Materials Science Forum Vol. 494 (2005) pp 513-518
online at http://www.scientific.net

Online available since 2005/Sep/15

Biopolymer Chain Folding and Biomolecular Recognition: A Quantum Decoherence Theory Approach

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Keywords: Biomolecular Recognition Processes, Biopolymer Kinetics, Chain Folding Problem, Conformational Stability, Conformational Transitions, Quantum Decoherence.

Abstract. In this paper we describe the biopolymer chain folding problem in the framework of the so-called quantum decoherence theory. As we propose a rather qualitative scenario yet bearing generality, it seems this provides promising basis for the solution-in-principle of the (semi) classically hard kinetic problem of biopolymer chain folding from coiled to native conformation in highly selective ligand-proteins/target-receptors biomolecular recognition processes, implying underlying macroscopic quantum nonlocality on the level of biological cell.

Introduction

Conformation is one of the most important features of polymer chains, and due to properties dependent on conformation, very important in consideration of polymer materials, as well [1]. The calculation methods of conformational dependent chain properties [2] describe conformational states of the polymer based on possible rotational states of chain bonds; but they do not describe transitions between possible states of the polymer, i.e. transitions from one conformation to another. The first is thermodynamic (stationary) and the second is kinetic (nonstationary) aspect of the problem.

The conformation change of long flexible chain, by random rotations around chain bonds due to thermal vibrations under the influence of the environment, has been considered understandable by itself, but leads to the so-called Levinthal-paradox [3] (semi)classically predicting unreasonably long time to explore all chain conformations (immensely more than the apparent age of the Universe), while some experiments clearly demonstrate that proteins can fold to their native conformation in less than a few seconds [4] - this being one of the most crucial questions in all life sciences. It has been subsequently proposed that conformational changes of proteins, due to solvent, thermal, optical, and other influences of the environment, does 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 [5]. On this line, it has been subsequently shown that a protein can be trained to recognize several conformations (with upper limit dependent on the size of the 20-letter amino acid alphabet as $\ln 20 < 5$, independent of protein length) analogous to an associative memory [6] - admitting the possibility of certain proteins, such as prions, evolving to fold into independent stable conformations [7], as well as novel possibilities for protein and heteropolymer design.

The problem of ordered set of pathways some authors translate to the problem of estimations of some long range-interactions responsible in a given moment for the direction of the process [8], while we recently proposed a *quantum decoherence model* [9] as a promising basis to reproduce both existence and stability of the (stationary) polymer conformations $\{k_j\}$ *and* the short time scales for the quantum-mechanical processes resulting effectively in (nonstationary) conformational transitions $k_i \to k_f$ from initial to final state (with corresponding conservation laws and selection

rules fulfilled). It should be pointed out, that the proposed quantum-decoherence model (with the related quantum-holographic Hopfield-like polymer (many-electron) energy-state plot, $E_e(\phi_k)$, in Feynman's representation [10]) implies characteristic times and frequencies only slightly dependent on dimensions of the polymer, as well as a *fuzzy borderline* between quantum coherent (nonstationary) and semi-classical decoherent (stationary) manifestations of any macroscopic condensed-state system (see for instance [11]). On the contrary, *(semi)classical* kinetic (nonstationary) predictions imply a continuous map/conformation change $k_i \rightarrow k_f$ which *requires* a sequence of n local *non-commuting* successive 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 ($\tau_n \sim n\tau_o \gg \tau_o$) and the frequency of corresponding global transition much lower than the frequency of a local rotation ($f_n \sim 1/n\tau_o \sim f_o/n \ll f_o$) - strongly dependent on a degree of polymerization n (in clear *contradistinction* with the experimentally *observed* poorly dimensionally-sensitive dispersion laws of the internal more or less delocalized quasiparticle excitations in any condensed-state quantum system: electrons, optical phonons, conformones, etc. [12,13]).

Additionally, the rules governing biological processes in any living organism, based on selective interactions between particular biomolecules i.e. their ability to selectively interact with each other - are also not completely understood. It still remains the question of the very physical nature of the long-range directivness of the biomolecular recognition process - to which a quantum decoherence model might also be applied to reproduce both existence and stability of the (stationary) biomolecular protein/targets matching conformations *and* the short time scales for the quantum-mechanical processes resulting effectively in (nonstationary) particular conformational protein/target biomolecular recognition transition.

In this paper, we shall initially review our general quantum-decoherence model for the existence and stability of polymer conformations *and* conformational transitions [9], and then provide its application on the conformational protein/target biomolecular recognition matching processes, thus revealing their underlying *macroscopic quantum* nonlocality on the level of biological *cell*.

