Chapter 31
Different Types of Molecular Docking Based on Variations of Interacting Molecules:
Variations of Molecular Docking

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ABSTRACT

Molecular docking plays an important role in drug discovery research by facilitating target identification, target validation, virtual screening for lead identification and lead optimization. Depending upon the nature of the disease of interest, targets can be either protein or DNA while drugs are mostly organic small molecules. Different types of molecular docking techniques like protein-protein or protein-DNA or protein-small molecule or DNA-small molecule are employed for achieving the above mentioned objectives. This chapter provides a clear idea of the position of molecular docking in drug discovery with detailed discussion on different types of molecular docking based on the varieties of interacting partners. Subsequently the authors provide a detailed list of tools that can be used for docking in drug discovery and discus some examples of molecular docking in drug discovery before concluding with a remark on future areas of improvement in molecular docking related to drug discovery.

1. INTRODUCTION

Present day drug discovery faces several major issues like rising cost, high development time and high failure rate at different stages of development. On average it takes 10-12 years and around one billion US dollar to market a drug but less than 5% of the compounds which are selected to undergo the drug-discovery pipeline, only end up being marketable. This high failure rate is associated with every stages of drug development starting from initial screening to final patient trial. Since the marketed drugs are

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only available for revenue generation which has to cover the development cost of all the trials, including the ones which failed at different developmental stages. Thus it is easily understandable that optimizing strategies that save both time and money are of significant interest to the drug-discovery world. It should also be kept in mind that subsequent stages of drug development are also associated with exponential increase of cost. To counteract these issues, computer aided drug development (CADD) has played significant role to reduce cost and time for the last two decades and has established itself as an essential part of modern day drug discovery.

Combined with the above mentioned issues, the ever rising compound library has imposed another challenge in terms of selection of proper compounds which can be used for initial screening. While a few thousand compounds can be screened using standard high throughput screening (HTS) methods, the challenge remains to find these few thousands from the immensely large compound library which houses several tens of thousands of compounds, sometimes in the ranges of hundreds of thousands. CADD plays an important role not only in this aspect but also in two other ways – a) by computationally generating secondary modifications of compounds which saves both time and money in comparison to synthesizing them in real world, b) by analyzing the quantitative structure-activity relationship (QSAR) of the compounds of interest. All the three above mentioned ways, in which CADD plays an important role in drug discovery, require the association of the compound with the target of interest which can be either DNA or protein and the technique which facilitates this association in a computational way is known as 'Molecular Docking'. However the benefit of molecular docking extends beyond this small molecule–DNA/protein interaction as it facilitates the docking of DNA with proteins as well as of proteins with proteins.

The benefit of molecular docking is exhibited at several stages of drug-discovery. Even before the beginning of drug-discovery pipeline, molecular docking facilitates the proper understanding of several potential target molecules by facilitating DNA-protein and protein-protein interactions. Later this technique facilitates virtual screening which enables screening of compound libraries to find the potentially promising ones as well as helps in understanding of the best suitable secondary modifications. Thus it can be clearly envisioned that different types of molecular docking depends on the types of interacting molecules. Keeping in mind the scope of this chapter, further discussion on molecular docking with respect to drug discovery will be limited to different types of molecular docking.

As we have previously discussed, small molecules or ligands, DNA, proteins and short peptides are four different individual components with which molecular docking can be performed. Based on the combinations of participating components, drug discovery can be of several types. In case of protein-ligand docking, molecular docking is performed with a small molecule ligand and a protein receptor. Interaction of 'dorzolamide', used for treatment of glaucoma, with carbonic anhydrase is an example of protein-ligand docking. It should be highlighted at this point that most of the known or developed drugs fall in to this category. Platinum containing cancer drugs interact with DNA and thereby results in cell death. Studies of interactions of such drugs with DNA are facilitated through DNA-ligand type molecular docking. Azacitidine and decitabine containing drugs which are used for treatment of myelodysplastic syndrome and acute myeloid leukemia act through several mechanisms that ultimately inhibit DNA-methyltransferases. Understanding the mechanism of actions of such drugs require proper knowledge of interaction of DNA, it's bases and base analogues with DNA-methyltransferases.DNA-protein docking analyses such interactions. The tyrosine protein kinase BCR-Abl when mutated can become constitutively active and thereby causes uncontrolled target phosphorylation which ultimately causes abnormal cell growth. Imatinib effectively blocks this constitutive BCR-Abl phosphorylation activity by binding to