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Review Article

A REVIEW ON COMPUTER ADDED DRUG DESIGN

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Computer aided drug design uses computational approaches to discover, develop, and analyze drugs and similar biologically active molecules. The ligand-based computer-aided drug discovery (LB-CADD) approach involves the analysis of ligands known to interact with a target of interest. These methods use a set of reference structures collected from compounds known to interact with the target of interest and analyze their 2D or 3D structures.

Key Words: CADD, ligand-based computer-aided drug discovery (LB-CADD).

INTRODUCTION

Computer-aided drug design (CADD) is a strategy to meet the challenges faced in the drug discovery process. CADD is an organized guide to provide chemical insight into drug activity by helping in the drug discovery and predicting the drug properties. CADD works at the intersection of structural biology, biochemistry, medicinal chemistry, toxicology, pharmacology, biophysical chemistry and information technology. Computational assessment of the binding affinity of enzyme inhibitors prior to synthesis is an important component aided drug design paradigms.

DRUG DESIGN:

Drug design, sometimes referred to as rational drug design or simply rational design, is the inventive process of finding new medications based on the knowledge of a biological target. The drug is most commonly an organic smallmolecule that activates or inhibits the function of a bio-molecule such as a protein, which inturn results in a therapeutic benefit to the patient. Drug design frequently but not necessarily relies on computer modeling techniques. This type of modeling is often referred to as computer-aided drug design. Finally, drug design that relies on the knowledge of the three-dimensional structure of the bio-molecular target is known as structure-based drug design.

Types:

There are two major types of drug design. The first is referred to as ligand-based drug design and the second, structure-based drug design.

Ligand-based:

Ligand-based drug design (or indirect drug design) relies on knowledge of other molecules that bind to the biological target of interest. These other molecules may be used to derive a pharmacophore model that defines the minimum necessary structural characteristics a molecule must possess in order to bind to the target. The QSAR relationships may be used to predict the activity of new analogues.

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Structure-based:

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. Using the structure of the biological target, candidate drugs that are predicted to bind with high affinity and selectivity to the target may be designed using interactive graphics and the intuition of a medicinal chemist. Alternatively, various automated computational procedures may be used to suggest new drug candidates.

Methodology of CADD:

The basis or conventional drug discovery process starts with lead identification, modification by synthesis, biological testing, structure-activity studies, and further analogue design and synthesis. Methods of CADD are of two types depending upon whether the target protein structure is known /involved or not. Computational design of new ligands is conventionally the more widely employed method. Structure activity relationship studies play an important part of the ligand design.

The methods involve in ligand-based design includes the following:

- Quantitative structure –activity relationship (QSAR)
- Pharmacophore modeling
- 3D QSAR

Molecular Mechanics:

A force field is used to minimize the bond stretching energy of this ethane molecule.

Molecular mechanics uses classical mechanics to model molecular systems. The potential energy of all systems in molecular mechanics is calculated using force fields. Molecular mechanics can be used to study small molecules as well as large biological systems or material assemblies with many thousands to millions of atoms.

All-atomistic molecular mechanics methods have the following properties:

- Each atom is simulated as a single particle
- Each particle is assigned a radius (typically the van der Waals radius), polarizability, and a constant net charge (generally derived from quantum calculations and/or experiment)
- Bonded interactions are treated as "springs" with an equilibrium distance equal to the experimental or calculated bond length.

Variations on this theme are possible; for example, many simulations have historically used a "united-atom" representation in which each terminal methyl group or intermediate methylene unit was considered a single particle, and large protein systems are commonly simulated using a "bead" model that assigns two to four particles per amino acid.

Parameter of CADD:

Some important parameters of computer-aided drug design are described as below.

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HOMOLOGY MODELING:

Unknown 3D Protein Structure (Query sequence)

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Identification of One or More Known protein structures (Homologues protein)

⇩

Produce a Structural Model of the Target (Sequence Alignment)

⇩

Protein Model Building

⇩

Refinement & Validation

Fig. 1: Structure prediction by homology modelling.

