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A Review on Molecular Docking Techniques

Priti N. Tarade *, Savita D. Sonawane, Sanjay K. Bais
Fabtech College of Pharmacy, Sangola, Solapur, Maharashtra, India
*Corresponding Author: prititarade222@gmail.com

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Abstract

A popular the computer method used in drug development and molecular biology is known as "molecular docking," which estimates the ideal orientation of small molecules, or "ligands," when they attach to a target protein, or "receptor." Understanding the mechanisms of therapeutic action and improving lead compounds depend on this interaction. Molecular docking is a technique that efficiently tests large compound libraries by using algorithms that duplicate the binding process to identify possible therapeutic candidates with high affinity and specificity. Its predicted accuracy has been greatly enhanced by developments in scoring algorithms and molecular docking software, making it an essential instrument for recent pharmacological research. Important elements of the docking process include online examining techniques, molecules energetic models, along with calculations of binding energies.

Keywords - Lead optimization, virtual screening, computational biology, Ligand-Receptor Interaction, Molecular Docking, and Binding Affinity.

INTRODUCTION

This structure-based drug design method is called molecular docking. [1], it mimics atomic exchange along with estimates the affinity and mode of binding between receptor and ligands. Research on drug design has utilized this method extensively in the last few years. It is basic for investigators to obtain, mix, and finish further pharmacological testing when they use the Database of chemicals to be screened for expected phenols. This method further boosts productivity and decreases costs of research. Also, the development of reverse molecular docking technology [2] may greatly enhance the ability to project therapeutic targets as well as understand the basic molecular basis for drug design. ligands and receptors are rigidly docked to establish the correct position regarding the "key" in order into unlock the "lock" in the first suggested "lock-and-key model"[3]. The geometric complementarity has been highlighted in this model. A computer is used in molecular docking - based modeling process that projects also structure of the interaction of a ligand and receptor. either, the tiny molecule known as the ligand or another protein, while the receptor is either a protein or nucleic acid molecule (DNA or RNA). Another term for it would be a model process which the role of the ligand in a predetermined or anticipated binding location is estimated.

Protein-ligand or protein-protein conformations can be developed in silico& compared to structure created. Which able to replicate experimental data through simulations of molecular docking and docking validation algorithms. As ligands and receptors, they must change their structures to properly contrast one another, however, as the real Docking mechanism is quite adaptable. We

produce the "induced fit model" as a result [4] . In accordance with geometric complementarity, pre-organization and energy complementarity help ligands and receptors combine into the strongest structure available in a way that reduces the amount of free energy [5]. The past few years have seen a notable increase also the amount of data accessible on natural activity, structure, and inhibition.[6] With over 50,000 protein structures.[7] structure databases like Database of Proteins (PDB)[8] & The WWPDB[9] or Worldwide Protein Data Bank[10] may be useful for drug discovery.[11] Some databases, such as PDBBIND[12] , PLD[13], AffinDB[14], and BindDB[15], also provide information about the structures both of binary complexes and to their affinity for binding.

