Volume 3, Issue 3, 2025

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

COMPUTATIONAL MODELING AND PHYSICS IN DRUG DISCOVERY

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DOI: https://doi.org/10.5281/zenodo.15524297

Keywords
Computational Modeling, Drug Discovery, Molecular Docking, Virtual Screening.

Article History
Received on 17 April 2025
Accepted on 17 May 2025
Published on 27 May 2025

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Abstract

Computational modeling and physics will play an important role in drug discovery, because it allows researchers to hypothesize the efficacy and safety of potential drugs without investing international regulatory approval time and large amounts of money. Computational modeling and physics-based approaches are changing the drug discovery space and have provided some powerful possible methods for reducing time and accelerating (failed) drug discovery. More than just reflecting on discovery methods, this review describes and situates the science of computer modelling and physics and the pharmaceutical sciences, collectively emphasizing the roles of each science relative to creating new drugs. This article provides a review of contemporary results regarding the ability to develop new pharmaceuticals using computer modelling, and physics that executed, taken literally, includes molecular docking, molecular dynamics simulation, quantitative structure-activity relationship (QSAR) modelling, virtual screening and machine learning. Within this review, I explore the challenges and limitations of undertaking computer modelling and physics-based approaches, as well as the applications the pharmaceutical industry may improve upon. A systematic search was performed for the review using the following electronic databases: PubMed, Scopus, Science Direct, Springer, Cureus, Elsevier, and Web of Science. The searches produced publications published within the past 10 years related to the topic of interest. At first, 40 articles were located but only 25 articles were selected for the review, because their content was relevant. Finally, computational modelling and physics are indispensable in drug discovery by providing valuable information on how molecules interact with each other, and they also aid in the design, development, and optimization of new therapeutic candidates.

INTRODUCTION

Computational modelling and physics-based approaches have transformed scientific research in many areas, facilitated drug discovery. These techniques enable researchers to comprehend and predict complex phenomenon, characterize molecular interactions, and expedite therapeutic invention. By integrating physics with computation, researchers are able to examine drug-target interactions more deeply within the context of drug design. Computational modelling is the process of simulating and analyzing complex systems with mathematical and computational techniques. Computational modelling provides a way to understand how drug molecules behave and relate to biological targets in drug discovery. Examples of techniques are: quantitative structure-activity relationship (QSAR) modelling, molecular docking, and molecular dynamics simulations. [1, 2, 3].

Frontier in Medical & Health Research

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Combining physics with drug discovery illustrates the potential of sciences in an interdisciplinary manner, the fundamentals of physics allows us to understand the theoretical approach and describe how energy and matter behave. When examine drug-discovery applications, physicist is able to get a greater context to all the physical forces and interactions found within biological systems. in computational drug-discovery, classical mechanics, quantum mechanics, and statistical mechanics are part of the computational models used to study how molecules behave, the binding affinities of the bottoms of interest, and simulations of the dynamics of drug-target interactions. in drug-discovery, the cooperative principles of computational modelling in the study of physics has contributed to our understanding and optimization of drug candidates. The obstacles of traditional experimental drug discovery search can be time-consuming effort for limited and costly investigations that guide future experiments involving drug-candidates, likewise, experimental drug-discovery approaches may not always address certain scope to intuitive understand the biophysical mechanism outcome of drug-candidates. Computational models, while not the same as experimental models, provide an alternative examination of certain physical aspects by permitted to simulated that could consist of screening libraries of compounds, predicting drug-target interactions, and optimizing lead compounds. [1, 4].

By using computational models and physics-based approaches researchers can explore the chemical and physical properties of drug molecules, predict their behavior within biological systems, and improve their effectiveness as well as safety. These approaches identify promising drug candidates, decrease the cost and time associated with using expensive and time-consuming experimental approaches, and provide critical information on how the drugs work. The incorporation of computational modelling and physics into drug discovery has transformed the research landscape into a more scientific, rational, and efficient drug-design process. In particular, these methods allow for a better understanding of drug-target binding, virtual screening, and comprehension of the molecular dynamics of drug molecules themselves. By employing computational modelling and physics researchers can hasten the discovery of safer and more effective drugs that may have a profound impact on clinical outcomes.

