Review Article

Computer aided drug designing

Sehgal VK, Das S, Vardhan A

[1]Dr Vijay Kumar Sehgal
Associate Professor
[2]Dr Supratik Das
Post Graduate Student
suprateek123@yahoo.co.in
Dr Anand Vardhan
Senior Resident
Andaman and Nicobar Institute of Medical Sciences
Port Blair, India
varanand.26@gmail.com
[1,2,3]Department of Pharmacology
[1,2]Govt. Medical College, Patiala
Punjab, India

Received: 23-08-2016
Revised: 29-09-2016
Accepted: 26-10-2016

Correspondence to:
Dr Vijay Kumar
vijayksehgal@yahoo.com

ABSTRACT

Designing of drugs and their development are a time and resource consuming process. There is an increasing effort to introduce the role of computational approach to chemical and biological space in order to organise the design and development of drugs and their optimisation. The role of Computer Aided Drug Designing (CADD) are nowadays expressed in Nanotechnology, Molecular biology, Biochemistry etc. It is a diverse discipline where various forms of applied and basic researches are interlinked with each other. Computer aided or in Silico drug designing is required to detect hits and leads. Optimise/ alter the absorption, distribution, metabolism, excretion and toxicity profile and prevent safety issues. Some commonly used computational approaches include ligand-based drug design, structure-based drug design, and quantitative structure-activity and quantitative structure-property relationships. In today's world, due to an avid interest of regulatory agencies and, even pharmaceutical companies in advancing drug discovery and development process by computational means, it is expected that its power will grow as technology continues to evolve. The main purpose of this review article is to give a brief glimpse about the role Computer Aided Drug Design has played in modern medical science and the scope it carries in the near future, in the service of designing newer drugs along with lesser expenditure of time and money.

Keywords: *Computer-aided drug design, structure based drug design, ligand-based drug design, pharmacophore model, molecular modelling*

Introduction

Drugs are essential for the prevention and treatment of disease. Thus, ideal drugs are in great demand. But the process of Drug design is a tedious, time-consuming and cost intensive process. Thus several approaches are required which collectively would form the basis of Computer Aided or In Silico Drug Designing.[1] Use of computational methods in drug discovery and development process are nowadays gaining popularity, implementation and appreciation. Different terms are being applied to this area, including computer-aided drug design (CADD), computational drug design, computer-aided molecular design (CAMD), computer-aided molecular modeling (CAMM), rational drug design, In Silico drug design, computer-aided rational drug design.[2] All the world's major pharmaceutical and biotechnology companies use computational design tools. At their lowest level the contributions represent the replacement of crude mechanical models by displays of structure which are a much more accurate reflection of molecular reality capable of demonstrating motion and solvent effects. Beyond this, theoretical calculations permit the computation of binding free energies and other relevant molecular properties.[3] Extensive genome decoding of various organisms, including man, proteomic investigations, discoveries of molecular mechanisms of many diseases, advances of protein chemistry lead to dramatic increase of number of new potential targets.[4] During the last decades the field of drug discovery process that direct to new ligands finding turns into the modern science employing of computer, bioinformatic and experimental approaches, which are denominated as rational drugs design which consist of computational drug designing.[4]

Computer Aided Drug Design (CADD) and Delivery Systems offers an in-depth discussion of the computer-assisted techniques used to discover, design, and optimise new, effective, and safe drugs.[5] The objective of drug design is to find a chemical compound that can fit to a specific cavity on a protein target both

geometrically and chemically.[5] The use of computers and computational methods permeates all aspects of drug discovery today and forms the core of structure-based drug design.[6] The day is not far away when Computer Aided Drug Designing will be dominant in modern medical services, thus the purpose is to bring forward, the significant advancements, which Computer Aided Drug Designing has made to serve mankind in producing newer drugs with improved effects.

A Brief History of CADD

In 1900, the concept of receptor and lock-and-key was given by P.Ehrich (1909) and E. Fisher. In 1970s, the concept of Quantitative structure-activity relationships (QS- AR) was established, it had Limitations: 2- Dimensional, retrospective analysis; in 1980s there was Beginning of an era of CADD Molecular Biology, X-ray crystallography, multi-dimensional NMR Molecular modeling alongwith computer graphics. In1990s more modern techniques like Human genome Bioinformatics alongwith Combinatorial chemistry and High-throughput screening were introduced in the world of innovative medical science.[3]

How Does CADD Work?

Computer aided drug designing process consists of 3 stages:

Stage 1: Involves identification of therapeutic target and building a heterogenous small molecule library to be tested against it. There is development of virtual screening protocol initialised by docking of small molecules

Stage 2: The selected hits are checked for specificity by docking at binding sites of other known drug targets.

