bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Collective Excitations in α-helical Protein Structures Interacting with the Water Environment

Vasiliy N. Kadantsev[1], *Alexey Goltsov*[1,2*]

[1] *Russian Technological University (MIREA), Moscow, Russia*

[2] *Modeling &Simulation Decisions LLD, Moscow, Russia*

[*]Corresponding authors: Alexey Goltsov, *alexey.goltsov@gmail.com*

ORCID ID: 0000-0001-6725-189X

Abstract

Low-frequency vibrational excitations of protein macromolecules in the terahertz frequency region are suggested to contribute to many biological processes such as enzymatic catalysis, intra-protein energy/charge transport, recognition, and allostery. To explain high effectiveness of these processes, two possible mechanisms of the long-lived excitation were proposed by H. Fröhlich and A.S. Davydov which relate to either vibrational modes or solitary waves, respectively. In this paper, we developed a quantum dynamic model of vibrational excitation in α-helical proteins interacting with the aqueous environment. In the model, we distinguished three coupled subsystems, i.e. (i) a chain of hydrogen-bonded peptide groups (PGs), interacting with (ii) the subsystem of the side-chain residuals which in turn interacts with (iii) the environment, surrounding water responsible for dissipation and fluctuation in the system. It was shown that the equation of motion for phonon variables of the PG chain can be transformed to nonlinear Schrodinger equation which admits bifurcation into the solution corresponding to the weak damped vibrational modes (Fröhlich-type regime) and Davydov solitons. A bifurcation parameter is derived through the strength of phonon-phonon interaction between the side-chains and hydration-shell water molecules. As shown, the energy of these excited states is pumped through the interaction of the side-chains with fluctuating water environment of the proteins. The suggested mechanism of the collective vibrational mode excitation is discussed in connection with the recent experiments on the long-lived collective protein excitations in the terahertz frequency region and vibrational energy transport pathways in proteins.

Keywords: α-helical protein; collective excitation; phonons; solitons; Fröhlich condensation; biological effect; terahertz radiation.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

1. Introduction

The concept of proteins as active dynamic systems integrates experimental and theoretical investigation of the interrelation between protein structure, dynamics, functions, and interaction with cellular environment. Currently, intense efforts are undertaken to realise the contribution of internal protein motion to protein functions such as enzymatic activity, charge/energy transport and allosteric regulation of proteins (Niessen *et al.*, 2017a), (Lindorff-Larsen *et al.*, 2005), (Kamerlin and Warshel, 2010). A study of the protein interaction with aqueous environment showed the link between the internal protein motion and the fluctuating of the hydration-shell water molecules and suggested an impact of this interaction on the internal protein dynamics and protein functioning (Agarwal, 2006). Protein vibration excitations spread over a wide frequency range include high-frequency localised vibrations and rotation of atom groups (e.g. C=O and N-H stretching) and the large-scale vibrations of subdomains of the proteins (Xie, Yao and Ying, 2014), (Balu *et al.*, 2008).

Different types of the collective modes are reported to be excited in protein molecules, i.e. normal vibration modes (Acbas *et al.*, 2014; Turton *et al.*, 2014), sound waves (phonons) (Liu *et al.*, 2008), and coherent vibrational states (Del Giudice *et al.*, 1986; Rolczynski *et al.*, 2018) which are observed on a timescale from picosecond to microsecond. Vital cellular processes are suggested to be controlled by the excitation of the long-lived collective degrees of freedom which are characterised by a weak coupling to the other ones and related to the substantially non-equilibrium processes in proteins (Mohseni *et al.*, 2014). Investigation of weakly relaxing excitations discribed by the quaiparticle dynamics such as phonons, exitons, polarons and others have given an insight into a vast amount of experimental facts in solid and soft matter physics (Venema *et al.*, 2016). Similarity of the non-linear mechanisms underlying formation of the collective excitations in different molecular systems suggestes that long-lived non-equilibrium states can be realised in the living systems and the concept of quasiparticles plays a crucial role in effectiveness of energy transformation, transport and storage in cells (Lambert *et al.*, 2013), (Davydov, 1985). The concept of quasiparticles in biophysics was developed by Davydov and Frohlich to explain effective energy and cardge transprt in biosystems. Investigation of the physical mechanisms of the formation and physiological functions of the coherent exitations in cellular molecular structures are one of the formidable challenges in molecular biophysics and the subject of intensive experimental and theoretical works over the

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

past decades (Engel *et al.*, 2007; Acbas *et al.*, 2014; Turton *et al.*, 2014; Goncharuk *et al.*, 2017; Niessen *et al.*, 2017b), (Kuramochi *et al.*, 2019).

The physical mechanism of the collective coherent excitations have been proposed and investigated early by H. Fröhlich (Fröhlich, 1968a). He has developed a phenomenological kinetic 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, protein-protein interaction, and the interaction of biosystems with microwave radiation (Fröhlich, 1970, 1980).

The general idea underlying the suggested mechanism of long-lived coherent vibrations in biosystems is in an assumption that the vibrational modes are capable of condensation 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 (Mesquita, Vasconcellos and Luzzi, 2004). Thus, excitation of the Fröhlich mode, in the form of the coherent dynamic structure, can be considered as the emergence of a space-temporal dissipative structure in accordance with Prigogine's theory (Prigogine and Lefever, 1973) which is governed by the self-organization principals of Haken's synergetics (Haken, 1983). At present, further investigation of the Fröhlich condensation in quantum dynamics and quasi-classical approaches were undertaken in order to determine the physical conditions of phonon condensation in proteins functioning far from thermal equilibrium (Vasconcellos *et al.*, 2012), (Salari *et al.*, 2011), (Preto, 2017), (Reimers *et al.*, 2009), (Nardecchia *et al.*, 2018).

Another type of coherent excitations in the form of solitary waves in α-helical protein structurews has been proposed theoretically by A.S. Davydov in order to describe highly effective long-distance transport of energy/charge within macromolecules (Davydov, 1985). As a result of a series of his works, the theory of soliton transport of energy/charge in the α-helical proteins has been developed (Davydov, 1977, 1985). Additionally, it was concluded that the α-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 the 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 (PGs) at room temperature (Davydov, 1985). Mechanisms of energy transport of are defined in the model as the non-linear interaction of the high-frequency amide-I excitation (1667 cm^{-1}) and low-frequency acoustic modes in the α-helical protein structure.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Various theoretical aspects of soliton dynamics in α-helical proteins, including soliton stability, thermalisation, solitons' interaction and others were investigated in various approximations (Takeno, 1984), (Lawrence *et al.*, 1987), (Lupichev, Savin and Kadantsev, 2015). Dadydov model was further extended to the multisoliton solutions in discrete nonlinear Schrodinger equation of amide-I excitation dynamics in the PG chain (Tchinang Tchameu, Togueu Motcheyo and Tchawoua, 2014), (Issa *et al.*, 2018). An exact quantum dynamical description of intra amide group vibration transfer coupled with the low frequency longitudinal vibrations in an α-helical polypeptide was developed in the multi configuration time-dependent Hartree (MCTDH) (Tsivlin and May, 2007) and the mixed quantum–classical Liouville (MQCL) equation approximations (Freedman and Hanna, 2016). The unified theoretical approaches to the description of both Davydov soliton mode and Fröhlich condensation mode excitations at the conditions far away from thermal equilibrium in proteins were developed (Del Giudice *et al.*, 1986; Bolterauer and Tuszyński, 1989; Bolterauer, Tuszyński and Satarić, 1991; Mesquita, Vasconcellos and Luzzi, 2004).

