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Review Article

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A Review on Computer-Aided Drug Design

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Abstract

Drug design through computer, a recent, very effective technique in modern era. Now a day's Computer Aided Drug Design (CADD) technologies are used in nanotechnology, biochemistry, molecular biology. The main benefit of the CADD is cost effective in research and development of drugs. There are wide range of software's are used in CADD. There are different techniques used in CADD visualization, homology, molecular dynamics, energy minimization molecular docking, QSAR etc., Computer aided drug design is applicable in cancer diseases, transportation of drug to specific site in body, data collections and storages of organic and biological. Conformational properties and energetic of small molecules and DNA cleavage are widely used this technique for the development of this technique.

Keywords: computer-aided drug design, pharmacodynamic, software, drug

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1. Introduction

Computer Aided Drug Design (CADD) and Delivery frameworks offers an in-profundity exchange of the computer-assisted techniques used to discover, design, and optimize new, viable and safe medications. Late technological improvements in biochemistry, biomedical science, and nanotechnology have made computer aided drug design and delivery systems conceivable on a molecular support. This in-profundity treatise blankets this pioneering advances [1]. The destination of the drug design is to discover a chemical compound that can fit to a particular cavity on a protein target both geometrically and chemically [2]. The most basic objective is to anticipate whether a given atom will tie to a target and if so how positively. It utilizes computational science to find , improve or study drugs and related living dynamic molecules.[3] Ideally, the computational system will have the capacity to anticipate partiality before a compound is blended and consequently in principle one and only compound needs to be combined, sparing colossal time and expense. Without a doubt present computational systems are flawed and give, at the very most, just qualitatively exact assessments of proclivity. In practice in any case it takes a few emphases of design, blend,

and testing before an ideal drug is uncovered.[4] Computer methodologies to drug design fall into two general classifications: those that don't expect data on the structure of the target particle , and the structure based methodologies that do make utilization of such information.[1] In the post genomic time , CADD has respectably developed its extend of provisions, traversing very nearly all stages in the drug disclosure pipeline , from target ID to lead finding , from lead improvement to preclinical to clinical trials [6]. Utilization of computational systems in drug finding and advancement procedure is quickly gaining in notoriety, usage and appreciation. Both the computational and exploratory procedures have imperative parts in drug revelation and improvement and represent complimentary methodologies.

CADD involves

Use of computing force to streamline drug disclosure and improvement process. Leverage of synthetic and natural information about ligands/or focuses to distinguish and upgrade new drugs. The integration of the information gathered in pre-clinical toxicokinetic (TK), pharmacokinetic (PK), pharmacodynamic (PD), and the digestion system studies are vital for providing a learning - based drug improvement edge work in people particularly in admiration to the recognizable proof of the measurement regimens that bring about ideal restorative result in verification of idea studies preliminary to full clinical drug advancement (Peck et al., 1997).[5]

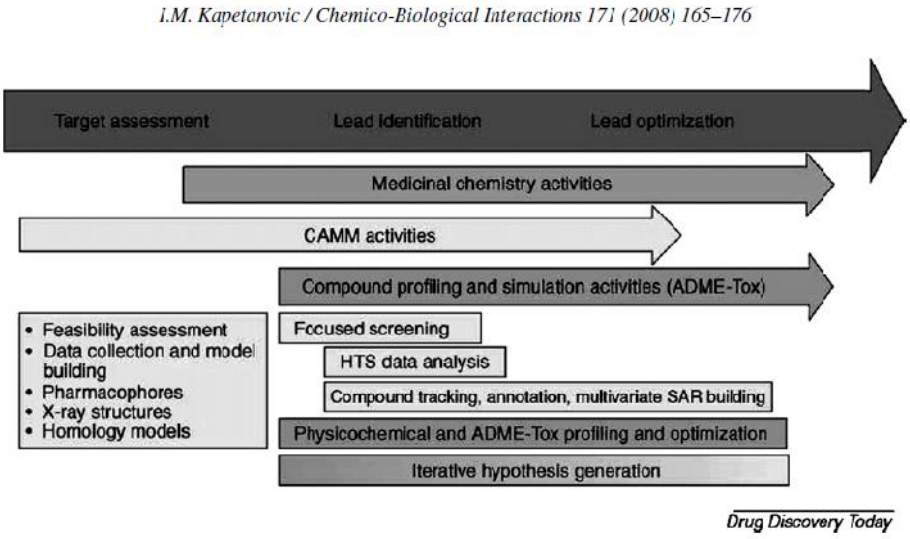

Figure 2. Modern drug discovery and development process including prominent role of Computational modelling.[3]

