(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

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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

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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

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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

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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

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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

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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

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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

communication include analysis of energy landscapes and network models. These models are not independent and molecular dynamics (MD) can provide knowledge of both. In this study, thermally populated substates on the free energy surface of MutS proteins are defined using all-atom MD simulations and principle component analysis (PCA). Our investigation reveals that DNA binding facilitates both, adjustment of thermal populations and major reshaping of the surface. Analysis of the collective atomic fluctuations within the protein framework of MutS establishes possible allosteric networks, which are highly dependent on the substate.

2936-Pos

Ovine Prion Polymorphisms Investigated by Threading to a Model Left Handed Beta Helical Structure using Molecular Dynamics Simlation

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We use AMBER all atom molecular dynamics (MD) to assess the stability of a model of the prion protein in its disease-causing conformation, PrPsc. The model is based upon threading the ovine prion sequence onto a template left-handed beta-helical (LHBH) structure with 18 residues per turn. Five polymorphisms in the sheep prion protein, VRQ, ARQ, ARH, AHQ, and ARR, have been identified at residues 136, 154, and 171 respectively, which are roughly 18 amino acids apart which thus align approximately on the LHBH. Threading of the sequence was thus done with an emphasis on the locations of these special sites as a means to investigate their possible role in disease susceptibility as well as investigating the overall viability of the LHBH as a structural candidate for PrPsc. In comparison to known left handed beta-helical proteins, the resulting model for VRQ is shown in all atom MD to 10 ns to exhibit similar stability as indicated by a low root mean square deviation, the presence of substantial side-chain to side-chain hydrogen bonding, and volume packing fraction. Interestingly, and in corroboration with experimental data that it is a disease resistant variant, the same model for ARR exhibits much less stability. Each polymorphic site was also investigated individually by comparing results from models with only one site different and showed a good correlation to experimental data regarding the relation of the variants to disease susceptibility.

2937-Pos

The Functional Role of Membrane Bound Proteinase 3

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Proteinase3 (Pr3) is a serine protease of the neutrophils involved in inflammation processes. Its membrane expression is a risk factor for chronic inflammatory diseases such as vasculitis or emphysema. A recent study demonstrated that Pr3 is co-localized with scramblase at the membrane and might thus be related to the externalization of phosphoserine-lipids in apoptotic cells.

Biophysical data shows a significant hydrophobic contribution to the binding of Pr3 to lipid bilayers, which is not observed for its close homolog the Human Neutrophil Elastase (HNE).

Here, we applied all-atom MD simulations to study the interactions of Pr3 and HNE with equimolar mixtures of DMPC with DMPG, DMPA and DMPS. Pr3 and HNE were introduced into previously calibrated lipid bilayers. These all-atom models enabled us to identify hydrophobic interactions of Pr3 with the lipid tails, which we did not observe for HNE. Further, we identified charge pairing of specific basic residues of Pr3 with DMPS lipids, not found for bilayers containing DMPG or DMPA. Although the substrate specificity of soluble Pr3 has been extensively studied, the influence of the membrane on its enzymatic activity is still a matter of debate. We docked peptides onto our models of membrane-bound Pr3 (mPr3). A thorough comparison of the peptide-protein interactions of mPr3 and soluble Pr3 revealed the changes in Pr3 substrate specificity induced by the membrane.

In conclusion, our MD simulations revealed the atomic details of the membrane binding of Pr3, and especially its strong affinity to phosphoserine-lipids. This allows us to propose a hypothesis on the role of Pr3 in apoptosis of neutrophils. In addition, this study contributes to the understanding of the enzymatic activity and substrate specificity of mPr3.

2938-Pos

Characterization of Electron Density Profiles and Area Per Lipid from MD Simulation of Large Undulating Bilayers

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Determination of the electron density profile (EDP) and area per lipid (A_L) from MD simulations of large lipid bilayers requires the characterization and isolation of the mesoscopic undulation dynamics. Typically, for small, flat bilayer patches, EDPs are calculated assuming a uniform bilayer normal across the trajectory. When common EDP algorithms are applied to larger systems, the undulations convolve an averaging function with the underlying "flat patch" EDP, introducing artifacts into the profile. It is necessary to decouple these undulation modes from both the protrusion and peristaltic dynamics in order to characterize an accurate EDP. We apply a 2-dimensional low-pass spatial filter, with frequency response optimized to a characteristic wave-number, q0 (as determined by Lindahl and Edholm), to define a mid-plane reference position for every atom. We present two approximations for the local curvature that are necessary when referencing this new surface. Results of both methods are in good agreement with the "flat patch" EDP. Common approaches for determining a simulated A_L underestimate the true A_L by not accounting for the out of plane components. As an alternative, we have developed two separate A_L schemes, both of which produce an increase in A_L of 1-2 $Å^2$ over the projected *xy-area*.

2939-Pos

A Coarse Grained Molecular Dynamics Study of the Formation and Structure of Bicelles

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Our goal is to study interactions between bicelles and membrane associated proteins by computer simulations. In this preliminary study we have tested different representations of the bicelle lipids within the MARTINI coarse grain (CG) model. Bicelles are lipid disk-shaped systems with properties that are believed to resemble those of a native lipid bilayer. This has made them useful for studies of membrane associated proteins by a range of biophysical techniques, such as circular dichroism, liquid and solid state NMR and in diffraction studies. Bicelles normally consist of two different kinds of lipids, one with short hydrophobic tails and one with longer tails. The structure and composition of a bicelle depends on both the temperature and the ratio between the long and short tailed lipids, also known as the q-factor. The results from the CG molecular dynamics (MD) simulations are compared to NMR data, and by that revealing that this method can account for the experimental observations made of bicelle structures. Furthermore, reversed CG united atom MD simulations using the GROMOS96 force field indicate that the bicelles formed are stable on the time scale simulated. The results from the CG MD of bicelles also underline the importance of choosing a proper mapping of atoms to the CG beads.

2940-Pos

Coarse-Grained Molecular Dynamics Simulations of Pegylated Lipids

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Polyethylene oxide (PEO) and polyethylene glycol (PEG) are polymers with the subunit C-O-C. Due to their low toxicity and high solubility in water, they have been conjugated (or PEGylated) to the drug transporters such as vesicles and micelles. Experimental results have shown the phase behavior of lipid/PEG-lipid mixtures and characterized their sizes using a disk model with apparent hydrodynamic radius. In this work, we perform coarse-grained molecular dynamics simulations of self-assemblies of a mixture of lipids and PEGylated lipids. Simulations with various concentrations of PEGylated lipids lead to formation of liposomes, bicelles, and micelles, and their sizes were characterized. Phase diagrams show dependence of PEG concentration, length, and temperature.

2941-Pos

Improving Internal Peptide Dynamics in the Coarse-Grained Martini Model: Application to Amyloid Peptides

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The assembly of misfolded protein aggregates into amyloid fibrils is at the heart of the development of neurodegenerative disorders such as Alzheimer's disease and prion diseases [1, 2]. Despite its significance, the driving forces behind the aggregation of peptides and protein misfolding are not well understood. To gain molecular insight into the aggregation of amyloid peptides, we carry out computer simulations using the recently developed MARTINI coarse-grained (CG) model [3]. Compared to the more traditional atomistic simulations, CG models offer the possibility of following protein folding events, which typically occur on the millisecond timescale. The current MARTINI model, in particular, is able to reproduce a wide range of lipid properties as well as lipid-protein interactions for rigid proteins. Protein folding and aggregation however often involves significant transitions between secondary structures and hence requires that the proteins be flexible during the simulations. We will present recent