Review article

Computer aided drug design: A mini-review

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ABSTRACT

New drug discovery and development process is considered much complex process which is time consuming and resources accommodating too. So computer aided drug design are being broadly used to enhance the effectiveness of the drug discovery and development process which ultimately saves time and resources. Various approaches to Computer aided drug design are evaluated to shows potential techniques in accordance with their needs. Two approaches are considered to designing of drug first one is structure-based and second one is Ligand based drug designs. In this review, we are discussing about highly effective and powerful techniques for drug discovery and development as well as various methods of Computer aided drug design like molecular docking at virtual screening for lead identification, QSAR, molecular homology, de-novo design, molecular modeling and optimization. It also elaborate about different software used in Computer aided drug design, different application of Computer aided drug design etc. Major objectives of Computer aided drug design are to commence collaborative foundation of research activities and to discover new chemical entities for novel therapeutics drugs.

INTRODUCTIION

New drug discovery and drug development is much time-consuming, lengthy, expensive and highly unpredictable risky process that has little peers in global commercial market. And that's why this approach of computer aided drug design is used in pharmaceutical sectors to enhance the process. Especially cost effective approach by using computer tools in the lead optimization phase of drug development is considerable. On average, 10 to 15 years and $ 500 to 800 million are required to introduce a drug to the market, and the synthesis and testing of lead analogues is great contributor that total budget [1]. Henceforth, by using computational tools in successful optimization which can save broad chemical space with reduced amount of compounds that has to be synthesized and tested in vitro. Computational optimization of an affected compound involves an analysis based on the structure of coupling postures and energy profiles for impact analogues, ligand-based detection for compounds with similar chemical structure or improved predicted biological activity, or favorable affinity prediction. Optimization of the metabolism and pharmacokinetics of the drug or absorption, distribution, metabolism, excretion and toxicity potential properties. Cost of biological characterization of compound and synthesis is more higher than compared to very much low cost of CADD make a make more acceptability diversity of chemical space [2].

CADD is capable to accelerate the rate of new drugs by using a much additional targeted search than conventional high-throughput screening (HTS) and optimization of lead compounds to enhance ADME. Design new compounds by either "growing" one functional group after the other as parent molecules or by joining fragments into new chemo types [3].

CADD can be categorized into two approaches: Structure-based and Ligand-based on knowledge of target protein structure for interactions energies calculation for all compounds to be tested are done by structure based CADD which is functioning on information of the target proteins structure which further expose the activeness of molecules through chemical similarities search or quantitative or predictive construction [4,5,6,7].

FACTORS AFFECTING DRUG DISCOVERY

Medicinal requirements
Screening facilities
Drug development facilities
Drug development process operating cost
Designing of drugs are depends on various parameters, some parameters are listed as below:
Safe and effective
Bioavailable at site
Metabolically stable
Minimal side effects
Selective target tissue distribution [8]

RECEPTOR THEORY

This hypothesis gives "lock and key" speculation. This speculation clarifies drugs as receptor ligands or catalyst substrates that change the capacity of obscure molecular target focuses to deliver helpful impacts. Receptor theory contains classical enzyme kinetic models based on the law of mass action. The interaction between receptor and ligand can be seen as follows [9].

Receptor + Ligand [RL] R + Cellular Effect

Ligand L binds to receptor R and alters the function of cells and tissues by modifying the nature of the interaction membrane components and receptor. Ligand interactions have two unique properties: affinity and effectiveness. Affinity is the capability to distinguish and bind to the receptor, and efficacy is the capability of the ligand to cause changes in cellular processes by activating trans-membrane transduction mechanisms including G protein complexes [10].

QUANTUM MECHANICS AND MOLECULAR MECHANICS

There is couple of approaches with some difference to knowing the energy of a molecule. First, quantum mechanics in this approach, nuclei are placed in space and the corresponding electrons are spread throughout the system with a continuous electron density. Classical mechanics can explain the performance of a bimolecular system when it is not necessary to simulate a chemical reaction. Molecular mechanics known to be mathematical model and can be used to calculate the energy of systems with many atoms, such as biochemical and biomedical molecules and complex systems.

