EXPLORING MOLECULAR DOCKING: TECHNIQUES, TOOLS, AND THERAPEUTIC INSIGHTS.

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Abstract:
Molecular docking is a vital computational technique in drug discovery and structural biology, used to predict the interaction between small molecules and their biological targets. This review explores the fundamental principles of molecular docking, highlighting its main types—rigid and flexible docking—and the algorithms that drive them. A comparative overview of widely used docking tools such as AutoDock, AutoDock Vina, Biovia Discovery Studio Visualizer and Open babel is provided. The advantages of molecular docking, including its efficiency, scalability, and cost-effectiveness, are discussed alongside key challenges such as scoring accuracy, receptor flexibility, and solvation effects. Finally, the review outlines major applications across drug development, virtual screening, and biomolecular interaction studies, emphasizing the role of docking in advancing modern biomedical research.

Index terms: Docking, Autodock, Drug discovery.

INTRODUCTION:

Docking is a process of positioning molecules in the best possible configurations to engage with a receptor. When molecules are joined to form a sustained complex in a cell, a mechanism known as docking occurs. Docking is a mathematical method that predicts which molecule will be oriented more favourably than the others when they are joined to form a stable complex. Based on their favoured orientation, scoring functions can be used to determine the strength of the bond or binding affinity between two molecules [1]. The docking process usually consists of multiple steps, each of which adds a new level of complexity. Small molecules are positioned in the enzyme's active area using docking techniques [2]. Molecular docking is a computational method that makes easier to forecast the optimal binding orientation of a ligand to a receptor when the two interact one another to create a stable complex [3]. The two terms that are most commonly linked to molecular docking are ligand and protein. A ligand may attach to a protein to produce a certain activity [2]. It is feasible to conduct molecular docking studies between proteins, ligands, and nucleotides. Several molecular docking stages includes ligand production, protein 3-D structure preparation, and protein-ligand complex binding energy estimate [3,4]. The field of drug design research has made extensive use of this technology in recent years. In addition to being practical for researchers to buy, using the chemicals database to filter the possible pharmacophores, synthesize and finish further pharmacological testing, but it also significantly boosts productivity and lowers research expenses. Furthermore, the development of reverse molecular docking technology has the potential to greatly enhance drug target prediction abilities and comprehend the associated molecular process for drug design [5,6].

MOLECULAR DOCKING:

Molecular docking is a bioinformatics-based theoretical simulation technique that examines how molecules interact (e.g., ligands and receptors) and uses a computer platform to predict the binding modes and affinities of those molecules. In medicinal chemistry, such as structure-based rational drug design, this technique represents a promising medium [6]. Both automated and manual molecular docking are possible. In manual docking, the ligand is paired with its corresponding group in the binding site, and the binding groups on the ligand and binding site are known. Every possible interaction has a predetermined bonding distance. The program tries to find the optimum match as specified by the operator by moving the molecule around inside the binding site. Instead of being immediately overlapped, the matched groups are fitted so that they are within each other's recommended bonding distances. It is possible to use automatic docking, in which the software determines how to dock the ligand.

I. It must position the ligand in various binding modes or orientations within the active site.
II. In order to determine which binding modes are optimal, it must score each one [7].

I. STEPS INVOLVED:

- The first step in docking process is protein preparation in which the protein's three-dimensional structure from the Protein Data Bank (PDB) is obtained; the structure should then be pre-processed. Depending on the available parameters, this should allow for the removal of the water molecules from the cavity, the stabilization of the charges, the filling of the missing residues, the formation of side chains, etc.

