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Hiện trạng của lĩnh vực nghiên cứu và phát triển thuốc có sự trợ giúp của máy tính

The current status of computer-aided drug design

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Tóm tắt

Nhiều căn bệnh nguy hiểm hiện nay chưa có thuốc chữa trị. Theo WHO, năm 2019 bệnh tim mạch gây 9 triệu người chết chiếm 16% tổng số người chết của năm, ngoài ra bệnh tiểu đường và Alzheimer cũng nằm trong số các bệnh gây nhiều cái chết nhất. Do đó, việc tìm kiếm và phát triển các thuốc chữa bệnh hiệu quả luôn là cần thiết. Tuy nhiên, quy trình nghiên cứu và phát triển thuốc hiện nay tốn rất nhiều chi phí và thời gian. Để một loại thuốc mới ra đến được thị trường phải mất hơn 12 năm nghiên cứu và phát triển, chi phí tài chính hơn một tỉ đô la Mỹ. Vì vậy, mô phỏng máy tính được ứng dụng vào để tiết giảm chi phí tài chính và thời gian. Bài báo này khái quát các nguyên lý hoạt động, những đóng góp của ứng dụng máy tính trong nghiên cứu và phát triển thuốc. Chúng tôi cũng thảo luận những thử thách cần vượt qua để việc ứng dụng máy tính trong nghiên cứu và phát triển thuốc hiệu quả hơn.

Từ khóa: Nghiên cứu thuốc; phát triển thuốc; thiết kế thuốc trên máy tính; gán phân tử; tương tác thuốc với protein.

Abstract

There are many diseases desperately needed treatment. In 2019, WHO reported that cardiovascular disease caused 9 million deaths and accounted for 16% the total mortality. The report also indicated that diabetes and Alzheimer are among the most deathly diseases, and pharmacotherapy has been known to be among the most effective treatment methods to combat against diseases. Thus, demand for the new drug has been always high and urgent, unfortunately, traditional method for drug discovery and development is time-consuming, expensive and inefficient. It takes more than 12 years and costs up to billions of USD to bring a new drug to patients. These drawbacks have been compensated for by Computer-aided drug design (CADD). This review summarizes the core working principles, the contributions, challenges and trends of CADD including structure-based and ligand-based drug design together with relevant softwares and databases of protein as well as ligands.

Keywords: Computer - aided drug design; Structure - based drug design; Ligand - based drug design; Molecular docking.

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1. Introduction

New medication is extremely necessary because of many unmet medical needs such as cancer, cardiovascular diseases and antibiotic resistance. Finding drugs by following the traditional process is a lengthy, costly, difficult and inefficient process regardless of the advancement of biotechnology and analytical sciences. This process consumes over 1 billion dollars and takes more than 12 years to bring a new drug to the patients [1]. Figure 1 shows the workflow of the traditional process in drug discovery and development (DDD).

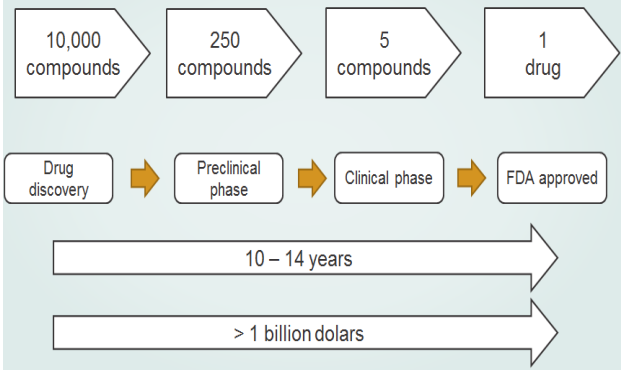

Figure 1: Traditional process of drug discovery and development [1]

To streamline that process, computer- aided drug design (CADD) has been applied widely in pharma and biotech companies to reduce cost and time involved in traditional method and nowadays CADD is an indispensable part of pharmaceutical industry [2].

CADD has been used to find hit and lead compounds, which is also the goal of high - throughput screening (HTS). CADD sometimes shows more effectiveness than HTS, for example Doman et al. compared hit lists from molecular docking with HTS and reported that the docking hits were more druglike than those from HTS [3]. In traditional DDD process, a lead compound might be obtained out of around 80,000 compounds and then goes through lead optimization to improve its bioactivities and reduce toxicity [4]. This long and expensive process can be optimized by using CADD, reducing number of compounds that must be synthesized and tested [5]. Two major approaches in CADD are structure-based and ligand-based.

