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RESEARCH ARTICLE

A REVIEW ON MOLECULAR DOCKING AND IT'S APPLICATION

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Abstract

Molecular Docking is powerful computer strategy, critical in drug development, structural biology, and biomolecular interaction researchproviding a thorough grasp of its importance in modern scientific study. Molecular docking involves forecasting how a small molecule, often a potential medication, will interact with a target biomolecule like DNA or a protein. This process examines the spatial and energetic compatibility of the ligand with the active site of the receptor, assisting in the discovery of new drug candidates, refining existing compounds, and understanding the intricate interactions between drugs and receptors. Molecular Docking a computational tool that evaluates and ranks different ligand-receptor conformations based on their binding energies. An accurate scoring function is imperative for distinguishing high-affinity ligands from low-affinity ones, this makes it possible to identify potential medication candidates for validation in experiments. Molecular docking finds application in various domains of Drug Progress, comprisingstructure-based medication development, virtual screening,lead optimization.When creating a medicine based on structure, the target biomolecule's three-dimensional structure is employed to guide the ligand selection that will communicate with the region that is active. Virtual examination accelerates the discovery of potential drug properties by rapidly evaluating large compound libraries. Lead optimization, on the other hand, is facilitated through iterative docking studies aimed at enhancing binding affinity and pharmacological properties. The field of molecular docking has seen a proliferation of diverse techniques designed to address the unique challenges of structure-based drug design and biomolecular interaction analysis. This report provides an in-depth examination of thedistinct methodologies of docking, it's principles, applications, and their importance in advancing our understanding of molecular interactions in different contexts.The diversity of docking methods arises from the need to accommodate different types of molecules, target structures, and research objectives.

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Introduction:-

The discipline of molecular docking has risen in demand over last few decades, primarily to be determined by the need of molecular biology structures and drug discovery based on structure.An enormous boost in computational capacity and accessibility, along with the simplicity with which tiny chemical and protein libraries have become readily accessible, have significantly assisted in this process [1]. Finding a novel medication is not just a resource-intensive task, but also a costly one due to its length, difficulty, and arduous nature. Providently, computational technique have intervened and unquestionably proven essential in streamlining the procedure for drug development [2]

Prior to the formal establishment in the 1980s, technological developments within computing IT equipment's power, along with the rise in number and accessibility of exposure to tiny particle and structures of protein, have resulted in the development of superior ways, facilitate docking progressively in educational as well as in professional environment. According to a 2016 estimate provided by The Tufts Centre for The Study of Drug Development, the expense for producing and introducing a novel medicine to the consumer has climbed approximately 145% in the past ten years.Since the median length of period neededfor incorporating a medicine to research studydeclined, the portion of excel of pharmaceuticals receiving FDA clearance has declined to 12%. By steering research towards ideal chemical more quickly, CADD (COMPUTER AIDED DRUG DESIGN) helped to lower medication discovery cost along with timelines [3].

Multiple Docking software schedules was created during last few years for both research and industrial purposes. Similarly, thevariety of articles mentioning "docking" has expanded dramatically in the preceding 20-25 years. A great number of quality review papers and comparison studies have enhanced the theoretical understanding and practicability of the existing programs[4].

Current approaches in medicinal chemistry:

Molecular Modeling have become more important while examining the relationships between structure and activity i.e., structure-activity relationship or correlation(SAR) in the research-based pharmaceutical sectors, to study pharmacokinetic features like (ADMET) additionally to pharmacodynamic facts (e.g., affinity, potency, selectivity, effectiveness).

The discipline has advanced in tandem with improvements in biomolecular spectroscopic techniques including Nuclear Magnetic Resonance Spectroscopy and X-rays crystallization have permitted remarkable breakthroughs in structural and molecular biology. Over one hundred thousand 3-D arrangements of proteins have been resolved using these techniques, yielding vital insights on significant large molecular shaped therapeutic goals [5].

Throughout the province of computational chemistry, docking is a course of action which prophesy the most effective orientation or spatial arrangement of one molecule to other at the very moment small molecule (liganddrug) interact with target protein (receptor) to form a undeviating combination [6]. The ligand might be any macromolecule yet this technique is typically carried out among proteins of eminent 3-D structure [7]. Additionally, docking of molecules is a popular virtual evaluation method if a desired protein's 3-D structure has been determined [8]. Molecular docking predicts non-covalent bonds between molecules, such those between a ligand and a protein receptor. The subsequent forecast generates the configuration and, in most cases, the reactivity of tiny molecule in the projected lowest vitalityform, & it's employed to digitally filter enormous libraries of substances[9]. The MD technique has two primary steps: search algorithm and scoring function [10].

