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A REVIEW ON COMPUTER AIDED DRUG DESINE IN DRUG DISCOVERY

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ABSTRACT:

Computer aided Drug Design (CADD) is an ever-evolving research area that encompasses many facets. Computer Aided Drug Design (CADD) is an exciting and diverse discipline in which different aspects of basic and applied research flow together and stimulate each other. Computer Aided Drug Design (CADD) provides various tools and techniques that help in different phases of drug design, thereby reducing research costs and drug development time. Drug discovery and the development of a new drug is a long, complex, costly and extremely risky process unparalleled in the commercial world. For this reason, Computer-Aided Drug Design (CADD) approaches are widely used in the pharmaceutical industry to speed up the process. The theoretical basis of CADD includes quantum mechanics and molecular modeling studies, such as B. structure-based drug design; ligand-based drug design; Database search and affinity binding based on knowledge of a biological target. In this report, we present the areas where CADD tools support the drug discovery process.

KEYWORDS: Computer, Development, Discovery, Modeling, Database, Quantum mechanics, Desine, Complex.

INTRODUCTION:

Drug discovery is a long process that takes between 10 and 15 years and it costs up to $2,558 million to get a drug to market. It is a multi-step process that begins with proper drug target identification, drug target validation, hit-to-lead discovery, lead molecule optimization, and pre-clinical and clinical studies. Despite the large investment and time involved in discovering new drugs, clinical trials have only a 13% success rate with a relatively high dropout

rate. In most cases (40-60%), drug failure was reported at a later time point due to lack of optimal pharmacokinetic properties of absorption, distribution, metabolism, elimination and toxicity (ADME/Tox).The use of computer-aided drug discovery (CADD) techniques in preliminary studies by leading pharmaceutical companies and research groups has helped accelerate the drug discovery and development in process and minimize the failure in last stage.Computer Aided Drug Design (CADD) provides various tools and techniques that help in different phases of drug design, thereby reducing research costs and drug development time. Drug discovery and the development of a new drug is a long, complex, costly and extremely risky process unparalleled in the commercial world. For this reason, Computer-Aided Drug Design (CADD) approaches are widely used in the pharmaceutical industry to speed up the process.

The cost and cost benefit of using computational tools in the main optimization phase of drug development is significant. Drug discovery labs are expensive and time consuming in the various phases of drug discovery, from therapeutic target identification, drug candidate discovery, drug optimization to pre-clinical and large-scale clinical experiments to evaluate drug efficacy, potency and safety of recently developed drugs.Major pharmaceutical companies have invested heavily in routine ultra-high-throughput (uHTS) screening of large numbers of "drug-like" molecules. In parallel, computers are increasingly being used for virtual screening in the design and optimization of drugs. Recent advances in DNA microarray experiments explore thousands of genes involved in a disease that can be used to gain insight into disease targets, metabolic pathways, and drug toxicity. Theoretical tools include empirical molecular mechanics, quantum mechanics and, more recently, statistical mechanics. This latest advance has made it possible to incorporate explicit solvent effects.

DRUG DISCOVERY PROCESS:

Drug discovery may be a series of processes which when followed identify the drug compounds for the effective treatment or control of disease targets. It starts with the screening of huge number of chemical compounds to optimize the disease targets. It requires insight information about the structure of the drug receptor in order that the drug molecules will be adjusted to the binding site.

Drug discovery process consist of following step:

1.Understand the disease for which drug to be developed

2. Candidate drug delivery :

a) Selection of therapeutic target

b) Lead discovery

c) Lead optimization

3) Preclinical and clinical trials

4) Drug

Drug discovery process starts with understanding the disease for which the drug to be designed. It consists of the following steps.

1.Candidate Drug Discovery

a) Selection of Therapeutic Target
b) Lead Discovery
c) Lead Optimization

2.Pre clinical and clinical trials to evaluate the safety, efficacy and adverse effects of the drug

a) nimal Studies
b) Clinical Trials

3.FDA approval process for the newly discovered drug and bringing the drug to market for public use.

a) Additional post marketing testing
b) Further improvement of the drug

Typically, drug discovery and preclinical development takes three to six years. Or Clinical trials can take up to 10 years or more before a product hits the market.Takes about 12 to 15 years to succeed and costs over $1.3 billion Over-the-counter drugs.On average, out of 5000-10000 compounds screened, there are about 250 compounds.Compounds are selected for preclinical studies. Only 5 of them survive and enter the infirmary After rigorous review of newly discovered studies, he was the only one approved by the FDA.

CADD Strategies in the Drug Discovery Process :

CADD strategies depend on the amount of structural and other information. Regarding targets (enzymes/receptors) and ligands. “direct and indirect” design is the two main modeling strategies currently used in the pharmaceutical design process. Among them indirect Approach Design is based on comparative analysis of structural features. Known active and inactive compounds. Direct design, three-dimensional features.The target (enzyme/receptor) is directly considered.