2. Structure-based drug design

Structure–based drug design (SBDD) relies on structures of biological target, which is normally a protein whose 3D structure can be determined by X-ray crystallography and Nuclear Magnetic Resonance spectroscopy. Target and ligand molecules in molecular docking are considered as “lock - and - key”, where the target is the “lock” and the ligand is the “key”. The ligand adapts the conformation to achieve the best fit with the target. This fitness is expressed as binding modes and binding affinity between the target and the ligand. The ligands that show the highest interaction with the targets are selected, evaluated and ranked by scoring function. Figure 2 shows the simplified workflow of SBDD process.

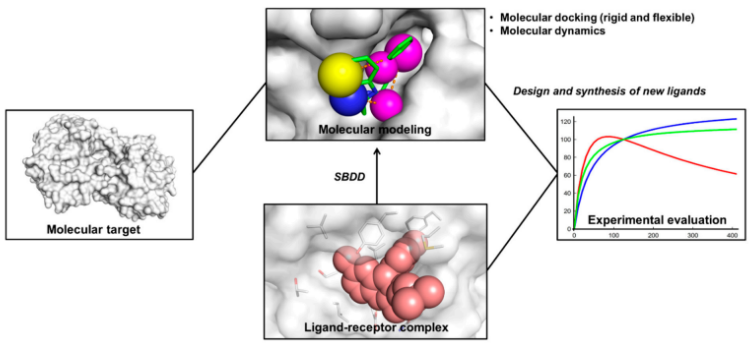

Figure 2: Process of structure-based drug design [6] consists of (i) choosing target molecule, (ii) preparing the ligand library, (iii) docking the ligands into the target to model the interaction and finally (iv) identifying hit compounds.

One fundamental concept in molecular docking is scoring functions that are used to rank ligand molecules based on the binding affinity of these molecules to the target. There are 4 types of scoring functions: physical based, empirical based, knowledge based and machine learning. The first three are classified as classical scoring functions, using linear regression model, whilst the latter incorporates nonlinear regression machine learning methods [7]. The force - field based scoring function identifies binding energy by total of bonded, electrostatic and van der Waals interactions [6], while empirical and knowledge - based functions calculate binding energy by hydrogen-bonding, ionic and apolar interactions, as well as desolvation and entropic effects [8]. Machine learning employs a variety of machine learning algorithms such as super vector machine, random forest, artificial neural network, and deep learning.

3. Ligand-based drug design

Ligand-based drug design (LBDD), on the other hand, relies on knowledge of certain ligands that show biological activities with a drug target. Based on structures of these ligands, a pharmacophore model is built. Then, chemical databases are scanned against the pharmacophore to find molecules that have similar structure to the pharmacophore. These molecules will be experimentally tested to confirm their biological activities, then follow further development phases in drug discovery process. Figure 3 shows the steps in LBDD process.

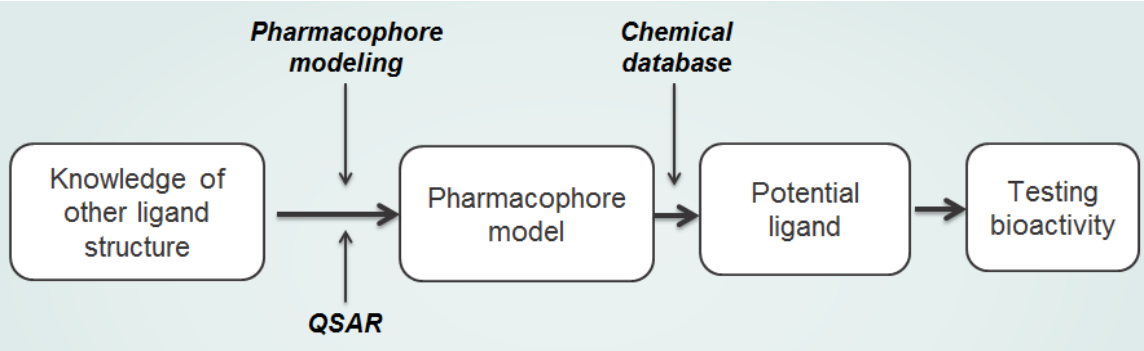

Figure 3: Outline of the process in LBDD

The critical factor of LBDD is pharmacophore modeling. An ideal pharmacophore model represents all features that are necessary to ensure the optimal molecular interactions with a target [9]. Six pharmacophoric features used to build a pharmacophore are hydrogen bond donors, hydrogen bond acceptors, acidic centers, basic centers, hydrophobic regions and aromatic ring centroids (Figure 4) [10]. Some popular pharmacophore searching softwares are Pharmer, PharmMapper, PharmaGist and ZINCPharma.

