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Current advances and new mindset in computer-aided drug design: A review

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Abstract
In this modern and digital era, Computer Aided Drug Design (CADD) plays a crucial role in the process of discovery and development of drugs. CADD represents the computational techniques and resources that are used to facilitate the design and discovery of new leads which reduces the cost up to 50% in the drug design process. When executed on the manual basis, discovery and development of new drug becomes an interdisciplinary, highly expensive and time consuming process. Consequently human minds are replaced by the machines where CADD technology has given rise major significant factor in the field of chemo informatics. An eye over these Computer Aided Drug Design techniques broach this paper, which shows the brief overview on the current advancement and new mindset in the field of chemistry to design new leads.

Keywords: CADD, Structure-Based Drug Design, Virtual Screening, Molecular Docking

1. Introduction
There are numerous known compounds and new one discovered each year which is not introduced in market indicating that the need of storage the electronic information of these probable compounds in databases and attaining a better overview of known chemistry. The consequences of the molecular cognizance or interaction between the ligand (i.e., drug) and the protein (i.e., receptor) leads to the effect of the drug in human body [1-6]
Computer Aided Drug Design is the process which facilitates computational approaches and resources that are used in design and discovery of new feasible therapeutic agents. The process of drug discovery, development and commercialization are a long, tedious, complex and highly cost effective. It is stated that typical drug discovery cycle from the lead identification through clinical trials, takes 10-15 years and US$ 500-800 million to introduce in market place. This is why Computer-Aided Drug Design (CADD) has been widely used in pharmaceutical field to accelerate the designing process in most efficient way [7-9] Therefore it is worthwhile to apply these computational tools in hit-to-lead manner to get the most out of desired leads to cover a wider chemical space while reducing the lot of compounds that must be synthesized and tested *in vitro* [10-14]
In the past few years, Computer-Aided Drug Design (CADD) has grown up rapidly, enhancing the perceptive of multifaceted and difficult biological process. With the help of these computational tools, it is now possible to find out new pharmacologically active agents in a short duration of time.
Here are few examples of drugs that comes in the race of drugs through the process of Computer Aided Drug Design in table 1 [15-18]
CADD plays crucial role in the development of effective new feasible molecular entities

