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Abstract:

Molecular recognition plays an important role in biological systems. The purpose of this study was to get a better understanding of the process by incorporating computational tools.Molecular Mechanics-Generalized Born Surface Area (MM-GBSA) method and Molecular Mechanics-Poisson Boltzmann Surface Area (MM-PBSA) method, the end-point free energy calculations provide the binding free energy the can be used to rank-order protein–ligand structures in virtual screening for compound or target identification. Free energy calculations were performed on a diverse set of 11 proteins bound to 14 small molecules was carried out for. A direct comparison was taken between the calculated free energy and the experimental isothermal titration calorimetry (ITC) data. Four and three systems in MM-GBSA and MM-PBSA calculations, respectively, reproduced the ITC free energy within 1 kcal•mol–1. MM-GBSA exhibited better rank-ordering with a Spearman ρ of 0.68 compared to 0.40 for MM-PBSA with dielectric constant (ε = 1). The rank-ordering performance

of MM-PBSA improved with increasing ε (ρ = 0.91 for ε = 10), but the contributions of electrostatics became significantly lower at larger ε level, suggesting that the only nonpolar and entropy components contribute to the improved results. Our previously developed scoring function, Support Vector Regression Knowledge-Based (SVRKB), resulted in excellent rank-ordering (ρ = 0.81) when applied into MD simulations. Filtering MD snapshots by prescoring protein–ligand complexes with a machine learning-based approach (SVMSP) resulted in a significant improvement in the MM-PBSA results (ε = 1) from ρ = 0.40 to ρ = 0.81. Finally, the nonpolar components in the free energy calculations showed strong correlation to the ITC free energy while the electrostatic components did not; the computed entropies did not correlate with the ITC entropy. Explicit-solvent molecular dynamics (MD) simulations offer an opportunity to sample multiple conformational states of a protein-ligand system in molecular recognition. SVMSP is a target-specific rescoring method that combines machine learning with statistical potentials. We evaluate the performance of SVMSP in its ability to enrich chemical libraries docked to MD structures. Seven proteins from the Directory of Useful Decoys (DUD) were involved in the study. We followed an innovative approach by training SVMSP scoring models using MD structures (SVMSPMD). The resulting models remarkably improved enrichment in two cases. We also explored approaches for a prior identification of MD snapshots with high enrichment power from an MD simulation in the absence of active compounds. SVMSP rescoring of protein–compound MD structures was applied for the search of small-molecule inhibitors of the mitochondrial enzyme aldehyde dehydrogenase 2 (ALDH2). Rank-ordering of a commercial library of 50,000 compounds docked to MD optimized structures of ALDH2 led to five small-molecule inhibitors. Four compounds had IC50s below 5 μM. These compounds serve as leads for the design and synthesis of more potent and selective ALDH2 inhibitors.

Description:

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