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COMMENTARY

Biophysical Reviews' "Meet the Councilor"—a profile of Anastasia A. Anashkina

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Abstract
As one of the twelve Councilors of the International Union of Pure and Applied Biophysics elected in summer 2021, I have been asked to provide this short biographical sketch for the journal readers. I am a new member of the IUPAB Council. I hold a specialist degree in Applied Physics and Mathematics from the Moscow Institute of Physics and Technology and PhD in Biophysics from Moscow State University. I have spent my entire professional career at Engelhardt Institute of Molecular Biology of the Russian Academy of Sciences in Moscow, where I am currently a senior researcher. I am Associate Professor at the Digital Health Institute of the I.M. Sechenov First Moscow State Medical University since 2018, and have trained undergraduate students in structural biology, biophysics, and bioinformatics. In addition, I serve as the Guest Editor of special journal issues of *International Journal of Molecular Sciences* and Frontiers in Genetics BMC genomics. Now I joined Biophysical Reviews Editorial Board as IUPAB Councilor. I am a Secretary of National Committee of Russian Biophysicists, and have helped to organize scientific conferences and workshops, such as the VI Congress of Russian Biophysicists.

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Contributions to biophysics

In all my studies, I considered biological objects from a physical point of view, since the laws of physics work in biology at the molecular level. In my dissertation work, I have analyzed the PDB structures of protein–protein complexes of different types by the Voronoi-Delaunay method and showed that the distribution of contact areas both at the atomic and at the amino acid-amino acid levels corresponds to the sum of the distributions of stochastic and specific contacts (Anashkina et al. 2007). It was found that the share of specific contacts is from a quarter to a third of all contacts in the complex, and stochastic contacts are formed due to the spatial approach of atoms. Maximum pairing preference index was found for Cys-Cys contacts and for oppositely charged residues. Thus, it is the charges on the protein surface that ensured the correct geometry of the complex, while hydrogen bonds, van der Waals, and hydrophobic interactions are formed at the protein–protein interface due to the approach of atoms and stabilize the complex. A significant difference in residue contacts was observed between homodimers and heterocomplexes, because interfaces in homodimers were enriched with contacts between residues of the same type due to the effects of structure symmetry.

Based on the results of the study of protein-DNA complexes from PDB, it was demonstrated that share of specific

contacts is also about a third, same as in proteins. It is worthy to note that about one-third of the contacts are the contacts with positively charged residues Arg and Lys. However, DNA contacts with Arg and Lys show a pairing preference index corresponding to random contacts, while contacts with negatively charged amino acid residues Asp and Glu show a specific pattern of interactions. From this, it can be concluded that it is the negative charges in the protein-DNA interface that provide the specificity of the interaction, and, in addition, facilitate the subsequent dissociation of the positively charged protein from the negatively charged DNA (Anashkina et al. 2008, 2009, 2013).

I was lucky to take part in a number of studies on Na, K-ATPase. We have shown that ATP binding to Na, K-ATPase in contrast to ADP binding generates a structural transition in the enzyme, which is consistent with the movement of a significant portion of the surface area to a solvent-protected state. We propose that ATP binding leads to convergence of the nucleotide-binding and phosphorylation domains transferring the enzyme from the "E1-open" to "E1-closed" conformation ready for phosphorylation (Petrushanko et al. 2014). We have found also that Na, K-ATPase is highly sensitive to changes in the redox state, and the mechanisms of its redox sensitivity are S-glutathionylation of the Cys-454, -458, -459, and -244 residues. It is dose- and time-dependent reversible suppression of the enzyme function up to its complete inhibition (Petrushanko et al. 2012). These amino acid residues were replaced with alanine, and the inhibitory effect of GSSG was observed for wild-type murine Na, K-ATPase, but was less pronounced in Cys454-458-459Ala mutant and completely absent in the Cys244Ala and Cys244-454–458-459Ala mutants. In cells, expressing wild-type enzyme, ouabain induced activation of Src and Erk kinases under normoxic conditions, whereas under hypoxic conditions this effect was inversed (Petrushanko et al. 2017). It was found also that Na, K-ATPase α-subunit has a basal glutathionylation which is not abrogated by reducing agent. We have shown that acute hypoxia leads to increase of total glutathionylation level of Na, K-ATPase α-subunit; however, basal glutathionylation of α-subunit increases under prolonged hypoxia only. We provided evidence that this modification is co-translational and bears a label of the hypoxic conditions in which the cell was at the time of protein synthesis. We have suggested that many proteins may have basal glutathionylation (Mitkevich et al. 2016). We developed the method for predicting new glutathionylation sites, especially in proteins with an unknown structure (Anashkina et al. 2020). As an ion pump, Na, K-ATPase specifically binds cardiotonic steroids (CTS), which leads to inhibition of the enzyme activity and activation of signaling network in the cell. We have studied interaction of Na, K-ATPase with CTS of two different types—marinobufagenin and ouabain. We have shown that both CTS inhibit activity of Na, K-ATPase with the same Ki values, but binding of ouabain is sensitive to the conformation of Na, K-ATPase while binding of marinobufagenin is not. Furthermore, binding of ouabain and marinobufagenin results in different structural changes in Na, K-ATPase. Our data explained the diversity of effects on the receptor function of Na, K-ATPase caused by different types of CTS (Klimanova et al. 2015).

