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Molecular dynamics study of solvent water behavior in giant hemoglobin of *Oligobranchia mashikoi*.

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The beard worm *Oligobranchia mashikoi* (*Oli. mashikoi*) only lives in Tsukumo Bay, Noto Peninsula, Ishikawa Prefecture, Japan. *Oli. mashikoi* has giant hemoglobin which transports oxygen and hydrogen sulfide. From experimental study, hollow-spherical structure of the giant hemoglobin and large space are confirmed inside of giant hemoglobin. Water molecules are trapped inside and surround of giant hemoglobin. Particularly, internal water molecules behavior is interesting. In previous study, we have analyzed dynamical properties of proteins and water behavior around protein through the molecular dynamics (MD) simulations and quantum chemical calculations. Oli_Hb_24mer entered in Protein Data Bank, which is determined by X-ray crystallographic analysis, is adopted for initial structure of using quantum chemical calculations and MD simulations. We have estimated the charge distribution of active site models of Oli_Hb_24mer and analyzed the dynamical properties from MD simulations. On the other hand, in blue copper protein azurin, we have studied hydration water behavior near the protein surface. In this study, we focus on the water behavior around the giant hemoglobin. We construct initial structure composed by Oli_Hb_24mer with hydrogen sulfide to cysteine residues. MD simulations are carried out using AMBER03 force field under some temperature conditions. We discuss the internal water molecule behavior through the MD simulations.

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A Computational Study of Monoamine Oxidase A Dynamics

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Monoamine oxidases are enzymes that catalyze the degradation of excess of neurotransmitters such as serotonin and dopamine, and are crucial for the regulation of the central nervous system. Although the crystal structures of several oxidases have been solved, the mechanisms of their functions are not clearly understood. To address this important question we performed molecular dynamics simulations of the monoamine oxidase A (MAOA) monomer bound with the flavin adenine dinucleotide (FAD) cofactor solvated in water and with membrane. No inhibitor or substrate was included in the simulation system. Calculations were performed using the cosgene module of the myPresto simulation package. For the soluble domain principal component analysis was performed on a trajectory of 4.5 ns. Three domains were found to define the dynamics of the protein in the low frequency modes. Interdomain fluctuations allow for relaxation of the interactions between residues surrounding the substrate cavity. Such fluctuations may lead to conformational changes which open a route to the active site for substrate uptake and release. We are currently also performing simulations of a system of the MAOA monomer embedded in a solvated POPC lipid bilayer. The system is stable after 200 ps, with average RMSD of the backbone atoms 1.5 Å relative to the crystal structure. Membrane insertion may have an important effect on the enzyme dynamics but longer simulation times are needed in order to observe the relevant motions.

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Molecular dynamics simulations of lysozyme variants lacking some of the disulfide bridges: a comparison with NMR observations

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So far, we have carried out molecular dynamics (MD) simulations of two species of three-disulfide variants of lysozyme, C64A/C80A and C76A/C94A, in order to explain the difference in structural flexibility of the β -sheet observed by NMR. Although three-disulfide variants well preserve the native structure at a room temperature, MD simulations were carried out at 500K or 600K to increase the sampling in a conformational space, so that 3SS-variants began to unfold after 1ns. Therefore, in MD simulation we observed the very early stage of protein unfolding. We realized that MD simulations give us a useful insight into the change in the dynamic properties induced by the deletion of a disulfide bridge. NMR observations suggested that 2SS-variants are on the border between ordered and disordered structures. 2SS[6-127,30-115] with two disulfide bridges of Cys6-Cys127 and Cys30-Cys115 preserves the native structure in the α -domain, but 2SS[64-80,76-94] is unstructured overall the entire molecule. On the other hand, the structural stability of 2SS-variants at 550K and 600K afford a good insight into the role of each disulfide bridge in maintaining the tertiary structure of lysozyme. For example, Cys64-Cys80 contributes toward preserving the β -sheet structure in 2SS[64-80,76-94] and 2SS[6-127,64-80] irrespective of the large deformation of loop and β 310; regions within the β -domain. On the other hand, Cys30-Cys115 is important for protecting B-helix against the transformation into an extended structure due to the deformation of D-helix.

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Mechanism of Ion Permeation in Model Channel; Free Energy Surface and Dynamics of K⁺ Ion Transport in Anion-doped Carbon Nanotube

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The mechanism of the ion permeation is investigated for an anion-doped carbon nanotube, as a model of the K⁺ channel, by analyzing the free energy surface and the dynamics of the ion permeation through the model channel. It is found that the main rate-determining step is how an ion enters the channel. The entrance of the ion is mostly blocked by a water molecule locating at this entrance. About ten percent of K⁺ ions which reach the mouth of the channel can really enter the channel. The rejection rate sensitively depends on the location of this water molecule, which is easily controlled by the charge of the carbon nanotube; for example, the maximum permeation is obtained when the anion charge is at a certain value, -5.4e in the present model. At this charge, the facile translocation of the ion inside the channel is also induced due to the number fluctuation of the ions inside the channel. Therefore, the so-called "Newton's balls", a toy model should be modified. The present analysis thus suggests that there exists an optimum combination of the length and the charge of the carbon nanotube for the most efficient ion permeation. The physical origin of the free energy barrier is also discussed.