802-Pos Board B39

Abrogating Ras Abnormal Function by Targeting Membrane Bound Ras Monomers and Oligomers
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Ras is a lipid-modified GTPase that acts as a molecular switch by cycling between active and inactive conformational states and is involved in a plethora of cell signaling pathways. Somatic mutations in Ras are associated with a variety of cancers and are found in ~15% of human tumors such as pancreatic, colorectal, lung, breast cancer to name a few. Of the three major human Ras isoforms H-, N- and K-Ras, cancers associated with mutant K-Ras are the most lethal. Characterization of hot-spot residues required for the dynamic assembly of Ras on the plasma membrane could be of therapeutic relevance and may yield isoform-specific drugs. To this end, we performed microsecond-level atomistic molecular dynamics (MD) simulations of full-length, oncogenic K-Ras monomers bound to a heterogeneous membrane. We also carried out extensive protein-protein docking combined with all-atom MD to determine the homo-dimeric interface of the protein. MD-derived populations from the monomer simulations reveal K-Ras residues interacting directly with the membrane, predominantly in two different modes. Different docking approaches resulted in the identification of several dimer models. In silico mutagenesis and MD-optimization of these models in membrane revealed hot-spot residues that likely form the dimer interface. We will discuss these results in terms of their potential usefulness for anti-cancer drug design.

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Identifying Transient Binding Pockets in Protein Dynamics for Allosteric Drug Design
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Allosteric modulators that regulate the activity of the orthosteric ligands are emerging as cutting-edge strategies in drug design. Unlike orthosteric ligands, allosteric modulators bind to topographically distinct domains from those utilized by orthosteric ligands. Allosteric modulators offer unique therapeutic advantages such as high selectivity thereby causing reduced side effects. However, allosteric pockets are difficult to find since they are often formed transiently during the protein dynamics and hence could be absent in the crystal structures. This poses a challenge in designing allosteric modulators using structure based drug design methods that rely solely on crystal structures or homology models. Moreover not all transient pockets are suitable for allosteric modulation, since the allosteric pocket must communicate with the orthosteric site for functional modulation. Thus there is a dire need for novel techniques that utilize information from protein dynamics to detect allosteric sites for drug design. We present here a comprehensive method for designing allosteric modulators using protein dynamics trajectories or NMR data. We have developed a method, VoidVol, to identify transient binding cavities during protein dynamics. Next, using mutual information calculated from the dynamics trajectories, we map the allosteric pipelines communicating with the orthosteric site. The transient pockets having strong allosteric communication with the orthosteric site can be used for screening allosteric modulators. These sites can be further tested for druggability using the program FindBindSite, also developed in our laboratory. The resulting druggable sites can then be used for high-throughput screening of small-molecule database. We have validated this approach using several kinases and GPCRs with known allosteric modulators. Ethical and methodological considerations demonstrate how molecular dynamics can be useful for allosteric drug design. Our method is applicable to any water-soluble or membrane protein with an available crystal structure or homology model.

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Learning about Transitions: Adaptive Control in the Molecular Marshal (M2) Framework
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Improvements in sampling on the events leading to transitions can provide significant insights into what drives biomolecular change. We present additions to our Molecular Marshal (M2) software framework for the adaptive sampling of biomolecular transitions. As an example, we work with the transitions seen in BPTI from DEShaw Research (Science, 2010) using their long-running 1 ms trajectory as the basis for states and transitions analyzed from the Anton production trajectory. Our algorithm works by resampling snapshot conformations known to be right before transition events, creating an ensemble set of transitions preconditioned on sampling in the space near to the transitions. This enables us to explore the reduced degrees of freedom that drive the transitions and to examine the statistical foundations of the description for state transitions in BPTI. To achieve these goals we use an adaptive framework for resampling built around a parallel relational database system and with scripts controlling molecular dynamics codes running on XSEDE sponsored national supercomputers. In addition to BPTI, we will show results that start from other trajectories defined from peptides and from other long-running protein simulations. Our initial scripts for the final analysis and the resampling thus readily generalize to both long and short trajectory runs and can be used to increase sampling on a broad range of transition events.

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Characterizing Dynamics of Anion/Pi Interactions through Molecular Dynamics Simulations
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Proteins are not static structures, but undergo dynamical variations at room temperature that can lead to changes in the number and strength of different non-covalent interactions. The negatively charged (Asp/Glu) and aromatic (Phe/Trp/Tyr) amino acid groups in proteins can form anion/pi interactions, that have been shown to have a distance and angle dependency. This study characterizes the dynamic stability of these interactions in RmlC (PDB:1EP0), a homodimeric epimerase showing a cluster of six anion/pi pairs in crystal structure, as a function of time using Molecular Dynamics (MD) simulations. The dynamic variations found in these interactions correspond to a potential of mean force (PMF) that exhibits a relatively wide range of distances (~4.5 to~8.5Å) and angles (0 to~45deg) sampled by these anion/pi pairs. The corresponding PMF indicates an associated free energy change that can be more stabilizing (up to ~5kcal/mol) than the ab initio-calculated interaction energy for the pairs in the crystal structure (~2.2kcal/mol). Possible anion/pi pairs and triplets (anion/anion/pi or anion/pi/pi) not seen in the crystal structure are also observed in other conformations sampled by the protein- both at the dimer interface and active site of the protein, forming an extensive network of anion/pi interactions covering most of the protein structure. Initial site-directed mutagenesis (SDM) experiments targeting one of these pairs, Asp84-Phe112, show that the single Phe/Met mutation decreases the stability of the protein compared to the wild type. Together these results suggest that anion/pi interactions can play an important role in maintaining both the structural stability and function of the proteins.

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Simultaneous Identification, Visualization, and Comparison of Complex Events in Molecular Dynamics Simulations
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With the ability to perform all-atoms Molecular Dynamics (MD) simulations of complex biological systems on the micro- and even millisecond time-scales, the need to extract the interesting features of the molecular behavior inherent in the resulting trajectories has become more pressing. For the large molecules, short simulations on the order of nanoseconds are often considered to be metastable and quasi-harmonic, representing small fluctuations around a...