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Review Article

UNREVEALING THE COMPLEX INTERPLAY: MOLECULAR DOCKING: A COMPREHENSIVE REVIEW ON CURRENT SCENARIO, UPCOMING DIFFICULTIES, FORTHCOMING INITIATIVES, AND VIEWPOINTS

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ABSTRACT

The computer modelling of structural complexes generated from two or more interacting molecules are referred to as molecular docking. It is an indispensable tool in computer-aided drug design and structural molecular biology. Using this technology, large libraries of compounds may be digitally screened, and the results can be graded along with structural assumptions about how the ligands impact the target's reduction. Recent advances in the synthesis of anti-infectious medicines prompted by structural insights have enabled the application of computer-assisted drug design in the quest for innovative mechanism-or structure-based drugs. Molecular docking is an important phase in the drug development process because it determines the best positions for molecules to occupy when they are coupled together and predicts how effectively two molecules will bind once they have been docked. The input structure's design is also critical, and the results are assessed using sampling methods and scoring systems. The recently developed docking software Local Move Monte Carlo provides a strong choice for customizable receptor docking strategies. Docking is a technique for determining how ligands and proteins interact. It is structurally sound and compatible with computer-assisted medication design. Successful docking discovers high-dimensional spaces and ranks function utilisation, resulting in a candidate docking rating that is acceptable. It may also be used to screen vast libraries of molecules and offer structural hypotheses for the process.

Keywords: Molecular docking, Ligand, Receptor, Drug design, Docking tool, Mechanism of docking, Protein

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INTRODUCTION

Docking is a widely employed technique in the field of molecular modelling, which aims to predict the optimal pathway by which one molecule can attach to another molecule, ultimately leading to the development of a stable complex. The technique is depicted in fig. 1 [1]. Molecular docking holds significant value in the realm of structure-based drug design due to its ability to forecast the manner in which small molecule ligands would attach to the appropriate target binding site. As a result of its widespread usage, this has become highly prevalent throughout the field. The assessment of binding efficacy plays a pivotal role in pharmaceutical development and in comprehending the fundamental biochemical mechanisms [2]. The primary aim of engaging in docking research is to generate predictions pertaining to the intended three-dimensional configurations. The process of docking automatically establishes appropriate incentive structures. There are multiple computational docking methodologies that are accessible for utilisation [3, 4].

Prospective of molecular docking

Molecular docking is mostly accomplished using two methods

Stimulation approach

This method works by physically separating the ligand and the target and then allowing the ligand to attach to the groove of the indented target after a number of movements in their conformational space. The movement involves structural modification of the ligand, which might be internal or external, and the total movement restricts the release of energy. The technique is proven to be better suited for accepting ligand flexibility. Furthermore, it facilitates the molecular identification of ligand and target. Although a longer period of time is necessary to estimate a good docked conformer due to the large quantity of energy removed from a specific conformational shift, Currently, rapid optimisation techniques and grid-based methodologies are revolutionising this [5].

Shape complementarity

This method uses ligand and target as structural surface characteristics to provide molecular interaction. The target surface was linked to the solvent-accessible surface area, and the ligand molecular surface should exhibit a matching illustration with the target surface area. Shape matching between two surfaces aids in finding the ligand indentation for ligand on its intended surface. Protein hydrophobicity, for example, was discovered to be analysed by twists contained in main chain atoms. This approach is recommended because it is faster and includes scanning a large number of ligands in a short period of time to find the predicted binding characteristics of the ligand on their intended target of molecular surface [6].

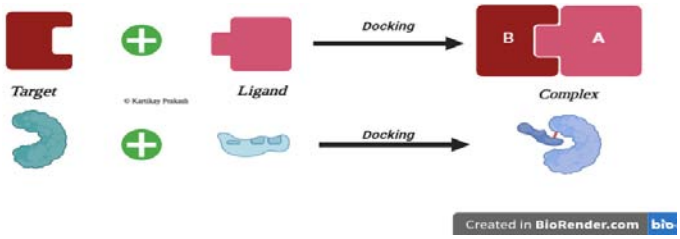

Fig. 1: Schematic diagram of docking (©Kartikay Prakash)

Types of molecular docking

There are 2 types of docking (fig. 2).