2. Brief History of CADD

1900 The receptor and lock and key concepts were developed by P.Ehrich (1909) and E.Fisher (1894),
1920 Quantitative Structural- Activity Relationship (QSAR) was developed. Limitations were 2-Dimensional, retrospective analysis of the drug moieties
1960 Viz -Review the target - drug interaction.
1980 Beginning of CADD, Databases (information technology) - combinatorial libraries Fast computers - docking.
1990 Fast computers - genome assembly - genomic based target selection.
2000 Vast Information handling - Pharmacogenomics.

Computer-Aided Drug Design: Early Methods

Initially, the design of new drugs was based on starting with prototypical molecule, usually a natural product and making structural modifications. Example include steroidal harmones based on naturally occurring cortisone, testosterone, progesterone and estrogen; adrenergic drugs based on epinephrine; local anaesthetics based on cocaine; opiate analgesics based on morphine; antibiotics based on penicillin, cephalosporin and tetracycline. Although prototypical molecules have produced significant advancements in treating diseases, this approach to drug development is limited to the initial discovery of the prototypical molecule. Today it is more common to take a holistic approach that, where possible, involves understanding the etiology of the disease and structure of the receptor where the ligand bind. Increasing computer power coupled with applicable software, both at reasonable cost, has lead to more focussed approaches for the development of new drugs. Computational methodologies include mathematical equations correlating structure with biological activity, searching chemical databases for leads and rapid docking of ligand to the receptor. This latter requires 3D structural information of the receptor. Originally

crystallized enzymes wee the common receptors, and their spatial arrangements determined by X-ray crystallography. Today's softwares can calculate possible 3D structures of protein starting with amino acid sequence.

Computer- Aided Drug Design: Newer Methods

Because of powerful computing power, high resolution computer graphics, and applicable softwares has reached the desktop, computational drug design methods are widely used in both industrial and academic environments. Through the use of computer graphics, structure of organic molecules can be entered into a computer and manipulated many ways. Computational chemistry methods are used to calculate molecular properties and generate pharmacophore hypotheses. Once a pharmacophore hypothesis has been developed, structural databases of 3D structures can be searched rapidly for hits. It has become popular to carryout in silico screening of drug-receptor candidate interactions, known as virtual high - throughput screening (HITS), for further development. The realistic goal of HTS is to identify potential lead compounds.

Today's computers and softwares give the medicinal chemist the ability to design the molecules on the basis of an estimated fit onto a receptor or have similar spatial characteristics found in the prototypical lead compound. Of course, this assumes that the molecular structure of the receptor is known in enough detail for a reasonable estimation of 3D shape. When a good understanding of the geometry of the active sites is known, databases containing the 3D coordinates of the chemicals in the databases can be searched rapidly by computer programs that select candidates likely to fit in the active site.

How Does CADD Work :

