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Computer Aided Drug Design:
A Novel approach in Drug Discovery

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Abstract

Background: Computer aided drug design (CADD) is the use of computational techniques in the process of drug discovery and development. It is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. The fast development is due to increase identification of molecular targets, elucidation of the 3D structures by X- ray crystallography and Nuclear magnetic resonance (NMR), availability of commercial, private or public data bases (for biological targets and ligands) and availability of CADD software's. The goal of computational approach in drug discovery is to identify and optimize drug-like molecules for a given target. This review was aimed to describe the various approaches to computer-aided drug design.

Methods: The universally recognized databases; Scopus, PubMed, ScienceDirect, and Google Scholar were used for the online search. Specific keywords were used for the search.

Results: Molecular docking- and pharmacophore based- virtual screening are the two commonly employed computational approach in drug discovery. Molecular docking is a computer simulation procedure that predicts the binding orientations or conformations of a receptor-ligand complex and use this knowledge to predict the binding affinity between the molecules in the complex. Pharmacophore on the other hand, is a molecular framework that carries the essential features responsible for a drug's biological activity. Pharmacophore modelling can be structure or ligand- based virtual screening. In hierarchical approach, the database of ligands can be pre-filtered using a pharmacophore query followed by molecular docking simulation.

Conclusion: Computational drug design is a cost- effective and less time-consuming approach.

Keywords: Computer-aided drug design, molecular docking, Pharmacophore modelling

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Introduction

Computer aided drug design (CADD) also called computational drug design, computer aided molecular design, computer aided molecular modeling, rational drug design, in silico drug design or computer aided rational drug design (1). It is the use of computational techniques in the process of drug discovery and development. Its fast development is due to increase identification of molecular targets, elucidation of the 3D structures by X- ray crystallography and Nuclear magnetic resonance (NMR), availability of commercial, private or public data bases (for biological targets and ligands) and availability of CADD software's (2).

Examples of available protein data bases include protein data bank, Pubmed, pubchem, DNA data base of Japan (DNAJ), European molecular biology laboratory (EMBL), Protein information resources (PIR) and Swiss protein while data bases for ligand include Drug bank, Zinc, LIGAND, Availability chemical directory (ACD) and chemDB (3).

The traditionally drug discovery method is a trial and error approach of lead identification from natural sources or high throughput screening of large chemical libraries. This method is time and cost expensive with a low success rate (4). Computer aided drug design expedite and facilitate the process of target elucidation, lead compound identification and the optimization of promising lead compound. It is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery. It also decreases the use of animals in the process of lead identification and optimization (5). This review was aimed to describe the various approaches to computer-aided drug design.

Methodology

The universally recognized databases; Scopus, PubMed, ScienceDirect, and Google Scholar were used for the online search. Specific keywords containing minimum of two of the following words; "Computer-aided drug design/computational drug design/insilico drug design, approaches/types/components/methods, molecular docking and pharmacophore" were used. The citation of each article was transferred into Mendeley reference Manager, and any duplicates were removed. Titles and abstracts of each article were screened for relevance. The full text of each relevant article was downloaded and the information were extracted.

Approaches to Computer-aided Drug Design

The two commonly employed computational design include molecular docking- and pharmacophore based- virtual screening.

Molecular Docking Simulation

Molecular docking is a computer simulation procedure that predicts the binding orientations or conformations of a receptor-ligand complex and use this knowledge to predict the binding affinity between the molecules in the complex. It is the main tool for virtual screening (6). The advantage of molecular docking virtual screening when compared to the traditional experimental method is that it saves time and resources (6). This technique was pioneered in early 1960's and remains the generally acceptable method in drug discovery (7). The rapid rise in the number of the known three-dimensional structures of protein targets through X-ray crystallography has made structure-based virtual screening more prominent in drug discovery (7). Molecular docking involves two components: search algorithm and scoring functions (8). Search algorithm predicts the conformation or orientation (pose) of a ligand in the target binding site while scoring functions predicts the binding affinity between the ligand and target protein (8).

Search algorithm

If we consider flexibility of ligand and/or receptor, search algorithm can be classified into, rigid body docking and flexible docking (8). Rigid body docking does not take into account the flexibility of either the ligand or the receptor- a factor that limits its specificity and accuracy (8). Because it is quite fast, rigid body docking is usually employed during virtual screening process of large library of compounds after which flexible docking can be used for lead optimization (8). On the other hand, flexible docking considers several possible conformations of a ligand and/or receptor. Several search methods are employed in flexible docking, each using different parameters. Shape matching, Monte Carlo simulation and incremental construction are the commonest methods of search algorithm employed by various docking soft-ware's/programs. Others include distance geometry, evolutionary programming, genetic algorithm, tabu-search and simulated annealing (8).

