hematopoietic cells, is significantly overexpressed in GBM. It is believed that LYN promotes migration of cancer cells, thus advancing the malignancy. This research addresses computational design of small druglike molecules that could potentially inhibit LYN and thus stave off the cancer advancement. LYN has a very similar binding site to the polo-box domain (PBD) in Polo-like kinase 1 (Plk1). Plk1 is a main regulator of mitosis. Considering the key cellular roles of both LYN and Plk1, it is important to design inhibitors that will specifically bind to LYN. In this work, physical and chemical properties of the binding sites of LYN and Plk1 were investigated and compared. Pertinent atomic distances within the LYN binding site were found to be smaller than those within the PBD of Plk1. The two sites also differed in their flexibilities. By utilizing the differences, novel molecules were designed that could potentially bind LYN with higher affinities than they could Plk1. Previously designed molecules that bonded both LYN and Plk1 were used as initial templates to design more specific inhibitors. Potential toxicities and drug-likeness of the molecules were evaluated. Molecules with no implied toxicities and optimal druglike properties were used for docking studies. Molecules that made the most stable docking configurations with LYN and with no other kinases were identified as LYN-specific. Binding energies of the stable complexes that these molecules formed with LYN were calculated. Possible utilization of the designed molecules against tumors with overexpressed LYN is discussed.

2068-Pos Board B798

Effect of Crystal Meth and Ecstasy Enantiomers on Function of Dopamine Transporters

Igor Zdravkovic, Sergei Y. Noskov.
University of Calgary, Calgary, AB, Canada.

The complexities of the brain are hidden in the always active neuron communication. The propagation of the neuron signals is carried out by neurotransmitters. It is obvious why the signals activation is important but the signal quenching is just at important in proper brain function. The length of the stimuli and in turn the intensity are controlled by the neurotransmitter transporters.
The clearing of the neurotransmitters from the synapse is the responsibility of transporters. Each neurotransmitter has its specific transporter. The main ones being Serotonin, Dopamine, and Norepinephrine Transporters (SERT, DAT, and NET). As a class of secondary transporters the sodium:neurotransmitter symporters utilize a sodium ion gradient to co-transport a neurotransmitter molecule against its gradient. The coupling of the ions favourable free energy to the unfavourable recycling of the neurotransmitters is the crucial step in deciphering the mechanism of transport.
The interaction between the substrate and protein are key to proper transport. However these transporters are very common targets not only for the neurotransmitters but many medicinal and psychedelic drugs. Our focus is on exploring similarities between the substrates and what properties make them likely to target transporters. Also we wish to explore the binding differences experimentally observed in different enantiomers of methamphetamines (crystal meth) and 3,4-methylenedioxymethamphetamine (ecstasy). We have used homology modelling to model hDAT and hSERT in three different conformations (open-to-out, open-to-in, and occluded). These six structures will be used to explore the differences between the S and R enantiomers. Like many biological systems preference is given to one conformation over the other, with S enantiomer being the highly preferred one.

2069-Pos Board B799

Predicting Druggable Sites in Protein-Protein Interfaces using *FindBindSite*

Hubert Li, Vinod Kasam, Nagarajan Vaidehi.
Immunology, Beckman Research Institute, City of Hope, Duarte, CA, USA.

Significance: Aberrant protein-protein interactions are a hallmark of disease and many cancers. Disrupting these interactions is a current therapeutic strategy. However, developing inhibitors for protein-protein interfaces (PPI) remains challenging due to large surface area over which these interactions occur. Computational methods can greatly aid in identifying druggable sites on the PPI enabling rational inhibitor design for PPI.
Approach: We have developed a computational method termed *FindBindSite* (FBS), to identify druggable sites in the PPI starting from free monomer structures. Our method virtually screens a small database of compounds or dipeptides over the entire protein surface and identifies regions with high docked ligand atom density. Densely populated regions are then clustered and scored based on cluster size. The clustering allows us to identify binding surfaces in the interface regions.
Results: FBS was validated 41 protein-protein structures crystallized in complex form. Structures were selected giving preference to free, protein-inhibitor, and then protein-protein complex when structures were not available. We predicted binding sites in interface regions of 71% with a high confidence and 90% with a low confidence using our test set. We tested the performance of FBS on homology models of free monomers achieving a hit rate of 68% when using templates with sequence identity between 20-97%. Applying a 60% sequence identity cutoff we achieved a hit rate of 86%. Using a library of dipeptides we were able to achieve 85% hit rate. We demonstrate that FBS is a useful computational method to predict binding sites in protein-protein interfaces because it uses the probe molecule diversity to span beyond well formed pockets and identify regions where one could likely disrupt any PPIs are likely to occur.