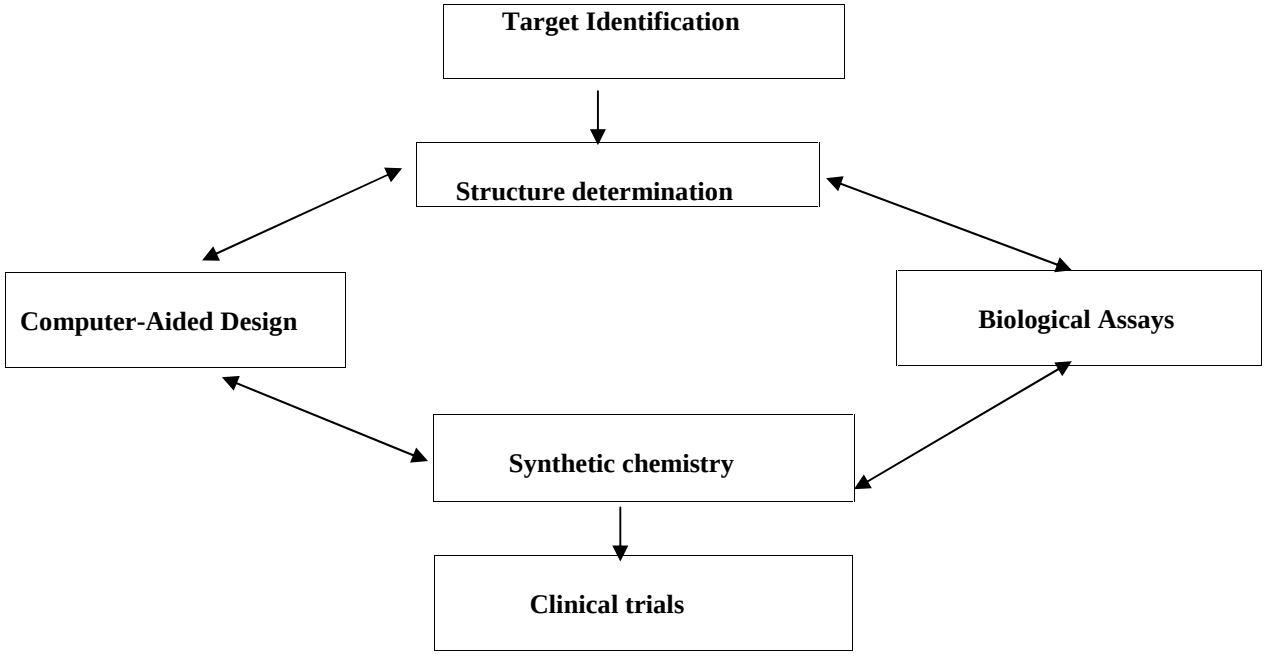

Figure 2: Working process of CADD

3. Software's used in CADD

Structure-based drug design

To design a medicinal product for treating a disease or relieve symptoms, a clear understanding of the disease pathway and relevant process is crucial for selecting a therapeutic target. Thus, in the past we have employed programs such as GeneCo and KEGG to build pathway maps of hypoxia-inducible factor in brain injury, as shown in Fig.2, for identifying critical signal or transcription pathways, specific protein-protein interactions and relationships between upstream and downstream proteins. This background knowledge has proven helpful to us for selecting key therapeutic target.[9]

Protein structure determination

For structure - based drug design, a priority before investigating receptor-ligand relationship is to obtain the target structure. There are two major methods for protein structure determination by physical measures, X-ray diffraction and NMR (Marti-Renom et al, 2000). The solved protein structure can be readily found at Protein Data Bank (www.rcsb.org/); however, modeling approach can be used.[10]

Homology modeling

Homology modeling is a fast method to obtain protein structures that cannot be used in studying rational drug design but also for protein-protein interaction and site-directed mutagenesis (Josa et al., 2008; Mohan et al, 2009; Sujatha et al., 2009). Proteins lacking structural information could be constructed if they have over 30% sequence identify with their related homologous proteins (templates) (Marti-Renom et al., 2000). This modeling strategy has been widely applied in many researches and in our past studies as well (Chen, 2008a,b,c; Chen, 2009a,b,c,d).[11]

Folding recognition

As known as "threading" folding recognition was brought up in 1991 by Bowie and colleagues whom employed this method to describe the environment of residues interactions. Folding recognition calculates the probability of the 3D structures could form by given protein sequence (Mishra , 2009). Both the environment of residue interactions and the protein surface area considered in the threading protocol. Structure with the highest probability is recommended to construct the protein model.[9]

Molecular Dynamics

Molecular dynamics is the study of movement of molecules. Every molecule has its own frequency of vibration. It can oscillate position one to two through zero, where the molecule has high potential energy at one and two position and least at zero position.[10]