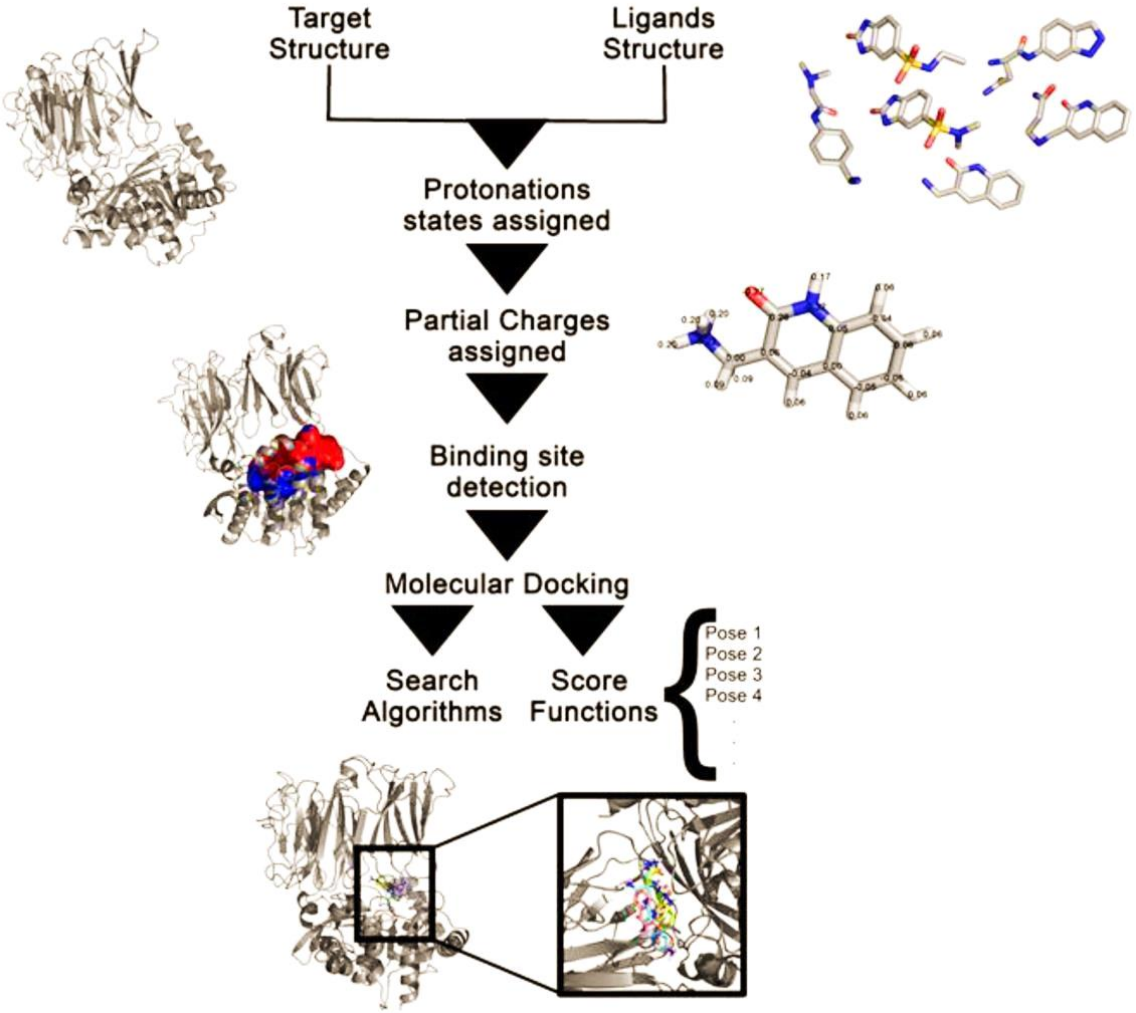

***Figure 1*:** *A major field in drug development using molecular docking*

OBJECTIVE

Predicting the interaction between two molecules, like a drug & its target (usually a protein), is the goal of docking approaches, especially in computational biology and drug development. The following are the goals of docking technique.

The process of predicting binding modes involves determining the ideal location and orientation (pose) regarding a ligand to bind to some target receptor.[22]

The binding Affinity Prediction: This involves estimating the extent to which the ligand interacts & Receptor, typically by means of scoring functions that is correlated with the binding energy.

Virtual Screening

To find possible therapeutic candidates that can bind to a target location efficiently, quickly evaluate vast libraries of chemicals.

The aim of this section is to offer an understanding of the molecular interactions, such as hydrophobic effects and hydrogen bonds that control the binding of ligands to receptors.

Rational Drug Design

To help discover new compounds by figuring out how to modify a ligand to improve its binding affinity or specificity for the intended target.

Intellectual Property Optimization

To investigate different chemical changes and binding configurations in order to optimize and refine lead molecules for drug discovery.

Application

Predicts potential ligands

Drug development is helped by the use of molecular docking, which finds different ligands that may bind to a specific protein target.

Saves time and resources

Docking simulations save time and money by reducing need for experimental screening.

Understanding binding mechanisms

Understanding molecular interactions and binding mechanisms is made possible through docking.

Virtual screening

Makes it possible to virtually screen large compound libraries.

Lead optimization

By estimating binding affinity and orientation, lead compounds can be optimized with its assistance.

Structure-based drug design

Provides guidance by pointing out important relationships.

Protein-ligand interactions

Explains in-depth the interactions between proteins and ligands.

Flexibility and adaptability

Takes into consideration the molecules' ability to adjust and change during binding.

Cost-effective

Decreases the requirement for assays that are preliminary.

Complementary to experimental methods

Strengthens and expands upon experimental structural biology methods.

