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ON MACROSCOPIC QUANTUM PHENOMENA IN BIOMOLECULES AND CELLS

FROM LEVINTHAL TO HOPFIELD

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Abstract. In the context of the macroscopic quantum phenomena of the 2nd kind we hereby seek for a solution-in-principle of the long standing problem of the polymer folding, which was considered by Levinthal as (semi)classically intractable. To illuminate it, we applied quantum-chemical and quantum-decoherence approaches to conformational transitions. Our analyses imply the existence of novel macroscopic quantum biomolecular phenomena, with far reaching implications regarding chain folding and biomolecular recognition processes, which cannot be considered kinetically understood based on (semi)classical predictions. For instance, biomolecular chain folding in an open environment might be considered as a subtle interplay between energy and conformation eigenestates of this biomolecule, governed by quantum-chemical and quantum-decoherence laws. On the other hand, within an open biological cell, a system of N_k identical (non-interacting and dynamically non-coupled) biomolecular proteins (and their biomolecular targets) might be considered as corresponding spatial quantum ensemble of N_k identical biomolecular processors, providing spatially distributed quantum solution to a single corresponding biomolecular chain-folding (and key-lock recognition process) – whose density of conformational states might be represented as Hopfield-like quantum-holographic associative neural network too. Thus, to generalize, a series of coupled environment-driven (compositionally/chemically or thermally/optically) intra-cellular and extra-cellular local biochemical reactions might be considered globally as a series of correspondingly coupled intra-cellular and extra-cellular distributed Hopfield-like quantum-holographic associative neural network layers – providing an equivalent global quantum-informational alternative to standard molecular-biology local biochemical approach in biomolecules and cells (and higher hierarchical levels of organism, as well).

1. INTRODUCTION

1.1 On macroscopic quantum phenomena

Initially, ***quantum mechanics*** appeared as a theory of *microscopic physical systems* (elementary particles, atoms, molecules) and phenomena at small space-time scales; typically, quantum phenomena are manifested at dimensions smaller than 1 nm and time intervals shorter than 1 μs. However, from the very beginning of the quantum-mechanical founding the question of ***universality of quantum mechanics*** was raised, i.e. the question of general validity of the quantum-physical laws for ***macroscopic phenomena*** as well, usually treated by the methods of classical physics.

In the history of quantum physics, and especially quantum mechanics, this question has been temporarily put aside for very different reasons, being considered as a *difficult scientific problem*. The situation is additionally complicated by the existence of different schools of quantum mechanics, arguing about physical-epistemological status of the so called *collapse (reduction) of the wave function*. In this respect the situation is not much better today, and it can be said freely that the *problem of universal validity of quantum mechanics is still open* [1-15]. To this end, Primas [16] emphasizes:

“If we consider quantum mechanics as *universally valid* in the atomic, molecular, mesoscopic and engineering domain, then we have to require that a proper mathematical codification of this theory must be capable to describe all phenomena of molecular and engineering science. Already rather small molecules can have classical properties, so that a classical behavior is *not* a characteristic property of large systems. The existence of molecular superselection rules and of molecular classical observables is an empirically well-known fact in chemistry and molecular biology. The chirality of some molecules, the knot type of circular DNA-molecules, and the temperature of chemical substances are three rather different examples of molecular classical observables. Such empirical facts can be described in an ad hoc phenomenological manner, but it is not so easy to explain these phenomena from the first principles of quantum mechanics. A universally valid theory of matter has not only to describe but also to *explain* why the chirality of biomolecules (like the L-amino acids, the D-sugars, lipids or steroids) is a *classical* observable. The reality of this breakdown of the superposition principle of traditional quantum mechanics on the molecular level is dramatically demonstrated by the terrible Vontergan tragedy which caused many severe birth defects.”

Starting from the 1980's, mainly in the papers of Leggett [1,2], a new period in investigation of quantum-mechanical phenomena on the macroscopic level began. Namely, a clarification of the notions and planning of experimental situations for observing some physical effects started. The central problem in this respect is a notion of macroscopic differentiation of the states of quantum system whose quantum-mechanical behavior is explored.

More precisely, Leggett argues that the term ***macroscopic quantum-mechanical effect*** must be related to macroscopically different states, i.e. the system states (and observables) that carry macroscopic properties (and behaviors) of the system as a whole. These states (i.e. observables) must carry classical-physical behavior of the system as well, this posing a task for choosing physical conditions giving rise to observation of typical quantum effects related to these states.[1]

[1] Paradigm of macroscopic, *macroscopically differentiated states*, are proper *states of position (and impulse) of the* ***center of mass*** of many-particle system. On the contrary, so called ***relative coordinates*** (as observables) *neither define macroscopically differentiated states nor carry classical* behavior *of the system*, in any known physical theory or experimental situation.

Hence a difference between ***two types*** of *macroscopic quantum phenomena*:
(i) ***macroscopic quantum phenomena of the 1st kind*** (explored by the methods of quantum statistical physics, and not regarding macroscopically differentiated states (like solid state phenomena));
(ii) ***macroscopic quantum phenomena of the 2nd kind*** (explored by the methods of quantum mechanics, and regarding macroscopically different (differentiated) states (being interesting to us)).