In recent years, there have been several notable advancements in the use of computational modeling and physics in the process of drug discovery. These include enhanced Molecular Dynamics Simulations, integration of Quantum Mechanics and Molecular Mechanics (QM/MM) Approaches, Machine Learning in Drug Discovery, and Advances in Free Energy Calculations. MD simulations have benefited from advances in computing power, algorithms, and force fields, making them more effective in studying protein dynamics and ligand binding. QM/MM methods combine quantum mechanics with molecular mechanics, providing a computationally efficient representation of the surrounding environment. Machine Learning techniques have been increasingly utilized in drug discovery to analyze large datasets, predict compound properties, and optimize lead compounds [3, 5].

Over the past several years, there have been several notable developments with important implications for future applications of computational modeling and physics in drug discovery: new and improved Molecular Dynamics Simulations, deployment of Quantum Mechanics and Molecular Mechanics (QM/MM) Approaches, Machine Learning in Drug Discovery, and Advances in Free Energy and free energy Permutation Calculations. MD simulations include enhanced treatment due to the significant improvements in computing power, algorithms, and available force fields, which collectively now make MD simulations more capable of analyzing protein dynamics and ligand binding. QM/MM methods provide a way to treat a specific interaction using quantum mechanics while retaining a more neutral but computable representation of the surrounding environment. Furthermore, the available studies of Machine Learning applications have grown exponentially in size and range while using self-learning inductive approaches from large data sets. Machine learning techniques are becoming more widely adopted for drug discovery because they can better analyze and predict compound properties as well as advance lead compound optimization capabilities. [4, 5].

High-Throughput Virtual Screening has been increased in scale to allow for high- throughput

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

virtual screening of large compound libraries. These advancements have improved accuracy and efficiency of computational methods that facilitate better decision making, while also enhancing the development process at a lower time and expense for experimental iterations. Ongoing developments likely will continue to advance the field and aid in the development of safer and more efficacious drugs [6].

Molecular docking is a computer-based modeling system in drug discovery, used to predict and analyze binding interactions of small molecules (ligand) with target proteins (receptor). This modeling system is very important in the early phases of drug development, as it can show the potential binding modes and affinities of small molecules to identified protein targets. Molecular docking is comprised of two main phases, conformational sampling, and scoring. Within the conformational sampling phase, many possible orientations and conformations of the ligand in the receptor's binding site are explored. In conformational sampling, this will be accomplished by placing the ligand into the binding site, at a given orientation, and algorithms will be used to evaluate its compatibility with the receptor's structure. Following the creation of ligand poses the scoring phase can begin - this utilizes scoring functions to rank and evaluate binding affinity of each pose. These scoring functions provide a quantitative value of the binding affinities of the ligand poses - these functions provide an estimation of the energetic and geometric complementarity of the ligand/receptor complex. The scoring procedure helps consolidate binding modes into the most favorable state when doing a drug discovery endeavor, leading to potentially investigating drug candidates in experimentation [7, 8, 9].

Molecular docking has a vast range of applications in drug discovery. It can be used to rapidly screen large libraries of small molecules and identify potential lead compounds that have a high probability of binding to our target of interest. This means researchers can better identify and focus their time on the most prospective drug candidates. Also, docking can give us some insight into how ligands are oriented and positioned in the active site, which helps predict the binding mode. Knowing the binding mode will help us understand which interactions are the most relevant between the ligand and the receptor and aid in the optimization of lead compounds. Finally, by screening a large database of compounds, we will be able to identify novel small molecules that also possess a high probability to bind to a specific target. Virtual screening accelerates the process of identifying possible drug candidates and minimizes the time and cost of experimental screening. Docking may be used in an iterative manner to direct the modification and optimization of lead compounds as part of a structure-based drug design. With the knowledge obtained from the ligand's and receptor's interactions, scientists can rationally design and predict the effects of chemical modifications, for example, improving the potency, selectivity, and pharmacokinetic properties of a drug. Therefore, docking methods could be used to study protein-protein interactions in addition to ligand-protein docking. Predicting binding interfaces and affinities between proteins can lead to evaluation of potential strategies to modulate specific protein-protein interactions, a crucial step in developing therapeutics that target protein complexes. [8, 10, 11].

Molecular dynamics (MD) simulations explore atoms and molecules throughout time. Protein-ligand complexes, protein-protein interactions, and lipid bilayers are studied using MD simulations in drug development. MD simulations reveal structural changes, binding kinetics, and stability by modelling atom movement and interactions. MD simulations monitor atom locations and velocities by numerically integrating Newton's equations. A force field describes the system's behavior, including bond stretching, angle bending, torsional rotations, electrostatic, and van der Waals interactions. MD simulations build time-evolving trajectories through repeated calculation of forces and updates to atomic locations. [12, 13].