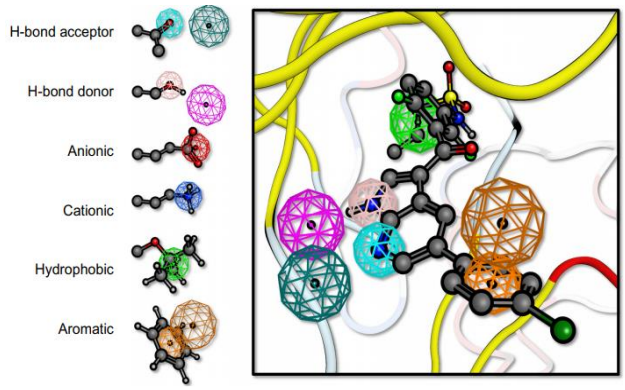

Figure 4: Example of an pharmacophore model [11]

4. Ligand and protein databases for CADD

CADD needs ligand and target databases to work. Ligand databases store molecular features, drugs' mechanism of action, drug indications, clinical data and other essential information of small molecules. There are numerous sizable chemical databases available today. ZINC, for example, has the greatest number of ligands, containing over 200 million 3D leadlike molecules and more than 700 million 2D structures. Chemspider, Pubchem, and REAXYS also have a large number of molecules: 88, 103 and 118 millions, respectively [12].

Similarly, protein databases contain the essential information of protein such as physical, chemical and biological information, three-dimensional structures, fold assignments, active site, function, and protein - protein interaction. Some important databases are Protein Data Bank (PDB), RefSeq, UniProt, and IntAct. Nowadays, PDB contains about 173,537 biological macromolecular structures and includes four members such as Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB), Biological Magnetic Resonance Data Bank (BMRB), Protein Data Bank in Europe (PDBe) and Protein Data Bank Japan (PDBj). RefSeq provides a comprehensive, integrated, non - redundant, well - annotated set of sequences, including 191,411,721 proteins, 35,353,412 transcripts and 106,581 organisms. UniProt is also a popular of sequence databases, containing UniRef, UniParc and Proteomes with 441,942,016 sequences, 373,907,456 sequences and 305,529 proteomes, respectively. IntAct focuses on protein - protein interaction, containing 22,037 publications, 1,130,596 interactions and 119,281 interactors. All these databases are public accessed.

5. Contributions of CADD

CADD economizes DDD process. Application of CADD can save 30% the total cost and time invested in developing a new drug [13]. Research reports that CADD market is increasing, from $1,540.4 billion in 2018 to $4,878.5 billion in 2026 [14]. Nowadays, CADD has been extensively applied in almost every phase of DDD process such as detecting targets, validation, lead discovery, and optimization and preclinical tests [15]-[17]. Comparing to HTS, CADD can provide knowledge about molecular interaction between proteins and ligands, therefore interaction merchanism [18].

Searching for treatment of covid-19 in 2020, for instance, has used CADD [19]. Ahmed et al. used CADD to demonstrate the potential of a remdesivir and its derivatives in treating SAR-CoV-2 infection [20]. De et al. succeeded in using CADD for development anti-cancer drugs [21]. The contributions of CADD has been demonstrated by the large amount of medicines tested with supports of CADD. Table 1 shows some medicines that are developed with the support from CADD.

