Chapter 12
Docking Methodologies and Recent Advances

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ABSTRACT

Docking, a molecular modelling method, has wide applications in identification and optimization in modern drug discovery. This chapter addresses the recent advances in the docking methodologies like fragment docking, covalent docking, inverse docking, post processing, hybrid techniques, homology modeling etc. and its protocol like searching and scoring functions. Advances in scoring functions for e.g. consensus scoring, quantum mechanics methods, clustering and entropy based methods, fingerprinting, etc. are used to overcome the limitations of the commonly used force-field, empirical and knowledge based scoring functions. It will cover crucial necessities and different algorithms of docking and scoring. Further different aspects like protein flexibility, ligand sampling and flexibility, and the performance of scoring function will be discussed.

INTRODUCTION

Molecular docking is an entrenched computational technique which can accurately predict the orientation of a ligand and its binding affinity within the constraints of a receptor binding site (Bachwani & Kumar, 2011). Docking of a ligand into the receptor pocket involves several degrees of freedom. Besides the six degrees of translational, rotational, as well as conformational degrees of freedom, some algorithm only uses the translation and orientation degrees of freedom. By increasing computer’s performance and using various new algorithms we can explore the ligand conformational degree of freedoms. There are simple methods for docking of rigid ligand with rigid receptors and flexible ligand with rigid receptors,

DOI: 10.4018/978-1-5225-0115-2.ch012
but the general method of docking conformations of flexible ligand and receptors is problematic (Leach, Shoichet & Peishoff, 2006).

Besides protein ligand docking, there are protein-protein docking, ligand-nucleic acid docking and protein-nucleic acid docking. Protein-protein docking is important for knowing the structural and functional features of the cell. It is similar to protein ligand docking; scoring and searching algorithms are used. The softwares available for this kind of docking are ZDOCK, HADDOCK, GRAMM-X, Hex protein docking etc. (Ehrlich & Rebecca, 2001). Ligand-nucleic acid docking involves the docking of ligand with nucleic acid like DNA and RNA. Less attention has been made in regard to docking with nucleic acid. Cisplatin, actinomycin and netropsin are example of drugs that shows ligand-DNA docking but less effort has been done in designing of ligands that binds to RNA targets (Mohan, Gibbs, Cummings, Jaeger, & Desjarlais, 2005). Protein-nucleic acid docking requires a set of well defined test cases that forms a common ground for development, validation and comparison of docking method. Software that carried out this kind of docking is HADDOCK (Dijk and Bonvin, 2010).

Earlier ‘soft-potential docking’ and rotamer libraries were used for flexible receptor docking methods (B-Rao, Subramanian, & Sharma, 2009). Currently X-ray crystallography, NMR, Monte Carlo sampling, Normal Modes-based methods and Molecular Dynamics methods are being focused on constructing an ensemble of structures produced in flexible type docking (Feixas, Lindert, Sinko, & McCammon, 2014; Sousa et al., 2013; Durrant, & McCammon, 2010; Cavasotto, Orry, & Abagyan, 2005). Principle techniques for docking methods use various searching and scoring algorithms like molecular dynamics, Monte Carlo methods, genetic algorithms, fragment-based methods (Mohan, Gibbs, Cummings, Jaeger, & Desjarlais, 2005), point complementary methods, distance geometry methods, tabu searches, evolutionary algorithm, particle swarm optimization and ant colony optimization which are mentioned in detail in later part of this chapter (Taylor, Jewsbury, & Essex, 2002).

FUNDAMENTAL NECESSITIES

Molecular docking program emphasize on the following basic requirements (Mahajan, & Gill, 2014; Krovat, Steindl, & Langer, 2005):

1. A target protein structure with or without a bound ligand is detected by various experimental techniques like NMR or X-Ray crystallography, but if protein structure is not present then protein prediction is done by any technique like threading modelling, homology modelling.
2. Database containing existing or virtual compounds for the docking process
3. Sampling and scoring method, desired scoring and searching algorithms require a computational framework for its efficient working
4. The three-dimensional structure of the protein ligand complex has to be studied in depth of atomic resolution.

MOLECULAR DOCKING MODELS

1. **Lock and Key Model:** Emil Fischer, in 1890, proposed this model which explains the functioning of biological systems. Ligand fits into the active site of the macromolecule as depicts in Figure 1.