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Review Article

Precision in Binding: An Insightful Review on Molecular Docking Techniques and their Applications

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Abstract: The numerical modelling of structural compounds made up of two or more interacting molecules is known as molecular docking. Predicting the desired three-dimensional structure is the aim of molecular docking. Software for molecular docking is mostly utilised in drug development. Easy access to structural databases and molecules have become crucial mechanisms. Molecular docking is a potent computer technique that is essential for structural biology, drug development, and bio-molecular interaction research, giving a comprehensive understanding of its significance in contemporary scientific research. Predicting how a small molecule, frequently a possible drug, would interact with a target biomolecule, such as DNA or a protein, is known as molecular docking. In order to help find novel drug candidates, improve already-existing molecules, and comprehend the complex interactions between medications and receptors, this procedure looks at the ligand's energetic and spatial compatibility with the receptor's active site. Because it predicts how well two molecules will bind after docking and identifies the optimal places for molecules to occupy when linked together, molecular docking is a crucial step in the drug development process.

Keywords: Molecular Docking, Types of Docking, Ligand Receptor, Software's, Scoring Function, Mechanism of Docking, Applications.

INTRODUCTION

Docking is a technique used in molecular modelling that predicts the direction a molecule will prefer to go in when it jumps to another molecule to form a stable complex [1]. The need for molecular biology structures and structure-based drug discovery has led to an increase in demand for the field of molecular docking in recent decades. This technique has been greatly aided by a huge increase in computing power and accessibility as well as the ease with which small chemical and protein libraries are now easily available [2].

These molecular docking techniques are now widely used in drug development, biological research, and other domains. They provide a number of functions in addition to finding new compounds that attach to proteins and nucleic acids. Docking, for instance, can assist in identifying the structural mechanism through which a ligand—a chemical that is known to bind a certain biological target—influences the function of the target. A crucial step in drug development, docking also commonly makes it possible for more effective ligand optimisation, which starts with a ligand and looks for related molecules with more desirable qualities—not just greater binding but also increased efficacy, less toxicity, and less adverse reactions [3, 4].

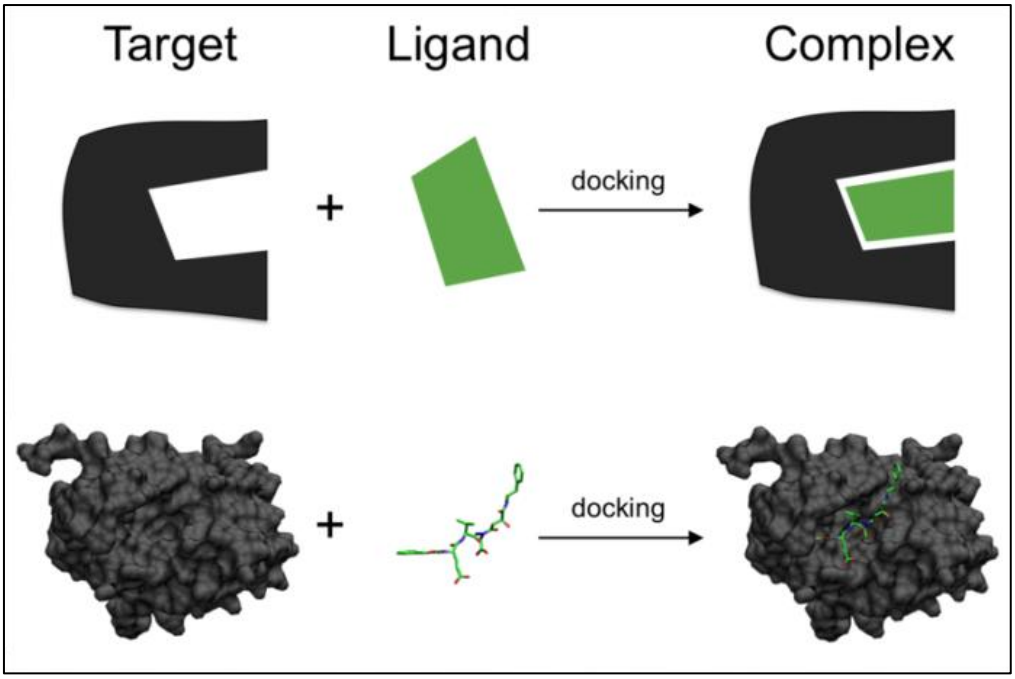


Fig. 1: Schematic diagram of docking a undersized molecule ligand (green) to a protein target (black) produce a steady compound

In addition to clarifying biomolecular interactions, docking holds great promise for evaluating novel drugs and therapeutic targets. Public initiatives like OpenZika, which analyse potential medications against Zika protein structural models, may demonstrate its broader applications. In the early screening of potentially hazardous pharmacological compounds, the mechanical method of docking may also aid in predicting adverse drug reactions (ADRs), which are caused by the administration of pharmaceuticals to an off-target protein, whether freely, clearly, or carefully.

