Review Article

APPLICATION OF COMPUTATIONAL METHODS IN DRUG DISCOVERY

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ABSTRACT

Rational drug design, is the inventive process of finding new medications based on knowledge of the biological target. Drug design involves the design of small molecules that are complementary in shape and charge to the bimolecular target to which they interact and therefore will bind to it. In the experiment based approach, drugs are discovered through trial and error. With high R&D cost and consumption, computational drug discovery helps scientists gain insight into drug receptor interactions and reduce time and cost. Scientists can predict whether the molecule will succeed or fail in the market. Currently, the process of drug designing increasingly relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design. In computational drug discovery, different computational tools, methods, and software are used to simulate drug receptor interactions. Using computational drug discovery helps scientists gain insight into drug receptor interactions with less time and cost.

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INTRODUCTION

Drug research and discovery is a complex process that takes a long time to complete. Various medications fail for a variety of reasons, such as poor pharmacokinetics, unfavourable side effects, insufficient efficacy, and commercial concerns. The expenses related to this process have increased significantly during the last few decades. The time it takes for a medicine from synthesis to market has also significantly increased.

Pharmaceutical Research and Manufacturers (2021) estimated that the total cost associated with the drug discovery process is approximately US$880 million, with a duration of up to 14 years from the initial research phase to the successful launch of a new medication (Mullard, 2024). In 2023, the Centre for Drug Evaluation and Research has

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granted approval for the use of 55 new drugs (www.fda.gov).

The Computer-Aided Drug Design (CADD) Centres in the academic sector and pharmaceutical industry are being established to support collaborative research between scientists from different disciplines, including computational scientists, biophysics, structural biology, and biology (Schneider and Fechner, 2005, Yu and MacKerell, 2017). The primary aim of the CADD centre is to initiate collaborations that facilitate the execution of research projects aimed at identifying new compounds that may be developed into innovative therapeutic agents. The fields of basic research and real-world applications intersect and have an impact on one another in the broad field of *in silico* drug design. This field uses sophisticated techniques such as cheminformatics, bioinformatics, structure-based design, combinatorial library design, Quantitative Structure-Activity/ Property Relationships (QSAR/QSPR), and a growing number of biological and chemical databases. Furthermore, the wide range of instruments available provides a strong basis for the development of particular ligands and inhibitors. A recent study suggests that the cost to develop a new drug ranges from approximately US $ 43.4 million to US$ 4.2 billion (Médecins Sans Frontières (MSF) 2024). This review seeks to explore the intricacies of the *in silico* drug design process.

Drug design

Finding and creating new medications is a difficult, drawn-out, and multi-disciplinary process. Drug discovery is frequently portrayed as a simple, sequential process that starts with identifying a target and a lead compound, then optimizes the lead and performs *in vitro* and *in vivo* experiments to determine whether the compounds meet certain requirements for proceeding with clinical trials. In the past, the process of discovering new drugs involved a long set of procedures, a variety of *in vitro* tests on living things, and a closer look at the most promising ones to see how they functioned in the body, how they broke down, and whether they were potentially dangerous. This strategy has resulted in a high failure rate, with the most frequent causes being inadequate bodily movement (39%), failure to function as intended (30%), injury to tested animals (11%), adverse reactions in humans (10%), and a variety of business related and other problems.

These days, new fields of study like genetics, protein analysis, and computer science, along with sophisticated tools like chemical mixing, rapid test screens, computer-based searches, new design techniques, in-lab tests, computer-based tests on the drug's toxicity and how it moves through the body, and designing drugs based on their structure, have completely changed the way drugs arediscovered. The fields of basic research and real-world application intersect and have an impact on one another in the vast field of *in silico* drug design. This field makes use of sophisticated techniques such as cheminformatics, bioinformatics, structure-based design, combinatorial library design, QSAR/QSPR (Quantitative Structure-

Activity/Property Relationships), and a growing number of biological and chemical databases (Kwon *et al*., 2019). Furthermore, the wide range of instruments at one's disposal provides a strong basis for the development of particular ligands and inhibitors (Chang *et al.,* 2022).

Three main functions of computation in drug discovery are: (1*) In silico* ADME/T prediction; (2) Virtual Screening and *de novo* design; and (3) Sophisticated techniques for determining protein-ligand binding (Kapetanovic, 2008).

In silico drug designing

The need for computational tools that can detect and analyse active sites and identify therapeutic compounds that can bind to them is increasing as more protein target structures are revealed through crystallography, Nuclear Magnetic Resonance (NMR), and bioinformatics techniques. A global pusheffort is also needed to fight deadly diseases such as AIDS, tuberculosis, malaria, and others. Millions spent for development of Viagra and pennies for the development of drugs for the diseases of the poor is the current situation of investment in Pharma R&D. The time and cost required to design a new drug is very high and an unacceptable level. Before a new drug is released into the market, it takes 14 years of research and an estimated $880 million to be developed (Mullard, 2024). To reduce the time and expense involved in the drug discovery process, computers must be used in several ways (Chang *et al.,* 2022).

