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Analysis of protein - small molecule interactions using probilistic approach

Analysis of protein - small molecule interactions is crucial in the discovery of new drug candidates and lead structure optimization. Small biomolecules (ligands) are highly flexible and may adopt numerous conformations upon binding to the protein. Using computer simulations instead of sophisticated laboratory procedures may significantly reduce cost of some stages of drug development. Inspired by probabilistic path planning in robotics, stochastic roadmap methodology can be regarded as a very interesting approach to effective sampling of ligand conformational space around a protein molecule. Protein - ligand interactions are divided into two parts electrostatics, modeled by the Poisson-Boltzmann equation, and van der Waals interactions represented by the Lennard-Jones potential. The results are promising since it can be shown that locations of binding sites predicted by the simulation are in agreement with those revealed by experimental x-ray crystallography of protein-ligand complexes. We would like to extend our knowledge beyond scope available to most of the current molecular modeling tools toward better understanding of the ligand binding process. We try to accomplish this goal using two-level model of protein-ligand interaction and sampling of ligand conformational space covering the entire surface of protein target.

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