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Recent Perspectives in Molecular Docking for Research

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Abstract: With the progress in computational power and developing approaches, new horizons are now opening for accurate prediction of molecular binding affinity. In the current book chapter, recent strategies for Computer-Aided Drug Designing (CADD) including virtual screening and molecular docking, encompassing molecular dynamics simulations, and binding free energy calculation methods are discussed. Despite the emergence of more degrees of freedom, several flexible conglomerates have not been well developed, and there are still computational limitations to solve, including several features in the focused technique. The present goals, such as molecular flexibility, binding entropy, and the presence of ions and solute conditions, are revisited with the purpose of anticipating the challenges, goals, and achievements in this field over the next few years or decades.

Keywords: CADD, Molecular Docking, Entropy.

Introduction: Advanced computational techniques such as MDO and MD involving virtual screening (VS) enable in-depth experimental drug discovery research, searching larger databases comprising chemicals to detect new ligands, and potential anti-inflammatory inhibitors. MDO is a structural analysis performed to detect protein binding sites and assess binding affinities between small particles and macromolecules, which can potentially be used as drug targets.

The drug discovery process and development are commonly time-consuming for almost 20 years and have an immoderate cost. Drug discovery can be introduced by screening lots of compounds into lesser sizes and, finally, the best compound, the hit or lead compound, is found. New methods are still being developed to shorten the time and save money and for this purpose, virtual screening has gained a lot of popularity lately. [1] Virtual screening comprises two approaches: structure-based drug design (SBDD) and ligand-based drug design (LBDD). LBDD is based on the principle that compounds with similar structures tend to exhibit similar biological activity. Thus, the screening will focus on finding compounds like the known active compounds. Meanwhile, in SBDD, it is assumed that biologically active compounds will be able to bind to target molecules (proteins, enzymes, DNA, RNA). Molecular docking is one of the structure-based virtual screening methods commonly used in drug discovery. [2]

Target Structure Selection: Computer-aided Drug Design (CADD) is an extensively used term since 1980. It represents the computer-based approaches as a tool and a source for the storing, managing, analyzing and modeling of compounds. Various features of drug discovery can be explored by the CADD approach like the designing of compounds, studying chemical interactions and assessment of potentially leading candidates. CADD can be principally applied to achieve the identification, validation, and optimization of the target molecule and even for the preclinical trials. The cost for the development of drugs can be decreased up to 50%by the CADD

approach. [3] The virtual screening involves the examination of a large no. of databases of compounds to search for the binding capacity for a target. Out of the huge databases, an appropriate subset of compounds is selected. This technique thus reduces the amount of compounds to be tested by conducting various experiments and enhancing the hit rate of novel drugs. [4]

Various interactions involved in the docking procedure There can be four different types of Interaction forces: (1) Electrodynamics forces-Van der Waals interaction. (2) Electrostatic forces-dipole-dipole, charge-dipole and charge-charge (3) Solvent-related forces-Hydrogen bond and hydrophobic interactions (4) Steric Forces-Caused by entropy. The docking procedure aims at predicting one of the best approaches of binding ligands with its suitable macromolecular partner which is most often a protein. This technique thus generates possible orientations in the form of ligand poses in a huge amount inside the binding site of the protein. Thus, it necessitates the presence of the 3-d structure of the targeted molecule. This structure can be any of the type, either achieved after conducting various experiments like X-ray crystallography/Nuclear Magnetic Resonance or by utilizing various computer-aided techniques like homology modelling. Molecular docking involves two main stages: a search algorithm and a scoring function, which is associated with a score predicting every conformation. [5] Search algorithm the searched algorithm must be able to generate the most favourable number of configurations to be admitted by conduction of many experiments to determine modes of binding. There exist many relevant algorithms for analysing docking procedures like Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry etc.,. [6]

Various docking approaches

Monte carlo approach:

This approach is beneficial in generating an initial orientation of a ligand at the active site which possesses translation, random conformation rotation. The starting orientation can be scored from it and it can also score a new configuration after generating it. A metropolis criterion is useful in the determination of the retaining ability of a new configuration. (Metropolis criterion is based on the immediate acceptance of new solution scores only when it is better than the previous one. In case a configuration is not found to be new, the application of a Boltzmann-based probability function is done, which finally decides if the configuration is accepted or rejected based on the passing of the probability function test.

Fragment-based method:

This method as the name suggests, mainly depends on the division of ligands in the form of fragments or small protons followed by the docking procedure and finally the linking of docked fragments is performed.

Distance geometry:

Information about the structure has been utilized by the Distance Geometry to be conveyed as intra or intermolecular distances. First, this geometry assembles the distance and then the consistency of 3-d structures is calculated with these distances.

Matching approach:

The main basis of this approach is the complementarity between the ligand and the protein. In this approach, the ligand-receptor configuration is generated by placing the ligand atom at the best site of the protein. This configuration, thus formed may need to be optimized further.

Ligand fit approach:

The base of this approach is the shape resemblance between ligand and protein active sites. Hence, it is beneficial in the rapid and accurate methods for docking of smaller molecule ligands into the active sites of protein.

Point complementarity approach:

This approach aims at evaluating the shape and chemical complementarity between the molecules forming specific interactions.

Blind docking:

This docking approach is used in the detection of binding sites which are possible. Also, in identifying the fashion of peptide ligand by overall surface scanning of the targeted proteins.

Inverse docking:

This docking procedure utilizes computational methods to detect the toxicity and side effect of small molecular protein targets. The understanding of these proteins facilitates the side effects and toxicities of the drug molecules by the combined effects of proteomics and pharmacokinetic profile. [7-9]

Conclusion:

The molecular docking measures have come out to be one of the most favourable techniques in the field of drug designing, especially in the past few years. This could be possible by the increased availability of various software used in docking, its advanced approaches, and the rapidly growing users. Along with all the enhancing benefits, some problems are also to be faced while performing molecular docking. This mainly involves the achievement of efficient protein flexibility during searching algorithms and the presence of water molecules along with entropy treatments during scoring function. But there are a varied number of software available to overcome these problems and new alternatives are also continuously appearing in each upcoming year. Though in this rapidly growing field all the alternatives will become outdated sooner or later especially if not updated timely. So, the early adopters own a special benefit here as it is difficult to master a newly formed software.

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