Indian Journal of Biochemistry & Biophysics
Vol. 63, November 2026, pp. 1304-1312
DOI: 10.56042/ijbb.v63i11.1335

Co-relating experimental evidences of protein-protein interaction with analytical approach to protein vibration in living organism

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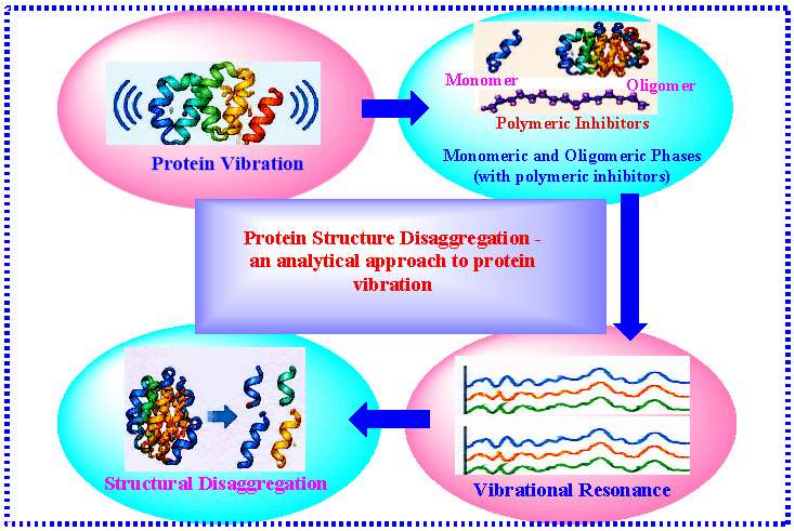
Received 10 May 2023; *revised 08 October 2026*

An in-depth analytical investigation was conducted to correlate diverse *in vitro* and *in vivo* experimental findings regarding the interaction of specific inhibitors with target proteins namely α-synuclein, tau proteins, and misfolded amyloid peptide oligomers associated with Parkinson's and Alzheimer's diseases. The mechanistic framework is evaluated through the lens of protein vibrational dynamics, which are driven within native cellular microenvironments by endogenous electrostatic potentials or external stimuli. This analytical model provides insight into the biophysical mechanisms governing inhibitor-mediated protein disaggregation and conformational modulation.

Keywords: Misfolded proteins, Parkinson, Protein vibration, Synuclein protein, Tau protein

Erwin Schrödinger first proposed the concept that proteins might exhibit vibrational dynamics. Connecting quantum mechanics with biological systems has since remained a major area of investigation, rooted in the long-held hypothesis that proteins vibrate analogously to the strings of a violin or the pipes of an organ[1]. Early theoretical frameworks suggested these vibrational motions occur at extremely high frequencies. Despite experimental challenges, several groups have attempted to characterize protein vibrational spectra. Niessen *et al*[1] successfully demonstrated protein vibrations *in vitro* using orientation-sensitive Terahertz (THz) near-field microscopy. Their study on the antibacterial enzyme lysozyme revealed that the protein exhibits collective vibrational modes (ringing) within the low-terahertz frequency range. These global vibrations extend throughout the macromolecular structure, facilitating efficient energy transfer across the protein domain[2]. This ultra-high-frequency ringing dynamic enables prolonged inter-protein interactions. Because biochemical reactions occur on a picosecond time scale and these resonant motions persist for comparable durations, evolutionary selection may have optimized enzymes to sustain vibrational modes for functional time windows[2]. Physiologically, intracellular protein vibrations are driven by endogenous electrostatic potentials ranging from 0.8 to 30 mV depending on localized pH variations[3] as well as external stimuli.The functional significance of protein vibrations in living organisms encompasses several key mechanisms: Structural Coordination and Dynamics: Molecular dynamics (MD) simulations by Iakhaiev *et al*[4] indicated that protein molecules possess coordinated dynamic networks capable of integrating structural transitions. Protein dynamics essential for biological function encompass atomic vibrations, residue-level motions (*e.g.*, bond stretching and angle bending), secondary structure fluctuations, and correlated domain movements[5]. Conformational Transitions and Ligand Binding: Sub-nanometer internal motions impart the conformational flexibility required for ligand binding and catalysis. These structural rearrangements are critical for cell signaling across membrane channels, as well as oxygen binding and release in hemoglobin. Global vibrational modes extending across the protein scaffold play a pivotal role in regulating these conformational transitions[1]. However, the *in vitro* THz microscopic observations reported by Niessen *et al*.[1] were restricted to crystalline lysozyme, which may not fully reflect the dynamic physiological state of proteins *in vivo*. The physical parameters governing crystallographic states alter the vibrational density of states compared to native cellular environments. Although direct *in vivo* measurements remain technically challenging, ongoing studies utilizing cell cultures, animal models, and disease models (including neurodegenerative, infectious, and

