

**(C.A.D.D.) - A NEW - MODERN SOFTWARE BASED APPROACH IN
DRUG DESIGN AND DISCOVERY**

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ABSTRACT

Computer-assist drug design uses computational chemistry to discover enhance or study drugs and related biologically active molecules. Two distinct approaches are possible in the area of computer-aided drug design. If the molecular structure of the target macromolecule is known the methods are obvious and direct and have achieved a high level of sophistication. That area may be extended by using computational techniques to predict protein structure like Cancer-Causing H-Ras p21 Mutant Protein and to stimulate drug-receptor interactions. CADD methods are heavily dependent on bioinformatics tools, applications and databases. As such, there is considerable overlap in CADD research and bioinformatics. When the only lead is a set of known active compounds or knowledge of a biochemical transformation which is to be interrupted, then the path is less direct. Currently favored tactics include the use of molecular similarity methods and the employment of neural networks. Recent advances include the prediction of the relative potency of different chiral forms of drugs.

KEY WORDS: Structure based study, Bite site study, De novo drug design, Virtual High-Throughput Screening , Bioinformatics

1. INTRODUCTION^{1,2,3}

Computer –assist drug design (CADD), also called computer assist molecular design (CAMD), and represents more recent applications of computer as tools in the drug design process and many new soft ware used in modern days ,And in the fields of biochemistry, molecular biology ,and cell biology, facilitated by developments in genomics and proteomics, are producing a large number of novel biological targets that may be exploited for therapeutic intervention. To facilitate the discovery of novel therapeutic agents, rational drug design methods in combination with structural

biology offer great potential. The Computer-Aided Drug Design (CADD) Center was created to foster collaborative research between biologists, biophysicists, structural biologists and computational scientists¹. The major goal of the CADDC enter is to initiate these collaborations leading to the establishment of research projects to discover novel chemical entities with the potential to be developed into novel therapeutic agents. Computer-aided drug design².

(CADD) is an exciting and diverse discipline where various aspects of applied and basic research merge and stimulate each other². The latest

technological advances (QSAR/QSPR, structure-based design, combinatorial library design, cheminformatics & bioinformatics); the growing number of chemical and biological data bases ;and an explosion in currently available software tools are providing a much improved basis for the design of ligands and inhibitors with desired specificity in drug discovery.

2. STRUCTURE-BASED DRUG DESIGN⁴

Structure- based drug design(or direct drug design) relies on knowledge of the three dimensional structure of the biological target obtained through methods such as x-ray crystallography or NMR spectroscopy. If experimental structure is not available. With in many of the rational drug design projects in the group, computer-aided methods, such as virtual screening and *de novo* design techniques, play an important role in follows 3-D structure Three dimensional structure of compounds can generated and studied using molecular modeling software package such as ChemDraw, then imported into a molecular modeling software package such as Chem3D . the 2-D structure is converted into a 3-D structure is converted into a 3-D structure, which is quite clever, but is not error free, since the structure created is usually distorted (the bond lengths and the bond angles are not ideal).There once a 3-D structure has been built or generated, it is important to carry out an operation called energy minimization .This involves running a program that modifies the bond angles and lengths in the structure, then calculates the static energy of the new model compared to the previous one. If the energy changes significantly, it means that neither

structure is particular stable and the process is repeated. Changes that decrease the total energy of the structure are retained, while those that increase the energy are not, and this continues until any modifications carried out have little effect energy on the total energy of the molecule. This corresponds to a stable structure or an energy minimum. Obtained, the molecules can studied, its dimensions measured (eg.bond angle, bond leangth, torsion angles,atom-atom distances).

An overlay operation is carried out where the program attempts to match up each defined pair of atoms.once the overlay has been carried out ,it is possible to measure how closely the corresponding atom in each structure overlap with each other. this sort of operation is crucial when aligning molecules for 3D QSAR studies and for comparing pharmacophores in different molecules.