Advantages

Predicts potential ligands
Saves time and resources
Understanding binding mechanisms
Virtual screening
Optimizing leads
Ligand protein interactions
Flexibility & adaptability
Cost effective
Complementary to experimental methods
Predictive Power

Exploration of Chemical Space
Structure-Based Insights

Disadvantages

Scoring Function
Lack of standardization
Identifying hot compound
Ligand chemistry
Rigid receptor

Limitations

Lack of confidence in the effectiveness of the scoring function provides joining with an appropriate Energy needed is the primary disadvantage of the molecular docking technique. The capacity to bind molecules together is not as easily predicted as the solvation effect. Together with multiple intermolecular interactions that have importance but rarely taken into account in scoring functions, For example- the transthyretin thyroxin complex- Kuntz

Accurately handling the water molecule during the binding process remains available issue that is still available receive a lot of attention due to several factors in the near future: X-ray crystal structures lack of details of hydrogen, because inefficient passing through smaller atoms.

When identifying a water molecule that may be serving as a molecule that bridges between a ligand & receptor, it becomes insufficient due to the unknown exact position of hydrogen. There is a theoretical approach available for precisely forecasting the impact of the ligand on water molecules and the strength of that action.

Rigid receptors are one of the main problems facing the docking field.

When a protein binds with a rigid receptor, it takes multiple confirmations based on the ligand's features [16].

This results in confirmations from a single receptor, which is negative. [17]

PRINCIPLES

Molecular docking is a process by which a small molecular ligand attaches itself to a particular location within a bigger molecule.

Molecular docking can be separated into two sections

The process of docking involves placing molecules in the positions that will allow them to interact with receptors as efficiently as possible. . Docking is a problem that occurs bind forces to create a stable complex within a matter of minutes.[18]

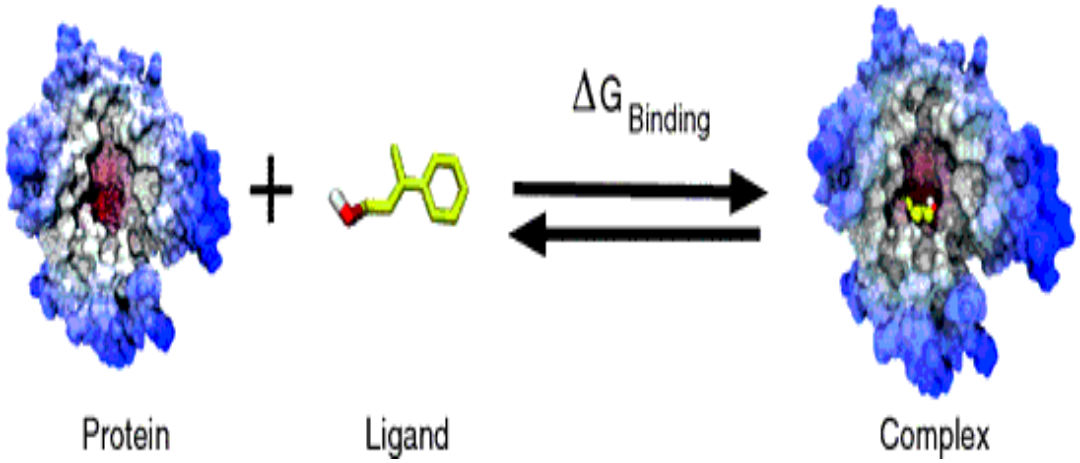

Figure 2*: *Protein Ligand complex

The significance of docking

The secret to logical drug design is it.

Docking data can be used to identify inhibitors for particular target proteins, which can lead to the creation of new medications.

With more proteins having known structures, it is becoming more significant. determining the proper binding geometry [position] of the ligand in the binding location transduction of signals.

ESSENTIAL PHASES OF DOCKING

Selection of the target and preparation

Ligand a particular choice

The docking -Evaluation docking results

Ways to bind two molecules together

Need to quantify or rank together

Scoring function or force field

Experimental structure may be amongst one of several predicted solution

Selection of method

MOLECULAR MODELING

Molecular modeling is the study of the structure, behavior, and interactions of molecules using simulations and computational methods. In chemistry, biochemistry, pharmacology, and materials research, it is essential because it offers insights that are hard or impossible to get from experimentation.[19]

