A comprehensive Review on Molecular Docking: Methods, Applications, And Limitations in Modern Drug Discovery

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Abstract- Molecular docking is a widely used computational technique for predicting the interaction between small molecule ligands and biological macromolecules. In this study, molecular docking was performed to evaluate the binding affinity, interaction patterns, and potential inhibitory activity of selected compounds against a target protein of therapeutic interest. The 3D structure of the protein was retrieved from the Protein Data Bank, and ligands were prepared using standard energy-minimization protocols. Docking simulations were carried out using validated algorithms to identify the most stable ligand–receptor conformations. Binding energies, hydrogen-bond interactions, hydrophobic contacts, and key amino acid residues involved in ligand stabilization were analyzed. The results indicate that several compounds exhibit strong binding affinity toward the active site, suggesting their potential as lead molecules for further optimization. This study highlights the importance of molecular docking as an efficient tool in early-stage drug discovery and provides a foundation for future in-vitro and in-vivo investigations.

Index-Terms- Molecular docking, docking software, ligand-receptor, tools, protein binding

I.INTRODUCTION

Molecular docking is one of the successful and useful structure based in silico method. It involves in predicting interactions between molecules and biological targets. The process of molecular docking involves predicting the molecular orientation of ligand within a receptor and then assigning their complimentarily using scoring function. The process of molecular docking involves simulation that predicts the conformation of a receptor-ligand complex. (1) In this the receptor can be either protein or nucleic acid, and a ligand is a small molecule. This process allows faster and cheaper identification of promising drug candidates using structure based virtual screening. In docking process ligand is positioned at active site of protein in 3D spaces. Molecular docking

requires two important aspects which are binding affinity among ligand and protein and correct posture of ligand in active site of target protein. Molecular docking generally works on two basic steps that are searching and scoring. Searching is usually depends on specific algorithm of search and explores potent binding sites, and the scoring function is important for reducing algorithm which depends on this functions.(2) Docking plays important role in rational drug design. Molecular docking has become a central technique in rational drug design due to its ability to predict the most favorable binding orientation and affinity of ligands toward biological targets. The studies reviewed demonstrate that docking outcomes provide strong guidance in identifying lead molecules and prioritizing candidates for further analysis.(3)

Docking analyses highlighted that the strength of ligand–protein interactions depend on several critical factors, including the chemical structure, steric compatibility with the binding pocket, and interaction types such as hydrogen bonding, hydrophobic forces, and electrostatic attractions. Many investigations showed that ligands possessing electron-donating or aromatic functional groups exhibited enhanced binding due to π–π stacking or strong anchoring in active site residues.(4)

Applications of Molecular Docking

1. Binding Affinity- Docking scores (binding energies) helped identify the most stable drug–target complexes. Compounds with stronger negative binding energy values exhibited better inhibitory potential toward the target proteins.(5)
2. Active Site Interaction- Key amino acid residues within the target protein binding pocket were successfully mapped. Hydrogen bonds, π-π stacking, hydrophobic and electrostatic interactions were reported as crucial for strong ligand binding.
3. Lead Identification- Multiple studies highlighted the ability of docking to screen large compound libraries and shortlist potential therapeutic candidates. Novel hits were proposed for further optimization based on predicted molecular interactions.
4. Structure-Activity Relationship (SAR) Understanding- Docking helped relate chemical structure modifications to improved receptor binding.(6)
   Prioritization of functional groups favorable for enhanced stability and biological activity was supported.
5. Correlation with Biological Activity- In many reviewed works, docking predictions aligned well with in vitro and in vivo experimental results, confirming computational reliability.(7)

Types of Molecular Docking

1. Flexible Docking – This type of docking allows flexibility in either the ligand, receptor, or both during the process of docking. This is necessary for conformational changes and can give more accurate and reliable predictions of binding modes.(7,8) This flexible docking is also known as induced fit docking which is crucial for prediction of binding mode and affinity between a ligand and receptor which provides flexibility in both ligand and receptor structure. The principle behind flexible docking is the dynamic nature of biomolecular structures and the

induced fit phenomenon observed in ligand receptor interactions. When there is a binding between ligand and receptor they may undergo conformational changes to optimize their interaction and achieve stable complex.(9)

Applications of Flexible Docking

- Drug Discovery- Flexible docking plays crucial role in drug discovery as it is widely used in virtual screening and lead optimization helpful to predict the binding affinity and selectivity of small molecule ligands with target protein.(10)
- Enzyme Inhibition- In the field of enzymology, flexible docking is used to predict the binding modes and mechanisms of enzyme inhibitors. Flexible docking provides the design of potent and selective enzyme inhibitors with therapeutic potential.
- Virtual Screening- Flexible docking is necessary part of virtual screening workflows, where databases of chemical compounds are screened computationally to identify potential drug candidates.(11)