Role of Computer in designing a drug molecules

Transportation of drug

The transport of the drug molecules in the biological membrane is one of the most important. The compound must be able to have the properties that its becoming soluble in lipid so that its can penetrate in to the skin. But it should not be so soluble. In the field of pharmaceutical chemistry the use of the partition co-efficient between the water and oil-family (butanol,octanol etc) help in transport to the membrane. Furthermore the use of cholesterol and proteins can act as the transportation for the drug molecules into the cell.[15]

Table 1: Data taken from Journal of Computational Drug Design

S.NO	Softwares	Application
1.	AMBER	Classical molecular modelling program
2.	ArgusLab	A molecular modelling, graphics, and drug design program
3.	Ascalaph Designer	Common molecular modeling suite
4.	BOSS	OPLS inventor
5.	Discovery Studio	A molecular modelling environment for both small and macromolecular systems
6.	DOCK	DOCK algorithm
7.	eHiTS	eHiTS docking and virtual screening suite
8.	Firefly (PCGAMESS)	An initio and DFT computational chemistry program
9.	FoldX	A force field for energy calculations and protein design
10.	INDDEx	Ligand-based scaffold hopping using SVILP machine learning
11.	Lead Finder	Lead Finder molecular docking package
12.	Maestro (Schrodinger)	Molecular modeling and visualization program for drug design and material science
13.	Materials Studio	Software environment
14.	MedeA	Software environment for inorganic materials science
15.	MOE	Molecular Operating Environment
16.	VlifeMDS	Vlife Molecular Design Suite
17.	NAB	Molecular manipulation language for nucleic acids
18.	PCMODEL	Common molecular modelling tool
19.	SCIGRESS	General purpose molecular modelling molecular suite
20.	SPARTAN	Molecular modeling tool with molecular mechanics and quantum chemical engines
21.	StruMM3D	Molecular modelling tool
22.	TINKER	Freeware, tool for protein design
23.	Tmolex	ab initio and DFT computational chemistry program

Arbitrarily categorized CADD into three major sections: (a) structure based drug design, (b) ligand-based drug design, and (c) molecular dynamics.

Agent for anticancer properties

The available of the human genome (alternative form of genes) is one of the major aspects in scientific research. The uses of this major aspect as one of the information will be able to use the particular type of genes for the treatment of cancer or cancer chemotherapy. Its has also been found out that the antibiotics such as Netropsin have the properties to bind with the A-T pairs of an amino acid sequence. So based on this, researchers have been tried to design a bio reductive ligand that netropsin based. This bio reductive is an anti-cancer agents, this its believe that the in tumours it receive a less blood and also a less oxygen than the normal tissue. This is possible only when the ligand consist of two foerms ie, the oxidized form and reduced form. The oxidized form is act on the normal tissue where as reduced form act on the tumours. There are cases also that when the reduced form bind to the target molecular causes the cell to become death (apoptosis) and destroy the normal cells there by reducing the side effects. Another classes of compound can also be use as anticancer agent ie, organometallic compound/molecules associated with the chiral properties.[12] Example like ruthenium tris-phenanthroline complexes shoe that its can bind to the A-T and G-C of amino acid sequence and also acts as the site for DNA molecules. [13]

Information Base on Receptor

The presence of the target site on the protein structure is help for identifying the ligand interactors. This type is involve the binding of the ligand to the receptor in the receptor site. This can be predict by the binding of a ligand to different receptor. However predicting the ligand bind to the protein active site is not easy. First we have to know the structure of the molecules which has already been shown by NMR or X-ray crystallography. Secondly, we should know the correct position of the compound in the site of the protein. Thirdly, we should know that the molecules will fit just like lock and key. [14]

Selectivity of Ligand and Fragment link

The developed of the molecular entities for improvement is a highly combination due to the diversity of the target proteins. The number of protein is about 25000, but the number of the real organic compounds with the molecular weight greater than 2000 Da is becomes more than 1060. Because of the big chemical space the studies for systematic is high. The use of computer can be done for the selection, analysing, modelling, and optimization of lead potential candidates. The use of this computational method can be able to predict the selectivity of the ligand.[16]

Suppose we want to plant any seed we need a fragments database so that we can be able to choose from. Thus the term fragment use to describe as the building blocks as a process of construction. This is base on the fact that the organic structure is decompose into small fragments. The first step of fragment is that the seed is put in the pocket which is bind and the rest of the fragment is being added one after the other.

