Sortase A cleaves a C-terminal sorting signal of the surface proteins at a conserved LPXTG motif with the help of a calcium ion, leading to adhesion to the cell wall peptideglycan. The solution structures with and without a peptide (LPAT) reveal that a disordered loop undergoes a disorder-to-order transition upon peptide binding. Comprehensive conformational sampling of the disordered loop has been performed to elucidate how flexible the disordered loop in the peptide free form is and how the peptide and calcium binding affect the flexibility. The free energy landscape thus calculated clarifies the role of the calcium ion in the enzyme activity.

795-Pos Board B595

Molecular Dynamics Simulations of Anionic Lipid Bilayers in Presence of Calcium Ions

Wei Zhao, Valentina Corradi, Peter Tieleman.

The negatively charged phosphatidylserine (PS) lipid molecules contribute up to 17% of the lipid composition in mammalian cell membranes. Experiments have shown that PS lipids, in presence of Ca^{2+} ions, are involved in a number of membrane-mediated processes such as phase separation, membrane fusion, and protein topological changes.

However, although experiments have been performed aimed at understanding the interactions of Ca^{2+} ions with PS lipids, the detailed mechanism of Ca^{2+} induced changes in PS-containing membranes is not well established. This is, in part, due to the lack of conformational information at the atomistic level in experimental measurements.

Molecular dynamics (MD) simulation is a powerful tool in elucidating phenomena at the molecular level and has been used widely in the field of biophysics. Specifically, several atomistic MD simulation studies have been performed to study the properties of model membranes containing PS in absence and presence of Ca^{2+} ions. However, it remains challenging to observe changes in membrane structure due to the presence of Ca^{2+} ions.

We are using atomistic and coarse-grained MARTINI simulations of membranes containing PS to study the role of Ca^{2+} ions in modifying structural and dynamic properties of the membranes.

796-Pos Board B596

Lipid Protein Interactions and Dynamical Properties of VDAC 1 channel

Rodolfo Briones, Saskia Villinger, Vytautas Gapsys, Ulrich Zachariae, Giller Karin, Christian Griesinger, Bert de Groot, Markus Zweckstetter.

VDAC-1 (Voltage Dependent Anion Channel) is one of the main components of the outer mitochondrial membrane. It is responsible for the transport of ATP and other anions, and it is involved in apoptosis and cancer [1]. The X-ray and NMR structures [2-4] showed VDAC as a 19 beta-barrel structure with an N-terminal alpha-helix bound to its interior. Mutations of E73 facing the membrane could be associated with local perturbations of the surrounding lipids. Remarkably, these changes are coupled to the intrinsic VDAC dynamics. To address this we measured the the local average thickness of the membrane and several structural properties of several E73 mutants of VDAC-1. Solution NMR in LDAO and molecular dynamics of VDAC-1 inserted in DPMC phospholipid patches were carried out. Mutation or chemical modification of E73 strongly reduces the micro- to millisecond dynamics in solution. The results show the main distortions of the membrane are located around E73. The major fluctuations of VDAC barrel were found to be correlated with the charge of E73. The motion amplitude described as PCA eigenvectors show structural deformations of VDAC mainly around E73X. The motions correspond to changes of the whole beta-barrel structure and align with the position of E73X. These results help to understand the intrinsic dynamic of VDAC and its possible interaction mechanism with lipid membranes.

[1] Zaid et al., Cell Death Differ. 12, 751 (2005)
[2] Hiller et al., Science 321, 1208 (2008)
[3] Ujwal et al., PNAS 105, 17742 (2008)
[4] Bayrhuber et al., PNAS 105, 15370 (2008)

797-Pos Board B597

Development of a Coarse-Grained Model for the Surfactant Family of Linear Alkylbenzene Sulfonates

Xibing He, Wataru Shinoda, Russell Devane, Olgun Guvench, Kelly L. Anderson, Alexander D. MacKerell, Michael L. Klein.

