IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

A REVIEW ON MOLECULAR DOCKING: NOVEL TOOL FOR DRUG DISCOVERY

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Abstract: The burgeoning field of computer-aided drug design and discovery (CADDD) has witnessed substantial growth, leveraging structural informatics, genomics, and proteomics to propel advancements in modern drug development. Molecular docking, a cornerstone technique within this domain, facilitates structure-based virtual screening (SBVS) by positioning small molecule structures within target proteins, thereby exploring potential binding orientations and conformations. This approach plays a vital role in various applications such as structure-based drug design (SBDD), lead optimization, evaluation of biochemical pathways, and de novo drug design. Through molecular docking, the binding mode and affinity of resultant complexes are estimated, aiding in the molecular recognition process and facilitating the discovery of novel drug leads.

Index Term: Molecular Docking, Types of Docking, Applications of docking, Docking, Docking for Drug Discovery, Drug Discovery, CADD, Drug Receptor Binding force.

Introduction: In recent decades, there has been a notable paradigm shift in drug design methodologies, transitioning from conventional, resource-intensive approaches towards more expedient and cost-effective virtual screening techniques. These advancements have been necessitated by the limitations inherent in traditional methods, prompting the adoption of more rational and efficacious strategies. Among these, virtual screening can be delineated into two principal categories: structure-based and ligand-based methodologies, each leveraging distinct computational frameworks. Notably, the former encompasses molecular docking, elucidating the energetically favorable conformations of ligand-protein complexes, whereas the latter encompasses quantitative structure-activity relationship (QSAR) analyses and pharmacophore modeling techniques. The proliferation of structurally resolved biomolecular targets, facilitated by advancements in chemical synthesis, purification, and spectroscopic methodologies such as X-ray crystallography and Nuclear Magnetic Resonance (NMR) spectroscopy, has underpinned the efficacy of these computational approaches [1]. Molecular docking, a cornerstone of structure-based drug design, elucidates the intricate non-covalent interactions governing ligand-protein binding events, encompassing hydrogen bonding, ionic interactions, hydrophobic effects, and van der Waals forces [2]. Notably, molecular docking endeavors encompass a diverse array of interaction modalities, including protein-protein, protein-ligand, and protein-nucleotide interactions [3]. The procedural workflow of molecular docking encompasses several discrete steps, including the preparation of three-dimensional protein structures, ligand pre-processing, estimation of ligand-protein binding energies, and subsequent analysis of docking results [4].

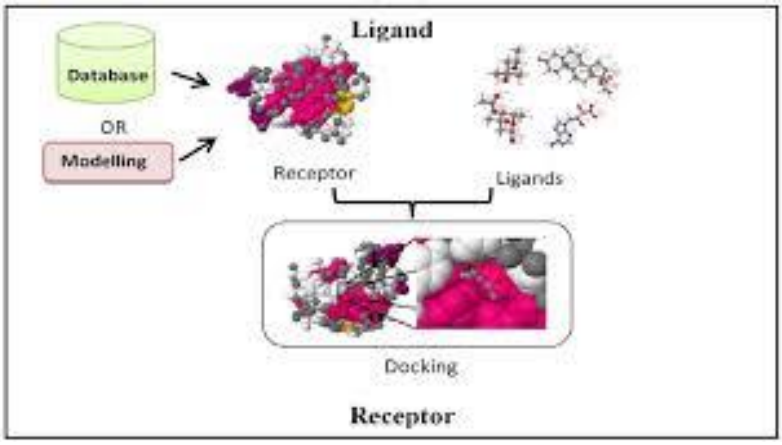

Fig no: 1 (https://www.google.com/imgres?q)

CADD (COMPUTER AIDED DRUG DISCOVERY):

a. Computational ability enhances the drug discovery and development process by accelerating tasks like virtual screening and molecular modeling.

b. Access to chemical and biological information about ligands and targets enables the discovery and optimization of novel drugs by facilitating rational drug design and structure-activity relationship analysis.

c. In-silico filters are designed to exclude chemical compounds with undesirable properties, such as poor activity or absorption, distribution, metabolism, excretion, and toxicity (ADMET), allowing for the selection of the most promising candidates for further development.

d. Computational methods like Computer-Aided Drug Design (CADD) utilize databases of target protein structures, such as the Protein Data Bank (PDB), to identify novel drug targets and discover potential drug candidates.

e. Virtual screening techniques are applied to identify novel drug candidates from diverse chemical scaffolds by searching through databases, offering a cost-effective and efficient approach to drug discovery.

