a backshift in the activation pathway [3]. Additionally, recent ^{2}H nuclear magnetic resonance (NMR) studies on retinal bound to rhodopsin hint towards a much lower methyl rotation activation barrier than observed in previous MD simulations [4]. Here we report quantum chemical calculations of torsional surfaces of model compounds and molecular dynamics (MD) simulations of the proteolipid complex in full atomic detail, to aid in the interpretation of the body of experimental data. Specifically, by using larger retinal fragments and a higher level of theory (MP2/cc-pVDZ), we are able to accurately reproduce the rotational behavior observed from ^{2}H NMR relaxation data [4]. For example, the relaxation data indicate an unusually low activation energy (E_a) for C9-methyl rotation, due to intraretinal interactions with H7 and H11 of the retinal polyene chain. These results in turn should lead to the ability to begin to simulate the coupling of small- to large-scale motions in rhodopsin activation. Ultimately, these efforts are aimed towards modeling more accurate comparisons to other GPCR proteins. [1] P.-W. Lau *et al*. (2007) *J. Mol. Biol.* 372(4) 906-917. [2] K. Martínez-Mayorga *et al*. (2006) *J. Amer. Chem. Soc.* 128(51) 16502-16503. [3] R. Vogel *et al.* (2006) *Biochemistry* 45(6), 1640-1652. [4] M.F. Brown *et al.* (2009) *Biochim. Biophys. Acta*, in press.

2924-Pos

Towards a Computational Model of Lignocellulose: Molecular Simulation of Lignin

Loukas Petridis, Jeremy C. Smith.
Oak Ridge National Lab, Oak Ridge, TN, USA.

Atomic-detailed computational models of lignocellulose can complement experiments in understanding its structure and dynamics. Here, we present results of Molecular Dynamics simulation of the plant cell wall polymer lignin. Polymer theory is employed to interpret these results. Finally the steps towards a realistic model of lignocellulose are discussed.

1. L. Petridis and J.C. Smith (2009); A molecular mechanics force field for lignin; Journal of Computational Chemistry 30 457-467
2. R. Shulz, B. Lindner, L. Petridis and J.C. Smith (in print); Scaling of Multimillion-atom Biological Molecular Dynamics Simulation on a Petascale Supercomputer; DOI: 10.1021/ct900292r

2925-Pos

Molecular Simulations of Dodecyl-D-Maltoside Micelles in Water: Influence of the Headgroup Conformation and the Force Field Parameters

Stéphane Abel[1], François Yves Dupradeau[2], E. Prabhu Rahman[3],
Alexander D. Mackerell Jr.[3], Marchi Massimo[1].
[1]Commissariat à l'Energie Atomique, DSV/iBiTEC-S/SB2SM/LBMS,
Saclay, France, [2]Laboratoire des glucides, UMR CNRS 6219, Amiens,
France, [3]Department of Pharmaceutical Sciences, School of Pharmacy,
University of Maryland, Baltimore, MD, USA.

Dodecyl-D-maltoside (DDM) is a non-ionic glycolipid detergent with a maltose headgoup and a dodecan chain. It is used for the extraction and purification of membrane proteins from their natural environment. DDM has two anomers: one with a linear conformation (beta) and one with a right angle bend between the headgoup and the alkyl tail (alpha). Experiments show that the headgroup conformations change the micelle properties. However, little is known about the influence of the surfactant conformation on the micelle internal structure and hydration properties. To examine these aspects, we have used molecular dynamics (MD). MD was performed with micelles containing 75 and 132 alpha-DDM and beta-DDM monomers, respectively, at ambient conditions with different parameters (CHARMM22 and a newly developed force field (ff) compatible with GLYCAM06). We analyse the simulations in terms of the aggregate structure, surfactant conformations and interfacial water dynamic properties. Our results show that micelle properties vary with the force field used and that the simulations performed with the GLYCAM reproduce better the experimental findings from SANS or NMR. The micelles are slightly ellipsoidal with dimensions around 20.0 and 26.4 Å. The structures of the aggregate do not change significantly with the ff. Surfactant and the headgroup conformations show similar behaviour with an exception for the ether link between the headgroup and the tail. The dynamics of the interfacial water are 7-10 times slower than that of bulk water and seem, surprisingly, to be independent of the headgroup conformation. Finally, to evaluate the robustness of the simulations, we also performed additional runs with a new release of the CHARMM ff for disaccharide with new optimized parameters for the ether link. Comparison of these runs with the preceding simulations will be presented.

