

A Review of Computational Tools for Designing Drugs Used by General Practitioners

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Abstract

The presented review is based on the survey of various computational tools that are being used to design novel compounds commonly referred as drugs. These drugs are commonly used in general practice by licensed professionals including physicians, chemists, pharmacists, doctors, etc. These drugs include drugs for depression, stress, fever, etc.

Keywords: General practitioners; General practice; Computational tools

Introduction

The process of designing new molecules and compounds in order to get new biological, chemical and physical properties is a very long and laborious process. Drug is a key molecule used to inhibit a particular molecular pathway or for the enhancement in the synthesis of biological macromolecules. In general practice, the general practitioners [1] use several kinds of drugs to deal with the common diseases and health problems. These drugs sometimes get resistant to the human body. In order to avoid antibiotic resistance, scientists have been trying to develop newly designed drugs with more efficiency. Designing a drug molecule against any disease needs the knowledge of both the protein which is responsible for its occurrence together with the molecular pathway of its transmission in the human body. This knowledge is further implemented and used in order to get a compound or molecule against the target protein. Traditionally, the process of drug designing was very time consuming, tedious and cost effective. Previously, many molecules and compounds were needed to be synthesized and tested in different organisms to obtain a suitable class of compound that can have the desired profile for a drug with lesser side effects. The random screening of a large number of compounds and a chance discovery of a lead compound out of them is a typical process that takes approximately 14 years and over \$800 million [2]. It was length expensive and intellectually inelegant.

Computer aided drug design (CADD) is a widely-used term that represents computational tools and servers used for the modeling, analysis and storage of compounds [2]. It includes development of databases for the study of chemical interaction relationships, computer programs for designing compounds with interesting physicochemical properties, as well as tools for the identification of potential lead candidates before they are synthesized and tested in wet laboratories. CADD is broadly categorized into two groups- a) Ligand based drug design and, b) Structure based drug design. In the ligand based drug design, a model, say, QSAR model, of the target protein is built based on the knowledge of the ligand that binds to it, and this model is then used to design new molecules that interact with the target protein for their inhibitory or stimulatory activity [3]. On contrary, structure

based drug design has the knowledge of the structure of target protein obtained through X-ray Crystallography and NMR spectroscopy [4]. This knowledge is used to design a ligand that can have the best binding affinity with the target and can be further used as a lead compound against the protein.

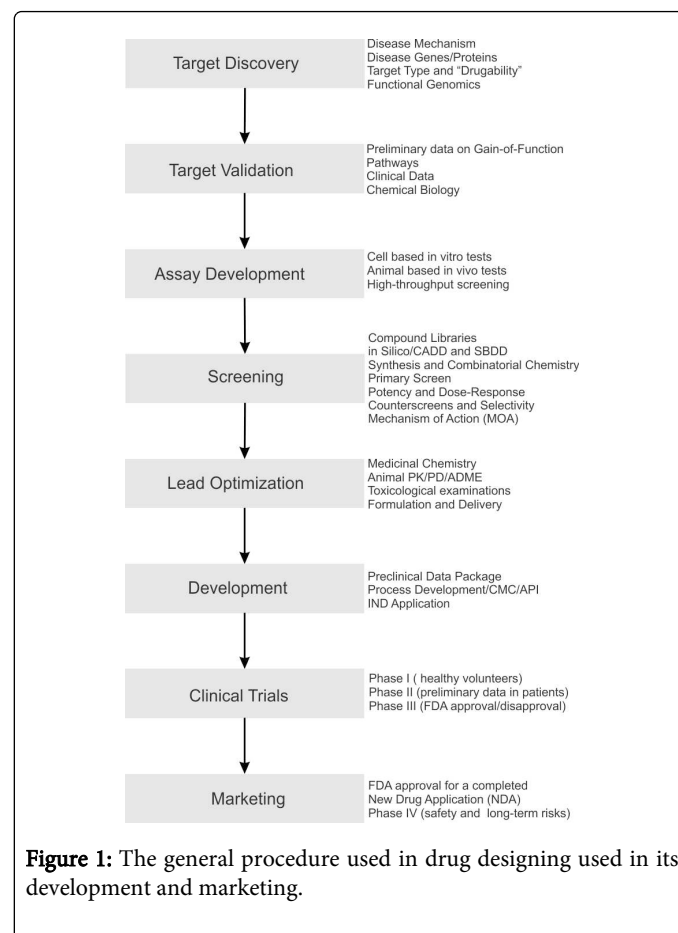


Figure 1: The general procedure used in drug designing used in its development and marketing.

Molecular Modeling

Molecular modeling is a computational technique to design the structure of novel compounds. It mimics the behaviour of molecules to design a newer molecule with better activity [4]. It is used in the fields of computational chemistry, drug design, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules [5]. The common feature of molecular modeling techniques is the atomistic level description of the molecular systems. Molecular modeling has become an important technique in the study of various biological pathways that include protein folding, protein stability, enzyme catalysis and identification of novel proteins, and other macromolecules [6]. There are various modeling softwares available online that have allowed the researchers to create biological models and modify them by the addition or removal of moieties and change in the covalent bonds, bond angles, interactions, etc as per their need. Table 1 is a list of modeling softwares that are generally used in the modeling of 3D structures of proteins.

