, that the resonance absorption spectrum in the terahertz frequency region for alpha-helical protein structures was defined by one of the authors (VNK) in the framework of the quantum mechanical model which describes the direct transfer of electron captured by the moving acoustic soliton (electrsoliton) along the molecular chain [47]. In our model, the resonance in the frequency range of 0.3 THz observed in the experiment [23] can be treated as threshold like excitation of collective modes in the form of either soliton (Davydov mode) or collective vibrational modes (Fröhlich mode) of frequency close to the normal modes calculated in our model (see Fig. 2).

In conclusion, the developed quantum dynamics model of the alpha-helical structure interacting with the environment can be useful in the analysis of the current experimental data on the molecular mechanisms of the long-lived, low-frequency collective vibrations in alpha-helical protein structures. The further expansion of the model to the dynamics of alpha-helix in native protein, protein-membrane systems, superhelix structures such amiloids fibers, and microtubules is needed that might support experimental investigation of the role of quasi-linear dynamical structures in extraordinary effectiveness of protein functions such as energy storage, transport and transformation.

Conflict of interest

The authors report no conflict of interest.

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Figure legends

Fig. 1. (a) The polypeptide chain. (b) The chain of hydrogen-bonded peptide groups. (c) Structure of alpha-helical protein, where one of the three hydrogen-bonded PG chains with side radicals (R) is shown. Hydrogen-bonds are depicted by dots.

Fig. 2. Dispersion curves for the chain of hydrogen-bounded PGs calculated at the following elastic constants [27]. (a) s=1, $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$, $\chi_{0,1} = 5.0\ \mathrm{N}m^{-1}$, $\chi_{0,2} = 0\ \mathrm{N}m^{-1}$. (B) s=2, $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$, $\chi_{0,1} = 5.0\ \mathrm{N}m^{-1}$, $\chi_{0,2} = 0\ \mathrm{N}m^{-1}$. (b) Dependence of the frequency Ω_{01} (C) and Ω_{02} (D) (k=0) on constant χ_{02} at the fixed values of elastic constants $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$ and different constant $\chi_{0,1}$: line 1 - $\chi_{0,1} = 0.0\ \mathrm{N}m^{-1}$, line 2 - $\chi_{0,1} = 3.0\ \mathrm{N}m^{-1}$, and line 3 - $\chi_{0,1} = 25.0\ \mathrm{N}m^{-1}$. Dispersion curves were calculated in MATLAB package (MathWork Inc).