Biophysical Reviews
https://doi.org/10.1007/s12551-023-01150-w

ABSTRACT

The 7th Congress of Biophysicists of Russia - conference proceedings

Abstracts

S1. Molecular biophysics. Structure and dynamics of biopolymers and biomacromolecular systems

S1.1. Molecular dynamics of α-helical poly-l-glutamic acid in water solution

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α-Helix is a basic element of secondary structure from which the globular proteins are built. Since true native protein exists in water solution the structural behavior of protein is determined essentially by their dynamic properties. However, the problem is rather complicated because a majority of protein structures has been obtained in the crystal state. Here we have studied the dynamic properties of poly-L-glutamic acid model in a helical conformation in water solution. It includes 16 Glu residues placed in 4.5 turns of right-handed α-helix structure built with the data of Pauling & Corey (1951). In acidic water solution at pH about 3.5 poly-L-glutamic acid undergoes the helical conformation. Thus, our model has non-ionized side carbonyl Glu groups, as COOH, and ionized terminal groups, as NH3+ and COO-. An analysis of all the atomic groups makes no special sense. So, we have concentrated solely on dynamic study of peptide skeleton from Cα-atoms. Computational system included helical fragment, water solution molecules, and ions of sodium and chlorine. There were introduced 11 Na and 9 Cl ions which supply zero total charge of the sysytem. Numerical simulations were performed on the hybrid supercomputing system K-60 at the Keldysh Institute of Applied Mathematics, Russian Academy of Sciences. The initial part of trajectories, from 0 to 500 psec, corresponds to the refinement and relaxation of the model. A dynamic trajectory of α-helical poly-L-glutamic acid has been calculated from 0.0 to 25.0 nsec. We have inspected fluctuations of the Cα-chain at each integer numbers of time, in nanoseconds. That has been done by calculating the absolute shift values of Cα-atom positions at the next 1.0 nanosec intervals. The model has displayed several fluctuation modes along the dynamic trajectory. The most interesting modes show the distinctive shifts of Cα-atoms. These modes include two adjacent in the turns clusters of Cα-atoms which are placed approximately at one side of the helix. The observed modes are intrinsically dynamic feature of a single fragment of α-helix structure. And they suggest playing a key role in dynamics of protein molecules.

S1.2. Multiscale modelling of DNA repair by photoenzymes

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Photolyase photoenzymes, binding to damaged DNA sites, repair the main DNA photoproducts formed under the action of UV radiation. The functioning of photolyases is based on the reaction of photoinduced intermolecular electron transfer. Especially interesting from the point of view of the chemical mechanism is (6-4) photolyase, which repairs the most cytotoxic (6-4) pyrimidine-pyrimidone photoproducts of DNA. Despite the extensive study of the (6-4) photolyase mechanism using the high-end experimental and computational methods, the chemical details of the repair reaction have not been definitively established. Multiscale modeling, combining classical molecular dynamics and quantum chemical calculations of photoexcited states and reaction coordinate, is able to resolve some of the contradictions existing today in understanding the (6-4) photolyase mechanism.
The present study considers the main stages of the (6-4) photoprodroduct repair by (6-4) photolyase including photoinduced electron transfer leading to the formation of a photoprodroduct radical, breaking and formation of covalent bonds in the photoprodroduct radical and back electron transfer. Using density functional theory calculations, optimized geometries were obtained for modeling the repair reaction involving various forms of the critically important amino acid residue His365, whose role in the repair has been extensively discussed in the literature. In the case of neutral His365, the photoproduct radical rearranges by the OH-group transfer, for which the enzyme reduces the reaction energy barrier. In the presence of protonated His365, electron transfer coupled to proton transfer takes place leading to the formation of a protonated (neutral) photoproduct radical. In order for the repair reaction to proceed along this path, it is necessary to adjust electron affinity of the photoproduct. Estimates of the effect of the macromolecular environment on electronic energies were carried by computing excited electronic states for structures comprising the repair rection coordinate using the multiconfiguration quantum chemical method XMCQDPT2-CASSCF. Within the framework of these calculations, the electronic coupling matrix elements were also evaluated. The influence of the macromolecular environment on electron transfer energies was evaluated using classical molecular dynamics. To assess the electron transfer reaction rate, the results of the quantum chemical and molecular dynamics calculations were combined. The estimated electron-transfer rates indicated that the rapid recombination of the radical pair takes place in the presence of neutral His365. The presence of protonated His365, acting as a proton donor for the photoproduct radical, may substantially slow down back electron transfer. Thus, the