In contrast to quantum mechanics, molecular mechanics ignores electrons and calculates the energy of the system only as a function of the nuclear position. Second, the electronic components of the system by appropriate parameterization of the potential energy function. The arrangement of conditions and boundaries that characterize the possible surface of an atom is called force field [6,7,11].

FORCE FIELDS

The estimation of the complete power of a molecule in terms of atomic coordinates contains of the sum of various contributions that calculate the deviation of the bond length and bond angle values from equilibrium, and the corresponding force constant used in the potential energy function in that force field which defines a set called force field parameters.

The increase in the total energy of the molecule depends on these deviations from equilibrium. Thus, intra molecular strain is measured by total energy for a virtual molecule with perfect equilibrium geometry. Although the total energy itself does not have a strict physical meaning, two different conformations of the similar molecule can be compared with the aid of disparity in total energy [5,12].

THE HYPOTHETICAL BASIS OF CADD

CADD relies upon the degree of course of action and different subtleties accessible with respect to the objective (compound/receptor/protein) and the Ligand. Theoretical basis of CADD are as follows.

Structure-based Drug Design

- Docking and virtual screening
- Homology modeling
- de novo ligand growth and optimization

Ligand-based Drug Design

- Pharmacophore modeling and virtual screening
- Conformational analysis
- QSAR

In silico Absorption, Distribution, Metabolism, Excretion, Toxicity and drug–like property calculations

- Fast prediction of physical properties
- Ligand-based or structure-based modeling for hERG and P450 enzymes [12]

Ligand based drug design

In this approach, a target recognition process that provides efficient information in relation to the target candidates and location information to biological networks is significant. Diseases caused by external pathogens, such as microbes and viruses, may find pathogen-specific targets by comparing human functional genomics to the corresponding genomics of the pathogen.

For example, the subtractive genome method is used to find the complete genome of Helicobacter pylori (H. pylori) and identifies a set of genes that are essential for pathogens but not present in humans. In the case of endogenous disease, the target can be found by analyzing the difference between the normal and abnormal tissue genomics. This determines and evaluates whether ligand-based (QSAR and

pharmacophore) or structure-based approaches (docking, de novo ligand design) generate new lead compounds [13].

Structure based drug design

3D structure drug development of potential drug binding site is defined by the structure based design in which, the known 3D structure of the target bound to its natural ligand or drug is determined by either X-ray crystallography or NMR to identify its binding or active site. Lead discovery is initiated by this approach of structure-based design of a known target. Virtual screening of large collection of compounds can be performed after knowing the ligand bound 3D structure e.g. ZINC. Such screening can identify potential new drugs by performing docking experiments on this molecular collection. To increase binding and thus improve binding affinity / specificity, groups of molecules with similar docking are commonly used for potency determination. This is high-throughput screening (HTS).

After determining biological potency, you can perform a number of properties such as statistical analysis and other relationships (QSAR between and potency docking score) to identify the molecules required for lead drug discovery. Prior to optimization, the lead molecule was tested for reactivity with ADME. Spectral studies such as reactivity (electrophilicity, nucleophilicity or radical attack studies) and large molecule UV-visible can be performed by applying quantum mechanical procedures. Target identification of powerful drugs with unknown targets provides a exceptional break for lead discovery [13].

Peptidases are the largest class of enzymes used as targets for structure-based drug design. Among the most successful applications to date are drugs for HIV protease and human rennin, each of which stops viral replication and regulates blood pressure. A structure-based approach is important for binding to a protein of a specific compound from a genomic or protein database, and then using experimental procedures to validate the computational results. One inverse computational approach to docking a series of ligands to a definite target is to dock a compound with a recognized biological activity to the binding site of all three-dimensional (3D) structures in a specific protein database [12].

Docking

Docking is a much more important process which acts when multidimensional structures of macromolecules and molecular models of available site of ligand binding sites. This approach is very helpful in determining the proper conformation and orientation of the ligand to the receptor binding site. Applying docking makes it easy to predict and simulate favorable and stable ligand-receptor interactions.

Docking begins with the logical placement of small molecules at receptor binding active site using a docking algorithm. In addition, these docking algorithms are supported by scoring functions. The scoring function is intended to actually predict the biological activity of a molecule in the energy process of ligand-receptor interaction.

