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REVIEW ARTICLE

Integrated Omics Approaches for Computer-Aided Drug Designing

Shraddha Pandey[1], Shrijal Singh[2], Prachi Srivastava[3]

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ABSTRACT

Omics technologies and Molecular biology have advanced so quickly that they have completely changed the process of finding and developing new drugs. A thorough understanding of the molecular mechanisms behind diseases can be gained by integrated omics techniques, which include transcriptomics, proteomics, metabolomics, epigenomics, and genomics. Insight about the probable genetic causes of diseases can be gained from genomic data. Combining this data with CADD can help direct the hunt for potential therapeutic targets, particularly in diseases like some types of cancer that have a significant genetic component. Together with Computer-Aided Drug Discovery (CADD) methods, these high-dimensional datasets allow to predict chemical activity, find new drug targets, and optimise therapeutic candidates with unprecedented accuracy. Molecular docking and virtual screening for lead development, the use of machine learning for complicated dataset analysis, and the function of multi-omics integration in target identification. Personalised medicine is made possible by the integrated framework, which also speeds up the creation of safe and efficient treatments.[1]

KEYWORDS

• CADD • Omics techniques • Molecular docking

AUTHOR'S AFFILIATION:

[1]Student, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.
[2]Student, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.
[3]Associate Professor, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.

CORRESPONDING AUTHOR:

Prachi Srivastava, Associate Professor, Amity Institute of Biotechnology, Amity University, Lucknow, Uttar Pradesh, India.

E-mail: psrivastava@amity.edu

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INTRODUCTION

A fascinating and multifaceted field, computer-aided drug design (CADD) is where many facets of basic and applied research come together and inspire one another. Early in the drug development process, experts can encounter scant or no structural activity relationship (SAR) data. The process of bringing a novel medication to market is known by several names, although it has several distinct stages and is most generally referred to as the development chain or "pipeline." The first step in creating a logical medication is determining which proteins in pathogenesis could be the targets of the medication.[2]

Potential new medicinal entities are found through the process of drug discovery, which combines computational, experimental, translational, and clinical models. Drug development and discovery involves preclinical studies on animal and cell models, human clinical trials, and ultimately securing regulatory approval to put the medication on the market. The process of modern drug development includes the identification of screening hits, medicinal chemistry, and optimisation of those hits to improve their oral bioavailability, metabolic stability (to lengthen the half-life), efficacy/potency, selectivity (to lower the risk of side effects), and affinity.[3]

Computational methods are widely proving rapid successes in biological related problems, including diagnosis and treatment of diseases. Omics studies such as genomics, epigenomics, transcriptomics, proteomics and metabolomics are key resources for understanding issues. Different computational and artificial intelligence (AI) methods can be used to process omics data separately or in combination to provide a variety of biological insights, including origin, genetic variations, protein structures, and identification.For the development of vaccines, repurposing, and drug discovery, these biological insights are crucial. [4]

Understanding the complex interactions and functioning of biological systems mandates omics approaches. These omics techniques enable an extensive understanding of the molecules responsible for building up cells, tissues, or organisms and are produced using high-throughput procedures. The use of omics data techniques is essential while researching the field of drug discovery.

Combining CADD with omics data

The study of an organism's entire DNA, including all of its genes and how they work. It helps in determining possible therapy responses, recognizing genetic variants, comprehending inherited illness and predisposition to certain ailments. Additionally, insertions, deletions, and copy number variation which refers to the loss or amplification of the expected two copies of each gene (one from the mother and one from the father at each gene locus) can be found using genomic analysis. The use of genomics technologies to investigate the relationship between health and disease and an individual's microbiome the collection of microbes that live within the human body is also gaining traction.[5]

Analysis of RNA transcripts generated by the genome in certain cells or under specific conditions. It helps in recognising genes that are differentially expressed in illnesses, comprehending patterns of gene expression, and investigating how cells react to different therapies. Transcriptomics provides an alternative to genome sequencing by allowing comparison of gene expression under various conditions and transcriptome assembly, which includes the identification of new genes, non-coding RNAs, and novel splicing variants of existing genes. The transcriptome of humans only contains 1.5–2% of the genome's protein-coding genes.[5]