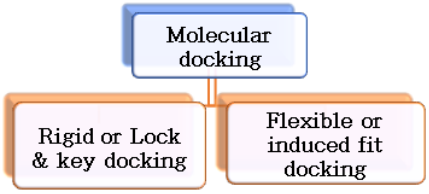

Fig. 2: Types of docking (© kartikay Prakash)

Rigid

The receptor and ligand molecules are both fixed in this docking. Docking is carried out. We are searching for a 3D space conversion of one of the molecules that will bring it to the best match with the other molecules in terms of a scoring function. The ligand's conformation may be generated in the absence of a receptor or in the presence of receptor-binding activity (fig. 3, 4).

Flexible

In this docking the ligand and the receptor both are movable. It is conformationally flexible. Each rotation the energy is calculated. Each conformation surface cell occupancy is calculated (fig. 3,4). After that, the most optimum binding pose is selected [7].

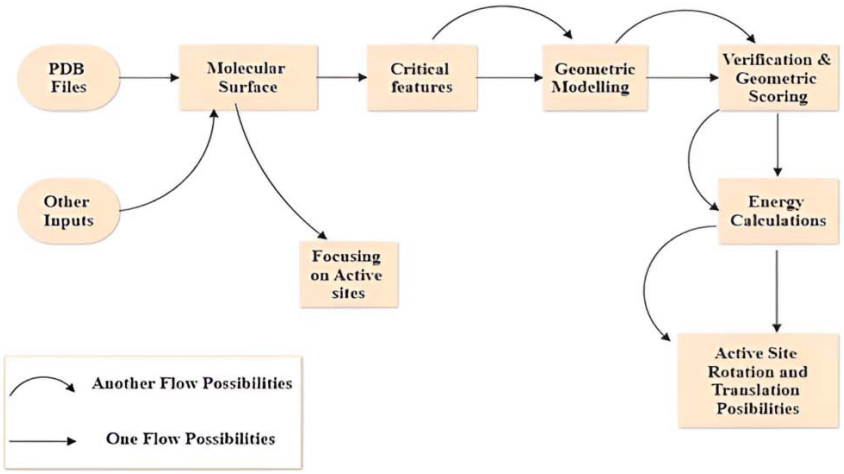

Fig. 3: Rigid and flexible docking (© kartikay Prakash)

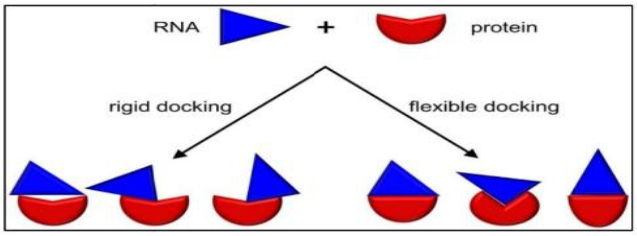

Fig. 4: Rigid and flexible docking

Application of molecular docking

Hit identification

Docking in combination with a scoring function, allows for speedy *in silico* screening of enormous databases of potential pharmaceuticals to locate molecules capable of binding to a specific target of interest.

Lead optimization

Docking is a technique for predicting the location and relative position of a ligand's interaction with a protein [also known as the binding mode or pose]. The aforementioned data can be used to generate more powerful and precise mimics.

Bioremediation

Enzymes and their modes of activity can be identified through molecular docking. It is additionally feasible to identify interactions between proteins. Using the restoration treatment, molecules are electronically examined. Other applications of molecular docking (fig. 5)