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 (Reimers *et al.*, 2009; Salari *et al.*, 2011; Preto, 2017), (Nardecchia *et al.*, 2018), (Weightman, 2014), (Austin *et al.*, 2009). Experimental investigation of the coherent vibrational states in proteins was carried out by the IR, Raman, terahertz spectroscopy and their combinations (Nardecchia *et al.*, 2018), (Lundholm *et al.*, 2015) and included analysis of the possible resonance effects of microwave and terahertz irradiation on cellular functions predicted by Fröhlich (Pokorný, 1999), (Foletti *et al.*, 2013), (Markov, 2015), (Fröhlich, 1980). Theoretical investigation in this field of electromagnetic biology also aims at the identification of biological structures enabling to maintain collective vibration states (α-helical protein structure, cytoskeleton microtubules, biomembranes and others) and calculation of the vibration spectrum of collective excitations containing specific frequency domains to inform an experimental search for the resonance effects of terahertz irradiation on cells (Fröhlich, 1988), (Pokorný, 2004), (Kadantsev and Savin, 1997), (Nardecchia *et al.*, 2018). The resonance interaction of cells with terahertz irradiation is considered as the possible biophysical mechanism which can be explored in the development of medical applications for the non-invasive diagnostics and therapy (Foletti *et al.*, 2013), (Markov, 2015), (Siegel, 2004), (Foletti *et al.*, 2013).

Another type of the protein interaction with environmental factors relates to the interaction with solvent surrounding native proteins. The surface interaction of proteins with the fluctuating hydration-shell and bulk water molecules has been shown to contribute

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

significantly to their internal vibrational dynamics and functional properties (Bellissent-Funel *et al.*, 2016) , (Doster, 2010).

In this work, we develop further the molecular models of the collective excitations in α-helical peptide macromolecules (Kadantsev, Lupichov and Savin, 1987; Kadantsev, Lupichcv and Savin, 1994; Lupichev, Savin and Kadantsev, 2015), (Kadantsev and Goltsov, 2018) and extend quantum dynamics approach to take into account protein interaction within the aqueous environment. In the model development, we distinguished three subsystems i.e. (i) a chain of hydrogen-bonded peptide groups (PGs) interacting with (ii) the subsystem of the side-chain residuals which in turn interact with (iii) surrounding water molecules though the phonon-phonon mechanism. We showed that consideration of vibrational coupling between macromolecules and their water environment significantly changes dynamic behaviour of the α-helical protein structures and contributes to the formation of coherent vibrational states in the PG chain. We used the quantum dynamics approach which have been developed earlier in the modeling of autolocalized states (polaron) in the intramolecular excitations of the PG chain (Kadantsev, Lupichov and Savin, 1987; Kadantsev, Lupichcv and Savin, 1994; Lupichev, Savin and Kadantsev, 2015). The developed model is used to investigate conditions when the molecular interaction between the PGs, side chains and water environment leads to the excitations of vibrational and soliton types in α-helical protein structures.

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

The secondary protein structure, α-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 α-helix has a form of a coil, and its inner part consists of a tightly twisted backbone with amino acid residues 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 (Davydov, 1977).

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

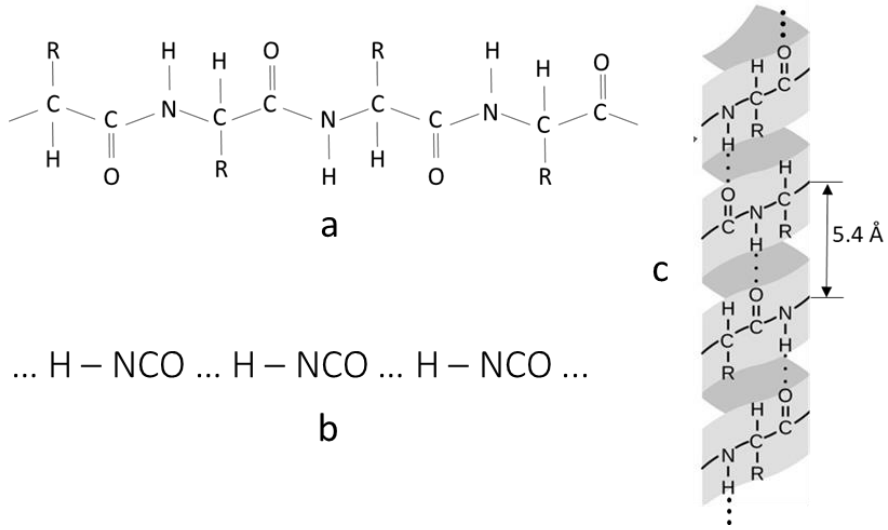

Fig. 1. (a) A polypeptide chain with amino acid residues (R). (b) The chain of hydrogen-bonded peptide groups. (c) Structure of α-helical protein structure, where one of the three hydrogen-bonded PG chains with the side-chains of amino acid residues are shown. Hydrogen-bonds are depicted by dots.

In the model of the α-helical protein structure we considered a one-dimensional chain of hydrogen-bonded peptide groups with hydrogen bonds between (NH)- and CO-groups (Fig. 1b). We also assumed intrinsic motion of proton and the rest of the PGs (NCO) and defined equilibrium positions of the PGs in the *l*-site z=*la* (*l*=0, 1, 2, …) along the α-helix backbone (the z-axis), where *a*=5.4 Å is chain spacing. We denoted 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 the interaction between the nearest PGs and nearest chain-side of residues R is expressed by a quadratic form:

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

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 of residues, respectively. In the model, we chose the following cyclic boundary condition for the PG chain

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

where N is a number of GPs in the chain.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

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

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

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

$$[b_{k,s}, b^{+}_{k',s'}] = \delta_{kk'}\delta_{ss'} \text{ and } [b_{k,s}, b_{k',s'}] = 0. \tag{4}$$

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

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

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

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

where two function $\Omega_s(k)$ defines dispersion relationship for frequencies of acoustic and optic branches of the vibration in the PG chain with s = 1 and 2 respectively.

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

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

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. The dispersion relation (8) can be derived using the methods applied to lattice oscillation of a diatomic linear chain (Animalu, 1977). Dispersion curves calculated at the values of elastic constants of the PG chain (Lupichev, Savin and Kadantsev, 2015) 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 vibrations $\Omega_s(k)$ in the terahertz frequency range.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Similarly, we introduced the phonon Hamiltonian for the side-chains of the residues which can be represented as a system of N oscillators of mass M having own frequencies of oscillation $\Omega_t(q)$

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

Here $c_{q,t}^{+}$ and $c_{q,t}$ are the operators of the creation and annihilation of phonons in the side-chains which correspond to the displacement of the residues from their equilibrium positions $\varsigma_l(t)$. $\Omega_t(q)$ are the phonon frequency of type t in the side-chains and q is the wave number. The representation of the side-chain dynamics as a set of oscillators is based on experimental data on the amino acid residue dynamics obtained by the X-ray diffraction, NMR methods and spin labelling EPR spectroscopy that provides detailed information on the side-chain order parameter and their mobility on the nanosecond timescale (Columbus and Hubbell, 2002), (Go, Noguti and Nishikawa, 1983), (Sivaramakrishnan *et al.*, 2008). 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 in the range of 120-200 cm^{-1} (Go, Noguti and Nishikawa, 1983). The analysis of the complex EPR spectrum of a spin labeled side chain in α-helixes showed that the side-chain dynamics is modulated by the interaction with the backbone as well as environment (Columbus *et al.*, 2001). Below we consider the interaction of the phonons in the backbone and residue side-chains in the α-helical protein, and then we include the interaction of the side-chains with aqueous environment of the proteins.