The comprehensive study of proteins, encompassing their structures and activities It helps in determining diseases related to protein biomarkers, comprehending protein protein interactions, and evaluating how medication affect protein expression. An increasingly significant part of the multi-step drug-development process is played by proteomics. The procedure consists of toxicity testing, small-molecular screening and optimization, lead selection, target identification, and validation. Protein expression and changes linked to biological disturbances under acquired settings are described in detail and quantitatively by proteomics analysis.[6]

Chemical changes to DNA and histone proteins that control gene expression without changing the DNA sequences are analysed. It helps in comprehending how genes are regulated, investigating how environmental influences affect gene expression, and researching alterations linked to illnesses. It

helps us to understand various components of pathology and cell physiology in both healthy and distressed conditions. Numerous approaches have been developed to forecast the location of epigenetic changes. In addition to genetic alterations, such modifications in DNA and histones can modify the fate and activities of cells.[7]

The exploration of metabolites, or microscopic compounds, identified in tissues, cells, or living things. It helps in researching metabolic pathways, discovering illness biomarkers, and comprehending how medications and therapies affect metabolism. With applications ranging from monitoring media content to enhance the efficiency of biologics manufacturing to evaluating unexpected biochemical aftereffects of target engagement in transgenic models, metabolomics technology is having a significant impact on drug discovery and development.[8]