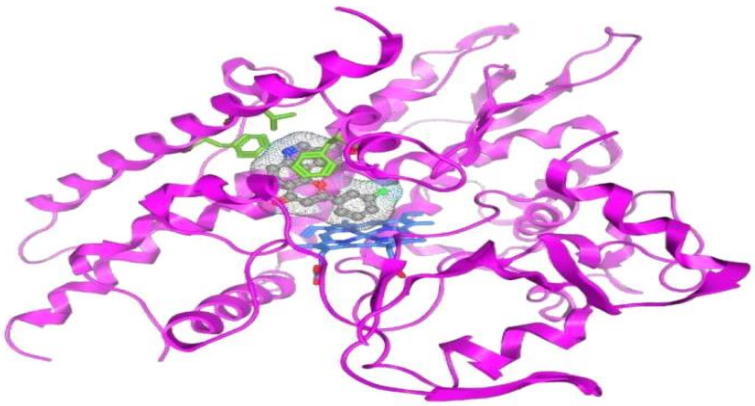

Figure 3*: *Molecular illustration modeling

The Molecular docking models

The theory of locks and keys

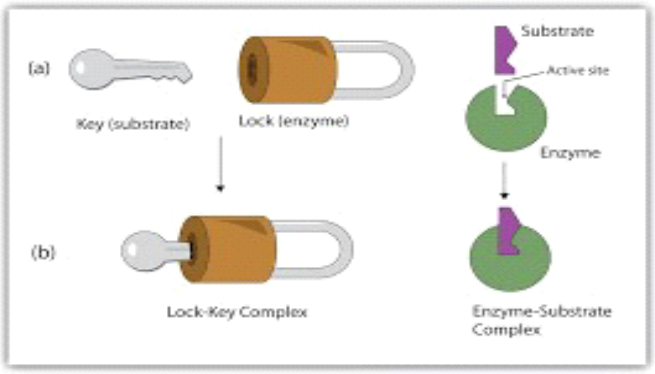

Figure 4*: *Lock & key theory

One of the oldest and most basic theories to describe the mechanism of interactions between enzymes and substrates is the lock & key theory. In 1894, Emil Fischer, a German chemist, made the suggestion. As per this hypothesis, the relationship between an enzyme and its substrate is comparable to that of a lock and key, in which the substrate (the "key") precisely and properly fits into the enzyme's active site, while the enzyme (the "lock") has a certain, inflexible form. [20]

The theory of induced fit

An explanation of how enzymes interact with their substrates during a chemical process is provided by the induced fit theory. Daniel Koshland first proposed the theory in 1958. It is an improvement on the Lock and Key Theory and gives a more realistic picture of catalysis and enzyme-substrate interaction. The induced fit theory explains that an enzyme's active site is a flexible structure that changes shape[21].

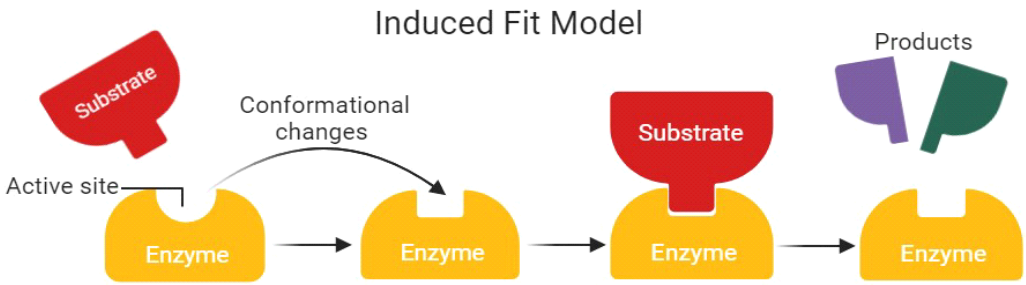

Figure 5*: *Induced fit model

Molecular docking approaches

The various developed molecular docking applications are powered by multiple algorithms. This area provides a review of the most popular algorithms along with each one's advantages. Also, we show the primary programs that are developed using every method. In docking programs, one or more search algorithms that are specific may be used.

Coordinating approach

One of the most basic algorithms that maintains in mind the geometric overlap of two molecules is the coordinating algorithm. In order to align the receptor and ligand in multiple ways, different strategies are used.[22]

Monte Carlo method

It employs a conformational search strategy using affinity of molecules potentials for a ligand to dock with a structure. The maintenance of the new arrangement is assessed using the Metropolis criterion.

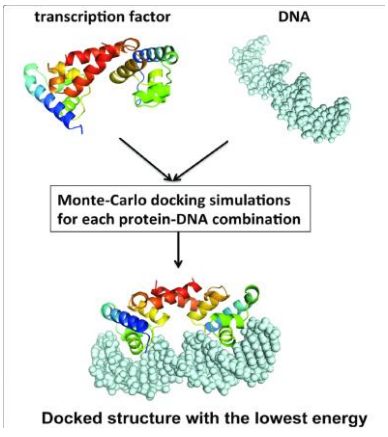

Figure 6*: *Monte Carlo method

Genetic approach

Genetic algorithms (GAs) are popular optimization approaches that are applied in a variety of situations, and the docking problem is one of them that is commonly solved. To accelerate the estimations & identify the most effective settings determining the medicinal molecule under study's activity, the GA technique was used. Natural evolution as proposed by Darwin provides the basis for GA] which proposes that a operator for genes can be utilized to connect parent chromosomes (two) to create a fresh chromosome that may Improve to the parents.[23]

Particle Swar optimization

The PSO algorithm or particle swarm optimization was created in 1995 by Kennedy and Eberhart. Swarm optimization techniques are a type of metaheuristic that is Molecular docking uses it as a way to Check for the docking issue., where the problem is defined as an issue with optimization of values linked to a clearly specified random flexible.

