thus putatively weakened for cleavage by ADAMTS13. MD simulations of the ADAMTS13-vWF A2 complex allowed us to identify residues adjacent to the cleaved peptide bond that are relevant for efficient A2 binding. Subsequent QM calculations using semi-empirical PM6-DH method provided relative binding energies in good agreement with experiments. The force-dependent hydrolysis of the Y-M peptide bond was explored by QM and hybrid QM/MM calculations. Mechanical stretching, induced by a shear stress, facilitates the cleavage reaction. Finally, the enzyme reduces the entropic cost of substrate binding by increasing fast-scale dynamics in the regions distant from the catalytic site (e.g. disintegrin domain).
Overall, our study reveals the subtle details of ADAMTS13 biomechanical function.

3288-Pos
Mapping the Proton Conduction Pathways in the Inner Membrane Multi-Drug Translocase AcrB
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With increasing frequency the emergence of new drug resistances constitutes a serious problem in cancer therapy or the treatment of bacterial infections. A major mechanism bacteria employ against antibiotics is based on multidrug efflux pumps extruding the drugs before they can reach their targets. In Escherichia coli the major efflux system comprises the inner-membrane translocase AcrB, the membrane-fusion protein AcrA and the outer-membrane channel TolC. AcrB functions as the engine of this complex, using proton motive force to expel a wide variety of unrelated toxic compounds such as antibiotics, disinfectants or detergents. The molecular details of how proton conduction through AcrB is coupled to drug expulsion are not fully understood yet. To gain insight into the AcrB proton conduction pathway we performed a series of 5 independent molecular dynamics simulations of AcrB in a phospholipid/water environment at a 150mMol NaCl concentration. Each monomer was considered in a different protonation state as suggested in (1), and in each run the system was simulated for at least 50 ns, using GROMACS 4.0.3 and the GROMOS96 53a6 forcefield. We report three possible proton conduction pathways through the trans-membrane domain. The pathways were identified based on the dynamics of protein-internal water molecules and monitoring their frequency of hydrogen bond formation to adjacent residues. That way we also determined residues likely involved in AcrB's hydrogen bonded network. Each residue was further characterized by its specific hydrogen bond frequency to protein-internal water. Additionally a new method was applied to analyze AcrB-internal cavities and transport tunnels in each monomer's porter domain.

3289-Pos
Application of an Inter-Protein Coarse-Grained Force Field to Binding Process of Actomyosin
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Protein-protein interaction is important for many biological processes. Especially, when molecular motors fulfill their functions, they sometimes form multi-subunit complex or move through alternate binding and unbinding processes. Therefore, it is important to model inter-protein interaction appropriately in order to reveal working mechanism of molecular motors. Coarse-grained model is often used to analyze working mechanism of molecular motors for computational efficiency, but modeling of inter-protein interaction sometimes becomes difficult problem. In this study, we apply a sequence dependent inter-protein coarse-grained force field (each amino acid is coarse-grained to one bead) that considers electrostatic interaction between charged residues and sequence dependent contact interaction [Kim and Hummer, JMB (2008)] to a molecular motor, actomyosin. Myosin is known to take detached, weakly bound and strongly bound state to its rail protein, actin, during ATP hydrolysis cycle, and the force is thought to be generated during the weakly-to-strongly transition. These binding states should be coupled to nucleotide dependent conformational changes of myosin such as open-close motion of the actin-binding cleft and rearrangement of surface loops like loop II. We will discuss the effect of the myosin conformational changes on the binding process.

