considered, and the energy functions used to estimate binding affinities are poor. This work investigated how implicit ligand and solvation theories as well as the linear response approximation may be combined to better describe the effect of protein flexibility on ligand binding affinities.

T4 lysozyme mutants, HIV-1 reverse transcriptase (HIVRT) and human FK506 binding protein 12 (FKBP) were chosen as model systems. An adaptive energy function based on the linear interaction energy approximation was parameterized and used to estimate partial affinities. Parameters were adapted according to ligand and protein surface polarities. Proteins were represented as an approximate conformational ensemble derived from molecular dynamics simulations. Interaction energies were obtained using the OPLS-ALA force field with modified partial charges for ligands. A generalized Born model was used for implicit solvation.

The parametrized energy function resulted in average deviations between experimental and calculated affinities of 1.0 kcal/mol and a correlation coefficient R²=0.8 for a test set of complexes with known binding sites. Discrimination of false-positive poses was also substantial. Then, approximations to the implicit ligand theory were proposed in order to obtain total binding affinities by combining interaction energies calculated for ligand complexes with the protein conformational ensembles. Several configurations contribute with the same weight for the FKBP protein. But, for lysozyme and HIVRT proteins, total affinities are dominated by one configuration. These results suggest that a faithful representation of protein conformational flexibility and an adequate statistical treatment based on implicit theories may be used to rapidly estimate reliable binding affinities.

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Development of Efficient Energy Function for Protein-Small Molecule Interactions in MedusaDock
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MedusaDock [1, 2] is a flexible docking approach in which both the ligand and the receptor conformational flexibilities are modeled simultaneously. A prede

termined discrete set of amino acid rotamers is used for representing receptor flexibility while for ligands, stochastic rotamers are generated on-the-fly during the simulation. Previous benchmark studies and CSAR 2012 blind prediction tests suggested [2] that MedusaDock is able to rapidly sample the binding poses and accurately predict near-native binding scores with the scoring function, MedusaScore. However, CSAR2012 benchmark results suggested that the MedusaScore cannot satisfactorily predict the binding affinities [3]. In this work, we developed new scoring functions by introducing free energy penalties of both proteins and ligands upon binding. Specifically, we included ligand entropy loss as well as receptor energy strains induced by binding. We benchmarked the ability to reproduce experimentally determined affinities of 148 protein-ligand complexes [4]. With the inclusion of new energy terms and use of new methods, Medusa’s performance was significantly improved in terms of recapitulating the binding affinities.

References

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Conformational Contribution to Thermodynamics of Binding in Protein Complexes Through Microscopic Simulations
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The biomacromolecular interactions are primarily governed by the conformational changes. We show that the thermodynamics of these conformational changes in biomacromolecular complexes can be extracted from the distributions of the dihedral angles of the macromolecules. These distributions are obtained from the equilibrium configurations generated via all atom molecular dynamics simulations. The conformational thermodynamics data we obtained for the system of calmodulin bound to different peptide complexes using our methodology corroborate well with the experimentally observed conformational and binding entropies. The conformational free energy changes and its contributions for different peptide binding regions of calmodulin are evaluated microscopically. We also extend the histogram based methods for calculation of conformational thermodynamics to calcium ion binding to calmodulin. This gives the microscopic information on the participation of different residues in the metal binding process.

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Structure-Based Predictors of Resistance to the HIV-1 Integrase Inhibitor Elvitegravir
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HIV-1 integrase (IN), an enzyme that incorporates reverse transcribed viral DNA into the human host cell genome, is a relatively new drug target. Elvitegravir (EVG) is the second IN inhibitor in its class approved for clinical use, to be used in combination with drugs targeting additional enzymes essential to the HIV-1 replication cycle. A multi-drug regimen generally blocks viral replication are the standard of care for treating HIV-infected patients, which minimizes the occurrence of random or drug-selected mutations. Amino acid substitutions in patient viral protein sequences, which may confer resistance to certain drugs, pose a challenge to prescribing appropriate medications. By developing a structure-based model that predicts phenotype (EVG drug susceptibility) from translated IN genotypes, clinicians can better target HIV-1 and avoid drug resistance.

A dataset of 157 mutant IN protein sequences with known susceptibility levels to EVG, each containing only amino acid substitutions relative to native IN (i.e., no indels), were obtained from the Stanford HIV-1 Drug Resistance Database. These data were used to train four classifier (decision tree, random forest, neural network, support vector machine) and two regression (reduced error pruning tree, support vector regression) models with the Weka software package. Each mutant IN sequence was characterized by a distinct feature vector of input attributes, achieved by quantifying ensuing environmental perturbations at sequence positions in the native IN structure upon mutation. Tenfold and leave-one-out cross validation performance reflected balanced accuracy as high as 87% for the classifiers and a correlation coefficient of up to 0.85 for the regression models, indicating promise for this computational mutagenesis approach as a supplementary clinical decision-making tool and as a method to efficiently predict any detrimental effects of unexplored IN mutations on EVG drug susceptibility.

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Elucidating Ephrin-Induced Intersecting Signaling Pathways in the Nipah Virus G Protein using Machine Learning
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The fusion of Nipah viruses with host cells is facilitated by two of their membrane proteins, the attachment protein (G) and the fusion protein (F). G binds to specific ephrin receptors on the host membrane. Ephrin binding changes the conformational density of G that activates F, which, in turn, mediates fusion. To understand how ephrin binding causes G to activate F, we use molecular dynamics in conjunction with machine learning to filter out the set of residues in the G head domain whose conformational densities are shifted equivalently by different ephrins, B2, B3, and a double mutant of B2. These three ephrins all trigger viral fusion, but with different potencies. We find that these three ephrins induce statistically equivalent shifts in the conformational densities of about one-quarter of the residues in the G head domain. This surprising and unexpectedly communal change in G includes most of the residues that have been shown experimentally to be important to F activation. This suggests that this set of residues contain the signaling pathways that connect the G-ephrin interface to the G stalk domain that activates F. The distribution of these residues in the G head domain is consistent with two models of signal transduction: one in which the ephrin-binding signal transduces to the F-activating G stalk domain via changes in the head-stalk interface, and the other in which the signal transduces via changes in the G head domain dimer interface. In general, this study shows how machine learning can be utilized along with molecular simulations to filter out quantitatively conserved patterns in changes in protein structure and dynamics.


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Design of Druglike Small Molecules with LYN-Specific Binding
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Glioblastoma multiforme (GBM), a very aggressive brain tumor, has a median survival of only 14 months. LYN, an important kinase involved in regulation of