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A REVIEW ON MULTI- COMPONENT REACTION AND DATA BASE SEARCHING FOR DRUG DESIGN

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ABSTRACT

It takes greater than 10 years to deliver a drug to the marketplace and expenses an average fee people $2.6 billion. Computer-aided drug design (CADD) saves up to 30% of the money and time of a drug improvement technique and has become an imperative part of research and improvement in pharmaceutical industries. CADD has been extensively divided in organizations: ligand-based drug design (LBDD) and shape-based drug design (SBDD). This bankruptcy covers fundamental standards, general workflows, associated equipment, applications, and modern challenges of various techniques in SBDD and LBDD.

KEYWORDS: Structure based drug design, Ligand-based drug design, Computer-aided drug design.

INTRODUCTION

Drug design is an inventine process of finding new medication based on knowledge of a biological target. computer aided drug design uses computational approaches to discover, develop and analyze drug and similar biological active molecules.[1]

Drug design especially therapeutic antibodies are an growing important class of drugs and computational methods for improving the affinity, selectivity, and stability of these protein-based therapeutics have also been developed.[2]

It is estimated that a typical drug discovery cycle, from lead compound an identification through to clinical trials, can take 14 years, with cost of 800 million US dollars.[3] The pharmaceutical industry is continuing to attempt double-digit growth rates driven by high market capitalization. Standard responses to this challenge have only provided limited impact. Besides scaling-up businesses through mergers or selective worship of platform technologies or drug candidates, an increase of Research and Development (R&D) productivity still represents a sure approach to address this challenge.[4]

The design of new antibiotics, computer-aided drug design (CADD) can be combined with wet-lab techniques to clarify the mechanism of drug resistance, to search for new antibiotic targets and to design novel antibiotics for both known and new targets. Notably CADD methods can produce an atomic level structure-activity relationship (SAR) used to facilitate the drug design process thereby minimising time and costs.[6,7]

Computer-aided drug design (CADD) provides a variety of tools and techniques that assist in the various stages of drug design, thereby reducing the cost of drug research and development time. Drug discovery and the development of a new drug is a long, complex, costly and highly risky process that has no equal in the commercial world.[5]

Computer-aided drug design (CADD)

It is computer-based technique used in the computational chemistry to discover, enhance or study of drug and related biologically active molecule is called as (CADD) Computer Aided Drug Design.

1. It is most useful in new drug design.
2. It provides knowledge about the chemical and biological properties of ligands and targets.
3. It is used to find and improve novel drug.
4. These are useful in new drug design.
5. It provides knowledge about the chemical and biological properties of ligands and targets.
6. It is used to find and improve novel drug Discovery of in-silico filters for prediction of
7. Undesirable properties like poor activityand poor Pharmacokinetic and Toxicity of drug molecule.
8. It is used for the optimization of novel drug targets.
9. By using chemical scaffolds to find out novel Virtual screening is applied for new drug molecules.