Quantum-Decoherence Model of Conformational Transitions and Biomolecular Recognition Processes

Due to the Born-Openheimer adiabatic approximation, the molecules can be ascribed to the *definite geometrical structure* [14]. *Geometrically*, the shape of a molecule can be continuously changed in 3D space, but *only* a restricted set of possible geometrical shapes are found experimentally, preserving *spatial distances and angles* between the adjacent vertices in the geometrical shape of a molecule, referred to as *conformations*. Every conformation is determined by the relative position in space of the vortices, thus representing a *physical characteristic*, K, of a molecule *as a whole*. Therefore, as to the conformation of a molecule, one actually deals with the *one-dimensional system*, i.e. different conformations $\{k_j\}$ of the variable K can be ascribed to different values of the molecular electronic energy, as presented by local minima of the (many-electron) potential energy vs. conformation plot, $V_e(K)$ ($\approx E_e(\phi_k)$), for the adiabatically decoupled (vibrational and) one-dimensional conformational system K. In a *"stationary state"* when no external action on the polymer solution is performed, the local minima are the (semi)classically stable *conformations* in the K-space due to, among other things, high energy barrier between the adjacent local minima; physically, this means that a macromolecule does not have enough energy to skip over the barrier in order to change its geometrical shape. However, some *"nonstationary"* external actions on the solution (e.g. compositional/chemical, thermal, optical etc.) result in a change of macromolecular conformation $k_i \rightarrow k_f$ (the indices i and f standing for *initial* and *final* conformations, respectively). These transformations can take different time intervals to effect themselves, which can be estimated from the experimental data: first, there are the *spectroscopic* data suggesting (dimensionally-non-

sensitive and locally non-commutive) conformational changes in macromolecules of the orders of 10^{-12}-10^{-9} s [12,14], and second, the duration of *protein renaturing* experiments in this regard is of the order of 1 s [4]. Needless to say, the order of magnitude of the time interval (10^{-12} s, 10^{0} s) is in *sharp contradistinction* with the existing *(semi)classical* predictions.

And this is the very heart of the problem of *polymer conformation transitions* (PCT). Our *quantum-decoherence model* of PCT bears *complete generality* [9]: we neither refer to the specific polymers (or solutions), or to the specific conformations.

Fulfilling the conditions of *existence and of stability of conformations* is our first objective [9]: fortunately, a straightforward application of the so-called decoherence theory [15] suffices in this respect. The general physical situation may be presented as follows. A quantum system *S* is in unavoidable interaction with its environment *E*. The composite system *S*+*E* is subject to the Schrodinger law, but neither *S* nor *E* is subject to the Schrodinger law, such systems being referred to as *open quantum systems*. The task is to calculate (open) system's (*S*'s) state - the so-called "reduced statistical operator", denoted by $\hat{\rho}_S$ - after integrating over the environmental degrees of freedom. Under the set of special conditions [16], in the representation of a special "pointer basis" of the (Hilbert) state space of *S* (fulfilling requirement of *robustness*, $\hat{H}_{\text{int}}|i\rangle_S|\varphi\rangle_E = |i\rangle_S|\varphi_i\rangle_E$), one obtains *disappearance of the off-diagonal elements* of $\hat{\rho}_S$, which is referred to as the *occurrence of the decoherence effect.* Effectively, there appear the *environment-induced superselection rules (decoherence)*, which *forbid the coherent superpositions of certain states of the system S*: in other words, decoherence *establishes existence and robustness* of a preferred set of states - e.g. of the "pointer basis" - of an open system. If the initial state of *S* is a coherent superposition, $|\psi\rangle = \sum_i c_i |i\rangle_S$, then the decoherence process can be presented as: $|\psi\rangle = \sum_i c_i |i\rangle_S \xrightarrow{\tau_D} \hat{\rho}_S = \sum_i |c_i|^2 |i\rangle_{S\ S}\langle i|$, where τ_D, the *decoherence time*, is the order of magnitude of the unfolding decoherence process; the above process exhibits the loss of initial coherence - which justifies the term *de*coherence [15]. Now, as to our task, it suffices properly to model the interaction Hamiltonian, $\hat{H}_{\text{int}}$, in order to deduce decoherence process for the composite system "conformation + environment" (*S*+*E*) - and virtually independently on the model of the system *E*, the following simplest separable interaction Hamiltonian fulfills our requirements (being necessary condition for the decoherence effect) [16]: $\hat{H}_{\text{int}} = C\hat{K}_K \otimes \hat{D}_E$, where *C* stands for the coupling constant (determining the strength of interaction), $\hat{K}_K = \sum_i k_i |k_i\rangle_{K\ K}\langle k_i|$ is the conformation observable of the quantum system *S*, and $\hat{D}_E$ is arbitrary observable of the environment *E*. So, by applying the fundamentals of the quantum decoherence theory, we were able to reproduce the *existence and stability of conformations* - the basics of the (semi)classical model for the macromolecule conformations in *stationary situation* - when no external action on the system was performed!