- Second step is Active site prediction: Following protein synthesis, the protein's active site needs to be estimated. The receptor may have many active sites; just the one that is of concern should be chosen. The majority of the water molecules and, if any, heteroatoms are eliminated [8,9].
- Step three is Ligand preparation where ligands can be obtained from a variety of databases, including Pub Chem and ZINC, or they can be drawn using the Chem sketch tool. When selecting the ligand, it is best to apply Lipinsky's Rule of Five. The Lipinski rule of five aids in differentiating between candidates who are drug-like and those who are not.
- The ligand is docked against the protein in step four, and the interactions are examined. The scoring function assigns a score based on the selection of the best docked ligand complex. [10]

II. TYPES:

1. RIGID DOCKING: The conformation of the docking system (ligand and receptor) remains unchanged in rigid docking. Large systems like protein–protein and protein–nucleic acid can benefit from it. Moreover, rigid docking is the easiest approach because it eliminates the need for several computations [11,12].
2. FLEXIBLE DOCKING: The docking process makes it possible to easily alter the conformation of the docking system (receptor and ligand) during this process. Since the number of atoms increases along with the receptor and ligand variables, a number of other elements must be taken into account. Among these are the computation's size and the docking procedure's excessive complexity. Flexible docking is typically used to precisely analyse molecular interactions [13].
3. SEMI FLEXIBLE DOCKING: The bond length or angle of the noncritical part of the ligand structure can be fixed because the conformation of the ligand is changed while the fixed receptor's conformation stays the same during the semi-flexible docking process [14]. Semi-flexible docking is appropriate for the docking of small molecules and macromolecules, like proteins or nucleic acids, and small ligand molecules. It considers the impact of changes on the ligand structure and can be used in a wider range of applications [15,16].

III. MOLECULAR DOCKING TOOLS:

Docking programs combine a scoring mechanism with a search method. Finding the exact ligand 3D geometry, or poses, within a specific targeted protein is the goal of the search process. In order to assess how well the ligands bind to the protein, the scoring function predicts the binding affinity [17].

Many methods and protocols have been created for the goal of evaluating protein receptor interactions with tiny ligands In silico, which is now a routine element of the drug discovery pipeline. A wide range of techniques and software have been created and improved over the last four decades to produce increasingly accurate forecasts. Simultaneously, advancements in docking have been suggested to tackle more focused issues like the hunt for fragment-based strategies, allosteric medications, or protein–protein interaction (PPI) inhibitors [18,19,20].

The installation of programs and libraries has been made easier and more straightforward by significant advancements in computer science; package managers like apt-get, brew, pip, and conda are just a few examples.

However, the installation and use of visualization programs like VMD (Humphrey et al., 1996), PyMOL (The PyMOL Molecular Graphics System, Delano Scientific, San Carlos, CA, USA), or Chimera or docking programs like Auto Dock, AutoDock Vina, and MGLTools may be too complicated for a user unfamiliar with Unix command lines [21,22,23].

Some of the above mentioned in silico techniques have been made available online via web servers in an effort to increase the accessibility of such computational resources. The following are some instances of web services for small molecule docking: SwissDock is a web interface based on EADock docking software; Webina enables the user to run AutoDock Vina; DockThor is a web server centered on SARS-CoV-2 therapeutic targets; and MedusaDock is a docking methodology that can incorporate structural constraints [24,25,26].

1) **Seam Dock:** We suggest a novel method to make small molecule docking more accessible to nonspecialists, including students, using the Seam Dock web server. For simple interaction site identification, the Seam Dock online service combines various docking techniques into a single framework that enables ligand global and/or local docking as well as a hierarchical method that combines the two. Advanced technical skills are not necessary to use this service, and it operates without the installation of any software other than a standard web browser.

   The user may navigate the Seam Dock web page with ease and interactive capabilities thanks to the Seamless framework, which connects the RPBS computation server to the user's browser. The 3D display of docking poses, ligands, and receptors as well as their interactions with the receptor has been the focus of much work. A user can share a docking session, its complete visualization states, and an infinite number of collaborators due to the sophisticated visualization features and the smooth library.

   Seam Dock is therefore a free, straightforward, didactic, and developing online docking tool that is ideal for training and education [27].

2) **Autodock Vina:** One of the most popular and quick open-source molecular docking programs is probably AutoDock Vina. It does not, however, support modeling certain features like macrocycles or explicit water molecules, in contrast to other AutoDock Suite products [28].