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

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

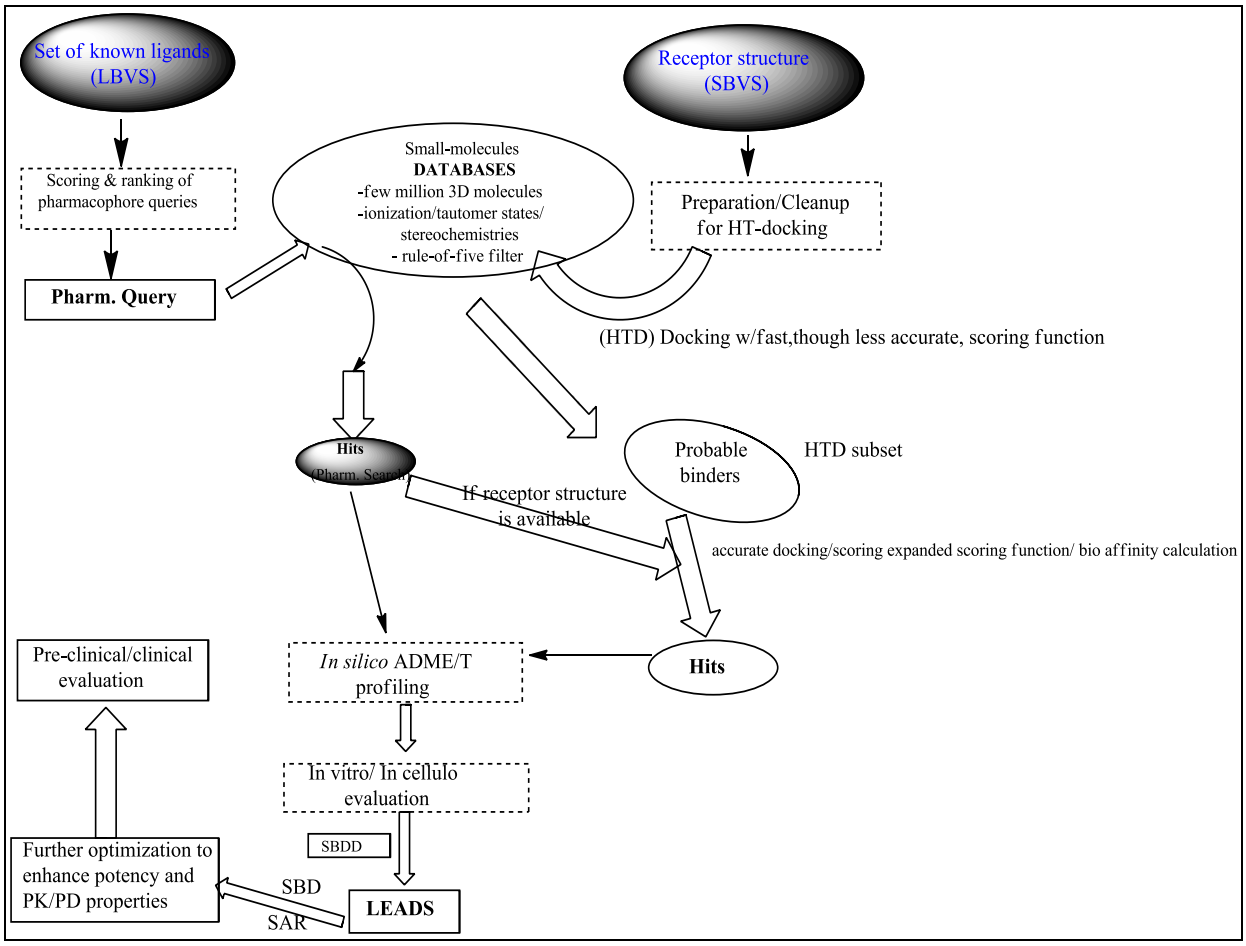

Fig 1: Workflow of the Computer-Aided Drug Design

Currently focused on searching new and advanced databases, management of data resources, creation of new computer based programs and software to generate vast compound libraries which contain number of pharmacologically active biomolecules, elaborate new algorithm to measure the potency and selectivity the new lead candidate molecules [19] Here we will discuss about the current topics addressing with new mindset and advancement in CADD technology.

Topics and Advances in Drug Design

Target Protein molecules

Generally Drug receptor now referred as the term target protein molecule, classified into enzymes, various types of receptors, ion channels and transporters and other protein targets. Majority of drugs which are therapeutically used, are membrane-bound proteins or enzymes as a site of action. Moreover, the detailed 3D structures of many membrane-bound proteins are still unknown. An eye on this, Homology modeling is a great alternative for determining the structure of the protein molecule. For the future aspects, lots of specially designed software and hardware programs will enable comprehensive studies of the target structure and dynamics of new potential target molecules. These approaches leading to new challenges in the validation and calibration of the bio simulation methods [20-23] In Discovery of new methods and drugs, identification and validation of viable targets are the first step. Support Vector Machine (SVM) and *In-silico* method, integrated approaches are continuously explored the rate of discovery and exploration of new targets [24, 21]

Statistical methods and QSAR

Quantitative Structural Activity Relationship (QSAR) is mathematical relationship for better understanding the chemistry (i.e., the structures) and biological effects (i.e., the activity) of each chemical in a quantitative manner for a series of compounds [25].

QSAR method is an incredible tool developed by Hansch and Fujita. The fundamental assumption in QSAR is that the biological activities of a series of cogeneric molecules that possess a common mechanism of action are correlated with variations in their structural, physical, and chemical properties. Quantitative Structure-Activity Relationship employs mathematical relationship between biological activity and physico-chemical properties of the compound like hydrophobicity, electronic and steric factors etc. One of the most powerful 3D QSAR methods, Comparative Molecular Field Analysis (CoMFA) now has been widely explored method to design new therapeutically active compounds. CoMFA correlates the molecular properties to biological activity through calculating the steric and electrostatic fields for each molecule by interaction with a probe atom at a series of grid points surrounding the aligned database in 3D space and then performing the statistical analysis and property of interest by using the partial least square in data set. In contrast to QSAR and QSPR, other statistical methods like neural network and SVM has been widely explored [26, 27]

Data Sources

Large numbers of organic molecules, amino acid sequences and biological sequences related information have been

compiled in scientific literature. All these data are collected and stored in an informative and structured way in various types of databases. Most important databases are reviewed in this section.

Small molecule databases

Small molecule databases play an important role in modern discovery with compilation of data. Huge number of compound libraries contains the large number of authenticated FDA approved compounds. All these databases provide the valuable information about the chemical compounds, carbohydrates, enzymes, chemical reactions and reactants. Here numbers of databases and programs are tabulated in table 2.

Biological databases

Huge amount of data relevant to the study of human diseases have produced through the sequencing of human and other model organism genomes. These databases synchronize their records on a daily basis. Number of databases included like PIR (Protein Information Resources), Swiss-Prot, PDB, EMBL contains comprehensive and expertly annotated protein sequences and information, Nucleotide sequences and the structural data of biological macromolecules respectively. Apart from this information, other variety of databases has also been developed. Collectively, all these data sources represent comprehensive and accumulated knowledge on human biology and disease [28]

Chemoinformatics and Bioinformatics in CADD

The new and rising field Chemoinformatics is the *de facto* standard for the application of computer and informatics technology methods in chemistry. Both are included in information resources to transform data into information and information into knowledge for the purpose of lead identification and organization for the betterment of the designing process. For the solving of chemical problems, informatics methods now have been widely used. Besides on this, other approaches like chemical structure representation, searching of new molecule, design and synthesis, QSAR, Structure elucidation and calculation algorithm, database retrieval, identification of new leads, etc. have been done through this [29].