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Graphical abstract

oncological conditions) seek to bridge this gap. Recently, a protein vibration model was proposed to explain the resonance-induced disaggregation of pathologically aggregated proteins driven by native and exogenous protein resonators[6]. Specifically, analytical models[7,8] demonstrated that the upregulation of Heat Shock Protein 70 (HSP70)—induced by phytopharmaceutical extracts of Indian medicinal herbs such as *Bacopa monnieri* and *Withania somnifera* (Ashwagandha) promotes the disaggregation of α-synuclein and tau protein aggregates associated with Parkinson's and Alzheimer's diseases, respectively. Furthermore, the modulating effects of heat shock proteins on immune responses against malignant proteins have been evaluated within the framework of THz protein dynamics[9]. Continued exploration of protein vibrational spectra holds strong potential for developing novel therapeutic modalities targeting age-related neurodegenerative disorders, infectious diseases, and tumor immunomodulation[11-14].

Numerous studies globally have investigated the disaggregation of pathologically aggregated proteins in neurodegenerative disorders using targeted protein inhibitors or Heat Shock Protein (HSP) inducers derived from Indian Medicinal Herbs (IMH)[15]. Due to limitations in conducting direct *in vivo* human trials, these investigations are primarily performed *in vitro* using affected cell lines, *Caenorhabditis elegans*, or murine models. Three representative experimental studies one on Parkinson's disease (PD)[14] and two on Alzheimer's disease (AD)[11,17] highlighted these therapeutic strategies.

Nazir *et al.*[16] demonstrated that HSP70 upregulation induced by *Bacopa monnieri* (BM) extract significantly reduced α-synuclein aggregation in a transgenic *C. elegans* model (NL-5901). Treatment with BM extract reduced the mean green fluorescent protein (GFP) intensity from 8.95±0.6195 arbitrary units in untreated control worms to 2.550±0.2500 arbitrary units in treated worms. Ravindranath *et al.*[15] evaluated the therapeutic efficacy of Withania somnifera (Ashwagandha) root extract in AD transgenic mouse models obtained from Jackson Laboratory[11]. Administration of the crude extract reversed memory deficits, suggesting that *W. somnifera* phytochemicals hold potential for clinical AD therapeutics. Das Mukhopadhyay *et al.*[11] synthesized tripeptide-based PEGylated block co-polymeric inhibitors and evaluated their efficacy against amyloid-beta (Aβ42) aggregation. Incubation of Aβ42 fibrils with inhibitors at equimolar to 1:3 molar ratios led to a steady decrease in emitted fluorescence intensity over 5 days, indicating inhibitor binding and subsequent fibril disassembly. Hydrodynamic Particle Size Reduction: Dynamic Light Scattering (DLS) measurements showed a reduction in Aβ42 fibril dimensions following a 1:1 molar treatment with inhibitors over 5 days. Atomic Force Microscopy (AFM), Field Emission Scanning Electron Microscopy (FE-SEM), and Transmission Electron Microscopy (TEM) confirmed the breakdown of macro-aggregates into smaller oligomeric/monomeric species[12,17]. Conformational Transitions: Circular Dichroism Spectroscopy (CDS) demonstrated a conformational shift in Aβ42 peptides from a native α-helical state to a β-sheet-rich motif during aggregation, which was