Numerous different *macroscopic quantum phenomena of the 2nd kind*, some of them belonging to the fast developing field of the *quantum computing & information*, unequivocally sharpen the overall problem of universal validity of quantum mechanics.

In the context of the ***macroscopic quantum phenomena of the 2nd kind***, we shall present a *solution-in-principle of the long standing problem* of the ***polymer folding*** (which was considered by Levinthal as *(semi)classically intractable* [17], as shortly reviewed bellow) – implying the existence of novel ***macroscopic quantum biomolecular phenomena***, with far reaching implications.

1.2 Levinthal paradox revisited

Contemporary methods for ***calculation of conformational dependent chain properties*** are based on ***thermodynamic aspect of the problem***, which *explores (semi)classically the folding free energy landscape* for protein with several successful attempts to model these processes *in silico* using *molecular dynamics simulations* with full atomic representation *of both protein and solvent* [18-22], producing *continuous (semi)classical trajectories* with the potential to connect *static structural snapshots* generated from experimental data.

This is incorporated into ***(semi)classical viewpoint***, that ***conformational changes of proteins***, *due to solvent, thermal, optical, and other influences of the environment*, ***do not occur in a random way*** (as e.g. movements of gas particles) – ***but fold to their native conformation*** *of deep global minimum* ***in some (semi)classical funnel*** *of low-energy conformations leading toward it* [23]. Even in recently reported *implementation of quantum annealing* (on the programmable superconducting quantum device) for lattice protein folding problems, *nothing quantum-mechanical is implied about protein or its folding process* [24] (rather quantum fluctuations are a tool used for solving the optimization problem of protein folding, considered classically intractable [25-27]).

Hence, *these (semi)classical calculation methods* ***do not describe*** properly ***transitions from one conformation to another***, which is ***kinetic aspect of the problem***, exploring the conformation change of long flexible chain. This has been illustrated by ***Levinthal***, who considered ***probability of folding a protein molecule from coiled to native conformation*** [17]:

Assuming $2n$ torsional angles of a n-residue protein, each having three stabile rotational states, this yields $3^{2n} \approx 10^{n}$ possible conformations for the chain; if a protein can explore new conformations in a random way, at the rate that single bond can rotate, it can find approximately 10^{13} conformations per seconds;

Then the time t(s) *required for a protein to explore all the conformations* available to it is: $t = 10^{n}/10^{13}$; for a rather small protein of $n = 100$ residues, one obtains $t = 10^{87}$ s, which is immensely more than the apparent age of the Universe ***("Levinthal paradox")***.

Yet, ***according to experiments*** *proteins can fold to their native conformation in less than a few seconds* [28].

It should be added that *(semi)classical* kinetic (nonstationary) predictions imply the continuous map/conformation change $k_i \rightarrow k_f$ which *requires* a sequence of n local ***non-commuting*** succesive elementary transformations (***local rotations*** of characteristic time τ_o), with the time necessary for the net transformation much longer than characteristic time necessary for a local rotation ($\tau_n \sim n\tau_o >> \tau_o$) and the ***frequency of corresponding global transition*** *much lower than the frequency of a local rotation* ($f_n \sim 1/n\tau_o \sim f_o/n << f_o$) – strongly dependent on a degree of polymerization n (in clear *contradistinction* with the ***experimentally poorly dimensionally-sensitive dispersion laws*** of the internal more or less delocalized quasiparticle excitations in any condensed-state quantum system: electrons, phonons etc. [29]).

Thus, ***chain folding*** based on *(semi)classical* (nonstationary) predictions ***cannot be considered kinetically understood***; the same apply to ***biomolecular recognition*** based on *(semi)classical* selective ligand-proteins/target-receptors key/lock interactions.

2. CONFORMATIONAL TRANSITIONS IN BIOMOLECULES & CELLS AS MACROSCOPIC QUANTUM EFFECTS

2.1 Quantum-chemical approach to conformational transitions in biomolecules

Within the framework of standard ***quantum-chemical Hamiltonian*** (including kinetic energies and Coulomb interactions of all biomolecular electrons and nuclei) and Born-Openheimer ***adiabatic approximation*** (of separated biomolecular electronic and vibrational degrees of freedom), the ***(semi)classical problem of many-electron hypersurface*** $E_e(\phi_e^{(k)})$, not adiabatically well-defined when traversing between two adjacent local minima, ***is replaced by*** *better defined problem of two (virtually intersecting) isomeric many-electron hypersurfaces (hyper-paraboloids)* serving as *potential hypersurfaces for two vibrational (isomeric) problems* – within the ***Theory of Non-Radiative Resonant Structural Transitions*** [30]. In this approach, the conditions for ***electronic-vibrational non-radiative resonant transitions*** between the *i*-th and *f*-th isomeric states are possible only for ***close states*** with *non-vanishing electronic and vibrational dipole moments & non-vanishing electronic and vibrational overlap integrals* (cf. ***Figure 1***) .