To consider interaction of the PG chain and residue side-chains in the α-helical proteins, we added the following anharmonic operator of phonon-phonon 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

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

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Experimental data on the α-helix backbone and side-chains interaction was derived from the analysis the EPR spectra of a spin labeled side chain that showed the tight coupling between backbone and side-chain dynamics in α-helical protein structures (Columbus *et al.*, 2001)(Columbus and Hubbell, 2002).

Substitution of eqs. (3) and (11) into eq. (10) 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:

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

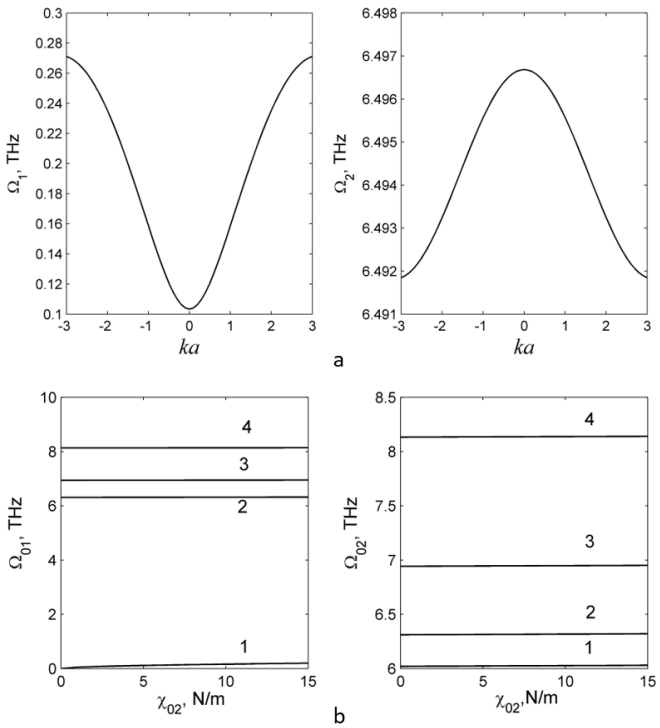

Fig. 2. (a) Dispersion curves of acoustic (s=1, left plot) and optic (s=2, right plot) branches for the chain of hydrogen-bounded PGs calculated at the following elastic constants (Lupichev, Savin and Kadantsev, 2015): $\chi_{1,2} = 13.0\ \mathrm{N}m^{-1}$, $\chi_{2,1} = 17.0\ \mathrm{N}m^{-1}$, $\chi_{0,1} =$

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

5.0 Nm^{-1}, $\chi_{0,2} = 0$ Nm^{-1}. (b) Dependence of the frequency Ω_{01} (left plot) and Ω_{02} (right plot) (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 - $\chi_{0,1} = 0$ Nm^{-1}, line 2 - $\chi_{0,1} = 3.0$ Nm^{-1}, and line 3 - $\chi_{0,1} = 25.0$ Nm^{-1}.

3. Interaction of α-helical protein structure with water environment

In the model, we considered the interaction of the α-helical protein with its environment, surrounding water molecules which form a heat reservoir with a non-zero temperature *T*. The protein-water interaction defines dissipation processes in the system and contributes to the structure and functions of proteins (Bellissent-Funel *et al.*, 2016), (Kurian *et al.*, 2018a), (Agarwal, 2006). In the model, we represented dynamics of the surrounding water molecules by a large set of harmonic oscillators and suggested that this system possesses collective excitation modes with dynamics like that of an oscillators' ensemble. This approximation can be justified by experimental observation of the collective vibrational subpicosecond dynamics (phonons) of the hydrogen bond network of water molecules in hydration shells of proteins in terahertz and IR spectra (Conti Nibali and Havenith, 2014).

Note that we considered the α-helical protein interaction with water molecules only through the amino acid residues and omitted hydration of the backbone carbonyl (–C=O) and amide (–N–H) groups in the model. This approximation is reasonable in case of large charged side chains of amino acid residues which shield backbone hydrogen bonds from water molecules and stabilise α-helix protein structure in aqueous environment (Ghosh, Garde and García, 2003). Furthermore, salt-bridge formation between amino acid residues additionally stabilises α-helix and prevents it from folding. A chain of the salt-bridge can also facilitate the excitation of vibration modes along these chains as discussed in the previous section. Additionally, in the model, we neglected different dynamic properties of the hydration shells and bulk water molecules of proteins.

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 $\omega_t(p)$

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

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

To calculate energy, W_B, of the 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 residue side-chains. So, we suggested that the PG chain interacts with the environment through amino acid residues R (Fig. 1). Then, interaction operator W_B can be written as

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

Parameter $\sigma_{tt\prime}(g,p)$ defines strength of the interaction between heat reservoir's oscillators of types t' and the residue side-chain oscillators of type *t*. Note that the operator (15) describes a wide class of relaxation mechanisms related to collective excitations (Lupichev, Savin and Kadantsev, 2015). 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 particularly in the Wu-Austin Hamiltonian approximation (Columbus and Hubbell, 2002), (Vasconcellos *et al.*, 2012), (Wu and Austin, 1981).

For simplicity, we dropped indexes which define phonon type, and below indexes *s*, *t*, and *t'* of variables mean that the specific variable belongs either to the PG chain or the side-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 system instability with respect to either one or several variables (dynamic modes) when attaining a critical condition (Haken, 1983). If the rest of the modes damp the different exclusion procedures of the stable variables can be applied. As a result, the system behaviour as a whole is defined by the dynamics of a few unstable variables which governs all the damped modes. In real systems, a hierarchy of relaxation times takes place that allows applying adiabatic approximation for the exclusion of fast-relaxing variables. In the case of protein molecules, the fast-relaxing variables c_g^{+} and c_g relate to the side-chains which directly interact with the environment (structured water). This approximation is based on the NMR experimental data on the relaxation of order parameter in backbone and side-chains dynamics (Columbus and Hubbell, 2002), (Wu and Austin, 1981). The experimental results revealed that the side-chains exhibit faster nanosecond dynamics than microsecond motion of the backbone.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Moreover, solvent exposed side-chains showed more mobile and faster dynamics than those fully buried in the protein hydrophobic core.

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

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

where

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

Equations of motion for dynamic variables of the PG chain and heat 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) in the forms

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

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 used 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 described 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 protein macromolecule

As known, all basic (microscopic) equations of motion are invariant with respect to time reversal, that is the motion is entirely reversal, and dissipative forces, violating this invariance, cannot be expressed in the original equations. But under certain assumptions, the Langevin equations can be derived from the Heisenberg equation for a system interacting with a heat reservoir which is represented by a set of harmonic oscillators (Shibata and Hashitsume, 1978).

Heretofore, we considered the model of α-helical protein interacting with the heat reservoir and turned to classical representation of this system. Such conversion can be justified by a large number of phonons in strongly exciting modes in the protein as well as a large number of oscillators in the heat reservoir. This allowed us to represent phonon amplitudes by

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

c-numbers and substitute operators b_k, b_k^+, B_k , and B_k^+ in eqs. (28) and (29) for c-numbers β_k, β_k^*, B_k, and B_k^* respectively. Amplitude $\beta_k(t)$ can be considered as the generalised coordinates with corresponding generalised 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, eq. (29) can be integrated as the classical one that gives the solution for variable $B_p(t)$ (see details in Appendix (eqs. (A1-A7)). Substitution $B_p(t)$ (eq. A5) into eq. (28) for b_k (β_k) gives us the Langevin equation for phonon amplitudes $\beta_k(t)$ in the form

$$\frac{d\beta_k(t)}{dt} = -\frac{i}{\hbar}(\varepsilon_k + e_k)\beta_k(t) + \frac{iN^2|V_k|^2}{\hbar^2\Omega_t}\sum_{g,k\prime}\beta_{k-g}(t)\beta_{k\prime-g}(t)\beta_{k'}^*(t) - \\ -\frac{1}{2}\gamma_k\beta_k(t) + iF_p(t)\,, \tag{30}$$

where

$$e_k = \frac{1}{\hbar}\sum_{p,k\prime} G(k,p)G^*(k',p)\beta_{k\prime-p}\beta_{k'}^* P\left(\frac{1}{\Lambda}\right), \tag{31}$$

$$\gamma_k = \frac{2\pi}{\hbar^2}\sum_{p,k\prime} G(k,p)G^*(k',p)\beta_{k'-p}\beta_{k'}^*\delta(\Lambda), \tag{32}$$

and

$$F_k(t) = \widetilde{F_k}(t)e^{-i\Omega_k t} = \frac{1}{\hbar}\sum_p G(k)\beta_{k-p}(t)B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t}. \tag{33}$$