modulated upon inhibitor binding[18]. Molecular Dynamics (MD) Simulations: MD simulations (50 ns) targeting the central KLVFFA hydrophobic core of monomeric Aβ42 revealed that leucine, valine, and phenylalanine moieties on the PEGylated polymers acted as competitive inhibitors[11,18]. In the absence of inhibitors, six KLVFFA units coalesced spontaneously; in the presence of inhibitors, strong hydrophobic interactions disrupted this self-assembly, preventing further assembly. Recently, an analytical framework based on THz protein vibrational dynamics was developed[7–9] to explain the disaggregation phenomena reported by Nazir *et al*.[16] and Ravindranath *et al*.[15]. The model posits that vibrational resonance serves as a driving mechanism for disaggregating pathological α-synuclein and tau protein assemblies. Furthermore, protein-ligand binding affinity is correlated with matching vibrational mode frequencies. Here, this protein vibration model is extended to evaluate the structural disaggregation mechanics observed in Aβ42 monomeric and oligomeric phases treated with polymeric inhibitors[3,10-11].

Materials and Methods

It is an established fact that proteins vibrate *in vivo* either due to inherent electrostatic force (potential) of the order of 0.8 to 30 mV with respect to variable pH or due to external stimuli[17]. In previous studies[9] the author suggested that the vibration characteristics of protein depend on the magnitudes of molecular weights of the concerned protein. It was also held by the authors[9] that more is the molecular weight of protein, the less is the number of vibration frequency. On the other hand, less the value of molecular weight of protein is, the more is the number of frequency. Thus the vibration pattern of protein may be described as.

The vibration frequency and vibration energy of the concerned protein can be evaluated by using one dimensional Schrodinger's Equation. The reason of considering one dimensional Schrodinger's Equation lies in the fact that an electrostatic force can control atomic motion in a protein (Fig. 1). For a protein this can be divided into two components – a large and a small.

Conformational substrates for the protein in its native state may correspond to the same position 'r' of the particle at time't'. Thus r (t) can be split into two independent components.

$$r(t) = rv(t) + rt(t)$$

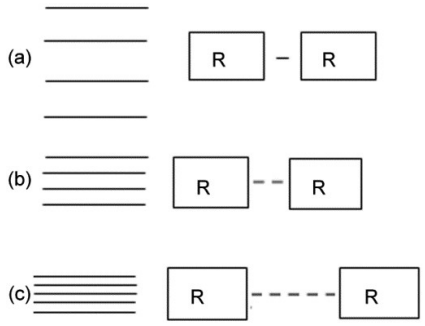


Fig. 1 — Vibration energy spacing of protein molecules

where rv (t) stands for the vibration component about the equilibrium position with the host molecule and rt(t) stands for transient component about the equilibrium position at time t. The electrostatic force required for this purpose may be deduced from the relation.

$$F = -dv/dr$$

Which means force is nothing but rate of change of potential.

$$V(r)=V(rvrt)=1/2[kv(r1)rv^2]+U(r1) \quad \text{... (1)}$$

where Kvr_1 is the vibration component of the force and U(r) stands for the translational component of the same. Since the translational component of the force is very small with respect to the vibration component of the same, the second term of equation (1) may be neglected. So equation (1) may be rewritten as:

$$V(r)=V(rvrt)=1/2[kv(rv)rv^2] \quad \text{... (2)}$$

The magnitude of this transformed energy may be evaluated by following quantum mechanical treatment of harmonic oscillator. By inserting vibration potential energy function, we may write f = -dv / dr, which stands for the rate of change of potential energy with change of co-ordinate. Let us now state with f = -kr which on integration leads to potential energy v = ½ kr^2. This potential energy rises parabolic on either side of the equilibrium as illustrated in (Fig. 2).