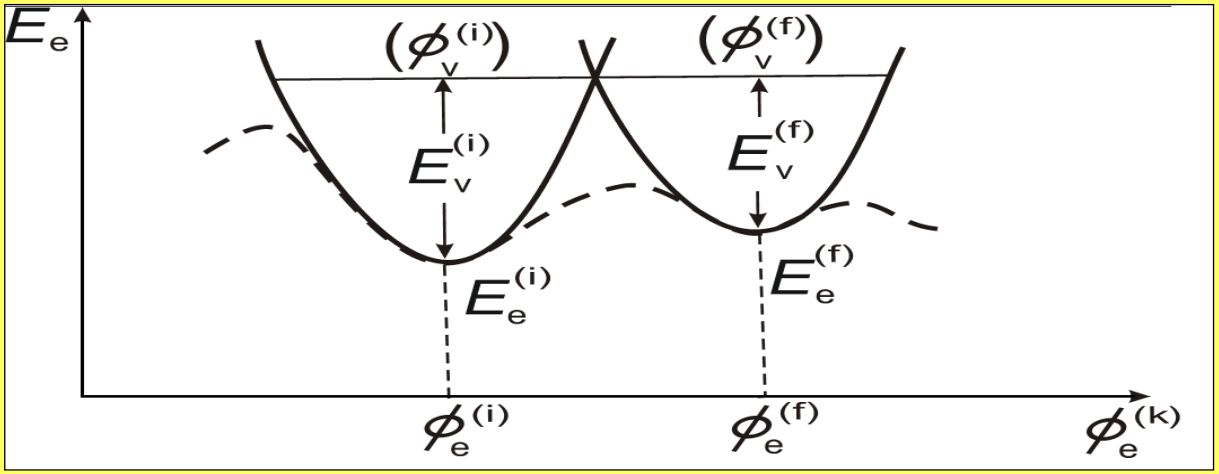

Figure 1. *The (semi)classical problem of many-electron hypersurface $E_e(\phi_e^{(k)})$ as a potential energy for adiabatically decoupled Q1D vibrational and conformational system (with local minima as (semi)classical 'positions', i.e. many-atomic isomer configurations on many-electronic hypersurface (broken line in the figure)) – not adiabatically well-defined when traversing between two adjacent local minima – is replaced in the framework of theory of non-radiative resonant transitions* [30,31] *by better defined problem of two (virtually intersecting) isomeric many-electronic hypersurfaces (hyper-paraboloids) serving as potential hypersurfaces for two vibrational (isomeric) problems (full line in the figure). In this approach, by time-dependent external perturbation of the isomers, at this very intersection the conditions for electronic-vibrational non-radiative resonant transitions between the two isomers (i, f) are achieved: in the first approximation, the matrix element of dipole transition from i-th to f-th isomer is given by $\boldsymbol{\mu}^{(i,f)} \approx \boldsymbol{\mu}_e^{(i,f)} S_v^{(i,f)} + \boldsymbol{\mu}_v^{(i,f)} S_e^{(i,f)}$. It is obvious that allowed transitions between isomeric states (i, f) are possible only for close states with non-vanishing electronic and vibrational dipole moments, $\boldsymbol{\mu}_e^{(i,f)}$ and $\boldsymbol{\mu}_v^{(i,f)}$, and non-vanishing electronic and vibrational overlap integrals $S_v^{(i,f)}$ and $S_e^{(i,f)}$, or in cascade resonant transitions between close intermediate participating isomeric states, which might be related to non-dissipative polaron/soliton-like transport* [32,33]. *Also, during these resonant transitions the perturbed biomolecular system is shortly described by quantum-coherent superposition $(\phi_e^{(i)} \phi_v^{(i)} \pm \phi_e^{(f)} \phi_v^{(f)})/\sqrt{2}$, before its quantum decoherence into final electronic state $\phi_e^{(f)}$ or into initial electronic state $\phi_e^{(i)}$ (with subsequent de-excitations into lower vibrational states).*

2.2 Quantum-decoherence approach to conformational transitions in biomolecules & cells: From Levinthal to Hopfield

Quantum decoherence approach to conformational transitions [34-42] (cf. *Appendix*) generally allows reproduction of both ***existence & stability*** of the (*stationary*) ***conformations***, and the ***short time scales*** for the quantum-mechanical processes resulting effectively in (*nonstationary*) ***conformational transitions*** under external influences on the complementary environmental solution.

This approach might also be applied to (*nonstationary*) mismatching-to-matching quantum-mechanical ***conformational transitions*** in selective ligand-proteins/target-receptors key/lock ***biomolecular recognition*** under external (e.g. compositional/chemical, thermal, optical ...) influences on the cell's complementary cytoplasmatic environment [36,37,41,42].

In the context of existence and changes of conformations of biomolecules, it should be particularly pointed out that biomolecular operators of ***Hamiltonian*** & ***Conformations*** ***do not commute***, $\left[\widehat{H},\widehat{K}\right]\neq 0$! Hence, *quantum-chemical approach* described in the previous section (with *simultaneously defined* energies and conformations of biomolecules) is *essentially (semi)classical*.