Published online: 11 October 2023

mM His, in the presence of 100 μM copper, significantly reduces the supply of metal to the root by 4.3 times. 5 mM Gln in the presence of 100 μM of the metal decreased by 86.6% to the variant without the ligand.
In the case of isolated cell walls, a similar tendency was observed to increase metal sorption as the concentration of copper in the medium increased. Under conditions of 10 μM copper, His did not affect the adsorption of copper by root CW. The addition of 5 mM Gln, on the contrary, increased copper adsorption by 13% relative to the ligand-free variant. In the presence of 100 mM copper in the solution, the addition of amino acids reduced adsorption by 16% in the variants with Gln and by 25% in the variants with 1 mM His, 0.5 mM His had no effect. In the case of the cell wall of the shoots, the ligands did not affect the adsorption of copper ions per gram dry weight of the shoot.
When treated with solutions of CuCl2 at a concentration of 10 μM and in the absence of ligands, the root CW adsorbs 2 times more metal ions than is absorbed by the transpiring plant. As the concentration of ligands in the solution increases, the difference between the copper content in the root and the adsorption of isolated root CW increases. At the maximum concentration of His and Gln, the adsorption of CW is 4.4 and 13.4 times higher than the internal concentration of copper in the roots of experimental plants per gram of root dry weight.
Thus, the studied ligands reduce the uptake of copper by intact plants. At the same time, it does not affect the adsorption of copper ions by isolated root CW, which, in turn, exceeds by several times the endogenous concentration of the metal in the experimental roots. The obtained results give grounds to believe that: 1) CW is the main site of HM deposition in the plant; 2) the studied ligands limit the intake of copper ions by intact plants without affecting the adsorption capacity of cell walls.
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S8.559. The model of the phytoplankton population functioning in the arctic regional seas in the summer period

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Sunlight and the availability of mineral nutrition are the main factors that ensure the existence of phytoplankton communities. Their impact primarily affects photosynthetic activity, which can be assessed using fluorescent methods. By measuring the parameters of algal chlorophyll fluorescence, one can determine the potential efficiency of photosynthesis, find out its dependence on different light intensities, detect a deficiency of mineral nutrients, establish the degree of algae adaptation to light intensity in the phytoplankton habitat. According to the expeditions data in the basins of the Kara Sea and the Laptev Sea, in situ measurements of the chlorophyll content by the fluorimetric method demonstrate extremely diverse depth distributions [1]. The maximum can be near the surface and at depths below the jump in water density, or in the upper and lower layers simultaneously. At the same time, some cells from samples of the upper horizon demonstrate adaptation to dark conditions, and from samples of the lower horizon, to high illumination. It should be noted that diatoms make up a significant part of the phytoplankton biomass in the Arctic seas in summer, they are not capable of active movement. The water column consists of two practically non-mixing layers of water - the upper desalinated, deficient in nutrients, and the lower, more saline and enriched in nutrients. The upper layer of water is sufficiently well lit, while in the lower layer the light intensity is too low for photosynthesis. A natural question arises: how are diatom populations maintained in a stationary state in such a system? In mathematical models, the vertical movement of phytoplankton in the absence of directional transport can be described, for example, by turbulent diffusion [2, 3]. However, under conditions of stratification of the aquatic environment, this process cannot explain the observed distributions. In the present work, the following hypothesis is suggested [4]. In the illuminated layer of water, the cell accumulates biomass due to photosynthesis and increases its density by maintaining the volume due to the presence of solid silicon valves. As density increases, the cell gradually sinks until its density equals that of more saline and denser water. In this layer, rich in minerals, the cell replenishes its intracellular reserves. Once in the absence of light, the cell begins to spend the accumulated carbohydrates on various metabolic processes, including respiration. The released carbon dioxide is retained around the cell in the resulting mucus sac. At the same time, the specific gravity of this "formation" (cell + "bag") gradually decreases. Upon reaching the critical density value, the cell floats to the surface, and the gas bubble collapses. Based on the proposed hypothesis, an agent-based model of the phytoplankton population dynamics was built in the NetLogo environment (http://ccl.northwestern.edu/netlogo/). Cells-agents are divided into two groups - upper and lower. For each cell increase/decrease of its density; storage/expense minerals; division; death; transition from one group to another; moving are available. Cells of the upper group photosynthesize increasing density, while consuming intracellular minerals. The cells of the lower group replenish the intracellular content of minerals and carry out the main metabolism, their density decreases. The medium is divided into 2 layers: in the upper layer, the nutrient content is assumed to be zero, the light intensity decreases with depth in accordance with the exponential law. In the lower layer, there is no illumination, nutrients are evenly distributed. It is assumed that all "resources" are in abundance, their content does not change when consumed by agent cells.
The behavior of model solutions was analyzed. The key parameters were the level of near-surface illumination and the distance by which cells are displaced in a random direction at each moment of time. By changing these parameters, one can obtain different distributions of cells—numbers in the upper and lower layers—typical for expeditionary observations. With small displacements of cells, the population demonstrates a periodic change in abundance. The constant predominance of cells in one of the layers or the successive change in dominance is determined by the given illumination. Moving cells over long distances smooth out population fluctuations. The model experiment demonstrates a decrease in the total number of cells compared to a similar experiment in the absence

of significant cell movements, since the "availability" of sunlight is reduced. Under conditions of higher surface illumination, the total number of cells moving over long distances becomes higher, since they are less susceptible to photodegradation. The dynamics of the numbers in each of the layers also changes: at a normal level of illumination, the maxima of the numbers of the upper and lower cells replace each other, which is typical for cells that move weakly in low light conditions. Further studies will be aimed at refining the parameters of the model and a more detailed comparison of the results with experimental data.

