Public Abstract
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Protein-ligand docking methods streamline the process of drug design by helping identify new chemical entities that bind to proteins. These methods provide a simplified model of protein-ligand interactions that may be used to predict the affinity and binding mode of a ligand for a protein receptor of interest. The protein receptor in question can be an important disease target, permitting docking methods to play the important role of hypothesis generation in early-stage drug discovery. The success of such methods depends greatly on the extent to which they can provide a good tradeoff between accuracy and computational efficiency, so researchers are very interested in the relative advantages of models that attempt to approximate the physical processes involved in protein-ligand binding. In this dissertation, we review the literature on protein-ligand docking methods, focusing especially on those methods used for structure-based drug design. We develop new methodology for deriving knowledge-based scoring functions, which are used in protein-ligand docking and many other applications. We present a large-scale evaluation of our docking methods, with special emphasis on the importance of accurate sampling of protein and ligand flexibility during docking. Finally we present a structure-based virtual screening study that serves as a practical application of the docking methods.