The vibration energy and vibration frequency of concerned proteins may be evaluated by using the solution of one dimensional Schrodinger's Equation:

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + \nu\,(r)\psi = \varepsilon\,\psi \quad \text{... (3)}$$

Which turns to

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + \frac{1}{2}\,\mathrm{kr}^2\psi = \varepsilon\psi \quad \text{... (4)}$$

$V = \frac{1}{2} kr^2$,

With potential energy while other symbols stands for usual meaning.

$$\varepsilon_{vib} = (\nu + \frac{1}{2}) \frac{h}{2\pi} \sqrt{\frac{k}{m}}, \nu = 0,1,2 \quad \text{... (5)}$$

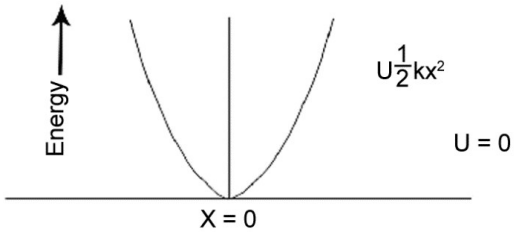


Fig. 2 — Oscillation of vibrating particle

The energy of the allowed vibration states derived from the solutions of the Schrodinger's Equation are:

$$\nu_{vib} = \frac{1}{2\pi} \sqrt{\frac{k}{m}} \quad \text{... (6)}$$

While the expression for vibrational frequency stands as.

Results and Discussion

Based on equations 6 and 5, vibration frequencies and vibration energies of protein of different molecular weights involved in disaggregation of $A\beta_{42}$ fibril as mentioned by Das Mukhopadhyay and others[11] are evaluated and these are tabled in (Table 1-3). These have been calculated by considering electrostatic

Table 1 —Vibration Frequencies ($\times 10^{10}$ Hertz) of different protein with respect to electrostatic potential (E.S.P) in mV

E.S.P	KD	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
$A\beta_{42}$	4.5	0.6	0.72	1.01	1.24	1.44	1.61	2.28	2.79	3.22	3.60	3.95
$A\beta_{42}$	10	0.43	0.48	0.68	0.83	0.96	1.08	1.53	1.87	2.16	2.42	2.65
fibril	15	0.35	0.39	0.55	0.68	0.80	0.88	1.24	1.53	1.76	1.97	2.16
	20	0.30	0.34	0.48	0.59	0.64	0.76	1.08	1.32	1.53	1.71	1.87
	50	0.19	0.21	0.30	0.37	0.43	0.48	0.68	0.83	0.96	1.08	1.18
	60	0.17	0.19	0.27	0.34	0.39	0.44	0.62	0.76	0.88	0.98	1.00
	70	0.16	0.18	0.25	0.31	0.36	0.40	0.57	0.70	0.81	0.91	1.08
	80	0.15	0.17	0.24	0.29	0.36	0.38	0.50	0.62	0.76	0.85	0.88
	90	0.14	0.16	0.22	0.27	0.32	0.36	0.50	0.62	0.72	0.80	0.83
	100	0.13	0.15	0.21	0.26	0.30	0.34	0.48	0.59	0.68	0.76	0.83
Inhibitors	8 KD	0.48	0.54	0.76	0.93	1.08	1.20	1.71	2.09	2.41	2.70	2.96
	11	0.41	0.46	0.65	0.79	0.92	1.03	1.45	1.78	2.06	2.30	2.52

Table 2 —Vibration energies (in10^{-21} KJ) of different proteins with respect to electrostatic potential (E.P.S) in mV

E.S.P	Mol Wt.	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
$A\beta_{42}$ Fibril (Monomer)	4.5 KD	4.26	4.77	6.68	8.20	9.53	10.65	15.09	18.46	21.31	23.83	26.14
Oligomers	10 KD	2.85	3.19	4.52	5.54	6.40	7.14	10.12	12.37	14.29	15.95	17.54
Of $A\beta_{42}$fibril	15 KD	2.32	2.61	3.69	4.52	5.22	5.83	8.26	10.12	11.68	13.06	14.24
	20 KD	2.03	2.22	3.13	3.84	4.45	5.06	7.54	8.70	10.12	11.22	12.00
	50 KD	1.27	1.42	2.02	2.44	2.85	3.19	4.52	5.54	6.40	7.14	7.81
	60 KD	1.15	1.30	1.84	2.26	2.61	2.91	4.13	5.04	5.84	6.53	7.19
	70 KD	1.07	1.24	1.71	2.09	2.42	2.70	3.81	4.68	5.41	6.06	6.63
	80 KD	1.01	1.11	1.59	1.95	2.25	2.52	3.51	4.38	5.08	5.66	6.19
	90 KD	0.95	1.06	1.50	1.84	2.12	2.38	3.37	4.10	4.70	5.29	5.82
	100 KD	0.90	1.01	1.42	1.75	2.02	2.26	3.19	3.91	4.50	5.06	5.54
Inhibitors	8 KD	3.19	3.59	5.12	6.15	7.14	7.94	11.32	13.83	15.95	18.00	19.59
	11 KD	2.71	3.05	4.31	5.28	6.10	6.81	9.59	11.78	13.63	15.22	16.68
Molucular weights between 11 KD and 10 KD	5.2 KD	3.96	4.43	6.27	7.68	8.87	9.92	14.03	17.10	19.86	21.93	24.30
Molucular weights between 8 KD and 10 KD	4.44 KD	4.30	4.81	6.82	8.35	9.65	10.79	15.25	18.69	21.58	24.12	26.88