2926-Pos

Dynamics in Tethered Particle Motion: Interpreting the Observations

Sanneke Brinkers[1], Heidelinde R.C. Dietrich[1], Jurriaan J. Mes[2],
Sjoerd Stallinga[1], Bernd Rieger[1].
[1]Delft University of Technology, Delft, Netherlands, [2]Wageningen UR,
Wageningen, Netherlands.

Tethered Particle Motion (TPM) enables the researcher to examine the properties of semi-flexible polymers at the single molecule level. In TPM, a small reporter particle is tethered to a substrate using the polymer of interest. The particle motion reflects the mechanical properties of the tethering polymer.

We will present a framework in which the influence of the different experimental aspects on the measurement outcome are quantified. The key elements are tether length, particle size, exposure time, fluid properties and frame rate.

Here, we use 80 nanometer diameter gold particles, tethered to a glass slide by double stranded DNA, that are visualized by dark field microscopy. The recorded images of these highly scattering particles have a high contrast and signal-to-noise ratio; therefore the particle can be tracked with high spatial resolution (5-20 nm).

High temporal resolution is necessary to distinguish between different diffusion regimes. At very short time scales the particle is freely diffusing and on longer time scales its motion is influenced and eventually restricted by the retracting harmonic force of the tether. We will show that the diffusion coefficient of the free motion on short time scales is composed of the diffusion properties of both the particle and tether and that the harmonic potential stems from the entropic elasticity of the tether molecule. Motion blur caused by the finite exposure time has to be considered for computing the diffusion constant. Lastly, the choice of tether length and particle size play an important role as well. They determine how often the particle will be in proximity of the substrate where particle-substrate interactions such as van-der-Waals and electrostatic forces play a bigger role.

2927-Pos

Md-Based Method for Computing Configuration Integrals Provides Ability to Test Force Fields

Gevorg Grigoryan.
University of Pennsylvania, Philadelphia, PA, USA.

Modern force fields allow the study of biological molecules in atomistic detail. However, too often computational limitations prohibit one from computing many biologically relevant measures such as folding energies and rates, differential population of alternate biological states, and binding affinities. This makes it difficult to test and improve upon the accuracy of force fields for such thermodynamic applications. In this work, new methods are presented for computing the configuration integral of biological molecules both around specific structural states as well as over all of phase space. These methods are based on Molecular Dynamics simulations and can be applied with any force field, including ones with explicit solvent. The methods are applied to study several problems. First, as a proxy for the random-coil state, free energies of hexa- and hepta- peptides are studied as a function of their sequence. Surprisingly, it is demonstrated that the Random Energy Model describes quite well the relationship between sequence and energy, indicating that individual amino acids contribute to the overall free energy largely in a context-independent manner. Second, the ability of EEF1 force field to reproduce experimental helix propensities is studied by computing relative helix folding energies of short peptides. Values computed for polar and non-polar amino acids, separately, show moderate correlation with experimental data. However, the two groups are out of scale with one another, indicating an imbalance between polar and hydrophobic interactions in the force field. Further, each group has two clear outliers - Val/Ile for non-polar amino acids and Lys/Arg for polar ones, suggesting additional avenues for improvement of EEF1. The success of the presented methods has far reaching implications not only for force field development and validation, but also for such areas as computational protein design and drug discovery.

2928-Pos

Molecular Dynamics Simulations of the AAA Protein P97

Jeff Wereszczynski, James Andrew McCammon.
University of California, San Diego, La Jolla, CA, USA.

The mechanocoupling of energy stored in triphosphate nucleosides provide the power necessary for many fundamental *in vivo* processes. The highly abundant protein p97 (also known as valosin-containing protein) is one of the most widely studied members of the AAA protein family (ATPases Associated with various cellular Activities), and is involved in numerous cellular functions such as nuclear envelope assembly, retrotranslocation of misfolded proteins from the endoplasmic reticulum to the cytosol, reformation of the Golgi following mitosis, and the IκBα pathway. Structurally, each monomer is composed of two hydrolysis domains (D1 and D2 with only D2 being catalytically active under standard cellular conditions), an N-terminal domain that interacts with effector proteins, a C-terminal domain, and linker regions between them. In solution, proteins hexamerize into stacked-ring shaped complexes with rings formed by each of the hydrolysis domains. Here, we present results from molecular dynamics simulations on each of the four predominant hydrolysis states (no nucleotide, ATP, transition state, and ADP). Initial *in silico* work focused on resolving differences between high- and low-resolution experimentally determined structures through the use of the molecular dynamics flexible fitting (MDFF) method. From these simulations, unrestrained all-atom, long time scale molecular dynamics simulations were performed on each state. Results show important differences in structure and dynamics of the protein in each hydrolysis state and assist in characterization of the p97 hydrolysis pathway.