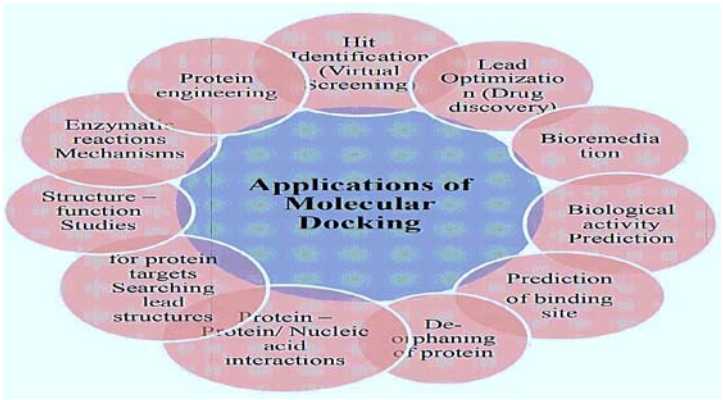

Fig. 5: Applications of molecular docking

Mechanism of molecular docking

The sequence of the specified protein is the first criterion for running a docking screen. A biophysical method, such as x-ray crystallography or, less commonly, Nuclear Magnetic Resonance spectroscopy, is frequently used to discover the structure. As inputs, a docking tool employs this protein function and a database of chemicals. The success of a docking programme is dependent on three components: the search algorithm, the scoring system, and the docking programme itself. is typically identified by a biophysical method like x-ray crystallography or, less commonly, Nuclear Magnetic Resonance spectroscopy. As inputs, a docking tool employs this protein function and a database of chemicals. The success of a docking programme is dependent on three components: the search algorithm, the scoring system, and the docking programme itself [8].

Steps involved in mechanism

Step I–Preparation of protein and ligand

Downloading the 3D-structure of the Protein from the Research Collaboratory Structural Bioinformatics Protein data bank. Following that, the downloaded structure should be pre-processed. Water molecules' cavities are removed, charges are stabilised, missing residues are filled, and hydrogen atom side chains are generated.

Step II–Preparation of ligand

Ligands can be downloaded from databases like ZINC and Pub Chem, or they can be drawn. Make use of the Chemistry Sketch tool. Lipinski's Rule of five aids should be applied when identifying the ligand. Lipinski's rule of five aids in distinguishing between non-drug-like and drug-like compounds. The computer-aided drug design and detection approach It guarantees a high likelihood of success or failure owing to drug similarity for molecules that remain inside two or more of the conforming rules.

Allow Lipinski's rule for directing the ligand choice:

- A maximum of five hydrogen bond donors.
- Fewer than ten hydrogen bond acceptors.
- A molecular mass below 500 Da.
- High lipophilicity [expressed as a log not exceeding.
- The molar refractivity ought to fall between 40 and 130 [9].

Step III-Grid generation

All variables, such as location, rotatable group, excluded volumes, and limitations, were held constant. The amount of genetic processing done [crossover, migration, and mutation] is the most important factor in determining if binding cavity predictions should be made.

Step IV–Active site prediction

The active site of protein must be anticipated once it has been prepared. The receptor strength has several active sites; just the one of concern should be chosen. Water molecules and heteroatoms tend to stay apathetic if present [10].

Step V-docking

Ligand and protein interactions are analyzed. Best docking score should be selected.

Molecular docking approach

Monte carlo approach

It generates a ligand's randomized conformation, translations, and rotation in an active site. It determines the initial configuration value. It then creates and scores a new configuration. Using the Metropolis criteria, it assesses if the new configuration should be preserved [11, 12].

Metropolis criterion

If a new reply has a higher score than the previous one, it is instantly approved. A Boltzmann-based prospect function is beneficial if the setup is not novel. If the solution passes the possibility function test, it is accepted; otherwise, the configuration is rejected [13].

Matching approach

These methods emphasize complementarity. The ligand atom is placed in the "best" location in the site, resulting in a ligand-receptor configuration that may need to be optimized.

Ligand fit approach

Ligand sturdy phrases present a fast and dependable approach for docking small particles of ligand into protein active sites to investigate shape complementarity between ligand and protein active sites.

Point complimentarily approach

These approaches are focused on assessing the form and/or chemical complementarity of molecules that interact.

Fragment-based method

Fragment-based techniques may be characterised as dissolving the ligand into single photons or particles, attaching the fragments, and finally joining the fragments.

Distance geometry

Many different types of sequence characteristics can be expressed using intra-or intermolecular dimensions. The distance geometry framework allows these distances to be assembled and three-dimensional structures that are compatible with them to be calculated.

Blind docking

It was developed to discover potential peptide ligand binding sites and modes by scanning the full surface of protein targets.

