A Mini Review on Computer-Aided Drug Design

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Amal Das[a]

Tonmoy Doley[b]

Pubalee Sarmah[b]*

Department of Chemistry, Guwahati College,

Guwahati, 781021, Assam, India[a]

Department of Chemistry, Royal Global University,

Guwahati-781035, Assam, India[b]

***Correspondence:** psarmah2007@gmail.com

ABSTRACT

Computer-Aided Drug Design (CADD) has significantly revolutionized the pharmaceutical industry; expedite the design and development of drugs. This paper reviews a range of methods from computer-aided drug design such as molecular docking, molecular dynamics simulation, and quantitative structure activity relationship (QSAR) modeling. Herein, we additionally discussed the application of artificial intelligence (AI) and machine learning (ML) in CADD, its real-world operationalization, and its predicted future. The identification of a new set of pharmaceuticals was aided through AI powered predictive models which completely shifted the traditional approach that previously relied on extensive testing. In addition, the sharing of knowledge through the collaboration of different fields and the use of freely accessible databases speed up the rate of drug development. Even though there are still concerns on the level of computation and the reliability of the data, the continuous progression of computational chemistry, AI, and bioinformatics in tandem is very promising for the future.

KEYWORDS

Computer-Aided Drug Design, Molecular Docking, AI in Drug Discovery, QSAR, Molecular Dynamics

INTRODUCTION

The development of new pharmaceuticals is a time consuming, expensive and highly complex process. Trial and error experimentation based on traditional methods has limited efficiency and are not effective. With the introduction of computational software, CADD has played a significant role in modern drug discovery. By employing these computational programs, researchers are now able to predict interactions at the molecular level, and thus optimize lead compounds, and thereby reduces time and cost imposed on drug development [i].

CADD software provides researchers the freedom to perform virtual screening to help reduces the need for extensive wet lab experiments [ii]. This screening methods helps to identify the promising drug candidates by guiding structural refining to enhance their efficacy. The combination of high throughput screening (HTS) with computational CADD has substantially role in the early stages of drug discovery; provides mechanistic insights to design molecules that selectively target disease related to proteins [iii]. Yang et al. describes the crucial role of SARS-CoV-2 viral proteins as therapeutics targets, and provides the application of CADD- based screening techniques for these viral proteins [iv].

The increasing availability of structural data from sources like Protein Data Bank (PDB) has significant role in the development of CADD [v]. The utilization of homology modeling helps scientists and researchers to figure out the protein structures that have not yet been experimentally tested and determined, and thereby broadens up the scope to design target-based drug [vi]. Moreover, new advancement in artificial intelligence and deep learning helps in enhancing the predictive accuracy of CADD models; improves the efficiency in drug discovery pipelines [vii]. The structural data particularly available in the sources like the Protein Data Bank (PDB) has immense contribution in the advancement of CADD. Through homology modeling, scientists can able to predict and estimate the structure of proteins for which experimental data are not available, and thereby broadening the scope of target based drug designing. Moreover, new development in artificial intelligence and deep learning helps in enhancing the predictive accuracy of CADD models, improving the efficiency of drug discovery pipelines. Recent research on anticancer compounds have illustrated that AI-based CADD tools are capable of accelerating hit identification by 70%. [viii]. Also, significant improvement in quantum computing technologies hold promise in solving complicated molecular interactions with unprecedented accuracy [ix]. CADD, although have significant advantages, faced several challenges due to limited datasets leading to inaccurate predictions. Also, the complexity of biological systems in addition to computational constraints further adds to its complications, thus making drug discovery more cost-effective and precise.

METHODS IN COMPUTER-AIDED DRUG DESIGN (CADD)

CADD employs various computational programs to discover and optimize potential drug candidates; broadly classified into SBDD (structure-based drug design) and LBDD (ligand-based drug design) [x]. Furthermore, AI (artificial intelligence) and ML (machine learning) have also become important tools in enhancing predictive models and optimizing drug properties. Recent study highlights the critical role of hybrid approaches that integrates multiple CADD techniques to further improved accuracy and efficiency in drug discovery. Chen et al. have reported the blended approach to in silico drug design; holds great promise for creating more effective anti-virulence drugs against dental caries [xi].

Advancements in cloud computing and distributed computing frameworks have further expanded the reach of CADD by enabling large-scale virtual screening and computational modelling. G. Kamuntavičius and his team have demonstrated the combination of high-throughput screening (HTS) data with computational methods; which includes machine learning-driven virtual screening and automated robotic laboratories, and thereby enhances hit identification rates and lead optimization [xii]. Also, using multi-objective optimization algorithms in CADD has greatly improved the selection of drug candidates with favourable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties [xiii].