The pharmaceutical industry's current strategy of using in vitro toxicity screens to analyse specific molecular interactions is inadequate, as evidenced by significant examples of phase IV failures like rosiglitazon and rofecoxi. Instead, docking technologies need to be investigated in order to create safer medications. Another area where docking is used is in medication repositioning, where previously established combinations may be reused to future potential useful targets [5].

Creating predictions about the desired three-dimensional configurations is the main objective of docking research. The proper systems of rewards are automatically created during the docking method. A variety of computational docking techniques are available for application [6, 7].

Principle of Molecular Docking

The principle of mutual matching, which states that the geometry, electrostatic, hydrogen bonding, and hydrophobic interactions of the ligand and receptor must all be complementary, must be met for ligand-receptor binding to occur [8].

Model of Molecular Docking

1. Lock and Key:

Emil Fischer was the first to propose this theory in 1894. Both enzymes and substrate molecules have distinct geometric shapes, according to this theory. The enzyme's structure or conformation is rigid, and the substrate fits into the binding site (now the active site) in the same way that a key fits into the right lock or a hand fits into the right glove. Therefore, an enzyme's active site is a stiff, pre-shaped template that can only bind a particular substrate. This model completely fails to explain numerous facts about enzymatic processes because it does not account for the flexible nature of enzymes.

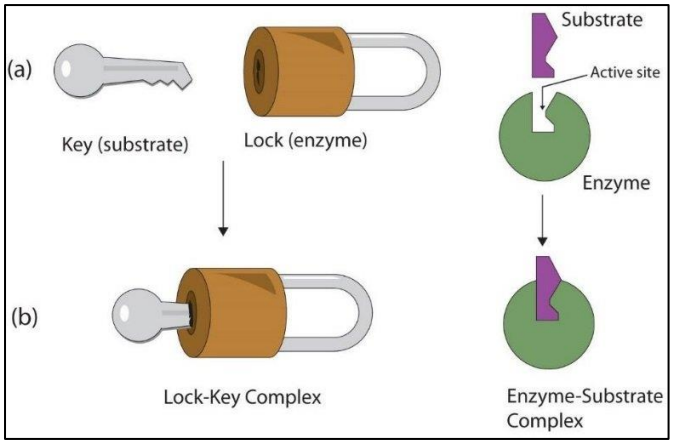


Fig. 2: Lock & Key Model

2. Induced-Fit theory or Koshland's model:

Daniel Koshland first put out this idea of enzyme function in 1959. The active site is not stiff and pre-shaped, in accordance with this paradigm. According to this hypothesis, the enzyme is flexible rather than stiff. In this case, the geometry of the substrate molecules affects how the enzyme molecules' active site alters. Conformational change is the term used to describe such a change in the enzyme molecules based on the size of the substrate molecule. Equivalent to a hand-in glove, it may be challenging to get the first finger in the right spot, but once it is, the glove is correctly aligned, making it easy to get the other fingers in. In this instance, the substrate that causes the glove's shape to alter is the hand (enzyme).

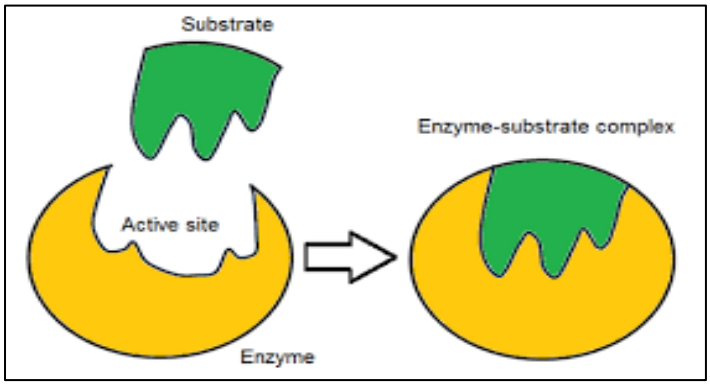


Fig. 3: Induced fit theory

3. Substrate strain theory

According to this theory, the enzyme's induced change in conformation causes strain on the substrate. A further possibility is that the enzyme causes strain on the substrate when it places to the ready active site. A product appears as outcome of the strained substrate [9].