In recent years, the Molecular Docking approach helped in drug designing by assisting with the estimation of binding affinity and scrutinize the interaction mode, owing to design and commonly utilized drug design tool and for anticipating the dynamic between ligand and receptor [3] [5] [11].

Molecular Docking investigates numerous attaching mechanisms of agonist to a specific biological receptor(usually protein) in orderto evaluate the most effective interaction mechanism. Predicting agonist (drug) binding affinity may be made using knowledge about the ligand binding mechanism. Large chemical libraries can be computationally screened first using molecular docking, and in the experiment, only possible binders to the desired complexing agent will be confirmed. Thisinexpensive"virtual screening" technology developed into a prominent method foras ademand generation tool in academic as well as commercial settings [12].

Later, docking is used asa mathematical tool to prophesy an attractive interaction or the degree to which two molecules are associated i.e., scoring function [13]. In the realm of structure-based drug discovery, scoring functions play a critical role in molecular docking[14]. These functions are essential throughout the process for two main purposes: (a) discerning the correct binding orientation from numerous computer-generated docking models (decoys), and (b) assessing the binding affinity of each molecule [15]. In molecular docking, tens of thousands of potential ligand poses are generated using protein structures, and scoring functions are employed to evaluate these poses, guiding the determination of ligand positioning. Scoring functions are frequently utilized to discover potential drug candidates for specific protein targets, predict binding affinity, understand ligand attachment mechanisms, and determine ligand locations [16]. In a study comparing 10 docking systems, 37 scoring functions, and 8 proteins from 7 different protein types for the objectives of lead optimization affinity ranking, lead identification through virtual screening, and estimation of binding modes, all docking algorithms could produce ligand conformations like those established by crystallography for at least one of the targets [17].

Score algorithms are typically divided into numerous categories:- (a) Force Field scoring function[18][19] (b) knowledge-based [20], (c) empirical [21] and (d) machine-learning based [22]. All the mentioned scoring algorithm have been authenticated on multiple set of complex configuration and may theoretically be incorporated into a docking tool. So, it's both fascinating and crucial to determine that which scoring function outperform the other [23].

The interactions of physiologically important components like proteins,lipids,N.A and carbohydrates are essential to the transmission of signals. The type of signal created may also depend on the relative alignment of both the interacting correlates (for example:- agonism and antagonism). In this way, docking is used to predict the nature as well as intensity of signal generated[24].

Docking is frequently utilized to regulate the small molecule's affinity and activity by anticipating the alignment of therapeutic candidates with certain target molecules. Docking is therefore essential for characterizing the structural makeup of therapeutic candidate. The purpose of docking research is to lower the the free vitality of the system as a wholeby optimizing the relative positioning and structures of the binding agent and enzyme [25].

Recognition of molecules provides an essential purpose for promoting basic biomolecular proceedings. This expression "molecular recognition" pertains to a particular noncovalent bonding contact among a few molecules, such as a H-bond, metal coordination, Lipophilic force,london force, - interaction, halogen bond, electrostatic effect, and/or electromagnetic effect. It can happen between a receptor and a ligand, an antigen and an antibody, a chain of amino acids and a DNA molecule, a peptide and a protein, a small molecule and a protein or peptide, etc. A thorough grasp of the nature of the interaction between pharmacopore and their proteintarget or nucleic acid targets may offer a foundation for creating pharmacological leads with the optimal potency and specificity for a particular therapeutic target [6][26][27][28]. Complementarities in the form and electrostatics of the binding site surfaces with the ligand propel these specialized interactions in biological systems [29].

Types of interaction in molecular docking

1. Electrostatic interaction [30]
2. Electrodynamic interaction [31]
3. Steric factor / steric force [32]
4. Solvent related force:H-bond and lipophilic interaction [33]
5. Other physical aspects: Conformation changes for either ligands or proteins is important for successful docking.

Types of docking

There are several free online programs accessible to create 3D ligand and target interaction profiles, including Biovia DSV, Pymol, Chimera, Rasmol, SwissPDB viewer, etc[34].

