

Density of chloroform and water

3 immiscible liquids of different densities are in a sealed cylinder. Chemicals and Solutions Bis(2-chloroethyl)ether Water Mineral oil Materials One large cylinder with the above mentioned liquids Procedure This is a display. The column consists of 3 liquid layers with dyes. The cylinder can be shaken and it will separate over time. The order of density from least dense to most dense is: Liquid/Solid Density in g/mL or g/cm³ Bis(2-chloroethyl) ether 1.456 Water 0.998 Mineral Oil 0.8 Hint It takes a while to separate fully. If you shake the cylinder, do so early in the lecture. References Shakhashiri Chemical Demonstrations Vol 3 pg 225, 1989, The University of Wisconsin Press, Madison Wisconsin Density Column 2 Summary Three level density column is made in class. Hazards Iodine can cause burns. Chloroform is a possible carcinogen Copper Sulfate is an irritant Chemicals and Solutions Ethyl Acetate Water Chloroform Iodine CuSO₄ Materials 2 Ungraduated Cylinders deflagrating spoon Procedure Two Ungraduated cylinders will be provided with the three liquids inside. Liquid Density in g/mL or g/cm³ Ethyl acetate 0.897 Water 1.00 Chloroform 1.48 Using the deflagrating spoon Copper Sulfate is only miscible in the aqueous layer and will show a floating blue layer. Iodine is then added to the other cylinder which is miscible in the organic layers. An orange and red solution will be separated by the colorless middle aqueous phase. The iodine and copper sulfate will then be added to the corresponding cylinder to make an orange/blue/red column. Hint Do not mix the organic layers as they are miscible. Disposal Organic layers will be combined and sent to EH&S as 1% iodine 99% Ethyl acetate/chloroform. Aqueous layer will be sent as 1% CuSO₄ and 99% water. 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Phys. 2009, 11, 2592-2596, DOI: 10.1039/b822395e Page 3Derivation of free energy of binding calculations employed in study; Table S1, bonded parameters for all di/trisaccharides; Table S2, bead type selection for N-glycans; Table S3, lectins with residues interacting with glycans; Table S4, residues and Martini bead composition; Table S5, window spacing; Figure S1, bonded distributions; Figure S3, M3 dihedral distributions; Figure S4, effect of elastic network on self-interaction properties; Figure S5, dependence of PMF on scaling nonbonded interactions in Martini v2.2; Figure S6, size dependence on solubility of glycans; Figure S7, crystal structures of lectin-glycan binding simulations; Figure S11, surface dependence of PMFs Figure S12, unrestrained simulations of PAL and M5 ligand; and Figure S13, unrestrained simulations of CVN and M9 ligand. Forcefield files and scripts for generating glycan topologies and coordinates are freely available from the authors upon request (PDF)Page 4LEARN ABOUT THESE METRICSArticle Views are the COUNTER-compliant sum of full text article downloads since November 2008 (both PDF and HTML) across all institutions are the number of other articles citing this article, calculated by Crossref and updated daily. Find more information about Crossref citation counts. The Altmetric Attention Score is a quantitative measure of the attention that a research article has received online. Clicking on the score and the score and the score is a quantitative measure of the attention Score and how the score is a quantitative measure of the attention that a research article has received online. calculated. Page 5Small molecule compounds which form colloidal aggregates in solution are problematic in early drug discovery; adsorption of the target protein by these aggregates can lead to false positives in inhibition assays. In this work, we probe the molecular dynamics simulations. Specifically, we examine in aqueous solution the adsorption of the enzymes β-lactamase and PTP1B. When complexed with aggregate, the proteins do not exhibit significant alteration in protein tertiary structure or dynamics on the microsecond time scale of the simulations, but they do indicate persistent occlusion can occur via surficial interactions of protein with miconazole but also potentially by envelopment of the protein by miconazole. The heterogeneous polarity of the miconazole aggregate surface seems to underpin its activity as an invasive and nonspecific inhibitory agent. A deeper understanding of these protein/aggregate systems has implications not only for drug design but also for their exploitation as tools in drug delivery and analytical biochemistry. Page 6Protein-protein interactions (PPIs) are attractive targets for drug design because of their essential role in numerous cellular processes and disease pathways. However, in general, PPIs display exposed binding pockets at the interface, and as such, have been largely unexploited for therapeutic interventions with low-molecular weight compounds. Here, we used docking and various