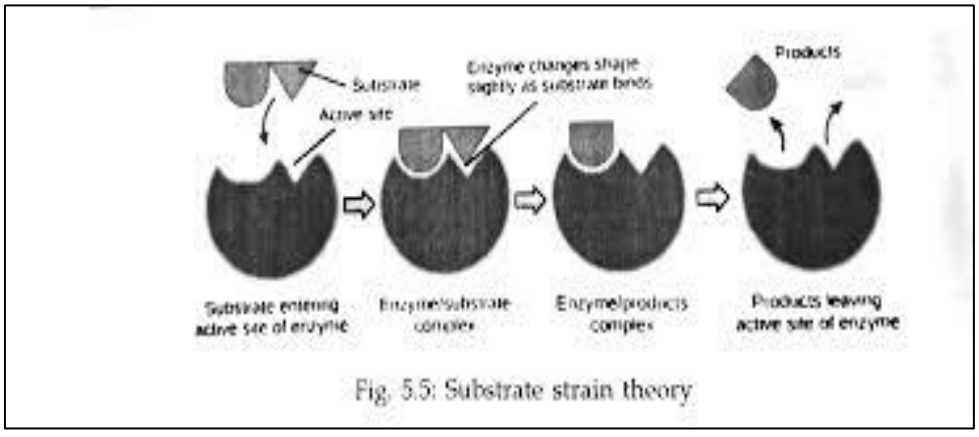


Fig. 4: Substrate Strain Theory

Types of Docking

1. ***Rigid docking:*** We are seeking for a transformation in 3D space of one of the molecules which allows it to the best fit with the other molecules in terms of a scoring function if we believe that the molecules are rigid. The ligand may be constructing its conformation while there is no receptor present or once there is receptor binding activity.
2. ***Flexible Docking:*** Our goal is to find the confirmations of the receptor and ligand molecules as they evolve in complex situations by considering molecular flexibility in addition to transformation [10].
3. ***Semi flexible docking / Flexible ligand docking:*** The ligand molecule is the only flexible component in this process; the protein is rigid. This kind of molecular docking allows a ligand to be flexible in molecular docking simulations by allowing rotatable bonds. This allows the ligand to accept many conformations while the protein structure stays rigid [11]. Keeping the protein rigid while taking into account the ligand's conformational flexibility is known as semi-flexible docking [12]. Although this assumption isn't always true, semi-flexible docking is commonly employed to study molecular identification because it uses more processing resources than rigid docking but less than fully flexible docking [13].

Molecular Docking Between:

The method used to investigate molecular binding and how molecules bind is called molecular docking. The word "docking" mostly refers to interactions between protein molecules. Molecular docking for protein interactions comes in a variety of forms:

- If a protein interacts with a ligand: protein-ligand interaction.
- If a protein interacts with another protein: protein-protein interaction.
- If a protein binds to DNA: protein-DNA interactions of all these Protein ligand interaction techniques are the most widely used techniques.

Advantages: One of the major advantages conferred by docking is that it allows researchers to quickly screen large databases of potential drugs which would otherwise require tedious and prolonged work in the lab using traditional drug discovery procedures.

Protein – Ligand
Protein- Protein
Protein- Nucleotide [14]

Different types of interactions:

Interactions between particles can be defined as a consequence of forces between the molecules contained by the particles. These forces are divided into four categories:

- **Electrostatic forces -** forces that have an electrostatic origin because of the charges that are present in the material. Charge-charge, charge-dipole, and dipole-dipole interactions are the most prevalent.
- **Electrodynamics forces**- It **is** commonly known as the *Van der Waals interactions*.
- **Steric forces -** When atoms in distinct molecules come into extremely close contact with one another and begin to alter one another's reactivity, steric forces are created. The forces that occur can have an impact on a system's free energy and chemical reactions.
- **Solvent-related forces -**These forces are produced when the solvent and the protein or ligand complete chemical reactions. Hydrogen bonds, which are hydrophilic interactions, and hydrophobic interactions are two examples.
- These forces have an electromagnetic in nature, which binds together.
- **Additional physical factors**: Successful docking often needs structural modifications between the ligand and the protein.

Molecular docking theory:

Molecular docking can be divided into two separate sections:

1. Search Algorithm: These algorithms determine the position and orientation of both molecules in connection with each other, i.e., any possible best the forms for a given complex (protein-protein, protein-ligand) in the environment. They are also able to determine the energy of each individual interaction as well as the resulting complex.

The different types of algorithms that can be used for docking analysis are given below:

- Molecular dynamics
- Monte Carlo methods
- Genetic algorithms
- Fragment-based methods
- Point complementary methods
- Distance geometry methods
- Systematic searches

2. Scoring Function: Following docking, these mathematical techniques are used to forecast the capacity for the non-covalent interaction, known as the binding capacity between two molecules. The strength of various kinds of intermolecular interactions, such as those between two proteins, proteins and DNA, or proteins and drugs, can also be predicted using scoring functions. To differentiate the simulated binding modes from every other mode investigated by the searching algorithm, these configurations are assessed using scoring functions.

For example:
*Empirical scoring function of lgemdock
Fitness= vdW + Hbond + Elec

- Binding Energy
  $\Delta G_{bind} = \Delta G_{vdw} + \Delta Gh_{bond} + \Delta G_{elect} + \Delta G_{conform} + \Delta G_{tor} + \Delta G_{sol}$

Receptor selection and preparation

Step I – Building the Receptor

This step involves downloading and modifying the receptor's 3D structure from PDB. Depending on the available parameters, this should involve removing the water molecules from the cavity, stabilising charges, completing the missing residues, generating side chains, etc. The receptor need to remain stable and biologically active following modification.