So, *it is only* ***quantum decoherence (QD)*** [2] *that enables* ***appearance of conformational eigenstates*** (labeled by upper index *K* in Eq. (1)) ***from the energy eigenstate of the isolated biomolecule*** (labeled by upper index *E* in Eq. (1)) – ***via quantum decoherence non-potential interaction*** of the *biomolecular quantum system* (*QS*) *& quantum environment* (*QE*), when *one of the conformational* K_k *eigenstates is stochastically selected from the initial many-electronic energy eigenstate* $E_e^{(i)}$ *of the isolated biomolecule.* [As only *self-Hamiltonian* of the biomolecule was switched-on initially, like a *proper approximation when interaction with quantum environment might be accounted* ***via self-Hamiltonian potential term***] [3]

It should be noted that the ***most probable conformational eigenstate*** is the one labeled by K_i, ***corresponding to initial many-electronic energy*** of the biomolekule $E_e^{(i)}$ (with same index *i*, in accordance with usually adopted quantum-chemical computations within the framework of adiabatic approximation).

Subsequently, ***one of stochastically QD-selected conformational K_k eigenstates*** (K_i, in *Fig. 1*) might be ***externally excited by nonstationary perturbations*** (photons…) ***into some resonant electronic-vibrational energy eigenstate***: $E_e^{(i)} + E_v^{(i)} = E_e^{(f)} + E_v^{(f)}$ (see *Fig. 1).* [When self-Hamiltonian of the biomolecule is again a *proper approximation,* and interaction with quantum environment might be again accounted *via* ***self-Hamiltonian potential term***] Then, in subsequent quantum deexcitation / decoherence [3] there are finally at least ***two possible conformational eigenstates*** (see *Fig. 1*): K_i related to biomolecular *deexcitation back into* ***initial*** *many-electronic state i*, or K_f related to biomolecular *deexcitation into* ***final*** *many-electronic state f.*

And such fluctuations between eigenstates of energy & conformation of biomolecules are repeating:

$$\left|\Phi_i\right\rangle_{QS}^{E}\left|\Psi_i\right\rangle_{QE}^{E} = \sum_j c_j \left|\Phi_j\right\rangle_{QS}^{K}\left|\Psi_j\right\rangle_{QE}^{K} \xrightarrow{QD} \left|\Phi_k\right\rangle_{QS}^{K}\left|\Psi_k\right\rangle_{QE}^{K} \quad [\rightarrow \rho_{\Phi\Psi}^{K}] \xrightarrow{+\Delta E_{exc}}$$

$$= \sum_l c_l' \left|\Phi_l\right\rangle_{QS}^{E}\left|\Psi_l\right\rangle_{QE}^{E} \xrightarrow{-\Delta E_{deec} / QD} \left|\Phi_f\right\rangle_{QS}^{E}\left|\Psi_f\right\rangle_{QE}^{E} \quad [\rightarrow \rho_{\Phi\Psi}^{E}] = \ldots \qquad (1)$$

and ***might be observed*** by applying methods of ***experimental macro-molecular biophysics*** [43] – thus becoming a ***paradigm of macroscopic quantum phenomena of the 2nd kind***.

[2] In general, the stipulated ***decoherence-preferred degrees of freedom*** (biomolecular ***conformations*** in our case) are considered to be *accessible* (directly measurable) and therefore ***objective for an environmental observer*** (which is thus a part of the structure he observes). Are there some *general rules and/or limitations for all* ***possible bi-partitions*** $QS_k + QE_k$ in the Universe, *is not generally answered in QD theory*, *and still needs* ***additional fenomenological assumptions*** [13].

So, ***in the manner of quantum chemistry*** [29,30] it might be ***plausibly proposed*** that many-atomic quantum systems QS_k are fenomenologically limited to ***structures with dynamically coupled (identical) fermions***, *described by permutationally-antisymmetric many-electronic eigenstates*, *which encompasses all existing* ***molecules & electronic condensed state objects*** *described by general quantum-chemical electronic self-Hamiltonian*; in case of ***structures with dynamically coupled (identical) bosons***, they are described by *permutationally-symmetric many-bosonic eigenstates* and corresponding self-Hamiltonian).

[3] In general, only ***closed composite system QS + QE*** is subject to the *Schrödinger law* (although this *does not hold true separately* for neither ***QS*** nor ***QE***, as ***open quantum systems***), with Hamiltonian $\hat{H} = \hat{H}_{QS} + \hat{H}_{QE} + \hat{H}_{\text{int}}$ where *interaction Hamiltonian* $\hat{H}_{\text{int}}$ depends on observables of both *QS* and *QE*. However, when $\hat{H}_{\text{int}}$ can be *reduced to the "external field",* its ***potential term*** $\hat{V}$ can be added to $\hat{H}_{QS}$ providing *new self-Hamiltonian* of the *QS,* dynamically decoupled from the observables of the *QE*, and then ***QS*** can be treated as the ***closed quantum system***.