Types of Molecular docking:

The elucidation of molecular docking methodologies delineates three primary modalities:

I. Induced fit docking entails the simultaneous flexibility of both the ligand and receptor, wherein the ligand dynamically conforms to the active site of the receptor, optimizing bonding interactions. This mechanism underscores the principle of complementarity between the protein and ligand.

II. Lock and key docking, rooted in the Lock and Key theory, assumes rigidity for both ligand and receptor, facilitating tight binding [5]. This concept emphasizes three-dimensional complementarity as the foundation for molecular recognition.

III. Ensemble docking elucidates the complexity of protein conformational states by leveraging multiple protein structures as an ensemble for ligand docking. This approach accommodates the inherent flexibility and diversity of protein structures.

Recent investigations have spotlighted covalent docking, particularly in the context of irreversible inhibitors binding to target receptors. Covalent docking facilitates the formation of robust chemical linkages between electrophilic ligands and nucleophilic residues on proteins, endowing chemical probes with heightened potency and selectivity. Noteworthy examples of FDA-approved drugs employing covalent bonding include Aspirin, Warfarin, and Azacytidin [6,7].

The utility of covalent bonding extends to various applications, including virtual screening, lead optimization, quantitative structure-activity relationship (QSAR) studies, and molecular dynamics simulations.

The process of molecular docking encompasses both manual and automated approaches. Manual docking involves the explicit identification of binding groups on the ligand and binding site, followed by the pairing of complementary groups and the definition of bonding distances. Automatic docking, on the other hand, delegates the task of ligand placement and

orientation to software algorithms. The primary objectives of docking programs include the exploration of ligand binding orientations and the subsequent scoring of binding modes to ascertain optimal configurations,

1. It has to place the ligand within the active site in different orientations or binding modes.
2. It has to score the different binding modes to identify the best ones.

Major steps involved in mechanics of molecular docking:

Molecular docking, an in-silico approach, investigates the intermolecular interactions between two molecules: a protein receptor (macromolecule) and a ligand molecule, often serving as an inhibitor. The docking process entails several steps:

Step I – Protein Preparation: The three-dimensional structure of the protein is retrieved from the Protein Data Bank (PDB) and subsequently pre-processed. This involves tasks such as removing water molecules from the cavity, stabilizing charges, filling missing residues, and generating side chains in accordance with predefined parameters.

Step II – Active Site Prediction: Following protein preparation, the active site of the protein is predicted. Amongst potentially numerous active sites, the relevant one is identified. Typically, water molecules and hetero atoms are removed if present, to focus on the target site.

Step III – Ligand Preparation: Ligands are sourced from databases like ZINC or PubChem, or synthesized using chemical sketching tools. In selecting a ligand, Lipinski's Rule of 5 is applied. This rule distinguishes between drug-like and non-drug-like candidates, offering insights into potential success or failure based on adherence to two or more of the specified rules, which include criteria such as hydrogen bond donors and acceptors, molecular mass, lipophilicity, and molar refractivity.

Step IV – Docking: The ligand is docked against the protein, and the resultant interactions are analyzed. A scoring function is applied to evaluate the docking outcomes, with the best-docked ligand complex being selected based on the score.

