Chapter 15

Computational Techniques in Binding Affinity Prediction of Drugs

Kshatresh Dutta Dubey
DDU Gorakhpur University, India

Rajendra Prasad Ojha
DDU Gorakhpur University, India

ABSTRACT
Computational techniques are widely used in the chemoinformatics and bioinformatics. Most of the drugs produce their effect by interacting with the target molecules via different interactions. However, these interactions are tough to be calculated without use of robotics techniques. The potentials of these drugs depend upon their binding affinity. Due to huge number of such drugs, the measurement of their relative potency is a hard task. In present chapter the authors have discussed about some most common techniques which are widely used in bioinformatics and chemoinformatics.

INTRODUCTION
Discovering and developing any new drug is a long and expensive process because the novel drug should not only produce optimum potency but it should exhibit minimum side effect. After the advancement in the development of high throughout screening and combinatorial techniques, the data of bioactivity and structure of a drug also increased abruptly. Therefore, analysis of bioactivity of such huge data becomes very ridiculous. A newly discovered drug may have to pass some filtering criterion like toxicity, selectivity and binding affinity. This explosion of data has increased the need for integration of chemical information with molecular modelling techniques. After the successful invention of a drug, the demands of discovery of lead series are also expected. A lead series comprises a set of related molecules that usually share some common
structural features, and shows some variation in the activity as the structure is modified. However, discovering a novel lead series by experimental techniques becomes more complicated than discovery of a single molecule. For example, after discovery of penicillin by Alexander Fleming, pharmaceutical companies screened soil and other biological samples to find a new lead, but it was proved very difficult to extract and purify a lot of bioactive ingredient. However, presently, due to robotic techniques, high throughout screening is very common which enables high number of compound to be screened. In this way, the scope of chemoinformatics has increased drastically in the field of drug discovery. Presently, there are more than 5000 drugs approved according to the Drug Bank (www.drugbank.ca). The relative potency of these drugs for a selected target has vast scope for medicinal chemists and practitioners. Due to huge number of such drugs, it is very difficult to examine relative potentials by experimental techniques. Therefore the computational techniques are widely used for this purpose. Drug-receptor binding is the most fertile field of study for biochemists and bioinformatics. Receptors are the macromolecules involved in chemical signaling between and within cells. Molecules (drugs, DNA, proteins etc) that bind to a receptor are called ligand. Although the drugs are targeted for a specific receptor, most have relative selectivity. Selectivity is the degree to which a drug acts on a given site relative to other sites. The probability of a drug occupying the receptor at any instant is known as binding affinity. In the present chapter we have discussed all popular methods which are used as binding affinity predictors.

**BACKGROUND**

In this section we will discuss about the commonly used techniques for the prediction of binding affinity of drug protein complexes.

**Molecular Docking**

In this section, we shall discuss computational methods for modeling the interaction of small molecule ligands with protein receptors in aqueous solution. Such interactions form the basis of the mechanism of the great majority of pharmaceutically active compounds. Figure 1 shows an example of the interaction by molecular docking. The ability to determine the structures and free energy of binding of protein ligand complexes is, therefore, the key objective of computational structure-based drug design. Molecular docking attempts to predict the structure of the intermolecular complex formed by two or more molecules. Docking is widely used to suggest the binding mode of bioactive inhibitors. Most docking algorithm is able to generate a large number of possible structures, and so they also require a means to score each structure to identify those of the most interest. Usually the docking algorithms generate different possible modes of binding of inhibitors for a selected target which are further ranked according to some filtering criteria which is known as docking score.

Theoretically a molecular dynamic simulation can be used to predict the free energy of a pharmaceutically active protein ligand complex, but due to large computational time and force field accuracy limitation, this method is ridiculous for straightforward usage. These considerations have led to the development of approximate methods that based on physical chemistry principles, endeavor to embody such principles in empirically optimized models and determine structures via specially designed conformational search algorithms. The optimized models are known as scoring function and conformational search algorithms are often called docking algorithm. When the scoring function is combined with docking algorithms, it constitutes docking program. Various docking programs have been developed to tackle the docking problem. The first docking program, DOCK (Kuntz et al. 1982), was developed in the
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