Chapter 32
The Comparison of Docking Search Algorithms and Scoring Functions: An Overview and Case Studies

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ABSTRACT

This chapter, composed of two parts, firstly provides molecular docking overview and secondly two molecular docking case studies are described. In overview, basic information about molecular docking are presented such as description of search algorithms and scoring functions applied in various docking programs. Brief description of methods utilized in some of the most popular docking programs also applied in our experimental work is provided. AutoDock, CDOCKER, GOLD, FlexX and FRED were used for docking studies of the DC-SIGN protein, while GOLD was further used for docking studies of cathepsin K protein. Methods and results of our studies with their contribution to science and medicine are presented. Content of the chapter is therefore appropriate for public of Medicinal and Organic Chemistry as an overview of docking studies, and also for Computational Chemists at the beginning of their work as the introduction to application of molecular docking programs.

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INTRODUCTION

Those who devote their time to molecular science are well aware of the amount of molecular data available that has rapidly increased in the past few decades due to breakthrough in structural biology. Since 1975 development of high-throughput protein purification, crystallography, and nuclear magnetic resonance spectroscopy techniques predominantly contributed to structural details of macromolecules and complexes with ligands. In 2014, after less than four decades, the number of structures exceeded the 100.000 with 10.000 structures per year being deposited in Protein Data Bank (PDB). PDB is the single worldwide repository of information about the 3D structures of large biological molecules, including proteins and nucleic acids (Berman et al., 2000; Berman, Kleywegt, Nakamura, & Markley, 2014).

These advances are responsible for computational methods to become indispensable in all aspects of drug discovery including the structure-based drug design and computer-based analysis of molecular interactions. Interactions between biomolecules are fundamental to biological processes; using these interactions, living organisms maintain complex regulatory and metabolic mechanisms responsible for the life course. Experimental research work is fundamental for a better understanding of biological processes; however, computer simulations and analysis are of mayor importance to extract information from large amount of multivariate experimental data. Application of these scientific methods provides exploration of molecules that can be utilized as bioactive substances able to modify and control molecular interactions. For bioactive substances, molecular recognition of the constituents is imperative. Binding mode, binding affinity, and kinetics play the crucial role in molecular recognition as they characterize intermolecular interaction.

Due to the limitations of experimental methods for determining the structure of molecular complexes, as they are expensive, time consuming and not always feasible, computational methods are preferable for predicting putative binding modes and binding affinities. Nowadays, the main advantages of rational drug discovery approaches, such as virtual screening, are low costs and effectiveness when compared to high-throughput screening. Molecular docking is one of the virtual screening methods used since 1980's. It is based on modeling of interactions between two molecules, a small molecule (ligand) and its receptor/protein (target). The predicted interactions allow us to characterize the binding mode and binding affinity of the ligand-target complex.

Currently there are more than 50 molecular docking programs available, which all have similar implementations. This chapter provides explanation and comparison of computational approaches, specifically different algorithms enclosed in software for molecular docking, considering several of the most commonly used program tools (AutoDock, FRED, CDOCKER, FlexX and GOLD). Authors also present the use of these algorithms in the comparative study for docking of small ligands to specific protein, lectin Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin (DC-SIGN) and covalent docking of cathepsin K.

BACKGROUND

Molecular docking, in the case of small molecules also known as ligand docking, can be defined as computational method for prediction of the structure of ligand-receptor complexes. Ligand docking process involves two basic steps: prediction of ligand conformation and orientation (the pose) by search algorithms and assessment of binding affinity by scoring functions.