The study was carried out within the framework of the scientific project of the state task of Lomonosov Moscow State University No. 121032500060-0.

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S9. Medical biophysics. Neurobiophysics

S9.560. 2-Ethyl-6-methyl-3-hydroxypyridine N-acetylcysteinate prevents stress-indused mitochondrial dysfunction

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Various stresses lead to disruption of the bioenergetic functions of mitochondria and excessive generation of ROS, which underlie the development of pathological processes [1]. Since mitochondria are the main source of ROS under stress conditions, it is possible that the main mechanism of action of adaptogen drugs is to reduce the excessive generation of ROS by these organelles. This function can be performed by antioxidants, in particular 3-hydroxypyridine derivatives, which have a wide spectrum of biological activity [2].They are heterocyclic analogs of aromatic phenols and, therefore, exhibit antioxidant and antiradical properties [3]. In our work, we used 2-ethyl-6-methyl-3-hydroxypyridine N-acetylcysteinate, which is a derivative of 3-hydroxypyridine and acetylcysteine, as an object of study. The aim of our study was to study the antiradical properties and biological activity of this drug. 2-ethyl-6-methyl-3-hydroxypyridine N-acetylcysteinate in the concentration range of 10-6-10-11M and 10-13M prevented LPO activation in the membranes of mouse liver mitochondria in the model system of mitochondrial "aging". At the same time, the chemiluminescent method showed high values of the antiradical activity of this drug, which could indicate the presence of adaptogenic properties in 2-ethyl-6-methyl-3-hydroxypyridine N-acetylcysteinate. The study of these properties was carried out on models of acute hypobaric hypoxia (AHH) or acute alcohol poisoning (AAP). At the same time, the influence of these effects on the functional state of mouse liver mitochondria was studied. AHH and AAP caused the activation of lipid peroxidation in mitochondrial membranes, which was accompanied by changes in the content of fatty acids (FA) having 18, 20 and 22 carbon atoms and swelling of mitochondria. The content of linoleic acid, one of the main fatty acids that make up cardiolipin, in the total lipid fraction of mitochondrial membranes decreased by 6%. Pool 20:3ω6 and 20:5ω3 decreased by 18% and 32% respectively. Considering that eicosanoids are signaling molecules and have a wide range of biological functions [4], a decrease in the content of these FAs, possibly, as well as a decrease in the content of linoleic acid, affected the body's resistance to stress. A 5-day administration of the drug at a dose of 10-6 M/kg before stress prevented the activation of lipid peroxidation, changes in the FA composition of membranes, and swelling of mitochondria.

Changes in the functional state of mitochondria affected the body's resistance to stress factors. The injection of 10-6M drug to mice for 5 days increased the lifespan and survival of mice under conditions of various types of hypoxia by 57-92% and 15-40%, respectively. At the same time, the lifespan and survival of mice under conditions of acute alcohol poisoning increased by 3.9 and 12 times respectively.

The adaptogenic properties of the drug, apparently, are due to its high antiradical and antioxidant properties.

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S9.561. A new approach to evaluate the effective intracellular concentration of bioactive molecules on the example of modular nanotransporters capable of interacting with the Nrf2 system of cells

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When studying intracellular interactions of bioactive molecules with target proteins, the problem of determining the concentrations of these molecules in a cell often arises. Of particular interest in this case is the concentration of only those molecules that are able to interact with the target protein, i.e., their effective concentration. In the cytoplasm, it can differ significantly from the average concentration, for example, due to the fact that the bioactive molecule and the target protein can be spatially separated, for example, in different cellular compartments. To determine the effective concentration, we developed an approach based on the processing of data from cellular thermal shift assay using a simple equilibrium mathematical model of interaction between molecules. This approach was tested on the example of protein constructs capable of interacting with the Keap1 protein, thereby leading to the release of the transcription factor Nrf2 from the complex with Keap1.

Our laboratory is actively developing polypeptide modular delivery systems for bioactive molecules that can bind to a selected receptor on the surface of target cells, internalize into cells by endocytosis, and exit endosomes. In this work, an antibody-like molecule, the R1 monobody, is delivered to the Keap1 protein. For binding to cells and subsequent internalization, another antibody-like molecule, affibody to the epidermal growth factor receptor (EGFR), was used. The translocation domain of diphtheria toxin (DTox) was responsible