Function $F_k(t)$ (33) can be considered as a random force with the correlator (see details in Appendix, eqs. (A8-A14)):

$$< F_k^*(t)F_k(\tau) >= \frac{2\pi}{\hbar^2}|G(k)|^2 n_p N_p \delta(t-\tau) = D_k\delta(t-\tau), \tag{34}$$

where value D_k can be obtained in the form (see Appendix)

$$D_k = \hbar^2\gamma_k N_p. \tag{35}$$

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

To investigate vibrational modes in the α-helical protein at the various parameters of its interaction with the environment, we applied a long-wave approximation to derive the equation for undamped modes and investigated system dynamics in the vicinity of an unstable point. For small values $ka \ll 1$, phonon frequencies according to eq. (8) can be written in the form

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

$$\Omega_s(k) = \Omega_{0s} + I_s k^2 a^2, \tag{36}$$

where

$$I_s = (-1)^{s+1} \frac{\chi_{1,2}\chi_{2,1}}{4m_1 m_2 \Omega_{0s}\sqrt{A^2 - B(0)}}. \tag{37}$$

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

$$\sqrt{A^2 - B(0)} = \frac{1}{2}(\Omega_{02}^2 - \Omega_{01}^2) \tag{38}$$

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 turned to continuum limit in eq. (36) after Fourier transformation by multiplication of all terms in eq. (36) by $N^{-1/2}e^{ikz}$ and summing up over k according to eq. (36). In continuum limit, eq. (36) for photon modes with the dispersion relation (47) takes the form

$$i\hbar \frac{\partial \beta_s(x,t)}{\partial t} + \hbar a^2 I_s \frac{\partial^2 \beta_s(x,t)}{\partial z^2} - E_s \beta_s(x,t) + Q_s |\beta_s(x,t)|^2 \beta_s(x,t) = F_s(x,t), \tag{39}$$

where

$$E_s = \varepsilon_{0s} - e_{0s} - \frac{i\hbar\gamma_s}{2} = E_{0s} - \frac{i\hbar\gamma_s}{2} \tag{40}$$

and Q_s is an energetic parameter of the phonon-phonon interaction between water molecules surrounding the protein and the side-chains of amino acid residues:

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

A solution of eq. (39.50) can be represented in the form

$$\beta_s(z,t) = \Phi_s(\rho) exp\left\{i(q_s z - \omega_s t) - \frac{\gamma_s}{2} t\right\}, \tag{41}$$

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

$$\frac{1}{a}\int_{-\infty}^{+\infty} \Phi_s^2(\rho)\, d\rho = N_0 . \tag{42}$$

Then we considered solutions of eq. (39) 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, ordered water clusters possessing

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

slow dynamics (Xie, van der Meer and Austin, 2002; Squire *et al.*, 2013). 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 (Xie, van der Meer and Austin, 2002). 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 α-helical structures.

In this condition ($\gamma_s \approx 0$), according to eq. (35) and fluctuation-dissipation theorem, fluctuations are small and can be neglected. Then eq. (50) takes the form:

$$\left[\Xi_s + \hbar a^2 I_s \frac{\partial^2}{\partial z^2} + Q_s |\Phi_s(\rho)|^2\right] \Phi_s(\rho) = 0, \tag{43}$$

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

$$\hbar\omega_s = \Xi_s + E_s + \hbar q^2 a^2 I_s \,. \tag{44}$$

Eq. (43) has solution $\Phi_s(\rho) = const$:

$$\Phi_s(\rho) = 0 \quad \text{at } \lambda_s = \frac{\Xi_s}{Q_s} > 0 \tag{45}$$

and

$$\Phi_s(\rho) = 0 \text{ and } \Phi_s(\rho) = (-\lambda_s)^{1/2} \quad \text{at } \lambda_s < 0, \tag{46}$$

where parameter λ_s defines interaction of the PG chain 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 of the system. Note that solutions (45) and (46) were obtained under conditions of the smallness of dissipation and fluctuations in the system. Thus, living time τ_s of the dynamic modes in the PG chain corresponding to nontrivial solutions (46) is less than the inverse-time of relaxation

$$\tau_s < \gamma_s^{-1} \,. \tag{47}$$

Thus, dynamics of this system is defined by weak damped (long-living) phonon modes. More detailed analysis of the dynamic equation of the type (39) is given in (Glauber, 2006), where it was shown in particular that the right-hand side of this equation can be obtained from the potential

$$U(|\Phi_s|) = \Xi_s |\Phi_s|^2 - \frac{1}{2} Q_s |\Phi_s|^4 \,. \tag{48}$$

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

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

$$\Psi(\Phi_s) \sim exp\left\{-\frac{2U(|\Phi_s|)}{D_s}\right\}, \tag{49}$$

where parameter D_s defines intensity of fluctuating force according to eqs. (34) and (35) at $k = 0$ for both phonon branches. From eq. (49) 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 (Haken, 1983). At the sign change of parameter λ_s, solution $\Phi_s(\rho) = 0$ remains one of the solutions of eq. (43). 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 in the environment.

Nonlinear Schrodinger equation (43) besides the solutions considered above has a solution in the form of solitary wave (soliton) travelling along the z-axis and satisfying normalisation condition (42). For any positive values of Q_s, eq. (43) has the normalised partial solution in the form

$$\Phi(\rho) = \left(\frac{a\Theta_0 N_0}{2}\right)^{1/2} \frac{1}{ch[\Theta_0(z - z_0 - V_{sol}t)]}, \tag{50}$$

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

$$\Theta_0 = \frac{Q_s N_0}{4\hbar a I_s}. \tag{51}$$

In the presence of dissipation, when $\gamma_s \neq 0$, a solution of eq. (50) in view of eqs. (40) and (41) is written in the form:

$$\beta(x,t) = \left(\frac{a\Theta_0 N}{2}\right)^{1/2} \frac{e^{i(q_s z - \omega_s t)}}{ch[\Theta_0 e^{-\gamma_s t}(z - z_0 - V_{sol}t)]}, \tag{52}$$

where

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

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

$$d(t) = \frac{\pi}{\Theta_0} e^{\gamma_s t}. \tag{53}$$

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

7. Discussion: Vibrational modes and self-organization in α-helical protein structures interacting with the environment

In the present paper, we further developed the quantum dynamic model of the collective excitations in α-helical protein structures (Davydov, 1977), (Kadantsev, Lupichov and Savin, 1987; Lupichev, Savin and Kadantsev, 2015), (Takeno, 1984). We extended this approach to taking into account the dynamics of the side-chains which is suggested to be responsible for the protein interaction within the environment and modulation of the internal dynamics of the PG chain. In the model, a side-chain-dependent coupling of the vibration excitations in the PG chain and surrounding hydrogen bond network of water molecules was considered. The model development was based on a series of approximations which are either the typical ones in the theoretical modeling of molecular chains or based on the experimental data on protein dynamics. The parameters of the model were extracted from experimental data on the structure and strength properties of peptide bonds of the α-helix.