Table 3 —Vibration frequencies of certain amino acids in $\times 10^{11}$ Hertzs

	E.S.P.	Mol. wt	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
Amino acids	Amine(A)	89D	0.45 8	0.5 12	0.7 25	0.8 86	1.0 25	1.1 46	1.6 21	1.9 86	2.2 93	2.5 64	2.8 09
	Leu(L)	131D	0.37 8	0.4 22	0.5 97	0.7 32	0.8 45	0.9 54	1.3 36	1.6 37	1.8 09	2.1 13	2.3 15
	Lysine(K)	146D	0.35 8	0.4 00	0.5 66	0.6 93	0.8 00	0.8 95	1.2 66	1.5 50	1.7 90	2.0 02	2.1 93
	Phenglala Nine (F)	165D	0.33 6	0.3 76	0.5 32	0.6 51	0.7 52	0.8 41	1.1 90	1.4 58	1.6 83	1.8 81	2.0 62
	Valine(V)	117D	0.39 9	0.4 46	0.6 31	0.7 74	0.8 93	0.9 99	1.2 13	1.7 31	1.9 97	2.2 35	2.4 49
	Combined form (KLVFFA)	813D	0.15 1	0.1 68	0.2 35	0.2 93	0.3 38	0.3 77	0.5 35	0.6 56	0.7 57	0.8 47	0.9 29

Table 4 — Statistical analysis partaining to Table– 1 data

Mean	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
	0.27	0.25	0.42	0.44	0.60	0.63	0.60	1.16	1.26	1.35	1.64
SD	0.21	0.18	0.19	0.66	0.35	0.39	0.35	0.58	0.66	0.63	0.32
CV	77.0	72.0	45.0	66.0	58.0	62.0	58.0	50.0	53.0	45.0	20.0

Table 5 — Statistical analysis partaining to Table– 3 data

Mean	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
	0.44	0.43	0.61	0.75	0.86	0.96	1.32	1.67	1.91	1.16	1.56
SD	0.09	0.17	0.46	0.64	0.25	0.19	0.47	0.39	0.28	0.48	0.83
CV	24.0	39.0	76.0	88.0	29.0	20.0	32.0	23.0	20.0	25.0	53.0

force of the cells in the range of (0.8 to 30) mV only. The effects of other parameters within the cells and also the cell membrane have not been considered for the sake of the present study.

Column wise statistical parameters like SD and CV Co-efficient of variation of the values of different frequencies as shown in (Table 1 & 3) have been evaluated. It is found from Table 1 that CV values of almost all frequencies are lowere except a few for lower magnitude of electrostatic potential in the range of (0.8 to 4.0) mV. Similar findings ar also observed in case of cv values of the frequencies evaluated for some amino acids except for (2.0, 3.0 and 30) mV of electrostatic potential. These are shown in (Table 3). Lower values of cv. indicated that magnitude of frequencies as evaluated (Table 1 & 3) are statistically stable (Table 4 & 5).