Shape matching/complementarity describes the protein and the ligand as complementary surfaces. It helps to identify possible regions (called 'Sphere centers') or binding sites where ligand atoms may be located. It is used by several docking software's/programs including PyRx, DOCK, MS-DOCK, SYSDOC and MOLEGRO (8). Monte Carlo simulation is a complicated approach, here protein and ligand are separated by some physical distance and the ligand finds its position in the protein's active site after a certain number of "moves" in its conformational space (8). Each moves in the conformational space of the ligand induce a total energetic lost to the system. The total energy of the systems is calculated for every move. The ligand with the minimal energy lost is the lead compound (8). This method is time consuming and expensive. Incremental construction splits a ligand into fragments that are docked separately on the receptor followed by subsequent fusion of the fragments. Fragmentation, also referred to as anchor and grow method, allows the consideration of ligand flexibility in docking. It is employed by softwares such as Surflex, Flexx, and Dock (8).

Scoring functions

These are mathematical models for estimating binding affinity between a ligand and the target protein (8). It helps to predict the ligand with the best binding affinity. Scoring functions are broadly classified into two (2) different types; the knowledge- based and energy component method. Knowledge-based scoring function uses the statistics of the observed inter-atomic contact frequencies in a large database of crystal structure of protein-ligand complexes (8). Molecular interactions close to the maximum frequency of interactions in the data-base will have a high binding affinity while a molecular interaction with low frequency of interaction in the Database will have a low binding affinity. The energy component scoring method is based on the mathematical assumption that change in free energy (DGbind) is the sum of the free energy for ligand-protein interaction (DGint), ligand-protein and solvent interaction (DGsol), conformational changes in the ligand- protein interaction (DGconf.) and the motion in the ligand-protein target complex formation (DGmotion). It is worth noting that individual terms are highly related to each other and can affect binding energy in more than one way. Factors like hydrogen bonding, flexibility of ligands and ion pairing can also affect binding affinity of a ligand-protein complex (8).

Pharmacophore Modelling

Paul Ehrlich define the term pharmacophore as 'a molecular framework that carries the essential features responsible for a drug's biological activity (9). The international union of pure and applied chemistry (IUPAC) define pharmacophore as a steric or electronic feature that ensure optimal interactions of a ligand- target complex (10). Fundamentally, pharmacophore simulations can be a ligand-based, extracting shared or merged chemical features of a set of bioactive chemical compounds or a structure-based, by probing possible interaction points between the macromolecular target and ligands (10). Pharmacophore simulations is an important tool of virtual based screening, rational drug design, lead

optimization and multi-target drug design (10). Several pharmacophore softwares available includes Ligand Scout, HipHop, HypoGen, DISCO, GASP, GALAHAD, PHASE and MOE, Drug Discovery studio etc.

Ligand-based pharmacophore modelling
The ligand-based pharmacophore simulation is usually employed in the absence of a putative macromolecule or receptor for the query compounds (11). It involves extracting the shared or merged chemical features of a set of bioactive chemical compounds (11). In general, pharmacophore generation from multiple ligands comprises of two major stages: conformational area creation for training set ligands and multiple training set ligand alignment (12). The creation of different conformations or orientations of a flexibility ligands with subsequent alignment of each of the conformation are the the key challenges as well as the main difficulties in ligand-based pharmacophore modeling (12).

Structure-based pharmacophore modelling
The structure-based pharmacophore simulation employed the ligand-receptor complex as template to generate a screening model. It involves the 3D structure of both macromolecule and the ligand (13). The design of structure-based pharmacophore simulation includes the determination of the complementary electronic component of the binding site and spatial arrangement for the ligand-receptor complex and a subsequent extraction of the interacting chemical features (13). The structure-based pharmacophore simulation is subdivided into two: macromolecule-ligand-complex based and macromolecule (without ligand)-based (13). This approach is reliable and more effective in identifying the active pockets of the receptor/macromolecule as well as evaluating the different interaction points of a lead compounds and receptor target. Ligand Scout is an excellent representation that incorporates the macromolecule-ligand-complex-based scheme (10). This approach is only possible in the presence of 3D structures of both the macromolecule and the ligands, hence it is not applicable in instances where the receptor or macromolecule for the query compounds is unknown. This limitation can be overcome using the macromolecule- based approach (10).

