Chapter 32

Current Trends in Docking Methodologies

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ABSTRACT

Molecular docking was earlier considered to predict the binding affinity of the receptor and ligand molecules. With the progress in computational power and developing approaches, new horizons are now opening for accurate prediction of molecular binding affinity. In the current book chapter, recent strategies for Computer-Aided Drug Designing (CADD) including virtual screening and molecular docking, encompassing molecular dynamics simulations, and binding free energy calculation methods are discussed. Brief overview of different binding free energy methods MMPBSA, MMGBSA, LIE and TI have also been given along with the recent Relaxed Complex Scheme protocol.

1. INTRODUCTION

The potential of computer aided drug design was recognized earlier. Fortune magazine in 1981 published a cover article titled “Next Industrial Revolution: Designing Drugs by Computer at Merck” (Van Drie, 2007). Initially, high throughput screening (HTS) was used to find novel therapeutic molecules in drug discovery. It is the process of testing a large number of diverse chemical structures against disease targets to identify ‘hits’ (Liu, Li, & Hu, 2004). Later, in silico techniques have acquired the competitive edge to filter out the lead molecules. Virtual screening is used for filtering molecules of interest from large chemical libraries. Screened molecules obtained as results are further evaluated using molecular docking. Moreover, the binding free energy methods viz. MMPBSA/MMGBSA, LIE, TI and FEP are used for stringent filtering from the molecular docking results. Lead molecules obtained from the in silico screening are used for biological evaluations (Figure 1).

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2. HIGH THROUGHPUT SCREENING (HTS)

HTS is characterized by taking the ligand-target interactions as the principle, leading to a higher information harvest (Liu et al., 2004). HTS lists contains a large percentage of false positives, making follow-up assays necessary to distinguish active from inactive substances (Jenkins, Kao, & Shapiro, 2003). HTS hit rate can be increased by using advance computational methods. Computational methods have several advantages over HTS as they are less time consuming, cost effective and require minimal compound design or prior knowledge. For example, researchers have used computational methods along with HTS to screen inhibitors of tyrosine phosphatase-1B, an enzyme implicated in diabetes. Virtual screening yielded nearly 35% hit rate as compared to 0.021% hit rate produced with HTS, demonstrating the power of computer aided drug designing (CADD) in drug discovery (Doman et al., 2002). Traditionally, HTS produces poor hit rate but in combination with CADD, its efficiency is greatly enhanced due to removal of false positives in less time and at lower computational cost.

One of the most remarkable uses of CADD in drug discovery process is the discovery of new targets for already existing drugs, a vice-versa approach. A few examples of approved drugs that owe their discovery...
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