Molecular docking is the prediction of conformational complementarity between ligand and receptor molecule. The process of docking integrates two schematic approaches namely sampling of ligand conformations and ranking of selected conformations based on scoring functions. The authors have discussed established methodologies for molecular docking and well-known tools implementing these methods. A brief account of different classes of scoring functions such as force field based, empirical, knowledge based, and descriptor based scoring functions is given along with the exemplary implementations of these scoring functions. By replacing test and trial based ligand screening with structure based virtual screening, molecular docking has helped in shortening the duration of novel drug discovery up to some extent. However, the developments made in the field of drug discovery are assisted by the advances in the techniques of molecular docking, but there is strong need of enrichment in the techniques, especially in scoring functions, to tackle the inbound problems of de novo drug discovery.

INTRODUCTION

All biological processes and molecular functions are carried out by diverse classes of macromolecules such as nucleic acids, proteins, carbohydrates, etc. Sometimes macromolecules perform certain activity on their own, but certain functions are carried out due to the intermolecular interactions in which the activity of a molecular species is induced by other molecules and vice versa. The concept of molecular docking is based on the phenomenon of intermolecular interactions between leading molecular species that play a key role in the working mechanisms of various biological processes and molecular functions. Basically, the event of docking upholds the binding of one molecule into the conformational space of another molecule leading to a specific activity or function. Docking can be seen between two proteins

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having conformational complementariness such as protein-protein docking, or between one small molecule (usually called ligand) and a protein, DNA-protein docking, etc. In the context of computer-aided drug design, ligand-protein docking holds significant status. Therefore, in the upcoming paragraphs the authors will objectively discuss various aspects of ligand-protein docking in particular and molecular docking in general.

Several reviews and evaluation reports have been published in recent years covering important aspects of molecular docking, recent advances in methods of docking, evolution of search algorithms, developments in scoring functions, and advancements in docking tools (Ferreira, Dos Santos, Oliva, & Andricopulo, 2015; Kitchen, Decornez, Furr, & Bajorath, 2004; Meng, Zhang, Mezei, & Cui, 2011; G. M. Morris & Lim-Wilby, 2008; Oshiro, Kuntz, & Dixon, 1995; Verdonk, Cole, Hartshorn, Murray, & Taylor, 2003). In this chapter, the authors have tried to bring forward the objective study of small molecule-protein docking in the context of computer-aided drug design including brief idea of various preceding events of molecular docking such as target identification, lead optimization, and virtual screening. This chapter further elaborates the historical perspective of molecular docking, role of docking in computer aided drug design, an introduction to various methods and established tools for molecular docking and underlying scoring functions that assess the quality of conformational complementarity between ligand and receptor molecule. In this way, the flow of the chapter (Figure 1) goes with an introduction and historical background of molecular docking along the brief description of docking methodologies, docking tools, search algorithms and scoring function. In context of drug discovery, the authors have discussed the role of molecular docking in drug discovery by discussing some case studies. The authors also have discussed modern perspective of molecular modeling including the present day challenges of the area with respect to its involvement in drug discovery.

HISTORICAL PERSPECTIVE

Though, in post genomic era molecular docking has met revolutionary developments making it a more advanced concept aided by other fields of study such as computer science, physics, and statistics, etc., but the traces of the basic idea of docking way back to “Lock and Key Hypothesis” proposed by Emil Fischer in 1894 in the context of enzyme – substrate geometric interaction. During the development phases of molecular biology, several modifications have been proposed to understand the inbound complexity of docking. In 1958, Koshland came forward with the idea of “induced fit” in his modification of “Lock and Key Hypothesis”. He proposed that the conformational changes in the active site of the receptor are induced by the binding of the substrate (Koshland, 1958).

Before the period of late 1970s and 80s, molecular docking was studied more as a phenomenon of molecular interaction between the molecules having binding affinity. The idea of docking as a distinguished concept originates in the works of late 1970s. The term docking also has its origin in the studies conducted in late 70s (Wodak & Janin, 1978). The developments made in the 70s were more or less confined to interactions between a large molecule such as protein-protein docking (Wodak & Janin, 1978). More polished idea of docking of small molecules with proteins emerged in the early 1980s in the work of Kuntz et al., (Kuntz, Blaney, Oatley, Langridge, & Ferrin, 1982).

The field of molecule docking as a distinguished field of study has been developed parallel to the developments in computer science and technology. Molecular docking emerged significantly in the context of computer-aided drug design hand in hand with several techniques like target identification,