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Review of Modern Computer-aided Drug Design Methods

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Abstract: Computer technology has developed rapidly in recent decades, and it is also widely used in the field of drug research and development. Computer-aided drug design (CADD) has appeared in the form of assistance to drug discovery process in this background. Computer-aided drug design can save time which is spent in the experimental process in the real world. Since appearance of computer-based drug design strategies, the concepts of HTS, structure-based and ligand-based drug design (SBDD and LBDD), and virtual screening (VS) have been proposed. These technologies have their own advantages and disadvantages, and have different scope of application. This review provides an introduction of modern drug design strategies which are based on computer technology, classifies different methods and finds out the basic working principle of each one, the applicability and limitations of these methods are discussed and recommendations are provided in the application of each method.

Keywords: High-throughput screening (HTS); Structure-based drug design (SBDD); Ligand-based drug design (LBDD); Structure-based virtual screening (SBVS); Ligand-based virtual screening (LBVS).

1. Introduction

The research and development process of drug discovery is lengthy, and considering the costs in every stage of the process is essential. In the past, the most popular ways for agencies to test the effects of some kinds of chemicals on certain diseases are adding the number of animal tests and altering animal-based toxicity tests, but the approaches are costly, lengthy and use too many animals. A large number of animal experiments are not only expensive but also do not meet the ethical requirements of animal experiments. Innovation by combining computational and experimental approaches is driving drug discovery, modern medicinal chemistry methods are increasingly adopted by the research-based pharmaceutical industries, the methods are developing with bimolecular spectroscopy methods represented by X-ray crystallography and nuclear magnetic resonance (NMR), modern medicinal chemistry methods have led to significant advances in molecular and structural biology. To solve difficulties and high expenses caused by experimental approaches, computer-aided drug design (CADD) which can make effective assistance to experiments by coordinating the experimental data available is currently developed to make the drug discovery process more efficient.

2. Current research about CADD

2.1. High-throughput screening

As to any drug discovery project, identifying promising hits and generating high-quality leads are critical in early stages. High-throughput screening (HTS) method, a kind of traditional computational drug design and discovery methods which depend on 3D structure of biological macromolecules, has improved the process of drug discovery efficiently. As an indispensable and essential part of research of big pharmacology discovery company, HTS which is based on various compound libraries has been used by a large number of companies and researchers. Based on various compound libraries, high degree of automation makes HTS to meet increasing demand for quantity of compounds. One of the advantages of using HTS technology is to filter out unsuitable compounds in preclinical tests and reduce health risks caused by occurrence of unsuccessful adverse drug reactions during clinical tests, another advantage of the HTS screening test is the significant reduction in cost and animal use by strong mechanical assistance. After HTS, the remaining compounds will be screened by selectivity assays and in vitro efficacy assays to find more suitable drug candidates.

However, this technology is also controversial. The criticism to HTS focuses on the quality of the information obtained, there can be lots of data points which are false-positive or false-negative exist in the result which can cause the lose of opportunity to get high quality of chemicals, the uncertainty information provided by HTS can cause high operating cost. At the same time, false positive and false negative results also cause problems for the entire drug screening process. Misjudgment of the affinity of the drug and the receptor will most likely cause the candidate compound to fail to achieve the expected effect. In the meantime, compared with the expensive cost and low hit rate of HTS, new computational alternative methods are developing to achieve a cheaper and faster goal.

2.2. Computer-aided drug design

CADD, which is short for computer-aided drug design, is the strategy which plays a role in the early stage of drug discovery and development. Based on the different basic principles, CADD can be roughly divided into two types: SBDD and LBDD. SBDD and LBDD have evolved and transformed modern drug discovery methods which allow hit identification and lead optimization into powerful tools that make a huge impact on modern drug discovery.

2.2.1. Structure-based drug design

SBDD, which is short for structure-based drug design, is structure based CADD relies on interaction energies which are calculated by the relevant understanding of the target protein structure to test compounds. X-ray crystallography, NMR (nuclear magnetic resonance) and 3-D structure