MD simulations support drug discovery in numerous ways including binding free energy calculations, examination of protein dynamics, analysis of protein-ligand interactions, solvation effects, and amount of membrane protein dynamics associated with drug discovery. Binding free energies are used to make estimates of ligand binding affinities and rank candidate medications, while protein dynamics and conformational changes are utilized to map out the

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

folding, unfolding, and domain movements of proteins. Protein-ligand interactions and binding modes are used to rationalize and optimize ligand-protein interactions, whereas the impacted solvation effects and drug permeability are probably used to help optimize the medication candidates with better pharmacokinetic properties. Membrane protein dynamics and drug design applications are utilized to study membrane proteins and lipids. Overall, MD simulations can reveal useful information regarding the dynamics of bimolecular systems in drug development as they give information on the binding free energy ranges, protein dynamics, protein-ligand interactions, relevant solvation effects, and form of the membrane proteins. MD simulations and other computational and experimental methods can help identify positive traits of possible drug candidates, optimize drug candidates by understanding their potential drug-target molecular pathways more, inferior drug-pathway interactions, whether protein-ligand interactions of relevant protein drug design perturbations can affect possible drug candidates during such phases of clinical research. Overall, together they can fast-track discovery of new medications and puts relevant strain on the exposure of knowledge relating to optimizing drug candidates alters when conduction drug discovery and/or development. [14, 15].

Quantitative Structure-Activity Relationship (QSAR) modeling is a computational approach that is used in drug discovery to establish quantitative connections between the structural characteristics of molecules and their biological activity. QSAR modeling involves multiple steps, that include data collection, descriptor calculations, model creation, and validation. Data collection consists of experimental biological activities or properties of a set of compounds, descriptor calculations, model creation, and model validation - which employs statistical and machine learning algorithms for model construction and independent test sets or cross-validation schemes for validation. QSAR modeling has many applications and can be used in a variety of valuable ways in drug discovery. [16, 17].

QSAR modeling is a key component of the drug discovery process, in which quantitative relationships between compound structure and activity or properties is defined. QSAR modeling assists in compound prioritization, lead optimization, toxicity predictions, and ADME (absorption, distribution, metabolism, and excretion) property predictions, and compound design. QSAR modeling in conjunction with other experimental and computational techniques can help researchers accelerate the drug discovery process and inform decisions on which drug candidates to select or optimize. A few examples of how QSAR models can be used are: Virtual Screening/Compound Prioritization- QSAR models can be used to screen through a large compound library and then prioritize the compounds with predicted high activity or desirable properties. Lead Optimization- QSAR models can assist in the optimization of lead compounds by giving insight into what structural features were key to the activity. Toxicity Prediction- QSAR models can help predict the potential toxicity of the compounds based on structural properties. ADME Properties: QSAR models can estimate the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of compounds. Scaffold Hopping/Compound Design: QSAR models can also assist in gaining insight into scaffold hops, where new compounds with different core structures can be designed based on the predictions from the QSAR model. [17, 18].

Machine learning is a field of artificial intelligence that encompasses algorithms and models that can learn and predict or make decisions without being specifically programmed. It has received considerable attention in regard to drug discovery because it has the potential to facilitate the identification of new drug candidates and optimize the drug development process. Some of the most prominent applications of machine learning to drug discovery are virtual screening, predictive modelling, and de novo drug design. The algorithms of machine learning make pharmaceutical development much more efficient by promoting data-driven decision making, fast chemical-screening, and simplifying the identification of potential new therapeutic candidates, including essentially synthesizing new molecules that are highly likely to have the activity or property of interest. Predictive modelling and machine learning potentially can predict toxicity based on chemical characteristics of the compounds instead of laboratory testing, identify possible new uses for existing drugs, and identify biomarkers, optimize

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

clinical trial design/execution, and improve patient selection, endpoint prediction, and trial outcomes. By utilizing machine learning, researchers can better navigate the vast chemical and biological universe and hasten and improve the drug discovery process [19, 20, 21].