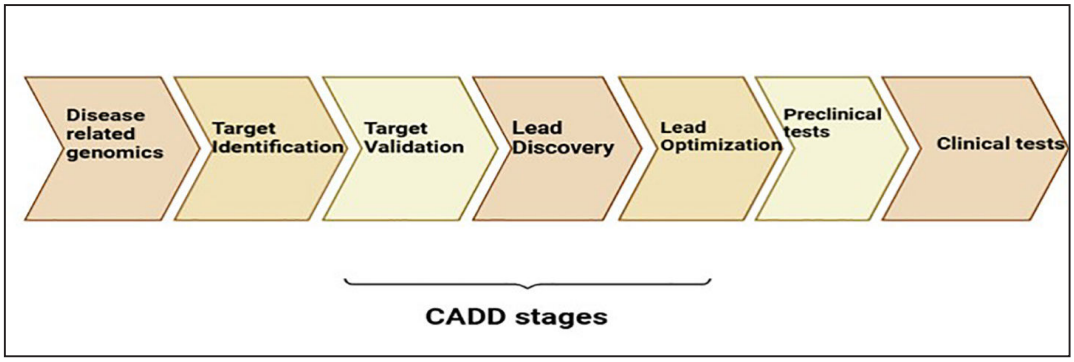


Figure 1: Schematic representation of Computational Aided Drug Designing stages

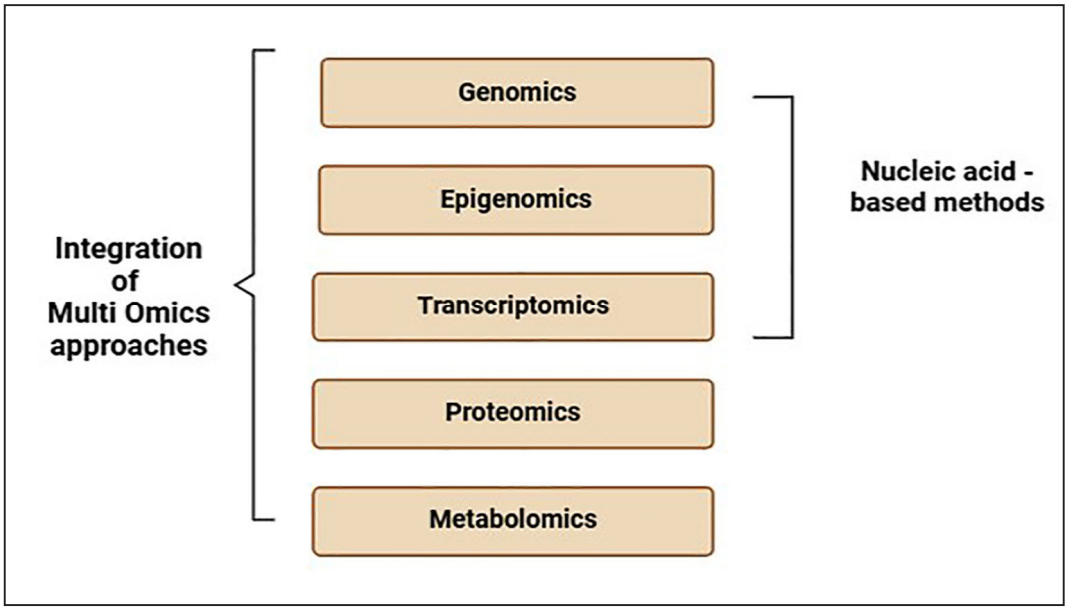


Figure 2: The multiple omics that constitute integrated multi-omics are shown in this diagram. Nucleic acid-based omics techniques comprise the top three omics techniques.

Integration of AI/ML for Omics approaches in CADD

Artificial intelligence and machine learning identify patterns and generate precise predictions by analysing massive amounts of data to advance these abilities. More quickly and accurately than other traditional methods, these sophisticated algorithms can forecast therapeutic efficacy, detect potential side effects, and optimise drug prospects. These computational domains, which are well-known for their capacity for data-driven decision-making, have started to have a substantial impact on the field of Computer-

Aided Drug Design (CADD), changing the context of drug discovery. Algorithms that can identify patterns in large data sets without being specifically trained for a specific purpose are the cornerstone of machine learning, an element of artificial intelligence. Predicting molecular characteristics, comprehending drug-receptor interactions, and predicting biological reactions based on chemical structures have all benefited greatly from machine learning in the drug development process.[9]

Drug- drug interaction (DDI) prediction: One of the obstacles in drug discovery is figuring out how a new treatment can affect other prescriptions a patient may be taking. Large datasets of established drug-drug interactions can be processed by ML systems for predicting potentially hazardous combinations for new substances. [10]

Drug Repurposing: The technique entails giving already-approved medications new therapeutic uses. Machine learning can find possible new targets for current drugs by evaluating large datasets, which reduces the time and expense involved in traditional drug discovery. When there is access to drug data, such as transcriptome data, drug-based methods are recommended. Despite the various obstacles that each of these strategies must overcome, effective repurposing strategies frequently make use of both medication and illness data.[11]

Predictive toxicology: Unanticipated toxicity is one of the main causes of drug candidates' failure in clinical trials. By examining past data on drug-induced toxicities, machine learning models can assist in anticipating possible negative effects and weeding out potentially hazardous substances early in the discovery process. Furthermore, QSAR models correlate a molecule's structure with its probable toxicity by using descriptors such as molecular weight, lipophilicity, and electronic characteristics to predict toxicological effects. In computational toxicology, additional characteristics including solubility, metabolic stability, and toxicophores identification offer thorough insights that help prioritize chemicals for experimental testing and identify hazards early.[12]

Structure based CADD (SB-CADD)

Determining and analyzing the three-dimensional (3D) structures of biologic molecules is essential to the process of structure based computer-aided drug design, or SB-CADD. The fundamental premise of this strategy is that a molecule's capacity to engage favorably with a specific binding site on a protein determines its capacity to interact with that protein and produce the intended biologic impact. Numerous 3D structures of human and pathogenic proteins have been clarified as an outcome of extensive use of biophysical techniques including X-ray crystallography and NMR spectroscopy. It should be considered that structure-based drug design guides the search for a drug lead that is, a chemical having at least micromolar affinity for a target rather than a drug product should also be considered. An optimized medication candidate is brought to clinical trials through the iterative process of SBDD, which goes through several cycles. The four stages of a drug discovery process are typically the discovery phase, development phase, clinical trial phase, and registry phase.[12,13]

Ligand-based CADD (LB-CADD)

In the ligand-based computer-aided drug discovery (LB-CADD) method, ligands that are known to interact with a target of interest are assessed. These approaches examine the 2D or 3D structures of compounds that are known to interact with the target of interest using a collection of reference structures. Analysis of ligands known to interact with a target of interest is part of the ligand-based computer-aided drug development strategy. These techniques evaluate the 2D or 3D structures of compounds by using a set of reference structures gathered from compounds known to interact with the target of interest.