databases are the methods used to obtain reliable information which shows the active sites and 3-D structure of the target protein. By knowing the structure of a target, potential ligands can be identified by silico studies, then the most feasible compounds can be synthesized; after getting the biological properties of structure of targets and ligand-receptor complexes, the observation of several intermolecular features can provide support for molecular recognition process. The techniques which are mainly used by SBDD are docking and molecular dynamics simulation. The method which is the most widely used is molecular docking, this method mainly predicts the interaction energy of the molecule with the active site of the target by defining how the ligand binds to the target active site, and then find the conformation of ligand which has overall binding free energy in the formed complex. Molecular dynamics simulations is essential in drug design process because of the insights into protein motion which is offered by this technique. Molecular dynamics simulations are useful for finding the characteristics of protein behavior and protein-ligand interactions during disease, this characteristic makes molecular dynamics simulations as an effective method to find out the molecular behavior under different mechanical stresses which happen in a cellular environment. As in research of the team of Li in 2021, they found the key clearance mechanism for Indoleamine-2,3-dioxygenase-1 (IDO1), a kind of attractive target for cancer immunotherapy, is amide hydrolysis in the D-pocket based on the method of SBDD. However, SBDD is not perfect, if the 3D structure of the target is not valid, SBDD cannot work. Since the 3D structure of all ligands cannot be obtained at this stage, it also leads to the low efficiency of SBDD in the actual application process. This also inspired researchers to try different methods to find more suitable hits and candidate compounds. When the 3D structure of the target protein has missed, ligands which are active to a relevant target can support information to identify structural and physicochemical properties of biological activity which we want to observe.

2.2.2. Ligand-based drug design

LBDD, which is short for ligand-based drug design, is the methodology which aim to predict and design new and more efficient compounds based on ligand-derived computational model, this method can find compounds with the same functional structure and show activity against the desired target, make the process of chemical drug discovery development into a new level. Therefore, as the most applied technique, LBDD method is widely used in the initial stages of drug design and discovery. LBDD is mainly used when the three-dimensional structure of target protein is not available, instead of using structure, the known ligands of the target protein can be used to make the process of drug design starts. The methods which are widely used in LBDD are molecular similarity approaches, QSAR and pharmacophore models.

As shown in figure 1, molecular similarity approaches can find out the molecules which have fingerprints that are similar to known ligands. Pharmacophore modeling provides opportunities to discover the general structural features of ligands, these features promote the process of screening for molecules with these features.

A good pharmacophore model which can provide essential basic common features of molecules in three-dimensional space can make rational hypothetical three-dimensional model in which the main chemical features are responsible for activity to be possible. Quantitative structure-activity relationships models can indicate the relationship between ligand and biological activity of their chemical and physical properties. LBDD provides more methodological support for drug discovery, and this method, different from SBDD, gives more opportunities to discover results that are otherwise limited by technology. For example, in the research of team of Hirono in 2005, the complete ligands 3D structures of rat multidrug-resistance–associated protein 2 (Mrp2) had not been determined by any transporters, to solve this problem, Hirono and his team uses binding conformation, key functional groups and 3D quantitative structure-activity relationships between ligands and rat Mrp2 to identify two types of ligand-binding conformations of rat Mrp2 by LBDD.

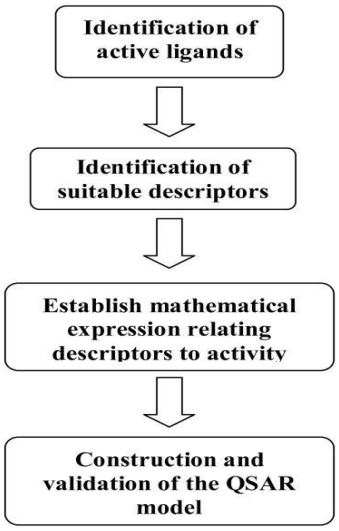

Figure 1. The overall process of LBDD.

SBDD and LBDD have been improved and developed over few decades separately, but some statements show that combining these two drug design strategies can complement their advantages and disadvantages, make the process of drug discovery be more effective than only using one approach. For example, when the 3D structure is not available in the target protein, Ligand-Based Drug Design can make the process continue normally when Structure-Based Drug Design cannot work, make the discovery of drug be more multifarious.

2.3. Virtual screening

To solve the problems caused by expensive, time-consuming and inaccurate properties of HTS, virtual screening, which provide opportunities to reduce the number of compounds to be screened in the process of bioassays has emerged as a supplementary technology to HTS technology in order to deduce time and cost greatly. Compared with HTS, virtual screening can save time and cost, based on huge size and content of database, virtual screening cannot be limited by physic, so this method can be essential partner of physical screens. As shown in figure 2, virtual screening (VS) can separate active samples from inactive samples quickly based on large number of samples, synthetic chemists can modify the hits which are searched by virtual screening methods to develop them into lead series.