3290-Pos
Fluctuation Theorem Applied to F1-ATPase
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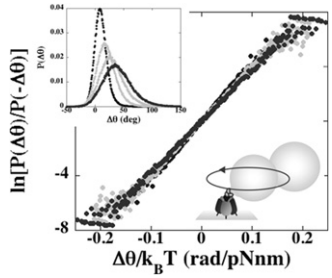
The fluctuation theorem (FT), which is one of fluctuation theories based on non-equilibrium statistical mechanics and represents the property of an entropy production in a small system, was experimentally verified in a motor protein F_1-ATPase (F_1). The theorem has been applied to several experimental systems such as colloidal particle systems and RNA hairpins. Those systems were in non-equilibrium when the operations were added to the systems and the entropy productions were measured for those non-equilibrium processes. Unlike those systems, F_1 is an autonomously non-equilibrium system in which the rotor γ subunit rotates in the stator $\alpha_3\beta_3$ ring upon ATP hydrolysis. Can FT be applied to such an autonomous system? Noting that the entropy production of the probe visualizing the rotation of F_1 is a product of the rotary torque and the angular velocity, we introduced the representation of FT appropriate for the torque measurement. The torque measured through our method was compared with that measured conventionally. In addition to the verification, we applied the theorem to a mutant F_1 and another motor protein V_1. The applicability of FT should be expanded to the wide range of biological systems *in vitro* and *in vivo*.



Protein Folding & Stability: Computational Approaches

3291-Pos
Computational Search of Evidence for the Division of Amino Acids into Transitional Groups in a Virtual State Protein. Phase I: Equilibrium Fluctuations
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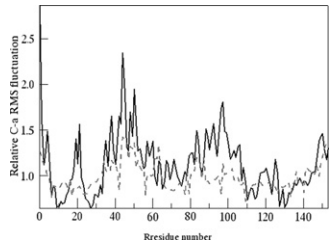
Core-Shell model postulates that beyond certain resolution, non-equilibrium states are virtual, non-testable as proteinous, because they are not ''domesticated'' by evolution. We propose that during (un)folding, the {Cα, Cβ, Cγ, Cδ, Cε}-backbone of residue does an elementary move, transverse to peptide backbone. Sliding mechanism assigns amino acids into three transition groups based on residue stereochemistry. According to model, this division is masked in folded conformation. Search of evidence for such division begins with study of fluctuation of folded molecule, using united-residue protein model of sperm whale myoglobin to simulate Monte Carlo conformational trajectories. For alpha-carbon fluctuations along polypeptide chain, reasonable qualitative agreement between simulated and crystallographic B-factor (PDB ID: 108M) profiles is reached. Nearly equal amount of average rms-fluctuation contribution is found for T-groups: T1 (1.13 ± 0.12Å); T2 (1.17 ± 0.14Å); T3 (1.18 ± 0.09Å); with 1.13 ± 0.11Å being for the whole molecule. Model predicts constant-rate built-up of rms-fluctuation amounts as protein unfolds. Myoglobin has high symmetry of architecture and unusual sextet of amino acid pairs. For comparison, their rms-fluctuation amounts are:
[Trp(2),Asn(2)] (1.38 ± 0.57Å);
[Met(3),Tyr(3)] (0.85 ± 0.00Å);
[Pro(4),Arg(4)] (1.25 ± 0.14Å);
[Gln(5),Thr(5)] (1.14 ± 0.09Å);
[Ser(6),Asp(6)] (1.25 ± 0.18Å);
[Phe(7),Val(7)] (1.08 ± 0.12Å).



3292-Pos
Multiscale Modeling and Design of Molecular Conformational States
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Some of the emerging goals in modern medicine are to uncover the molecular origins of human diseases, and ultimately contribute to the development of new therapeutic strategies to rationally abate disease. Of immediate interests are the roles of molecular conformational ensembles and dynamics in certain cellular processes leading to human diseases and the ability to rationally manipulate these processes. We developed a multiscale approach, which utilizes rapid Discrete Molecular Dynamics (DMD) simulations. We demonstrate that by using this approach we can predict protein structure, conformational ensembles of the unfolded protein states, and uncover the folding kinetics of biological molecules. Furthermore, using computation and experiment, we demonstrate that by using computational molecular design we can manipulate these states. We will describe several recent studies that demonstrate our multiscale modeling and design approach.