2070-Pos Board B800

Understanding the Interactions of Three Integrins with a Library of Peptides

Matt McKenzie, Aravind R. Rammohan.
Corning Inc, Corning, NY, USA.

Integrin receptors play a critical role in mediating early events in cells adhering to ECM and synthetic peptides on surfaces. To better understand the sensitivity of peptide sequences to a specific integrin types and between integrins we performed a computational analysis. Specifically we began by sequence based homologies between the three integrin receptors (3VI4, 3ZE2, and 1L5G) for which crystal structures are available. Using the homology study as a starting point we developed some hypothesis on potential similarities and differences to be expected with respect to their function. As the next step we performed computational docking simulations of the library of peptides (19) against each of these peptides using Autodock. For these simulations we primarily used the co-crystal structure (integrin/RGD PDB name 3ZE2) implicated binding pocket as the focus of our studies. Based on these docking simulations we have generated a number of different binding ensembles for each peptide for a given integrin receptor. From the top docking configurations (based on visual inspection, grouping, and Autodock Binding scores), we then performed steered molecular dynamics simulations to generate a potential of mean force for the peptides against the receptors. These values then serve as starting point into a multi-scale simulation study being used to estimate the adhesion of the entire cell to an ECM/functionalized surface.

2071-Pos Board B801

Re-Docking Scheme to Explore Docking Search Space by using Interaction Profiles

Nobuyuki Uchikoga[1], Yuri Matsuzaki[2], Masahito Ohue[2], Takatsugu Hirokawa[3], Yutaka Akiyama[2,4].
[1]Department of Physics, Chuo University, Tokyo, Japan, [2]Department of Computer Science, Tokyo Institute of Technology, Tokyo, Japan, [3]molprof, AIST, Tokyo, Japan, [4]Education Academy of Computational Life Sciences, Tokyo Institute of Technology, Tokyo, Japan.

In protein-protein interaction predictions, there are various approaches to obtain near-native 3D structure of protein complexes. One of the most available methods is rigid-body docking process, generating many protein complexes (decoys) as candidates of the native complex.
However, we sometime faced with one of the critical problems to solve, which is a situation of no near-native decoys including a decoy dataset. Even if the bound-state case, in 9 out of 44 protein pairs, we could not obtain near-native decoys. To overcome this situation, we applied interaction fingerprint (IFP) to this problem. IFP method in docking process is originally developed for cluster analysis by comparing among decoys in our previous work [Uchikoga & Hirokawa, (2010) BMC Bioinfor. 11:264]. This method can applied to proteins with large conformation changes, for example, calmodulin. IFP composed of frequencies of interaction between amino acid residues. Therefore, much more different structures can compare each other.
The critical situation of no near-native decoys results from a fact that docking search space is not large enough to obtain near-native decoys. Therefore, we proposed re-docking scheme for exploring docking search spaces by restricting protein surfaces after assembling interaction surfaces of decoys using IFPs. We applied re-docking scheme to several docking cases and will discuss the results.

2072-Pos Board B802

Model of the Nogo: Nogo Receptor Complex

Ali Alhoshani[1], Rosemarie Vithayathil[1], Gregory A. Weiss[2], Melanie J Cocco[1].
[1]Departments of Molecular Biology and Biochemistry, University of California, Irvine, Irvine, CA, USA, [2]Department of Chemistry, University of California, Irvine, Irvine, CA, USA.

Several myelin-associated proteins, the neurite outgrowth inhibitor (Nogo), myelin-associated glycoprotein (MAG), and oligodendrocyte-myelin