Computer aided drug design: advancement and methodology

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Abstract: Computer-Aided Drug Design (CADD) and manufacturing are computer applications for also industrial and academics that significantly impact the chain of processes from initial design to final product realization it also plays a crucial role in modern era for development and discovery. It is a diverse research field that integrates applied and basic aspects, utilizing structural study and molecular modeling. These systems include prototyping, reverse engineering, additive manufacturing, and intelligent management. CADD technology has become a significant factor in chemo informatics, replacing human minds with machines. These systems are sophisticated for both large and small industries, and are essential for managing processes, operations, manpower, resource handling, and meeting delivery deadlines. This paper provides an overview of CADD techniques and their advancements in the field of chemistry to design new leads. CADD helps identify suitable drug characteristics and compatibility, enabling easier access to pre-clinical trials. CADD focuses on two types: structure-based drug design and ligand-based drug design. Structure-based design involves identifying binding sites, docking, virtual screening, compound selection, and lead optimization, while ligand-based design involves quantitative structure activity relationship. The ligand-based drug design shows the relationship between the structure active site and the potent pharmacophore ligand. That complex gives the docking score for various chemical and pharmacological activity. This review article aims to help clinicians and researchers harness the potential of CADD in drug design and disease management. Also it explains methodology for drug design and its development with their actual action of potent drug.

Keywords: Artificial intelligence, Biological Database, CADD, Methodology, QSAR.

INTRODUCTION

Computer Aided Drug Design (CADD) is a modern strategy in the biomedical arena, enabling the discovery and design of new therapeutic agents using computers. A drug target is a key molecule involved in a specific metabolic pathway associated with a disease or pathology. The complex process of drug discovery and development can cost billions and take 12 years to complete. (1)

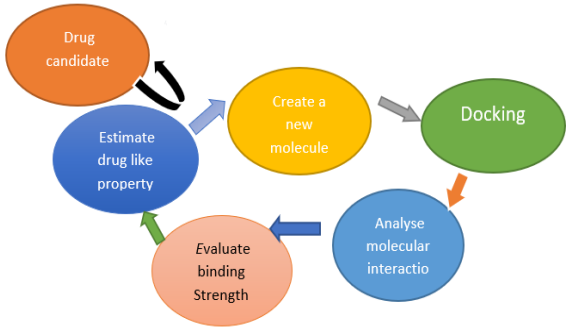


Fig1. General principle of CADD

Computer Aided Design (CAD) and Computer Aided Manufacturing (CAM) are two terms often used together to describe the use of computers in designing and manufacturing processes. CAD applications help make designs of engines, bridges, buildings, spare parts, and aircrafts both fail-proof and fail-safe. AI has revolutionized the field with advanced software, such as SOLIDWORKS, which can identify mistakes and suggest the best ways for designers and manufacturing firms. Machine learning techniques are developed to fight complex relationships based on empirical inputs. In numerical simulations, machine learning techniques are used to prepare simulation models based on CAD models, which can be helpful in addressing complex problems. CAD/CAM can sometimes be used together, with some software providing interface and functionality for both design and manufacturing purposes. In the global market, competition is a major factor, and different products have varying time-to-finish times. CAD/CAM software can help address these challenges and improve the overall efficiency of the manufacturing process. (2)

AI uses computer memory to store and suggest corrections to users. Machine learning techniques are

developed to tackle complex relationships and generate outputs for complex algorithms. In numerical simulations, idealization processes based on CAD models are used to prepare simulation models, addressing complex problems requiring high-level expertise. Machine learning techniques are helpful in adaptation scenarios. (3)

Computer-Aided Drug Design (CADD) is a process that facilitates computational approaches and resources used in designing and discovering new therapeutic agents. The process of drug discovery, development, and commercialization is long, complex, and expensive. CADD accelerates the designing process, allowing for more efficient leads and reducing the number of compounds needed for in vitro testing. With the rapid growth of CADD, it has enabled the discovery of new pharmacologically active agents in a short time, improving the understanding of complex biological processes. (4)

Table 1: Example of some drugs which came to existence with the help of CADD

Year	Drug name	Used as
1989	Zanamavir	Anti-HIV
1997	Nelfinavir	Anti-HIV
1998	Raltitrexed	Anti-Cancer
1999	Amprenavir	Anti-HIV
2007	Raltegravir	Anti-HIV

(4)