3. BINDING SITE STUDIES

Several proteins have been crystallized allowing their structure to be identified by X-ray crystallography. However, this is of limited use in drug design for the following reasons: the structure of an enzyme or receptor gives no indication of the induced fit that arises following the binding of a ligand to its binding site; it also gives no indication of how the ligands binds to the binding site.For these reasons, it is better to bind a ligand (usually an antagonist or inhibitor, as they bind more strongly) to the proteins binding site, and then crystallize the protein-ligand complex. The X-ray structure of the complex then reveals where the ligand is bound to the protein, thus identifying the binding site ,The structure of the complex can be downloaded into a computer and a

molecular modeling software used to study how the ligand binds to the protein. First of all, the program allows the operator to hide most of the protein so only the binding site and the bound ligand are visible on the screen. The binding interactions can then be identified by measuring the distances between the atoms of the ligand and the closest atoms in the binding site. The later can be studied to see if any vacant spaces not filled by the ligand. And identified it. Then it is possible to design analogs of the ligand with extra substituents or groups attached that would fit into these vacant regions allow the ligand to fit the binding site more snugly. More ever identified the amino acid residues and peptide links that line these vacant regions would indicate what types of substituents could be added to the ligand in order to get further binding interactions. Alternatively , docking experiments can be carried out to explor the various ways in which a ligand could bind to the model site and calculate which is the most stable docking interaction. In these experiments the possible binding groups in the binding site and in the ligand are identified, but there is no constraint as to which binding groups are used in the ligand or the binding site.

4. DE NOVO DRUG DESIGN

It should be possible to design a drug based on the structure of a binding site – a process known as the de novo drug design . by knowing which amino acids are present in the binding site and where they are positioned, it should be possible to identify the binding interactions that could take place and then design a molecule that will fit and have the necessary functional groups to interact with the amino acids residues, there has

been successin designing lead compounds by de novo dasign , especially in the area of thymidylate kinase inhibitors.

5. PROTEIN STRUCTURE

The protein structure can be determined it by x-ray crystallography if suitable crystals can be obtained. The structures of proteins belonging to the same family can be modeled using a known protein as a template. These projects involve the School's computational chemistry group, led by Dr Richard Bryce⁴. His group also develops new computational approaches, with a focus on molecular dynamics, solvation, hybrid QM/MM methods and carbohydrate modeling. NMR spectroscopy in conjunction with molecular modeling and other spectroscopic methods allows in the investigations to be made into molecular mechanisms of ligand-target recognition at the atomic level. This provides a description of the region of target and drug surfaces involved in the interaction, and important contacts between drug and target responsible for affinity and specificity. The structural analysis of DNA/RNA-ligand interactions by high-field NMR is crucial to define structure-function correlations. This information is a necessary component in the design of novel therapeutics and in prediction of interactions of drugs with the targets .*For example*, the group can analyze the shapes of macrolide antibiotics bound to ribosomes. Also over the years, the group has studied details of binding of ligands to the minor groove of DNA, such as Hoechst 33258, or to tRNA. NMR methods are also used by the group to study interactions of proteins with ligands. There is 300 MHz instrumentation in the School, and the group has shared usage of 500 MHz high-field instruments housed in

the Department of Chemistry. The group collaborates extensively with Professor Gareth Morris, inventor and pioneer of many modern NMR techniques, there by bringing novel techniques to bear on red biological problems.

6. BIOINFORMATICS IN COMPUTER-AIDED DRUG DESIGN⁶

A few years ago, the National Institutes of Health (NIH) created the Biomedical Information Science and Technology Initiative (BISTI) to examine the current state of bioinformatics in the United States. BISTI's working definition of bioinformatics included its use in biomedical research, in particular for drug discovery and development programs. Bioinformatics was seen as an emerging field with the potential to significantly improve how drugs are found, brought to clinical trials and eventually released to the market place .Computer-Aided Drug Design (CADD) is a specialized discipline that uses computational methods to simulate applications and data bases. As such, there is considerable overlap in CADD research and bioinformatics.

7. BIOINFORMATICS HUB

The bioinformatics and computational biology are often used interchangeably .however bioinformatics more properly refer to the certain and advancement of algorithms, computational and statically techniques, and theory to solve formal and practical problems posed by or inspired from the analysis of biological data. Bioinformatics can be thought of as a central hub that unites several disciplines and methodologies .On the support side of the hub, Information Technology ,Information Management,

software applications, databases and computational resources all provide the infrastructure for bioinformatics. On the scientific side of the hub, bioinformatics methods are used extensively in molecular biology, genomics, proteomics, other emerging areas (*i.e.* metabolomics, transcriptomics) and in CADD research. There are several key areas where bioinformatics supports CADD research.