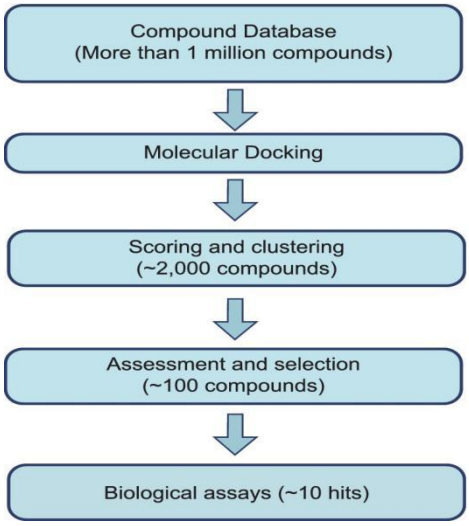

Figure 2. Basic process of virtual screening.

As shown in figure 3, LBVS, which is short for ligand-based virtual screening, includes technologies such as pharmacophore-based methods, quantitative structure–activity relationships (QSAR), and three-dimensional shape matching. SBVS, which is short for structure-based virtual screening, is based on X-ray crystallography, nuclear magnetic resonance (NMR), or homology modeling to determine the docking situation of molecules with three-dimensional (3D) structures of the biological target. Both of LBVS and SBVS are two traditional strategies of virtual screen [18,19].

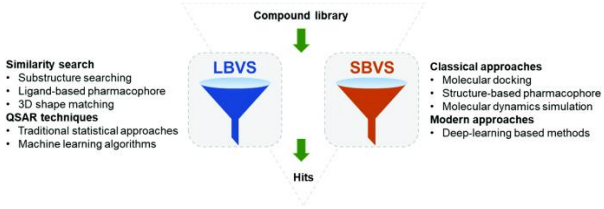

Figure 3. Essential techniques used by LBVS and SBVS during the process of hits discovery.

As in research of Lim, Rahman and Tejo in 2011, they have used SBVS and LBVS to find several potential compounds which is active against dengue virus NS5 MTase and lower the cost of screening in poor countries laboratories in the same time. LBVS methods are based on known bioactive molecules and commonly use a single reference ligand to search and analyze the relationship between active and database. In the meantime, pharmacophore methods can be applied when there are more available data to create a three-dimensional model to find essential key interactions between binding and receptor by substructural features between known actives. As in the research of Chen in 2009, they found the dual target inhibitor of H1N1 by using pharmacophore theory to virtual screening. To prevent the trouble caused by situations such as different assays have same ligand-target interaction when evaluate millions of drug-like compounds targeting thousands of targets, quantitative structure–activity relationships (QSAR) models is a method to make the screening process effective. Because the properties of known ligands are the basic working principle for ligand-based strategies, the limitations of this method during the discovery of the hits are also existing, structure-based strategies which aim to find chemical entities which can bind strongly which the biologically relevant targets by exploiting the molecular recognition between a ligand and a target protein is a useful method to exploit more ligands which have similar interactions with known ligands. Therefore, virtual screenings are mainly focus on the identification of micromolar ligands which are necessary to be improved. However, only a few numbers of people and institutions can have chance to use virtual screening techniques because of the high level of knowledge and expense of the technology as the difficulties of calculation of stereo- and regiochemical molecule 3D structure and multiple protonation. This has led to the low penetration of this technology. The biggest barrier to make virtual screening techniques be widely used is the lack of small molecules databases which are suitable to screen.

3. Conclusion

Computer-aided drug design has become an indispensable method in drug design process now. As a relatively traditional method, although high-throughput screening (HTS) method can screen out unsuitable compounds in preclinical tests and lower the price in the process of animal experiment, false result and high price limit the development of this technique. To find better way, computer-aided drug design, broadly classified as LBDD and SBDD, has received increasing attention. Based on the target structure, potential ligands can be obtained by SBDD and support the process of molecular recognition. However, the technique can only work when 3D structure of the target is valid; in the meantime, LBDD can continue to predict and design new compound based on ligand. Therefore, it is a better way to combine SBDD and LBDD together to make advantages and disadvantages be complementary. Virtual screening which also be classified as structure-based and ligand-based has been considered as a supplementary technology to HTS and has been used in a large number of researches. Although virtual screening uses less time and cost compared with HTS, it is still expensive and based on high level of knowledge which has been a huge barrier to popularize it. There is not a method which is perfect and people still need to focus on the development of drug design. However, we have had excellent understanding on engineering tight binding ligands now, as computer power increases we can better predict ligand-protein binding and make medicinal chemistry be more efficient and accurate.

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