rescoring strategies in an attempt to recover PPI inhibitors from a set of active and inactive molecules for 11 targets collected in ChEMBL and PubChem. Our focus is on the screening power of the various developed protocols and on using fast approaches so as to be able to apply such a strategy to the screening of ultralarge libraries in the future. First, we docked compounds into each target using the fast "pscreen" mode of the structure-based virtual screening (VS) package Surflex. similarity and (ii) interaction fingerprint similarity with a co-crystallized inhibitor, (iii) solvent-accessible surface area, and (iv) extent of deviation from the geometric center of a reference inhibitor. The derivatized descriptor-scaled scoring functions, were utilized to investigate possible impacts on VS performance metrics. Moreover, four standalone scoring functions, RF-Score-VS (machine-learning), DLIGAND2 (knowledge-based), Vinardo (empirical), and X-SCORE (empiric under the receiver operating characteristic curve for some targets, and in early stages, with up to a 4-fold increase in enrichment factors at 1% of the screened collections. Outstandingly, DLIGAND2 emerged as the best scoring function on this data set, outperforming all rescoring techniques in terms of VS metrics. The described methodology could help in the rational design of small-molecule PPI inhibitors and has direct applications in many therapeutic areas, including cancer, CNS, and infectious diseases such as COVID-19.Page 7Although molecular dynamics simulations allow for the study of interactions among virtually all biomolecular entities, metal ions still pose significant challenges in achieving an accurate structural and dynamical description of many biological assemblies, particularly to coarse-grained (CG) models. Although the reduced computational cost of CG methods often makes them the technique of choice for the study of large biomolecular systems, the parameterization of metal ions is still very crude or not available for the vast majority of CG force fields. Here, we show that incorporating statistical data retrieved from the Protein Data Bank (PDB) to set specific Lennard-Jones interactions can produce structurally accurate CG molecular dynamics simulations using the SIRAH force field. We provide a set of interaction parameters for calcium, magnesium, and zinc ions, which cover more than 80% of the metal-bound structures reported in the PDB. Simulations performed on several proteins and DNA systems show that it is possible to preclude the use of topological constraints by modifying specific Lennard-Jones interactions. Page 8Translocator protein (TSPO), a mitochondrial membrane protein, has been extensively studied, and its role is still debated and continues to be enigmatic. From a structure remains elusive. In the present study, we attempted to study dynamics of TSPO from the perspective of oligomerization. In this are enigmatic. aim, we examined if and how TSPO monomers could assemble to form a dimer. Accordingly, we performed several coarse-grained molecular dynamics simulations, one with a pair of TSPO monomers distantly placed in a model of a bilayer composed of DMPC/cholesterol mixture and the other with preformed dimer models with different starting interactions. We identify stable TSPO dimers with diverse interfaces, some of which were consistent with earlier experimental observations on putative TSPO oligomer interfaces. For most of the stable ones, interactions between aromatic residues were significantly overrepresented in diverse oligomeric organizations. Interestingly, we identified different communication pathways that involve dimer interfaces. Additionally, we observed that cholesterol molecules in close interaction with the TSPO dimer were able to translocate through the bilayer. increased and favored by the dimer formation. Overall, our observations shed new light on TSPO oligomerization and bring new perspectives on its dynamics, as well its interactions with protein and ligand partners. Page 9Dopamine (DA) transporter (DAT) is a major target for psychostimulant drugs of abuse such as cocaine that competitively binds to DAT, inhibits DA reuptake, and consequently increases synaptic DA levels. In addition to the central binding site inside DAT, the available experimental evidence suggests the existence of alternative binding sites on DAT, but detection and characterization of these sites are challenging by experiments alone. Here, we integrate multiple computational approaches to probe the potential binding sites on the wild-type Drosophila melanogaster DAT and identify a new allosteric site that displays high affinity for cocaine is primarily dominated by interactions with hydrophobic residues surrounding the site. We show that cocaine binding to this new site allosterically reduces the binding of DA/cocaine to the central binding of cocaine to this site stabilizes the conformation