However, our problem refers to *nonstationary situations* when the external action on the system results in the *change of the conformations*, which is the subject of our *quantum-decoherence model* of PCT [9] - *sufficiently general* to account for the effect of change of conformation in *short time intervals*, in obvious contradistinction with the results of the (semi)classical physics analysis - this generality allowing applicability of the model for different yet *realistic* physical situations. A special characteristic of the decoherence process is its tendency to freeze dynamics of an open system, once the system is in a preferred state; therefore, our task here reads: to model the external influence on the system *S*+*E* so as to both first to break and later to re-establish the effect of the decoherence due to the interaction $\hat{H}_{\text{int}}$. Hence, we introduce the following, *physically and phenomenologically plausible* assumptions: (i) the external influence is much stronger than the

interaction $\hat{H}_{\text{int}}$, and (ii) after the external action, the composite system relaxes to equilibrium (a stationary state) determined by the model interaction $\hat{H}_{\text{int}}$. Then, *before the external action*, *S*'s stationary state reads: $\hat{\rho}_K = \sum_i |c_i|^2 |k_i\rangle_{K\ K} \langle k_i|$; *subsequent strong external action* on the *S+E* system of the duration T_{ext} (providing, for instance, the external energy $\Delta E'$ to skip over a barrier in order to change its conformations from k_i to k_f, in two-conformational example) gives rise to the following nonstationary state transformation for the system *S*: $\hat{\rho}_K \rightarrow \hat{\rho}_K'$, such that *in general* $[\hat{\rho}_K, \hat{\rho}_K'] \neq 0$; *after the external action*, the composite system *S+E'* is subject to the nonstationary *relaxation process* of the duration T_{rel} (taking-off, for instance, the excess external energy $\Delta E''$ to fulfill the energy conservation law in two-conformational transition $k_i \rightarrow k_f$), which in general gives rise to another state change of *S*: $\hat{\rho}_K' \rightarrow \hat{\rho}_K''$; the completed relaxation process *re-establishes* the stationary state defined by the interaction $\hat{H}_{\text{int}}$, which - *and this is the point strongly to be emphasized* - guarantees the existence and stability of conformations; that is, the final state of the system *S* reads: $\hat{\rho}_K''' = \sum_i w_i |k_i\rangle_{K\ K} \langle k_i|$, which can be easily proved [16] - where transition $\hat{\rho}_K'' \rightarrow \hat{\rho}_K'''$ refers to decoherence effect of duration τ_D. Now, the point is in the difference of the initial $\hat{\rho}_K$ and the final $\hat{\rho}_K'''$: both states refer to the conformations $|k_i\rangle_K$ guaranteeing their existence and stability, *but* the relative number (concentration) of different conformations - i.e. "statistical weights", w_i - are likely to be different, $w_i \neq |c_i|^2$; *in effect*, there has occurred a *change of conformation*, at least for a sample of molecules in a solution - *which is exactly the effect we search for*! The total duration of the *nonstationary effect* reads: $T = T_{ext} + T_{rel} + \tau_D$, but since it is expectable $T_{ext} + T_{rel} >> \tau_D$ [15], the *duration of the conformation change in our model is of the order of* $T \approx T_{ext} + T_{rel}$ - in obvious contradistinction with the estimates based on the (semi)classical analysis.

Finally, we shall apply our quantum-decoherence interpretation of biomolecular transitions on biomolecular recognition processes - as the rules governing biological processes in any living organism, based on selective interactions between particular biomolecules i.e. their ability to selectively interact with each other, are not completely understood to date. It still remains the question of the very physical nature of the *long-range directivness of biomolecular recognition processes* - to which our quantum decoherence model might be also applied. Concretely, in the context of necessary conditions for decoherence process, it should be pointed out that defining of open quantum system and its (complementary) environment is a simultaneous process - providing also conditions for the decoherence process in the context of existence of *relative borderline* [17]: $|\text{open quantum system}\rangle_S$ $|\text{(complementary) environment}\rangle_E$. So, we can redefine open quantum system *S* to include not only biomolecular ligand-proteins but also their biomolecular target-receptors, and their new (complementary) cytoplasmatic environment *E* - which can then reproduce both *existence and stability* of the (stationary) biomolecular protein-and-target matching and non-matching conformations (described by corresponding minima of the re-defined quantum-holographic Hopfield-like (many-electron) energy-state plot, $E_e(\phi_k)$, of the open quantum system ligand-proteins/target-receptors in Feynman's representation [10]), *and* the short time scales for the quantum-mechanical processes resulting effectively in (nonstationary) enhanced particular conformational protein/target matching *biomolecular recognition transitions* under an external influence (compositional/chemical, thermal, optical, ...) on the cell's cytoplasmatic environment. All this implies underlying *macroscopic quantum nonlocality* on the level of biological *cell*, which will be discussed further in the following section.

