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THE ROLE OF MOLECULAR DOCKING IN DRUG DISCOVERY: CURRENT APPROACHES AND INNOVATIONS

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Background:
Molecular docking is a crucial computational technique used to predict the binding mode and affinity between ligands and target macromolecules, playing an integral role in drug discovery and development. This review delves into the methodologies, challenges, and advancements in molecular docking, emphasizing its application in virtual screening, drug repurposing, and lead optimization. The process of molecular docking relies on accurate pose and affinity predictions, which are influenced by the choice of docking program, test set diversity, and algorithmic approaches. Various docking software tools, each with their strengths and limitations, are compared to highlight their performance in different contexts. The review also explores recent trends in molecular docking, particularly its contribution to combating emerging diseases like COVID-19. Additionally, it addresses the integration of deep learning (DL) algorithms into docking experiments, enhancing pose selection and improving the accuracy of binding affinity predictions. Despite the progress, the identification of near-native binding poses remains a significant challenge, with current scoring functions often falling short in predicting the correct ligand conformation. As molecular docking methods evolve, the combination of computational techniques and DL-driven innovations holds great promise for more efficient and precise drug discovery. This review aims to provide valuable insights for researchers and clinicians in the bioinformatics and pharmaceutical industries, offering guidance on the use of docking techniques to design and optimize therapeutic agents for various diseases.

Keywords: Mechanism of docking, CADD, drug discovery, computational methods, ligand, scoring function, algorithm, pose selection.

Introduction

Computer-aided drug design (CADD) is an area that consists of many computations strategies for the discovery, design, and development of novel therapeutic agents. CADD has crucial role in improving active ligands, discovering novel drugs and understanding biological processes at a molecular level [1]. Nowadays, good accountable techniques like NMR (Nuclear Magnetic Resonance) spectroscopy, crystallography, high throughput protein purification etc. which can attain these targets are handy quiet easily. It is a process through which small molecules are docked into the macromolecular structures for scoring its complementary values at the binding sites. Amidst of well-known liabilities, molecular docking has predicted novel ligands for more than 50 targets during the last decade. There are several approved drugs in the market that are developed through CADD. For example, the anti-HIVs raltegravir, saquinavir, indinavir, and ritonavir, the anti-influenza oseltamivir, the antihypertensive captopril, the carbonic anhydrase inhibitor dorzolamide and the neuraminidase inhibitor zanamivir are developed by using CADD methods if new solution score improved than the preceding one, it is immediately accepted. If the configuration is not new one, a Boltzmann-based prospect function is useful.

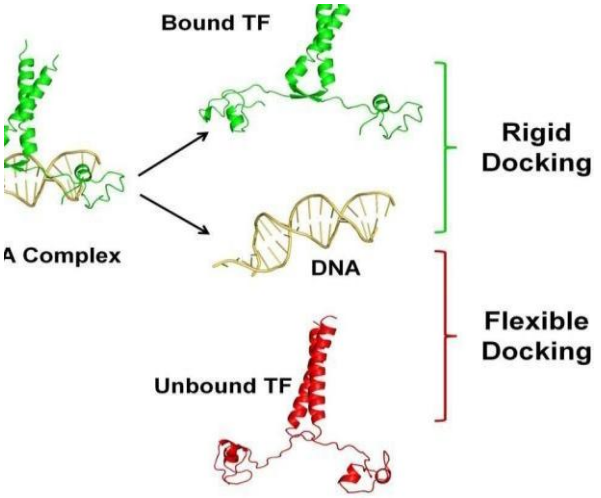

Fig 01: Structural images of rigid docking and flexible docking

The scoring power describes the ability of the SF to compute a score that is linearly correlated with the experimentally measured BA value of solved protein-ligand complexes [2]. The Person's correlation coefficient is the metric used to estimate the correlation between the computed score and the experimental value. The ranking power refers to the capability to correctly rank a set of ligands bound to the same protein and is measured by the Sperman's rank-correlation coefficient. Instead, the screening power is related to the ability to retrieve true binders among a set of random compounds, usually denoted as decoys, and it is expressed as an enrichment factor (EF) which measures the number of active molecules identified among the top n ranked compounds. Finally, the docking power represents the ability of the SF to select the native binding conformation of a ligand among a set of computer-generated poses [3].

Background

The scientific and commercial quantum leap gave birth to proteomics with which the world has witnessed the computational outbreak infecting every nook and corner of the drug discovery process. A great deal of biological information is coded in each human gene and such information is translated to function only through proteins.

Protein flexibility added a new dimension to this complexity that has a direct impact on drug discovery as it leads to different results each time and so it has become a major challenge of molecular docking as discussed in several reviews [4]. Scoring functions assess the quality for millions of docked poses generated by estimating the strength of the binding interaction given as binding energy with respect to a binding mode. The binding constant (Kd) and the Gibbs free energy (ΔGL) give the energy variation value due to the formation of protein-ligand complex. However, it is a matter of fact that no true scoring function exists which is universal to all docking programs. Identification and use of such a scoring function best suited for the problem under investigation is the rule of the game for obtaining efficient and reliable results. For this, the different atom types set for both the ligand and protein must be carefully examined and a scoring function that incorporates test class of protein or ligands in the parameterization process is highly recommendable [5].