of DAT but alters the conformation and thereby reduces the accessibility by DA, providing molecular insights into the inhibitory mechanism of cocaine. In addition, our results indicate that the conformations induced by cocaine binding to this site may be relevant to the oligomerization of DAT, highlighting a potential role of this new site in modulating the function of DAT. Page 10G-Protein coupled receptors (GPCRs) are involved in a myriad of pathways key for human physiology through the formation of complexes with intracellular partners such as G-proteins and dynamical determinants of these complexes are still largely unknown. Herein, we developed a computational big-data pipeline that enables the structural characterization of GPCR complexes with no available structure. This pipeline was used to study a well-known group of catecholamine receptors, the human dopamine receptors, the human dopamine receptors, the human dopamine receptors of all members of the DXR family (D1R, D2R, D3R, D4R, and D5R) and the corresponding protein interfaces of their binding partners (Arrs: Arr2 and Arr3; G-proteins: Gi1, Gi2, Gi3, Go, Gob, Gq, Gslo, Gssh, Gt2, and Gz) was generated. To produce reliable structures of the DXR family in complex with either G-proteins or Arrs, we performed homology modeling using as templates the structures of the \$2-adrenergic receptor (M2R) bound to Gi, and the recently acquired neurotensin receptor-1 (NTSR1) and muscarinic 2 receptor (M2R) bound to arrestin (Arr). Among others, the work demonstrated that the three partner groups, Arrs and Gi-proteins, are all structurally and dynamically distinct. Additionally, it was revealed the involvement of different structural motifs in G-protein selective coupling between D1- and D2-like receptors. Having constructed and analyzed 50 models involving DXR, this work represents an unprecedented large-scale analysis of GPCR-intracellular partner interface determinants. All data is available at www.moreiralab.com/resources/dxr.Page 11Figure S1, multiple alignment of SLN deletion constructs; Figure S12, helical content of SLN deletion constructs; Figure S13, TM domain orientation and time-averaged local membrane thickness of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedral angles of SLN deletion constructs; Figures S15-S18, backbone dihedr constructs simulated with the CHARMM36 force field; Figures S19-S22, backbone RMSD, RMSF, TM insertion, tilt angle, φ/ψ torsion angle distribution, mutual correlation analysis, helical content, contacts with the lipid headgroups, and membrane thickness analysis of three SLN deletion constructs simulated with the Amber ff14SB force field in the DMPC lipid bilayer; and Figure S23, backbone RMSD and per-residue RMSF of SLN phosphorylated at residue T5 (PDF)Page 13FMS-like tyrosine kinase 3 (FLT3) is mutated in ~30% of patients, in-frame insertions are observed in the sequence. Most of those insertions are internal tandem duplications (ITDs) of a sequence from the protein. The characteristics of such mutations in terms of length, sequence, and location were hitherto studied in different populations, but not in a comprehensive mutation database. Here, in-frame insertions into the FLT3 gene were extracted from the Catalogue of Somatic Mutations in Cancer (COSMIC) database. These were analyzed with respect to the length, location, and sequence of the mutations. Furthermore, characteristic strings (sequences) of different lengths were identified. Mutations and first tyrosine kinase domain (TKD1), upstream of the phosphate-binding loop (P-loop). Interestingly, there are specific hot spot residues where insertions are more likely to occur. The insertions vary in length between one and 67 amino acids, with the largest insertions spanning the phosphate binding loop. Insertions that occur downstream of the P-loop are shorter. Our analysis further shows that acidic and aromatic residues are enriched in the insertions. Finally, molecular dynamics simulations were run for FLT3 with ITD insertions in the hinge and tyrosine kinase domains. On the basis of the findings, a mechanism is proposed for activation by ITDs, according to which there is no direct coupling between the length of the insertion and the activity of the mutated protein. The effect of insertions on the sensitivity of FLT3 to kinase inhibitors is discussed based on our findings. Page 14 Molecular dynamics (MD) simulation has become a powerful tool because it provides a time series of protein dynamics at high temporal-spatial resolution. However, the accessible timescales of MD simulation are shorter than those of the biologically rare events. Generally, long-time MD simulations over microseconds are required to detect the rare events. Therefore, it is desirable to develop rare-event-sampling methods. For a rare-event-sampling method, we have developed parallel cascade selection MD (PaCS-MD). PaCS-MD generates