The possibility of the fragment is huge. At the same time we can be able to find out the lowest binding of potential energy surface. Between the plant fragment and the pocket receptor. The calculation can be done for every step during the conformational changes of fragments derived from every type of combination. This method required a lot of the computational, but we can use different tricks for the less use of the computer and let the program work more efficiently. When the ligand is being bind to the receptor in a specific pocket, so those that can be bind strongly can be have the high priority in lowest energy conformation. This can help us by allowing the seed in to the program and optimize the changes of those seed that has been interact with the receptor and connect in such a way so that can be able to produce a ligand that have a lowest energy. This method is being helpful in the reduction of calculation for fragment construction. It can also reduced the combination of fragments, which reduces the number the ligand which is possible for this part in the program. The two major method base on the structure base drug design program. They are described as the GROW and LINK . The combination of both can give a better results.[17]

Rational Drug Design

Rational drug design begins with the modulation of the specific target biological molecules that have the therapeutic value. In order to select the bio molecule as the drug target two types are needed. Firstly the modulation of the target molecule will have the therapeutic value. For example the linkage of disease that shows the associate between the mutation and the certain state of disease. The second is that the target site is durable. This tells us that the small molecule capable of binding and the activity can be mediate by the small molecule only. The begin of the small molecule to bind to the target site is the screening of the drug potential compound. This can also be done by using the screening assay. But if the structure of the target site is available a screen may be performed for a drug. The candidate of the drug molecule should be drug-like that should have the properties of bioavailability, metabolic stability, and minimal toxic effect. There are many method for the likeness of drug molecule such as Lipinski's rule and lipophilic efficiency. [19]

Changing of the Biochemical process

We have no or a little knowledge on the target macromolecule but still we can work out by using the computer aided-drug design techniques. This will be able to compute the different biochemical transformation for the desirable to inhibit. Thus by locate the intermediate state and then create a mimic which is stable which has been recognise by the enzyme that can be able to lead the reaction and then acts as a inhibitor. Such type of a mimic has a two steps ie, transient structure and then design a mimic which is stable. The first step can be done by perform by using the triosephosphate isomerise reaction. The second step is involve the use of the molecular similarity that is to

measure how similar the molecules are. But one of the most important is that by comparing the similarity of shape and similarity of electrostatic potential of a molecule. Both of these can be achieve by follow the Gaussian function.[18]

Similarity of the molecules

There has been many achievement in the similarity of the measurement in SAR and QSAR relationship. Good et al has been consider that the series of steroids acts as the binding site. The validated cross correlation coefficient that has been get from statistical analysis has been compared with the more commonly used. More over there is no need of arbitrariness of the extent of surface of a molecule or the size of the three dimensional box in the placed in which the molecule has been incorporated.[16]

Dissimilarity of the molecules

The dissimilarity between the two molecules can be define as the 1-Similarity. Its cans has a range of 0-1 with the identity which is unity. The dissimilarity can be seen in the comparison between the chiral of the same molecule. Thus we can be used the 'chirality coefficient' a number of which will be able to give the range of value of chirality. When they produce a chiral compound for use in the pharmaceutical agents; thus the more active form is called 'eutomer' and the less active form is called as 'distomer'. The ratio is called as eudismic ratio. It's has been shown that the correlation between the eudismic ratio and chirality coefficient.[20]

Determination Of Protein structure

In order to determine the structure of protein we have to consider the use of genes and sequence of proteins to predict the three-dimensional of proteins ie, primary, secondary and tertiary. One of the method that can be done is that on finding the similarities between the protein of a known sequence and the unknown one. So the sequence are based on how similar the short length of the polypeptide in a unknown case compare with the known case. One the best method is that base on the small protein endothelia was proposed, by using properties and hydrophobicities.[21] Now a days they has been used the colour graphics to penetrate to the human eye and detect the similarities. It's has many advantages by using this method. The computer program or software has been used for predict the structure of interleukin-4 receptor called as *CAMELEON*.