Inverse docking

Considering all of these goals, when juxtaposed with a particular pharmacokinetics characteristic, may be helpful to identify a drug candidate's possibility of toxicity and side effects. For docking investigations on an individual ligand, a unique technique is implemented.

Theory of molecular docking

The goal of molecular docking is to anticipate the ligand-receptor complex structure using computer approaches. Docking is accomplished through two interconnected processes [14].

Sampling algorithm

There is a profusion of different binding modes between two molecules with six degrees of translational and rotational flexibility, as well as the conformational degrees of freedom of both the ligand and protein [15]. Unfortunately, computationally generating all potential conformations would be prohibitively costly. In terms of shape attributes and chemistry facts, Matching Algorithms employing molecular shape can map a ligand onto a binding site of a protein [16, 17].

DOCK, FLOG, Lib-Dock, and SANDOCK all provide ligand docking matching algorithms. Using incremental construction methodologies, the ligand is embedded in an active site in a scattered and innovative way [18-21]. DOCK 4.0 and Flex-X and Hammerhead and SLIDE and eHiTS have employed the incremental building approach [22-26]. Through bond rotation, rigid-body translation, or rotation, Monte Carlo techniques create ligand positions [27, 28]. This transformation's conformation is evaluated using an energy-based selection criterion [29, 30].

Monte Carlo algorithms were used in an early version of Auto-Dock [31], ICM [32], QXP [33], and Affinity [34]. Another well-known family of stochastic approaches is genetic algorithms [34-36]. Auto Dock employs five genetic algorithms. GOLD, DIVALI, and DARWIN are the top five [38-40].

Scoring function

The scoring function's purpose is to discriminate between correct poses from inaccurate movements or binders from inactive compounds in an adequate amount of time. However, scoring functions suggest rather than predict the binding affinity between the protein and ligand, and they use numerous presumptions and simplifications. Scoring functions can be categorized as force-field-based, theoretical, or knowledge-based [41].

Model of molecular docking

Lock and key theory

Emil Fischer developed the "lock-and-key model" in 1890 to demonstrate how biological processes function. A substrate is placed into a macromolecule's active site in the same way a key is inserted into a lock. Biological locks, as seen in the picture below, have specific stereochemical attributes that are critical to their functioning (fig. 6).

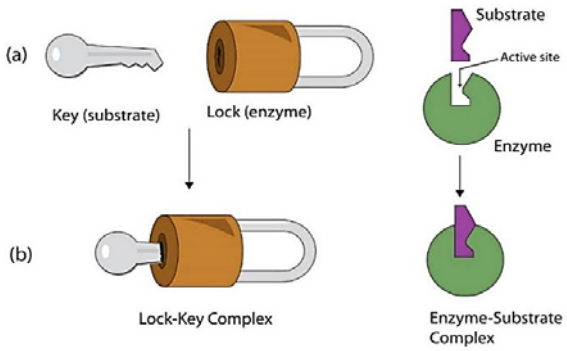

Fig. 6: Lock and key theory

Induced fit theory

The "Induced fit theory" was presented by Daniel Koshland in 1958. The basic principle is that during character recognition, both the ligand and the target adapt to one another through minor conformational changes until an optimal match is found (fig. 7) [42-45].

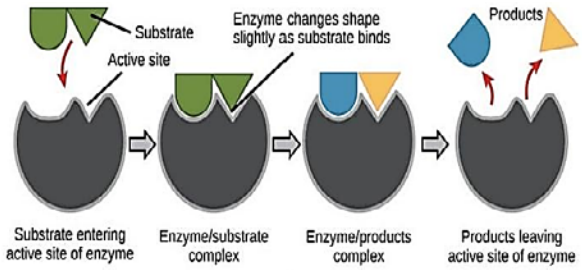

Fig. 7: Induced fit theory

Confirmation ensemble model

Proteins have been found to suffer substantially bigger structural alterations than small induced-fit adjustments. Proteins, according to a new theory, are made up of a pre-existing ensemble of conformational states. The protein's flexibility allows it to change states [46-48].