It was showed that the equation for phonon dynamics of the PG chain interacting with the water environment can be considered as the equation for the order parameter which admits a bifurcation of its solutions. Thus, this molecular system can function in different dynamic modes, which are defined by the order parameter. Transition of a protein behavior between different states occurs at a change in the bifurcation parameter λ_s which, according to eq. (45), determines the interaction of the macromolecule with its environment. The PG chain dynamics below and above a switching threshold are significantly different. At $\lambda_s > 0$, the system is characterized by the absence of excited modes, when the PGs fluctuate with a zero-mean amplitude of the phonon modes.

At the bifurcation parameter $\lambda_s < 0$, the behaviour of the system changes so that either one or several vibrational modes become unstable and their amplitudes can grow to macroscopic values. Thus, the dynamics of the macromolecule is defined by i) the interaction of the side-chains with the fluctuation of the environment and ii) switching behaviour defined by the bifurcation parameter controlled by the protein interaction with the environment.

As shown in the model, the collective vibration modes are excited through the energy pumping to the system from fluctuating water environment (see eq. (39)). It is suggested that the vibrational energy can be channelled to the protein through the vibrational interaction of the side chains with the water molecules surrounding the protein. According to the model, the motion of the side chain residues is correlated with the motion of the hydration-shell and bulk

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

water molecules that defined the internal dynamics of the α-helical proteins. In general, the molecular mechanisms of energy transfer from the solvent exposed side-chains on the protein surface to their internal protein motion are the subject of intense experimental and theoretical investigation (Agarwal, 2006), (Wang *et al.*, 2018). As the results of this study, it has been established the vibrational energy transport pathways within enzymes which are capable of transferring required energy to the catalytic-site from dynamical fluctuations of the solvent. The mechanisms of energy pumping and transferring can be determined by the interaction of ordered water clusters bound to the hydration shell of proteins and polar amino acid residues (Goncharuk *et al.*, 2017). Additionally, the hydrogen bond networks of water molecules which possess the collective vibrational sub-picosecons dynamics and propagating phonon-like modes in terahertz and IR spectra can also contribute to this mechanism (Conti Nibali and Havenith, 2014; Niessen *et al.*, 2017b).

According to our model, the emergence of space-temporal structures in the form of solitary waves (Davydov regime) are possible in the PG chain. Analysis of the soliton mode showed that (i) soliton formation is governed by phonon-phonon interaction of the PGs with radical chains in α-helical proteins and (ii) the Davydov regime realises at the bifurcation parameter value corresponding to the excitation of collective vibrational modes (Fröhlich-like regime). This result showing the coexistence of the Frohlich-like vibration and Davydov soliton excitation in the same region of the bifurcation parameters agrees with similar results obtained in different approaches such as Fröhlich kinetic rate equations, Wu-Austin Hamiltonian and other methods (Del Giudice *et al.*, 1986; Bolterauer and Tuszyński, 1989; Bolterauer, Tuszyński and Satarić, 1991; Mesquita, Vasconcellos and Luzzi, 2004).

The obtained results showed that instability of vibrational modes, which are induced by a change in the parameter of protein-environment interaction, can cause a formation of the new macroscopic space-temporal structures in the protein system. The joint action of random and deterministic forces leads to the switching of the system to a dynamic state, characterised by cooperative behaviour of its subsystems. i.e. the backbone, side-chains of amino acid residues, and hydrogen bond networks of surrounding water molecules.

Note, that the developed model of the α-helix interacting with its environment needs further development to build a more realistic model by considering tertiary interactions of α-helical structures in native proteins. As the α-helical structure is not stable in aqueous solution in the absence of tertiary interactions, our model in the current version can be directly applied to unfolded α-helical structures which are stable in solution. Such stable structures are the α-helical proteins and the α-helical Fs-peptide enriched with polar amino acid residues (e.g. an

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

alanine-rich peptides) which are stable in water environment due to shielding of backbone hydrogen bonds from water molecules (Ghosh, Garde and García, 2003). These α-helical structures interact with water molecules through only amino acid residues that was considered in our model (section 3). Moreover, α-helical structures form more complex ones stable in the solution such as the coiled-coil ones, supercoils (a superhelix) as well as α-helix barrel structures due to hydrophobic interaction of the non-polar side-chains (Lupas and Bassler, 2017). The amphipathic α-helical coiled-coil structures 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 (Lupas and Bassler, 2017). Excitation of the vibrational modes in the superhelices can be applied to explain the molecular recognition mechanism, long-range protein-protein (Fröhlich, 1968a) and protein-DNA interaction (Kurian *et al.*, 2018b), (Christopher J. Oldfield *et al.*, 2005).

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 (Pokorný, 2004; Weightman, 2014). Recently, a search for experimental evidence of long-range quantum coherent states in the proteins was undertaken in experimental investigation of the lysozyme protein interaction with terahertz irradiation of 0.4 THz (Lundholm *et al.*, 2015). Authors observed the excitation of longitudinal compression modes of microsecond lifetime in the α-helix and attributed this underdamped low-frequency collective vibration to the Fröhlich condensation mode, excited by terahertz radiation.

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 (Engel *et al.*, 2007). 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 (Kolli *et al.*, 2012; Chenu *et al.*, 2013; Duan *et al.*, 2017; Rolczynski *et al.*, 2018). It is notable that Fröhlich in 1968 proposed the role of coherent longitudinal electric modes (polarization waves) of low frequency (0.01 THz – 1 THz) in the storage of light energy in photosynthesis (Fröhlich, 1968b).

In the 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 α-helical structures (Nardecchia *et al.*, 2018).

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

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. Authors also developed a classical version of the Fröhlich model and showed that phonon condensation is possible in nonequilibrium state of the protein.

Note, that the resonance absorption spectrum in the terahertz frequency region for α-helical protein structures was defined by one of the authors (VNK) in the framework of the quantum dynamics model which described the transport of electron captured by the moving acoustic soliton (electrsoliton) along the PG chain (Kadantsev and Savin, 1997).

In this work, we further developed the quantum dynamics model of the α-helical protein structure and extended it to taking into account protein interaction with the water environment. This model can be applied to the analysis of the current experimental data on the collective vibration excitations in α-helical protein structures under the different mechanisms of energy supplying and the vibrational energy transport along the quasi-linear dynamical pathways in proteins.

Conflict of interest

The authors report no conflict of interest.

Appendix: Exclusion of the variables related to the side-chain dynamics.

Eq. (29) can be integrated as the classical one that gives the solution in the form:

$$B_p(t) = B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t} + i\int_{-\infty}^{t}\sum_k \frac{G^*(k,p)}{\hbar}\beta_{k-p}(\tau)\beta_k^*(\tau)e^{-i\frac{\varepsilon_p}{\hbar}(t-\tau)}d\tau\,, \tag{A1}$$

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

Then we introduced new variable $\widetilde{\beta_k}(t)$

$$\beta_k(t) = \widetilde{\beta_k}(t)e^{-i\Omega_k t} \tag{A2}$$

and used below the previous notation $\beta_k(t)$ for $\widetilde{\beta_k}(t)$. Then we applied 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. (A1) and obtain it in the form

$$B_p(t) = B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t} + \tag{A3}$$

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

$$+i\sum_{k}\frac{G^{*}(k,p)}{\hbar}\beta_{k-p}(t)\beta_{k}^{*}(t)\int_{-\infty}^{t}exp\left\{-i\left[\frac{\varepsilon_p}{\hbar}-\Omega_{k-p}+\Omega_k\right](t-\tau)\right\}d\tau\,.$$