2929-Pos

CHARMM-GUI: Brining Advanced Computational Techniques to Web Interface

Sunhwan Jo, Wonpil Im.
The University of Kansas, Lawrence, KS, USA.

CHARMM-GUI, http://www.charmm-gui.org, has been developed to provide a web-based graphical user interface to generate various input files and molecular systems to facilitate and standardize the usage of common and advanced simulation techniques in CHARMM. We have made a significant amount of efforts to implement basic and common molecular dynamics simulation techniques into web interface and the web interface has generated a multitude of positive feedback from our users. In this work, we describe our latest efforts to bringing more advanced molecular modeling and simulation techniques to the web interface, such as membrane system building with more lipid types, ligand binding free energy calculation, electron microscopy density map fitting, protein-protein docking, transition path finding and free energy along the path, and NMR structure calculation.

2930-Pos

Molecular Mechanisms How Mercury Inhibits Water Permeation of Aquaporin-1: Understanding by Molecular Dynamics Simulation

Yoshinori Hirano[1,2], Noriaki Okimoto[1], Kenji Yasuoka[3], Makoto Taiji[1], Makoto Suematsu[1], Masato Yasui[2].
[1]RIKEN, Yokohama, Japan, [2]Keio University, Shinjuku-ku, Japan, [3]Keio University, Yokohama, Japan.

Aquaporin (AQP) functions as a water-conducting pore. Mercury inhibits the water permeation through AQP. Although site-directed mutagenesis has revealed that mercury binds to Cys189 during the inhibition process, it is not fully understood how this inhibits the water permeation through AQP1. Here, we performed 40 ns molecular dynamics simulations of bovine AQP1 with mercury (Hg-AQP1) or without mercury (Free AQP1). In Hg-AQP1, Cys191 (Cys189 in human AQP1) is converted to Cys-SHg$^+$ in each monomer. During each last 10 ns, we observed water permeation events occurred 23 times in Free AQP1 and never in Hg-AQP1. Mercury binding did not influence the whole structure, but did induce a collapse in the orientation of several residues at the ar/R region. In Free AQP1, backbone oxygen atoms of Gly190, Cys191, and Gly192 lined, and were oriented to, the surface of the water pore channel. In Hg-AQP1, however, the SHg$^+$ of Cys191-SHg$^+$ was oriented towards the outside of the water pore. As a result, the backbone oxygen atoms of Gly190, Cys191, and Gly192 became disorganized and the ar/R region collapsed, thereby obstructing the permeation of water. We conclude that mercury disrupts the water pore of AQP1 through local conformational changes in the ar/R region.

2931-Pos

Molecular Dynamics Studies of the ERK2 Tyrosine Kinase

Daniel Barr[1], Arjan van der Vaart[2].
[1]Arizona State University, Tempe, AZ, USA, [2]University of South Florida, Tampa, FL, USA.

The extracellular-regulated kinase (ERK) belongs to a class of mitogen activated protein kinases (MAPKs) which respond to growth signals in the environment and regulate cell growth and division. Consequently, these signal pathways are often implicated in various cancers and growth diseases. Using molecular dynamics simulations, we studied the ERK protein in various stages of activation. By studying the quasiharmonic modes, correlation maps, and information flow in the system, we developed a coherent picture of the structural and dynamic changes upon activation of the protein.

2932-Pos

The Effect of Genetic Mutations on Structural and Mechanical Properties of Collagen: Molecular Dynamics Simulations

Ashley E. Marlowe, Yaroslava G. Yingling.
North Carolina State University, Raleigh, NC, USA.

Osteogenesis Imperfecta is a disease characterized by too little collagen in the body, causing brittle bones, permanent disfigurement, and often death. To provide fundamental understanding of the molecular basis of these diseases, extensive molecular dynamics simulations were conducted using the AMBER 10.0 suite. A Glycine-Proline-Hydroxyproline tropocollagen molecule was used as a building block for a fibril. The central tropocollagen molecule was later modified to corresponding mutations. Electrostatic measurements, hydration and ion patterns were determined, garnering an observation of a hydrophobic dipole. Our simulations indicate that the mutations significantly affect binding and mechanical properties of the collagen fibrils. Moreover, we predict that the high death rate related to lysine mutation can be explained by the increase in diameter and significant loss of mechanical properties in collagen fibril.