Software available for molecular docking

- GOLD [49]
- AUTODOCK
- FLEX-X [50]
- DOCK
- FRED [52]
- GLIDE
- LIGAND FIT [53]

Current scenario of molecular docking

Molecular docking is a crucial computational technique in drug discovery and structural biology. In the current scenario, it has evolved significantly due to advances in computing power and improved algorithms. Docking programs like Auto-Dock, Auto-Dock Vina, and Glide have become more efficient and user-friendly. Machine learning and artificial intelligence have been integrated to enhance accuracy in predicting ligand-receptor interactions, reducing the time and cost of drug development. Cloud-based docking platforms have also gained popularity, making it more accessible to researchers worldwide. Furthermore, molecular docking has expanded beyond traditional small molecule-protein interactions to include protein-protein docking and protein-ligand binding kinetics. It plays a pivotal role in understanding the molecular basis of diseases, such as COVID-19, by identifying potential drug candidates. In summary, molecular docking continues to evolve, facilitating drug discovery and advancing our understanding of molecular interactions in various fields of research [54]. Molecular docking is a computational technique widely used in drug discovery and molecular biology to predict the binding interactions between molecules, typically a small molecule (ligand) and a larger biomolecule (receptor), such as a protein. In recent years, molecular docking has undergone significant advancements and has become a crucial tool in various fields, including drug design, protein-protein interaction analysis, and understanding molecular mechanisms. In this article, we will explore the current scenario of molecular docking, including its applications, challenges, and emerging trends.

Role of molecular docking in pharmaceutical sciences

Drug discovery and development

Molecular docking plays a central role in pharmaceutical research by aiding in the identification of potential drug candidates. Researchers use docking simulations to predict how small molecules interact with target proteins, helping prioritize compounds for experimental validation.

Protein-ligand binding studies

Docking helps elucidate the binding modes and affinity of ligands to their respective protein receptors. This information is crucial for understanding molecular recognition processes and designing more effective ligands.

Virtual screening

High-throughput virtual screening using molecular docking allows researchers to screen large chemical libraries quickly, identifying potential drug candidates that may bind to a specific target.

Structural biology

Docking is used to model protein-protein interactions, protein-nucleic acid interactions, and protein-ligand interactions, aiding in the structural characterization of biomolecular complexes.

Rational protein engineering

Researchers use docking to design mutations or modifications in proteins to enhance their binding affinity for ligands or substrates [55].

Challenges in molecular docking

Scoring functions

Accurate prediction of binding affinity remains challenging due to limitations in scoring functions used in docking simulations. Developing more robust scoring functions that account for solvation, entropy, and enthalpy is an ongoing challenge.

Conformational flexibility

Proteins and ligands can adopt multiple conformations, making it essential to account for conformational flexibility during docking. Advanced techniques such as ensemble docking and molecular dynamics simulations are used to address this challenge.

Treatment of solvent effects

Modelling the effects of solvents accurately is critical, as water molecules and ions can significantly influence binding interactions. Advanced solvent models and implicit solvent methods are continually evolving to improve accuracy.

Sampling efficiency

The search space in molecular docking is vast, and efficient sampling of ligand and receptor conformations is a computational bottleneck. Enhanced sampling methods, like Monte Carlo-based techniques and genetic algorithms, are being developed to address this issue.

Membrane proteins

Docking membrane proteins remains challenging due to their complex environments. Researchers are developing specialized methods to account for lipid bilayers and membrane protein stability [56].

Emerging trends in molecular docking

Machine learning integration

Machine learning techniques, including deep learning, are being integrated with molecular docking to improve scoring functions and enhance prediction accuracy. These models learn from large datasets of experimental binding data.

Free energy calculations

Advances in free energy calculations are improving the accuracy of binding affinity predictions. Techniques like alchemical and thermodynamic integration are becoming more accessible for researchers.

AI-driven drug discovery

Molecular docking is an integral component of AI-driven drug discovery pipelines, where AI algorithms help identify promising drug candidates and predict their potential toxicity and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties.

Fragment-based docking

Fragment-based docking approaches are gaining popularity as they allow for the efficient screening of fragment libraries, facilitating the discovery of novel lead compounds.

Cryo-EM integration

The combination of molecular docking with cryo-electron microscopy (cryo-EM) data is revolutionizing the study of large macromolecular complexes, enabling the determination of high-resolution structures [57].