8. VIRTUAL HIGH-THROUGHPUT SCREENING (vHTS)

Ligand based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest .Pharmaceutical companies are always searching for new leads to develop into drug compounds. One search method is virtual high-throughput screening. In vHTS , protein targets are screened against databases of small molecule compounds to see which molecules bind strongly to the target. If there is a "hit" with a particular compound, it can be extracted from the database for further testing. With today's computational resources, Several million compounds can be screened in a few day son sufficiently large clustered computers. Pursuing a Handful of promising leads for further development can save researchers considerable time and expense. ZINC is a good example of a vHTS compound library.

9. SEQUENTIAL ANALYSIS

In CADD research, Major parts of bioinformatics. under knows the genetic sequence of multiple organisms or the amino acid sequence of proteins from several species. It is very useful to determine how similar or dissimilar the

organisms are based on gene or protein sequences. With this information one can infer the evolutionary relationships of the organisms, search for similar sequences in bioinformatics databases and find related species to those under investigation. There are many bioinformatics sequence analysis tools that can be used to determine the level of sequence similarity.

10. HOMOLOGY MODELING

Another common challenge in CADD research is determining the 3-D structure of proteins. Most drug targets are proteins, so it's important to know their 3-D structure in detail. It's estimated that the human body has 500,000 to 1 million proteins. However, the 3-D structure is known for only a small fraction of these. Homology modeling is one method used to predict 3-D structure. In homology modeling, the amino acid sequence of a specific protein (target) is known, and the 3-D structures of proteins related to the target (templates) are known. Bioinformatics software tools are then used to predict the 3-D structure of the target based on the known 3-D structures of the templates. MODELLER is a well-known tool in homology modeling, and the SWISS-MODEL Repository is a database of protein structures created with homology modeling.

11. SIMILARITY SEARCHES

A common activity in biopharmaceutical companies is the search for drug analogues. Starting with a promising drug molecule, one can search for chemical compounds with similar structure or properties to a known compound. There are a variety of methods used in these searches, including sequence similarity, 2D and 3D shape similarity, substructure

similarity, electrostatic similarity and others. A variety of bioinformatics tools and search engines are available for this work.

12. DRUG LEAD OPTIMIZATION

When a promising lead candidate has been found in a drug discovery program, the next step (a very long and expensive step) is to optimize the structure and properties of the potential drug. This usually involves a series of modifications to the primary structure (scaffold) and secondary structure (moieties) of the compound. This process can be enhanced using software tools that explore related compounds (bioisosters) to the lead candidate. Open Eye's WABE is one such tool. Lead optimization tools such as WABE offer a rational approach to drug design that can reduce the time and expense of searching for related compounds.

13. PHYSICOCHEMICAL MODELING

Drug-receptor interactions occur on atomic scales. To form a deep understanding of how and why drug compounds bind to protein targets, we must consider the biochemical and biophysical properties of both the drug itself and its target at an atomic level. Swiss-PDB is an excellent tool for doing this. Swiss-PDB can predict.

14. BASICS OF DRUG DESIGN

It is a process which involves the identification of a compound that displays a biological profile and ends when the biological profile and chemical synthesis of the new chemical entity are optimized¹. Drug designing is other wise

known as rational drug design and it is a method of finding new medications based on the biological receptors and target molecules. It involves the designing of small molecules which is complementary to the biological receptor to which they bind and interact to cause the pharmacological actions. 2. Modern method of drug designing is done with the aid of computers and hence the process is known as Computer Assisted/Aided Drug Design (CADD). It uses computational chemistry to study about the drugs and related biological active molecules. The major aim is to find whether the given molecule bind to the target and causes pharmacological actions or not. The basic steps involved in CADD are:

- Hit identification using virtual screening.
- Hit-to-lead optimization of affinity and selectivity.
- Lead optimization of other pharmaceutical properties maintaining affinity.
- In the present article, we discussed about structure based drug designing and ligand based drug designing softwares and their therapeutic potential in the field of medical research.

15. DRUG DESIGNING SOFTWARES^{17,18}

A computer needs software for its functions such as programs. This software makes our work simpler and faster. Various companies such as Accelrys, Schrodinger, Auto Dock and Argus Lab offering drug designing softwares.

15.1. Accelrys

Accelrys is a software company with its headquarters in US, along with its

organization in Europe and Japan. It provides softwares especially for drug discovery and materials science. Their products and technologies create solutions for several stages in the drug discovery and developmental process⁴. The different softwares produced by Accelrys are:

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

15.2. Insight II

Insight II is a graphical molecular modeling program. Using this software we can build and manipulate virtually any class of molecules or molecular systems. Some of these insight II computational engines have the capacity to restart calculations from in formations in the saved files.

