folding, domain movement, and so on, due to the computational limitation. Therefore the enhanced sampling methods to overcome the computational limitation are so important.
This study aims at the reduction of the computational cost for sampling through combined use of the simulations with the implicit and explicit solvent; the former is used for broad sampling of the conformational space and the latter for correcting the conformational space sampled by the former simulation. The system with the explicit solvent was coupled with the subsystem solvated with the implicit solvent, which accelerate the conformational sampling. The replica exchange molecular dynamics (REMD) was adopted for the subsystem in this study. For estimating the ability of the new method, chignolin, 10-residue mini protein, was chosen as a model system. The results show that the ability of conformational sampling by this method is higher than that of the conventional MD simulation and nearly corresponds to the temperature REMD simulation with the explicit solvent. Furthermore the computational cost was reduced by approximately six-fold as compared as the temperature REMD on this system.

875-Pos Board B644
Ligand-Perturbed Allosteric Communication within the Human A_{2A} Adenosine Receptor
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The human A_{2A} adenosine receptor ($A_{2A}R$) is a member of Class A G protein-coupled receptors (GPCRs). Activation of A_{2A} adenosine receptor leads to the stimulation of adenylyl cyclase (AC), and thereby increases the formation of cyclic adenosine monophosphate (cAMP). It has been recognized that A_{2A} adenosine receptor is a potential therapeutic target for the treatment of Parkinson's disease, Huntington's disease, schizophrenia, and other neurodegenerative diseases. In 2008, the first human A_{2A} adenosine receptor was crystalized in complex with its high affinity selective antagonist ZM241385. In 2011, six more A_{2A} adenosine receptor structures were published. Three of them co-crystallized with its agonists (UK432097, adenosine, and NECA) and three of the others co-crystallized with its antagonists (ZM241385, xanthine amine congener, and caffeine). In this study, the changes of allosteric communication inside the A_{2A} adenosine receptor induced by these agonists and antagonists are examined by molecular dynamics simulations. We found that agonists are able to switch the torsion angle of $W246^{6.48}$, and the correlated motions within the A_{2A} adenosine receptor are also perturbed by this rotamer toggle switch. In addition to conventional dynamical cross-correlation matrix analysis, we also investigated the time-lagged correlated motions to see the persistence time of autocorrelation and cross-correlation, and to examine the causality relationships between different dynamics states of the receptor.
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2. Chen, J.-B.;. ….Lin, J.-H., Fang J.-M. Design and synthesis of novel dual-action compounds targeting adenosine A_{2A} receptor for neuroprotection. ChemMedChem 2011, 6, 1390-1400.

876-Pos Board B645
Exploring Protein Energy Landscapes with Time-Dependent Principal Component Analysis
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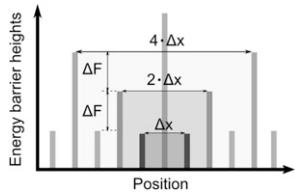
Protein function crucially depends on protein dynamics. Large-scale molecular dynamics simulations of small globular proteins show an anomalous diffusion behavior for the principal motions of proteins over multiple time scales. Specifically the variance of the essential principal components increases with a power law $\sigma \sim T^{\alpha}$ with trajectory length T. This behavior suggests a hierarchical structure of the energy landscape as first proposed by Frauenfelder.
To quantify how the anomalous diffusion exponents found in the molecular dynamics simulations give insight into the hierarchical structure of the underlying energy landscape, we compared our results to the simple discrete energy landscape shown in the figure. In this model, a hierarchy of energy barriers separating adjecent states is assumed. This hierarchy is characterized by its ''ruggedness'' ΔF as shown in the figure. We show that ΔF can be derived from the power law exponent α measured in the simulations via $\Delta F = \log(2)(2/\alpha - 1)$. Typical values of 5-7 kT are obtained.



877-Pos Board B646
Dynamics of the Distal Cavity in Myoglobin Variants
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The non-coordinated water molecule in the distal pocket of a myoglobin (Mb) can be a dominant factor in controlling the binding of CO to the active site. Experimental data showed that the mutations of the distal-pocket residues (V68F, V68L, L29F and L29W) modified myglobion's reaction rates with nitrite and water occupancy after photodissociation of CO. In this work molecular dynamics (MD) simulations revealed pronounced changes in the distal cavity volume for all variants and wild-type (WT), particularly when water leaves or enters the cavity. A 10% reduction in mean cavity volume was observed for WT when water exits the cavity (60.8 $Å^3$ and 55.4 $Å^3$ occupied vs. unoccupied respectively). In contrast, the L29F substitution resulted in 75% contraction in unoccupied volume making it less accessible, correlating with lower experimental water occupancy reported for L29F as compared to WT. The main dynamical pathway for water migration in and out of the distal cavity for all five systems was via H64. The imidazole ring of H64 acted as a gate to the cavity and was stabilized by the cavity bound waters. The exit of water molecules from the WT and V68F distal cavities increased the dynamics of H64 leading to significant population in the solvent exposed conformation. This conformational flexibility of H64 should ease the entrance of water molecules back into the distal cavity. In L29F and L29W variants which have lower experimental water occupancy in comparison to WT and V68F, the H64 showed reduced motions with the elevated population in the conformation precluding the entrance of water. This work demonstrated that the dynamics of residues lining the cavity play an important role in governing the water access to the distal pocket and the binding affinity for gaseous ligands to Mb.

878-Pos Board B647
Pressure Effect on the Secondary Structure of Peptides Studied by Generalized-Ensemble Molecular Dynamics Simulations
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Pressure effect on the structure of proteins and peptides has recently been studied theoretically and experimentally. Some proteins are denatured under high pressure conditions while some peptides are more stable in the folded state than in the random coil state at high pressure. It is important to understand the molecular mechanism of pressure-induced structural changes of proteins and peptides.
We studied pressure effect on the structure of peptides by using molecular dynamics simulations. Molecular simulations often get trapped in the local minimum states of the free energy. In order to overcome such difficulty, we used a generalized-ensemble algorithm, which gives more efficient sampling in a molecular simulation.
We performed molecular dynamics simulations with a generalized-ensemble algorithm for helical peptides in explicit water molecules. We found that the population of the secondary structure of the peptides changes as pressure increases. We also calculated the free energy as a function of pressure. The detail molecular mechanism of the structural change induced by pressure will be shown in the meeting.

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Understanding the Molecular Mechanism of Synergistic Inhibition in the Hepatitis C Virus (HCV) Polymerase via a Computational Investigation of Protein Dynamics
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A major challenge of treating HCV infection is the emergence of resistance to current treatment regimens. An approach to reducing the rate of drug resistance is to increase the inhibitory effects of allosteric inhibitors by using them in combination to target the HCV polymerase (NS5B). Although recent biochemical studies show the use of multiple allosteric inhibitors has a synergistic inhibitory effect on the HCV polymerase, the mechanism by which this synergistic inhibition occurs still has not been clearly elucidated. To garner insight into the mechanism of synergistic inhibition of NS5B, we employ molecular dynamics (MD) simulations of the enzyme simultaneously bound to two allosteric ligands. In concert with covariance and principal component analyses, the data from MD simulations allow us to compare specific structural and dynamic properties of the free and ligand-bound protein. Understanding the molecular mechanism that mediate synergistic inhibition in NS5B may allow us to optimize the inhibitory activity of these compounds against the