Integral in eq. (A3) gives

$$\int_{-\infty}^{t}exp\left\{-i\left[\frac{\varepsilon_p}{\hbar}-\Omega_{k-p}+\Omega_k\right](t-\tau)\right\}d\tau=-\frac{i}{\frac{\varepsilon_p}{\hbar}-\Omega_{k-p}+\Omega_k}=-\frac{i}{\Lambda}= \tag{A4}$$

$$=-i\left[P\left(\frac{1}{\Lambda}\right)+i\pi\delta(\Lambda)\right],$$

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

$$B_p(t)=B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t}+i\sum_{k}\frac{G^{*}(k,p)}{\hbar\Lambda(k,p)}\beta_{k-p}(t)\beta_{k}^{*}(t). \tag{A5}$$

Substitution of eq. (A5) into eq. (28) gives us equation for $\beta_k(t)$

$$\frac{d\beta_k(t)}{dt}=-i\frac{\varepsilon_k}{\hbar}\beta_k(t)+iN^2\sum_{g,k\prime}\frac{V_{k,g}V_{k\prime,g}^{*}}{\hbar^2\Omega_t}\beta_{k-g}(t)\beta_{k\prime-g}(t)\beta_{k'}^{*}(t)-$$

$$-i\sum_{g,k\prime}\frac{G(k,p)G^{*}(k',p)}{\hbar^2\Lambda}\beta_{k-p}(t)\beta_{k\prime-p}(t)\beta_{k\prime}^{*}(t)+ \tag{A6}$$

$$+i\sum_{p}\frac{G(k,p)}{\hbar}\beta_{k-p}(t)B_p(0)e^{-i\frac{\varepsilon_p}{\hbar}t}\,.$$

Eq. (A6) is the Langevin equation for phonon amplitudes $\beta_k(t)$ written in the form of eq. (30)

$$\frac{d\beta_k(t)}{dt}=-\frac{i}{\hbar}(\varepsilon_k+e_k)\beta_k(t)+\frac{iN^2|V_k|^2}{\hbar^2\Omega_t}\sum_{g,k\prime}\beta_{k-g}(t)\beta_{k\prime-g}(t)\beta_{k'}^{*}(t)- \tag{A7}$$

$$-\frac{1}{2}\gamma_k\beta_k(t)+iF_p(t)\,,$$

where e_k, γ_k and $F_k(t)$ are defined by eqs. (31-33).

The correlator of random force $F_k(t)$ (eq. 33)

$$<F_k^{*}(t)F_k(\tau)>=$$

$$=\frac{1}{\hbar^2}\sum_{p,p\prime}|G(k)|^2<\beta_{k-p}^{*}(0)\beta_{k-p\prime}(0)><B_p^{*}(0)B_p(0)>e^{-i(\Lambda(k,p)t-\Lambda(k,p\prime)\tau)} \tag{A8}$$

can be calculated if we assume that amplitudes $\beta(0)$ and $B(0)$ are not correlated at the initial time, i.e.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

$$< \beta^*_{k-p}(0)\beta_{k-p'}(0) >= n_p \delta_{pp'} \tag{A9}$$

and

$$< B^*_p(0)B_{p'}(0) >= N_p \delta_{pp'} \,, \tag{A10}$$

where

$$n_p = \left(e^{\theta\hbar\Omega_p} - 1\right)^{-1} \tag{A11}$$

and

$$N_p = \left(e^{\theta\hbar\omega_p} - 1\right)^{-1}. \tag{A12}$$

Here $\theta = 1/k_B T$.

Substitute eqs. (A9)-(A12) into eq. (A8) and take into consideration that the main contribution in a sum in eq. (A8) is given by terms $\Lambda(k,p) = 0$ at not too small values of a difference $(t - \tau)$. Then we finally obtained the correlator in the form of eq. (34)

$$< F^*_k(t)F_k(\tau) >= \frac{2\pi}{\hbar^2}|G(k)|^2 n_p N_p \delta(t-\tau) = D_k \delta(t-\tau). \tag{A13}$$

It can be shown that after averaging in eq. (32) for parameter γ_k with consideration of eq. (A12) and substitution of this result into eq. (A13), the value D_k can be written in the form of eq. (35)

$$D_k = \hbar^2 \gamma_k N_p. \tag{A14}$$

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

References

Acbas, G. *et al.* (2014) 'Optical measurements of long-range protein vibrations', *Nature Communications*. Nature Publishing Group, 5(1), p. 3076. doi: 10.1038/ncomms4076.

Agarwal, P. K. (2006) 'Enzymes: An integrated view of structure, dynamics and function', *Microbial Cell Factories*. doi: 10.1186/1475-2859-5-2.

Animalu, A. O. E. (1977) *Intermediate quantum theory of crystalline solids*. Prentice-Hall.

Austin, R. H. *et al.* (2009) 'Tilting after dutch windmills: Probably no long-lived davydov solitons in proteins', *Journal of Biological Physics*. doi: 10.1007/s10867-009-9130-7.

Balu, R. *et al.* (2008) 'Terahertz Spectroscopy of Bacteriorhodopsin and Rhodopsin: Similarities and Differences', *Biophysical Journal*, 94(8), pp. 3217–3226. doi: 10.1529/biophysj.107.105163.

Bellissent-Funel, M.-C. *et al.* (2016) 'Water Determines the Structure and Dynamics of Proteins', *Chemical Reviews*. American Chemical Society, 116(13), pp. 7673–7697. doi: 10.1021/acs.chemrev.5b00664.

Bolterauer, H. and Tuszyński, J. A. (1989) 'Fröhlich's condensation in a biological membrane viewed as a Davydov soliton', *Journal of Biological Physics*. Kluwer Academic Publishers, 17(1), pp. 41–50. doi: 10.1007/BF00393325.

Bolterauer, H., Tuszyński, J. A. and Satarić, M. V. (1991) 'Fröhlich and Davydov regimes in the dynamics of dipolar oscillations of biological membranes', *Physical Review A*. American Physical Society, 44(2), pp. 1366–1381. doi: 10.1103/PhysRevA.44.1366.

Chenu, A. *et al.* (2013) 'Enhancement of Vibronic and Ground-State Vibrational Coherences in 2D Spectra of Photosynthetic Complexes', *Scientific Reports*. Nature Publishing Group, 3(1), p. 2029. doi: 10.1038/srep02029.

Christopher J. Oldfield, *et al.* (2005) 'Coupled Folding and Binding with α-Helix-Forming Molecular Recognition Elements'. American Chemical Society . doi: 10.1021/BI050736E.

Columbus, L. *et al.* (2001) 'Molecular motion of spin labeled side chains in α-helices:

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Analysis by variation of side chain structure', *Biochemistry*. doi: 10.1021/bi002645h.

Columbus, L. and Hubbell, W. L. (2002) 'A new spin on protein dynamics.', *Trends in biochemical sciences*, 27(6), pp. 288–95. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12069788 (Accessed: 14 April 2019).

Conti Nibali, V. and Havenith, M. (2014) 'New Insights into the Role of Water in Biological Function: Studying Solvated Biomolecules Using Terahertz Absorption Spectroscopy in Conjunction with Molecular Dynamics Simulations', *Journal of the American Chemical Society*. American Chemical Society, 136(37), pp. 12800–12807. doi: 10.1021/ja504441h.

Davydov, A. S. (1977) 'Solitons and energy transfer along protein molecules', *Journal of Theoretical Biology*. Academic Press, 66(2), pp. 379–387. doi: 10.1016/0022-5193(77)90178-3.

Davydov, A. S. (1985) *Solitons in Molecular Systems*. Dordrecht: Springer Netherlands (Mathematics and Its Applications). doi: 10.1007/978-94-017-3025-9.