CADD is a specialized and multipurpose discipline that heavily dependent on the bioinformatics tools, software application and information technology, databases and computational resources all provide the substructure for bioinformatics. On the basis of scientific side of the network, bioinformatics methods are broadly used in molecular biology, proteomics and genomics and such other emerging areas like development of biological and gene ontologies, metabolomics. There are several key areas where bioinformatics supports CADD research Figure 2 [30, 31]

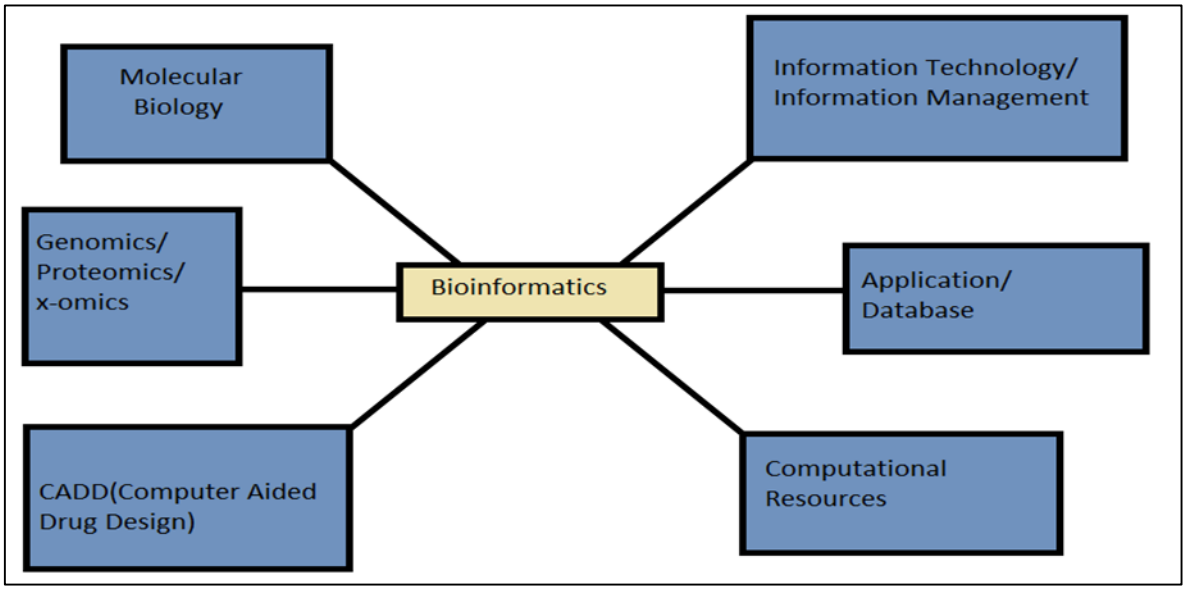

Fig 2: Role of Bioinformatics in Computer-Aided Drug Design

Virtual Screening

Virtual Screening is a computer-aided technique for searching the most probable compounds which are likely bind to the target molecule. These virtual screening techniques categorized into two viz Ligand based virtual screening and Structure based virtual screening. Pharmacophore modeling and QSAR exist in Ligand based and Docking comes under the Structure based virtual screening. Screening is just like eliminate the undesirable compounds by so called "garbage filter". Then through the Lipinski rule of five candidate molecule fulfill these four parameters demand that the log P value should be smaller than 5; molecular weight of a molecule should be less than 500 Dalton; hydrogen bond donor should not be more than 5; and hydrogen bond acceptor not exceed than 10. By applying these four parameters, selective molecules as taken for the further study [32].

Docking

Molecular docking helps to study the ligand-receptor interaction for identifying the active binding sites of target protein. Most energetically stable geometry of ligand-receptor complex is obtained through docking. The minimum energy of interaction can be represented by different scoring functions such as dock score, potential of mean force score, and steric and electrostatic score. This score is used to predict the binding affinity of a ligand towards receptor. The utility of molecular docking allows the screening of compounds for the lead identification [33]. The main aim of molecular docking is to find out the strength of the binding energy of the protein-ligand complex with least energy system.

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 representations	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,metaPocket,PocketAnnotate
Docking	Auto dock, DOCK, GOL, Docking Server, Swiss Dock, 1-ClickDocking,COPICAT
Screening	Pharmer, Catalyst, Pharma Gist, Swiss Similarity, Blaster, Anchor Query
Target prediction	Patch Search, IXCHEL, CABRAKAN, SEA,PPB Swiss Target Prediction
Ligand Design	GANDI,LUDI,BREED,SwissBioisostere,sc-PDB-Frag,GlideFragmentLibrary,e-LEA3D,eDesign
Binding free energy estimation	Hyde, X-score, NN Score, DSX_{ONLINE}, 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

Computer aided approaches to identify the new lead compounds via using the number of methodology like Structure based, ligand based pharmacophore modeling, molecular mechanics, molecular modeling, virtual screening with the availability of numerous types of databases. Also concluded the utility and role of Chemo informatics and Bioinformatics in the modern and digital era of the drug discovery and development. At that time computer-aided approach is the new and rising methodology for the development of drugs.

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