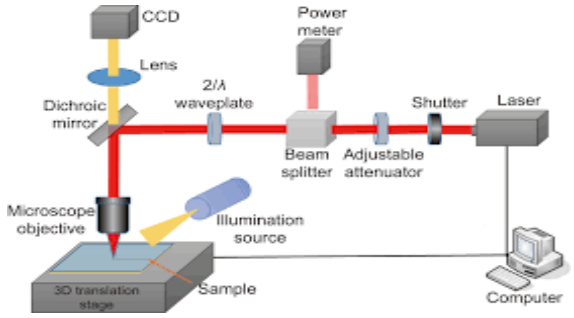
METHODOLOGY

1. CAD/CAM for Micro Laser Machining:

Laser machining is popular due to its delicacy, quality fabrication, and easy-to-use tools. Its CAD/CAM software packages reduce errors and improve company efficiency, making design more accurate and efficient.

The figure here shows a laser machining system attach to computer including laser object, control laser power density and command structure. neutral thickness filter are passed down to tune the product ray power to a felicitous amount. the particularities of fabrication can be supervised by a CCD camera upon a dichroic reflector.

The administered shade is used to carefully put the ray. The sample piece is coupled on a computer managed 3-axis platform. (5)



(6)

Fig2: Computer-controlled laser machining system

2. Developing managerial integration for CAD/ CAM

Over the past decade, Western European enterprises have adopted Advanced Manufacturing Technologies (AMTs) to meet demands for shorter development and delivery times, with the emergence of integrating technologies like CAD/CAM, impacting large organizational areas.

Rapid technology expansion and early costs have limited adoption experience, leading to focus on technical installation, resulting in failure to realize business benefits, despite successful implementation.

CAD/CAM technology integrates engineering and manufacturing sectors, saving time, money, and eliminating errors, thereby enhancing efficiency and reducing time waste.

Rapid product development is crucial for companies, focusing on cross-functionality, co-operation, and linking functions. Key points include minimization, differentiation, coupling, and familiarizing users with machine interfaces. (7)

3. Artificial Intelligence in CAD/CAM and Integration:

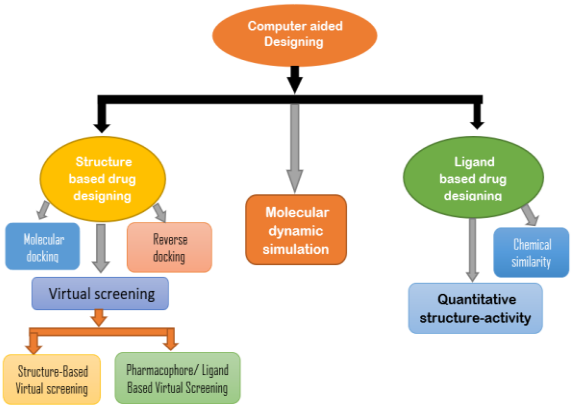
CAD software is essential for multi-stage manufacturing of everyday products like smartphones and planes, allowing designers to design, assemble, and test cars without switching between software for each detail and part.

AI in CAD/CAM has revolutionized manufacturing by automatically calculating materials' mass, durability, and elasticity, suggesting changes, and imitating engineer patterns, reducing errors and recording data.

The figure illustrates the integration of CAD/CAM, initially used for creating 2D drawings and diagrams, but now aims to eliminate human errors and improve work quality.

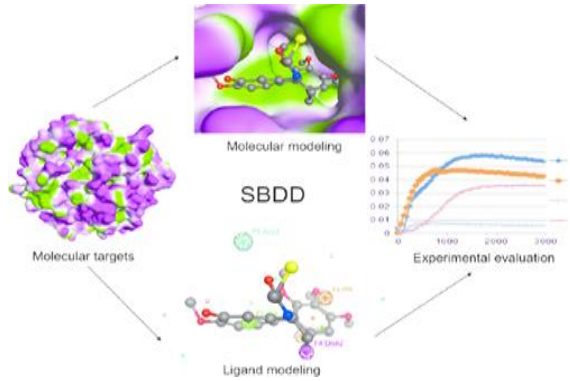
Manufacturing, Unigraphics, Catia, SDRC's IDEAS, and CADDS 5 are high-end, cost-effective solutions that offer seamless data interfaces, application integration, and 100% results without human errors. (7)

Types of Computer Aided Drug Design (CADD):



STRUCTURE BASED DRUG DESIGN:

Structure based drug design (SBDD)is the process which includes virtual screening and de novo drug design.