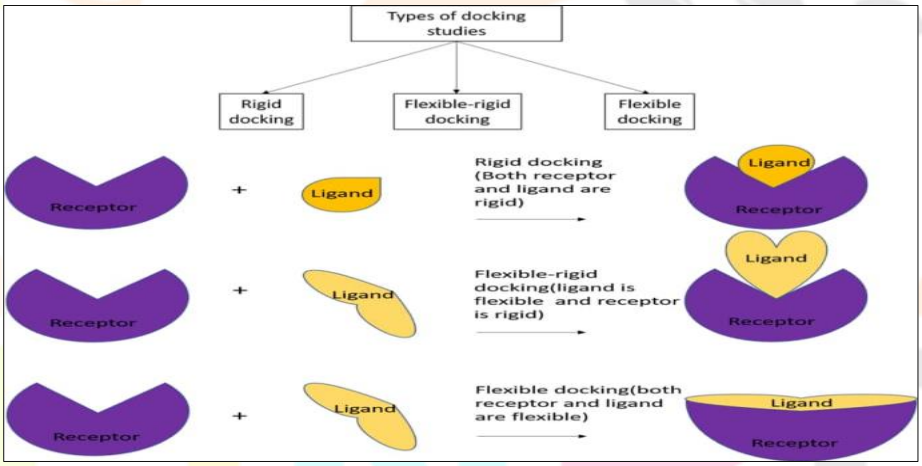

Fig no : 2 Types of docking

The Application of Molecular Docking:

Applications of molecular docking Molecular docking interactions may lead in activation or

inhibition of the protein, whereas ligand binding may lead in agonism or antagonism. Molecular

Docking possibly employed to:

1. Hit Identification (Virtual Screening)

2. Lead Optimization (Drug discovery)

3. Bioremediation

4. Prediction of potential targets

5. Protein engineering

6. Mechanisms of Enzymatic reactions

7. Protein – Protein/ Nucleic acid interactions

8. Searching for lead structures for protein targets

9. Studies of Structure – function

10. Binding site prediction (Blind docking)

11. Prediction of KA (Biological activity)

Virtual Screening to discover the lead compound and hit compound:

Virtual screening, facilitated by scoring functions, has significantly enhanced the identification of lead and hit compounds from molecular databases, thereby substantially augmenting screening efficacy compared to conventional methods. The ubiquity of virtual screening underscores the rapid progress in high-throughput methodologies [11], high-performance computing [12], and advancements in machine learning [13], including deep learning techniques [14]. For instance, Pereira et al. [15] deployed a deep learning approach to extract pertinent features from molecular docking data for the creation of distributed vector representations of protein-ligand complexes. Similarly, Pyzerknapp et al. [16] introduced virtual high-throughput screening methodologies.

Bioremediation:

Protein-ligand docking methodologies extend beyond drug discovery to predict enzymatic degradation of pollutants. Molecular docking facilitates drug discovery through diverse avenues, including target identification, screening for activators/inhibitors against diseases, lead optimization, and elucidation of binding modes and active site characteristics. Its efficiency renders it indispensable in medicinal chemistry, protein engineering, chemo informatics, bioremediation, and other biological and medicinal domains. Notably, molecular docking analysis has elucidated the role of Human Leukocyte Antigen (HLA) variants [17] in idiosyncratic adverse drug reactions, particularly HLA-B*57:01, implicated in abacavir hypersensitivity syndrome. Moreover, molecular docking predicts the functionality of G protein-coupled receptors (GPCRs) and identifies potent drug molecules to inhibit cancer stem cell growth, enhancing therapeutic outcomes [18]. Molecular docking outperforms High-Throughput Screening (HTS) in drug discovery due to its speed and cost-effectiveness in evaluating ligand binding affinity from large chemical libraries. However, challenges persist, including accounting for water molecules and solvation effects at the active site, crucial for accurate docking. Understanding the interplay between ligand desolvation energies and receptor-ligand association free energies provides mechanistic insights into molecular recognition processes, bridging theoretical predictions with experimental observations effectively.