The evaluation is performed using a scoring function based on the calculation of the shape and electrostatic properties during the interaction. In addition, a complex scoring scheme using solvation or entropy effects and simultaneous comprehensive analysis of electrostatic and Vander walls interactions are used to reevaluate optimal compound fit.

Docking performed one of the three ways:

- Rigid docking, in which the target and ligand are treated as rigid;
- Flexible ligand docking, in which the target is held rigid; or
- Flexible docking, in which both the target and ligand are considered flexible

Docking programs mainly serve three purposes:

- To identify potential ligands from molecular libraries
- Prediction of mode binding for selected ligands
- To provide scoring of compounds for their likeliness of binding with the binding site by calculating putative binding affinities [14]

Virtual Screening

Computer aided technique helps in identification or searching of nearest compound or molecule which is probably binding to target molecule, is said to be virtual screening. Screening of a large number of chemical compounds from the molecule libraries against biological targets using in-silico methods is called as virtual screening.

These virtual screening techniques categorized into two are as follows:

- Ligand based virtual screening: It consist of Pharmacophore modeling and QSAR.
- Structure based virtual screening: It consist of docking and virtual screening.

Screening eliminates unwanted compounds known as so-called “dust filters”. Second, the log P value must be less than five because these four parameters are satisfied by the Lipinski rule for the five candidate molecules. The molecular weight of the molecule must be less than 500 Daltons. The hydrogen bond donor must

not exceed [5]. By applying these four parameters, selected molecules are selected for further study [15].

Homology modeling

Molecular modeling that is useful for expressing molecular structures numerically and simulating their behavior with quantum physics and classical physics equations. Since most drug targets are proteins, it is essential to know their 3D structure in detail. It is predicted that the human body lacks 5 million proteins, but only a small portion of these 3D structures are known. 3D structure of proteins prediction is done by Homology modeling.

Homology modeling is nothing but a similarity search for drug analogs. Start with promising drug molecules. There are two calculation tools for similarity search and sequence alignment such as BLAST, FASTA, and multiple sequence alignment Clastal-W, Clastal X [13]

De novo drug design

New design structure for specific target site is programmed by De Novo design

De novo drug design include following steps for its methodology

Step 1: Determination of binding pocket on target receptor

Step 2: Prediction of interaction sites of target receptor through Ligplot

Step 3: Placing the fragments or other linking groups with pharmacophore models at pre-defined interaction site to provide possible interactions with the residues in the site of the target receptor.

Step 4: Structurally modification of the fragments to provide possible interactions with the residues in the site of the target receptor.

Step 5: Joining all fragments together to yield a complete single molecule [16]

Optimization

It is the second stage of drug discovery with hit correction to improve the biological properties of the compound by replacing the pharmacophore. With QSAR, changing lead compounds is less cumbersome than physically synthesizing compounds. In silico methods useful for modifying compounds to show their potency and selectivity, highest pharmacokinetics and minimal toxicity. QSAR mainly includes physical chemistry and molecular docking tools to derive tabular data and first and second order equations [17].

Quantitative structure-action relationship

Quantitative structure-action relationship (QSAR) displaying is the development of an extrapolated model of pharmacological movement as an element of compound library structure and molecular data. QSAR ideas are usually utilized in drug revelation and improvement and are generally applied to keep up a correspondence molecular data with other physicochemical properties just as biological activity

Molecular parameters that contribute to electronic properties, hydrophobicity, steric effects, and topology can be determined theoretically by experiment or by computational chemistry. Certain collections of datasets are subject to data preprocessing and data modeling using statistical and / or machine learning techniques.

Quantitative Structure-Activity Relationship (QSAR) and Quantitative Structure-Property Relationship (QSPR) have made it possible to predict activity / property as a function of the molecular substituent of a particular compound. This suggests that new untested compounds with similar molecular characteristics as those used to build the QSAR / QSPR model will have similar activity / properties [18].

Molecular modeling

Structure relationship elucidation from storing models of complex molecular structure, visualization, analyze, building are done by molecular modeling.

MOLECULAR MODELING FUNCTIONS

Several applications and methods of molecular modeling are possible

- **Structure creation**

Generation of structure is done by several of processes. If a crystal structure exists, it can be found in the Cambridge crystallographic data file and turned into molecular coordinates by a standard method.

