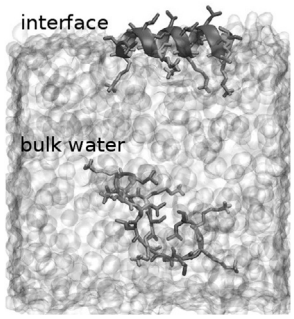
by the surrounding molecules. I will discuss our research on the interplay of intermolecular forces and influence of interfaces. In the first part the amphiphilic nature of short peptide oligomers and their behavior at the air/water interface will be discussed. The surface driving force and its decomposition will be analyzed. In the second part aggregation of peptides in bulk water and at an interface will be discussed. Different design features which can be tuned to control aggregation behavior will be analyzed. Finally, I will talk about the coarse-grain modeling of peptide-based materials.



References:
1) J. Phys. Chem. B 116 (7), 2198-2207 (2012).
2) Macromolecular Theory And Simulations 20, 451-465 (2011).

296-Pos Board B51

Pr65A Phosphorylaion Regulates PP2A Complexation and Signaling

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Serine-threonine Protein phosphatase 2 A (PP2A) is a major member of the PPP family of phosphatases. Increased PP2A activity/signaling regulates cardiac remodeling, contractility, and arrythmogenicity. The core PP2A complex is a hetero-trimeric holoenzyme consisting of a 36 kDa catalytic subunit (PP2Ac), a65 kDa scaffold subunit (PR65A or PP2Aa), and one of at least 18 variable regulatory proteins (B subunits) classified into 4 families. We have recently reported that cardiac PR65A is dephosphorylated in heart failure (Journal of Proteomics 77: 1-13, 2012). In the present study, three *in vivo* phosphorylations of cardiac PR65A were identified (S303, T268, S314) by MALDI-MS. In structural modeling, these are located at the concave surface and the bottom ridge of the A subunit and within HEAT repeats 7 and 8, suggesting that these residues do not directly contact PP2Ac or the regulatory subunits. Based on the structure of PP2A holoenzymes (PDB codes: 2NPP, 4I5L, 4I5N), Ser303 is buried between HEAT repeats 8 and 9 in all active PP2A holoenzymes, suggesting that significant structural shifts in HEAT repeat 7-9 are required to expose the phosphorylated Ser 303 (P-S303) and to accommodate the phosphate group, thereby alleviating the repulsive interactions between the phosphate group and internal hydrophobic structures and, as a result, stabilize the A subunit in an open conformation that hinders formation of the compact A subunit required for the holoenzymes. These phosphorylations indirectly reduce the interaction of PR65A with PP2Ac and PP2A activity was empirically demonstrated in HEK cells transfected with recombinant forms of PR65A with site-directed mutagenesis of these sites with phosphomimetic and non-phosphorylatable amino acids. Thus, phosphorylation of PR65A regulates PP2A signaling and PR65A dephosporylation may underlie increased PP2A activity in heart failure.

297-Pos Board B52

Retinal Makes Concerted Conformational Changes During Early Stages of Rhodopsin Activation

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G protein-coupled receptors (GPCRs) are a biomedically important class of integral membrane proteins. Many details of their activation mechanism are still unknown. Notably, the role played by protein-ligand interactions remains elusive. In the present work, we combined microsecond-scale all-atom molecular dynamics (MD) simulations with solid-state ^{2}H NMR to study the behavior of rhodopsin-the mammalian dim-light receptor-in the presence of either 11-*cis* or all-*trans* retinal. In order to validate our simulations, we directly calculated the theoretical ^{2}H NMR lineshape for retinal bound to rhodopsin in aligned bilayers [1]. To do this we applied ^{2}H NMR lineshape theory [2] with an iterative refinement procedure. These results corroborate our previous work, [3,4] revealing a highly dynamic ligand. Our data showed that retinal made a dramatic conformational change as the protein transitioned between the dark state and the Meta-I intermediate. A concerted elongation of the ligand defined this change. Simultaneously, (*i*) the ligand became more torsionally dynamic, (*ii*) conserved residues in the binding pocket reorganized, and (*iii*) there was a substantial influx of water into the G protein binding cleft. These changes occur only in simulations containing the all-*trans* form of retinal, revealing an intriguing picture of the early stages of GPCR activation. Importantly, our results reconcile two disparate experimental crystal structures, where retinal was found in the opposite orientation.

