1712-Pos Board B32
Machine Learning Guided Ligand-Protein Simulation Approach Elucidates the Binding Mechanism of Abscisic Acid
Saurabh Shukla[1], Moeen Meigooni[1], Chuankai Zhao[1], Diwakar Shukla[1,2].
[1]Department of Chemical and Biomolecular Engineering, University of Illinois at Urbana-Champaign, Urbana, IL, USA, [2]Department of Plant Biology, University of Illinois at Urbana-Champaign, Urbana, IL, USA.
Rising temperatures and climate change are threatening agricultural productivity and have motivated efforts to elucidate the molecular mechanisms of drought resistance in plants. Abscisic acid (ABA) is a key plant hormone that imparts drought resistance in plants. Crystal structures of receptors (PYLs) involved in ABA perception have shed light on the interactions ABA makes in the binding pocket of the receptor but these structures provide limited knowledge about the dynamic mechanism of ABA binding. Mechanistic understanding of ABA recognition by plants could provide new avenues for development of drought resistant agrochemicals. In this work, we have performed extensive atomistic molecular dynamics (MD) simulations using Markov state models (MSMs) based adaptive sampling protocols to characterize ABA binding pathway for two ABA receptors in *A. Thaliana*, *At*PYL5 and *At*PYL10 receptors belonging to different sub-classes of ABA receptors to identify the major bottlenecks in their binding pathways. Our results not only explain the binding mechanism of ABA molecule but also provide atomistic information about the intermediate states along the binding pathways. We have also identified a new non-productive pose, which we call the inverted state, where ABA gets trapped in the binding pocket while forming an unproductive complex. We validate our results with previously published NMR and Hydrogen/Deuterium exchange experiments to show that receptors retain their flexibility even after ABA binding. Our findings shed light on the role of specific receptor residues in ABA binding, explore role of water in binding and characterize major barriers to ABA binding. Our results demonstrate the efficacy of MD simulations and MSM framework in elucidating the mechanism of ABA signaling. Knowledge of ABA binding mechanism will help in improving drought resistance in plants by informing genetic manipulations and agrochemical discovery efforts.

1713-Pos Board B33
Hydration Effects on Binding Equilibria: Role of Desolvation Energy
Daryl K. Eggers.
Chemistry, San Jose State University, San Jose, CA, USA.
This study tests a new thermodynamic framework for aqueous binding equilibria that features an explicit consideration for the change in hydration that occurs when two solvated surfaces come into contact. As an outcome of this approach, the standard state free energy of binding is defined by the summation of two terms, the traditional term (-RTlnK) plus a desolvation free energy term that is weighted by the number of complexes formed at equilibrium. The governing equation suggests that the equilibrium ratio (K) is not a constant; this equation is supported firmly by results from isothermal titration calorimetry using the chelation of calcium(II) by EDTA as a model binding reaction. In addition, we demonstrate that secondary solutes can shift the equilibrium by altering the average free energy of bulk water; molar solutions of urea, sucrose, and trehalose result in significant changes in the equilibrium ratio without altering the standard state free energy, as defined by our working equation. This investigation provides a fresh approach for characterizing concentrated, nonideal solutions, as relevant for understanding the driving forces behind molecular interactions in a cell or tissue. Future investigations will target other examples of concentration-dependent equilibria that appear to follow the proposed equations.

1714-Pos Board B34
A Structure Based Framework to Identify Novel Targets of FDA Approved Kinase Inhibitors
Hammad Naveed.
Computer Science, Toyota Technological Institute at Chicago, Chicago, IL, USA.
The promiscuity of drugs towards protein binding sites and vice versa hinders our understanding of the metabolism of healthy and diseased states. The identification of all protein targets is therefore important to understand a drug's (side) effects, and to reuse existing drugs. Current FDA approved kinase inhibitors have significant side-effects, many of which might be due to the off-targets of these drugs. We have developed a novel computational approach for drug target prediction for large-scale discovery of new targets for existing drugs. For a given drug, we construct a probabilistic pocket ensemble that captures the promiscuous structural features of drug binding sites. We were able to predict the interaction of six FDA approved kinase inhibitors (Sorafenib, Imatinib, Gefitinib, Dasatinib, Sunitinib, Pazopanib) with its known targets with a sensitivity of 50% and specificity of 56%. Four out of the five top predicted targets for Sorafenib were shown to interact with it using *in vitro* experiments. Our method is broadly applicable for the prediction of protein-small molecule interactions with several novel applications to biological research and drug development.