Step II – Identification of the Active Site

Once the receptor has been constructed, it is necessary to identify its active site. Even though the receptor may have multiple active sites, the one of interest should be chosen. If there are any heteroatoms or water molecules, the majority should be eliminated.

Step III- Ligand Preparation:

Ligands can be drawn with programs like Chemsketch or acquired from a variety of databases like ZINC and Pub Chem. The LIPINSKY'S RULE OF 5 should be followed while choosing the ligand. When a pharmacologically active lead structure is gradually optimised for enhanced activity and selectivity as well as drug-like qualities, as explained, the rule is crucial for drug development.

For the selection of a ligand using LIPINSKY'S RULE:

1. Not more than 5 –H bond donors.
2. Molecular Weight NOT more than 500 Da.
3. Log P not over 5 for octanol water partition coefficient.
4. NOT more than 10 H bond acceptors.

Step IV- Docking:

The final step involves docking the ligand onto the receptor and examining the interactions. The ligand with the best match is chosen based on the scores produced by the scoring function [15].

Molecular Docking [36]

Mechanism of Molecular Docking

This method uses molecular docking to anticipate the atomic-level interactions between a tiny chemical molecule and a protein. This method helps in understanding molecular recognition mechanisms, optimising leads, and drug discovery. The substance, known as a ligand, has the ability to inhibit. This approach depends on a comprehensive three-dimensional model of the target protein, which can be acquired using methods such as Cryo-Electron Microscopy, X-ray crystallography, or Nuclear Magnetic Resonance Spectroscopy [16, 17].

Knowing the structure of the protein being studied is essential before starting a docking screen. This protein structure is used in conjunction with a ligand database by a docking program. The scoring function and the search strategy, which investigate Conformational Space, are the two primary determinants of a docking program's effectiveness. All possible protein and ligand orientations and conformations are included in this space. Extensive exploration of this domain

is not feasible due to existing computational limits. This would entail taking into account every conceivable molecule's distortion as well as every possible ligand rotational and translational orientation with respect to the protein at a certain degree of detail. While some docking systems aim to model a flexible protein receptor, many already in use use flexible ligands [18].

MOLECULAR DOCKING APPROACHES

There are number of approach survive for docking as follows:

1. *Monte Carlo Approach*
   i. It creates a ligand's initial configuration in an energetic location via rotation, conversion, and random conformation.
   ii. The basic arrangement is scored. It then creates a fresh arrangement and scores it.
   iii. The Metropolis criterion is used to determine if the new configuration should be kept.

2. *Metropolis Criterion*

A new solution is approved right away if its score is higher than the previous one. A Boltzmann-based prospect function is helpful if the configuration is not novel. If the solution is works out [19].

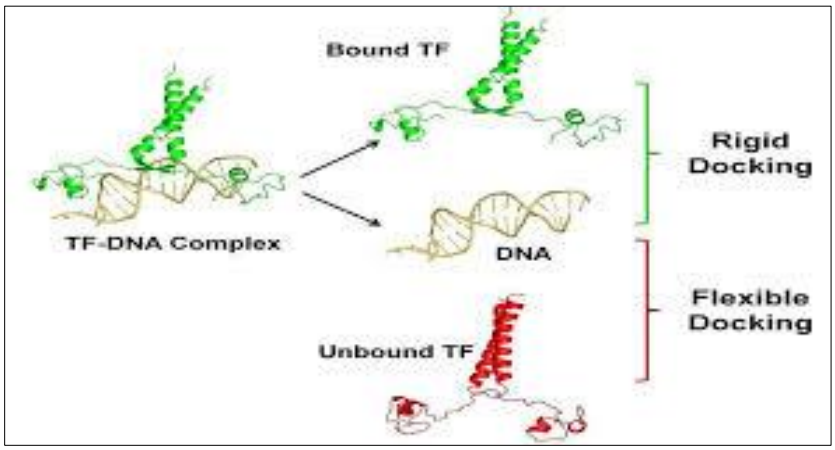


Fig. 5: Structural images of rigid docking and flexible docking

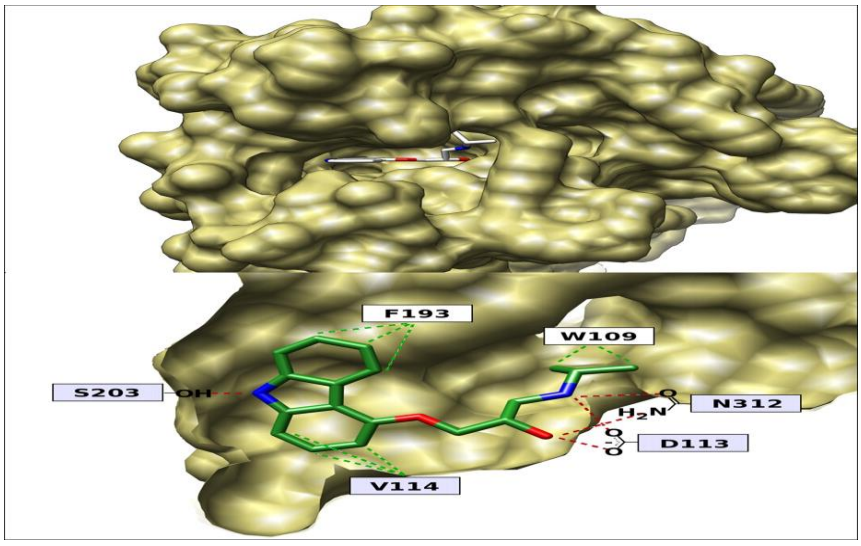


Fig. 6: Docking of a little molecule (green) into the crystal composition of the beta-2 adrenergic g-protein coupled receptor