From Tables 4 and 5, it reveals that both vibration frequencies and vibration energies are getting decreased with increase in molecular weights of $A\beta_{42}$ fibril by a segment of oligomer of approximately 10 KD molecular weight irrespective of magnitude of electrostatic potential. On the other hand, each oligomer seems to be formed with at least two monomers of 4.5 KD each molecular weight. The vibration frequencies of 9 KD or 10 KD oligomer are almost similar and all these are shown in (Table 1). The vibration frequencies of inhibitor having molecular weights 8 KD and 11 KD have also been evaluated and these are Shown in the (Table 1). Vibration frequencies of $A\beta_{42}$ fibril with oligomers of increased Molecular weight by10 KD each were also evaluated and these are shown in the (Table 1). Looking at the frequency levels of inhibitor with molecular weight 11 KD and an oligomer of molecular weight 10 KD, it is held that resonance of frequency may occur resulting in disaggregation of $A\beta_{42}$ fibril by 1st segment of oligomer of molecular weight 10 KD. Since all protein constituents of $A\beta_{42}$ fibril are considered as oligomers of 10 KD or combination of at least two monomers of each having molecular weight of 4.5 KD and since resonance may occur with respect to oligomer of 10 KD and inhibitor of 11 KD, disaggregation of related oligomers will continue segment wise or disaggregation of all

oligomers may be occurred even simultaneously including the native one (50 KD $A\beta_{42}$ fibril) also. The proposed phenomenon may be compared to earthquake where all constituent parts of abuilding collapse step by step or as a whole depending onthe strength (magnitude) of resonance frequency. On the other hand, frequency levels of oligomer and inhibitors being in parity, each will feel tendency to bind each other and were found to be compatible with the previous report[10].

The concerned monomers or oligomers consist of amino acid like 'Lys-Veu-Val-Phe-Phe-Ala' abbreviated as KLVFFA. The vibration frequency of each of the amino acids and their combined form (KLVFFA) are presented in (Table 3). Since the molecular weights of these amino acid are small, the magnitude of vibration frequencies will be high. On the other hand, the molecular weights of amino acid are almost in same range, the magnitude of vibration frequencies are also in the same range. As a result, these will feel tendency to come close to each other and thereby to get associated with native $A\beta_{42}$ fibril in the form of monomer or oligomer. But the inhibitors do not allow them to get united and hence to aggregate $A\beta_{42}$ fibril. This is because of the fact that vibration of higher frequencies will have small wavelength and those of smaller frequencies will have large wavelength. Since the vibration frequencies executed by inhibitors are smaller than those executed by amino acids and their combined form, the wavelength due to higher frequencies will be smaller than those of smaller frequencies and as such wavelength due to vibration frequencies of inhibitors will be larger than those created by vibration frequencies of amino acids. As a result, wavelength of vibration frequencies created due to amino acids and also their combined form (KLVFFA) will be modulated by the wavelength of vibration frequencies created due to inhibitors. This is because of the fact that here frequency modulation stands also for change in signaling path way of bio-chemical interaction. Hence, amino acids will have no change to get united and to aggregate the $A\beta_{42}$ fibril again. These are in good agreement with the observations as revealed in item No 'd' by Das Mukhopadhyay[11]. Das Mukhopadhyay[11] observed conformational changes of $A\beta_{42}$ fibril from α- Helix to β sheet in their experiment of treating $A\beta_{42}$ fibril with inibitors with the help of far UV Circular Dichroism (CD). The change into β sheet was confirmed by considering the shifting of wavelength in CD spectral lines.

In the literature report[11] it was opined that protein vibration plays pivotal role in conformational changes of protein from α-helixto β sheet. But no experimental data for comparing conformational changes based on protein vibration is available at present. The author attempts here to explain analytically the phenomenon of conformational change of protein fromα-helix to β sheet from the view point of protein vibration. Treating of inhibitors[11] with $A\beta_{42}$ fibril can be viewed by considering reduced Mass of $A\beta_{42}$ fibril in the form of oligomers/monomers as two vibrating particles in the light of one body phenomenon like.

$$\mathrm{M} = \frac{m_1 m_2}{m_1 + m_2}$$

where m_1 and m_2 stand respectively for molecular mass of oligomer(10 KD) and inhibitors (8 KD and 11 KD).

$$\mathrm{E_{vib}}(KJ/molecule) = h\nu = \mathrm{h}\frac{\mathrm{c}}{\lambda}$$

$$= \frac{(6.62 \times 10^{-34} JS)(2.99 \times 10^{8} ms^{-1})}{(1000 J/KJ)\ (\lambda \times 10^{9})}$$

$$= \frac{19.79 \times 10^{-20}}{\lambda}\ \mathrm{nm} \qquad \ldots (7)$$

Vibration frequencies and vibration energies of inhibitors have already been evaluated and those of reduced mass have also been evaluated with the help of equation 5 & 6 and these are shown in (Table 3). With numerical values of vibration energies, corresponding values of wavelength in nanometer have been evaluated from the relation.