Pharmacophore-model-based virtual screening
The generated pharmacophore model from either the ligand-based or structure-based, can be used to screen training set of the 3D structure of lead compounds for compound similarity, resemblance and electronic/stearic conformity. This is called pharmacophore-based virtual screening (14). Pharmacophore- based and docking-based virtual screening are the conventional tools for screening chemical library data bases. It minimizes difficulties associated with insufficient consideration of receptor flexibility or the use of insufficiently designed or optimized scoring functions by introducing a tolerance radius for each pharmacophoric feature (14). In the pharmacophore-based virtual screening approach, a pharmacophore hypothesis is taken as a template (14). The essence of pharmacophore screening is to find hit molecules with similar chemical features as the template. The screened hit compounds could be similar to existing compounds while others might be entirely novel in scaffold (14).

Pharmacophore-based de novo design
Another application of pharmacophore simulation is in de novo drug design. The hit compounds from pharmacophore-based screening are usually patent protected known compounds. Contrarily, the de novo design approach can be employed in the creation of an entirely original hit compounds generated structure- or ligand- based pharmacophores virtual screening (15). The first pharmacophore- based de novo design program is NEWLEAD. NEWLEAD import set of molecular ingredients compatible with a pharmacophore model connected by linkers (10). Nevertheless, it can only be possible in instances where pharmacophore components are actual functional groups and not imaginary features. Its limitations include non-consideration of the sterically abandon binding site region and the difficulty in chemically synthesizing the created de novo compounds (10).

Pharmacophore methods in docking simulations
Pharmacophore virtual screening simulations are reliable, validated and effective data base virtual screening tool. Nonetheless, a more robust and holistic in-silico approach is the "hierarchical method" in which dissimilar computational approaches are used successively. It is also called the "funnel computational technique". It involves successive computational screening of the chemical library database to remove less active or less promising compounds. The resultant hits are more likely to win the process of drug development (16). Characteristically, every successive step of this method involves a more multifaceted, robust and computationally challenging step than the preceding one. In this approach, pharmacophore models are frequently used to screen or detect promising hit query compounds that satisfy simple geometric and chemical functionality requirements followed by a more complicated and computationally demanding approaches such as molecular docking (16).

In this approach, the database of ligands can be pre-filtered using a pharmacophore query prior to a more

sophisticated molecular docking simulation (16). Contrarily, the molecular docking approach can be used as a pre-screening tool followed by a pharmacophore modelling to screen and remove compounds with poor pharmacophore compatibility and stearility (16). This approach can remove molecules that recorded excellent pharmacophore hit but have very poor binding energies in molecular docking studies. In this instance, the molecules are assessed based on total molecular orientation independent on the alignment with pharmacophore features (16). The second option is to apply the pharmacophore alignment features to detect the ranking of the molecular docking simulations. The pharmacophore simulation can in this instance be employed for the ranking of the ligand fitting into the pharmacophore query; or to guide the docking process using non-default parameters which could interfere and modify scoring at individual binding poses (3). Famously, pharmacophore models are very useful virtual screening tool used to pre or post filter results of molecular docking simulations (17).

Pharmacophore-guided drug target identification

While typically the aim of computer aided drug design is to screen and improve drug-like molecules at a known biological receptor, the reverse instance is possible. Most herbal or serendipitously developed drugs have unknown mechanism of action. In such instances, computational approach can be used to identify the targets responsible for the said actions (18). Chemo-informatical fingerprint-based similarity tools are employed to identify close analogue compounds with a known mechanism of action. Here the drugs with unknown mechanism of action is imported in the query area and screened against library of generated pharmacophores. The most likely pharmacophore model that match the compounds is identified and postulated as the possible mechanism of action of the drugs (19). The library of generated pharmacophores can be manually created or automatically generated.

Limitations of pharmacophore methods

Regardless of significant recorded success in computational drug discovery using pharmacophore modeling approach, it is not failed safe and one should be cautious about the limitations of this technique (20).

The foremost limitation is the absence of good scoring metrics (20). While molecular docking technique is based on predicting the binding affinity using scoring functions, pharmacophore queries do not have a reliable, general scoring metric (20). Usually, the pharmacophore fit of the ligand into a query is estimated by the root mean square deviation of the query and the atomic mass of the molecules.

This poor scoring metric does not take into account known compounds similarity and cannot predict the total compatibility of the flexible protein targets.

Secondly, compounds with good pharmacophore fit might not be complementary with the biological receptor making them inactive despite the excellent pharmacophore match.

The third limitation is the dependency of a pharmacophore-based virtual screening on a pre-computed conformation database (21). These databases have limited number of low-energy orientations hence likelihood that active compounds with missing orientation due to rotatable bonds will have low pharmacophore score fit. Again, different rotatable bonds would be very difficult to delineate during the orientation generation process using differences in the root mean square deviation (21). Lastly, there is no one well defined method to design a pharmacophore query (20).