The Advancement of Computer in Aided Drug Design.

The cycle for the discovery of drug has been undergo a clinical trials in by many researchers. Its suggested that it can cost for 800 million dollars for about 14 years. The development of the field of chemistry and screening technology has been a new field for the purpose of drug design that can be screen for a given period of time. The identification of lead can optimized into the actual lead and undergo a preclinical. It's also believe that 40-60% of a drug undergo the distribution, absorption, excretion, metabolism and also cause toxicity. Moreover as early in 1970s the CADD was established by the use of the biological structure which can lead to the modification of the activity of the hormones like insulin and simultaneously allowing the synthesis of the ligand of haemoglobin. In earliest time the X-ray crystallography was very costly and also taking time.[17] As the time going on, new technologies was developed such as modelling comparatively based on the structure of the natural homologues this can be use for designing a lead.[18] These along with the combination chemistry, computational infrastructures and screening technology has been bring a gap between the medicinal chemistry and the model of theory. There are number of the successful designing drug like Dorzolamide for the treatment of edema.[19] Zanamivir use for treating the infection of influenza.[21] Drug for the treatment of male erectile dysfunction called as Sildenafil.[19] And the drug use for the treatment of HIV infection is Amprenavir.[20]

The CADD use the computational branch of chemistry to enhance or discover the drug or to study the active biological molecules. The aim is to predict that the particular molecule will be able to bind with the active site or not. So the method use to determine the conformation of the of the molecules which are small and also to model the change during the conformation in the target site when the molecules bind to the target site called as the molecular mechanics or molecular dynamics[17]. Different methods have been use like semi-empirical etc, for providing the optimized paramaters for the mechanics calculation and the properties of the electronics of the drug that will bind into the target site or active site. Also the use of the scoring function may be estimate for the affinity of binding. This method use the different types like machine learning, neural net. Or the other techniques for the binding site of the small molecule in the target site. The computational method use for the purpose of predicting the compound when the compound is being synthesized saving the cost and time. However the use of the computational method is imperfect and provides the best estimate for affinity. But in practice its very difficult to synthesis, design, testing before the drug get discover[21]. The use of this method is gaining the discovery of the drug there by reducing the number of the iterations. With this we can come out with new discovery of drug with the unique structure.

So with the help of computer we can be able to design a drug and can be used for the following drug discovery:

1) By using the hit to lead method we can be able to optimized the selectivity and affinity ie, by QSAR, structure based on design etc.
2) The use of the virtual screening for identification ie, ligand based design.

3) The lead optimization for pharmaceutical properties there by maintain the affinity to overcome the prediction of the binding of the molecules. This has been calculate by the recent scoring functions,. For the structure base drug design several types of the post screening analysis on the protein-ligand has been developed.
   a) Cluster analysis
   Represent the candidates of the cluster base on the protein ligand 3D. Also required the meaning representation of the protein ligand action.
   b) Consensus scoring
   Candidates are being select by voting to the multiple function of scoring. There will be a lost of the protein ligand structure and scorin criterion.
   c) Geometric analysis
   There is a comparing of the protein ligand interaction by individual structure. When the number of the complexes is increasing then it can be interact [22].

4. Conclusion

From our review, we would like to convey that CADD drug design is more widely recognized and high complement to high throughput screening. Conversely, advances in molecular docking algorithms, combined with improvements in computational infrastructure, are enabling rapid movement in High throughput screening. By using CADD, we can reasonably consider that the predictions in man, generated using the same molecular approach. A survey of the integration of pharmacokinetics and pharmacodynamic principles in clinical drug development in major pharmaceutical company has been performed recently. It has shown that the use of the pharmacokinetic - pharmacodynamic guided approach had contributed to making clinical drug development. It is probable that the ability to model drug behaviour and effects more efficiently has greatly promoted the more scientifically based strategies of drug development, without forgetting their rational use in individual patients.

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