1715-Pos Board B35
A Synthetic Peptide from the N-Terminal of Hexokinase I Prevents the Interaction Between VDAC1 and SOD1 G93A Mutant Recovering the Viability of an ALS Cell Model
Andrea Magrì[1,2], Ramona Belfiore[3], Loredana Leggio[1], Francesca Guarino[3], **Angela Messina**[1].
[1]Biological G. & E. Sciences, University of Catania, Catania, Italy, [2]Biometec, University of Catania, Catania, Italy, [3]BIOMETEC, University of Catania, Catania, Italy.
Superoxide Dismutase 1 mutants associate with 20-25% of familial Amyotrophic Lateral Sclerosis (ALS) cases, producing toxic aggregates on mitochondria, notably in spinal cord [1,2]. The Voltage Dependent Anion Channel isoform 1 (VDAC1), the main pore in the outer mitochondrial membrane [3] is a docking site for SOD1 G93A mutant in ALS mice and the physiological receptor of Hexokinase I (HK1) [4], which is poorly expressed in mouse spinal cord [5, www.brain-map.org]. Our results demonstrate that HK1 competes with SOD1 G93A for binding VDAC1, suggesting that in ALS spinal cord available HK1-binding sites could be used by SOD1 mutants for docking mitochondria, producing thus organelle dysfunction [6]. We tested this model by studying the action of a HK1-N-end based peptide (NHK1). This NHK1 peptide specifically interacts with VDAC1, inhibits the SOD1 G93A binding to mitochondria and restores the viability of ALS model NSC34 cells [6]. Altogether, our results suggest that NHK1 peptide could be developed as a therapeutic tool in ALS, predicting an effective role also in other proteinopathies.
1. Magrì A et al, Biochim Biophys Acta (2016) 1857:789-98
2. Vande Velde C et al, *PNAS* (2008) 105:4022-7
3. De Pinto V et al, Biochim Biophys Acta (1989) 987:1-7
4. Tomasello MF et al (2013) PlosOne 8, e81522
5. Pastorino JG & Hoek JB *J Bioenerg Biomembr* (2008) 40:171-82
6. Magrì A et al, SciRep. 2016, *in press.*

1716-Pos Board B36
Multi-Conformer Hierarchical Virtual Screening Workflow to Identify Potential K-Ras Inhibitors
Amit K. Gupta[1], Priyanka Prakash[1], John A. Putkey[2], Alemayehu A. Gorfe[1].
[1]Integrative Biology and Pharmacology, UT Health houston, Houston, TX, USA, [2]Biochemistry and Molecular Biology, UT Health Houston, Houston, TX, USA.
K-Ras is a small GTPase that plays a critical role in the regulation of a variety of signaling pathways involved in cell growth and proliferation. Somatic mutations on K-Ras are associated with many different cancers, accounting for about 85% of all Ras-associated cancers or 15-20% of all human cancers. K-Ras is a very dynamic allosteric enzyme and our previous studies revealed that K-Ras harbors four allosteric ligand-binding pockets. This suggested that targeting K-Ras directly is a viable strategy to abrogate its abnormal functions. In the current study, we conducted extensive multi conformer hierarchical virtual screening to identify potential hits targeting each of these four pockets. In the first step we used clustering, structure-based pocket analysis and knowledge-based filters on conformers obtained from all-atom MD simulations of oncogenic mutant K-Ras to select representative structures for docking. The representative structures were further analyzed in terms of their physicochemical properties to gain an insight into the unique features of each pocket. Based on this the large purchasable chemical space of the ZINC database was tailored to generate complementary pocket-specific chemical libraries. We performed ensemble docking of these tailored ligand libraries against each pocket with the standard precision module of the Glide docking software, and used hierarchical post-docking analysis (PDA) to identify plausible K-Ras binders. In PDA the docking outputs of ligands were grouped based on their common residues interaction pattern (**A**) and chemical scaffold diversity (**B**) at the each binding site. A primary list of highest scoring hits per pocket was made from the ligands in the **B** subgroup that belonged to subgroup **A**, followed by visual inspection of the binding pose. This yielded a list of 761 potential hits. 217 of these were procured for experimental testing and about 100 were tested for their ability to bind to GDP-bound K-Ras using N^{15}-labeled heteronuclear single quantum coherence (HSQC) NMR. Of the 100 tested, 11 showed significant