Chapter 33
Recent Advancements in Docking Methodologies

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ABSTRACT
Nowadays molecular docking has become an important methodology in CADD (Computer-Aided Drug Design)-assisted drug discovery process. It is an important computational tool widely used to predict binding mode, binding affinity and binding free energy of a protein-ligand complex. The important factors responsible for accurate results in docking studies are correct binding site prediction, use of suitable small-molecule databases, consistent docking pose, high dock score with good MD (Molecular Dynamics), clarity whether the compound is an inhibitor or agonist, etc. However, still there are several limitations which make it difficult to obtain accurate results from docking studies. In this chapter, the main focus is on recent advancements in various aspects of molecular docking such as ligand sampling, protein flexibility, scoring functions, fragment docking, post-processing, docking into homology models and protein-protein docking.

INTRODUCTION
To accelerate the new drug discovery process, search of small molecules which bind to biological targets of interest, is rapidly increasing. Molecular docking is an important tool used in structure-based drug design which facilitates the drug discovery process with the aid of high speed computers. A typical docking program consists of two essential components viz. sampling and scoring. Sampling is generation of ligand orientations in the binding site of a protein, whereas scoring is prediction of its binding fitness. The top ranked orientation with lowest energy score is predicted as binding mode. Docking is
Recent Advancements in Docking Methodologies

now routinely used in hit identification, lead optimization and virtual screening. With the development of protein structure prediction techniques and high speed computers, several advancements have been made in molecular docking methodologies. However, several limitations still exist, which make CADD approaches less reliable than experimental approaches. Several research articles can be found on docking studies but only few of them have succeeded in the development of drug candidate of interest.

This chapter covers general introduction to molecular docking process, its components, limitations and advancements in docking methodologies including ligand sampling, scoring functions, protein flexibility, fragment docking, post-processing, docking into homology models and protein-protein docking along with examples.

BACKGROUND

Enzyme-substrate, drug-protein, drug-nucleic acid, protein-protein and protein-nucleic acid interactions play an important role in many important cellular processes, such as signal transduction, cell regulation, gene expression, enzyme inhibition, antigen-antibody reaction, assembly of multi-domain proteins etc. These interactions form stable protein-protein or protein-ligand complexes which are essential for various biological functions. But, it is quite difficult and expensive to determine the complex structure of proteins by experimental methods i.e. X-ray crystallography and NMR (nuclear magnetic resonance). Thus, structure-based drug design approaches especially docking methodologies are now being considered as an important approach for understanding the protein-protein as well as protein-ligand interactions (Halperin, Ma, Wolfson, & Nussinov, 2002).

In the beginning, structure-based drug design was not easy due to low computational speed and non-availability of 3D (three dimensional) structure of proteins. One key methodology “docking” was pioneered during early 1980s, and became a thrust area of research. The first docking program DOCK was developed in 1982 by Irwin “Tack” Kuntz’s group, which considered only geometric complementarities but not the ligand interactions (Kuntz, Blaney, Oatley, Langridge, & Ferrin, 1982). Subsequently, in 1985 Goodford developed a program GRID to understand and predict the ligand interactions in the binding site (Goodford, 1985). Further advancements in CADD resulted in development of various important computational approaches including high-throughput docking and virtual screening (VS). High-throughput docking is primarily used when only the structure of a target and its binding site is available while VS is used to identify a subset of chemical compounds from small-molecules database that contain relatively many hits against the target (Schneider & Böhm, 2002). Till date, several improvements have been made in the docking algorithm, and at the moment more than 50 docking programs are available. Now it is used as a tool not only for hit identification and lead optimization but also for understanding the drug metabolism as well as toxicity prediction (Halgren, 2007).

Development in structure determination techniques like high throughput X-ray crystallography, NMR, genomics and proteomics have increased the number of proteins with known 3D structure and are easily available as a repository of protein structures i.e. PDB (protein data bank). The 3D structure of a protein is an initial and prime requirement of docking program to estimate the binding mode and affinity of interacting ligands (Blundell, Jhoti, & Abell, 2002). Advancement in the structure-based drug design approaches has discovered a number of important drugs like inhibitors of HIV-1 protease, HIV-1 integrase, carbonic anhydrase, neuraminidase, protein kinases etc. Undoubtedly, docking methodologies
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