2933-Pos

Mechanism of Glycan Receptor Recognition and Specificity Switch for Avian, Swine and Human Adapted Influenza Virus Hemagglutinins: A Molecular Dynamics Perspective

Dong Xu, E. Irene Newhouse, Phineus R.L Markwick, Rommie E. Amaro, Hsing C. Pao, Kevin J. Wu, Maqsudul Alam, J. Andrew McCammon, Wilfred W. Li.
University of California, San Diego, San Diego, CA, USA.

Hemagglutinins (HA's) from duck, swine and human influenza viruses have previously been shown to prefer avian and human glycan receptor analogues with distinct topological profiles, pentasaccharides LSTa (α-2,3 linkage) and LSTc (α-2,6 linkage), in comparative molecular dynamics studies. Based upon detailed analyses of the dynamic motions of the receptor binding domains (RBD's) and interaction energy profiles with individual glycan residues, we have identified approximately 30 residue positions and secondary structural elements (SSE's) in the RBD that present distinct profiles with the receptor analogues. Glycan binding constrained the conformational space sampling by the HA. Electrostatic steering appeared to play a key role in glycan binding specificity. The complex dynamic behaviors of the major SSE and trimeric interfaces with or without bound glycans suggested that networks of interactions might account for species specificity in these low affinity and high avidity (multivalent) interactions between different HA and glycans. Contact frequency, energetic decomposition and H-bond analyses revealed species-specific differences in HA-glycan interaction profiles, not readily discernable from crystal structures alone. Interaction energy profiles indicated that mutation events at the set of residues such as 145, 156, 158 and 222 would favor human or avian receptor analogues, often through interactions with distal asialo-residues. These results correlate well with existing experimental evidence, and suggest new opportunities for simulation-based vaccine and drug development.

2934-Pos

Study of Interactions Between Neuron-Specific Enolase and B-Type Phosphoglycerate Mutase with Molecular Dynamics Simulations

Davit Hakobyan[1], Karen Nazaryan[1,2].
[1]Institute of Molecular Biology, Yerevan, Armenia, [2]Russia-Armenian (Slavonic) State University, Yerevan, Armenia.

Molecular dynamics simulations were used to examine the interaction of human B-type phosphoglycerate mutase (dPGM-B) and neuron-specific enolase (NSE). Specifically, we studied the interactions of 31 orientations of these enzymes by means of the effective energy function (EEF1) implicit solvation method available in program CHARMM. Interactions of the enzymes were grouped into five different NSE - dPGM-B complexes. Interactions between active regions of the enzymes occurred preferentially as in three of the five groups the enzymes interacted with their active regions. With periodically increased temperature dynamics the close conformation of dPGM-B was obtained as the C-terminal tail capped the active pocket in the presence of the 2-phosphoglycerate (2PG) substrate. Cleavage of 2PG through the residue loop Trp16-Gly24 was observed for a separate subunit of dPGM-B. Preferential interaction between active regions of the enzymes implicitly implies tendency of direct transfer of 2PG (channeling) between dPGM-B and NSE. Such phenomenon, however, needs additional study as interaction of the active regions of the enzymes might bring delays into conformation changes of dPGM-B which are necessary for proper direction of 2PG to the surface of the enzyme and consequent cleavage.

2935-Pos

Recognition and Signaling in DNA Mismatch Repair: Interdomain Communication in T. Aquaticus Muts Proteins

Susan N. Pieniazek[1], Moitrayee Bhattacharyya[2], Saraswathi Vishveshwara[2], Manju Hingorani[1], David L. Beveridge[1].
[1]Wesleyan University, Middletown, CT, USA, [2]Molecular Biophysics Unit, Indian Institute of Science, Bangalore, India.

Allosteric communication events involving multifaceted protein architectures are critical in complex biological processes, including DNA mismatch repair (MMR). MutS and its homologs, highly conserved proteins in both prokaryotes and eukaryotes, initiate MMR by recognizing mispaired DNA and signaling downstream repair. DNA binding is allosterically coupled to ATPase activity at the nucleotide binding sites ~70 Å away. Modern theories on allosteric