- **Structure visualization**

Molecular structure visualization and interaction by a different method. Demonstration of the structure is prepared with the stick model, Ball, and Stick model, Space filling and Surface model.

- **Conformation generation**

Used to calculate possible conformation. Monte Carlo technique formed conformations that can be analyzed statistically or energetically.

- **Deriving bioactive conformations**

For biologically active molecules, determination of 3D structure of molecule which is linked with that particular activity is most essential. If one, two, or more molecules bind in a common mode, then search for a general conformation is performed. To search for bioactive conformers, only low energy conformations are used, so an energy calculation is required.

- **Molecule superposition and alignment**

The calculation of molecular properties often involves a comparison of the entire homology series. This is done by superposition or alignment of the molecules, and the difference becomes clear and

interpretable. If the molecules have a common structure that is large and stiff, their alignment is relatively simple. In general, molecules are sufficiently different in structure and conformation, so their sequence is not obvious and probably not unique.

- **Deriving the pharmacophoric pattern**

The essential geometric arrangement of atoms or functional groups required to generate a specific biological response can be said as a pharmacophore. A given set of biologically active molecules that generate activity by the same mechanism is assumed to have the same important pharmacophore. Pharmacophore are described as topological (graph theory or connectivity-based structural fragments) and topographic (geometric, usually 3D patterns).

- **Receptor mapping**

The "receptor map" may be build by using the mechanism of receptor ligand complementarily for unknown receptor structure. Many algorithms are available for calculating the union of molecular volumes. An electron density function calibrated to reproduce the van Der Waals radius is mapped to a three-dimensional grid to calculate volume coupling, intersection, and subtraction.

- **Biological activities estimation**

In reality, drug activity can vary from very active or powerful to inactive. QSAR is a technique for quantifying the relationship between structure and biological data, and helps optimize groups that regulate the efficacy of molecules.

- **Molecular interactions**

Modeling the interaction between a drug and its receptor is a complex problem. This is because there are too many degrees of freedom, so there is not enough knowledge about the effect of the solvent on the binding and is determined stereo specifically by the fit of the molecule to the receptor. Many forces are involved in intermolecular associations, such as hydrophobicity, dispersion or van der Waals, hydrogen bonding, and static electricity [19]

DRUG DESIGNING SOFTWARE [20]

Basic needs of Software working are programme through computers. Several industries are providing different designing of software's like Accelrys, Schrodinger, Auto Dock and Argus Lab

- **Accelrys**

Accelrys is a software company with US based headquarters and elaborated its branches in Europe and Japan. It provides software's especially for drug discovery and materials science.

Their product helps and curtails the hurdles to proceed further for drug discovery and development process. Below mentioned several software's are created by Accelrys:

- Insight II
- Pipeline Pilot
- Discovery Studio
- Materials Studio
- Accord

Area of Research Software [21]

Sr No.	Area of Research	Software
1	Docking	ZINC, Auto dock, Dock, Gold, Ligand Fit, Dock blaster
2	Ligand design	Gandi, Sprout, Flex Novo
3	QSAR	cQSAR, clogP, Galahad
4	ADME Toxicity	Qik Prop, Q-ADME, ADMET Predictor
5	Lead optimization	Wabe
6	Physicochemical modeling	Swiss-PDB

Table no. 1: Different software of drug design

ADVANTAGES OF CADD

- To reduce the synthetic and biological testing efforts.
- Promising drug category is given by this by eliminating unwanted compounds properties like poor pharmacokinetics parameters (ADMET), poor efficacy through in silico filters.
- It is quick, automatic, time saving and cost efficient process
- To know about the drug-receptor interaction pattern.
- It determines the list of compounds with high best rates through vast libraries of compounds in silico as compared to traditional HTS.
- These approaches minimize chances of failures in the final phase [22]

APPLICATION OF COMPUTER IN DRUG DESIGN

Anticancer agent

Sequencing the human genome is one of the major scientific efforts of aspect. This major aspect, by using this information is the provision of small molecules that recognize selected sequences possibly for the purpose of switching off specific genes, such as cancer chemotherapy. For some time, antibiotics such as netropsin have been known to bind especially to sequences rich in A-T pairs. Therefore, we may consider ligands that can exist in two forms, oxidized and reduced, and it may be appropriate that the redox potential is oxidized in normal tissues but decreased in tumors.