With equation 7 wavelength of related oligomers having molecular weights 10 KD which are expected to be disaggregated by treating $A\beta_{42}$ fibril with inhibitors[13] having molecular weights 8 KD and 11 KD respectively and thereby the wavelength of reduced mass of vibrating oligomers and inhibitors are evaluated and these are soon in (Table 6).

From Table 6, it reveals that wavelength of 10 KD oligomer is higher than those of reduced mass between 10 KD oligomer and 11 KD and 8 KD inhibitors irrespective of the magnitudes of electrostatic potential when $A\beta_{42}$ fibril was treated with inhibitors. The numerical values of wavelength of 10 KD oligomeris λ= 69.4 nm. for 0.8 mV , while it is λ= 49.9 nm for reduced mass 5.20 KD (between 10 KD and 11 KD) and for reduced mass 4.44 KD

Table 6 — Wavelength in nanometre of oligomers (α-helix) and reduced mass of oligomers and inhibitors (changed β sheet) after treating $A\beta_{42}$ fibril with inhibitors

E.S.P.	Mol. Wt	0.8 mV	1 mV	2 mV	3 mV	4 mV	5 mV	10 mV	15 mV	20 mV	25 mV	30 mV
Oligomer Of 10 KD	10 KD	69.4	62.0	43.7	35.7	30.9	27.7	19.5	15.9	13.8	12.4	11.2
Reduced mass of 11 KD and oligomer 10 KD	5.20	49.9	44.2	31.5	25.7	22.2	19.9	14.1	11.5	9.9	9.0	8.1
Reduced mass of inhibitor 8 KD and oligomer 10 KD	46.0	46.0	40.4	29.0	23.7	20.5	18.3	12.9	10.5	9.1	8.2	7.3

Table 7 — Wavelength (in nm) for reduced mass of native (tau) protein, and aggregated tau protein evaluated in presence of electrode potentials (E.P.S.) in mV

I some rs of tau proteins	Mol.wt	Mol.wt of AP	Mol.wt of NP	Frequency ($\times10^{10}$Hertz) of reduced masses of proteins				Vibration energy ($\times10^{-24}$J of reduced masses of proteins				Wavelength of native proteins and aggregated portions			
				E.P.S.											
				0.8	10	20	30	0.8	10	20	30	0.8	10	20	30
1 native tau	45	45	-	0.20	0.72	1.01	1.24	1.34	4.77	6.74	8.20	147.060	41.048	29.036	24.013
2.h tau 23	48	93	30.32	0.24	0.89	1.24	1.52	1.64	5.81	8.22	10.006	120.067	34.006	24.007	19.067
3h tau 24	52	145	34.34	0.23	0.82	1.16	1.43	1.54	5.46	7.72	9.46	128.050	36.024	25.063	20.091
4h tau 37	54	199	36.70	0.22	0.79	1.12	1.38	1.48	5.27	7.46	9.14	133.071	37.055	26.052	21.065
5h tau 34	59	258	38.31	0.22	0.78	1.10	1.35	1.46	5.17	7.31	8.95	135.54	38.022	27.007	22.011
6tau. 39	62	320	39.45	0.21	0.77	1.08	1.33	1.43	5.09	7.20	8.83	138.39	38.088	29.048	22.041
7tau 40	67	387	40.31	0.21	0.72	1.07	1.31	1.42	4.80	7.08	8.73	139.36	41.022	27.095	22.066