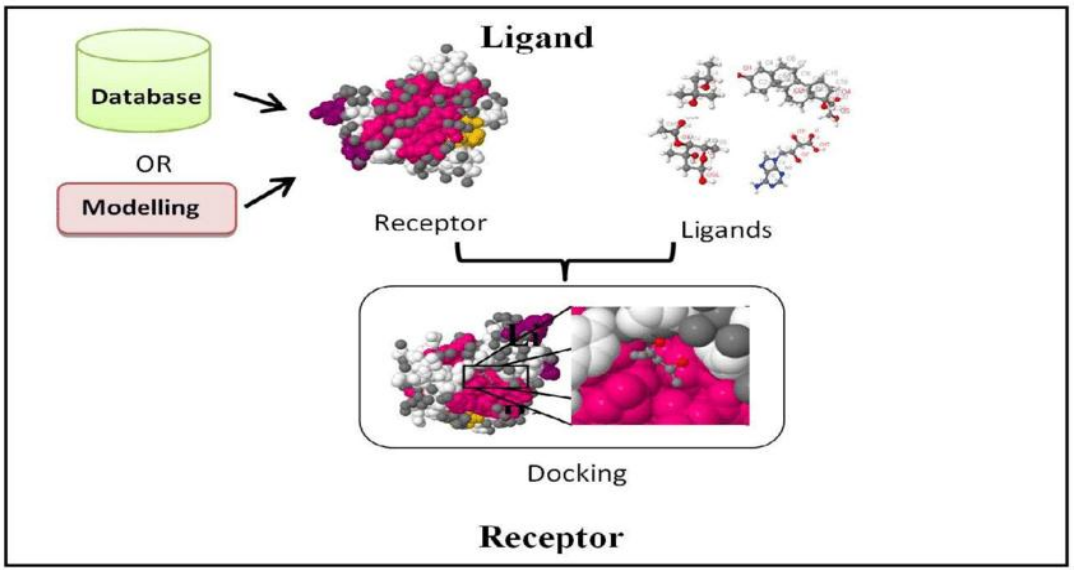

Fig. Molecular docking flow chart.

Pharmacophore

A pharmacophore describes the framework of molecular features that are vital for the biological activity of a compound.

Computer aided drug designe two types

1. Structure based drug design (SBDD)
2. Ligand based drug design (LBDD).

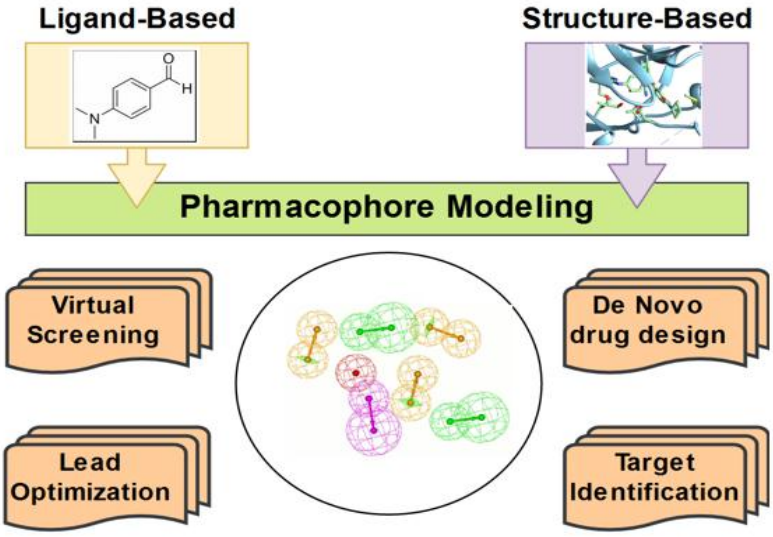

Fig. Pharmacophore modeling.

Structure based drug design (SBDD)

SBDD is an iterative process and it proceeds through multiple cycles leading an optimized drug candidate to clinical trials. Generally, a drug discovery process consists of four steps-

- Discovery phase,
- Development phase,
- Clinical trial phase,
- Registry phase.

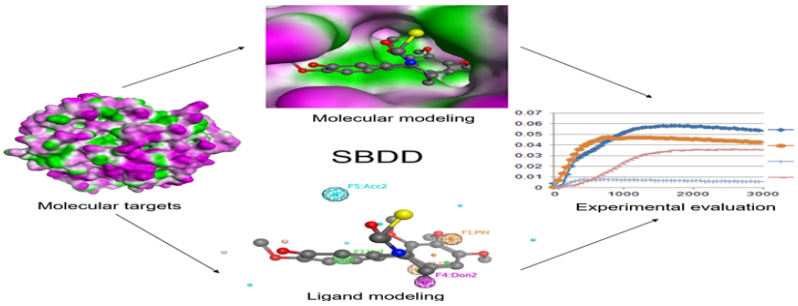

Fig. Structure based drug design (SBDD).

1. Homology modeling

Concept

Since the WHAT IF program (Vriend, 1990) performed well for the high-sequence-identity test cases in both CASP competitions, we decided to make this modeling program available as a WWW-based server that can be used for high-sequence-identity modeling tasks. The server is not as automatic as, for example, the SwissModel server (Peitsch, 1996); it does not search for the optimal template and it does not yet model insertions. The search for an optimal template will perhaps be implemented in the near future, but ab initio modeling of loops has, in the two CASP competitions, been proven to be too difficult for today's techniques (Dunbrack et al., 1997; Mosimann et al., 1995) (especially when limited CPU time is available, like in a WWWbased server set-up) and will only be implemented in the server after a major technical or scientific breakthrough. However, we are presently working on the incorporation of a module that will allow for the insertion of very short loops (one or two residues), and hope to make this module available soon.[8]