Scoring function

The intermolecular complex structure is identified by the docked orientation, which is estimated using the SF. Measuring the relative strength of ligands is another application for the SF. The first and the most crucial phase in the procedure is designing the SF. Because the SFs are employed to specify the ligand location and the mechanism of binding, their precision affects the docking reliability.

Force field scoring operation

A scoring function created according to atomic-level physically interactions, such as Torsion, bond angles & lengths is the force-field function. atomic level, including bond torsions, bond angles, and bond lengths (Vanommes laeghe & Guvench, 2014). In most cases, the experimental data and a mechanical calculation based on physics principles give the force-field functions and associated parameters.

Empirical scoring function

To determine the optimal molecular docking structure, empirical SFs are used. According to Guides et al. (2018), it calculates the binding affinity by adding together all of the significant energy components of the protein ligand. These empirical SFs were used in a number of studies. According to the total comparison.[24] In order to ascertain the most effective weights for the energetic variables, the empirical SF technique often uses a series of training with unidentified binding affinities. There are various optimization approaches that can be used for this, including linear regression analysis.

Requirements for molecular docking

The following elements make up a method for docking ligands: the design of the target protein, a database or the substances of interest containing real or synthetic substances regarding the docking procedure, & a mathematical basis certain allows the use of the proper docking and scoring methods. There are several methods for attaching solid compounds or parts of a protein's active site, including acceptance search, geometric hashing, and pose grouping [25].

Ligand representation

Typically, more Atoms of hydrogen are either added or deleted to identify the arrangement with the best chance of developing into predominant and determine the calculated values for pKa [26].

The representation of a receptor

In general, few amounts of docking seen increases with the precision of the crystal lattice applied. In general, A new study on the precision, restrictions, & risks associated with Refinement methods for ligand-protein complex structures offer a thorough examination of the present buildings. [27]

The docking mechanism

The method by which a tiny molecule (ligand) is anticipated to bind to a particular spot on a macromolecule (usually a protein) is known as the docking mechanism in molecular modeling. Finding the ideal ligand orientation, location, and interaction in the receptor's binding site is the aim of docking, which also helps forecast the binding affinity and comprehend the interactions that lead to complex formation.

Preparing the Ligand

It may create programs for every potential charge configuration inside a given calculate the pKa values for every charged element in the pH range. Generally, it's useful to reduce the chemical structure of applying a force field from quantum mechanics.

Software available for docking

Docking software is commonly used in computational biology and chemistry to predict how molecule, such as a drug, binds to a receptor. There are several software options available for docking, each with its strengths and features. Here are some of widely used:

Software available for docking

Gold

Many The usages of ligand subgroups in receptor docking and genetic improvement. There are 3 terms that comprise the scoring system based on force fields system: The term "H-bonding" describes the possibility of dispersion between molecules.[28] The potential for intramolecular dispersion is referred to as "intramolecular potential".

Auto dock

Has a three-dimensional lattice structure with tips that are regularly spaced that surround and is centered around the region of interest of the macromolecule.

Flex-x

To dock the base fragment, "position clustering" method is applied. To include related donor modifications into adjustments to the active site, one method of clustering is employed. To complete the ligand assembly, flexible fragments are successively inserted Utilizing MIMUMBA & evaluated with the overlap function. Calculations for energy then come in last. Final evaluations utilizing the hydrogen bond, ionic, aromatic, and lipophilic words included in Böhm's grading method.[29]