This is the case in ***most situations in quantum chemistry***, with ***Schrödinger equation applied*** ***to the explored closed many-atomic quantum system*** with appropriate boundary conditions and adopted computational approximations (giving rise to ***stationary*** ground and excited electronic-vibrational energy ***eigenstates*** of all possible many-atomic ***isomers***, corresponding to *minimuma* of the electronic potential hypersurface, depicted in ***Figure 1*** for ground electronic and corresponding excited vibrational energy eigenstates) [29,30].

It should be noted that ***Schrödinger equation cannot apply*** ***to nonstationary excitations & relaxations of the many-atomic quantum system***, *not only in-between different isomers but also within the same isomer* – when ***quantum deexcitation / decoherence must apply*** ***to non-potential interaction of the open many-atomic quantum system*** (*non-decribable fully by its self-Hamiltonian*) *with its* ***quantum environment*** (*generally field-related, including vacuum*) [12,13].

So, ***in an open environmental solution*** ***biomolecular chain folding*** might be considered as *a* ***subtle interplay between energy & conformation eigenestates of a biomolecule*** *(governed by local quantum-chemical and quantum-decoherence laws)*, and in this scenario the ***Levinthal's paradox disappears*** (cf. ***Appendix*** for some aspects of *quantum decoherence scenario* of conformational transitions, and ***Footnote 5*** therein for revealing *(semi)classical meaning* of the harmonic-like vibrating conformations).

On the other hand, ***within an open biological cell***, a ***system of N_k non-interacting & dynamically non-coupled identical proteins in their primary chemical structure*** (and *their biomolecular targets*) might be considered as corresponding ***global spatial quantum ensemble of N_k identical processors***, ***providing spatially distributed quantum solution to corresponding*** ***single local chain-folding*** (and *key-lock recognition process*) – whose ***time-adapting density of conformational states*** $\widehat{\rho}_{S_k}^{k}(t)$ *might be represented as* ***global cell's Hopfield-like quantum-holographic associative neural network***, as well [41,42] (cf. ***Figure 2***).

We hereby silently assumed ***ergodic hypothesis***, i.e. ***near thermodynamic equlibrium*** of the N_k proteins in their ***decoherence-selected (stationary) conformations*** (which is *not fulfilled in (nonstationary) conformational transitions*, induced by *strong environmental interactions* (cf. ***Appendix*** for more details) which might occur *far from thermodynamic equilibrium* (as is the case in *metabolic processes* in biological cells [43]).

Or to generalize, a series of all *k* intra-cellular and extra-cellular environmentally-driven (compositionally / chemically or thermally / optically) ***local biochemically coupled reactions*** might be ***equivalently considered*** as a series of all *k* corresponding intra-cellular and extra-cellular ***global Hopfield-like quantum-holographically coupled associative neural network layers*** – providing an ***equivalent global quantum-informational alternative*** *to standard molecular-biology local biochemical approach in* ***biomolecules & cells*** (***& higher hierarchical levels of organism***, as well).[4]

[4] The similar Hopfield-like quantum-holographic picture might also be applied to individual ***acupuncture system*** [41,42] (with *quantum-like macroscopic resonances*, fenomenologically observed in *microwave resonance therapy* [44,45], which implies corresponding bi-partition QS_{acu} + QE_{acu} i.e. that ***acupuncture system has macroscopic open quantum structure*** *with dynamically coupled electrons all-along macroscopic network of acupuncture channels* [41,42,44]). This then provides natural ***quantum-informational framework for psychosomatic medicine*** i.e. ***quantum-holographic downward coupling*** *of the higher macroscopic quantum levels of* ***acupuncture system & its projection zones*** (and presumably closely related *consciousness* [10,41,42]) *with lower macroscopic quantum* ***cell's biomolecular level***, so ***changing the expression of genes*** (starting from the first fertilized cell division which initializes differentiation of the acupuncture system of non-threshold electrical GJ-synapses ("gap-junctions")) [41,42,46].