3. *Matching approach*- Complementarity is emphasised by these approaches. The ligand-receptor-arrangement may require optimisation as a result of the ligand atom being positioned in the "best" spot within the site.
4. The Ligand Fit Method a quick and reliable method for docking tiny ligand particles into protein active sites to examine form complementarity between ligand and protein active sites is provided by ligand robust phrases.
5. Take a complimentary stance these methods concentrate on evaluating the shape and/or chemical complementarity of interacting molecules.

6. The fragment-based approach one way to describe fragment-based approaches is to dissolve the ligand into individual photons or particles, then attach the fragments and finally reunite them.
7. Geometry of distance Intra-molecular or inter-molecular dimensions can be used to express a wide variety of sequence properties. These distances can be put together and compatible three-dimensional structures can be computed using the distance geometry framework.
8. Docking blindly it was created to scan the entire surface of protein targets in order to find possible peptide ligand binding sites and modes.
9. Docking in reverse to determine a medication candidate's potential for toxicity and adverse effects, it may be useful to compare each of these objectives with a specific pharmacokinetics feature. A special method is used to conduct docking studies on a single ligand [20].

Factor Affecting Docking [21]:

1. Intra-molecular forces:
    - Bond length
    - Bond Angle
    - Dihedral Angle

2. Inter-molecular forces:
    - Dipolar
    - Electrostatic
    - Hydrophobicity
    - Vander walls forces

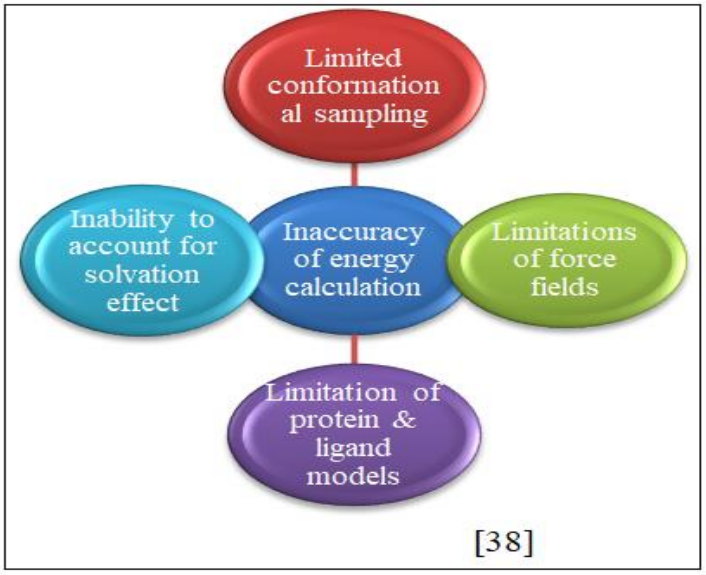
Software available for molecular docking [22-26]

• GOLD
• AUTODOCK
• FLEX-X
• DOCK
• FRED
• GLIDE
• LIGAND FIT
    - Sanjeevini- IIT Delhi [www.scfbio-iitd.res.in]
    - GEM Dock {Generic Evolutionary method for Molecular Docking} - A tool developed by jinn-Moon-Yang, a professor of the Institute of Bioinformatics, National Chiao Tung university, Taiwan (gemdock.life.nctu.edu.tw/dock/)
    - Hex Protein Docking- university of Aberdeen, UK(hex.loria.fr/)
    - GRAMM [Global Range Molecular Matching Protein Docking – A center for Bioinformatics, university of kanas, USA [www.bioinformatics.ku.edu/flies/vakser/gramm/]

Limitations of Experimental Techniques:

Several limitations restrict experimental methods despite significant advancements in structural genomics. The ability to replicate, purify, and cultivate a sufficiently high-quality crystal is necessary for X-ray crystallography. It may take several months to solve a structure. Only proteins that are relatively tiny (less than 25 k Da) can be analysed using NMR spectroscopy. The production of numerous individual mutants is a time-consuming step in mutagenesis experiments [37].

X-ray crystallography	• must be able to crystallize • must have 20 mg material solving a structure is not easy
NMR	• limited to 120 residue • must be soluble in aqueous solution environment at high concentration
Electron Microscopy	• low resolution • still emerging science



Role of molecular docking in pharmaceutical sciences

Drug discovery and development

Since this improves the discovery of possible medication candidates, molecular docking is essential to pharmaceutical research. Docking models assist researchers prioritise drugs for experimental validation by predicting how tiny molecules will interact with target proteins.