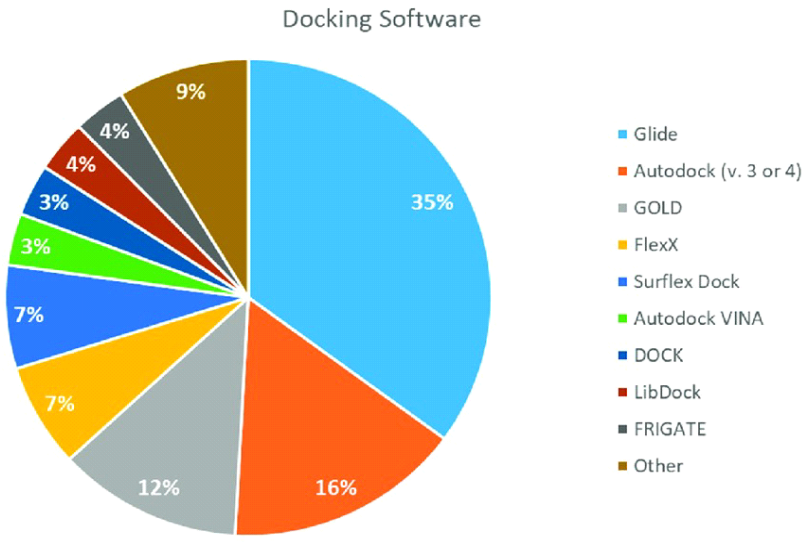

Figure 7*: *Docking software

Knowledge based scoring functions

According to Li, Ze, Lu, and Ballester (2020), knowledge-based SFs often make use of the structural details in the known protein-ligand complex. According to Rykunov and Fiser (2010), statistical potential based SFs is a different term for it. Knowledge-based energy potentials, or Knowledge-based SFs, are obtained by collecting structural information from experimentally calculated atomic structures. Many knowledge-based SFs were created and applied to protein ligand and protein structure estimation. Knowledge-based SFs have the capacity to have a good balance between efficiency (speed) and accuracy compared to the previously explained techniques [force field (Section 18.2.2.1) and empirical SFs], based on a variety of research studies.

Machine learning based SFs

Many machines learning (ML)-based support functions (SFs) available that can be used in together with docking algorithms to create SFs. ML-SFs are used to score and improve the accuracy of SFs, and they typically perform better than other classical SFs. To create MLSFs, a number of machine learning techniques are used, such convolutional neural networks (CNNs), random forests (RF), and support vector machines (SVM) (Wang et al.2017).

Methods for docking

Adjustable docking

According to Huang and Wong (2009) and Lexa and Carlson (2012), flexible docking, which is based on the induced-fit model, provides flexibility in the binding position prediction of the protein-ligand, protein-protein, or peptide-protein interactions. Flexible docking, in addition to rigid docking, takes into account a ligand's capacity to alter or rotate side chains of residues inside the target protein's binding site. [30] Multiple receptor combinations joined during flexible docking link to very difficult multidimensional data sets. Because of the many degrees of freedom linked with the residues of flexible protein structure, it allows the potential energy surface to have different coordinate functions. Stochastic and systematic incremental construction algorithms are the two main algorithms used in this methodology. for extremely flexible ligand docking on the protein-peptide dataset, the Dock Thor instrument is provided.

Semi flexible docking

It is appropriate to deal with protein and small molecule/Ligand interactions in semi flexible docking since the range of protein conformation changes and is allowed to flex with protein at specific torsional angles, but hard docking binds the protein configuration. To maintain computational efficiency, the structure configuration of macromolecules maintains rigid or holds any residues of the rotation amino acids, whereas small molecules undergo changes in structure.[31]

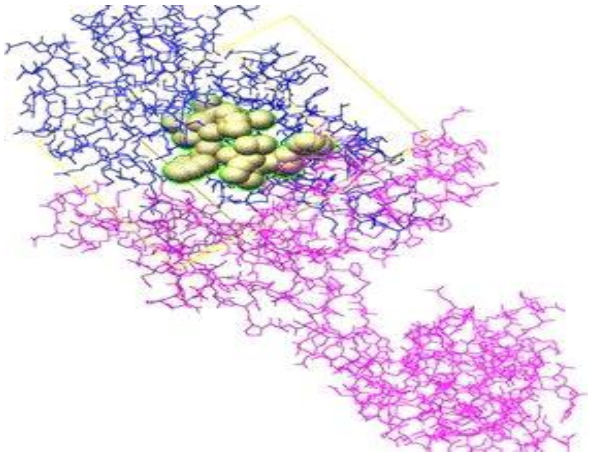

Figure 8*: *Semi flexible docking

High throughput docking virtual screening

Online screening refers to a group of computer techniques certain enable the analysis big chemical groups or searches in datasets in order to determine suitable potential target. That is separated divided into two categories: (1) based on structure and receptors, which depends on information obtained from one or more active ligands; (2) ligand founded, which depends Using the known locations of protein receptors. Inhibition tests can be used to produce the highest scoring computationally screened compounds to evaluate their activity in vitro. Using the protein-ligand structure using X-ray crystallography complex can be identified, providing information on the interacting residues. By using linkers to increase the binding interaction/affinity on the lead, Information about the interaction of proteins and ligands can be utilized to maximize the binding. site and improve interactions in the unused region.

