Chapter 1  
Molecular Docking at a Glance

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ABSTRACT

The current chapter introduces different aspects of molecular docking technique in order to give an overview to the readers about the topics which will be dealt with throughout this volume. Like many other fields of science, molecular docking studies has experienced a lagging period of slow and steady increase in terms of acquiring attention of scientific community as well as its frequency of application, followed by a pronounced era of exponential expansion in theory, methodology, areas of application and performance due to developments in related technologies such as computational resources and theoretical as well as experimental biophysical methods. In the following sections the evolution of molecular docking will be reviewed and its different components including methods, search algorithms, scoring functions, validation of the methods, and area of applications plus few case studies will be touched briefly.

INTRODUCTION

Molecules are seldom found in isolation and all over the chemical universe they are involved in intermolecular interactions in homogenous or heterogeneous systems observed in almost all of the materials around us. The biological systems are no exceptions to this rule and the life with no question is dependent on these interactions. One of the important types of the interactions takes place between biological macromolecules known as receptors and the corresponding ligands. Understanding the molecular modes of such interactions is one of the major goals in comprehending the mechanism of actions of drug substances and drug design and discovery pipeline. Designing bioactive compounds with a controlled interaction profile toward a target of interest with minimum level of adverse effects is of great importance. In this context, molecular docking as a valuable tool in structure based drug design provides a framework to
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engineer such molecules by visualizing structural requirements at the atomic level. Such useful information can significantly facilitate the rational drug design processes. The current chapter will introduce the molecular docking technique and its importance in computer-aided drug design. Moreover, different types of molecular docking methods, search algorithms as well as scoring functions will be presented briefly. Different examples of molecular docking applications will be also highlighted.

BACKGROUND

The inevitable need for developing new drugs originates from their inadequate efficiency and toxicity in the body. The history of drug discovery dates back to thousands of years ago wherein the ancient civilization used to employ herbal medicine as remedies for treatment of diseases. In spite of historical role of the serendipity factor throughout the traditional drug discovery, it is not regarded as a major component in modern drug discovery (circulation 2009). Drug development from inception to market requires an average time of 10-15 years and a cost of approximately a billion dollars (Campbell, Lamb, & Joseph-McCarthy, 2014; Ou-Yang et al., 2012). Being time consuming, costly, and risky, this process combines variety of tools to work more rationally in the process of introducing new drugs to the market. Late twentieth and early twenty-first century faced the substantial changes in drug design and discovery processes. The philosophy behind the rational drug design lies in logical reasoning before synthesizing any therapeutic agent for the biological evaluation. It provides a framework for prioritizing of potential lead compounds as early as possible, based on rational guidelines by employing the computational and experimental methods (Hung & Chen, 2014; Veselovsky & Ivanov, 2003). In this context, computer-aided drug design (CADD) is of great importance in shortening the development process in terms of cost and timeline. The CADD is mainly divided into two categories; ligand-based drug design (LBDD) and structure-based drug design (SBDD). In the case of LBDD, there is no information about the target of interest, and the chemical/biological features of a set of ligands are analyzed. Quantitative-structure activity relationship (QSAR) techniques and pharmacophore-based design are the typical examples of LBDD strategy. If the 3D structural information of the target of interest is available, SBDD can also be utilized. In this strategy, the main focus is the design of novel ligands guided by investigating the ligand-target mutual interactions (Gani, 2007; Hung & Chen, 2014; Wilson & Lill, 2011). The starting point of SBDD approach is to identify the active site of the target molecule based on the known 3D structure of the bound natural ligand and/or drug molecules, mostly via X-ray crystallography or NMR experiments (Campbell et al., 2014; Mandal, Moudgil, & Mandal, 2009). The availability of the geometry for the target binding site may provide useful information for designing novel ligands or screening ligands from a large collection of chemical compounds based on structural and chemical complementarity features between target and ligand molecules (Gani, 2007; Mandal et al., 2009; Veselovsky & Ivanov, 2003). The candidates for synthesis and further biological assays are chosen based on the predicted binding mode and affinity as well as synthetic feasibility (Campbell et al., 2014). The most routinely used techniques in the area of SBDD are but not limited to molecular modeling, molecular dynamics, and docking techniques (Wilson & Lill, 2011).

The molecular docking is one the crucial components of the in silico studies which is heavily used in modern drug design and discovery efforts. Current molecular docking techniques have passed the infancy period and taking into account the tremendous advances in terms of novel computational algorithms as well as high performance computing hardware have led to its maturity to the state that is considered
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