Limitation

This review only focuses on the various approaches to computer-aided drug design but does not cover a review of comparative analysis and product development from the various approaches.

Conclusion

Computational drug design is a cost- effective and less time-consuming approach. It is a validated and reliable alternative to the cost expensive and time-consuming conventional method of drug discovery.

References

1. Sabe VT, Ntombela T, Jhamba LA, Maguire GE, Govender T, Naicker T. Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: A review. *European Journal of Medicinal Chemistry*. 2021; 224:113705.
2. Mouchlis VD, Afantitis A, Serra A, Fratello M, Papadiamantis AG, Aidinis V. Advances in de novo drug design. *Computational and structural biotechnology journal*. 2021; 12: 145-156.
3. Pal S, Kumar V, Kundu B, Bhattacharya D, Preethy N, Reddy MP. Ligand-based pharmacophore modeling, virtual screening and molecular docking studies for discovery of potential topoisomerase I inhibitors. *Computational and structural biotechnology journal*. 2019;17:291-310.
4. Macarron R, Banks MN, Bojanic D, Burns DJ, Cirovic DA, Garyantes T. Impact of high-throughput screening in biomedical research. *Nature reviews Drug discovery*. 2011;10(3):188-95.
5. Kapetanovic I. Computer-aided drug discovery and development (CADDD): in silico-chemico-biological approach. *Chemico-biological interactions*. 2008;171(2):165-76.
6. Dias R, de Azevedo J, Walter F. Molecular docking algorithms. *Current drug targets*. 2008;9(12):1040-7.
7. Lin X, Li X, Lin X. A review on applications of computational methods in drug screening and design. *Molecules*. 2020;25(6):1375-1383.
8. Tripathi A, Bankaitis VA. Molecular docking: From lock and key

to combination lock. *Journal of molecular medicine and clinical applications*. 2017;2(1): 1567-1580.

9. Goyal S, Jamal S, Grover A, Shanker A. Drug discovery: An in Silico approach. *Bioinformatics: Sequences, Structures, Phylogeny*: Springer; 2018; 10(3):307-328.

10. Handler N, Buschmann H. Pharmacophore generation for multiple ligands. Drug selectivity: *An evolving concept in medicinal chemistry*. 2017; 40(3):275-312.

11. Vázquez J, López M, Gibert E, Herrero E, Luque FJ. Merging ligand-based and structure-based methods in drug discovery: An overview of combined virtual screening approaches. *Molecules*. 2020;25(20):4723-4737.

12. Cleverdon ER. Ghrelin Processing and Maturation: Developing a Molecular-Level Framework for Hormone Activation and Biological Function: *Syracuse University*; 2018.

13. Yang S-Y. Pharmacophore modeling and applications in drug discovery: challenges and recent advances. *Drug discovery today*. 2010;15(11-12):444-50.

14. Seidel T, Schuetz DA, Garon A, Langer T. The pharmacophore concept and its applications in computer-aided drug design. *Progress in the Chemistry of Organic Natural Products*. 2019; 25(2):99-141.

15. Huang Q, Li L-L, Yang S-Y. PhDD: a new pharmacophore-based de novo design method of drug-like molecules combined with

16. Pérez-Sianes J, Pérez-Sánchez H, Díaz F. Virtual screening meets deep learning. *Current computer-aided drug design*. 2019;15(1):6-28.

17. Hu B, Lill MA. PharmDock: a pharmacophore-based docking program. *Journal of cheminformatics*. 2014;6(1):1-14.

18. Rampogu S, Lee KW. Old Drugs for New Purpose—Fast Pace Therapeutic Identification for SARS-CoV-2 Infections by Pharmacophore Guided Drug Repositioning Approach. *Bulletin of the Korean Chemical Society*. 2021;42(2):212-26.

19. Zawahir Z, Dayam R, Deng J, Pereira C, Neamati N. Pharmacophore guided discovery of small-molecule human apurinic/apyrimidinic endonuclease 1 inhibitors. *Journal of medicinal chemistry*. 2009;52(1):20-32.

20. Qing X, Lee XY, De Raeymaecker J, Tame JR, Zhang KY, De Maeyer M. Pharmacophore modeling: advances, limitations, and current utility in drug discovery. *Journal of Receptor, Ligand and Channel Research*. 2014;7:81-92.

21. Muhammed MT, Esin A-Y. Pharmacophore Modeling in Drug Discovery: Methodology and Current Status. *Journal of the Turkish Chemical Society Section A: Chemistry*. 2021;8(3):749-62.

assessment of synthetic accessibility. *Journal of Molecular Graphics and Modelling*. 2010;28(8):775-87.