In the absence of experimental structures, computational methods are used to predict the 3D structure of target proteins. Homology modelling is a specific type of comparative modelling in which the template and target proteins share the same evolutionary origin.

Ligplot analysis:

Ligplot analysis a computer program that generates schematic 3D representations of protein-ligand complexes from standard protein data bank (PDB)' file input.

Moleculer Docking:

Molecular docking is the computational modelling of the structure of complexes formed by two or more interacting molecules. The goal of molecular docking is the prediction of the three dimensional structure. The aim of molecular docking is to achieve an optimized

conformation for both the protein and ligand so and relative orientation between protein and ligand so that the free energy of the overall system is minimized.

DE NOVO DRUG DESIGN:

De novo design is the uses of docking programmes to design new lead structures that fit a particular target site.

Step 1: Determination of binding pocket on target receptor

Step 2: Prediction of interaction sites of target receptor through Ligplot

Step 3: Placing the fragments or other linking groups with pharmacophore models at pre-defined interaction site to provide feasible interactions with the residues in the site of the target receptor

Step 4: Structurally modification of the fragments to provide possible interaction with the residue in the site of the target receptor

Step 5: Joining all fragments together to yield a complete single molecule

Fig. 2 : Steps of de novo drug design methodology

Pharmacophore-Based Drug Design:

A pharmacophore is an abstract description of molecular features which are essential for molecular identification and recognition of a ligand by a biological macromolecule. Typical pharmacophoric features include hydrophobic centroids, aromatic rings, hydrogen bond acceptors, hydrogen bond donors, positive charge and negative charge. Pharmacophore approaches have become one of the major

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tools in drug discovery after the past century's development.

A pharmacophore model can be established either in a ligand-based manner, by superposing a set of active molecules and extracting common chemical features that are essential for their bioactivity, or in a structure-based manner, by searching possible interaction points between the macromolecular targets and ligands. Pharmacophore approaches have been used extensively in virtual screening.

Uses:

Pharmacophores are frequently used as a tool for searching databases for compounds with similar pharmacophores.

Application and Advantage of CADD:

Application Of CADD:

1. Leverage of chemical and biological information about ligands and targets to identify and optimize new drugs.
2. Use of computing power to stream line drug discovery and development process.
3. Approaches to antiviral drug design.
4. Role of computer aided molecular modeling in the design of inhibitors of rennin.

Advantages of CADD:

- Through it we can reduce the synthetic and biological testing efforts.
- It gives the most promising drug candidate by eliminate the compounds with undesirable properties (poor efficacy, poor ADMET etc.) through in siliconfilters.
- It is a Cost-effective, time saving, Rapid and automatic process. Through it we can know about the drug-receptor interaction pattern.
- These approaches minimize chances of failures in the final phase.

CONCLUSION

Computer aided drug design (CADD) has been credited to the modern patterns in compound characterization in drug discovery following its inception in 1981. It represents advancement when compared to HTS as it requires minimal compound design or prior knowledge, but can yield multiple hit compounds among which promising candidates have been elected. The typical role of CADD in drug discovery is to screen out large compound libraries into smaller clusters of predicted active compounds, enabling optimization of lead compounds by improving the biological properties (like affinity and ADMET) and building chemo types from a nucleating site by combining fragments with optimized function.

The process of drug discovery and development is a long and difficult one and the cost of developing are increasing rapidly. Today it takes appropriately 10 years and 100 million dollars to bring a new drug to market.

Computer aided drug design uses computational approaches to discover, develop, and analyze drugs and similar biologically active molecules. The ligand-based computer-aided drug discovery (LB-CADD)

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approach involves the analysis of ligands known to interact with a target of interest. These methods use a set of reference structures collected from compounds known to interact with the target of interest and analyze their 2D or 3D structures.

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