In silico techniques for designing drugs

Homology modeling

Homology modeling, also known as comparative protein modeling, is a technique that uses an experimental three-dimensional (3D) structure of a related homologous protein (the "template") to create an unknown atomic-resolution model of the "target" protein from its amino acid sequence (Muhammed and Aki-Yalcin, 2019). In homology modeling, one or more identified protein structures are recognised, most likely because they resemble the structure of the query sequence. An alignment will be then created, mapping the residues in the query sequence to the residues in the template sequence. Proteins have similar sequences that follow evolution, and homologous proteins have similar protein structures. It has been found that the three-dimensional structure of a protein is more evolutionarily conserved than expected because of conservation to maintain functional conservation. Because protein structures are much more conserved than DNA sequences, the observed levels of sequence similarity are included in the extremes. Bioinformatics software tools are used to generate the 3D structure of the target based on the known 3D structures of the templates. The Modeller is a popular tool in homology modeling, and the SWISS-model repository is a database of protein structures created with homology modeling (Lee and Kim, 2005 and Vyas *et al.,* 2012).

Molecular docking (Interaction networks)

Docking is a technique used in molecular modeling that predicts a molecule's preferred orientation when it is joined to another molecule to form a stable complex (Agu *et al*., 2023). Ligand binding to its receptor or target protein is indicated by molecular docking. By analyzing and simulating the molecular interactions between ligand and target macromolecules, molecular docking is used to identify and improve drug candidates. Several ligand conformations and orientations are produced via molecular docking, and the most suitable ones are chosen. Molecular docking is a characterization technique used to determine the affinity of ligands for binding to a receptoractive site. In high-throughput screening, compounds are bound to the active site and thenselected to determine which onebindstothemacromolecule.Severalmolecular docking tools are available, including Biovia Discovery Studio, Schridinger, Argus Doc etc. (Leelananda *et al.,* 2016).

Virtual High-Throughput Screening (VHTS)

Using a computational method called virtual screening, a vast library of compounds is screened for good matches and their ability to bind particular sites on target molecules, like proteins. Virtual screening (VS), a computational technique used for the quick exploration of huge libraries of chemical structures to find those structures most likely to bind to a drug target, typically an enzyme or protein receptor and it is one of the research activities involved in the drug discovery process. A crucial part of the drug discovery process is virtual screening. The concept of "virtual screening" is a recent development when contrasted with the longstanding and broader notion of database searching. According to Walters and colleagues, virtual screening involves the "automated assessment of extensive libraries of compounds" through the use of computer software. This definition indicates that virtual screening operates on a large scale, primarily aiming to address questions such as how to narrow down the vast chemical space of over 10 potential compounds to a manageable quantity that can be synthesized, acquired, and evaluated. More realistic Virtual Screening (VS) scenarios centre on designing and optimising targeted combinatorial libraries and enriching libraries of available compounds from vendor offerings or internal compound repositories, although filtering the entire chemical universe might be an intriguing question. It is faster than traditional screening, less expensive than High-Throughput Screening (HTS), and can scan many possible drug-like molecules quickly. Although HTS is a trial-and-error method, virtual screening is a better complement (Ekins *et al.,* 2007).

Quantitative Structure Activity Relationship (QSAR)

Quantitative Structure-Activity Relationship (QSAR) techniques are employed to demonstrate the relationship between the structural and/or property descriptors of compounds and their biological effects. These descriptors, which elucidate the steric, topologic, electronic, and hydrophobic

characteristics of various molecules, have been established through experimental methods and recently via computational approaches (Anderson, 2003).

Hologram Quantitative Structure Activity Relationship (HQSAR)

In hologram QSAR, which is a unique QSAR technique, 3D information about the ligand is not required. In this method, the molecule is broken down into molecular finger prints that encode the frequency of the occurrence of different molecular fragments. Simply put, the size and length of the fragments depend on the size of the fragment to be included in the fingerprint hologram. Molecular holograms are created by the formation of linear and branched fragments, varying in size from four to seven atoms.

Comparative Molecular Field Analysis (CoMFA)

One innovative and useful method for elucidating structure-activity relationships is Comparative Molecular Field Analysis (CoMFA). CoMFA is a well-known 3D QSAR technique, and research on it started in the 1970s. It provides ClogP values, indicating that the solvent-repellent constrains the ligands and explains their electrostatic and steric values.

