changes in fibrinogen function are created by oxidative stress in both thrombotic and hemorrhagic diseases, particularly trauma induced coagulopathy. However, there is currently little understanding of which oxidized methionines are contributing to the observed gel characteristics or the molecular mechanism by which these oxidations change the fibrin structure at the molecular level. We have applied the recently developed well-tempered ensemble parallel tempering (PT-WTE) technique along with conventional molecular dynamics (MD) to investigate these changes in the structure and stability of the human fibrin D and αC regions. Both of these regions have indicated as key contributors to the mechanism of fibrin lateral aggregation. MD of the D region of human fibrin/fibrinogen shows no evidence that methionine oxidation disrupts the native state nor the stability of a bound knob 'b' surrogate peptide on the 350 ns time scale. PT-WTE simulations of a human homology model of the bovine N-terminal subdomain fragment from the αC domain reveal that methionine oxidation alters the conformational ensemble of the hairpin-linking region and decreases the proportion of closed structures compared to the non-oxidized αC domain. We attribute this alteration to the disruption of the hairpin-linking region's conformation, with oxidation increasing the radius of gyration for this segment.

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Database Guided Exploration to Determine Native Ligands for Orphaned Odorant Receptors

Sarana Nutanong[1], Kyle Wong[1], Yanif Ahmad[1], Jen Pluznick[2], Blythe Shepard[2], **Thomas B. Woolf**[2].
[1]Department of Computer Science, JHU, Baltimore, MD, USA, [2]Department of Physiology, JHMI, Baltimore, MD, USA.

Despite significant advances in purification and in high-throughput experimental design, the assignment of ligands to orphaned odorant receptors is difficult. We describe the development of a three stage computational database that is coupled with experimental measurements to aid the de-orphanization process. We posit that apo receptor conformations can be found that rationalize binding and non-binding ligands first measured in experiment. The challenge is to find the best receptor models in this large set of candidates. Our approach is to filter the search space throughout each of our stages. The initial stage of database control begins with a set of tertiary models for the receptor made with Rosetta and Modeller. All-atom molecular dynamics is performed for the apo receptor in an explicit bilayer for each model. Using OpenEye's Fred and UCSF's Dock6, we determine the subset of sampled conformations that maximally rationalizes the current experiments. In a second stage, using the filtered set of reduced conformations we perform re-scoring with Poisson Boltzmann and re-evaluation relative to experiment. Our third stage uses Amber and Charmm potentials to further evaluate the quality of the reduced subset to fit against experiment. Lastly, new ligand computations with this reduced set of candidate receptor models are used to computationally screen for new ligands to be tested by experiment. A loop between experiment and computation is thus created, with any results feeding back into the database and multiple cycles used. We will emphasize results achieved on olfr1393 and olfr1392.

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Probing Diffusive and Energetic Aspects of Ribosome Function

Jeff K. Noel[1], Vitor B.P. Leite[2], Jorge Chahine[2], **Paul C. Whitford**[3].
[1]Center for Theoretical Biological Physics, Rice University, Houston, TX, USA, [2]Physics, UNESP, São José do Rio Preto, Brazil, [3]Physics, Northeastern University, Boston, MA, USA.

As the scale of modern computers continues to grow, it is becoming possible to use theoretical models to quantitatively study of the energy landscapes and diffusive aspects of large-scale conformational transitions in molecular machines. One of the largest biomolecular assemblies, for which we have atomic-resolution structural data, is the ribosome. To elucidate the relationship between the structural, energetic, diffusive and kinetic aspects of large-scale collective dynamics, we use molecular dynamics simulations with simplified energetics models (40,000-150,000 atoms per simulation), in addition to explicit-solvent simulations of complete ribosomes (2-3 million atoms). Our simplified models are revealing coordinate-dependent diffusive properties of large-scale rearrangements in the ribosome, and are suggesting which coordinates most accurately capture the underlying barriers. Complementing this description, multi-hundred nanosecond explicit-solvent simulations suggest that the energy landscape of tRNA accommodation is relatively smooth. For translocation, we used a long (> 1 microsecond) explicit-solvent simulation to measure diffusion coefficients along collective (hundreds of residues) rearrangements in the ribosomal subunits. Grounded in energy landscape theory, as developed in the context of protein folding, these calculations provide a theoretical framework for understanding the relationship between experimental kinetics, single-molecule measurements, and theoretical predictions of the free-energy barriers that govern ribosome function.