[1] Martínez-Mayorga, K., *et al*., (2006) *JACS***128**,16502. [2] Nevzorov, A., *et al*., (1999) *JACS***121**, 7636. [3] Struts, A., *et al*., (2007) *JMB***372**, 50. [4] Struts, A., *et al*., (2011) *PNAS***108**, 8263.

298-Pos Board B53

Efficient Protein Structure Alignment Methods Based on a Structural Alphabet

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The increasing number of available protein structures requires efficient tools for protein structure comparison. Indeed, pairwise and multiple structural alignments are essential for the analysis of function, evolution and architecture of protein structures. We have developed methods for pairwise and multiple structure comparisons largely based on sequence alignment techniques. A widely used Structural Alphabet named Protein Blocks (PBs) was used to transform the information on 3D protein backbone conformation as a 1D sequence string. A sequence alignment procedure based on dynamic programming was developed and named iPBA. The main adaptations of the procedure consist in using a dedicated PB Substitution Matrix, by weighting local similar stretches and by coupling linearly amino acid substitutions scores with PB substitutions. The resulting pairwise alignments were compared with DALI and MUSTANG and showed a significant improvement in 81.3% of the cases (Joseph, Srinivasan, de Brevern, Biochimie, 2011). A progressive alignment strategy similar to CLUSTALW was adopted for multiple PB sequence alignment, namely mulPBA. Highly similar stretches identified by the pairwise alignments are favored by higher weights during the alignment. The residue equivalences from PB based alignments are used to obtain a 3D-fit of the structures followed by an iterative refinement of the structural superposition. The method was benchmarked on different datasets used by similar approaches. The alignment quality is better than with MULTIPROT, MUSTANG and those within HOMSTRAD, in more than 85% of the cases. Comparison with other rigid-body and flexible approaches demonstrate that mulPBA alignments are superior to most rigid-body approaches and highly comparable to flexible alignment methods (Joseph, Srinivasan, de Brevern, Biochimie, 2012). These methods are implemented in two dedicated web servers (Gelly, Joseph, Srinivasan, de Brevern, Nucl Acid Res, 2011; Leonard, Joseph, Srinivasan, Gelly, de Brevern, JBSD, 2013).

299-Pos Board B54

In Silico Assessment of Bundle Architectures of HCV P7 Protein

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Hepatitis C virus (HCV) p7 protein is a 63 amino acid polytopic (2 transmembrane domains (TMDs)) membrane protein which forms ion conducting homo-oligomers. It is crucial for effective assembly and release of infectious virions and an attractive target for antiviral therapy. Recently experimentally derived structures of p7 have been published. The present work compares computationally derived hexameric bundle structures of p7 from genotype 1a with those from NMR experiments of the protein from genotype 1b and 5a.

Monomeric protein p7 is assembled using a combination of docking approach and molecular dynamics (MD) simulations. Consequently six copies of the monomer are docked to form a bundle. The lowest energy structure found is used for further assessment. The lowest energy bundle shows TMD1 with His-17 facing the lumen of the pore. Monomeric p7 of 1b is also assembled accordingly while p7 of 5a is taken as a bundle. All bundles, computational and experimentally derived, tend to collapse during extended MD simulations. A change of pH, mimicked by protonating the histidines, prolongs the integrity of the bundles. MD simulation of each of the p7 monomers, leads to a good structural alignment of their TMD1s with each other.