Doster, W. (2010) 'The protein-solvent glass transition', *Biochimica et Biophysica Acta - Proteins and Proteomics*. doi: 10.1016/j.bbapap.2009.06.019.

Duan, H.-G. *et al.* (2017) 'Nature does not rely on long-lived electronic quantum coherence for photosynthetic energy transfer.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 114(32), pp. 8493–8498. doi: 10.1073/pnas.1702261114.

Engel, G. S. *et al.* (2007) 'Evidence for wavelike energy transfer through quantum coherence in photosynthetic systems', *Nature*. Nature Publishing Group, 446(7137), pp. 782–786. doi: 10.1038/nature05678.

Foletti, A. *et al.* (2013) 'Bioelectromagnetic medicine: The role of resonance signaling', *Electromagnetic Biology and Medicine*, 32(4), pp. 484–499. doi: 10.3109/15368378.2012.743908.

Freedman, H. and Hanna, G. (2016) 'Mixed quantum–classical Liouville simulation of vibrational energy transfer in a model α-helix at 300 K', *Chemical Physics*. doi: 10.1016/j.chemphys.2016.08.015.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Fröhlich, H. (1968a) 'Long-range coherence and energy storage in biological systems', *International Journal of Quantum Chemistry*. John Wiley & Sons, Inc., 2(5), pp. 641–649. doi: 10.1002/qua.560020505.

Fröhlich, H. (1968b) 'Storage of Light Energy and Photosynthesis', *Nature*. Nature Publishing Group, 219(5155), pp. 743–744. doi: 10.1038/219743a0.

Fröhlich, H. (1970) 'Long range coherence and the action of enzymes.', *Nature*, 228(5276), p. 1093. Available at: http://www.ncbi.nlm.nih.gov/pubmed/5483165 (Accessed: 7 June 2019).

Fröhlich, H. (1980) 'The Biological Effects of Microwaves and Related Questions', *Advances in Electronics and Electron Physics*. Academic Press, 53, pp. 85–152. doi: 10.1016/S0065-2539(08)60259-0.

Fröhlich, H. (Herbert) (1988) *Biological Coherence and Response to External Stimuli*. Springer Berlin Heidelberg.

Ghosh, T., Garde, S. and García, A. E. (2003) 'Role of backbone hydration and salt-bridge formation in stability of alpha-helix in solution.', *Biophysical journal*. The Biophysical Society, 85(5), pp. 3187–93. doi: 10.1016/S0006-3495(03)74736-5.

Del Giudice, E. *et al.* (1986) 'Collective Properties of Biological Systems', in *Modern Bioelectrochemistry*. Boston, MA: Springer US, pp. 263–287. doi: 10.1007/978-1-4613-2105-7_9.

Glauber, R. J. (2006) *Quantum Theory of Optical Coherence*. Weinheim, Germany: Wiley-VCH Verlag GmbH & Co. KGaA. doi: 10.1002/9783527610075.

Go, N., Noguti, T. and Nishikawa, T. (1983) 'Dynamics of a small globular protein in terms of low-frequency vibrational modes.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 80(12), pp. 3696–700. doi: 10.1073/PNAS.80.12.3696.

Goncharuk, V. V. *et al.* (2017) 'On the possibility of chiral structure-density submillimeter inhomogeneities existing in water', *Journal of Water Chemistry and Technology*. Pleiades Publishing, 39(6), pp. 319–324. doi: 10.3103/S1063455X17060029.

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Haken, H. (1983) *Synergetics : an introduction : nonequilibrium phase transitions and self-organization in physics, chemistry, and biology*. Springer. Available at: https://books.google.co.uk/books?id=KHn1CAAAQBAJ&source=gbs_similarbooks (Accessed: 14 January 2018).

Issa, S. *et al.* (2018) 'Fluctuations of polarization induce multisolitons in $$\alpha $$ α -helix protein', *Nonlinear Dynamics*. Springer, 91(1), pp. 679–686. doi: 10.1007/s11071-017-3902-6.

Kadantsev, V. N. and Goltsov, A. N. (2018) 'Collective excitations in α-helical protein structures', *Russian Technological Journal*, 6(2), pp. 32–45. doi: 10.32362/2500-316X-2018-6-2-32-45.

Kadantsev, V. N., Lupichcv, L. N. and Savin, A. V. (1994) 'Electrosoliton dynamics in a thermalized chain', *physica status solidi (b)*. Wiley-Blackwell, 183(1), pp. 193–199. doi: 10.1002/pssb.2221830115.

Kadantsev, V. N., Lupichov, L. N. and Savin, A. V. (1987) 'Intramolecular Excitation Dynamics in a Thermalized Chain. I. Formation of Autolocalized States in a Cyclic Chain', *physica status solidi (b)*. Wiley-Blackwell, 143(2), pp. 569–579. doi: 10.1002/pssb.2221430217.

Kadantsev, V. and Savin, A. (1997) 'Resonance Effects of Microwaves are Caused by their Interaction with Solitons in A-Helical Proteins', *Electro- and Magnetobiology*. Taylor & Francis, 16(2), pp. 95–106. doi: 10.3109/15368379709009835.

Kamerlin, S. C. L. and Warshel, A. (2010) 'At the dawn of the 21st century: Is dynamics the missing link for understanding enzyme catalysis?', *Proteins: Structure, Function, and Bioinformatics*, 78(6), p. NA-NA. doi: 10.1002/prot.22654.

Kolli, A. *et al.* (2012) 'The fundamental role of quantized vibrations in coherent light harvesting by cryptophyte algae', *The Journal of Chemical Physics*. American Institute of Physics, 137(17), p. 174109. doi: 10.1063/1.4764100.

Kuramochi, H. *et al.* (2019) 'Fifth-order time-domain Raman spectroscopy of photoactive yellow protein for visualizing vibrational coupling in its excited state', *Science Advances*. American Association for the Advancement of Science, 5(6), p. eaau4490. doi:

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

10.1126/sciadv.aau4490.

Kurian, P. *et al.* (2018a) 'Water-mediated correlations in DNA-enzyme interactions', *Physics Letters A*. North-Holland, 382(1), pp. 33–43. doi: 10.1016/J.PHYSLETA.2017.10.038.

Kurian, P. *et al.* (2018b) 'Water-mediated correlations in DNA-enzyme interactions', *Physics Letters A*. North-Holland, 382(1), pp. 33–43. doi: 10.1016/J.PHYSLETA.2017.10.038.

Lambert, N. *et al.* (2013) 'Quantum biology', *Nature Physics*. Nature Publishing Group, 9(1), pp. 10–18. doi: 10.1038/nphys2474.

Lawrence, A. F. *et al.* (1987) 'The nature of phonons and solitary waves in alpha-helical proteins', *Biophysical Journal*. Cell Press, 51(5), pp. 785–793. doi: 10.1016/S0006-3495(87)83405-7.

Lindorff-Larsen, K. *et al.* (2005) 'Simultaneous determination of protein structure and dynamics', *Nature*. Nature Publishing Group, 433(7022), pp. 128–132. doi: 10.1038/nature03199.

Liu, D. *et al.* (2008) 'Studies of Phononlike Low-Energy Excitations of Protein Molecules by Inelastic X-Ray Scattering', *Physical Review Letters*, 101(13), p. 135501. doi: 10.1103/PhysRevLett.101.135501.

Lundholm, I. V *et al.* (2015) 'Terahertz radiation induces non-thermal structural changes associated with Fröhlich condensation in a protein crystal.', *Structural dynamics (Melville, N.Y.)*. American Institute of Physics, 2(5), p. 054702. doi: 10.1063/1.4931825.