(8)

Fig3. Layout of SBDD

In SBDD, structure of target protein is known and interaction or bio-affinity for all tested compound calculate after the process of docking, to design a new drug molecule. (9)

SBDD involves multiple cycles, including protein isolation, purification, and structure determination using methods like X-ray crystallography, homology modelling, or NMR, and virtual screening of active protein regions. (9)

Virtual Screening:

(10)

Fig4: Overview of virtual screening process

Virtual screening is a computational method used in drug design and development, focusing on identifying promising target proteins. Methods like Structure-Based Virtual Screening (SBVS), molecular docking, and molecular dynamics (MD) are used in SBDD for lead discovery and optimization. SBDD has identified numerous drugs, including thymidylate synthase inhibitors, raltitrexed, and HIV protease inhibitors. Over 100,000 3D protein structures are provided in SBDD. (11)

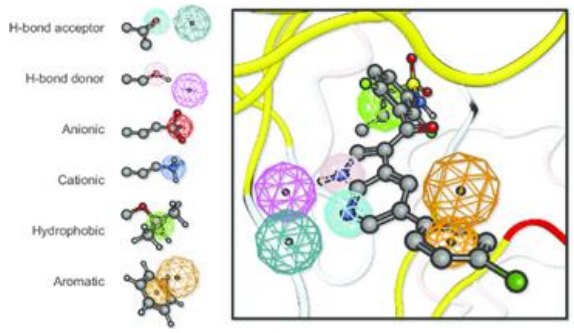
Molecular docking

Molecular docking is a virtual simulation technique used to model the interaction between a small molecule and a protein at the atomic level. It involves predicting ligand conformation and accurately binding the ligand within the target active site. This technique is commonly used in structure-based drug design (SBDD) to study molecular phenomena and improve docking efficiency. Online programs like -GRID and POCKET can help identify binding sites. (13,14,15)

Reverse docking:

Reverse docking is a method used in drug design to accurately study interactions between drug molecules and target proteins. It involves docking small molecules with known target databases and scoring the stability of the binding complex. This technology has been used in the development of drugs like Donepezil, Indinavir, Captopril, and Zanamivir. (16)

Pharmacophore:



(17)

Fig5: Pharmacophor Mechanism

The schematic representation of bioactive functional group's along with their interatomic distance is known as 'pharmacophore'.

Pharmacophore is a 3D model used to analyse the similarity between molecules or a library of molecules, organized into small molecule libraries, and used on screen for feature collection. (18,19)

History of pharmacophore:

The pharmacophore concept, first developed by Paul Ehrlich in the late 1800s, is a molecular framework that carries essential features responsible for a drug's biological activity. It plays a significant role in computer-aided drug design (CADD), involving hydrogen bond donors, acceptors, cations, anionic, aromatics, and hydrophobic molecules. (19,20)

LIGAND BASED DRUG DESIGNING (LBDD):

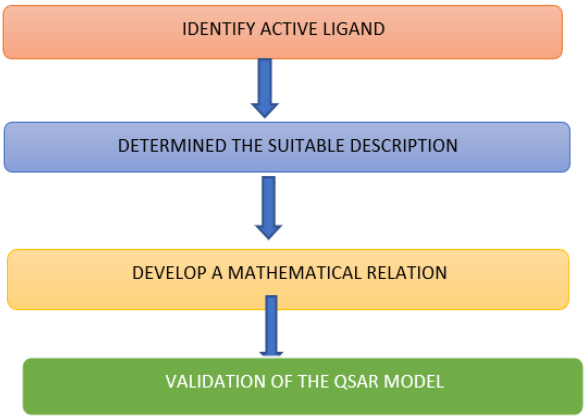
LBDD involves identifying ligands that bind to the desired target site, allowing for the development of a pharmacophore model or molecule with necessary structural features. (21)

QSAR

The QSAR technique is crucial in drug optimization, quantifying the correlation between chemical structure and biological process, aiding in compound identification, modification, and optimization for maximum biological activity.

The method some are used in QSAR

1. Experimentally measure value of desired biological activity and then identify the ideal ligand.
2. Determine molecular descriptor with physic-chemical properties of molecules.
3. Biological activity correlation discovers.
4. At the last test QSAR model for statistical stability. (22)



ADVANCEMENT IN CADD:

Target protein molecules

Drug receptors are target protein molecules, classified into enzymes, receptors, ion channels, and transporters. Most drugs are membrane-bound proteins or enzymes. Homology modelling is an alternative for determining protein structure. Future software and hardware programs will enable comprehensive studies of target structure and dynamics. Discovery of new methods and drugs involves identifying and validating viable targets using Support Vector Machine and In-silico methods. As 3D structure of membrane bind protein are not still known. (23)