Discussion

Two unresolved issues of the (semi)classically addressed problems in molecular biophysics are unreasonably long, time necessary for change of biopolymer conformations *and* long-range directivness of selective biomolecular recognition processes. In this paper, by employing the fundamentals of the quantum decoherence theory, we were able to reproduce both, *existence and stability* of the (stationary) polymers conformations, *and* the short time scales for the quantum-mechanical processes resulting effectively in (nonstationary) *conformational transitions* in selective ligand-proteins/target-receptors *biomolecular recognition processes* under an external (e.g. compositional) influence on the cell's complementary cytoplasmatic environment.

This obviously implies underlying *macroscopic quantum* nonlocality on the level of biological *cell* - which might be additionally supported by high effectiveness of the Resonance Recognition Model (RRM) [18] - based on findings that there is significant correlation between spectra of the numerical presentation of constitutive elements of primary sequences (amino acids, nucleotides) and their biological activity or interaction in corresponding biomolecules (proteins, DNAs). The RRM model interprets this linear information by assigning the electron-ion interaction potential (EIIP) value to each constitutive element of primary sequence thus describing their average energy states of valence electrons [19], with subsequent using of signal analysis methods in FFT transforming this numerical series into single-electron wavenumber/RRM frequency domain and determining the common frequency components as peak frequencies in the multiple cross-spectral function for a group of primary sequences [18]. The presence of peak with significant signal-to-noise ratio in a multiple cross-spectral function of a group of sequences with the same biological function means that all of the analyzed sequences within the group have this single-electron RRM frequency component in common, with the following general conclusions: (i) such a peak exists only for the group of biomolecules with the same function; (ii) no significant peak exists for biologically unrelated biomolecules; (iii) peak frequencies are different for different biological functions; (iv) ligand-proteins and their biomolecular target-receptors have the same characteristic frequency in common but almost opposite phase - providing also promising novel theoretical possibilities for protein *de novo* design with desired functions [18]. The same characteristic single-electron RRM frequency, and almost opposite phase, presumably characterizes not only biomolecular protein and target general function, but also their *macroscopic quantum biomolecular recognition/interaction* on the level of biological *cell* - possibly by externally *activated* (compositionally/chemically, thermally, optically, ...) protein/target (high-energy) RRM quantum-resonantly electron-electron coupling *accompanied* by k_i-annihilation and k_f-creation conformones' quanta in (low-energy) two-conformational transitions $k_i \rightarrow k_f$ (giving rise to (energy-favorable) protein/target many-electron energy-deepening of the final state ϕ_{kf} and protein/target many-electron energy-shallowing of the initial state ϕ_{ki} on the macroscopic quantum level of cell, i.e. to *dynamic modification of the many-electron hypersurface* $E_e(\phi_k)$ *of the cell's protein-target biomolecular macroscopic quantum system*, in full analogy with the situation of learning in Hopfield associative neural networks [10] as already revealed in associative-memory-like protein-conformation-recognition [6]).

Surprisingly, this underlying nonlocallity seems to be even extended on the *macroscopic quantum level* of biological *organism*, as supported by macroscopic quantum-like microwave resonance therapy of the acupuncture system [20,21], presumably based on long-range coherent microwave Frohlich excitations of strongly polarized molecular subunits in the cell membranes and cytoplasmatic proteins [22] - which might be of fundamental importance in understanding underlying macroscopic quantum (quantum-holographic Hopfield-like [10]) control mechanisms of morphogenesis and ontogenesis and their backward influence on the expression of genes, as well as macroscopic (quantum)holistic very nature of psychosomatic health and diseases [23] (implying also a *fuzzy borderline* between quantum coherent (nonstationary) and semi-classical decoherent

(stationary) manifestations of the acupuncture (as well as any other) macroscopic quantum condensed-state system).

Conclusion

Employing the fundamentals of the decoherence theory, we are able to reproduce both, *existence and stability* of the polymers conformations, *and* the short time scales for the quantum-mechanical processes resulting effectively in *conformational transitions* in selective ligand-proteins/target-receptors *biomolecular recognition processes*. This implies underlying *macroscopic quantum* nonlocality on the level of biological *cell* (additionally supported by high effectiveness of the Resonance Recognition Model), which seems to be even extended to the *macroscopic quantum* level of biological *organism* (as supported by macroscopic quantum-like microwave resonance therapy of the acupuncture system).

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Current Research in Advanced Materials and Processes
doi:10.4028/www.scientific.net/MSF.494

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doi:10.4028/www.scientific.net/MSF.494.513