Principles of Molecular Docking

Docking is a method based on the examination of the fitting of the designed compounds to target cavities and their interactions with the residues. The basis for the majority of the docking programs is molecular mechanics, which explains polyatomic systems using classical physics. Experimental parameters are used to reduce the deviation between the experimental data and molecular mechanics. Due to the limitations of the experimental methods, mathematical equations are converted into parameters using quantum mechanics semiempirical and ab initio theoretical calculations [6]. With the development of X-ray crystallography, NMR, Cryo EM, and similar structure determination methods, the number of proteins with known three dimensional (3D) structures is rapidly increasing and they are accessible to the public in databases like the protein d.

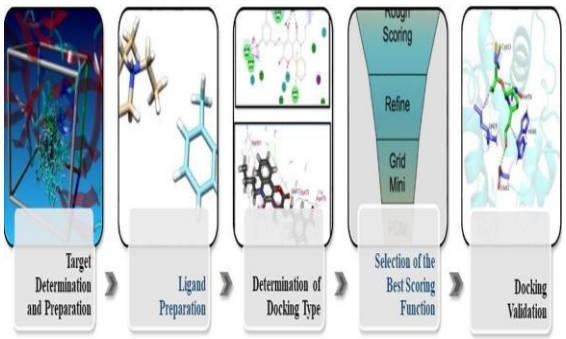

Fig 02: Steps of molecular docking. A higher resolution / colour version of this figure is available in the electronic copy of the article

This energy includes internal energies, coulombic interactions, including Van der Waals interactions and hydrogen bonding. The entropy and solvent energies are calculated separately. Knowledge-based scoring functions are calculated by converting the frequencies of ligand-protein atom interaction pairs into free energies using Boltzmann distributions [7]. Like any other technique, the docking process should also be validated. The docking results are validated by redocking of reference ligands with targets and comparing the RMSD (root mean square deviation) values, binding pose, binding affinity, and coverage of the estimated bindings with previously acquired results.

Approaches of Molecular Docking

Docking is used to predict the binding site of small molecule drug to their protein targets in order to predict the affinity and action of small molecule. Therefore,

docking is important in rational drug design. Docking is a method which involves prediction of selected orientation of one molecule to another when they bound to each other to form stable complex. Information of selected orientation is used to determine the strength and binding affinity between two molecules by using scoring functions. The goal of docking studies is to optimize the shape of both the ligand and protein, as well as the relative orientation of the protein and ligand, to reduce the total system's free energy. Many types of structural in sequence can be articulated as intra or intermolecular distances. The distance geometry formalism allows these detachment to be assembled & 3 dimensional structures dependable with them to be considered. It was introduced for detection of possible binding sites & modes of peptide ligand by scanning the entire surface of protein targets [8].

Advances in Molecular Docking

The opportunities provided by molecular docking in the drug discovery process are well known. However, intrinsic factors limit the prediction performance of docking. Ligand-based approaches have been used to identify appropriate target structures for docking-based screening. The ability of docking to differentiate active compounds from inactive ones may have a high dependence on the 3D structure of the target used and the degree of similarity of the selected ligands by screening against those compounds co crystallized in the target structure. Similarly, ligand based approaches have been utilized to increase the predictive potential of docking screening [9] The opportunities provided by MD in silico screening, especially, address flexible targets with few elucidated 3D structures. QM can also play its role in dealing with ionization and tautomerism. Thus, QM-based scoring functions provide a better correlation of calculated and experimental ligand affinities than the classical MM. This in turn, improves its role in lead optimization [10]. Therefore, they show low performance in cases that are not considered in their formulations. Machine learning, nonparametric learning, does not take the form of predetermined functions. Instead, outputs are extracted from the input data. It can give a continuous output as in nonlinear regression. This in turn allows for diverse and accurate scoring. Random forest (RF)-Score is one of the first machine learning scoring functions that outperform classical scoring functions. In addition, logistic regression and support vector machines (SVM) were used to improve docking-based binding affinity predictions [11].

Applications of Molecular Docking in Drug Discovery

A binding communication between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may. Result in agonist or antagonism. Docking is mainly used in the field of drug design. Most drugs are small organic molecules, and docking may be applied to: With advances in docking algorithms, an increase in open-access information on ligands and targets, the applications of molecular docking in drug discovery are rapidly increasing. The applications of docking in virtual screening have increased with the combination of the method with other new applications. For example, the combination of molecular dynamics and free energy binding estimation methods with docking has improved virtual screening. These days there is a great effort worldwide to discover a promising drug against the global pandemic, COVID-19 [12]. The results demonstrated that platelet-derived growth factor receptor (PDGFR), hepatocyte growth factor receptor (HGFR), IL-2 Receptor, and ErbB1 tyrosine kinase might be the potential off-targets. Furthermore, by combining docking with machine learning (ML) and statistical approaches, advanced screening methods, which also make drug side effect predictions more advanced, were developed [13].

