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Research on the application of computer in drug design

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Abstract. Virtual screening by computer is of great scientific significance for drug research and development. In recent years, a large number of computer simulation methods have been developed and applied to drug development for a variety of diseases. This paper summarized and prospected the application progress of computer aided drug design (CADD) in the research and development of new drugs, focusing on the working principle of CADD, related algorithms, and the advantages and disadvantages of existing methods. Although CADD has been successfully applied to a number of drug development projects, the accuracy of auxiliary drug structure optimization is still not high. Therefore, it is urgent to develop more accurate and efficient CADD models and algorithms to promote the process of new drug discovery.

Keywords: computer aided drug design, new drug research and development, computer algorithm, virtual simulation, drug screening.

1. Introduction

New drug research and development are a complex system project with long cycle, high investment and high risk [1]. With the rapid development of modern science and technology, it has been found that virtual screening by computer can not only improve the efficiency of drug design, but also improve the accuracy of drug analysis. Therefore, the use of computer aided drug design has aroused widespread attention and concern in society [2]. In recent years, drug molecular structure design assisted by computer virtual algorithm has made important progress in the field of new drug research and development [3]. Computer algorithms have been proved to be useful for molecular structure analysis, target structure construction, drug activity conformation, pharmacophore recognition, target-drug action model simulation and three-dimensional quantitative structure-activity relationship analysis of drugs, etc., and have been widely used in lead compound discovery and drug molecular structure optimization, greatly improving the level, speed and success rate of drug design [4]. So that drug design from the initial based on chance gradually tends to the orientation and rationalization. Computer-aided drug design not only expands drug discovery upstream, but also uses computer processing biological information to identify and confirm targets and discover new drug targets. It also extends downstream to drug discovery, by calculating drug-like properties of drugs and predicting drug-forming properties such as absorption-distribution-metabolism-excretion/toxicity, so as to eliminate unsuitable compounds early and improve the efficiency of drug design. Computer aided drug design is mainly supported by computer science, using computer algorithms to simulate, calculate and predict the ideal drug molecular structure, compared with candidate compounds, discover and select new compounds in drugs, and carry

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out reasonable drug research and development design. The current computer-aided drug design discipline is becoming more and more mature, and has promoted the process of new drug research and development to the maximum extent, and has gained a lot of successful experience [1]. Therefore, this paper will review the working principle of computer-aided drug design, related algorithms and the advantages and disadvantages of existing methods, and look forward to the future development trend and application prospects in drug development.

2. Working principle of computer-aided drug design

First, the structure of the binding site of the receptor macromolecule was obtained by X-single crystal diffraction and other techniques. Firstly, the hydrophilicity, electrostatic field, and hydrogen bond action site distribution of receptor molecules were analyzed by computer simulation. Then a computer search database was used to design the molecular structure of the receptor, and matching drug molecules were found according to the molecular shape and physical and chemical properties obtained from the search. The two were synthesized, and finally a batch of new lead compounds was developed. Computer-aided drug design can be divided into three categories: database search, novel drug design, and active site analysis [5].

Second, the relationship between structure and activity was basically analyzed based on the native properties of the drugs. Its core is molecular docking, which refers to the recognition of receptor and drug molecules through computer geometric matching, the establishment of quantitative structure-activity relationship, and the analysis and prediction of new compounds. The three-dimensional structure of the small molecule receptor complex is established by computer, so as to predict the small molecule receptor, and further design and develop new drugs targeting it [6].

3. Computer-aided drug design related algorithms

3.1. Indirect drug design

Based on the pharmacodynamic group model, the three-dimensional structure of the basic search is used, including the analysis of molecular shape, reactive analogues and pharmacodynamic group models. Why: most of the receptor structures are based on the ligand structure, and the structure of the structure is studied. Process: the conformation of the lower energy of the compounds is searched, and then the conformation of a certain rule is interposed, and the various conformation that can be overlaps in the series can be solved [7].

3.2. Direct drug design

Based on the target structure, the commonly used design methods include the dynamic algorithm, template localization method, molecular fragment method and atomic growth method. If the three-dimensional structure of the complex formed by the receptor or ligand and receptor has been known, the structure of the new drug can be designed according to the three-dimensional requirements of the recipient site. If only the amino acid composition sequence of the receptor protein is known, but its spatial arrangement is not clear, the local structure can be simulated according to the homologous protein [8].

3.3. High channel virtual filtering

After mastering the basic information about the target and its related compounds, the design can be carried out with the help of computer simulation. Reason: This design method has a certain degree of certainty and pertinency, which can maximize the simplification of the design process in each design process, and effectively shorten the cycle of new drug research and development. Process: Computer simulation of the ligand structure-activity relationship model, the ligand-receptor docking model, and the three-dimensional model of large molecules of the target were carried out first, and then small molecules were screened according to the characteristics of each model [9].