S.No.	Name of Software	Description	Reference
1.	DeepView-Swiss PdbViewer	It provides an user friendly interface allowing to analyze and model proteins	Johansson [7]
2.	CCP4	It is used for macromolecular structure determination	Winn et al. [8]
3.	Modeller	It involves homology or comparative modeling of protein three-dimensional structures	Eswar et al. [9]
4.	UCSF Chimera	It is a modeling program for interactive visualization and analysis of molecular structures	Lin et al. [10]
5.	Abalone	It is a modeling program focused on molecular dynamics of biopolymers	http://www.biomolecular-modeling.com/Abalone/
6.	Tinker	It is a package for molecular mechanics and dynamics, with some special features for biopolymers	http://dasher.wustl.edu/ffe/
7.	Geno3D	Geno3D is an automatic web server for protein molecular modelling.	Combet et al. [11]

Table 1: List of Molecular modeling softwares.

Virtual Screening

Virtual screening is a computational technique that is used in drug designing to search libraries of small molecules in order to identify the structures of those compounds that may act as lead compounds with maximum affinity for a drug target that may be a protein or an enzyme [12]. Its basic aim is to score, rank and filter a set of chemical structures using one or more computational databases or other techniques. Virtual screening has been defined as the "automatically evaluating very large libraries of compounds" using computer

programs [13]. This method is accurate and allows the researchers to get an authenticated structure that may be used as a drug after further validations. Due to this, virtual screening has become an integral part of the drug discovery process [14].

Protein-Ligand Docking

Protein-ligand docking methods are used to recognize most favourable positions, orientations and conformations of a ligand or small molecule in a protein (<http://www.intechopen.com/books/protein-engineering-technology-and-application/protein-protein-and-protein-ligand-docking>). As, most of the diseases occurring in human body is due to the improper functioning of enzyme or a protein, this method is widely used during virtual screening of a lead compound for a target protein. It is also used to predict the position of any ligand that is already bound to the target in order to calculate and identify the active site. There are various softwares that enable the researchers to do the protein-ligand docking. Table 2 is the list of molecular docking softwares.

S.No.	Name of Software	Description	Reference
1.	Autodock	It involves automated docking of flexible ligands to macromolecules	(http://autodock.scripps.edu/).
2.	CombiBUIL D	It is a structure-based drug design program that is created to aid the design of combinatorial libraries	sandia.gov
3.	DockVision	It carries Monte Carlo, Genetic Algorithm, and database screening docking algorithms	http://www.dockvision.com/
4.	QM Polarized Ligand Docking	It carries the function of both Glide and Q-Site applications of Schrodinger Suit	Varga et al. [15]
5.	GOLD	It identifies correct binding modes of the active target molecules	http://www.ccdc.cam.ac.uk/Solutions/GoldSuite/Pages/GOLD.aspx
6.	Docking Server	It provides a web-based, easy to use interface for the molecular docking of protein and ligand	Bikadi et al. [16]
7.	SwissDock	It is a protein ligand server that is accessed via ExPASy	http://www.swissdock.ch/
8.	Click2Drug	It is accessed via ExPASy server	http://www.click2drug.org/

Table 2: List of Molecular docking softwares.

In the present era, two docking softwares namely Autodock 4.2 and Glide are very frequently used for CADD study. Glide 4.0 XP scoring function has been developed and implemented as the docking protocol to estimate protein-ligand binding affinities [17]. On the other hand, Autodock is reported to have utility in analysis of covalently-bound ligands, using both a grid-based docking method and a modification of the flexible side chain technique [18].

MD Simulation

MD Simulation is a computational method that is used to examine the dynamicity of the biological macromolecules. It calculates the time dependent behavior of a molecular system. MD simulation provides detailed information on the fluctuations and conformational changes of proteins and nucleic acids. These methods are now routinely used to inspect the structure, dynamics and thermodynamics of biological macromolecules and their complexes. They are also used in the determination of structures from X-ray crystallography and from NMR experiments. Molecular dynamics simulations allow the study of interactions occurring between different macromolecules during various cellular life processes (http://www.ch.embnet.org/MD_tutorial/pages/MD.Part1.html) together with the analysis of biological processes occurring in a living system. These include, for example,

Protein stability

Conformational changes

Protein folding

Molecular recognition: proteins, DNA, membranes, complexes

Ion transport in biological systems

One of the most commonly used MD simulation softwares is Gromacs [19]. It takes input files in PDB format and produces trajectory files that carry the information of each and every conformational change that would have occurred on each atom during simulation. By the use of several commands, it has permitted the researchers to study the stability and minimization of energy of proteins as well as protein bound complexes.

Conclusion

Nowadays, various new drug entities have been designed used for general practices. These drugs include antihypertensive agents, anti-inflammatory agents, drugs for ulcer therapy, immunosuppressive agents, etc [20]. These drugs carry several side effects and reactions to the human body. In order to overcome them, bioinformaticians have tried to design newer and more efficient drugs with lesser side effects. For the drug designing, the tools discussed are playing a major role in the enhancement of these modified drugs development.

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