Statistical method and QSAR

Quantitative Structural Activity Relationship (QSAR) is a mathematical method developed by Hansch and Fujita to better understand the chemistry and biological effects of a series of compounds. It assumes that the biological activities of a series of cogeneric molecules with a common mechanism of action are correlated with variations in their structural, physical, and chemical properties. QSAR uses mathematical relationships between biological activity and physico-chemical properties like hydrophobicity, electronic, and steric factors. Comparative Molecular Field Analysis (CoMFA) is a powerful 3D QSAR method that correlates molecular properties to biological activity by calculating steric and electrostatic fields for each molecule. It performs statistical analysis using the partial least square in the data set. Other statistical

methods like neural networks and Support Vector Machines have also been widely explored. (24)

Data sources

Large amounts of organic molecules, amino acid sequences, and biological sequences related information have been the most important databases that collect and store scientific literature data in an informative and structure manner.

Small molecule databases

Small molecule databases are crucial for modern discovery, providing valuable information about chemical compounds, carbohydrates, enzymes, reactions, and reactants. These databases contain a large number of FDA-approved compounds, and their numbers are tabulated in tables for easy reference.

Biological databases

The sequencing of human and model organism genomes has produced a vast amount of data for studying human diseases. Databases like PIR, Swiss-Prot, PDB, and EMBL provide comprehensive annotated protein sequences, nucleotide sequences, and structural data of biological macromolecules. Additional databases have also been developed to further enhance this information.

Chemoinformatics and Bioinformatics in CADD

Chemoinformatics is a rapidly growing field that uses computer and informatics technology to transform data into information and knowledge for lead identification and organization in chemistry. It has been widely used in solving chemical problems, chemical structure representation, molecule search, design and synthesis, QSAR, structure elucidation and calculation algorithm, database retrieval, and lead identification. CADD is a specialized discipline heavily dependent on bioinformatics tools, software application, information technology, databases, and computational resources. Bioinformatics methods are widely used in molecular biology, proteomics, genomics, and emerging areas like biological and gene ontologies and metabolism. Bioinformatics supports CADD research in several key areas. (25)

Table 2: Some small molecule and biological databases are reviewed in this article

Type	Name
Small molecule databases	Zinc database, PD Bbind, Zinc15Database, Protein data bank (PDB), JChemfor Excel, ChEMBL, Chemdiff, Bingo, Binding MOAD (Mother of all Database), TTD, SMPDB, Drug bank, STITCH
Chemical structure representation	Chem Draw, Marvin Sketch, ACD/Chem Sketch jsMol Editor, Ketcher, UCSF Chimera, Pymol, Open Structure, DaylightSMILES, InChI, TriposMol2, OpenBabel, Corina, Indigo, Pose view, DSV isualizer, BINANA
Molecular Modeling	CHARMM, Swiss Side Chain, GROMACS, Amber, CHARMM-GUI, Swiss Param CHARMMing.org
Homology modeling	Modeller, I-TASSER,, LOMETS, SWISSMODEL, SWISS-MODEL Repository, Robetta
Binding site prediction	MED-SuMo, Caver, FINDSITE, sc-PDB, CAST-p, Pocketome,3DLigandSite, metalPocket, PocketAnnotate
Docking	Auto dock, DOCK, GOL, Docking Server, Swiss Dock, I-ClickDocking, COPICAT
Screening	Pharmer, Catalyst, Pharma Gist, Swiss Similarity, Blaster, Anchor Querry
Target prediction	Patch Search, IXCHEL, CABRAKAN, SEA, PPB Swiss Target Prediction
Ligand Design	GANDI, LUDI, BREED, SwissBiosostere, sc-PDB-Frag, GlideFragmentLibrary, e-LEA3D, eDesign
Binding free energy estimation	Hyde, X-score, NN Score, DSXonline, BAPPL server, BAPPL-Z server
QSAR	CQSAR, clogP, ClogP/CMR, MOLEdb, CHEMDB/Datasets, OCHEM, E-Dragon, Pattern Match Counter
ADME Toxicity	Qik Prop, Vol Surf, Gastro Plus, ALOGPS, Swiss ADME

CONCLUSION

In today's complex world, organizations need an errorless system to emerge from distress. Computers have been a friend of humans since their invention, and their integration across various industries is crucial for improved results. The role of Chemo informatics and Bioinformatics in the digital era is highlighted, making computer-aided approaches a rising methodology for drug development. Machine learning has further advanced CAD systems, making them more advanced. CAM (Computer-Aided Manufacturing) manages all manufacturing tasks. With current achievements, there is a promising future for computer-aided drug design

to aid in the discovery of more therapeutics in the future. The resolution of the protein structure, multiple structures binding multiple ligands, and the choice of protein conformation also affect the accuracy of reverse docking. A powerful database of the target protein is essential for accurate docking results.