15.3. Pipeline Pilot

Pipeline Pilot datas are based on powerful client-server platform that leads to construct graphical workflows for data retrieval, filtering, analysis, and reporting. Data modeling in this software is done by modeling tools, statistical filters and clustering components optimized for large real-world data sets. One can create additional components using various technologies such as Perl, Java, SOAP and basic command line access. This software is used for sequence analysis, gene expression, in cheminformatics to study the ADME properties of the drug and check the toxic constituents present in the drugs.

15.4. Discovery Studio

Discovery studio is the advanced software solutions for life science researchers and

is easy to use, a graphical interface for powerful drug design and protein modeling, sequence analysis, pharmacophore analysis and it is a structure based designing software. Discovery studio provides a visualizing tool ActiveXcontrol, which provides 3D molecular structures and sharing scientific results. The sequence analysis is done by using tools such as BLAST (Basic Local Alignment Search Tool) and protein modeling by DS Modeller. It can be operated in different operating system applications such as Linux and Windows based environment.

15.5. Materials Studio

Materials studio software is the most advanced technology and is used to solve the problems in R&D process. It is designed for structural and computational researchers in chemicals and materials R&D. Materials studio provides tools for modeling crystal structure and crystallization processes; property prediction for molecules, polymers, catalysts and for determining the structure activity relationship. They provide various ranges of quantum mechanics based tools for predicting structures, density functional methods, linear scaling and semi-empirical tools. QSAR integration in the Materials studio has wide range of descriptors such as topological and electro-topological descriptors, these helps the calculation process easier.

15.6. Accord

Accord is software specially designed for cheminformatics. They can capture, manage, analyze, and mine chemical data. Accord is oracle based software used for storage, retrieval, analysis of chemical structures and related biological, chemical and inventory data. Accord is user friendly and is powered by Robust and

well proven chemistry engine that can be used for any type of chemistry.

15.7. Schrodinger

Schrodinger software provides accurate, reliable and high performance computational technology and provides facilities to solve problems in life science research. It was used for molecular modeling and well suited for drug designing both structure based and ligand based methods. Most of the pharmaceutical companies, biotechnology companies, government agencies, universities and supercomputing centers are using this software¹⁰. The various products of Schrodinger are:

- Glide
- Prime
- Jaguar
- Macro Model

15.8. Glide

Glide offers a complete solution for ligand-receptor docking with speed and accuracy. Glide works with HTVS- High Throughput Virtual Screening mode in which it can retrieve million compound libraries, to Standard Precise (SP) mode in which it docks hundreds to thousands of ligands with high accuracy. From SP it switches to XP Extra Precision where the false results are changed by advanced scoring. They can also exhibit excellent range of docking accuracy across diverse range of receptors. This makes the glide universally applicable.

15.9. Prime

Prime is a package used for protein structure predictions. It is user friendly. Prime provides users complete control over calculational settings to increase the accuracy of the result, they provide accurate receptor models for structure based drug design. Homology modeling

and fold recognition can be done using prime. Comparative modeling is used to generate accurate homology models for further structure based studies. Threading and fold recognition techniques are used in cases of low or no sequence identity. Prime allows the users to specify and adjust parameters to optimize the quality of predictions.

16. DRUG BIOAVAILABILITY AND BIOACTIVITY

Most drug candidates fail in Phase III clinical trials after many years of research and millions of dollars have been Spent on them. And most fail because of toxicity or problems with metabolism. The key characteristics for drugs are Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET) and efficacy-in other words bioavailability and bioactivity. Although these properties are usually measured in the lab, they can also be predicted in advance with bioinformatics software.

17. BENEFITS OF CADD

CADD methods and bioinformatics tools offer significant benefits for drug discovery programs.

17.1. Cost Savings

The Tufts Report suggests that the cost of drug discovery and development has reached \$800 million for each drug successfully brought to market. Many biopharmaceutical companies now use computational methods and bioinformatics tools to reduce this cost burden. Virtual screening, lead optimization and predictions of bioavailability and bioactivity can help guide experimental research. Only the most promising experimental lines of inquiry can be followed and experimental

dead-ends can be avoided early based on the results of CADD simulations.