Preparation of a Target Structure:

The quality and quantity of structural data that is known about the target and the small molecules that are being docked are key factors in the success of virtual screening. Checking for an acceptable binding pocket on the target is the first step. Typically, this done by employing

in-silico simulations or by analysing known target-ligand co-crystal structures. Techniques for finding new binding locations. A target structure that has been experimentally determined using NMR or X-ray crystallography . The PDB serves as the appropriate beginning point for docking procedures. The process of identifying target structures has sped up thanks to genomics. No experimentally established structures, several successful virtual screening campaigns have been reported using target protein comparison models.

Homology Modeling:

Computational approaches are utilised to forecast the 3D structure of target proteins in the absence of experimental structures. Utilizing the fact that protein structure is better conserved than sequence, i.e., proteins with similar sequences have similar structures, comparative modelling is used to predict target structure based on a template with a similar sequence. A specific kind of comparative modelling called homology modelling involves using template and target proteins with the same evolutionary ancestry. The following steps are involved in comparative modelling: Identifying related proteins to use as template structures, aligning the target and template proteins' sequences, copying coordinates for firmly aligned areas, creating the target structure's missing atom coordinates, and fine-tuning and evaluating the model are the first five steps.

Molecular dynamics-based detection:

Utilizing a single static structure to predict potential binding sites is occasionally insufficient due to the dynamic nature of biomolecules. Targets' structural dynamics are frequently accounted by using a variety of target conformations. An ensemble of target conformations can be obtained starting from a single structure using traditional molecular dynamic (MD) simulations.

The MD technique calculates a protein's trajectory of conformations as a function of time using the laws of Newtonian mechanics. Traditional MD techniques frequently become stuck in local energy minima. To address this, a number of cutting-edge MD methods have been created, including replica exchange MD, targeted MD, conformational folding simulations, temperature accelerated MD simulations.

Steps involved in homology model building proces:

- Template recognition and initial alignment. …
- Backbone generation. …
- Loop Modeling. …
- Side Chain Modeling. …
- Model Optimization. …
- Model Validation.

Monte Carlo Search with Metropolis Criterion (MCM) Simulations:

MCM samples conformational space more quickly than molecular dynamics since it only needs to evaluate the energy functions, not their derivatives. Despite the fact that conventional MD pushes a system in the direction of a local energy minimum, the randomness jumping over the energy barriers is made possible by Monte Carlo, preventing the mechanism from sustaining a local energy minimum. Flexible MCM simulations have been adopted. docking software programmes like MCDOCK

Genetic Algorithms:

Molecular flexibility is added by genetic algorithms through the recombination of parent and child conformations. The "fittest" or highest scoring conformations in this artificial evolutionary process are preserved for a subsequent round of recombination. This is how the best potential solutions evolve by holding onto advantageous characteristics from one generation to the next. State variables in docking are a collection of values that describe the position of the ligand within the protein. A set of values describing translation, orientation, conformation, and other state ccharacteristics, Hydrogen bonds present, etc. The genotype and condition are correlated, and the outcome the protein's structural model of the ligand matches its phenotype, and binding energy reflects an individual's level of fitness.To create new people, genetic operators may randomly modify (mutate) the value of certain ligand states or swap huge portions of a parent's genes. Using a genetic approach, Genetic Optimization for Ligand Docking (GOLD)[25] investigates full ligand flexibility with limited target flexibility

Scoring Functions for Evaluation of Protein Ligand Complexe:

Applications for docking must quickly and precisely evaluate protein-ligand complexes, or approximate the interaction's energy. To rank these complexes and distinguish between predictions of valid binding modes and predictions of invalid binding modes, an effective scoring function is required. A ligand docking experiment may produce hundreds of thousands of target-ligand complex conformations.

Force-Field or Molecular Mechanics-Based Scoring Functions:

The energy estimates in force-field scoring functions are based on conventional molecular mechanics. These functions make use of parameters that were calculated using ab initio quantum mechanics and experimental data. Combining van der Waals and electrostatic interactions yields an estimate of the binding free energy of protein-ligand complexes. Using the Lennard-Jones potential to express van der Waals energy terms in the AMBER force fields, DOCK while coulombic interaction with a distance-dependent dielectric function accounts for electrostatic terms

Empirical Scoring Functions :

Experimental data are fitted with parameters by empirical scoring functions. Explicit hydrogen bond interactions, hydrophobic contact terms, desolvation effects, and entropy are weighted together to form binding energy, which serves as an illustration. terms for empirical functions are rely on approximations and are easy to evaluate. Different parameters' weights are based on experimental data derived from molecular data and regression analysis. Numerous docking suits that are available on the market now use empirical functions, including SURFLEX, FLEXX, and LUDI

Consensus-Scoring Functions :

Consensus methods use various scoring systems to repeatedly rescore anticipated poses. The answers can then be ranked using different combinations of these outcomes. A few methods for combining scores are: (1) weighted combinations of scoring functions, (2) voting, where decisions are made based on the number of poses a molecule has, (3) rank by number, where each compound is ranked according to its average normalised score values, and (4) rank by rank, where compounds are sorted according to average rank established by individual scoring functions.