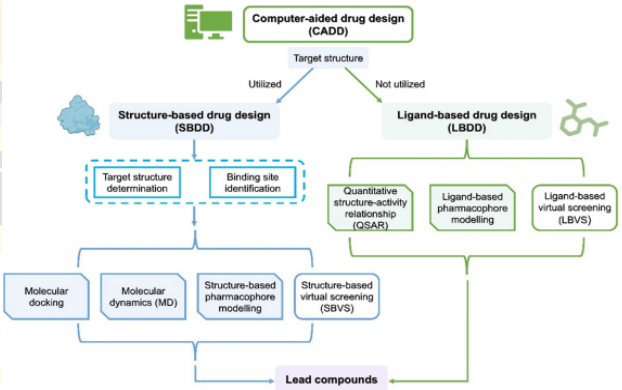


Fig.1 The main processes and sections of CADD [xiv].

2.1 Structure-Based Drug Design (SBDD)

SBDD depends on the three-dimensional (3D) structure of biological targets, elucidated through X-ray crystallography or cryo-electron microscopy. Molecular docking and molecular dynamics simulation are pivotal in analyzing ligand-receptor interactions [xv]. Recently, Shihoya et al. have highlighted the increasing and transformative role of cryo-EM (cryogenic electron microscopy) on structure determination for challenging targets of GPCR–G-protein complexes [xvi]. Moreover, improved and better docking

algorithms integrating AI-based scoring functions have displayed higher predictive accuracy in drug-target binding affinity [xvii].

Along with molecular docking, molecular dynamics (MD) simulations have become essential to understand the ligand-protein interactions over time. MD simulation provides helpful information in conformational flexibility, binding stability, and allosteric modulation of drug targets [xviii]. Enhanced sampling techniques like metadynamics and accelerated MD are now widely used to study complex biological systems with more accuracy [xix]. Moreover, hybrid approaches mixing docking with free energy calculations, like MM-GBSA (Molecular Mechanics/Generalized Born Surface Area) and FEP (free energy perturbation), have been more successful in lead optimization [xx]. These methods make it possible for more accurate ranking of potential drug candidates, and have been applied in recent antiviral and anticancer drug discovery efforts [xxi].

The integration of quantum mechanics/molecular mechanics (QM/MM) simulations further makes SBDD more accurate by modeling electronic effects that classical approaches cannot capture [xxii]. The synergy between SBDD and AI has led to the creation of deep-learning-based scoring functions that perform better than traditional scoring models in docking simulations [xxiii]. These new advancements continue to expand the boundaries of SBDD making it an indispensable tool in modern drug discovery process.

2.2 Ligand-Based Drug Design (LBDD)

LBDD, employed primarily for the unidentified biological structure. In such cases, QSAR modeling and pharmacophore modeling both provide common approaches in analysing potential drug candidates based on known active compounds. [xxiv]. Recent studies demonstrate that deep-learning based QSAR models outperform conventional methods in predicting bioactivity [xxv]. Also, AI-driven de novo drug design have further strengthened to generate novel scaffolds with better pharmacokinetic properties [xxvi]. Zeng et al. stressed the significant advancements in deep generative models to ligand-based drug discovery, facilitating the development of new molecular structures which are capable of binding effectively to their targets, and outlined future directions to enhance the applicability of these models in the drug discovery community [xxvii]. Moreover, with the integration of transfer learning techniques, the efficacy of QSAR model has significantly improved by leveraging information from extensive chemical databases [xxviii]. The application of GANs (generative adversarial networks) has indicate strong promise in predicting molecular properties and optimized lead compounds that works better with reduced toxicity [xxix].

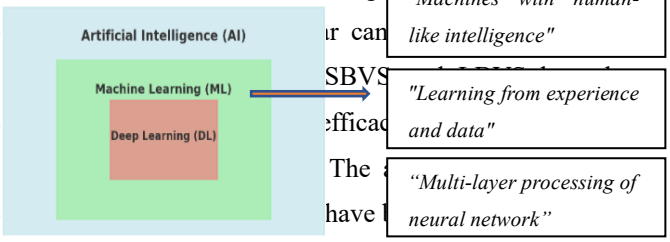
In general, the integration of AI to ligand-based approaches has made it easier to identify the promising candidates, while significantly cutting down both the time and cost associated for experimental validation [xxx]. Future studies in LBDD are expected to focus on enhancing model interpretability and incorporating multimodal data sources to achieve superior predictive accuracy and reliability.

2.3 Molecular Docking and Virtual Screening in Drug Discovery

Molecular docking and virtual screening are two important steps in modern drug discovery; quickly helps to identify potential therapeutic candidates [xxxi]. Molecular docking involves predicting the ideal orientation of a ligand within the active site of a target protein, enabling researchers to evaluate binding affinity and interaction patterns critical for drug efficacy [xxxii]. Virtual screening, on the other hand, employs computer based screening to analyze vast chemical libraries to identify promising lead compounds needed for further investigation [xxxiii].