Pharmacology: Poly pharmacology expresses the identification of ligands that interact with targets with a selected series of therapeutic values. The pharmaceutical industry has concentrated on the development of immensely selective drugs to avoid possible side effects [14]. There are docking- based web tools and platforms used to investigate polypharmacology and determine the ligands' multitarget activities. CANDO (computational analysis of novel drug opportunities) is an example for platforms and DRAR-CPI (drug repositioning and adverse reactions via chemical protein interactome) is an example for web servers.[15]. There are many docking approaches and algorithms for reverse screening of a ligand against protein structure libraries and evaluation of its binding affinities. However, the implementation of these methods needs a convenient target library [16].

Drug Repurposing

Drug repurposing is an established drug discovery way that provides the opportunity to identify new therapeutic applications for approved drugs, drug candidates under evaluation, natural products, or generally presynthesized ligands [17]. Considering the wealth of information available in public databases on ligands, targets, and diseases, efforts to increase the application of the discovery strategies based on in silico repurposing have increased over the last decades. In silico repurposing methods have been shown to offer valuable new opportunities in drug discovery and development. For example, researchers searched for commercially available drugs to repurpose them against SARS-CoV-2 using in silico approaches. The stability of the complexes was also checked by MD simulations [18]. In another study, researchers identified potential inhibitors of Mpro of the novel coronavirus using in silico drug repurposing. Molecular docking calculations were carried out using Auto Dock 4.2 to select top-ranking drugs from the Drug Bank database. After the top-ranked approved drugs from the database were filtered, 35 drugs with docking scores of lower than -11.0 kcal/mol were picked for further

investigations. Based on these promising results, it is possible to say that docking is a valuable approach in drug repurposing. Especially, when it is combined with other computational approaches, such as ligand-based methods, its value increases in another similar work, Remdesivir was found to be one of the hits for Mpro inhibitors [19].

Challenges in Molecular Docking

The field of molecular docking is confronted with challenges waiting to overcome with increase predictive power so as to widen the application aspect of this computational field. In the form of a research field, docking has undergone tremendous evolution since its inception. It does not always predict the correct binding modes of a ligand since the underlying algorithms are just approximations of the real world. So, a number of docked poses ranked subsequently by the docking score is produced during each docking run. Few attributes can correctly predict the binding modes such as: if only the binding site is small, small ligands, sufficient knowledge about the receptor, smaller constraints for binding sites and above all experienced hands [20]. The use of a scoring function for estimating binding affinity remains to be the mainstay of many virtual screening projects. One of such with force field based function is to deal with the solvent effect. In addition to it, the entropic effect is a much more serious problem while scoring. The former challenge can be solved by introducing a dielectric constant which is distance dependent that can screen the dielectric constant of water as tried in the DOCK force field scoring function Combining these regions, a volume envelop is made where the calculated van der Waals interaction remains low than a defined threshold, gives the probable binding site Again, HADDOCK guides the docking procedure by using biophysical and biochemical data. Upon binding, an increase chemical shift perturbation is observed which are considered critical residues by the program and is incorporated as AIR (Ambiguous Interaction Restraints) for exploring the potential sites on the protein surface and delivers the most optimal interacting atom-pairs. Future Prospective and Focus Drug Discovery As estimated recently, overall drug development cost is high, comprising the cost of failures, capital and launch per drug exceed $2.6 billion Molecular modeling, docking, VS can substantially reduce the burden of screening and has the potential for complementing the designing scheme. This silver lining of digitization in drugs is appreciable as FDA recently approved the first digital pill “Abilify MyCite” a 1 mm chip which is activated when comes in contact with stomach acids sends a signal to a band-aid sized patch attached to a Smartphone. Hence, developing reliable models for predicting binding affinities is the need of the hour. Although they are still in a proof- of-concept except in some isolated cases, soon they will overtake the conventional way of drug companies with the growth of artificial intelligence, big data and

“organ to chip” analysis which includes benefits of reducing errors and material consumption For example (−)-englerin A, a natural anticancer compound which was computationally obtained in 3 steps, otherwise takes 14 steps giving accurate activity as predicted.

Conclusion

In conclusion, molecular docking has emerged as a pivotal technique in structure-based drug discovery, enabling the rapid and cost-effective identification of novel bioactive compounds. This review has highlighted the broad spectrum of molecular docking, its underlying principles, and applications in drug discovery. Despite the challenges and limitations associated with molecular docking, its role in making the drug discovery process more efficient and effective is expected to rise. The integration of molecular docking with other computational approaches, such as molecular dynamics and machine learning, has significantly enhanced its predictive power and accuracy. The development of more advanced scoring functions and sampling algorithms has also improved the reliability of molecular docking results.. The integration of molecular docking with other emerging technologies, such as artificial intelligence and machine learning, will likely further enhance its predictive power and accuracy. In summary, molecular docking has emerged as a powerful tool in structure-based drug discovery, enabling the rapid and cost-effective identification of novel bioactive compounds. Its role in making the drug discovery process more efficient and effective is expected to rise, and its integration with other emerging technologies will likely further enhance its predictive power and accuracy.

Author Contributions

All authors are contributed equally

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Declaration of Competing Interest

The Authors have no Conflicts of Interest to Declare.

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