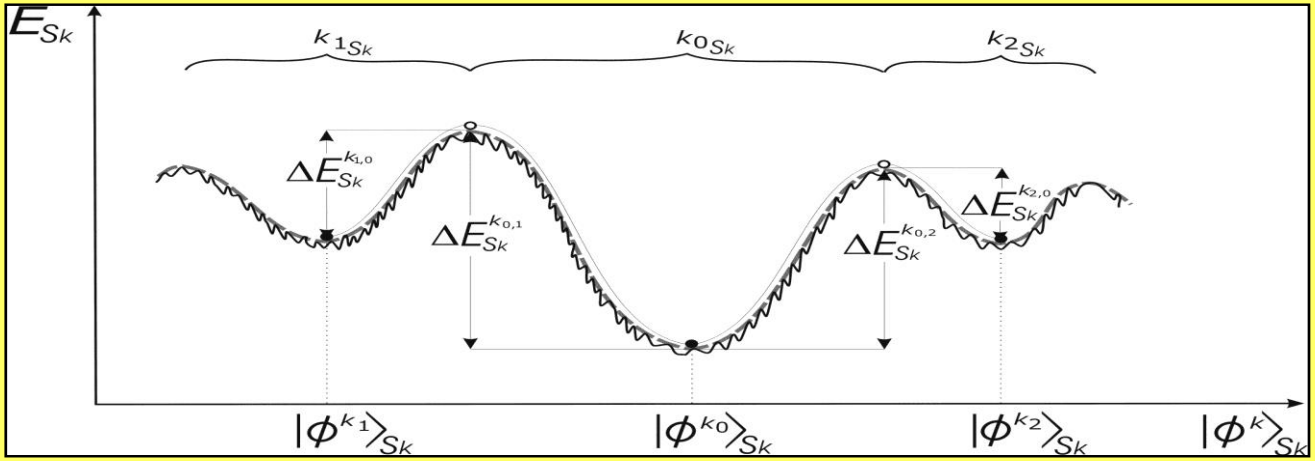

Figure 2. *Schematic presentation of the memory attractors in the (many-electronic) energy-state* $E_{S_k}(\phi^k)$ *hypersurface of the Hopfield-like quantum-holographic memory/propagator of the open macroscopic quantum (sub)system* S_k*, of cell'sparticular spatial quantum ensemble of (non-interacting and dynamically non-coupled)* N_k *chemically identical proteins of k-th type (and their corresponding biomolecular targets)* [41,42], *in Feynman's representation* [47]: $G(r_2,t_2;r_1,t_1)=\sum_i \phi^{k_i}(r_2,t_2)\phi^{k_i}{}^*(r_1,t_1)$ $=\sum_i A_{k_i}(r_2,t_2)A_{k_i}{}^*(r_1,t_1)e^{\frac{i}{\hbar}(\alpha_{k_i}(r_2,t_2)-\alpha_{k_i}(r_1,t_1))}$. *It should be pointed out that quantum decoherence presumably plays fundamental role in biological quantum-holographic neural networks, via energy-state hypersurface shape adaptation (in contrast to low-temperature artificial qubit quantum processors where it must be avoided until the very read-out act of quantum computation) – which implies that Nature presumably has chosen elegant room-temperature solution for biological quantum-holographic information processing, permanently fluctuating between eigenstates of energy and conformation of the proteins of k-th type (identical in their chemical structure) due to nonstationary environmental perturbations and subsequent decoherence by the environment,* described by *time-adapting density of conformational states (represented by corresponding depths of the minima in the figure above):* $\hat{\rho}_{S_k}^k(t))=\sum_i w_{k_i}(t)\left|\phi^{k_i}\right\rangle_{S_k}\left\langle\phi^{k_i}\right|$, $\sum_i w_{k_i}(t)=1$, *of cell's biomolecular open macroscopic quantum (sub)system* S_k.

3. DISCUSSION & CONCLUSION

Biomolecules in a living biological cell are subjected to ***non-equilibrium*** processes of huge complexity. Elaborate quantum mechanical descriptions of such processes are only a ***matter of recent considerations*** [48-50].

In this regard, the physical methods are a matter of intense current research [51,52]. A fully developed, quantitatively elaborate quantum mechanical background for such biological processes is a *remote goal yet*.

In the context of ***macroscopic quantum phenomena of the 2nd kind*** we proposed ***quantum-chemical & quantum decoherence approaches to biomolecular conformational transitions*** (*which cannot be considered kinetically understood based on (semi)classical predictions*).

Our qualitative proposal has a ***solid quantum mechanical basis of wide applicability*** (*there are not any particular assumptions on the chemical kind, structure or the initial state of the molecule, or any assumptions on the chemical kind or on the initial state of the molecule's environment*).

It seems that our ***matter-of-principle solution*** to the long standing ***Levinthal paradox*** offers a natural physical picture of a number of the important processes with ***biomolecules***, including ***chain folding & biomolecular recognition***. Actually, ***quantum decoherence*** is assumed to provide ***(quasi)classical behavior*** of the molecules conformation degrees of freedom, which can be further (semi)classically described (like in the recent (also) qualitative proposal of Dill & Chan [23]) to provide more details of the *molecule's conformation dynamics* in molecular biology & biochemistry.

On the level of an ***open biological cell***, our quantum-decoherence approach enables that a ***system of identical non-interacting & dynamically non-coupled proteins of particular type*** (*and their biomolecular targets*) might be considered as ***corresponding global spatial quantum ensemble of identical processors***, whose ***time-adapting density of conformational states*** *might be represented as* ***cell's Hopfield-like quantum-holographic associative neural network*** – and to generalize, ***a series of all types of intra-cellular & extra-cellular environmentally-driven local biochemically coupled reactions*** *might be* ***equivalently*** *considered as* ***corresponding global Hopfield-like quantum-holographic coupled associative neural network layers*** (*with extension to higher hierarchical levels of the organism as well*, providing possible missing *downward causation control mechanism of morphogenesis & psychosomatics* [41,42,44-46]).