Recent improvements in docking algorithms have significantly improved accuracy and reliability, rendering them more effective tools for finding new drugs. The incorporation of machine learning-based scoring functions has significantly enhanced the predictive performance of docking models [xxxiv]. Additionally, ensemble docking methods utilizing multiple conformations of the target protein highlights the superior performance in predicting ligand

binding poses [xxxv]. Virtual screening is primarily classified into structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS); distinct advantages benefits in the realm of drug discovery. SBVS looks for known 3D structure of a target protein to screen potential ligands, whereas LBVS uses the chemical pr



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in the discovery of promising drug candidates for diseases, like cancer, COVID-19, and neurodegenerative disorders [xxxviii-xxxix]. Moreover, AI-driven virtual screening has revolutionized the entire process significantly by accelerating the speed and expanding drug discovery efforts.

Despite significant advancements, challenges such as protein flexibility, inaccurate scoring functions, and false positives are still very concerning. To further address these limitations, future research is increasingly focussed on integrating quantum mechanics-based docking methods, which offer more precise modeling of molecular interactions and further refine virtual screening methodologies [xl].

2.4 Role of Artificial Intelligence and Machine Learning in CADD

The use of artificial intelligence (AI) and machine learning (ML) has revolutionized CADD by significantly making it faster, improving accuracy, and better prediction capabilities [xli-xlii]. AI-powered algorithms facilitate the rapid scanning of huge chemical libraries and thereby identify drug candidates with optimal binding affinities [xliii]. Advanced deep-learning models like convolutional neural networks (CNNs) and recurrent neural networks (RNNs) have demonstrated better performance at predicting molecular interactions and bioactivity profiles [xliv]. Moreover, recent studies indicate the utilization of GANs (generative adversarial networks) to create novel drug-like compounds with potential pharmacokinetic properties [xlv]. Uddalak Das in his research has highlighted the challenges and advances in GANs utilized in designing of drug and protein, and thereby indicates their significant role in generating realistic molecules and conditional property control [xxix]. AI-assisted molecular docking techniques have demonstrated improved precision in ligand-receptor binding affinity predictions. Gaudreault et al. demonstrated that the integration of AI-guided antibody modeling with physics-based docking significantly improved the accuracy of antibody-antigen complex predictions compared to traditional methods [xlvi]. Furthermore, reinforcement learning algorithms are now being utilized to optimize lead compounds by iteratively refining molecular structures based on feedback loops [xlvii]. Baduge et al. in his research paper aims to provide a comprehensive overview and critical analysis of the state-of-the-art advancements in machine-learning and deep-learning algorithms, their data collection approaches, as well as the applications of AI, ML and DL technologies in the context of Construction and Building 4.0, while also addressing their implementation challenges [xlviii]. Despite persistent challenges like data bias and interpretability issues, AI and ML continue to transform CADD; unlocking new possibilities in the development of personalized medicine and rare disease treatment.

Fig.2 Hierarchical Representation of AI, ML, and DL [xlix].

2.5 Pharmacokinetics and Pharmacodynamics Optimization Through CADD

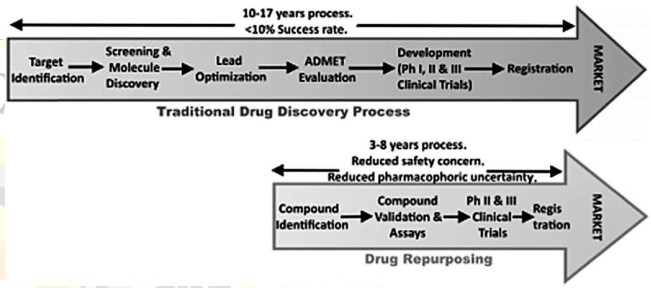
Recent studies highlight the increasing effect of machine learning and computational techniques in improving the predictions of pharmacokinetic (PK) and pharmacodynamic (PD) [l]. Machine learning models have demonstrated good accuracy in predicting drug clearance rates and bioavailability, which are crucial for establishing appropriate dosing and therapeutic efficacy [li]. Enhanced prediction of drug–protein interactions through computational methods has

been instrumental in lowering adverse drug reactions, thus making overall drugs safety. The incorporation of artificial intelligence with PK/PD modeling has further improved personalized medicine, allows the customization of drug dosages based on individual patient profiles and physiological parameters [lii]. These advancements further represent a significant progression making treatments safer and more effective for each patient.