I also had the opportunity to participate in a series of studies on the Aβ peptide in Alzheimer's disease. We found that interaction of Na, K-ATPase with exogenous Aβ(1–42) leads to a pronounced decrease of the enzyme transport and hydrolytic activity and Src-kinase activation in neuroblastoma cells SH-SY5Y. This interaction allows regulation of Na, K-ATPase activity by short-term increase of the Aβ(1–42) level. However, prolonged increase of Aβ(1–42) level under pathological conditions could lead to chronic inhibition of Na, K-ATPase and disruption of neuronal function (Petrushanko et al. 2016). One of Aβ modified forms, iso-Aβ (containing an isomerized Asp7 residue), shows an increased neurotoxicity in vitro and stimulates amyloidogenesis in vivo. We have shown that the isomerization of Asp7 enhances the inhibitory effect of Aβ on the functional activity of the α7nAChR, which may be an important factor in the disruption of the cholinergic system in AD (Barykin et al. 2019). We suggested also that 35 HAEE 38 is a potential binding site for Aβ on α4β2 nAChR and Ac-HAEE-NH 2 tetrapeptide corresponding to this site is a potential therapeutic for the treatment of α4β2 nAChR-dependent cholinergic dysfunction in AD (Barykin et al. 2020).

Having studied the known spatial structures of several peptides and proteins involved in proteopathies, the amyloid-beta peptides, protein tau, and prion protein, we have shown that polyproline-II helix is abundant here. We hypothesize that in prions and amyloids, in general polyproline-II helices can serve as structural elements of the normal structure as well as dormant nuclei of structure conversion, and thus play an important role in structure changes leading to the formation of fibrils (Adzhubei et al. 2017).

HIV-infected patients are at an increased risk of developing atherosclerosis, in part because of down-modulation and functional impairment of ATP-binding cassette A1 (ABCA1) cholesterol transporter by the HIV-1 protein Nef. We studied molecular details of Nef–calnexin and Nef–ABCA1 interactions and identified a compound, which blocked Nef–calnexin interaction and partially restored ABCA1 activity in HIV-infected cells (Hunegnaw et al. 2016), modified the compound for better solubility (Adzhubei et al. 2018), and predicted a series of compounds for potential development as inhibitors of Nef-mediated co-morbidities of HIV infection by virtual screening (Adzhubei et al. 2021). The QASDOM meta-server was designed to analyze large data sets of docking models and rank them by scoring criteria

developed in this study. The server allows visualizing residues that form interaction sites in the receptor and ligand sequence and displays 3D model structures of the receptor–ligand complexes (Anashkina et al. 2017).

In studies on hemoglobin, we calculated that hemoglobin molecules are very densely packed in the erythrocyte at physiological concentration; a very thin layer of solvent remains between the hemoglobin molecules (Latypova et al. 2020, 2021). With such a dense arrangement of hemoglobin molecules in the erythrocyte, the formation of a small hydrophobic patch on the surface of hemoglobin will lead to "sticking" of hemoglobin A into hemoglobin S and the appearance of sickle cell disease.

Analyzing the evolutionary and entropy properties of protein sequences, we have developed a method for revealing the hierarchical structure in the protein sequence (Anashkina and Nekrasov 2014; Nekrasov et al. 2014). Correlations between the hierarchical elements were studied. A total of 11 levels of protein organization with elements ranging from 7 to 56 amino acid residues were found in the protein sequence set. The organization levels were assumed to correspond to super-secondary structure elements of different topologies (Mikhalskii et al. 2020; Nekrasov et al. 2020, 2021).This method uses the pentapeptide as a unit of protein sequence and has been successfully used in the development of recombinant proteins, the study of the principles of enzyme functioning, and the finding of the minimum functional site in proteins. We analyzed 44,860 structures of peptides by the molecular dynamics method and found that 1,225 pentapeptides over 80% of the simulation time were in a stable conformation. Clustering of these conformations revealed 54 topological types of conformationally stable pentapeptides. These conformations relate to different combined elements of the protein secondary structure. So, we obtained a minimal set of amino acid structures of conformationally stable pentapeptides, creating a complete set of different topologies that ensure the formation of pre-folded conformation of protein structures (Nekrasov et al. 2019).

Since 2019, science community gave priority for studying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing an outbreak of coronavirus disease 2019 (COVID-19), and I was no exception. We proposed a hypothesis that the cytokine storm syndrome, which complicates COVID-19 in some patients, is a consequence of antibody-dependent enhancement of virus infection, which, in turn, happens due to a change in dominant antigenic determinants of SARS-CoV-2 S-protein. We believe that this conformational change is the major factor in the switching of antibody affinity, which triggers antibody-dependent enhancement (Nechipurenko et al. 2020). According to the molecular dynamics simulation, a key mutation N439K in the SARS-CoV-2 RBD region created a new salt bridge with Glu329 of hACE2, which resulted in greater electrostatic complementarity, and created a weak salt bridge with Asp442 of RBD. Furthermore, the N439K-mutated RBD bound hACE2 with a higher affinity than wild-type, so it may be more infectious. In addition, the N439K-mutated RBD was markedly resistant to the SARS-CoV-2 neutralizing antibody REGN10987, which may lead to the failure of neutralization (Zhou et al. 2021a). We summarized also the spatiotemporal distribution of mutations in spike protein, and present recent efforts and progress in investigating the impacts of those mutations on viral infectivity and antigenicity. As mutations continue to emerge in SARS-CoV-2, we strive to provide systematic evaluation of mutations in spike protein, which is vitally important for the subsequent improvement of vaccine and therapeutic neutralizing antibody strategies (Zhou et al. 2021b).

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Declarations

Conflict of interest The author declares no competing interests.

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