4. APPENDIX. ON GENERAL QUANTUM DECOHERENCE FRAMEWORK FOR MACROMOLECULAR CONFORMATIONS AND TRANSITIONS

We assume that the molecule's environment selects the molecule conformation as the "pointer observable". Following the general phenomenological results and understanding, we assume that decoherence takes place for virtually all kinds of macromolecules & the solvent environment ***while*** the composite system "molecule + environment" is not externally disturbed. This we call **"*stationary state*"**, for which we stipulate occurrence of ***decoherence***, i.e. *the environment-induced classicality of the molecule conformation*.

Typically, the ***conformation transitions*** occur due to a *severe external influence* exerted on the molecular degrees of freedom and / or to the molecule environment. In effect, this ***external influence redefines*** the *molecule environment*, and thereby also the influence exerted by the new environment to the *molecule degrees of freedom*. Such physical situations, which may take some time, we describe as **"*nonstationary state*"**. For the nonstationary state, no particular assumption is made. Rather, one may expect that the change in physical characteristics and state of the environment would typically violate the conditions assumed for the occurrence of decoherence.

In formal terms, the ***stationary state*** is defined by the *conformation-system „mixed“ state*,

$$\rho_K = \sum_i w_i \left| i \right\rangle_K \left\langle i \right|; \ \sum_i w_i = 1. \qquad (2)$$

where the states $\left| i \right\rangle_K$ represent the different conformational states. These (approximately orthogonal) states represent the preferred, (semi)classical ***“pointer basis” states*** for the molecule conformation system.[5] Therefore we stipulate the occurrence of decoherence as the fundamental quantum mechanical basis for the phenomenologically observed (semi)classical behavior of the large molecules conformation stability.

On the other hand, as emphasized above, the ***conformational transitions*** occur due to a severe external influence. The related non-stationary state is defined by *non-validity of Eq. (2)* for the duration of the external influence. Intuitively, one may say: the external influence redefines the physical situation, which is the molecule exerted to. In effect, the stationary state is disturbed and there is not any semi-classical conformation state for the molecule. Formally, the conformation system is in a state ρ_K', which cannot be presented by Eq. (2).

Of course, every external influence ***terminates*** *& leaves the (redefined) system "molecule + environment" to* ***relax***, i.e. to reach another stationary state with the final conformation state $\rho_K^{"}$, which is representable in the form of Eq. (3). The point strongly to be emphasized: it is highly non-expectable that $\rho_K = \rho_K^{"}$. That is, the final set of conformations need not be the same as the initial one, while for the conformations (i.e. the states $|i\rangle_K$) common for ρ_K and $\rho_K^{"}$, their statistical wights need not equal to each other, $w_i \neq w_m^{"}$. In effect, the following transition of the conformation state occurred:

$$\rho_K = \sum_i w_i |i\rangle_K \langle i| \xrightarrow{non\text{–}stationary} \rho_K^{'} \xrightarrow{stationary} \rho_K^{"} = \sum_m w_m^{"} |m\rangle_K \langle m|; \quad \sum_i p_i = 1 = \sum_m p_m^{"} \tag{3}$$

Duration of the whole dynamics presented by Eq. (3) is of the order of the time needed for the non-statinary state to terminate (note that decoherence, present for both stationary states, the most left hand and the most right hand sides of Eq. (3), is among the fastest physical processes known to date). So, in this scenario, the ***Levinthal's paradox disappears***. Furthermore, as the concept of "trajectory" (in configuration space) is not well-defined quantum mechanically, the very basis of the Levinthal's paradox (i.e. sampling of trajectiories in the configuration space) is absent in this quantum mechanical picture. This general scenario has been analysed [49,50] and a few possible scenarious of the external influence (i.e. of the non-stationary state) have been distinguished (see ***Figure 3*** for a possible one).

[5] ***Normalized "pointer basis" states*** for macromolecule conformation system of Eq. (2) are shown to be almost-classical one-dimensional harmonic oscillation ***"coherent states"*** $\left|\psi_{q_i(t)p_i(t)}\right\rangle$ [40]. Then Eq. (2) physically means that each macromolecule in a solution oscillates with probability w_i along classical harmonic trajectories $(q_i(t), p_i(t))$, where the time change of $q_i(t)$ and $p_i(t)$ is the ***classical law*** for the harmonic oscillator position and momentum:

$$q_i(t) = q_{0i}\cos\omega_i t + \left(p_{0i}/m\omega_i\right)\sin\omega_i t$$
$$p_i(t) = p_{0i}\cos\omega_i t - m\omega_i q_{0i}\sin\omega_i t \qquad (4)$$

in the vicinity of k_i-th local minimum (which can be *locally approximated* by harmonic potential, cf. Fig. 3), i.e. in the vicinity of k_i-th conformation.