There are 3 general categories for docking, which are covered below:

Flexible docking

Flexibility can be handled in a few different ways: The concept of flexible docking involves allowing both the ligand and the receptor to be flexible during the docking process, which can significantly improve the accuracy of molecular docking simulations. This flexibility can be achieved implicitly by permitting sidechain and/or

backbone flexibility or explicitly by executing multiple docking runs from different conformations, known as cross or ensemble docking. Additionally, soft docking strategies involve smoothing the protein surfaces or permitting some degree of interpenetration to account for flexibility and enhance ligand binding. In flexible docking, both the ligand and the receptor are kept flexible, allowing for a more realistic representation of protein-ligand interactions and increasing the chances of identifying optimal binding poses.[35].

According to Daniel Koshland's induced-fit theory, which he proposed in 1958 which often referred as "induced-fit docking," in which the binding energies of alternative conformations of the suggested ligand are computed at protein or receptor [36]. FlexX-Pharm is an advanced iteration of the flexible docking software FlexX, designed to incorporate crucial details about the characteristics of protein-ligand binding modes into the docking process. This enhanced version allows the inclusion of information derived from receptor-based pharmacophore characteristics as constraints in the docking calculations[37].

Semi flexible docking / Flexible ligand docking

In this method, the sole flexible part is the ligand molecule, whereas the protein is stiff. In this type of molecular dockingthe flexibility of a ligand in molecular docking simulations is achieved by permitting rotatable bonds, permitting the ligand to approve different conformations during the docking process, but the protein structure remains stiff [38]. Semi-flexible docking involves considering the ligand's conformational flexibility while maintaining the protein as rigid[39]. Semi-flexible docking is frequently used to investigate molecular identification since it requires more computing power than rigid docking but less than completely flexible docking, this assumption is not always validate[40].

Rigid docking

Rigid body docking is a kind of Molecular Docking in which protein as well as the ligand are assumed to be fixed and only the longitudinal and circular degrees of freedom are taken into account[41]. Rigid body docking is less computationally costly than flexible or semi-flexible docking,which permits adaptability in the ligand and the protein.Rigid body assumption plainly presents constraints in accuracy and dependability [42]. The main notion of Rigid Docking is based on Emil Fisher Lock &Key theory, which he proposed in 1898[43] [44].

Approachfor Molecular docking:

Monte carlo approach

The Monte Carlo method was used to solve the molecular docking issue, this entails anticipating the direction a molecule would prefer to faceone another upon joining to create an enduring structure[45].Monte Carlo (MC) methods use rigid-body translation, bond rotationor rotation in an active site to produce ligand randomized conformation. The conformation learned by this alteration is evaluated using an energy-based choicecriteria.If it satisfies the requirements, it will be retained and switched to create the next confirmation[46].

Metropolis Criteria

The Metropolis criterion assesses whether an updated configuration should be kept. According to this criterion, if a new strategy performs better than the previous one, it is immediately accepted.[47].

Fragment based method.

The fragment base approach is defined as follows: docking the fragments, joining them together, and dividing the ligand into separate protons or fragments. The pieces are independently docked on receptors, and the output is utilized to reconstruct aoutline of several potential docking conformations. The high degree of freedom (DOF) is effectively avoided by this strategy [48].

Distance geometry

It is possible to depict a wide variety of sequence features using intra- or intermolecular dimensions. These distances can be designed, and appropriate three-dimensional structures can be calculated thanks to the distance geometry framework. A lot of work has gone into creating models of molecules of different sizes, such as tiny molecules, peptides, and proteins, using distance geometry techniques [49].

Matching approach

These strategies underscore the importance of complementarity. If a ligand atom occupies an optimal position at the site, it may be crucial to fine-tune the configuration of the ligand-receptor interaction. From a certain

perspective, the protein and the ligand represent interdependent surfaces with matching capabilities. Describing their complementarity in terms of shape matching facilitates the identification of the most fitting orientation for docking the target and ligand molecules. [50].

Ligand fit approach

"Ligand fit" refers to a swift and precise method for docking small molecule ligands into the active sites of proteins, considering shape complementarity. The Ligand Fit docking process comprises two main steps: (a) identifying cavities to pinpoint and select the protein region designated as the active site for docking, and (b) docking ligands into the chosen site. [51].

Point complimentarily approach

This strategy seeks to assess the chemical complementarity and shape of the molecules involved in certain interactions [52].