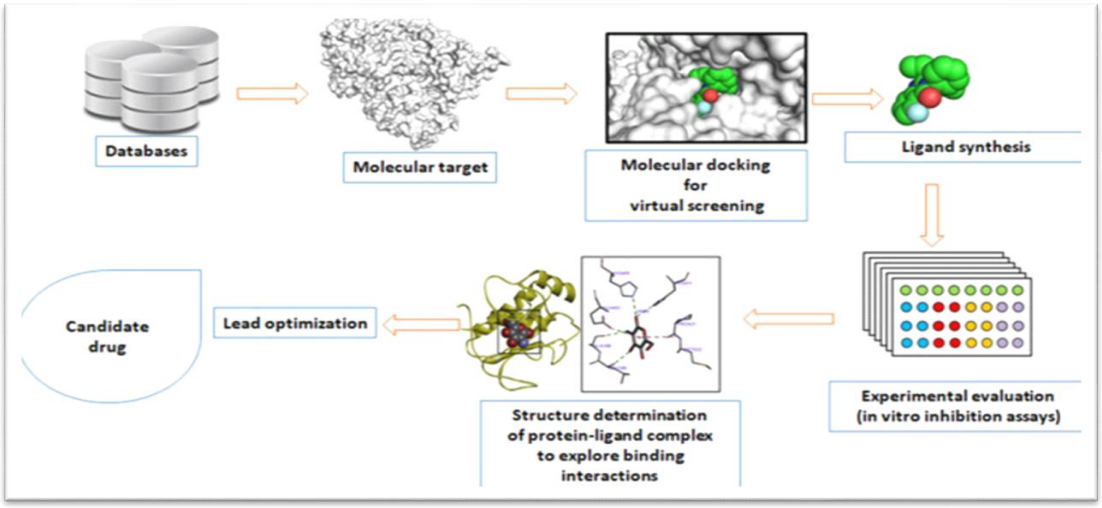

Figure 9*: *High throughput docking virtual screening

Docking of fragments

Compared to drug-like molecules, false positive findings, incorrect scoring, and problems involving multiple binding modes make fragment-based drug design difficult. One area of increasing research is the development of fragment-specific techniques. By predicting the proposed chemicals' binding positions, docking of fragments increases the development of fragment hits. The Graph theory's maximum clique algorithm is applied to determine exact relationships between a multifragmenting Ligand and a collection of docking positions with different fragment varieties. Using a fragment's known binding mode, de novo modeling software presents altered analogs with greater affinity for binding that are determined experimentally or computationally.

Docking with machine learning

Some SF's ability to evaluate binding affinity prediction accurately determines the rightness of docking effects. The atomic coordinates regarding the receptor-ligand combination structure is used to predict the binding affinity. The goals of machine learning (ML) is to create algorithms that have let Representative Datasets are used to teach computers. The three primary subcategories are three types of learning: supervised, unsupervised, and reinforced. The first machine learning support vector (ML-SF) to significantly outperform classical SFs Regression is used by RF-Score to link its capacity to bind to a complex's summary of the structure.

Features of docking tools

The methods (rigid, flexible, and fragment), and a few other elements form the basis of docking tools. The benchmark and an overview of the molecular docking tools are listed. In molecular modeling and computational biology, docking tools are software programs that simulate the

interaction of molecules, usually a protein and a ligand, to predict the preferred binding orientation and affinity.

Mechanism of docking

Finding the attention protein ordered is the first step towards producing a docking screen. Biophysical techniques like x-ray crystallography or, sometimes, NMR spectroscopy have regularly produced the structure. [32]

A docking program's success depends on two mechanisms, such as the scoring function and search algorithm. The protein's possible conformations and orientations make up the investigate space. linked by a ligand Packed with near computer devices.[33]

Many docking programs try to model a flexible protein receptor, but most of these account for bendable ligands. [34]

The main steps in the molecular docking mechanism include

Therefore, the docking process consists of the following steps

Step 1: preparation of protein

The Protein Data Bank (PDB) must be checked to obtain the protein's three-dimensional structure, which should then undergo preliminary processing. Based on the provided parameters, this should allow for the amputation of the water molecules from the cavity, stabilize the charges, effectively replace the missing residue, produce side chains, etc.

Step 2: Active site prediction

Protein manufacturing must be followed by an estimate of the protein's active site. There are many active sites in the receptor strength; only the one that is of concern should be selected. [35]

When they are present, heteroatoms and water molecules typically important. [36]

Step 3: Preparation of ligand

Ligands can be obtained from a variety of databases, such ZINC and Pub Chem, or they can be sketched using the Chem. sketch tool. The LIPINSKY'S RULE OF 5 should be applied while selecting the ligand. The drug design and detection computer-aided technique, or CADDD.

