Chapter 30
Molecular Docking Challenges and Limitations

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ABSTRACT

Today, the development of new drugs is a challenging task of science. Researchers already applied molecular docking in the drug design field to simulate ligand- receptor interactions. Docking is a term used for computational schemes that attempt to find the "best" matching between two molecules in a complex formed from constituent molecules. It has a wide range of uses and applications in drug discovery. However, some defects still exist; the accuracy and speed of docking calculation is a challenge to explore and these methods can be enhanced as a solution to docking problem. The molecular docking problem can be defined as follows: Given the atomic coordinates of two molecules, predict their "correct" bound association. The chapter discusses common challenges critical aspects of docking method such as ligand- and receptor- conformation, flexibility and cavity detection, etc. It emphasis to the challenges and inadequacies with the theories behind as well as the examples.

INTRODUCTION

Molecular recognition plays a key role in promoting basic biomolecular experiences such as drug-protein, enzyme-substrate and drug-nucleic acid interactions. Detailed understanding of the general principles that administrate the nature of the interactions (van der Waals, hydrogen bonding, electrostatic) between the ligands and their protein or nucleic acid targets may present a conceptual support for designing the desired potency and specificity of potential drug leads for a given therapeutic target. Practical application of this knowledge requires structural information for the target of interest and a route for evaluating

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candidate ligands. To this end, a variety of computational docking methods are available(Mohan, Gibbs, Cummings, Jaeger, & DesJarlais, 2005)

Among the vast studies, there are several reports that represent molecular docking as worthwhile strategy to predict 3D structures of complexes. Molecular docking can overcome to experimental complications surrounding the structure determination of complexes, and can give valuable structural insights on biomolecular interactions. However, the process of binding a small molecule drug to its protein target is not simple; several factors affect on the interaction between two molecules, so these methods can be improved as a solution to docking problem. Despite great developments and achievements, the widespread application of docking methods, and the accurate and rapid prediction of protein–ligand interactions is still a challenging area to explore and some downsides still exist. The flexibility or mobility of both ligand and target, the effect of the protein environment on the charge dispersal over the ligand, and their interactions with the surrounding water molecules, complicate the quantitative description of the process.

This chapter reviews the literature in the last decades to account for the various abilities, limitations and challenges of the currently widespread applied algorithms which presently characterize this methodology. It introduces some efforts of drug developers for the improvement of algorithms to overcome the shortcomings and to enhance the computations for the incorporation of both ligand and receptor flexibility in the docking process, careful exploration of the ligand conformation within the binding site and improving complementarity between them, refinement and stability evaluation of the final complexes and thus accounting for induced fit. The discussion will further be limited to protein-small ligand complexes, omitting macromolecular complexes; however, much of what is presented here is also valid for that class of complexes.

The chapter handles some critical problems of docking calculation such as the lack of speed, accuracy, protein flexibility and ligand sampling with somewhat aspects of fundamental basic concepts such as movements of side chains and the biased selection of ligands as a result of using ligand-bound protein structures during a docking process or mis-docking ligand. As mentioned before, something of the recent advances provide on the ligand sampling, protein flexibility, and scoring functions as important features in protein-ligand docking. Three types of ligand sampling algorithms will be discussed; shape matching, systematic search, and stochastic algorithms. Computational efficiency for each algorithm is represented according to their main advantages and disadvantages. Covalent docking is another issue of molecular docking which is to be considered in the last part. Authors hope that the recently published papers on covalent docking give insights on biomolecular interactions to the readers.

BACKGROUND

Mutual molecular recognition is the initial point for approximately all processes in biological systems. Today, molecular docking as a very demanding computational and algorithmic tool plays a fundamental and advanced role in structural molecular biology and drug design. These computational tools help us for understanding molecular interactions of two molecules such as protein–protein or protein–ligand that is a key for the understanding of chemical process in diseases and other life issue occurrence. Molecular docking has a wide range of potential uses and can be applied in the following fields of drug discovery:

- Structure–activity studies
- Lead optimization