REFERENCE

[1] Singh Dharampreet, Kaur Ramanjeet, Patil R. K, Patil H.C, "Computer Aided Drug Design" JETIR, March 2020:7;3.

[2] Zahid Maqsood, Dr P S. Rao, Tawseef Abdullah, "CAD/CAM with New Trends and Advancements using Machine Learning" IJTIMES, May-2019:5;5.

[3] Navjot Singh Matharu, Devesh Shrivastava, "Latest trends and improvements in CAD/CAM" Res. J. Engineering Sci, September-2021:10; 3.

[4] Sunita Pandey, BK Singh, "Current advances and new mindset in computer-aided drug design" The Pharma Innovation Journal, 2017:6;8.

[5] Navjot Singh Matharu, Devesh Shrivastava, "Latest trends and improvements in CAD/CAM" Res. J. Engineering Sci, September-2021:10; 3.

[6] https://www.oejournal.org/article/id/61f6021999d881528090e6dc

[7] Abdoleza Bayesteh, Junghyuk Ko, Farid Ahmad, Martin B. G. Jun "Improvement of Computer-Aided Manufacturing (CAM) Software for Laser Machining " J. Korean Soc. Manuf. Technol. Eng, August-2015:24;4.

[8] https://images.app.goo.gl/MhFWn8r565jEDUxF7

[9] Syed Sarim Imam, Sadaf Jamal Gilani, "Computer Aided Drug Design: A Novel Loom To Drug Discovery" Juniper publishers key to the researchers, February 2017:1;4.

[10] https://images.app.goo.gl/G4xYUhnN1oMnnDMKA

[11] A. Srinivas Reddy, S. Priyadarshini Pati, P. Praveen Kumar, H.N. Pradeep and G. Narahari Sastry, "Virtual Screening in Drug Discovery – A Computational Perspective" Current protein and peptide science, September 2007:8;4

[12] https://images.app.goo.gl/Ydbid9VTPYUTcsR6A

[13] Clark D.E, "What has computer-aided molecular design ever done for drug discovery?" Expert Opinion Drug Discovery, July 2006:1;2.

[14] Sheng-You Huang, Xiaoqin, "Advances and challenges in Protein-Ligand docking" MDPI, August-2010:11;8.

[15] Alexander Wlodawer, Jiri Vondrasek, "Inhibitors of HIV-1 protease: A major success of structure-assisted drug designI" Annual Review of Biophysics and Biomolecular Structure, June-1998:27;1.

[16] Hongxu Wang, Huiqin He, Tingting Zhang, and Jingwei Jiang, "Application of Reverse Docking in the Research of Small Molecule Drugs and Traditional Chinese Medicine" Jiangsu Key Lab of Drug Screening, October 2021:45;1.

[17] https://images.app.goo.gl/uS5CzxrjdriACiHF6

[18] Peter Itskowitz, Alexander Tropsha, "k Nearest Neighbors QSAR Modeling as a Variational Problem" Journal of chemical information and modelling, April-2005:45;3.

[19] Ajay N. Jain, Kimberle Koile, David Chapman, "Predicting Biological Activities from Molecular Surface Properties. Performance Comparisons on a Steroid Benchmark" Journal of Medicinal Chemistry, July-1994:37;15.

[20] D.C. Whitley, M.G. Ford, D.J. Livingstone, "Unsupervised Forward Selection: A Method for Eliminating Redundant Variables" Journal of Chemical Information and Computer Science, September-2000:40;5.

[21] Surabhi, B.K. Singh, "Computer Aided Drug Design" JDDT, August-2018:8;5.

[22] Rajeshwar P. Verma, Corwin Hansch, "Camptothecins: A SAR/QSAR" ACS Publications, January-2009:109;1.

[23] Taft CA, Silva CHTP, "Cancer and aids: New Trend in Drug Design and Chemotherapy" Current Computer-Aided Drug Design, 2006:2;3.

[24] Toshio Fujita, Takaaki Nishioka, Minoru Nakajima, "Hydrogen-bonding parameter and its significance in quantitative-activity studies" Journal of Medicinal Chemistry, August-1977:20;8.

[25] William Lingran Chen, "Chemoinformatics: Past, present and future" J. Chem. Inf. Model, November-December-2006:46;6.