NB: AP = Aggregated Proteins; NP = Native Proteins

(between 10 KD and 8 KD) it is λ= 46 nm. For the sake of controversy we may consider 10 KD oligomer as α-helix and 5.20 KD and 4.44 KD reduced masses as outcome of α-helix to β-sheet. This means wavelength of reduced mass (treated as β-sheet) is less than that of oligomer (α-helix). These are found alike with those observed experimentally by Das Mukhopadhyay and others[11] where numerical values of wavelength stand as λ= 216 nm for α-helix and λ=196 for β-sheet when $A\beta_{42}$ fibril was treated with inhibitors. Moreover, it also reveals that numerical values of wavelength as in case of 11 KD inhibitor is higher than that of 8 KD inhibitor which also supports the findings that the role of the inhibitor (11 KD) is more significant than other inhibitor (8 KD) as observed experimentally by Das Mukhopadhaya[11]. The numerical values of wavelength as evaluated by the author for electrostatic potential 0.8 mV. are found lower by 4 to 5 times of magnitude of the experimental values observed by Das Mukhopadhyay[11]. Similarly, wavelengths of different constituents of tau proteins are evaluated based on protein vibration energy (Equation 5) and its relation with wavelength (Equation 7) and these are presented in (Table 7).

From Colum No.13 of (Table 5), it reveals that wavelength of native tau protein (said to be α -helix) is λ= 147.60 nm and for reduced mass of aggregated tau protein and native protein (said to beβ -sheet) it is λ= 139.36 nm for electrostatic potential 0.8 mV. These values of wavelength are found more close to those of Das Mukhopadhyay[11]. These predict that tau protein approach and also the PE Gylated approach of disaggregation of aggregated proteins responsible for A. D. are found in close proximity with each other particularly for electrostatic potential of 0.8 mV in cells while numerical values of wavelength for higher values electrostatic potential do not hold good with respect to experimental values. However difference in numerical values of wavelength maybe due to the fact that protein vibration has been considered by the author based only on electrostatic potential of cells, other parameters which may take part *in vivo* protein vibration were not taken into account by the author. On the other hand, the experimental groups which have considered the role of B.M and Ashwagandha for treatment of Parkinson and Alzheimer in conducting *in vitro*/*in vivo* experiment with living cells, worms, mice and etc. may vary with those who have also considered the role of PE Gylated inhibitors for treatment of Alzheimer patients. Their experimental finding would vary with those of analytical values as effects of different parameters in living cells may appear invariably, even though they have not considered the role of protein vibration. On the other hand, protein vibration considered to be generated within the cells in presence of electrostatic potential by the author will be definitely smaller than those observed by A.K.Niessen and others[1]. It is to be noted that Niessen group[1] conducted laboratory experiment with crystallized lyzosome in presence of light with tera heartz frequency. It is evident that the frequency of vibration of crystallized lyzosome will be in order of tera heartz resulting frequency 10 cm^{-1} and above. This may be considered as a result of existence and mode of protein vibration outside the cells of living beings. So, these findings can in no case be considered as compatible with those of *in vivo in vitro* experimental findings on living beings.

Conclusion

The spirit of the present work is to correlate analytically the experimental findings of different groups on the role of different inhibitors (proteins) for treatment of certain old age diseases. Results related to *in vitro*/*in vivo* findings of different groups will also vary since different group may consider different parameters in cells of living organism. Since no universal experimental arrangement has yet been developed, no similar findings will come out. However, the present author conducted in-depth study on the role of EEG in learning and memory formation taking into account certain proteins responsible for learning and memory in the context of protein vibration. Arrangement for investigating the role of protein vibration related to different neurodegenerative diseases with EEG rhythms may be undertaken by the scholars. Similar experiment for measuring vibration frequency mainly concerned with antigen-antibody (protein-protein) interaction may also be developed. However, we are to wait till novel experimental arrangements for conducting *in vivo* investigation on the role of protein vibration responsible for number of functioning's in cells of living beings emerge out.

Acknowledgement

The author is thankful to Dr. C. Das Mukhopadhyay, associate professor, IIST, Kolkata, West Bengal and others for her proposal to examine the role of protein vibration. The author is thankful to Dr. U.C. De, Professor, Tripura University, Agartala Tripura for his helpful discussion. The author is also thankful to Mr. Sunil Debnath and Smt. Aparajita Majumder for their co-operation in different computation works.

Conflict of interest

The author declares no conflict of interest.

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