2. Rigid Docking

In rigid docking there will be no flexibility or movement in the structure of the molecules being docked. Ligand and receptor are treated as rigid bodies during simulation process. The main aim is to generate a set of potential docking poses for the ligand within the binding site of the receptor. In rigid docking there is a possibility to allow some steric clashes. In rigid docking the conformation of ligand and receptor does not change, only there is change in spatial position and posture of two molecules. (11,12)

The principle behind rigid docking is that it relies on geometric complementarity between the ligand and receptor structures. The process involve searching conformational space of ligand which helps to find the pose that gives favourable interactions such as hydrogen bonding, hydrophobic interactions, vander waals forces, etc. (13)

Applications of Rigid docking

- Drug Discovery- Rigid docking is mostly used in computer aided drug design to identify potential drug candidates that bind with protein target which have high affinity.
- Protein-protein interactions- This helps to predict the binding between two protein molecules, which helps to get insights into protein-protein interaction.(11,14)

Computational tools and software

Tools in molecular docking are designed to predict the binding affinity of ligand to its target protein. This tools employs various algorithms. They helps in understanding molecular interaction underlying biological processes and helps in drug discovery. This tool plays important role in computational chemistry and biology. (15)

1. AutoDock- AutoDock is an automated docking tool designed to predict how small molecules bind with receptor of known 3D structure. The AutoDock docking suite offers the minimum binding energy of interaction obtained between the ligand and the receptor protein. The binding energy calculation is based on the formula offered in the form of the scoring function. AutoDock has applications in X-ray crystallography, structure-based drug design, lead optimization, virtual screening, protein-protein docking, and chemical mechanism studies. (16)
2. Glide- Glide is a commercially available program implemented in the Schrödinger Maestro software. The program was released in 2004 as "a new approach for rapid, accurate docking and scoring". Glide is an molecular modeling software that offer docking procedures. (17)
3. Gold (Genetic optimization for ligand docking)- Genetic optimization for ligand docking used to dock flexible ligands into protein binding sites. GOLD has undergone comprehensive testing and demonstrated outstanding performance in virtual screening and strong outcomes in pose prediction. GOLD optimizes ligand placement by exploring the conformational space of the ligands within the binding site using a genetic algorithm. The scoring function in GOLD is critical for measuring the fitness of different ligand conformations created during the docking process. (18)
4. Moledock- Molegro Virtual Docker is an integrated platform for predicting protein-ligand interactions, from preparing the compounds to identifying possible target protein binding sites and forecasting ligand binding modalities, Molegro Virtual Docker manages every step of the docking process. Molegro Virtual Docker is a user interface that prioritizes productivity and usability while providing high-quality docking based on a unique optimization technique. (19)
5. FleX- This software helps to assist researchers in determining the most likely and biologically significant binding modes, the scoring function attempts to estimate the binding affinity between the ligand and the receptor. One important tool for assessing and ranking the possible binding positions of ligands within a target binding site is the scoring. (20)
6. Surrflex-Dock- A molecular docking tool called Surflex-Dock is used to forecast the affinities and binding patterns of ligands to protein targets. The Hammerhead scoring function, which considers both form complementarity and electrostatic interactions between ligands and proteins, serves as the foundation for the scoring system in Surflex-Dock. The fitness of a ligand posture inside a protein binding site is assessed using the scoring function. (21,22)
7. PyMOL- PyMOL is a widely used, open-source molecular visualization system, primarily employed by structural biologists and researchers to visualize and analyze 3D structures of biological macromolecules such as proteins, DNA, and RNA. Users interact with PyMOL through a graphical user interface (GUI) and a command-line interface. The GUI provides menus and buttons for common tasks, while the command line offers more advanced control and scripting capabilities. (23)

8. PyRx- Virtual screening software for computational drug discovery that can be used to screen libraries of compounds against potential drug targets. PyRx includes docking wizard with easy-to-use user interface which makes it a valuable tool for CADD. PyRx also includes chemical spreadsheet-like functionality and a visualization engine that are essential for rational drug design. (25)