Target Enzyme

When the structure of the enzyme is already identified then is easy to design inhibitors that can block in vitro activities. The free energy of binding of the

inhibitor to the enzyme is an important amount for which strong binding is essential.

Drug Transport

Transport across biological membranes is essential. The compound needs to dissolve in the lipid and enter the membrane, but it must not dissolve and stay there. The partition coefficient between water and n-Octanol is used as membrane transport. A free energy perturbation method useful for calculating partition coefficients. However, it is probable to model biological membranes. Starting with the crystal structure of a membrane containing DMPC (1,2-dimyristoyl-snglycero-3-phosphorychloro), a very realistic simulation involving a hydrated lipid bilayer is possible. The membrane is involved in lead separation and diffusion.

Structure determination of protein

The three-dimensional structure of a protein is determined from primary to tertiary structure and increases from a few cases to thousands, depending on the drug target whose binding site structure is known. The currently favored and only successful methods are all based on finding similarities and homologies between proteins of known topology but of unknown topology and known structure from 3D databases.

Biochemical Transformation

Computer-aided design methods can be used even if there is no knowledge of detailed polymer targets at the atomic level. A popular and ideal approach is to calculate the energy profile of the biochemical transformation that it is desirable to inhibit. It acts as an inhibitor, identifying transition states or intermediates, creating stable mimetics of these unstable transients recognized by enzymes that catalyze the reaction.

Molecular similarity

Even more striking is the achievement of structure-activity relationship and quantitative structure-activity relationship similarity measurement for example, steroids which gives comparative molecular field three-dimensional structure activity studies for which binding affinity data are available [23].

DISCUSSION

Drug discovery and development are very demanding, costly and time consuming which is accelerated by the development of calculation tools and methods. In recent years, computer aided drug design (CADD) has also been known as in silico screening. This technique is used at various stages of drug development through various overhang features. In-silico screening is also used for synthesis and screening of selected compounds for better treatment.

In many cases the QSAR approach is used in these cases where the structure-based approach is not applicable due to lack of target polymer structure information. QSAR provides information on chemical structure and biological activity in mathematical form. QSAR provides information on chemical target structure, eliminating the need for compound synthesis and testing. Research also associates all of them, such as compound structure descriptors, physiological properties, and biological activity.

CADD provides valuable information on target molecules, lead compounds, screening and optimization. Recent advances such as QSAR, combinatorial chemistry, various databases, and new software tools available provide the basis for the design of ligands and inhibitors that require specificity. The backbone of the CADD process included various approaches, design stages, docking, pharmacophore modeling, and homology modeling. Computational chemistry can also help understand the three-dimensional aspects of drugs-molecular-based receptor interactions accelerate medicinal chemistry in the design of new therapeutics. There will be improvement of quality of research and accelerate the development of numerous pharmaceuticals in the near future by CADD [8].

Genome and proteomic approaches are key tools for target identification. For example, proteomic approaches for identifying specific small molecule binding proteins include comparing protein expression profiles of specific cells or tissues in the presence or absence of specific molecules. The method is cumbersome and time consuming, so target discovery is not very successful. Therefore, a series of in-silico tools have also been developed for target identification to complement the experimental method. For target identification, it can be divided into a sequence-based approach and a structure-based approach [17].

CONCLUSION

Computer-based drug design is an efficient tool in the field of drug discovery and development, through which you can find the most promising drug candidates in a very cost-effective manner. It always gives hope for improvement in the drug discovery field.

Over the past few years, many impressive studies have been achieved through computer-aided drug design, which will play a very important role in the near future. With current achievements, there is a promising future for computer-aided drug design to support the discovery of more future therapeutics.

CADD's success story in drug discovery over the past few years has demonstrated its usefulness in the drug development process. CADD provides valuable information on target molecules, lead compounds, screening and optimization. Recent advances such as QSAR, combinatorial chemistry, various databases, and

new software tools available provide the basis for the design of ligands and inhibitors that require specificity. Various approaches, design phases, docking, pharmacophore modeling, and homology modeling are the backbone of the CADD process. The usefulness of computational chemistry is also to understand the three-dimensional aspects of drugs-molecule-based receptor interactions.

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