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1157-Pos Board B49

Druggability of Ionotropic Glutamate Receptor N-Terminal Domains

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Ionotropic glutamate receptors (iGluRs) are ligand-gated ion channels that mediate excitatory neurotransmission. All distinct classes of iGluRs (AMPA, NMDA, Kainate) harbor a ligand-binding domain (LBD), and an N-terminal domain (NTD) in their extracellular region. Glutamate binding to the LBD activates the ion channel. Allosteric modulation of iGluR activity by NMDAR NTD is well established; a similar function in AMPARs is still a matter of debate. Recently, we have shown that the bilobate architecture of iGluR NTDs favors similar global motions, and facilitates easy reconfiguration between AMPAR and NMDAR dimers [1,2]. This unexpected similarity in the intrinsic dynamics of these two subfamilies hints at the allosteric potential of non-NMDAR iGluRs and has propelled the evaluation of their ''druggability''. To achieve realistic detection of ligand-binding sites and their maximal binding affinities, we performed molecular dynamics (MD) simulations of iGluR extracellular domains in the presence of drug-like probe molecules and water. First, we benchmarked this method by exploring the well-known ligand-binding landscape of GluA2 LBD. We found that binding of one probe molecule in the endogenous ligand-binding site can drive domain closure necessary for channel activation. Subsequently, we explored the ligand-binding potential of all known iGluR NTDs. Our method captures with reasonable accuracy the known binding sites on NMDAR-GluN2B for modulators like Zn^{2+} and phenylethanolamine compounds, and furthermore provides insights into the chemical features and compound shape that may bind with better affinity than those known compounds. Another striking result from an extensive analysis of all iGluR NTDs is the accuracy with which the probe-binding hot spots overlap with known dimer interfaces of the monomers. This opens new avenues whereby we can accurately identify/predict druggable protein-protein interfaces.

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1158-Pos Board B50

Sampling Conformational Intermediates with Dynamic Important Sampling

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Hepatitis C virus (HCV) is a wide spread health concern and causes approximately 35,000 new infections in the U.S. each year. Though there are treatments available, they cause many side effects and are not completely effective for all genotypes. HCV contains a positive sense single-stranded RNA genome and replicates with the aid of RNA dependent RNA polymerase (RdRp). This polymerase is known to have at least two different conformations: open and closed. Our goal is to understand how this transition occurs in order to better understand how the enzyme is able to replicate RNA. To accomplish this goal we employ the Dynamic Importance Sampling Algorithm (DIMS). DIMS is a pathway finding algorithm that gives information about the intermediate states between defined starting and ending points. In our case of study this starting and ending points are the coordinates of the open and closed conformations taken from the 1YV2 and 1YUY structures (Biswall, B. K., Cherney, M.M., J. Biol. Chem. 280, 18, 18202-18210) DIMS allows us to sample the conformations of intermediates between the open and closed conformations to illuminate, at the molecular level. how this transition takes place, what motions facilitate the transition and what role conformational changes play in the function of the enzyme.

1159-Pos Board B51

Examining Protein Sequence Perturbations with Markov State Models

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Markov State Model (MSM) approaches model the conformational dynamics of proteins as a kinetic network of metastable states. This allows one to obtain long-timescale and equilibrium information from ensembles of much shorter non-equilibrium trajectories sampling local transition rates between states. To explore the possibility of using MSMs to efficiently characterize the effects of sequence perturbations, we construct ''wildtype'' and ''mutant'' MSMs built from molecular dynamics simulations of Fs peptide, the GB1 hairpin, and WW domain. We show that metastable states are generally robust to perturbation, although unfolded states may suffer from finite sampling. To assess the statistical significance of changes in observed transition counts that occur upon mutation, we develop a log-likelihood surprisal metric. We validate the metric in simple lattice models, and apply it to study sequence-dependent folding mechanisms and our ability to efficiently sample them.

1160-Pos Board B52

Structural Dynamics of Iowa, Dutch, and Arctic Mutations of the 21-30 Fragment of Amyloid Beta under Aqueous Salt Environments

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The amyloid β protein (Aβ) has been implicated in the pathogenesis of Alzheimer's disease. Previous in vitro experiments have shown that the central Aβ(21-30) fragment may have special importance because it may act as a folding nucleus of the full-length protein. Recently, experiments of the full-length wild type (WT) peptide under aqueous salt environments have revealed varied responses in both the structure and growth of aggregates of the full-length peptide under these environments. Here we use all-atom molecular dynamics simulations of monomeric Aβ(21-30) to examine pre-aggregate structural alterations under similar dissolved salt conditions (CaCl2 and KCl). Further, we make use of the wild-type and three common mutations of the decapeptide (Arctic[E22/G22], Dutch[E22/Q22], and Iowa[D23/N23]) to explore the possible dependence of charged side-chain and salt-ion interactions in driving structural changes under aqueous salt environments. Our results indicate that the production and stability of open (random-coil) structures is enhanced under CaCl2 for the wild-type decapeptide, and both Dutch and Iowa mutations; while KCl environments enhanced the production of turn structures for wild-type and β-structures for the Iowa and Dutch mutations. Additionally, we present a possible explanation for these differences in structural response as a combination of volume exclusion, ion-residue interactions, and ion effects on the hydration of the decapeptide.

1161-Pos Board B53

Intrinsic Transmembrane Flexibility of the Amyloid Precursor Protein Explored by Molecular Simulations

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Deposition of Amyloid-β (Aβ) is an early indicator of Alzheimer's disease (AD). Aβ is a 39- to 42-amino acid peptide released by the proteolytic cleavage of the C-terminal fragment of Amyloid Precusor Protein (APP). Recently, the backbone structure of the APP-C99 in detergent micelles was determined by nuclear magnetic resonance (NMR) restraints. The transmembrane (TM) domain resulted characterized by a highly kinked helix at position G708. We used molecular dynamics simulations to explore the conformational space of the APP transmembrane domain. Equilibrated models of APP inserted in micelles and lipid bilayers were produced and characterized; moreover the effect of experimental conditions on the APP TM free-energy landscape was investigated by using enhanced sampling techniques. Finally, the effect of small chemicals and pathogenic mutations were tested. Our findings were strongly correlated with *in vitro* experiments. We concluded that APP-C99 is intrinsically flexible at the hinge region defined by G708 and G709. Under in vivo-like conditions this is a key feature to explore multiple functional conformations implicated in proteolytic cleavage by γ-secretase and the generation of amyloidogenic species.

1162-Pos Board B54

Global Transitions or Proteins Explored by a Multiscale Hybrid Methodology: Application to Dopamine Transporter

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Efficient and accurate mapping of transition pathways is a challenging problem in allosteric proteins. We propose here a new methodology which facilitates the sampling of the conformational space by recruiting all modes of motions naturally encoded by the protein architecture, while evaluating the atomic interactions and energetics via full-atomic molecular dynamics (MD) simulation protocol. The basic approach is to deform the structure collectively along the modes of motion predicted by the anisotropic network model (ANM), similar