transition pathways from a given source structure to a target structure by repeating short-time MD simulations) with high potentials to make transitions toward the target structure. In the present study, based on principal component analysis (PCA), we propose PCA-based PaCS-MD to detect rare events of collective motions of a given protein. Here, the PCA-based PaCS-MD is composed of the following two steps. At first, as a preliminary run, PCA is performed using an MD trajectory from the target structure to define a principal coordinate (PC) subspace for describing the collective motions of interest. PCA provides principal modes as eigenvectors to project a protein configuration onto the PC subspace. Then, as a production run, all the snapshots with higher values of short-time MD simulations are ranked by inner products (IPs), where an IP is defined between a snapshot swith higher values. of the IP are selected as reasonable candidates, and short-time MD simulations are independently restarted from the PCA-based PaCS-MD repeats the short-time MD simulations from the reasonable candidates that are highly correlated with the target structure. As a demonstration, we applied the PCA-based PaCS-MD to adenylate kinase and detected its large-amplitude (open-closed) transition with a nanosecond-order computational cost. Page 15Using an all-atom explicit water model lipid bilayers. The first was formed of 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine, palmitoyl-sn-glycero-3-phosphoethanolamine, palmitoyl-sn-glycero-3-phosphoethan two bilayers has revealed qualitative similarities. Partitioning into the DMPC and BBB bilayers is thermodynamically favorable although insertion into the former lowers the free energy of benzoic acid by approximately an additional 1 kcal mol-1. The partitioning energetics for the two bilayers is also largely similar based on the balance of benzoic acid interactions with apolar fatty acid tails, polar lipid headgroups, and water. In both bilayers, benzoic acid retains a considerable number of residual water molecules until reaching the bilayers, benzoic acid retains a considerable number of residual water molecules until reaching the bilayers, benzoic acid retains a considerable number of residual water molecules until reaching the bilayers, benzoic acid undergoes several rotations primarily determined by the interactions with the lipid headgroups. Nonetheless, in addition to the depth of the free energy minimum, the BBB bilayer differs from the DMPC counterpart by a much deeper location of the free energy minimum, the BBB bilayer differs from the DMPC and BBB bilayers exhibit different structural responses to benzoic acid insertion. Taken together, the BBB mimetic bilayer is preferable for an accurate description of benzoic acid partitioning. Page 16The increased activity of monoamine oxidase (MAO) enzymes may lead to serious consequences since they reduce the level of neurotransmitters and are associated with severe neurodegenerative diseases. The inhibition of this enzyme, especially the B isoform, plays a vital role in the treatment of Parkinson's disease (PD). This study is aimed to find novel human MAO-B (hMAO-B) selective inhibitors. A total of 256.750 compounds from the Otava small molecules database were virtually screened gradually by employing several screening techniques for this purpose. Initially, a high-throughput virtual screening (HTVS) method was employed, and 10% of the molecules having high docking scores were subjected to binary QSAR models for further screening of their therapeutic activities against PD, Alzheimer's disease (AD), and depression as well as for their toxicity and pharmacokinetic properties. Then, enzyme selectivity of the ligands towards the A and B forms that passed through all the filters were studied using the induced-fit docking method and molecular dynamics simulations. At the end of this exhaustive research, we identified two hit molecules ligand3 (Otava ID: 7131545) and ligand4 (Otava ID: 7566820). Based on the in vitro results, these two compounds (ligands3 and 4) together with ligands 1 and 2 found in our previous study showed activity at the nanomolar (nM) level, and the results indicated that these four ligands 1 and 2 found in our previous study showed activity at the nanomolar (nM) level, and the results indicated that these four ligands 1 and 2 found in our previous study showed activity at the nanomolar (nM) level activity at the nactivity at the nanomolar (nM) level activity at th molecules (SCAMs) are the most common source of false positives in high-throughput screening (HTS) campaigns. Although SCAMs can be experimentally detected and suppressed by the addition of detergent in the assay buffer, detergent sensitivity is not routinely monitored in HTS. Computational methods are thus needed to flag potential SCAMs during HTS triage. In this study, we have developed and rigorously