Protein-ligand binding studies

The binding mechanisms and affinities of ligands to their corresponding protein receptors are clarified via docking. Understanding molecular recognition mechanisms and creating more potent ligands require knowledge of this information.

Virtual screening High-throughput

Researchers can fast test large chemical libraries mixing virtual screening with molecular docking to find possible drugs that may connect to a specific target.

Structural biology

Protein-protein, protein-nucleic acid, and protein-ligand interactions can be modelled using docking, which helps with the structural characterisation of biomolecular complexes.

Rational protein engineering

To increase a protein's binding affinity for ligands or substrates, researchers can design mutations or alterations in the protein via docking [39]. The difficulties in molecular docking Functions for scoring Because of the limits of the scoring systems employed in docking simulations, it is still difficult to predict binding affinity accurately. An continuing difficulty is creating more reliable scoring functions that take solvation, entropy, and enthalpy into consideration.

Conformational flexibility

Since proteins and ligands can take on many conformations, conformational flexibility must be taken into consideration when docking. To overcome this difficulty, sophisticated methods like ensemble docking and molecular dynamics simulations are employed.

Treatment of solvent effects

Since ions and water molecules can greatly affect binding interactions, it is essential to precisely model the effects of solvents. To increase accuracy, sophisticated solvent models and implicit solvent techniques are always being developed.

Sampling efficiency

Molecular docking has a large search space, and one computational bottleneck is the effective sampling of ligand and receptor conformations. To solve this problem, improved sampling techniques are being developed, such as genetic algorithms and Monte Carlo-based approaches.

Membrane proteins

Because membrane proteins have complicated surroundings, docking them is still difficult. Scientists are creating specialised techniques to take membrane protein stability and lipid bilayers into consideration [40].

Role of Molecular Docking in Drug Discovery [41-43]

- ✓ Conformational search
- ✓ Evaluation of binding energetics
- ✓ Structural-based methods

Emerging trends in molecular docking

Machine learning integration

Molecular docking is being combined with machine learning methods, like as deep learning, to improve scoring functions and increase prediction accuracy. Large collections of experimental binding data are used to train these models.

Free energy calculations

Predictions of binding affinity are becoming more accurate thanks to developments in free energy calculations. Researchers are increasingly able to use methods like thermodynamic and alchemical integration.

AI-driven drug discovery

AI-driven drug development pipelines rely heavily on molecular docking, where AI algorithms find interesting drug candidates and forecast their possible toxicity and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties.

Fragment-based docking

Fragment-based docking techniques are becoming more and more common because they make it possible to screen fragment libraries effectively, which makes it easier to find new lead compounds.

Cryo-EM integration

The study of massive macromolecular complexes is being revolutionised by the combination of molecular docking with cryo-electron microscopy (cryo-EM) data, which makes it possible to determine high-resolution structures [44]. Finally, molecular docking continues to be an essential tool in structural biology and drug development, and its influence on other scientific fields is expanding. The predictive power of molecular docking is continuously increasing due to continuous research efforts, machine learning integration, and improvements in free energy calculations, despite the difficulties with accuracy and processing efficiency. It promises to speed up the creation of novel medications and expand our knowledge of atomic-level molecular interactions as the field develops.

Upcoming difficulties, forthcoming initiatives, and viewpoints

A computer method called molecular docking is used in structural biology, bioinformatics, and drug discovery to forecast the interactions between tiny molecules (ligands) and proteins or other macromolecules (receptors). Although molecular docking has proven to be a useful technique in various domains, there are a number of upcoming obstacles, projects, and viewpoints [45, 46].

Improved accuracy and precision

Improving the precision and accuracy of docking predictions is still quite difficult. Current algorithms frequently have trouble correctly predicting ligand binding poses and binding affinities. One of the main initiatives in this field is creating sample methods and scoring systems that are more reliable.

Incorporating flexibility

Numerous dynamic biological macromolecules can change their shape when a ligand binds to them. To improve predictions, future docking techniques must better take protein flexibility into consideration. This could entail using sophisticated conformational sampling methods or molecular dynamics simulations.

Handling protein-ligand water interactions

Given water molecules have a major impact on binding, it is essential to accurately characterise their role in protein-ligand interactions. The development of techniques that can accurately forecast the locations and energetics of water molecules in docking simulations is still in progress.

Machine learning and AI integration

Molecular docking procedures are increasingly incorporating machine learning and artificial intelligence approaches. This includes enhancing docking methods, forecasting binding affinities, and employing AI to improve scoring systems.

Multi-target docking

Several targets must frequently be taken into account at the same time in drug discovery, particularly in network pharmacology and poly-pharmacology. There is increasing interest in creating docking techniques that can effectively manage multi-target circumstances.

Virtual screening and drug repurposing

In virtual screening and medication repurposing, docking is essential. Future research may concentrate on enhancing the scalability and speed of virtual screening methods to swiftly examine large chemical libraries.

