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Review on Computational Chemistry in Drug Discovery

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Abstract

By assisting pharmaceutical scientists and medicinal chemists in the creation of new, safe therapeutic ideas via the logical design and placement of current medicines, computational techniques help reduce the necessity for animal medical research. Examine the many studies on computational approaches in drug development that have been published in this article. According to this study, computational chemistry has transformed modern drug discovery by offering strong tools and techniques for predicting and examining molecular interactions. Drug development has been greatly expedited by computer approaches, from virtual screening to lead optimisation and toxicity prediction. Molecular docking, pharmacophore modelling, MD simulations, QSAR, and virtual screening are some of the computational chemistry technologies that are used to identify drug candidates with potential bioactivities. In order to improve the drug development process, these methods should be able to describe molecules that are effective, target-selective, and absorbable. New possibilities for creativity in drug discovery are presented by recent developments in AI, ML, and high-performance computers, which further expand the potential of computational chemistry.

Keywords: Computational chemistry, Drug discovery and development, Computational technique, Computer-aided drug discovery (CADD), Molecular docking (MD), Quantitative structure–activity relationship (QSAR) techniques, etc.

1 Introduction

To guarantee the safety and efficacy of the new drugs, the time-consuming and expensive process of drug development involves clinical studies, regulatory approval, and an examination of academic

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information. Numerous applicants may not be able to finish the lengthy procedure, which might take years, and there is no assurance that it will be successful. Despite the challenges, drug development is an essential part of the healthcare industry since it produces drugs that may cure illnesses, reduce symptoms, or cure medical problems [1]. For example, antibiotics revolutionised the treatment of infectious diseases, and new developments in cancer immunotherapy have offered patients whose illnesses were previously believed to be incurable hope [2]. Validating the target, identifying the lead compounds, improving and optimising these compounds, and then proceeding to preclinical research and clinical trials are common processes in the drug development process [3].

In order to address challenging chemical issues, computational chemistry uses computer simulation. Its emphasis on comprehending tiny molecules, medications, and intricate molecular systems like DNA, proteins, and other macromolecules makes it an essential component of the molecular-level examination of biological systems [4]. Principles from chemistry, biology, and pharmacology are often combined in the intricate multidisciplinary process of drug development. Researchers can anticipate molecular characteristics and uncover possible medication candidates more effectively by using computational methods. These technologies will also save the time and money that are normally needed for exploratory testing. Close cooperation between researchers with multidisciplinary knowledge and medical scientists is necessary for this [5], [6].

A. Computational chemistry

Computational chemistry uses "computers and physics-based algorithms" to simulate chemical processes and calculate the chemical properties of atoms and molecules. Drug design and discovery use a variety of computational chemistry tools to predict and calculate events, including "the drug's binding to its target and the chemical properties" needed to create potential new drugs [7].

B. Importance of Computational Drug Discovery

"Drug design, discovery, and development" are interdisciplinary processes that take a lot of time and effort and include several study areas. Traditional medication development and research is notoriously costly and time-consuming. There are only 200 to 250 chemical compounds out of 10,000 that will get to clinical testing. Ten of these 200–250 chemicals will be examined in animal models instead of human ones. The Tufts Centre for the investigation of Therapeutic Development conducted an investigation from 1995 to 2007 that found that around 11.83 % of all therapeutic compounds that progress to Phase I of clinical trials are approved for the market. Because traditional drug discovery is expensive and has a high failure rate, researchers have turned to a new method of drug development. A novel method for quickening the drug discovery process has been made possible using CADD [8].

C. Applications of computational chemistry in drug discovery

Computational techniques facilitate the methodical investigation of chemical alterations, directing synthetic endeavours and expediting the optimisation procedure. Lead optimisation driven by computational chemistry is shown by the discovery of selective kinase inhibitors for cancer treatment. Effective treatments design requires an understanding of the molecular underpinnings of drug-target

interactions [9]. Detailed information about the binding processes is provided by computational chemistry, which also identifies important residues and interactions that influence binding affinity and specificity. To clarify the binding mechanisms of different pharmacological targets, including as ion channels, enzymes, and G protein-coupled receptors (GPCRs), MD simulations and QM calculations have been used [10]. These realisations help rationally develop medications with better binding characteristics and fewer side effects. An important part of drug development is predicting a medication candidate's toxicity. On the basis of chemical structure and established toxicological data, computational models, such as machine learning algorithms, can forecast possible toxicities [11]. In the early stages of medication development, these forecasts aid in identifying and reducing safety hazards. Several negative consequences, including hepatotoxicity, cardiotoxicity, and genotoxicity, have been predicted using computational toxicology. Scientists may make well-informed conclusions about the safety profiles of potential drugs by combining these predictions with experimental evidence [12].

D. Limitation and challenges in computational chemistry

Despite the significant advancements in computational drug discovery, there are still several problems that jeopardise the reliability and utility of these methods. Protein flexibility and solvation effects are examples of biological complexity that may not be fully replicated by the approximations used in the computer approaches. Improved sampling methods, machine learning-driven scoring systems, and ensemble docking are among recent innovations that aim to overcome these limitations [13]. Research teams without access to high-performance computers face challenges since large-scale virtual screening and high-resolution simulations need significant processing resources. The incorporation of cloud computing, GPU acceleration, and artificial intelligence-powered prediction models have all been investigated as potential solutions. Additionally, experimental validation is required for computer predictions, which may be costly and time-consuming; some anticipated medications do not exhibit the predicted in vitro and in vivo activity [14].