A coarse-grained (CG) model has been developed for the anionic surfactant class, linear alkylbenzene sulfonates (LAS), which are the most widely used synthetic surfactants. The development work started from a systematic examination of tens of CG water models with different resolutions, interaction potentials (Lennard-Jones and Morse), and cut-off distances. The relationships between the parameters under specific choices of the above options and the thermodynamic properties, such as density, surface tension, and compressibility, were found to fit simple mathematical equations. The limits of applicability of these CG water models were explored by checking the melting temperature. Considering both efficiency and accuracy, a CG water model which includes three water molecules in one CG site was chosen. Correspondingly, the LAS molecules were mapped into CG sites each contains approximately three heavy atoms and connected hydrogens. Structural data obtained from atomistic simulations and thermodynamic data from experiments were used as targets to parameterize standard potential forms for bonded and non-bonded interactions. An extensive evaluation of the CG model for a series of different alkane molecules (aliphatic or aromatic, linear or branched) shows that the present model is not only reliable, but also transferable. This point is crucial to assure that the model is capable of representing different isomers and homologues in the LAS family. The resulting model is easily implemented into standard MD codes. The added computational efficiency permits the simulation of the self-assembly of LAS solutions starting from a random configuration. The model is shown to accurately reproduce the phase behavior of solutions of pure isomers of sodium dodecylbenzene sulfonate, despite the fact that phase behavior was not directly taken into account in the parameterization.

798-Pos Board B598

Analysis of Amino Acid Sidechain Chi1, Chi2 Conformational Properties Using Quantum Mechanical and Experimental Crystallographic Survey Data

Xiao Zhu, Pedro Lopes, Jihyun Shim, Alexander D. MacKerell Jr.

Amino acid side chain flexibility is an important property that influences the side-chain interactions in proteins as well as protein stability. In molecular mechanics, the conformational properties of sidechains can beis modulated, in part, by torsional parameters. In this study, we analyze the conformational properties of sidechains via quantum mechanical calculations. One and two- dimensional chi energy surfaces were performed on dipeptides representative of the amino acids. Analysis was performed for relevant peptide backbone conformations corresponding to the alpha helical (alpha R), beta stranded (extended) and alpha L conformations. Calculated QM energy surfaces are indicative of the conformational properties of the different amino acid sidechains and were used as target data for optimization of the CHARMM additive and polarizable force fields optimization as well as a the basis for explaining experimental observations the sampling of sidechain conformations in protein crystallographic structures.

799-Pos Board B599

Sequence Dependent Free Energy Estimates of Base Opening in Arylamine-Induced DNA-Adducts

Eva Darian, Vipin Jain, Bongsup Cho, Alexander D. MacKerell Jr.

Environmental mutagens are strong inducers of carcinogenesis and can cause DNA damage including single- and double strand breaks, DNA cross-links and DNA-adduct formation. DNA adducts formed by aromatic amines including 2-aminofluorene (AF) and 4-aminobiphenyl (ABP) can adopt one or two out of three distinct conformations: B-type (B), stacked (S) or wedge (W), related to the extent of opening of the base out of the DNA duplex. Notably, AF and ABP can assume either S or B conformations and the sampling of these states is dependent on sequence context. To obtain structural insight into this sequence-dependent phenomena, we have conducted potential of mean force calculations using molecular dynamics simulations of 11-mer 5'-CCATCG*C-XACC-3' duplexes with varying sequences, where X=A, T, C or G and G*=fluorine labeled-ABP or -AF. The analyses of the 15ns trajectories indicate that the stacking of adduct is greater in G*CT than G*CA. Calculated free energy of G* base flipping shows the presence of the second minima of the pseudo-dihedral angle at ~120°, which corresponds to the S conformer, though the ratio of S/B conformation is less than experimentally detected. Additional analyses are underway to try to better understand the mechanism of S/B conformational equilibrium and the impact of adduct-induced conformational heterogeneity on the stability of S/B conformations.

800-Pos Board B600

Disaccharide Binding to Galectin-1: Free Energy Calculations and Insight of the Molecular Recognition Mechanism

Ignacia Echeverria, L. Mario Amzel.

Galectin-1, a member of the conserved family of carbohydrate-binding proteins with affinity for β-galactosides, is an important modulator of several cell functions. In order to study the binding affinity and specificity of this protein, galectin-1 was modeled with eight different disaccharides: Galβ1,4glcNAc, Galβ1,4Glc, Galβ1,4Glcβ-OMe, MeO-2Galβ1,4Glc, Galβ1,4Man, Galβ1,4Frp, Galβ1,3Arp and Galβ1,3GlcNAc. Using molecular dynamics simulations each ligand was unbound from the binding site by a mechanical force. The free energy of binding (ΔG) was estimated using novel procedure based on combinations of multi-step trajectories (MSTC) (Echeverria I, Amzel LM. Proteins. 78(5):1302–10), which uses Jarzynski's equation (Jarzynski C. PRL. 1997;78(14):2690–3). Estimated binding free