Inverse docking

Inversedocking is a computerizing process fora particular tiny molecule of interest to be docked to a collection of receptor structures. The method might be used to discover fresh prospective biological targets for established drugs or to find chemical targets among a family of similar receptors [53]. Additionally, the method may be used to predict the pharmacological profile of a molecule orconstruct a virtual selectivity profile that reflects the inhibitors' promiscuity [54].

Using a structure-based computational approach, 'one ligand-many targets' is represented by inverse docking.[55]. The inverse procedure yields a list of probable protein targets for the ligand, sorted by projected affinity (docking scores) for the ligand [56].

Blind docking

Blind docking involves the docking of a ligand onto the entire surface of a protein without prior knowledge of the target binding pocket.[57].

Mechanism of docking

This approach involves predicting how a small chemical compound interacts with a protein at the atomic level by using molecular docking. This technique assists in drug discovery, optimizing leads, and comprehending molecular recognition processes. The molecule, called a ligand, can function as an inhibitor. This method relies on a detailed 3D representation of the target protein, which can be obtained through techniques like Nuclear Magnetic Resonance Spectroscopy, X-ray crystallography, or Cryo-Electron Microscopy. [58][59]

Before beginning a docking screen, it's crucial to have the structure of the protein under investigation. A docking tool utilizes this protein structure alongside a database of ligands. The effectiveness of a docking program depends on two main factors: the scoring function and the search method, which explore Conformational Space. This space encompasses all potential conformations and orientations of proteins and ligands. Due to current computational limitations, exhaustive exploration of this space is impractical. This would involve considering all possible distortions of each molecule and all potential rotational and translational orientations of the ligand concerning the protein at a specific level of detail. Many docking systems currently in use incorporate flexible ligands, while others are striving to model a flexible protein receptor.[60].

Critical phase in molecular docking

Preparation of protein

Brookhaven National Laboratory (BNL) established the Protein Data Bank (PDB) in 1971 to serve as a repository for the crystalline structures of biological subunits. The PDB is a vital resource for accessing the 3-D structures of proteins. After October 1998, management of the PDB was transferred to the Research Collaboratory for Structural Bioinformatics (RCSB). The RCSB aims to enhance the accessibility and understanding of structure-based data by leveraging cutting-edge innovations. Their objective is to develop a resource that fosters biological research and supports advancements in the field. [61].

Active side prediction

Once a protein has been shaped, its active site should be predicted. Protein 3D structure prediction is critical for predicting active sites [62].A receptor may have multiple functioning regions; only the most significant one needs to be chosen. Water molecules, inhibitors, and other mixed atom removed from the protein and utilized for docking[63].

Preparation of ligand

Preparing a ligand for molecular docking involves several steps, including generating a 3D structure of the molecule, determining appropriate bond orders, and considering accessible tautomeric and ionization states[64]. The choice of ligands for docking depends on the specific objectives of the study. These ligands can be sourced from various databases such as ZINC and PubChem, or they can be manually drawn using software like Chemsketch[65]. while selecting the ligand,The LIPINSKY'S RULE OF 5 should be tracked[66].

Analysis

The primary goal of docking analysis is to understand the interaction between a protein molecule and a binding agent. This interaction occurs at a specific binding site on the protein, and the strength of the interaction is typically quantified by the binding energy. Lower binding energies indicate stronger and more significant interactions between the protein macromolecule and the ligand, highlighting the most crucial binding events[67]. Molecular docking has been useful in determining protein-ligand interactions and pharmacological modes of action [68].

Docking Software

Molecular docking has changed into ancrucial tool and technique that contributes significantly to the efficacy of high-throughput computer-generated screening techniques utilized in educational institute and industrial drug screening and discovery processes. Significant advancements in advanced computers, improved software & atmospheric platforms, and enhanced publicly accessible chemical database have benefited computational screening approaches in becoming more accurate, effective, and valuable in recent year. Numerous docking software programs have been created over the last few decades for both academic and commercial applications. Similarly, the number of papers concerning "docking" has expanded significantly during the previous 20-25 years [69][70]. Table (1) highlights essential docking tool features such as approved platforms, license requirements, algorithms, and score systems.