Bearing in mind that "coherent states" *do not change their gaussian shape* in the course of time [53-55] $(\Delta\hat{K}_i = const,\ \Delta\hat{P}_i = const,\ \Delta\hat{K}_i\Delta\hat{P}_i = \hbar/2)$ Eq. (4) has (semi)classical meaning: ***defining conformations as harmonic-oscillation equilibrium positions*** (cf. local minimums k_i in Fig. 3) one obtains ***(semi)classical vibration of macromolecule conformation in the vicinity of local minimum k_i.***

This might enable ***coexistence of (quantum) stationary ground eigenstates of energy & (semiclassical) harmonic-like vibrating macromolecule conformations***, thus ***somewhat relaxing (quantum) severe restrictions of non-commuting observables***, $\left[\hat{H},\hat{K}\right] \neq 0$.

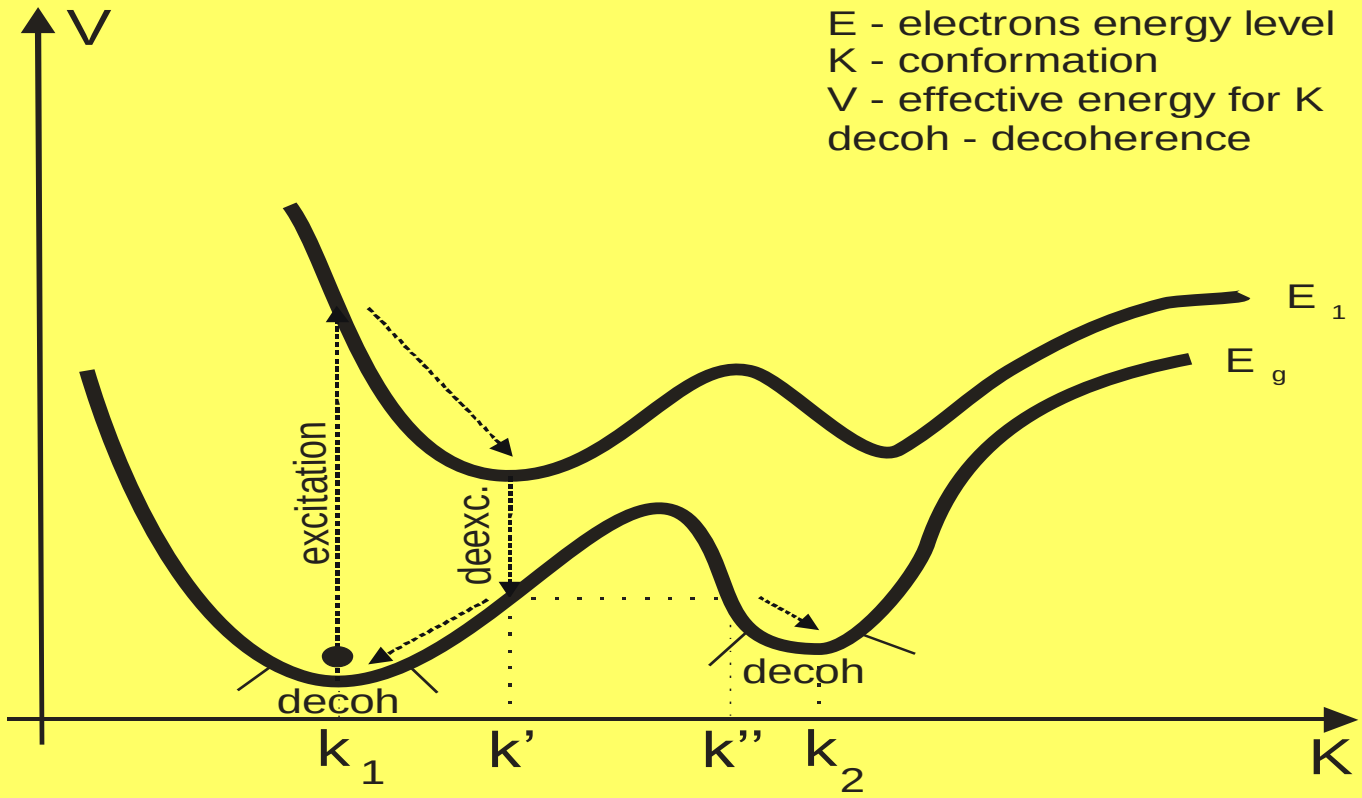

Figure 3. *The black dot represents one-dimensional "particle" (molecular electronic-conformational-vibrational system) which is excited to the upper hypersurface (electronic excited state E_1), and according to Ehrenfest theorem is descended down the slope towards the local excited state minimum, conformation k'. Then, the "particle" is deexcited to the lower hypersurface (electronic ground state E_g), when according to Ehrenfest theorem a superposition of the two possible "particle" states depicted by k' and k" is established, with subsequent coherent descent of the "particle" down both slopes of the barrier (which can be thought of as the interference of the two paths along the barrier walls), and final decoherence into local ground state minima k_1 and k_2 (with assumption that environmental influence dominates the dynamics in the vicinity of the local minima, corresponding to the acquired conformations k_1 and k_2 – with their statistical weights being changed, as a net effect). For more details see ref.* [50].

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