In order to address these issues, hybrid approaches—which combine automated high-throughput screening with computer forecasts—are being developed. AI-driven drug development is also fraught with issues, including overfitting, biassed datasets, and interpretability issues. These methods are becoming more resilient and open because to developments in federated learning, data augmentation, and explainable AI [15]. Ethical and regulatory concerns, such as data privacy, repeatability, and molecular evaluation produced by artificial intelligence, remain significant. These days, systems that emphasise transparency, reproducibility, and adherence to ethical standards are being examined by regulatory bodies [16]. These difficulties still exist, but they are gradually being overcome by continuous developments in "computer techniques, artificial intelligence, and integrated approaches". In order to define the future of computational drug development, it will be possible to expedite the discovery of novel drug candidates by improving experimental validation techniques, increasing computer efficiency, and improving prediction accuracy [3].

2 Literature Review

(Shah et al., 2024) [17] "Computer-aided drug discovery (CADD)" approaches not only reduce the time and cost of drug discovery and development, but also help to understand the molecular mechanisms of drug action and toxicity. The method known as QSAR creates mathematical connections between a group of chemicals' structural characteristics and biological activity. The current state and applications of CADD techniques are examined in this work, with a focus on "molecular docking and quantitative structure–activity relationship (QSAR) approaches". In addition to some current developments and instances of their use in drug discovery for different illnesses, this paper examines the fundamentals, benefits, drawbacks, and difficulties of these approaches. The study also discusses the potential future prospects of CADD techniques in the era of big data and artificial intelligence.

(Mahamat, 2022) [12] highlights the main computational techniques and resources utilised in drug development, such as machine learning, quantum physics, molecular docking, and molecular dynamics simulations. The article covers recent developments, examines potential future possibilities in the subject, and talks about how these approaches are used at different phases of drug development. New therapeutic candidates have been identified and optimised much more quickly thanks to the use of computational chemistry into drug development methods, which has also yielded considerable cost, time, and effectiveness gains.

(Lin et al., 2020) [18] highlighted the functions of multiscale biomolecular simulations in determining the target macromolecule's drug binding sites and clarifying the mechanics behind therapeutic activity. Virtual screening methods (such as pharmacophore modelling, QSAR, and molecular docking) were then discussed and presented, along with "structure and ligand-based classical/de novo drug design". Lastly, the evolution of machine learning techniques and their use in the previously described computational approaches to expedite the drug discovery process were examined. Additionally, a number of application scenarios involving the combination of several techniques were explored. The future of "drug screening and design" will undoubtedly involve the integration of multiple methodologies to collaboratively address the complex challenge across a variety of dimensions and sizes.

(Amrit, 2023) [19] Drug design and discovery have seen a revolution thanks to computational chemistry. Numerous benefits come with this method, such as the opportunity to explore a large chemical area and time and money savings. Examine some important uses of computational chemistry in drug design and discovery here. Thanks to the capabilities of computational chemistry, the area of drug discovery and design has seen a dramatic revolution in recent years as researchers look for safe and effective medications. Computational chemistry speeds up the drug discovery process by using sophisticated algorithms, high-performance computation, and large datasets. This ground-breaking method has made drug discovery more successful and economical, which has resulted in the creation of ground-breaking treatments that were previously thought to be unattainable.

(Schaduangrat et al., 2020) [16] provides a comprehensive analysis of the repeatability of computational drug discovery. This study covers the following topics: computer problems associated with model

building and deployment, model generation in computational drug discovery, and use case scenarios for improving the computational drug discovery procedure. To encourage partnerships and facilitate repeatability, it has become commonplace in computational fields to share data and programming codes for numerical calculations (i.e. to push the project farther by adding new ideas, extending the data, enriching the code, etc.). In the field of computational drug design, an open approach to data/code collection, curation, and sharing is thus essential.

(Xu, 2024) [15] With the Nobel Prize in Chemistry given for "protein structure prediction and design" and the Nobel Prize in Physics given for "artificial neural networks," 2024 has been a particularly interesting year for computational sciences. Given how quickly these fields are evolving, a publication summarising the current status of "computer-aided drug design (CADD) and artificial intelligence in drug discovery (AIDD)" as well as their future directions would be relevant and topical for the Journal of Medicinal Chemistry's readership. In order to contribute to current debates in the literature and on scientific blogs, this commentary attempts to highlight recent advancements, significant obstacles, and possible areas of overlap across various disciplines.

3 Conclusion

With its strong tools and methods for predicting and analysing molecular interactions, computational chemistry has completely changed the way that drugs are discovered today. Using computational techniques has greatly sped up the drug development process, from virtual screening to lead optimisation and toxicity prediction. Lately, in silico prediction techniques have shown quick results. In order to identify drug candidates with potential bioactivities, computational chemistry uses technologies such as molecular docking, pharmacophore modelling, MD simulations, QSAR, and virtual screening. By characterising molecules that are effective, target-selective, and absorbable, these methods should improve the drug development process. In order to improve effectiveness and reduce attrition in drug development, QSAR techniques are often superior for lead optimisation. "The pharmacodynamic and pharmacokinetic characteristics" of compounds may be determined using QSAR models throughout the drug research and development process. To assist optimise and prioritise drug prospects, these in silico evaluations anticipate a number of attributes (including physicochemical and ADME) and actions. Current developments in high-performance computers, artificial intelligence, and machine learning continue to expand the potential of computational chemistry and provide fresh chances for creative drug discovery. highlighted the expanding use of AI and machine learning in computational drug development, showcasing their capacity to improve molecular predictions, automate data processing, and expedite drug testing. Drug development efforts are greatly aided by hybrid techniques, which integrate machine learning and artificial intelligence with pharmacological and computational procedures.

Dr. G. Hemalatha

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