Lupas, A. N. and Bassler, J. (2017) 'Coiled Coils – A Model System for the 21st Century', *Trends in Biochemical Sciences*, 42(2), pp. 130–140. doi: 10.1016/j.tibs.2016.10.007.

Lupichev, L. N., Savin, A. V. and Kadantsev, V. N. (2015) *Synergetics of Molecular Systems*. Cham: Springer International Publishing (Springer Series in Synergetics). doi: 10.1007/978-3-319-08195-3.

Markov, M. (Marko S. . (2015) *Electromagnetic Fields in Biology and Medicine, Electromagnetic Fields in Biology and Medicine*. doi: 10.1201/b18148.

Mesquita, M. V., Vasconcellos, Á. R. and Luzzi, R. (2004) 'Considerations on undistorted-

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

progressive X-waves and Davydov solitons, Fröhlich-Bose-Einstein condensation, and Cherenkov-like effect in biosystems', *Brazilian Journal of Physics*. Sociedade Brasileira de Física, 34(2a), pp. 489–503. doi: 10.1590/S0103-97332004000300028.

Mohseni, M. *et al.* (eds) (2014) *Quantum Effects in Biology*. Cambridge: Cambridge University Press. doi: 10.1017/CBO9780511863189.

Nardecchia, I. *et al.* (2018) 'Out-of-Equilibrium Collective Oscillation as Phonon Condensation in a Model Protein', *Physical Review X*. American Physical Society, 8(3), p. 031061. doi: 10.1103/PhysRevX.8.031061.

Niessen, K. A. *et al.* (2017a) 'Moving in the Right Direction: Protein Vibrations Steering Function', *Biophysical Journal*. Cell Press, 112(5), pp. 933–942. doi: 10.1016/J.BPJ.2016.12.049.

Niessen, K. A. *et al.* (2017b) 'Moving in the Right Direction: Protein Vibrations Steering Function', *Biophysical Journal*, 113(11), p. 2573. doi: 10.1016/j.bpj.2017.10.038.

Pokorný, J. (1999) 'Conditions for coherent vibrations in the cytoskeleton', *Bioelectrochemistry and Bioenergetics*. Elsevier, 48(2), pp. 267–271. doi: 10.1016/S0302-4598(99)00016-1.

Pokorný, J. (2004) 'Excitation of vibrations in microtubules in living cells', *Bioelectrochemistry*, 63(1–2), pp. 321–326. doi: 10.1016/j.bioelechem.2003.09.028.

Preto, J. (2017) 'Semi-classical statistical description of Fröhlich condensation', *Journal of Biological Physics*, 43(2), pp. 167–184. doi: 10.1007/s10867-017-9442-y.

Prigogine, I. and Lefever, R. (1973) 'Theory of Dissipative Structures', in *Synergetics*. Wiesbaden: Vieweg+Teubner Verlag, pp. 124–135. doi: 10.1007/978-3-663-01511-6_10.

Reimers, J. R. *et al.* (2009) 'Weak, strong, and coherent regimes of Fröhlich condensation and their applications to terahertz medicine and quantum consciousness.', *Proceedings of the National Academy of Sciences of the United States of America*. National Academy of Sciences, 106(11), pp. 4219–24. doi: 10.1073/pnas.0806273106.

Rolczynski, B. S. *et al.* (2018) 'Correlated Protein Environments Drive Quantum Coherence Lifetimes in Photosynthetic Pigment-Protein Complexes', *Chem*. Cell Press, 4(1), pp. 138–

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

149. doi: 10.1016/J.CHEMPR.2017.12.009.

Salari, V. *et al.* (2011) 'Plausibility of quantum coherent states in biological systems', *Journal of Physics: Conference Series*. IOP Publishing, 306(1), p. 012075. doi: 10.1088/1742-6596/306/1/012075.

Shibata, F. and Hashitsume, N. (1978) 'Generalized Phase-Space Method in the Langevin-Equation Approach', *Journal of the Physical Society of Japan*. The Physical Society of Japan, 44(5), pp. 1435–1448. doi: 10.1143/JPSJ.44.1435.

Siegel, P. H. (2004) 'Terahertz Technology in Biology and Medicine', *IEEE Transactions on Microwave Theory and Techniques*, 52(10), pp. 2438–2447. doi: 10.1109/TMTT.2004.835916.

Sivaramakrishnan, S. *et al.* (2008) 'Dynamic charge interactions create surprising rigidity in the ER/K -helical protein motif', *Proceedings of the National Academy of Sciences*, 105(36), pp. 13356–13361. doi: 10.1073/pnas.0806256105.

Squire, R. H. *et al.* (2013) 'Comparison of various types of coherence and emergent coherent systems', *International Journal of Quantum Chemistry*. Wiley-Blackwell, 113(19), pp. 2181–2199. doi: 10.1002/qua.24423.

Takeno, S. (1984) 'Vibron Solitons in One-Dimensional Molecular Crystals', *Progress of Theoretical Physics*. Oxford University Press, 71(2), pp. 395–398. doi: 10.1143/PTP.71.395.

Tchinang Tchameu, J. D., Togueu Motcheyo, A. B. and Tchawoua, C. (2014) 'Mobility of discrete multibreathers in the exciton dynamics of the Davydov model with saturable nonlinearities', *Physical Review E*, 90(4), p. 043203. doi: 10.1103/PhysRevE.90.043203.

Tsivlin, D. V. and May, V. (2007) 'Multidimensional wave packet dynamics in polypeptides: Coupled amide-exciton chain-vibrational motion in an α-helix', *Chemical Physics*. doi: 10.1016/j.chemphys.2007.03.010.

Turton, D. A. *et al.* (2014) 'Terahertz underdamped vibrational motion governs protein-ligand binding in solution', *Nature Communications*. Nature Publishing Group, 5, p. 3999. doi: 10.1038/ncomms4999.

Vasconcellos, Á. R. *et al.* (2012) 'Fröhlich Condensate: Emergence of Synergetic Dissipative

bioRxiv preprint doi: https://doi.org/10.1101/457580; this version posted April 15, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder. All rights reserved. No reuse allowed without permission.

Structures in Information Processing Biological and Condensed Matter Systems', *Information*. Molecular Diversity Preservation International, 3(4), pp. 601–620. doi: 10.3390/info3040601.

Venema, L. *et al.* (2016) 'The quasiparticle zoo', *Nature Physics*. Nature Publishing Group, 12(12), pp. 1085–1089. doi: 10.1038/nphys3977.

Wang, W. B. *et al.* (2018) 'Energy transport pathway in proteins: Insights from non-equilibrium molecular dynamics with elastic network model', *Scientific Reports*. doi: 10.1038/s41598-018-27745-y.

Weightman, P. (2014) 'Investigation of the Frohlich hypothesis with high intensity terahertz radiation', in Jansen, E. D. et al. (eds) *Optical Interactions with Tissue and Cells XXV; and Terahertz for Biomedical Applications*, p. 89411F. doi: 10.1117/12.2057397.

Wu, T. M. and Austin, S. J. (1981) 'Fröhlich's model of bose condensation in biological systems', *Journal of Biological Physics*. Kluwer Academic Publishers, 9(2), pp. 97–107. doi: 10.1007/BF01987286.

Xie, A., van der Meer, L. and Austin, R. H. (2002) 'Excited-State Lifetimes of Far-Infrared Collective Modes in Proteins', *Journal of Biological Physics*. Kluwer Academic Publishers, 28(2), pp. 147–154. doi: 10.1023/A:1019986321524.

Xie, L., Yao, Y. and Ying, Y. (2014) 'The Application of Terahertz Spectroscopy to Protein Detection: A Review', *Applied Spectroscopy Reviews*. Taylor & Francis, 49(6), pp. 448–461. doi: 10.1080/05704928.2013.847845.