LB-CADD employs two basic methods:

1. through choosing compounds based on their chemical resemblance to known actives using a similarity metric.
2. Additionally, a QSAR model that uses chemical structure to predict biologic activity is being designed.

Numerous strategies are used through LB-CADD techniques to describe small molecule features using computational algorithms that strike a compromise between information content and efficiency. Numerous methods have been created and used for obtaining chemical information, with the best descriptor set depending on the biologic function

predicted and the LB-CADD approach.[14]

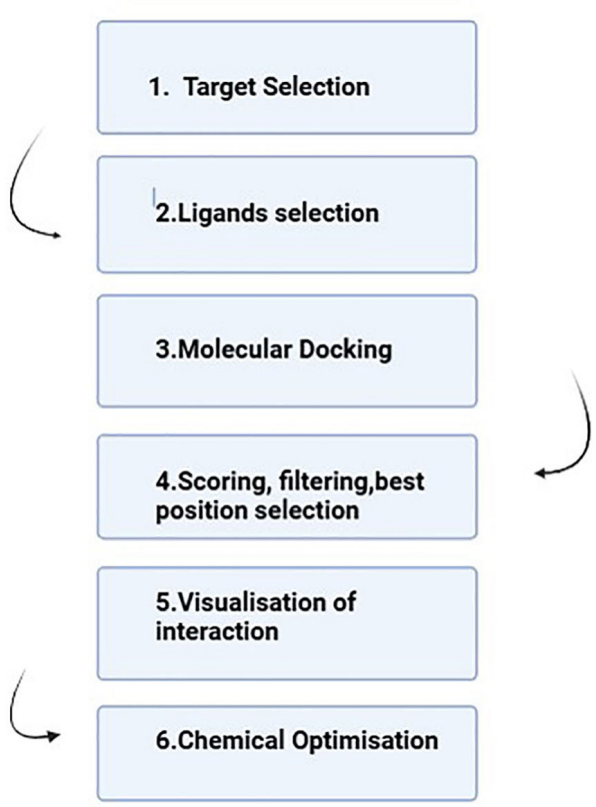


Figure 3: Flowchart of ligand-based computer aided drug designing

The broad spectrum of approaches and processes that support CADD contribute to its diversity and adaptability. CADD includes a wide range of instruments intended to speed up and improve the drug development process, from molecular modelling to drug metabolism prediction.[15]

Molecular Modelling: Molecular modelling, which includes a broad range of computational methods used to simulate or model the behaviour of molecules, is the foundation of CADD. This entails building three-dimensional representations of molecular structures, frequently involving ligands and proteins.

This method offers information about the structural and functional characteristics of molecules, leading to a better comprehension of how possible medications might act in the body. It helps in the design and optimization of possible medications by allowing researchers to see and examine how drug candidates interact with their target proteins. Molecular dynamics (MD) simulations are one type of tool that may predict how molecules will behave over time by recording their motions and interactions.[16]

Docking and Virtual Screening: Docking is the process of projecting a drug molecule's orientation and location upon binding to its target protein. A significant consideration in drug design is the estimation of the binding affinity between the medication and its target. Using a scoring mechanism that accurately rates candidate dockings, docking algorithms efficiently search high-dimensional spaces. In lead optimization, docking is an essential tool for virtual screening of an enormous database of compounds, ranking the results, and generating structural theories about how the ligands inhibit the target. Conversely, virtual screening entails searching through enormous libraries of compounds to find those that have the best chance of efficiently and highly attaching to the target protein. In the process of finding new drugs, its reliability as a source of chemical starting points keeps expanding.[17-19]

