Optimization of protein-ligand binding affinities based on integral equation theory

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The accurate and fast prediction of protein-ligand binding affinities is one of the remaining grand challenges of computational chemistry. [1] The need for reasonably accurate and fast methods to predict and optimize the binding affinity which can drive the design process of drug-like molecules is therefore very high. Furthermore, in order to optimize current drugs or promising candidates, it is helpful to determine the most sensitive sites along with a direction in chemical space defining how a specific ligand atom should be changed in order to gain a higher binding affinity (for instance, by replacing it with a larger or more negatively charged atom). Ideas for replacing or introducing atoms and functional groups in the ligand can be distilled from those insights and rationally steer the design of new drugs.

The three-dimensional (3D) reference interaction site model (RISM) integral equation theory can be formulated and applied in a way to address the problem of complex formation thermodynamics. [2-4] More specifically, by applying the so-called solute-solute (*uu*) form it is possible to calculate rapidly the potential of mean force (PMF) between a protein a ligand sites on grid points in a binding site. The PMF is the key quantity for characterizing chemical and biological processes since it represents the free energy change along a given reaction coordinate from which the binding free energy can be computed. Furthermore, it can be differentiated with respect to, for instance, Lennard-Jones parameters and partial charges, yielding the so-called free energy derivatives (FED) [3] which encode optimal design directions defined above.

We here present novel methodology for computing these quantities efficiently based on *uu*-RISM theory. The resulting algorithms are applied to model systems comprising matched molecular pairs, where exchange of single atoms leads to substantial modulations of the binding free energy. Results are compared to reference explicit-solvent molecular dynamics simulations and experimental data in order to evaluate scope and limitations of the methodology.

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