Despite having substantial advancements, accurate modeling of complex biological systems continues to pose a major challenge in CADD. The complexity of human physiology characterized by significant inter-individual variability, and dynamic interactions between pharmaceuticals and biological targets, complicate precise predictions. Even the best advanced models still have struggle to fully capture these multifaceted processes. Nevertheless, ongoing progress in algorithm development with the expansion of high-quality training datasets are steadily improving the reliability of computational models. These advancements hold lots of potential for further refining pharmacokinetic (PK) and pharmacodynamic (PD) optimization, which ultimately facilitates the development of safer, more effective and personalized drug therapies.

2.6 Drug Repurposing Using Computational Approaches

Drug repositioning or mostly referred as Drug repurposing, involves the process of identifying new therapeutic targets for existing pharmaceuticals available in the market. It represents a more expedient and less expensive way to conventional drug development [liii]. Rao et al. provides the timelines for drug repurposing which are significantly shorter than those associated with conventional drug discovery, and therefore makes it an increasingly attractive strategy for rapid therapeutic innovation [liv]. Computational methodologies such as molecular docking, network-based drug discovery, and AI-driven virtual screening have markedly expedited the identification of repurposed drug candidates. Machine learning algorithms, in particular, look goods in revealing the novel connections between drugs and disease in large biomedical datasets. Recent studies highlight the effectiveness of these methods in the identification of repurposed drugs for conditions such as COVID-19 and neurodegenerative diseases [lv - lvi]. AI-based screening platforms have exhibited notable accuracy at finding potential antiviral compounds in FDA approved drug libraries. Deep-learning models that integrate omics data have further enhanced the repositioning predictions more accurate. Together, these advancements underscore the increasing significance of drug repurposing as a powerful and efficient route to therapeutic discovery, particularly in addressing urgent global health challenges. [lvii].Singh et al. has



demonstrated the screening of an FDA-approved drug library for inhibition of ACE2-dependent pseudotyped SARS-CoV-2 entry; enable efficient prioritization of candidates for further preclinical and clinical evaluation [lviii]. Despite these advancements, a significant challenge persists in the experimental validation of computationally predicted candidates. Nevertheless, the integration of in silico techniques with high-throughput experimental screening offers a promising trajectory; broadening the scope of drug repurposing, reducing development timelines and costs, and expediting the transition of promising candidates to clinical application.

Fig.3 Comparative timelines of traditional drug discovery and drug repurposing [liii]

CHALLENGES AND FUTURE PERSPECTIVES IN CADD

Computer-aided drug design (CADD) presents numerous advantages to speed up and optimize the drug discovery process; however, several challenges still keeping it from reaching full potential. A major concern lies in the accuracy and reliability of computational models. Many predictive tools are biased caused by limited or imbalanced training datasets, leading to molecular docking and virtual screening

results less accurate. Sur and Hemlata has emphasized that CADD substantially improves the efficiency of drug discovery, but its full potential can be unlocked only through continuous methodological advancements, better data curation, and stronger integration with experimental workflows [lix]. Another major challenge arises from the dynamic nature of biological systems, which makes it significantly hard in accurately modeling of ligand–receptor interactions over time. Recent reviews highlight that existing CADD models encounter challenges in accurately representing biomolecular dynamics. Consequently, extensive laboratory testing remains essential to validate the precision and physiological relevance of computational predictions [lx]. Additionally, the high computational demands associated with advanced simulations such as molecular dynamics and quantum mechanics, which limit their application in drug discovery pipelines all the time.

Looking into future, CADD is poised to benefit from the rapid growth in artificial intelligence (AI) and machine learning (ML). These technologies are said to enhance predictive accuracy while lowering overall computational costs. The development of hybrid models that combine deep learning with molecular dynamics simulations is likely to improve the precision of drug–target interactions [lxi]. Ahuja's research further emphasizes the revolutionary impact of integrating cloud computing with artificial intelligence (AI) and machine learning (ML); offering scalable computational resources, rapid data processing, and secure global collaboration and significantly accelerating early-stage drug development [lxii]. At the same time, integrating CADD with multi-omics data encompassing genomics, proteomics, and metabolomics is expected to drive major improvements in personalized and targeted therapies. The emerging field of quantum computing also holds immense potential for solving complex biomolecular problems with unprecedented accuracy [lxiii-lxiv]. Additionally, innovations in AI-driven generative models and automated laboratory systems are expected to further revolutionize the entire drug development process by making it faster, more efficient, and more precise than ever before.

Conclusion

The integration of computational techniques in drug discovery has significantly changed the pharmaceutical research by speeding up the hit identification, lead optimization, and repurposing drugs, and consequently saving both time and cost. The incorporation of AI and ML makes CADD better and efficient in predictions. Although having persistent challenges like data reliability and computational limitations, ongoing significant development in computational chemistry and bioinformatics promises a bright future for CADD. With the gradual expansion in interdisciplinary collaborations and computational power growth, CADD is increasingly poised to play a bigger role in the development of personalized medicine with innovative way to treat people.

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