21.5 kJ/mol for the liquid phase of POPC and DPPC lipids respectively for an electric field of 0.3 V/nm, and reduces at higher fields. The activation energy in the gel phase of POPC increases to 28.8 kJ/mol at the same field. The pore closing time after the field is switched off was found to be longer in the gel phase than in the liquid phase. Remarkably, pores of radii ~0.7nm in the gel phase of POPC did not close even after 50ns, whereas they close completely within 10ns in the liquid phase.

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1581-Pos Board B532

The Carboxy Terminus of the Ligand Peptide Determines MHC Class I Complex Stability: A Combined Molecular Dynamics and Experimental Study

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Major Histocompatibility complex (MHC) class I proteins bind peptides of eight to ten amino acids to present them at the cell surface to cytotoxic T cells. The class I binding groove binds the peptide via hydrogen bonds with the peptide termini and via diverse interactions with the anchor residue side chains of the peptide. To elucidate which of these interactions is most important for the thermodynamic and kinetic stability of the peptide-bound state, we have combined molecular dynamics simulations and experimental approaches in an investigation of the conformational dynamics and binding parameters of class I molecules with optimal and truncated natural peptide epitopes. We show that the F pocket region dominates the conformational and thermodynamic properties of the binding groove, and that therefore the binding of the C terminus of the peptide to the F pocket region plays a crucial role in bringing about the peptide-bound state of MHC class I.

1582-Pos Board B533

Molecular Modelling in MRI Contrast Agents Interacting with Water Molecules: Hierarchical Clustering Method for Molecular Dynamics Data Analysis

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A revised method to compute mean residence time (MRT) from molecular dynamics (MD) simulations is reported. One of the most frequent scenarios in the modeling of biological related systems is to describe their interactions with the solvent that in most of the cases is water. This is important, for instance, in determining the three dimensional structure and function of proteins that will greatly depend on the affinity of certain sections of these biomolecules with water. The amount of interaction with water can be quantified by means of the so called MRT, which for this specific case is the average time that a water molecule stays within a certain distance (threshold) from a particular referential point of the model molecule. Determining this threshold and for how long it can be broken during a simulation and still counting as a single event is not a straightforward task. To calculate MRT from MD data our methodology uses hierarchical clustering analysis. We propose applying this methodology as a step for the computational design of novel contrast agents for Magnetic Resonance Imaging (MRI) taking into consideration that MRT of water interacting with a given contrast agent directly affects the quality of the MRI images. In addition, it is shown that the presented method is applicable in a wider range of scenarios in MD data analysis.

1583-Pos Board B534

His 95 Acts as a pH Gate in Aquaporin-4

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Aquaporins are trans-membrane channels that are responsible for the permeation of water across the cell boundary. Responding to environmental stresses such as osmolarity, voltage and pH is an important aspect of regulation of channel permeability. We demonstrate that aquaporin-4, a membrane water channel modulates water transport via pH sensing. Aquaporin-4 is expressed mostly on the cytoplasmic membrane of cells of the nervous system. It has been implicated in the formation of edema during stress caused to the brain and thus has medical relevance. In this work we combine a Molecular Dynamics based computational approach with empirical methods to identify the molecular mechanism involved in the regulation of the channel via pH . Using a Partial Least Squares (PLS) based machine learning algorithm, we perform Functional Mode Analysis (FMA) to elucidate collective motions in the protein that are responsible for opening and closing the channel pore. We find that the protonation of conserved histidine residue H95 opens the channel and locally increases the pore radius. We employ Essential Dynamics (ED) simulations to ascertain that the collective mode identified by the computational method can indeed switch the protein function on and off. This mechanism is then tested experimentally by expressing the protein on Xenopus oocytes. By controlling the pH on either side of the cell boundary the location of the pH sensor is identified with respect to the cell membrane. Finally using mutational analysis it is established that H95 is the residue responsible for the pH sensing.

1584-Pos Board B535

Structural and Dynamical Study of Bovine Carbonic Anhydrase II in the Presence of Substrate: An Essential Dynamics and Molecular Dynamics Simulation Study

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Activity, regulation and inhibition of Bovine Carbonic Anhydrase II (BCAII), like other enzymes, are associated with its conformational changes.Molecular dynamics simulation was performed for Free BCAII and BCAII in complex with Para-nitro phenyl acetate to investigate the effect of substrate binding on BCAII structure and dynamics. Each Simulation was done for 100ns, in water with GROMACS software package. DSSP and Essential Dynamics techniques were used for analyzing secondary structures and concentrated motions, respectively. Results of this study demonstrated that presence of Para-nitro phenyl acetate in BCAII active site increased RMSD in the secondary structure backbone resulting in increasing number of amino acids in alpha helix and beta sheet and as opposed to turns. Flexible regions are located in the N-terminal while, surface of the protein and its central domain and the c-terminal have low flexibility and high resistance against changes. Motions have been induced in protein surface and secondary structures. Reduced motion in several sites, including amino acids 52 to 58 and 173 to 175 was observed. Increased motion in several sites, including beta sheets and alpha helices was induced. Results are in good agreement with studies on BCAII knotted structure and resistance against conformational changes.

1585-Pos Board B536

Resolving the Mechanisms of Bacterial Resistance to Macrolide Antibiotics

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Macrolides are a class of commonly used antibiotics that target the bacterial ribosome and prevent protein synthesis in the affected cells. Ribosomal residues A2058 and G2505 in the protein exit channel are considered to be particularly important for macrolide binding. Unfortunately, due to extensive use of macrolides, bacterial resistance, caused by mutation or methylation of specific rRNA residues in the ribosome, has become a growing concern. How these changes in rRNA induce macrolide resistance on a molecular level is still unclear. Here, we investigated macrolide resistance using atomistic molecular dynamics simulations.

Presently, there are no force field parameters developed specifically for macrolides. Therefore, we have developed novel approaches for force field parametrization from first principles for large and bulky molecules, such as macrolides, using the Force Field Tool Kit plugin in VMD. Parameters were developed and validated for two commonly used macrolides: erythromycin and azithromycin. These macrolides were studied in wild-type and in two mutated ribosomes of E. coli: G2057A and A2058G. The simulation showed that both mutations caused rearrangements of the binding site and decreased hydrogen bonding between the macrolide and residue 2058. Surprisingly, the G2057A mutation prevented hydrogen binding to residue 2058 to a larger extent than the A2058G mutation.

1586-Pos Board B537

Molecular Modeling of Self-Assembly of Anticancer Drug Amphiphiles

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Recently, Drug amphiphiles (DAs) have been shown to form discrete and stable supramolecular nanostructures with high and quantitative drug loading1. A drug amphiphile consists of a hydrogen-bonding peptide sequence attached to a hydrophobic drug. Similar to peptide amphiphiles2, DAs also self-assemble into discrete and well-defined supramolecular structures. Using