At Last, molecular docking remains a vital tool in drug discovery and structural biology, with a growing impact on various scientific disciplines. Despite the challenges associated with accuracy and computational efficiency, ongoing research efforts, integration of machine learning, and advancements in free energy calculations are steadily improving the predictive power of molecular docking. As the field continues to evolve, it promises to accelerate the development of new drugs and deepen our understanding of molecular interactions at the atomic level.

Upcoming difficulties, forthcoming initiatives, and viewpoints

Molecular docking is a computational technique used in drug discovery, bioinformatics, and structural biology to predict how small molecules (ligands) interact with proteins or other macromolecules (receptors). While it has been a valuable tool in these fields, there are several future challenges, endeavours, and perspectives for molecular docking [58, 69].

Improved accuracy and precision

Enhancing the accuracy and precision of docking predictions remains a significant challenge. Current algorithms often struggle with accurately predicting binding affinities and the correct binding poses of ligands. Developing more robust scoring functions and sampling techniques is a major endeavour in this area.

Incorporating flexibility

Many biological macromolecules are dynamic and can undergo conformational changes upon ligand binding. Future docking methods need to better account for protein flexibility to improve predictions. This might involve incorporating molecular dynamics simulations or advanced conformational sampling techniques.

Handling protein-ligand water interactions

Accurately modelling the role of water molecules in protein-ligand interactions is crucial, as they can significantly influence binding. Efforts are ongoing to develop methods that can effectively predict the positions and energetics of water molecules in docking simulations.

Machine learning and AI integration

Machine learning and artificial intelligence techniques are increasingly being integrated into molecular docking workflows. This includes using AI for better scoring functions, predicting binding affinities, and optimizing docking protocols.

Multi-target docking

In drug discovery, it's often necessary to consider multiple targets simultaneously, especially in poly-pharmacology and network pharmacology. Developing docking methods that can handle multi-target scenarios efficiently is a growing area of interest.

Virtual screening and drug repurposing

Docking plays a crucial role in virtual screening and drug repurposing. Future endeavours may focus on improving the speed and scalability of virtual screening techniques to analyse vast chemical libraries quickly.

Personalized medicine

Molecular docking can be applied to personalized medicine by considering individual genetic variations. Developing methods to predict how genetic mutations affect drug binding and response is a promising area.

Accessibility and user-friendliness

Making molecular docking software more user-friendly and accessible to researchers without extensive computational backgrounds is important. User-friendly graphical interfaces and cloud-based solutions can help democratize its usage.

Big data and structural databases

Leveraging the wealth of structural data available in the Protein Data Bank and other repositories, as well as advances in big data analytics, can lead to improved docking methodologies.

Ethical and regulatory considerations

As molecular docking plays a pivotal role in drug discovery, there will be increased scrutiny regarding the ethical use of AI and machine learning in this context, as well as the regulatory approval process for drugs discovered using computational techniques [60, 61].

At last, molecular docking continues to evolve as a powerful tool in various scientific and industrial applications. Overcoming current challenges and pursuing these future prospectives will contribute to its ongoing success and its ability to address complex biological and pharmacological questions [62].

CONCLUSION

Molecular Docking provides a variety of methods for drug design and discovery. The medicinal chemist may easily visualise molecular structure databases. It accurately predicts ligand binding within receptors. It is both time and money-saving. It is utilised in the creation of new drugs. Complications of the molecular docking approach include lead molecule optimisation, biological pathway assessment, and de Novo drug creation. Include all information on molecular docking in this review. Malaria, heart failure, cancer, and other infectious illnesses have become public health issues in most nations as a result of the evolution of drug resistance strains, necessitating the development of more effective treatments.

Warning: The phenomenon of small-molecule ligands binding to proteins does not always provide the expected outcomes.

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AUTHORS CONTRIBUTIONS

Kartikay Prakash developed the theoretical formalism, performed the analytical calculations and performed the numerical stimulation. Dr Shashank Tiwari and Kartikay Prakash contributed to the final version of the manuscript. Dr Shashank Tiwari, Kartikay Prakash and Devbrat Soni supervised the project.

CONFLICT OF INTERESTS

Declared none

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