The present paper discusses the relationship between computer modelling, physics, and pharmaceutical sciences during the drug discovery process. It is mainly concerned with the applications of molecular docking, molecular dynamics simulations, quantitative structure-activity relationship (QSAR) modelling, virtual screening, and machine learning. It also examines the challenges and limitations presented by these methodologies, as well as the future of the industry.

Method:

For the purpose of the study, an exhaustive search was undertaken utilizing electronic databases such as PubMed, Scopus, Science Direct, Springer, Cureus, Elsevier, and Web of Science to discover articles that were published during the previous ten years that were relevant to the issue that was being considered. The objective of the review was to locate publications that were published in relation to the topic that was being considered. In the beginning, a total of forty articles were discovered; however, only twenty of those articles were chosen to be included in the review since the information that was included within them was pertinent.

Discussion:

In the process of drug development, computational modelling and physics-based methods, such as molecular docking and molecular dynamics simulations, have emerged as crucial tools. While molecular docking allows for the prediction of binding modes and interactions between small molecules and target proteins, molecular dynamics simulations give insights into protein-ligand interactions, protein dynamics, and membrane protein behavior [3, 22]. Molecular docking is a technique that allows for the prediction of binding modes and interactions. Approaches based on machine learning have led to improvements in areas such as virtual screening, chemical prioritization, toxicity prediction, and medication repurposing. The expediency of identifying potential drug candidates has been stimulated by the process of computer modelling, physics-based scoring functions, high throughput screening and the total effectiveness of the drug development process. [5, 8].

The review article elaborated on the value of molecular docking for predicting ligand binding modes and interactions with target proteins. Its importance continues to expand because of advances in drug development and design, and predictive modelling technology. The article further emphasized the value of molecular dynamics (MD) simulations as they represent the dynamic properties of bimolecular systems best. In virtual screening, chemical prioritization, and toxicology prediction, machine learning technologies like quantitative structure-activity relationship (QSAR) modelling and deep learning have grown in importance. The review paper further highlighted predictive outcomes using physics-based scoring functions (e.g., force fields and solvation models) for predicting binding affinities and enhancing chemical features or attributes. In addition, the invention of high throughput virtual screening has enhanced the identification of potential hits and lead compounds from large libraries in a timely and economical manner. In general, this article has highlighted the tremendous impact that computer modelling and physics-based methods have had in drug development in terms of improving predictions, accelerate compound screening, and improving the quality of decision-making. [8, 23].

Although there have been many advances in computational modelling and physics-based methods in drug discovery, there are challenges and limitations that need to be understood to fully realize the potential of these methods. These challenges include computational complexity, accuracy and reliability, data availability and quality, lack of standards, limited scope of models, and integrating experimental validation. Nevertheless, the prospects for the future of our industry remain optimistic. Although there have been many advances in computational modelling and physics-based methods in drug discovery, there are challenges and limitations that need to be understood to fully realize the potential of these methods. [15, 18].

Frontier in Medical & Health Research

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Understanding these challenges is important to occur so that we can overcome them to realize the full potential of these methods. Significant aspects of computational modelling include the advancement of machine learning, coupling of multi-scale models, incorporation of big data and omic technologies, developed networking and standardization efforts, and signs of expansion. The potential of continuously evolving machine learning techniques is that they may help circumvent some of the constraints of a lack of data and precision; by synthesizing different types of modelling, including from atomic to systems modelling, we could achieve a better understanding of drug-target engagement and complex biological process. Big data and omics technologies have the potential to enrich computational models and improve predictions of drug efficacy, toxicity and patient stratification when considering omic data and big data. For the issue of some issues in standardization and collaborative efforts that are needed in the field of computational modelling, it will take collaborative and standardization efforts. New applications can also help with the development of emerging therapies for difficult diseases. [24, 25].

Conclusion:

In conclusion, physics-based methods and computational modelling have become invaluable resources in the pharmaceutical industry. Methods including molecular docking, molecular dynamics simulations, quantitative structure-activity relationship modelling, and machine learning have all made major contributions to the discovery of new drugs. They have sped up the drug development process by aiding in the forecasting of chemical characteristics, binding affinities, and toxicity. Despite difficulties and restrictions like as computing complexity, accuracy limits, and the need for standardization, the future of the sector seems bright. These obstacles may be surmounted and the efficacy of computer modelling in drug discovery can be improved by developments in machine learning, multi-scale modelling, integration of large data, and enhanced cooperation efforts.

Statements & Declarations

FUNDING:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

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