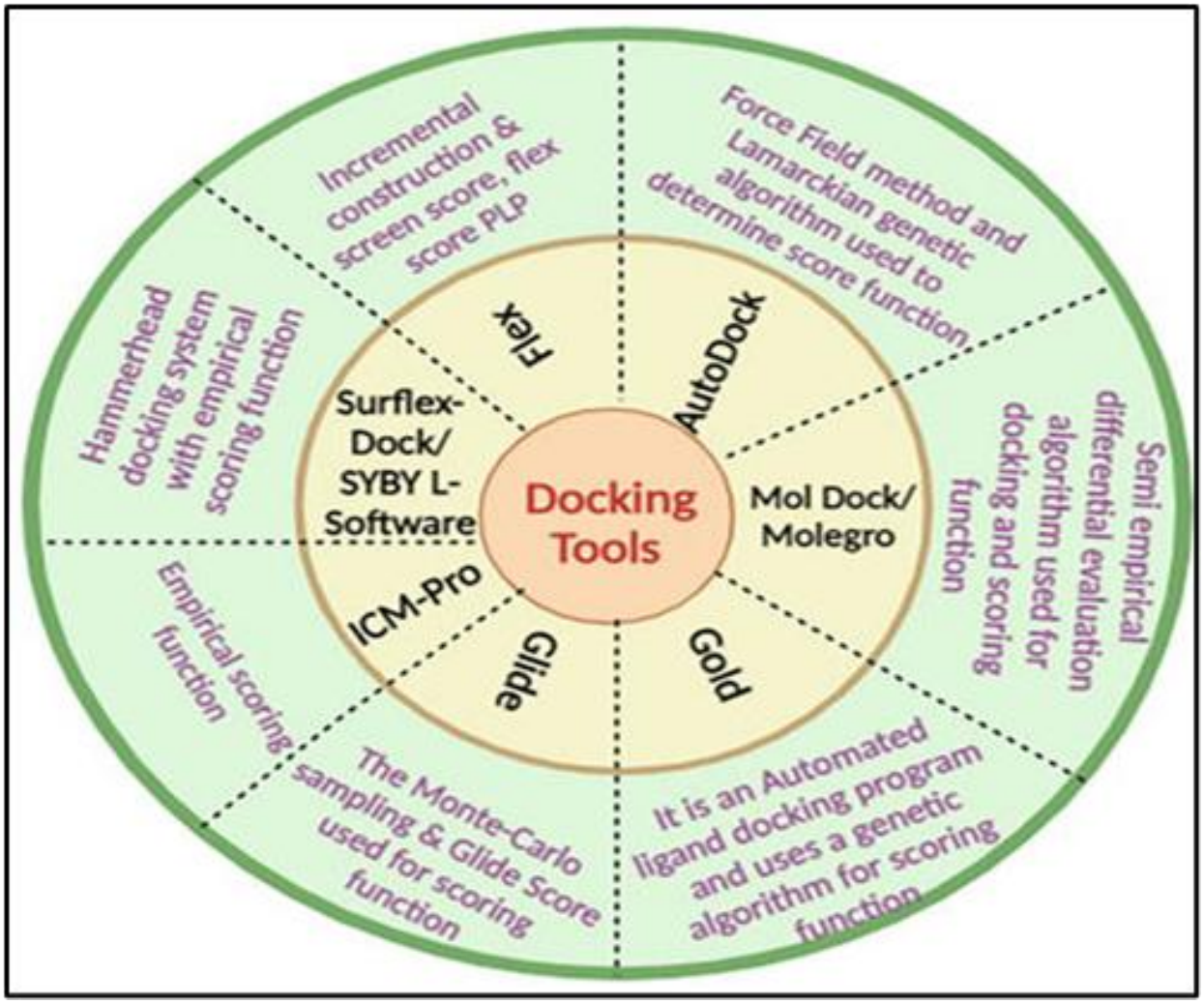

Fig. No.1. Different Software and Computational tools

Choosing the right software

Choosing the molecular docking software depends upon the type of work or research you are doing, your budget, your level of experience, and your unique needs will all play a role in selecting the best molecular software. When choosing molecular software, keep the following important factors in mind. (21,25)

Considerations for selecting docking software

- User interface (UI) and user-friendliness
- Integration and compatibility
- Compliance and data security
- Trial period
- Cost and licensing
- Compliance and data security
- Features and functionality.

III.CONCLUSION

Present review spotlight on molecular docking which has been emerged as an essential computational technique in modern drug discovery for understanding and predicting ligand–receptor interactions. The reviewed studies collectively highlight that docking enables rapid screening of bioactive compounds, estimation of binding affinities, and identification of key amino acid residues involved in molecular recognition. It supports structure-based drug design by providing insights into the structural and energetic requirements for effective binding.

Docking results, when integrated with pharmacokinetic and toxicity predictions, demonstrate strong correlation with experimental outcomes and help in prioritizing potential drug candidates for synthesis and biological evaluation. Therefore, molecular docking not only reduces the cost and time associated with laboratory research but also strengthens decision-making in the development of new therapeutic agents. Continued advancements in algorithms, scoring functions and computational resources will further enhance the accuracy and applicability of molecular docking in future pharmaceutical research.

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