Homology modeling is based on the hypothesis that the 2 notably comparable sequences have similar structures. Threading or fold reputation is the method of desire if the goal sequences have the equal protein fold as that of regarded forms however there may be no template (>40% collection identification) structure to be had within the protein shape database. Ab

initio is the technique of choice to are expecting a protein shape whilst the goal collection lacks any comparable known structure or comparable fold in the structure database. Ab initio modeling considers the physicochemical properties of amino acids to predict the least electricity and solid conformation and is presently constrained to small proteins (<a hundred and twenty amino acids).[8,9]

Homology modeling is based on the hypoth

Esis that the two highly similar sequences have similar structures. Threading or fold recognition is the method-of-choice if the target sequences have same protein fold as that of known structures but there is no template (>40% sequence identity) structure available in the protein structure database. Ab initio is the method-of-choice to predict a protein structure when the target sequence lacks any similar known struc- ture or similar fold in the structure database. Ab initio modeling considers the phys- icochemical properties of amino acids to predict the least energy and stable conformation, and is currently limited to small proteins (<120 amino acids).

Applications

- It is used to one of the computational structure prediction methods that are used to determine protein 3D structure from its amino acid sequence.
- Homology modeling considered to be the most accurate of the computational structure prediction methods.
- It consists of multiple steps that are easy to apply.[10]

2. Molecular docking

Concept

Molecular docking is a method to identify of compounds generated by two or more separate molecules computationally. These is objective of docking studies is to anticipate the desired three-dimensional structures These possibilities are sorted using scoring functions to determine which structures are most likely to be present in nature. It is present study outlines the state of the art in several computational elements of molecular docking-based virtual screening of a library of small compounds docking techniques' scoring functions, as well as their relevance to protein and nucleic acid therapeutic targets.[10]

Applications

- Molecular docking is usedto the process of computer aided drug design (CADD). It can be applied in different such as:
- Predict the binding mode of already known ligands
- Identify novel and potent ligands
- As a binding affinity predictive tool.[11]

3. Virtual screening

Concept

Virtual screening isintegral part of the drug discovery process in. Related to the more general and longer pursued concept of database searching the term 'virtual screening' (VS) is relatively young. Walters *et al*. define virtual screening used as 'automatically evaluating computer programs. As this definition suggests, VS has largely been a numbers game focusing on questions like how can we filter down the enormous chemical space of $>10^{60}$ conceivable compounds to a manageable number that can be synthesized, purchased and tested.[12]

Applications

- Virtual screening is a technique used in drug discovery to search of small molecules in order to identify those structures which are bind to a drug target, typically a protein receptor or enzyme
- Virtual Screening can be used to select in house database compounds for screening, choose compounds that can be purchased externally, and to choose which compound should be synthesized next.[13,14]

4. Receptor-based pharmacophore modeling

Concept

The pharmacophore defined as the essential 3D arrangement of the features of a compound they are responsible for a biological effect. Early software tools for perceiving pharmacophores were initially developed in the 1970s, resulting in the commercial 3D searching software that entered the market in the early 1990s.

Pharmacophore modeling is one of the most successfully used tools in computer-aided drug design (CADD) today. This approach aids researchers in achieving the main objectives of CADD, which are to discover and/or design new drug candidat

https://scholar.google.com/scholar_lookup?journal=Ann+Rev+Biophys+Biomol+Struct&title=Ab+initio+protein+structure+prediction:+progress+and+prospects&author=R+Bonneau&author=D+Baker&volume=30&publication_year=2001&pages=173-189&pmid=11340057&es for use as new treatments or to design new drugs that are expected to be superior to the existing treatments. Pharmacophore modeling provides some unique capabilities both in terms of discovery of novel compounds, as well as identification of novel applications for existing compounds.[15]

Applications

3D-LBP and VS: Researchers have used a cocrystallized ligand as a bioactive molecule to develop an LBP model. Using validated LBP, the authors screened a large dataset to identify novel, selective, and submicromolar-range active in- hibitors.