17.2. Time-to-Market

The predictive power of CADD can help drug research programs choose only the most promising drug candidates. By focusing drug research on specific lead candidates and avoiding potential “dead-end” compounds, biopharmaceutical companies can get drugs to market more quickly.

17.3. Insight

One of the non-quantifiable benefits of CADD and the use of bioinformatics tools is the deep insight that Molecular models of drug compounds can reveal intricate, atomic scale binding properties that are difficult to envision in any other way. When we show researchers new molecular models of their putative drug compounds, their protein targets and how the two bind together, they often come up with new ideas on how to modify the drug compounds for improved fit. This is an intangible benefit that can help design research programs.

CADD and bioinformatics together are a powerful combination in drug research and development. An important challenge for us going forward is finding skilled, experienced people to manage all the bioinformatics tools available to us, which will be a topic for a future.

17.4. Speed up Drug Development

Researchers in Germany report an advance toward the much awaited era in which scientists will discover and design drugs for cancer, arthritis, AIDS and other diseases almost entirely on the computer, instead of relying on the trial-and-error methods of the past. In the report, Michael C. Hutter¹² and colleagues note that

computer-aided drug design already is an important research tool. The method involves using computers to analyze the chemical structures of potential drugs and pinpoint the most promising candidates. Existing computer programs check a wide range of chemical features to help distinguish between drug-like and nondrug materials. These programs usually cannot screen for all features at the same time, an approach that risks overlooking promising drug-like substances. In the new study, researchers describe a more gradual and efficient system. Their new program uses an initial quick screen for drug-like features followed immediately by a second, more detailed screen to identify additional drug-like features. They applied this new classification scheme to a group of about 5,000 molecules that had previously been screened for drug-like activity. The new strategy was more efficient at identifying drug-like molecules “whereby up to 92 percent of the non drugs can be sorted out without losing considerably more drugs in the succeeding steps,” the researchers say.

18. CONCLUSION

The process of drug discovery and development is long and difficult one and the cost of new therapeutic agents are increasing rapidly. The use of new software in modern CADD technology has the ability to accomplish both of these goals and to improve the process as well, thus reducing cost. CADD approaches aim to increase the speed and efficiency in the drug discovery process. CADD is, however, not a direct route to new drugs, but it provides a somewhat more detailed map to the goal. The hope is that providing bit and pieces of information, and by helping to coordinate the information, CADD will help to make the

drug design process more rational. The many success stories of the use of CADD in the discovery of new drugs shows the utility of such analyses used in close coupling with traditional medicinal chemistry techniques. Computer-Aided Drug Design is a natural outgrowth of theoretical chemistry, the traditional role of which involves the creation and dissemination of a penetrating conceptual infrastructure for the bioinformatics, chemical sciences, particularly at the atomic and molecular levels. The mathematical sciences have been indispensable allies and have provided the vital tools for that role. Computer-Aided Drug Design is central to rational drug design, it contributes to the selection and synthesis of new materials, and it guides the design of catalysts. New quantum mechanical techniques underlie the understanding of electronic properties of materials and have advanced the level of precision at which molecules of at least moderate size can be modeled¹⁵. The marketed growth of Computer-Aided Drug Design inevitably has involved a substantial investment of skilled human resources and to expensive computing resources. Both of these types of commodities are relatively scarce and are subject to competition between alternative scientific and technological disciplines. Reports show that the heavy dependence of these chemistry codes on mathematical software such as LINPACK and EISPACK¹⁶. The productivity of these computational resources, broadly construed, must be an issue for continual analysis and informed action by policy makers. In particular, the strong mathematical flavor of Computer-Aided Drug Design leads to a natural examination of the efficacy of links between mathematical and the chemical sciences, and to the past, present, and

future roles of interdisciplinary research at the interface between these subjects. The issues constitute basis concerns for the present study.

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TABLE 1- Drug Designing Software

Drug Designing Software	Types	Therapeutic potential
Insight II	Structure based	Graphical molecular modeling
Pipeline Pilot	Structure based	Gene sequence analysis
Discovery Studio	Structure based	Protein modeling
Materials studio	Structure based	Modeling crystal structures
Accord	Structure based	Cheminformatics
Glide	Ligand based	High Throughput Virtual Screening
Prime	Structure based	Protein structure prediction
Jaguar	Structure based	Gas and solution phase reaction
Macro Model	Ligand based	Docking of ligand and target molecule
Argus lab	Ligand based	Build molecules using templates