Structure-Based Virtual High-Throughput Screening:

Structure-based virtual high-throughput screening (SB-vHTS), an in silico technique for selecting potential hits from among millions of compounds for targets with known structures, compares the small molecule's 3D structure with the potential binding pocket. In contrast to traditional HTS, which experimentally affirms a ligand's generic ability to bind, SB-vHTS chooses for ligands predicted to bind a specific binding site.The protein’s activity is inhibited or allosterically changed. To make it possible to screen enormous compound libraries in a finite amount of time. SB-vHTS frequently use a condensed estimate of binding energy that can be computed quickly and a limited conformational sampling of the protein and ligand. Preparing the target protein and compound library for docking, choosing a favourable binding pose for each compound, and ranking the docked structures are the main processes in SB-vHTS.

Ligand-Based Computer-Aided Drug Design:

The analysis of ligands known to interact with a target of interest is a component of the ligand-based computer-aided drug discovery (LBDD) method. These techniques examine the

2D or 3D structures of a group of reference compounds that are known to interact with the target of interest. The main objective is to represent these compounds in a fashion that preserves the physicochemical characteristics most crucial to their desired interactions while excluding unimportant details. Since it does not require understanding the structure of the target of interest, it is regarded as an indirect approach to drug discovery. The two primary LBDD strategies are(1) the creation of a quantitative structure activity relationship (QSAR) model that predicts biological activity from chemical structure. (2) the selection of compounds based on chemical similarity to known actives using some similarity metric. The techniques are used for hit-to-lead and lead-to-drug optimization, as well as the optimization of DMPK/ADMET characteristics. They are also used for in silico screening for new compounds with the desired biological activity.

The similar property concept, which holds that molecules with similar structural characteristics are likely to have comparable properties, is the foundation of LBDD. LBDD methods, as opposed to SBDD methods, can also be used when the biological target's structure is unclear. Furthermore, active substances found using ligand-based virtual high-throughput screening (LB-vHTS) techniques are frequently more potent than those found using SB-Vhts techniques.

Molecular Descriptors:

Properties like molecular weight, geometry, volume, surface areas, ring content, rotatable bonds, interatomic distances, bond distances, atom types, planar and nonplanar systems, molecular walk counts, electronegativities, polarizabilities, symmetry, atom distribution, topological charge indices, functional group composition, aromaticity indices, solvation properties, and many others can be included in a molecular descriptor. These descriptions are produced using molecular mechanical, knowledge-based, graph-theoretical. According to the dimensionality of the chemical representation they are computed from, quantum-mechanical tools and are categorized[.Scalar physicochemical qualities in one dimension (1D), such as molecular weight; descriptors generated from molecules in two dimensions (2D); in three dimensions (3D); and descriptors obtained from molecules in three dimensions. However, these various levels of complexity overlap, with the more sophisticated descriptions frequently including details from the simpler ones.

Software for General Purpose Molecular Modeling:

- AMBER—Peter Kollman and coworkers, UCSF.Computer assisted model building, energy minimiza-tion, molecular dynamics, and free energy perturbation calculations.
- Midas Plus—UCSF Computer Graphics Laboratory.
- CHARMM—Martin Karplus and cowrokers, Har- vard.
- QUANTA/CHARMm—Molecular Simulations Inc. (MSI) molecular/drug design, QSAR, quantum chemis- try.

- X-ray & NMR data analysis Insight/DISCOVER— Biosym, Inc. Now MSI and Biosym became Accelrys Inc.
- SYBYL—Tripos, Inc.
- ECEPP—Harold Scheraga and coworkers, Cornell
- MM3—Norman Allinger and coworkers, Georgia For personal computers (Apple, Compaq, IBM, etc.)
- Alchemy III—Tripos, Inc.
- Desktop Molecular Modeller—Oxford Elec. Publish- ing Molecular Modeling Pro—WindowChem Software Energy minimization, QSAR (surface area, volume, logP), etc.
- PC MODEL—Serena Software

CONCLUSION:

The multidisciplinary discipline of computer aided drug design (CADD) draws researchers from pharmacology, medicine, and other fields to develop new tools and techniques or improve those already in use to aid in the drug development process. These strategies outperformed more traditional approaches in terms of efficiency at various phases of the drug discovery process, which decreased the cost and length of time needed to produce a medicine. A few examples of pharmaceuticals that are currently on the market that were successfully designed utilising various CADD technologies are offered. These drugs were developed using these techniques. To help with the various stages of drug discovery, these tools can be used and improved.

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