Comparative Molecular Similarity Indices Analysis (CoMSIA)

One of the new 3DQSAR techniques is Comparative Molecular Similarity Indices Analysis (CoMSIA). Finding common traits that are necessary for appropriate biological receptor binding is typically done during the drug discovery process. This approach addresses the hydrophobic fields, acceptors and donors of hydrogen bonds, as well as steric and electrostatic properties. (Sliwoski *et al.,* 2014).

3D pharmacophore mapping

3D Pharmacophore mapping is an efficient, reliable, and adaptable technique for the rapid identification of surface compounds in proximity to an appropriate target. A pharmacophore is characterised as a distinct three-dimensional configuration of functional groups within a molecular structure that is essential for binding to an active site or macromolecule (Qing *et al*., 2014). The initial steps in characterising a pharmacophore involve understanding the interaction between the ligand and receptor.

Once a pharmacophore is identified, the pharmacologist uses 3D database search tools to retrieve new compounds that fit the pharmacophore pattern. Since search algorithms have improved over time to effectively find and optimize lead focus combinatorial libraries and support virtual high-throughput screening, the modern drug design process has been utilized to make it one of the most effective computational tools. The computational perspective and use of pharmacophores in compound libraries, database searching, and drug discovery have advanced significantly. For example, in order to efficiently divide the library into a test set of samples, a checklist of analytical statistics

has been developed that can be used. This sequence analysis makes it possible to handle large libraries and also to screen compounds that have been found to have many related information. In addition, new and time-consuming QSAR analysis techniques have been developed to convert drug-drug information into QSAR models, which can be used as high-resolution virtual screens for library performance display. Furthermore, by listing a variety of distance ranges and pharmacophoric characteristics, 10,549 three-point pharmacophores have been previously created using an efficient fingerprinting method. Consequently, the fingerprint uses partial least squares as a QSAR model descriptor. Using a variable selection QSAR as a division of molecular descriptors that afford the maximum statistically significant structure-activity relationship, a further general concept of descriptor pharmacophores was introduced. These methods include k-nearest neighbours and partial least squares. To identify compounds with predicted biological activities, chemical similarity searches utilising descriptor pharmacophores result in creative extraction from chemical databases or virtual libraries (Sadybekov and Katritch, 2023).

Conformational analysis

Through a variety of computation techniques and interaction networks, conformational analysis examines deformable molecules and their least energy configurations. This includes comparing a molecule's receptor site with another molecule and determining the most energetically satisfactory three-dimensional shape.

Monte Carlo simulation

Monte Carlo simulation, which employs statistical mechanics principles, generates numerous system conformations through computer modeling to ascertain the preferred thermodynamic, structural, and numerical properties as a weighted average across these conformations. A beneficial approach involves integrating Monte Carlo sampling with adjustable temperatures (simulated annealing) to enhance the binding of ligands to the active sites (Sliwoski *et al.,* 2014).

Molecular Dynamic (MD) simulation

Molecular dynamics is an effective technique that involves simulating the movement of molecules by resolving Newton's equations of motion for each atom and subsequently advancing the position and velocity of each atom by a small time increment (Badar *et al*., 2022). Utilising this principle, MD simulations explore various paths through the sample configuration space. At 'reasonable' temperatures (ranging from a few hundred to several thousand degrees), only the immediate surroundings of the sampled point are influenced, and solely minor energy barriers (approximately a few tens of kJ/mol) are overcome. The generation can vary locally, and the minimum can be achieved by choosing suitable configurations at specific times during the simulation, thereby reducing these structures. Molecular dynamics (MD) techniques utilise a system's inherent dynamics to investigate low-energy deformation modes

and are adept at exploring the conformational landscape of large confined systems (Shaker *et al.,* 2021).

Prospects for the drug discovery and development process

Significant investments have been directed towards drug discovery and development in recent decades; however, there remains a pressing need for expedited methods that reduce both the costs and time involved in advancing candidate drugs to market approval. Currently, computational methods present a viable solution by utilizing advancements in computational technology to enhance and accelerate the drug discovery process. These methods effectively identify promising drug candidates that are likely to meet functional criteria while discarding unsuitable molecules early in the process, thereby conserving resources that would otherwise be spent on clinical trials. In the forthcoming years, computational approaches to drug discovery are anticipated to remain a focal point for the pharmaceutical industry, with expectations of increased investment aimed at further enhancing these capabilities.

CONCLUSION

Bioinformatics has transformed the drug development process, allowing researchers to more rapidly and precisely identify and assess possible therapeutic candidates. In the years to come, bioinformatics should continue to play a significant role in drug discovery and development due to ongoing advancements in technology and data processing method.

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