Application Of Molecular Docking

Due to its application prior to any investigation's experimental phase, molecular docking can show if a certain biological reaction is feasible. There are various fields where molecular docking has transformed research. The specific relationship between ligands and protein targets, which might be enzymes, can be used to forecast to what extent an enzyme will be inhibited or activated. This knowledge might serve as a starting point for rational medication design [105].

The most significant applications of molecular docking are listed below:

Hit identification.

Structure-based computer-aided drug design (CADD) aids in hit identification, where docking, along with a scoring function, can efficiently screen large databases of potential drugs in silico. This process aims to identify compounds with a high likelihood of binding to a specific protein target of interest. However, there is limited research systematically assessing the success rate, also known as the hit rate, of docking campaigns. This hit rate refers to the percentage of compounds accurately predicted to bind to the protein target [106][107].

Lead Optimization

Docking is employed to ascertain the binding mode or posture of a ligand as it interacts with a protein, offering insights that aid in the design of more potent and selective analogs. Lead optimization involves refining initial hit or lead molecules to enhance their effectiveness and drug-like properties. In cases where structural details of the target are known, docking and scoring serve as valuable strategies for both hit identification and the optimization of hits into lead compounds[110].

Some other application are as follows :-

1. Bioremediation [111]
2. Prediction of Ka (biological activity) [112]

3. Binding side prediction [113]
4. Mechanism of Enzymatic reaction [114]
5. Protein -Protein / Nucleic Acid interaction [115]

Conclusion:-

Molecular docking is a dynamic and growing discipline that provides a foundation for understanding molecular recognition. As technology advances and our knowledge of biological systems develops, Molecular docking will remain an essential technique for the discovering novel treatments and the explanation of complicated molecular relationships. The ability to select the appropriate docking type, model, technique, and software for individual research aims, while carefully traversing the key phases, is important to realizing the full potential of this computational approach. The future of molecular docking seems hopeful, with potential treatment options and a greater knowledge of the complicated molecular dance that supports life itself.

The contemporary landscape of drug discovery has undergone a remarkable transformation, primarily attributed to the advent of molecular docking. This computational technique, centeredon the simulation of ligand-receptor interactions, stands as a beacon of hope for researchers and pharmaceutical scientists alike. Its foremost importance lies in its ability to accelerate the drug findingprocedure, greatly cutting down on the expenses and duration of experimental screening.

Looking forward, the future of molecular docking is brimming with promise. As computational techniques continue to improve&our understanding of biological systems deepens, this methodology is expected to evolve and expand its horizons. With the integration of machine learning, artificial intelligence, and the consideration of dynamic effects such as solvation, the accuracy and predictive power of molecular docking are poised to reach new heights.

In closing, molecular docking stands as a testament to the synergy between science and technology. It embodies the fusion of biological knowledge and computational prowess, offering a pathway to unlock the doors of therapeutic potential. As we journey forward in the pursuit of novel drugs and innovative treatments, molecular docking will remain an indispensable tool, guiding us towards a healthier and more vibrant future. Its impact transcends laboratory boundaries, shaping the very landscape of healthcare and pharmaceutical innovation. The promise it holds is not only significant but also boundless, ensuring its enduring relevance in the ever-evolving field of drug discovery.

Tabled 1:- Different types of docking program.

S.NO.	PROGRAM REF**	SUPPORTED PLATFORM	LICENSE TERM	DESIGNER/ COMPANY	DOCKING APPROACH	SCORING FUNCTION
1.	AutoDock [71][72][73] [74][75][76] [77][78][79]	Windows, Unix, Mac OS, Linux	Free and available under open source license	D.S. Good sell and A.J. Olson The Scripps Institute of Research	Lamarckian genetic algorithm Stimulated Annealing Genetic algorithm	Force field
2.	Flex X [80][81][82] [83][84][85]	Linux, SGI, SUN Windows	Commercially free evalution	T. Lengauer and M. Rarey Bio SolveIT	Incremental Construction	FlexXScore, PLP, screen score
3.	Glide [86][87][88] [89][90][91]	Unix, Linux, IBM AIX	Commercially free	Schrödinger Inc.	Monte Carlo Sampling	Glide Score
4.	GOLD [92][93][94] [95][96][97]	Linux, SGI	Commercially free	Cambridge Crystallographic Data Centre	Genetic Algorithm	PLP, Chem Score, Gold Score,

	[98][99] [100]					
Some other docking tools are :- Surflex[101], FRED [102], LigandFit[103], SLIDE[104]						

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