Stage 3: The selected hits are subjected to computational ADMET profiling studies and those who pass these studies are called leads.[6]

 # Target Identification

It is the first key stage in the drug discovery pipeline. Identification of correct targets from thousands of candidate macromolecules is a tedious process, which can be achieved by literature referring, Genomic analysis, pathway analysis.[6]

 # Target Validation

After target identification, a rigorous evaluation is needed to demonstrate that modulation of target will have desired therapeutic effect. Target validation process determines whether modulation of target will have desired therapeutic effect.[1]

 # Lead

Leads can be identified with the help of techniques like Structure based design. At this point, the structure of the target protein in complex with the lead molecule can be extremely useful in suggesting ways to improve the affinity of the lead for the target.

Leads which are used in this case may be far from perfect, thus they should be optimised in order to increase their affinity for the target sites. Optimisation may be obtained by altering their structural features.[7]

 # IN SILICO ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) Prediction

Techniques like molecular modelling, data modelling are used to study the interaction of proteins involved in ADMET process.[8]

Parameters considered for drug design

Whole Genome Sequence Analysis

Drug design is incomplete without human genome project. With the help of Genetic Code, the complete Genome has been utilised to find the nature and structure of the receptors. Once the structure of receptor is known it becomes easy to design a molecule (drug) which can bind to it.[9]

Structure activity relationship determination

This is done with the help of tool 3DQSAR (Quantitative Structure Activity Relationship). It is used to help guide chemical synthesis. It is responsible for quantifying relationship between structure and biological data and is useful for optimizing the groups that modulate the potency of the molecule.[10]

ADME (Absorption, Distribution, Metabolism, Excretion)

The description of drug distribution and elimination are often called drug disposition. Characterisation of drug disposition is important for determination of dosing intervals.[11]

The processs of structure based drug design comprises of the following points:

- A preparation of the chosen target should be made in a solution form and its structure should be determined by the help of Crystallography.
- Proper analysis of the structure should be made in order to determine the binding sites.
- Different compounds from databases should be docked at binding site and then scored regarding its affinity for the site.
- Compounds which show the best affinity with the site are selected.
- Biochemical asays comprise of application of Leads and Tests which are made to bind at the target sites.

a) If the lead is found to be posing as an inhibitor at the site, then it should be analysed by crystallography regarding its structure.
b) It should be further tested for potency and bioavailability in order to launch it.
c) In Structure Based Drug Design, the action of the leads can be modified or optimised which would ensure higher success rates.[12]

Ligand based Drug Designing

a) Ligand Based Drug Designing comprises of the knowledge of molecules which bind to the desired target site.
b) These molecules may be used to derive a Pharmacophore model
c) Pharmacophore model is defined as a molecule which is having necessary structural abilities to bind to a desired target site.
d) Once the Pharmacophore is identified, it is then determined whether it is fit for the receptor, otherwise Pharmacophore is modified further in order to make it a potential drug.[13]

Software requirement[6] : The commonly used softwares for Computer Aided Drug Designing are given below:

Programs	Company
TOPKAT, Tsar, LigandGel, ZDOCKPro, DS MedChem Explorer, AEI,	Accelrys
ACD/LogD Suite and ACD/Log Sol Suite, ACD/LogD Batch and ACD/Log Sol Batch, ACD/Structure Design Suite, ACD/PhysChem batch	ACD/Labs
ADMET Modeler, ADMET Predictor, Class Pharmer 4.0, GastroPlus, DDDPlus	Simulations Plus, Inc.
ToxML, LeadScope Toxicity Database, LeadScope Known Drugs Databases, LeadScope Enterprise, LeadScope Personal	LeadScope
Algorithm Builder, QSAR Builder, ADME Boxes v. 3.0, Tox Boxes v. 1.0, ADME/Tox WEB, DMSO Solubility, ADME Batches, Absolv	Pharma Algorithms

Sl. No.	Software name	Company/institution	Provided utilities and URL
1	Insight II, Discovery studio, Cerius	Accelrys	Molecular modeling and de novo drug design. http://www.accelrys.com/products
2	Sybyl	Tripos	Computational informatics software for drug discovery. http://www.tripos.com
3	Phase, Glide, Liasion	Schrodinger	Pharmacophore modeling, Ligand-receptor docking. http://www. Schrodinger.com
4	Bio-suite	Tata consultancy services	Genomics, Protein modeling, structural analysis, simulation and drug design. http://www. Atc.tcs.com/biosuite
5	Sanjeevini	Indian institute of technology, Delhi	Active site directed drug design http://www.scfbioitd.in/research/drugdesign.htm

Benefits of CADD

- Cost savings: Many biopharmaceutecal companies use CADD in order to reduce cost burden.[9]
- Traditional experimentation requiring animal and human models are now replaced by CADD, which saves both time and cost.[14]
- It is hoped that in case of certain diseases like Influenza, Computational Drug Designing will play an important role in reducing the chances of drug resistance and thus would lead to production of lead compounds which would target the causative factor.[14]
- Taking advantage of computational methods, potent hits can be obtained in a
- Matter of weeks.CADD has also led to construction of high quality datasets and libraries that can be optimised for high molecular diversity or similarity.[15]