3) **Open babel:** An open-source chemical toolbox that can understand the various languages of chemical data is called Open Babel. More than 110 formats can be interconverted with Open Babel version 2.3. A library that implements a broad range of cheminformatics techniques, from partial charge assignment and aromaticity detection to bond order perception and canonicalization, is necessary to represent such a diverse range of chemical and molecular data. We explain the Open Babel implementation in detail, highlight significant developments in the 2.3 release, and list numerous applications for scientific research and software solutions that go much beyond basic format translation [29].
4) **Biovia Discovery Studio Visualizer:** There is a lot of molecular docking software on the market right now, but a literature review revealed that Discovery Studio is a suite of programs for stimulating systems of small and large molecules. Accelarys is responsible for its development and distribution. It reduces the time and cost associated with bringing products to market by enabling the investigation and testing of hypotheses in silico before expensive experimental implementation. Dassault System BIOVIA (formerly Accelerys) is responsible for its development and distribution. The Discovery Studio program effectively advised the author with regard to biological activities, primarily anti-inflammatory, anti-tubercular, anti-bacterial, anti-viral, anti-diabetic, and antioxidant activities, according to the literature review [30].

IV. CHALLENGES:

Since the previous century, when the area was founded by the first significant efforts, protein docking has advanced significantly [31]. In light of the past, it is appropriate to consider the future of protein docking and discuss its challenges, both the more distant ones, for which it is crucial to develop fundamental paradigms and lay out strategic directions, and the ones that are closer to us, for which current research is advancing quickly. The goal of recent advancements in protein docking is to increase the modelling of macromolecular complexes' application, accuracy, and utility.

More focus on protein docking to various molecules, proper accounting for conformational flexibility upon binding, new promising approaches based on residue co-evolution and deep learning, affinity prediction, and the advancement of fully automated docking servers are some of the challenges. Crucially, recent advancements have placed a greater emphasis on accurately simulating protein interactions in vivo, including the packed environment inside a cell, which entails numerous fleeting contacts, and the system's temporal propagation [32].

There is an inherent trade-off between the precision and speed of the docking algorithm. More sophisticated scoring methods or a more thorough sampling of the potential binding modes and flexibility can be used in an effort to increase accuracy, however these changes typically increase the computing cost. The quantity of chemicals involved tends to place realistic restrictions on the available computational time per compound, making this trade off particularly noticeable in large-scale virtual database screening. Protein-ligand docking techniques have shown significant success in applications in spite of all these obstacles [33].

Fundamental challenges are scoring & sampling. The scoring function is a crucial part of docking procedures. The scoring function used in protein-ligand docking usually evaluates the overall favourability of a protein-ligand complex and is intended to be similar to the free energy of binding between the ligand and protein [34,35]. For practical reasons, one could also want to assess other characteristics, like toxicity and characteristics pertaining to absorption, distribution, metabolism, and excretion [36]. Additionally, it may be beneficial to employ multiple scoring functions even within the sampling method itself. For instance, a quick and straightforward scoring function might be used to eliminate the worst binding modes before evaluating the remaining ones in greater detail. But even though it's a very lofty objective, correctly forecasting binding free energy using a broad scoring function would transform the usefulness of docking approaches in drug research and other applications [37,38].

V. ADVANTAGES:

1. Efficient Screening of Compounds.
2. Insight into Molecular Interactions.
3. Flexibility in Modelling.
4. Cost and Time Efficiency.
5. Versatility in Applications. [39,40].

VI. APPLICATIONS:

Molecular docking plays an essential role in drug discovery research by simplifying target selection, target validation, virtual screening for lead identification and lead optimization. Drugs are primarily organic tiny molecules, however targets might be either proteins or DNA, depending on the ailment of interest [41]. Molecular docking has revolutionized discoveries in a number of domains. Molecular docking must be used in today's study. By examining the interactions between small molecules (ligands) and protein targets (which might be enzymes), one can predict whether an enzyme will be activated or inhibited [42]. This type of information may contain the fundamental components for logical medication design. Some of the primary uses for molecular docking are listed below [42, 43, 44].