Personalized medicine

By taking individual genetic variants into account, molecular docking can be used in personalised treatment. One interesting field is creating techniques to forecast how genetic variations impact drug binding and reaction.

Accessibility and user-friendliness

It's critical to improve molecular docking software's usability and accessibility for scientists without strong computational backgrounds. Its use can be made more accessible through cloud-based solutions and user-friendly graphical user interfaces.

Big data and structural databases

Improved docking techniques can result from utilizing the abundance of structural data found in the Protein Data Bank and other repositories, as well as developments in big data analytics.

Ethical and regulatory considerations

Given the importance of molecular docking in drug development, the ethical use of AI and machine learning in this setting, as well as the regulatory approval procedure for medications found by computational methods, will come under closer examination [47, 48]. Finally, molecular docking keeps developing into a potent instrument for a range of industrial and scientific uses. Its continued success and capacity to handle intricate biological and pharmacological issues will be facilitated by overcoming present obstacles and pursuing these future opportunities [49].

Application of Molecular Docking

Because molecular docking is used before the experimental phase of any inquiry, it can demonstrate whether a particular biological reaction is possible. Molecular docking has revolutionised research in a number of domains. The degree to which an enzyme will be blocked or activated can be predicted based on the particular interaction between ligands and protein targets, which may be enzymes. This information could be used as a springboard for logical drug development [27]. Below is a summary of the most important uses for molecular docking:

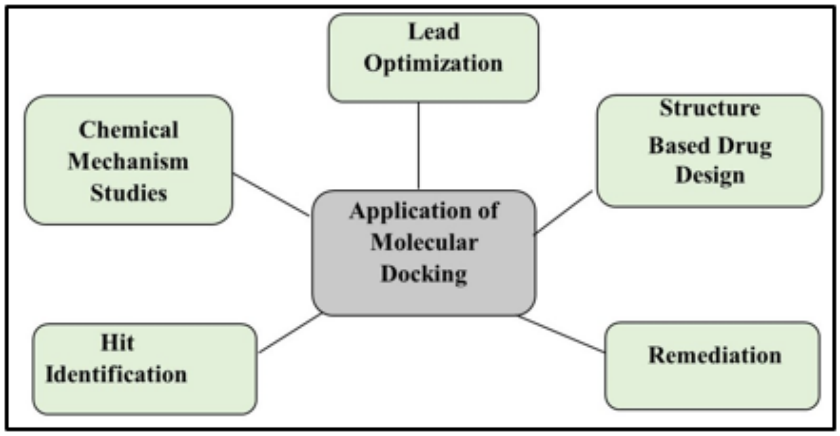


Fig. 7: Application of Molecular Docking

Hit identification

With the help of docking and a scoring algorithm, structure-based computer-aided drug design (CADD) facilitates hit identification by effectively screening sizable databases of possible medications in silico. The goal of this procedure is

to find substances that have a high probability of attaching to a particular protein target of interest. Nevertheless, little study has been done to systematically evaluate the hit rate, or success rate, of docking campaigns. The percentage of compounds that are correctly predicted to bind to the protein target is known as the hit rate [28, 29].

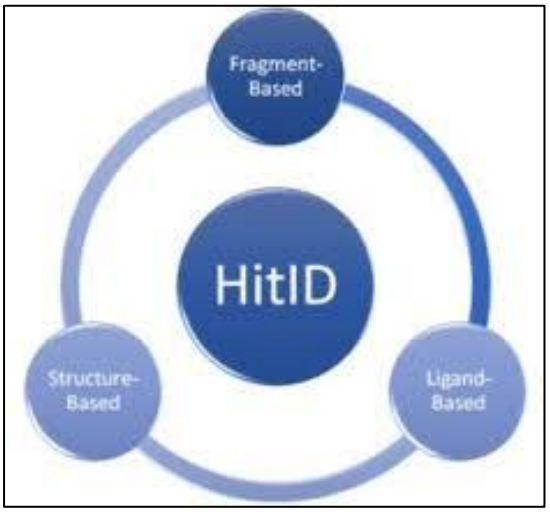


Fig. 8: Hit Identification

Lead Optimization

Docking is used to determine a ligand's binding mode or posture during protein interaction, providing information that helps create more powerful and specific analogues. Lead optimisation is the process of improving the efficacy and drug-like qualities of initial hit or lead compounds. Docking and scoring are useful techniques for hit identification and hit optimisation into lead compounds when the target's structural features are known [30]. Here are a few more applications:-