Limitations in CADD:

- Lack of accurate experimental data that restricts further advancement of CADD.[6]
- Some procedures concerning Computer Aided Drug Designing are time consuming, specially while looking for a proper lead component.[16]

Future prospects

- Computer Aided Drug Designing will be beneficial for pharmaceutical development, but the extent of that role needs to be seen.
- According to experts, the companies which can successfully implement CADD will probably beat those in competition which still use old fashioned ways.
- This technique is hoped to be more pocket friendly.[6]

Conclusion

In today's world, Computer Aided Drug Design, its application and development has made great progress in order to make a significant impact in both industry and academics. CADD approach provides valuable information for target identification and validation, lead selection, small-molecular screening and optimization, but still, it needs to be kept in mind that experimental tests have a role to play in this field. Due to large scale usage of CADD in industrial field, propelled by increasingly powerful technology and distributed computing for large-scale screening initiatives, the effective cost for making new drug molecules has reduced.cases of drug resistance against some diseases can also be dealt nowadays. Due to this gift of Computer Aided Drug Designing, new drug molecules can stil be designed by altering the structure of molecules of conventional drugs, which can play a beneficial role in counteracting drug resistance and improving patient compliance.

In the future, it is expected that Computer Aided Drug Designing will comprise of integration of computer aided chemistry and biology, along with chemoinformatics, bioinformatics, thus leading to creation of a new field Pharmacoinformatics. Nowadays, Computational approach for Drug designing is grabbing more attention as everyone is keen on saving time and money and aiming for more profit at lesser time, specially in case of industries. There was a time where design of newer drug molecules was tedious process, which would consume time and money, but due to advent of this technique and especially numerous researches on this topic we can say that the impossible has been made possible. Also, the new molecules designed by it may be used as a probe for further research thus ensuring CADD a bright future in coming years.

References

1. Kumar SC. An Insight to Drug Designing by in Silico approach in Biomedical Research. J Pub Health Med Res 2013;1(2):63-5.
2. Kapetanovic IM. Computer Aided Drug Discovery and Development: in silico-chemo-biological approach. Chem Biol Interact 2008; 171(2):165–76.
3. Kore PP, Mutha MM, Antre RV, Oswal RJ, Kshirsagar SS. Computer-Aided Drug Design: An Innovative Tool for Modeling. Open Journal of Medicinal Chemistry 2012; Nov2:139-48.
4. Veselovsky AV, Ivanov AS. Strategy of Computer-Aided Drug Design. Current Drug Targets - Infectious Disorders 2003;3:33-40.

5. Rahman MM, Karim MR, Ahsan MQ, Khalipha ABR, Chowdhury MR, Saifuzzaman M. Use of computer in drug design and drug discovery: a review. International Journal of Pharmaceutical and Life sciences 2012;1(2):1-21.
6. Bharath EN, Manjula SN, Vijaychand A. In Silico Drug Design tool for overcoming the innovation deficit in the drug discovery process. International journal of Pharmacy and Pharmaceutical sciences 2011;3(2):1-5.
7. Kumar GP, Pushpa A, Neeta S, Suhasini HB. In Silico modelling and drug design- A review. IRJP 2011;2(9):15-7.
8. Waterbeemd HVD, Gifford E. ADMET in silico modelling: Towards prediction paradise? Nature Reviews Drug Discovery 2003;2:191-204.
9. Galperin MY, Koonin EV. Comparative Genome Analysis. Baxevanis AD, Francis Ouellette B, editors. Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins. 2nd ed. New York: A John Wiley & Sons; 2001.p.359-92.
10. Borman S. New QSAR Techniques Eyed for Environmental Assessments. Chem Eng News 1990;68:20-3.
11. Verlinde CLMJ, Hol WGJ. Structure-based drug design: progress, results and challenges. Structure 1994;2(7):577-87.
12. Anderson AC. The process of Structure Based Drug Design. J Chembiol 2003;10:787-97.
13. Crasto AM. All About Drugs. Mumbai, India:[Publisher unknown]; Available from: http://www.allfordrugs.com/drug-design/
14. Mallipeddi PL, Kumar G, White SW, Webb TR. Recent Advances in Computer-Aided Drug Design as Applied to Anti-Influenza Drug Discovery. Current Topics in Medicinal Chemistry 2014;14:1875-89.
15. Ou- Yang SS, Lu JY, Kong XQ, Liang ZJ, Luo C, Jiang H. Computational drug discovery. Acta Pharmacologica Sinica 2012;33:1131–40.
16. Jorgensen WL. The Many Roles of Computation in Drug Discovery. Science 2004; 303:1813-17.

Cite this article as: Sehgal VK, Das S, Vardhan A. Computer aided drug designing. Int J Med and Dent Sci 2017; 6(1):1433-1437.