Quantitative Structure - Activity Relationship (QSAR**):** QSAR modeling investigates the connection between a molecule's chemical structure and biological activity. QSAR models may foresee the psychotropic properties of novel compounds using statistical techniques based on their structural characteristics, allowing chemists to make adequately informed changes to increase a drug's potency or lessen its negative effects. The affinities of ligands to their binding sites, inhibition constants, rate constants, and other biological end points have been correlated in classical QSAR studies with atomic, group, or molecular properties like polarizability, lipophilicity, electronic and steric properties (Hansch analysis), or with specific structural features (Free-Wilson analysis). With the use of QSARs, medicinal chemists can search the limitless "chemical and stereochemical space" and identify structures that may hold the key to discovering new "leads compounds," which will serve as the foundation for the development of possible medications following additional study on ADME-Tox properties (drugs' adsorption, distribution, metabolism, excretion, and toxicity).[20-22]

There are many publicly available omics datasets used in drug design such as small molecules databases are a valuable resource for researching biochemical interactions and are becoming more and more important in contemporary research as data grows Chemical compounds, medications, carbohydrates, enzymes, reactants, natural

products, and compounds generated from natural products are all included in these databases. Like PubChem it comes under National institute of health (NIH) Molecular Library Roadmap Initiative gives details on 19 million distinct structures and around 40 million tiny compounds' biological functions. The free database of commercial chemicals, ZINC, includes 20 089 615 3D structures of molecules with biologically significant attributes (number of rotatable bonds, estimated Log P, and molecular weight). Also, it includes biological databases in this A growing amount of data pertinent to the study of human disease has been generated by the sequencing of the genomes of model organisms, including humans. Some of the data sources are the international collaborative GenBank, DNA Databank of Japan (DDBJ), and European Molecular Biology Laboratory (EMBL) it serves as worldwide repositories for nucleotide sequences. Records from the three databases are synchronized upon a daily basis. Protein sequence and functional information are comprehensively and expertly annotated by Swiss-Prot and Protein Information Resource (PIR).[23]

Limitations in CADD

It is important to understand the inherent challenges of CADD, even while it provides unmatched benefits in terms of speeding and improving drug discovery

Low Quality Insights: Accurate predictions depend on trust worthy datasets (such as protein structures and binding affinities), but these are frequently sparse or lacking. Variations in the quality and structure of disparate data sources might make integration and analysis more difficult.

Restriction on Protein and Ligand Structural Properties**:** Protein structures that are incomplete. The 3D structures of many target proteins, particularly membrane proteins like GPCRs, are not experimentally resolved. Models based on homology may introduce errors.

Prediction model accuracy: Accurate predictions of binding affinities or interactions may not always be made by docking and scoring algorithms. Frequently, the intricacy of real-world chemical interactions is not adequately captured by simplified scoring algorithms.

ADMET Estimations: Accurately predicting these features in CADD is still quite difficult. A lot of computer models fall short in capturing the intricacy of in vivo pharmacokinetics.

The majority of biological molecules, including possible therapeutic chemicals and their target proteins, are incredibly flexible.[1]

CONCLUSION

The integration of omics approaches such as genomics, proteomics, transcriptomics, epigenomics into computational aided drug design is a revolutionary step in improving the effectiveness of drug discovery. Omics driven CADD has ability to predict drug-target interaction, toxicity, efficacy more reliably and provide an improved comprehensive of the molecular mechanism underlying diseases by integrating multi-dimensional biological data. Recent developments in systems biology, data integration methods, and machine learning are gradually enhancing the potential to use omics data in drug design in spite of these constraints. Drug development is enhanced by the bilateral interaction between experimental data and CADD, which emphasizes the complementary relationship between computational estimations and actual validations.[24] Computer based trials and virtual screening are becoming popular strategies to expedite drug development while cutting costs.[25] Tools must become more effective, interoperable, and user-friendly as they develop for computationally demanding analysis. Integrated omics is not merely a collection of tools; rather, it is a coherent framework for interpreting multi-omics data in a biologically meaningful way. This could lead to new discoveries about basic biology, health, and illness.[26]

Conflict of Interest: Nil

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