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3.4. Molecular docking method

In the process of computer aided drug design, drug design is carried out directly on the basis of receptors. For molecular docking method, if the binding interaction between the ligand and the receptor can be obtained, relevant software can be adopted to simulate, calculate, and measure the interaction process between the ligand and the receptor and then design the structure of the complex.. Process: The binding site is hypothesized, then calculated, the ligand is projected onto the surface of the receptor, and finally the binding effect is calculated, and reasonable evaluation and analysis are carried out [10].

4. Application of computer-aided drug design in new drug research and development

4.1. Computer aided toxicology and pharmacokinetics related studies

In the preclinical study of drugs, the most important parts include toxicology and pharmacokinetics, and the latter mainly reflect the absorption, distribution, metabolism and excretion of drugs in the body. In the past, more than 60% of the R&D drugs failed because of their toxicity or poor absorption, distribution, metabolism, and excretion properties, which not only wasted a lot of R&D costs, but also a lot of time and energy of R&D personnel [11].

4.2. Discovery and validation of drug target applications

In today's new drug research and development process, the discovery and confirmation of drug targets is the initial link, and it is the main link where most researchers in the past often encountered research and development bottlenecks. The application of computer-aided drug design will enable researchers to improve the speed and accuracy of drug target discovery, thereby improving the efficiency of the entire new drug development process [6].

4.3. Discover and optimize the application of lead compounds

For the research and development of new drugs, the discovery and optimization of lead compounds are key to their success. In the past, the main way to discover lead compounds was for pharmacologists to use various models or pharmaceutical chemists to develop a large number of compounds. Large scale screening is carried out by means of synthesis. After the application of computer-aided drug design, through LBDD (ligand-based drug design) and SBDD (structure-based drug design), lead compound discovery has been innovated, and the overall efficiency of this work has been comprehensively improved.

5. The advantages and disadvantages of current computer-aided drug design methods

5.1. Advantages

Computer-aided drug design provides an important basis and support for drug discovery as an analytical tool ("data mining") and a source of new ideas ("rational" molecular design); This design method is completely simulated by software on the computer, which becomes a new way of drug discovery. A complete break with traditional drug discovery and design methods that rely on massive experimental screening and parallel chemical synthesis; The introduction of computer-aided drug design has a certain "auxiliary" effect on the whole research and development process, and even becomes the key factor and main way to promote drug research and development or determine the success or failure of drug research and development.

5.2. Disadvantages

Molecular docking conditions and pharmacophore model construction may lead to a series of problems. In the process of molecular docking, the protein will move with the skeleton during the docking process, and its protein conformation is not the same, so the flexibility of the receptor should be fully considered during the docking. The development of molecular docking technology is not perfect, and its docking speed needs to be improved. Water ligands also play an important role in docking. The flow direction

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of water molecules should be paid attention to at all time during docking. The treatment of water molecules is a difficult problem. In the process of molecular docking, various forms of isomerization and ionization state appear in the ligands, and the choice of their structure also affects the success of molecular docking. The construction of the pharmacophore model of ligands affects the conformation of ligands. Due to the flexibility of the ligand molecule itself, how to accurately and effectively generate all possible conformations of the ligand is the primary problem in the construction of the pharmacophore model. The same computer will also produce different efficacy models for different training sets, so the training set should be rationally analyzed and selected. There are a similar number of molecules in the compound database, but not all of them are applied by biomedical research institutes. Therefore, high throughput screening also has important problems, such as false positives. Therefore, the virtual screening database should be established to improve its application quality, reduce material resources, and improve screening efficiency.

6. Conclusion

In summary, this paper makes a summary and prospect for the application progress of computer aided drug design in new drug research and development from the working principle, related algorithms, and the advantages and disadvantages of existing methods. From this review, we have found that computer-aided drug design, avoiding the blindness of traditional drug discovery, has positive significance in new drug research and development with strong feasibility, and shows a huge application prospect, which saves a lot of time, raw materials, and human resources in the process of drug development. Further, computer aided drug design has greatly improved the efficiency of new drug discovery. Although computer aided drug design has been successful in a number of drug development, it is difficult to completely replace traditional experimental research owing to its low accuracy in auxiliary drug structure optimization. In the future, computer algorithms and models will urgently need to be further refined and verified. The development of computer-aided drug design in China is early, which is equal to the international level, and gradually tends to mature after years of development. With the continuous progress and development of computer science, we believe that more and more accurate and efficient CADD methods will be constantly developed, which will bring great convenience to the medical industry and eventually promote the rapid development of the whole human society.

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