- **Lead Optimization:** Molecular docking can be used to predict the optimal location for a small molecule or ligand to bind to its target.
  It is possible to estimate the various ligand binding modalities in the target molecule's groove. Analogues that are more potent, distinct, and efficient could be made using the data acquired from these types of studies.
- **Hit Identifications:** In order to search through enormous databases to identify the potential drug candidates that can target the desired molecule, molecular docking can be utilized in connection with a scoring function [2,42,43,44,45].
- **Remediation:** It is also possible to anticipate which pollutants are enzyme-degradable using protein-ligand docking. It can be used to locate the best place to collect the strongest medications. Enzymes and their mechanisms of action can be determined using molecular docking. It can also be used to determine the connections between proteins. The remediation method is used to virtually filter molecules [2].
- **Bioremediation:** Protein ligand docking can be used to estimate which contaminants enzymes can degrade [43,45].
- The discovery of therapeutic medicines is facilitated by molecular docking in a variety of ways, including:
  a. Identification of potential target.
  b. Screening of potent drugs as activators/inhibitors against certain diseases.
  c. New drug development through lead optimization.
  d. Prediction of the nature of the active site and the binding mode.
  e. Less a time-consuming chemical compound synthesis.
  f. Drug-DNA interactions.
  g. Protein de-orphaning.
  h. Nucleic acid and protein interactions.
  i. Structure-function studies.
  j. Discovering the lead structures of potential protein.
  k. Enzymatic reaction mechanisms.
  l. Protein modification [44,45].

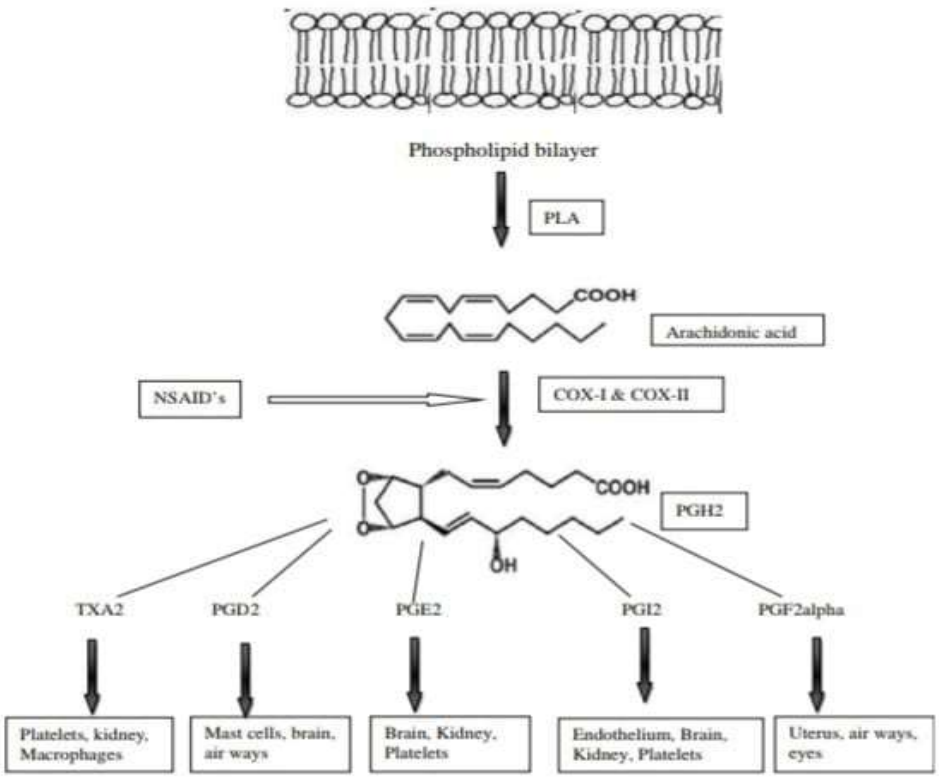

Fig 1: Molecular mechanism of COX-I & COX-II [46].

VII. CONCLUSION:

It is concluded that Molecular docking allows researchers to predict the binding mechanism and affinity of small compounds to proteins, it has completely changed the drug discovery process. This potent instrument has been effectively used in a number of domains, including as virtual screening, protein-ligand interactions, and drug development. Docking holds promise for improving treatment outcomes and advancing personalized medicine by finding possible lead compounds and refining their binding qualities. We may anticipate seeing even more creative uses of docking as the area develops, which will result in the creation of fresh and efficient cures for a variety of illnesses.

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