validated quantitative structure-interference relationship (QSIR) models of detergent-sensitive aggregation in an AmpC βlactamase assay, the preferred HTS counter-screen for aggregation, as well as in another assay that measures cruzain inhibition. Our models increase the accuracy of aggregation prediction by ~53% in the β-lactamase assay and by ~46% in the cruzain assay compared to previously published methods. We also discuss the importance of both assay conditions and screening concentrations in the development of QSIR models for various interference mechanisms besides aggregation. The models developed in this study are publicly available for fast prediction within the SCAM detective web application (.Page 18G-protein-coupled receptors (GPCRs) transmit signals into the cell in response to ligand binding at its extracellular domain, which is characterized by the coupling of agonist-induced receptor conformational change to guanine nucleotide-binding protein (G-protein), leading to the activation of the G-protein. The signal transduction mechanisms have been widely researched in vivo and in silico. However, coordinated communication from stimulating ligands to the bound GDP still remains elusive. In the present study, we used microsecond (µS) molecular dynamic (MD) simulations to directly probe the communication from the β2 adrenergic receptor (β2AR) with an agonist or ar antagonist or no ligand to GDP bound to the open conformation of the Ga protein. Molecular mechanism-general Born surface area calculation results indicated either the agonist caused a higher level of destabilization than the antagonist. This is consistent with the role of agonist in the activated systems. Interestingly, while GDP remained bound with the G α -protein for the agonist-bound and apo form), GDP dissociated from the open conformation of the G α -protein for the two inactive systems. Data obtained from MD simulations indicated that the receptor and the Gα subunit play a big role in coordinated communication and nucleotide exchange. Based on residue interaction network analysis, we observed that engagement of agonist-bound β2AR with an α5 helix play very important roles and the residues in the phosphate-binding loop, α1 helix, and α5 helix play very important roles and the residues in the phosphate binding loop. in the GDP release. The insights on GPCR-G-protein communication will facilitate the rational design of agonists that target both active and inactive GPCR binding pockets, leading to more precise drugs. Page 19LEARN ABOUT THESE METRICSArticle Views are the COUNTER-compliant sum of full text article downloads since November 2008 (both PDF and HTML) across all institutions are the number of other articles citing this article, calculated by Crossref and updated to reflect usage leading up to the last few days. Citation save the number of other articles citing this article, calculated by Crossref and updated to reflect usage leading up to the last few days. Citation save the number of other articles citing this article, calculated by Crossref and updated to reflect usage leading up to the last few days. a quantitative measure of the attention that a research article has received online. Clicking on the donut icon will load a page at altmetric.com with additional details about the score and how the score is calculated. Page 20The emergence of a large amount of pharmacological, genomic, and network knowledge data provides new challenges and opportunities for drug discovery and development. Identification of real small-molecule drug (SM)-miRNA associations is not only important in the development. the mechanisms by which small-molecule drugs achieve the purpose of treating diseases by regulating miRNA expression. However, challenges remain in accurately determining potential associations between small molecules and miRNAs using information from multiomics data. In this study, we the prediction of small molecule-miRNA associations with joint learning. First, we use enhancing matrix completions to obtain the network knowledge of small-molecule fingerprints and miRNA associations. Then, we extract the information of small-molecule fingerprints and miRNA associations. sequence information. Finally, we incorporate small-molecule structure information, miRNA sequence data, and heterogeneous network knowledge into a joint learning model based on a Restricted Boltzmann Machine (RBM) to predict association scores. To validate the effectiveness of our method, the SMAJL model is compared with four state-of-the

art methods in terms of 5-fold cross-validation. The results demonstrate that the AUC and AUPRC of the SMAJL are obviously superior to those of other comparison methods. The SMAJL model also achieved great results in terms of robustness and case studies, further demonstrating its strong predictive power. Page 22Page 23Page 24

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