Prediction of Potential Targets:

The aforementioned methods primarily involve general docking approaches, where various ligands dock with a single receptor. However, the reverse docking technique differs in its approach. Utilizing a single small-molecule ligand as a probe, reverse docking docks it with multiple receptors to uncover potential binding sites, thus predicting novel drug targets. For instance, Grinter et al. employed the reverse docking software Mdock to explore the potential target oxidized squalene cyclase (OSC) of PRIMA-1. Similarly, Chen et al. utilized reverse docking to identify target proteins of marine compounds with anti-tumor activity. Moreover, Chen et al. highlighted the complementary nature of reverse docking with in vitro assays, enhancing target identification efficacy. Lastly, structural biology analysis, such as pocket-based exploration, can shed light on the relevant mechanism of action or side effect profiles.

Binding site prediction (Blind Docking):

Blind docking involves the process of docking a ligand onto the entire surface of a protein without prior knowledge of specific target pockets. This method necessitates numerous iterations and energy evaluations until a favorable protein-ligand complex configuration is attained.

Mechanism of Enzymatic Reactions:

Enzymes facilitate chemical reactions by attracting substrates to their active sites, where catalysis occurs, resulting in the formation of products. Subsequently, the enzyme permits the dissociation of the products from its surface. The assembly of an enzyme with its substrates is termed the enzyme-substrate complex.

Protein Engineering:

Protein engineering involves the design and synthesis of unnatural polypeptides, frequently achieved by altering amino acid sequences present in natural proteins. Contemporary methods enable the creation of synthetic protein structures and functionalities either through computer-based design or via directed evolution in laboratory settings.

Conclusion: Considering the inherent limitations in scoring function approximations and incomplete conformational sampling, molecular docking may yield erroneously high scores for inactive molecules, leading to false positives. Moreover, significant disparities in physical properties between actual and database compounds can introduce aberrations in docking scores. Thus, the incorporation of thermodynamic features or retrospective validation is essential to evaluate the reliability of affinity predictions. Additionally, the utilization of three-dimensional structures for docking, removed from their native environments, may result in conformational alterations that inadequately represent experimental docking states. Looking forward, optimizing conformational search algorithms by accounting for greater bond flexibility, solvent states, and integration of recent biological data mining algorithms is imperative. Ultimately, with refined scoring functions and enhanced search algorithms, molecular docking stands poised to evolve into a dependable tool for drug design, capitalizing on the wealth of biological data available.

Table 1 : Basic characteristics for current protein- Ligand docking tools

Entry	Program Reff.	Designer/ Company	Licenses Terms	Supported Platforms	Docking Approach	Scoring Function
1.	Auto Dock	D.S.Good sell and A.J Olson The Scripps Research Institute	Free For Academic use	Unix, Mac OSX Linux, SGI	Genetic algorithm Lamarckian Genetic algorithm Simulated Annealing	Auto Dock (force- field Methods)
2.	Dock	I. Kuntz Univercity of California San Francisco	Free for academic use	Unix, Linux, Sun, IBM AIX, Mac OSX, Windows	Shape fitting (sphere sets)	Chem Score, GB/ SA solvation scoring,other
3.	Flex X	T. Lengauer and M.Rarey Bio SolvIT	Commercial Free evaluation (6 weeks)	Unix, Linux, SGI, Sun Windows	Incremental Construction	FlexXScore, PLP, Screen Score, Drug Score
4.	FRED	Open Eye Scientific Software	Free for academic use	Unix, Linux, SGI, Mac OSX, IBM AIX, Windows	Shape fitting (Gaussian)	Screen Score, PLP, Gaussian Shape score, User defined
5.	Glide	Schrodinger Inc,	Commercial	Unix, Linux, SGI, IBM AIX	Monte Carlo Sampling	Glide Score, Glide Comp
6.	GOLD	Cambridge Crystallographic Data Centre	Commercial Free evaluation (2 months)	Linux, SGI, Sun, IBM, Windows	Genetic Algorithm	Gold Score, Chem Score User defined
7.	Ligand Fit	Accelrys Inc.	Commercial	Linux, SGI, IBM AIX	Monte Carlo Sampling	Lig Score,PLP, PMF

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