Table 1: Successful medicines that have support from CADD

Medicine	Biological action	Approval year	Ref
Captopril	An angiotensin-converting enzyme inhibitor, treat high blood pressure.	1981	[22]
Dorolamide	Inhibits carbonic anhydrase II and reduces intraocular pressure. To treat ocular disease or glaucoma.	1994	[22]
Saquinavir	Inhibits protease of rotavirus, that can inhibit one of the last stages of viral replication.	1995	[22]

Zanamivir	Inhibits neuraminidase enzyme of influenza virus, used for treatment of influenza A or B viruses.	1999	[22]
Oseltamivir	Has similar effect with zanamivir with an improvement of bioavailability compared to zanamivir.	1999	[22] [23]
Aliskiren	Use for treatment of hypertension by impacting on renin-angiotensin system.	2007	[22] [24]
Boceprevir	Boceprevir is antiviral medication used to treat chronic Hepatitis C	2011	[22] [25]
Ritonavir	Inhibits HIV protease and interferes the reproductive cycle of HIV	1996	[22]
Tirofiban	Tirofiban is an antiplatelet drug by inhibiting between fibrinogen and platelet integrin receptor GP IIB/IIIa.	1998	[22]
Raltegravir	An antiretroviral medication used together with other medication, to treat HIV/AIDS.	2007	[22]
Loteprednol etabonate	An ophthalmic corticosteroid formulation	2020	[26]
Remdesivir	A SARS-CoV-2 nucleotide analog RNA polymerase inhibitor for the treatment of COVID-19 patients	2020	[20]
Fostesavir	Treat HIV	2020	[27]
Artesunate	Treat severe malaria	2020	[28]
Opicapone	Treat Parkinson's disease	2020	[29]
Amisulpride	Help prevent nausea and vomiting after surgery	2020	[30]

6. Challenges of CADD

Although CADD has been making great contribution, it still faces many challenges. Its algorithms should take into account the protein flexibility. Nowadays, most CADD studies assume a rigid protein structure which is not accurate [31]. Study of Lexa et al. shows that flexible docking can improve the prediction up to 80-95%, whereas the best performance of rigid docking only reaches 50% to 70% [32]. Another issue connects with false - positive reports [33] which is likely associated with scoring function [34].

The second challenge concerns the reliability and accessibility of database. Currently, the databases are fragmented, coming from various sources and this can cause inconsistency [35] due to different enumeration standards. For example, Audibert et al. had detected that there is a considerable inconsistency in reported data when they collected IND dates for 587 New Molecule Entities (NMEs) approved between 1994 and 2014 from FDA's drug database and Federal Register (FR) [36]. The scientific data often contain intellectually and mathematically information, therefore there is a challenge related to how to design data accessibly and understandably to users [37]. This makes large scale virtual screening difficult. In addition, many quality databases are commercial or restricted, which means expensive or impossible to access from academia. This challenge calls for an open access to chemical database, which is advocated by Irwin Lab and Shoichet Lab. Besides, nowadays big data has encountered new infrastructure challenges such as network resilience, network latency and unpredictable behaviour in cloud - based systems [38].

The third challenge faced CADD is the complex biological system. CADD is expected to describe effectively and accurately the interactions of drugs with this system at different levels from molecular, cellular, tissue

to organism. However, this is not a trivial task. Most of studies until today have been working at molecular level, describing the interaction between drug molecule and target macromolecule [39]. But this is a simplified model, in contrary to the real phenomenon happening in living organisms where multi-interactions occur and are unknown yet [40]. Recent research has tried at tissue and cellular level [41], given the prospect, more endeavors are needed.

To tackle above challenges, several research directions have been launched. Many groups have focused on building big and reliable databases [42], [43]. Go hand-in-hand with database is calculation method development. CADD has been increasingly applied machine learning (ML) to speed up the process and reduce failure rates in DDD [44]. Using ML, Farimani et al. has identified the pathway of opiates in binding to the orthosteric site, the main binding pocket of μ - Opioid Receptor [45]. Similarly, molecular dynamic (MD) simulation has been applied intensively to simulate the dynamic interaction between drugs and targets [46]. Nunes et al., for example, had applied successfully MD simulations to examine the interaction between a pyrazol derivative Tx001 and malaria target protein PfATP6 [47].

7. Conclusion

CADD has made significant contribution and is considered as an important approach in drug discovery. It can accelerate the process, save time and resources. For the last two decades, CADD has helped to bring many drugs to patients. In spite of having many successes, CADD faces several challenges including fragemented and inconsistent database and underperformance calculation methods. In order to improve the efficacy of CADD, more high-quality databases of drug targets and ligands are needed along with better algorithms and scoring functions. Furthermore, methods that can simulate living organism and perform animal testing *in silico* are in great demand because the public attitude to these conventional testings is becoming less supportive.

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