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Protein-Ligand Binding Simulation with the Martini Coarse-Grained Force Field

Tatsuki Negami, Kentaro Shimizu, Tohru Terada.
The University of Tokyo, Tokyo, Japan.

Clarifying the mechanism of protein-ligand interactions is one of the most important research subjects in the field of biophysics. However, most of the research efforts have been devoted to predicting the docking structures. The process of ligand binding remains to be clarified. Molecular dynamics simulation is a straightforward way to study the ligand-binding process. However, reproducing the ligand-binding process in an all-atom simulation is quite difficult because it requires a very long time simulation. For this reason, we have explored the possibility of coarse-grained simulation. In this study, we used the MARTINI force field, in which four non-hydrogen atoms are mapped to one particle on average. We performed ligand-binding simulations for two protein-ligand pairs, the levansucrase-glucose and LinB-1,2-dichloroethane, that differ in the shape of the ligand-binding pocket and in the physicochemical properties of the pocket and the ligand. Each simulation system was composed of one protein molecule, randomly placed ligands, and explicit water solvents. One-microsecond simulations were repeated 100 times with different initial placements of the ligands. For each protein-ligand system, we observed that ligand molecules entered into the correct ligand binding pocket. To obtain further details, we calculated the distributions and the flows of ligand molecules on the protein surface. The distributions of ligands revealed that the ligands were stable in the ligand binding pockets. The analyses of the ligand fluxes demonstrated that the CG ligand molecules entered the ligand-binding pockets through specific pathways. These results suggest that coarse-grained simulation is a good approach to studying protein-ligand binding processes. We will discuss the effects of the shape of the ligand-binding pocket and physicochemical properties of the pocket and the ligand on the binding process.

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Local Dynamics of FRET Dyes in an Intrinsically Disordered Protein Studied by MD Simulations

Reinhard Klement, Helmut Grubmueller.
MPI for Biophysical Chemistry, Goettingen, Germany.

Fluorescence resonance energy transfer (FRET) is widely used to track structural changes of biomolecules such as conformational transitions, aggregation or folding. The energy transfer efficiency between a donor-acceptor dye pair is a measure of their mutual separation.

However, several assumptions about the dynamics of the dyes have to be made to quantitatively interpret the data measured in single molecule or bulk experiments. In particular, the mutual orientation of their transition dipole vectors determines the FRET efficiency, and has to be disentangled from the inter-dye distance. To this aim, it is usually assumed that both dyes adopt an isotropic orientation and that their orientational fluctuations are fast compared to their excitation decay rate. In this case, an orientation factor of $\kappa^2 = 2/3$ is obtained. In extended molecular dynamics (MD) simulations we investigated the local flexibility of FRET pairs (tryptophan as donor, coumarin as acceptor) located in the N-terminal and NAC region of alpha-synuclein (aS) which is an entirely intrinsically disordered protein (IDP) of 14.4kD. MD simulations of FRET probes yield instantaneous information about their mutual orientation κ^2 and distance R_{DA} which are typically inaccessible to experiments.

The orientation factors obtained from our MD simulations deviated considerably from the isotropic value $\kappa^2 = 2/3$. Further, rotational autocorrelation functions obtained for both dyes reveal a slow diffusion on the surface of the protein. Unexpectedly, we found that slow internal structural fluctuations of aS can cause transient immobilization of one or both dyes, which markedly affects the interpretation of FRET data and might be a general feature of FRET probes attached to IDPs.

M. Hoefling, N.Lima, D.Haenni, C.A. M.Seidel, B.Schuler, H.Grubmüller, PLoSONE 6(5): e19791. doi:10.1371/journal.pone.0019791.
A.Grupi, E.Haas, JMB, 405:1267-1283 (2011).
B.W. van der Meer, Rev.Mol.Biotechnology, 82:181-196 (2002).

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Comparison of Side-Chain Motion of Calbindin D-9K in its Four Calcium Binding States by Molecular Dynamics Simulation

Mahendra B. Thapa[1], Mark Rance[2].
[1]University of Cincinnati, Cincinnati, OH, USA, [2]Molecular Genetics, Biochemistry and Microbiology, University of Cincinnati, Cincinnati, OH, USA.

Calbindin D-9k, a small single domain protein found predominantly in tissues involved in the uptake and transport of calcium, consists of a single pair of a helix-loop-helix motif(called EF-hand)that binds calcium with the ligands provided by the loop residues and helical residues immediately adjacent to the