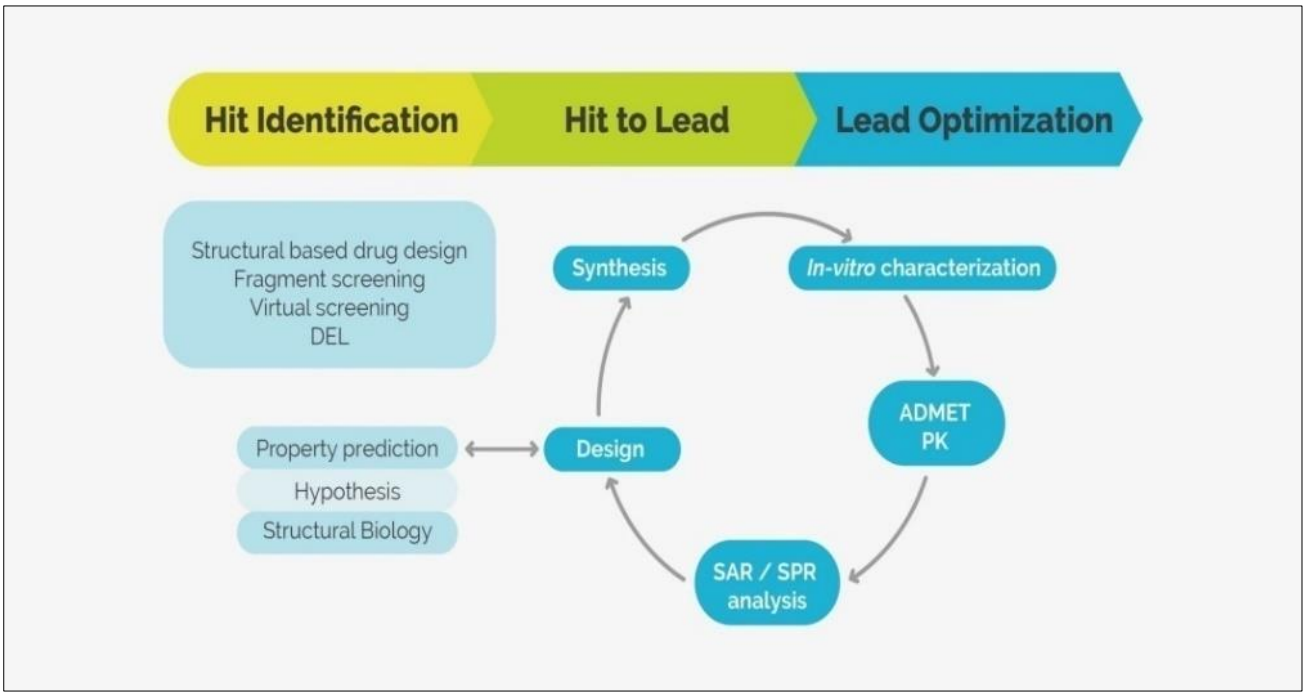


Fig. 9: Lead Optimization

Bioremediation- Protein ligand docking can also be used to forecast pollutants that can be despoiled by enzymes [31].

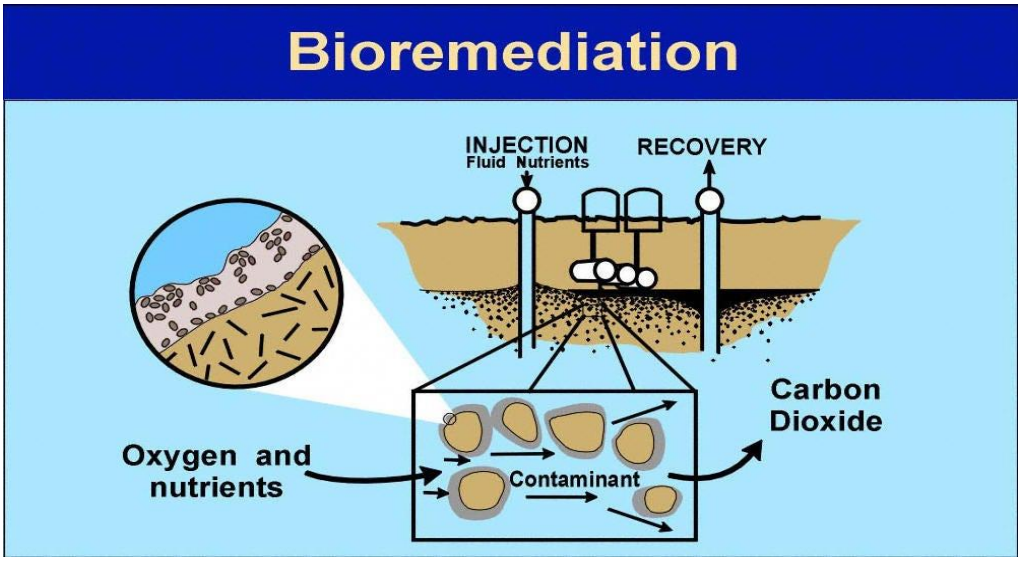


Fig. 10: Bioremediation

1. Prediction of Ka (biological activity) [32]
2. Binding side prediction [33]
3. Mechanism of Enzymatic reaction [34]
4. Protein -Protein / Nucleic Acid interaction [35]
5. Biological activity [36]
6. De-orphaning of a receptor
7. Surface function studies
8. Protein Engineering

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