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- It is used tobioactive molecule to develop an LBP modelUsing validated LBP.
- It is identity of micromolecular range.[8]

5. Molecular dynamics simulations

Concept

Computer simulation for the study of the dynamic behavior of molecules to understand the enigma behind the complexity of the biological world is a demanding task. It necessitates the need of optimally developed models capable of mimicking the cellular environment, physical forces that can simulate the laws of physics and thermodynamics, and provide dynamicity. Today, tools have been developed for molecular modelling, energy calculations, algorithms to simulate the chemical aspect of the real systems, docking-scoring techniques, etc., thereby

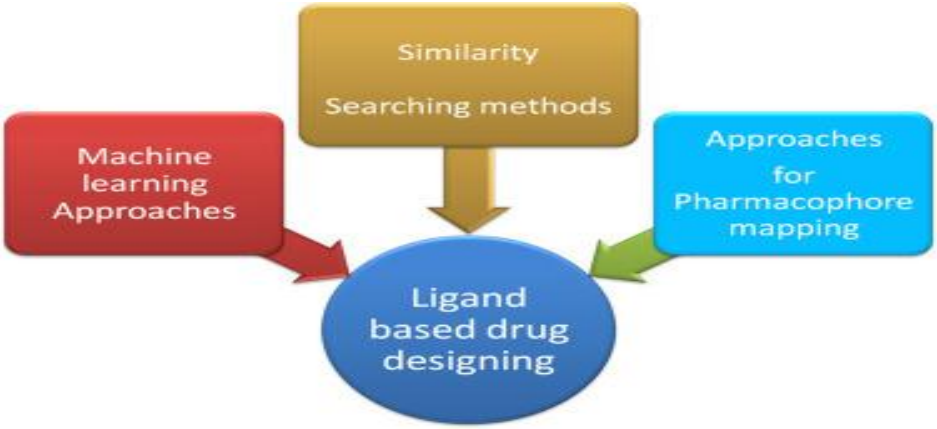
making the whole technique robust. To make the simulation realistic, the structure is placed in a "bath" of thousands of water molecules. Let us generate a fundamental idea about this incredibly amazing technology-enhanced technique.[16]

Applications

- Structure prediction has been one of the most ancient problems, including the longest simulations performed, has been extensively used for ab impact protein structure prediction.[17]
- The new amino acid sequence and a structure average the used templates. Indicate relaxation of the structure using normally molecular mechanics. In others, restrained simulations are used throughout all the process.[18]

Ligand based drug design (LBDD)

Ligand based drug design is an approach used in the absence of the receptor 3D information and it relies on knowledge of molecules that bind to the biological target of interest.



The principle of LBDD is that structurallysimilar molecules are likely to have similar properties (Hendrickson, 1991) molecular graph is a combination of nodes and edges in which atoms and bonds are represented as nodes and edges, respectively Amolecular graph is a combination of nodes and edges in which atoms and bonds are represented as nodes and edges, respectively The most common LBDD techniques include molecular similarity-based search, quantitative structureactivity relationship (QSAR), and pharmacophore modeling.

These techniques are discussed in the next section. The most common LBDD techniques include molecular similarity-based search,quantitative structureactivity relationship (QSAR), and pharmacophore modeling.[8]

Concept

"The ensemble of steric and electric function that is necessary to ensure the optimal molecular interaction with a specific biological target structure and to trigger a show biological response. Ligand based pharmacophore (LBP) is pharmacophore- based method of choice in the absence of any structural information available for therapeutic target.

A critical step in ligand-based pharmacophore (LBP) is to identify a "bioactive" conformation of an active molecule to align the rest of the molecular. In the absence of 3D bioactive conformation. data based are searched to find a conformation of a molecule these are similar to input ligands.

The most active molecule is geometrically optimized and thus the obtained minimum energy formation. It is validation the developed LBP before using it ateriorly, and similar to QSAR, a separate test of molecules is created to validate the prediction power of the LBP.[8]

Application

- Structure evaluation of new compounds
- Improve poor chemical structure
- Predict the bioactivity and ADMET properties of new compounds.

CONCLUSIONS

The structural based drug designe. This review article including the recent important contribution in these area, including the data survey of this interaction in biomolecules, the development of structural based on different model such as- Homology modeling, molecular docking, virtual screening and receptor-based pharmacophore modeling. The different orientation of the ligand in the active site, more over establishing bond may increased protein-ligand stable contribute to the binding affinity and selectivity.

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