Step 4

Analysis of the interactions occurs when the ligand is docked next to the protein.

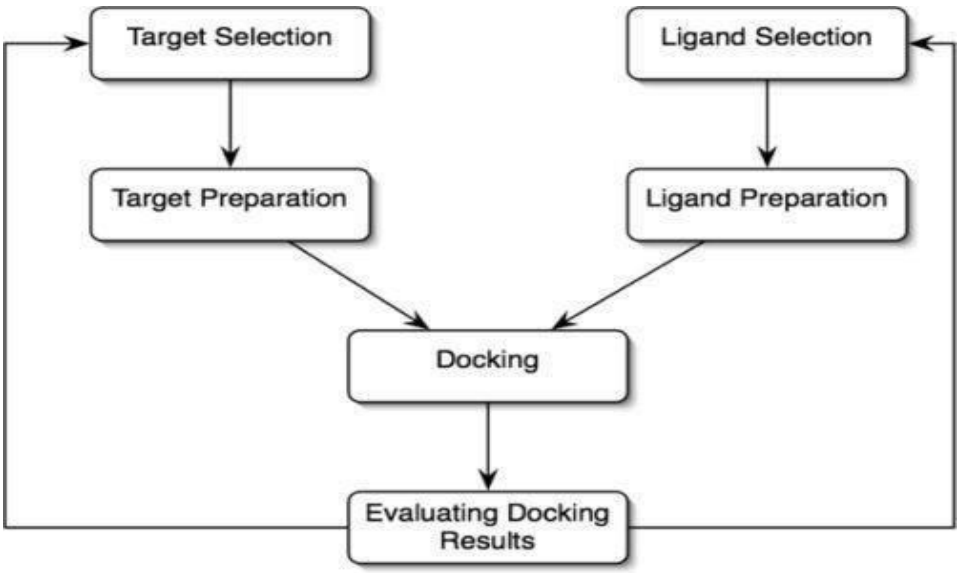

Figure 10*: *Flow chart of evaluation docking

Molecular dynamic simulation

Newton's motion rules are used by the MD simulation to handle the atoms' positions and velocities. As a kind of "computational microscope," a simulation may determine interactions between every peripheral in the system down to the atomic level in order to recognize the dynamic change over time in the protein structure specified amount in terms of time, MD modeling makes use of classical equations of motion. To explain the various attributes of the model system for specific times and residue, simulation-related trajectories are displayed as a graph. Protein conformational states at different times can also be determined via MD simulation. It offers information on thermodynamic and kinetic parameters.

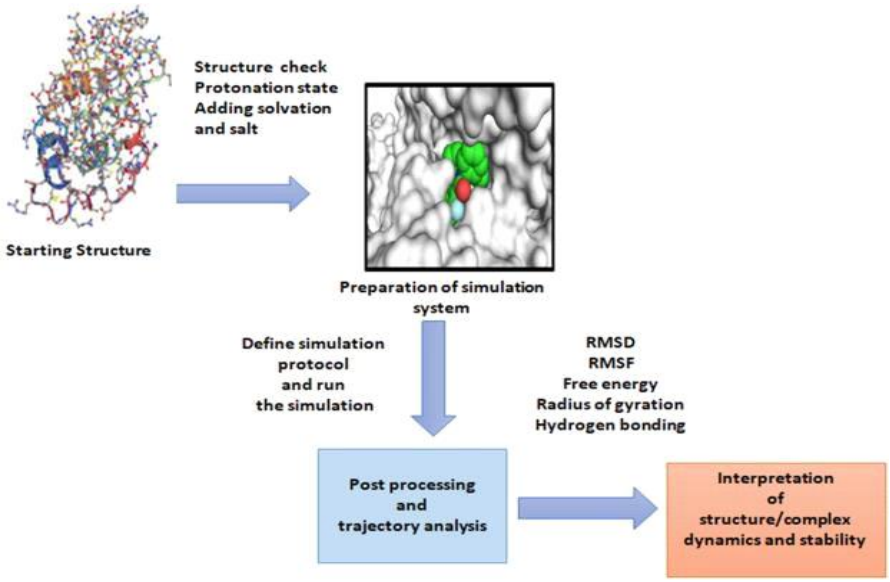

Figure 11*: *Important procedures for analysing molecular dynamic simulations

An understanding of a protein's Secret compartments or allosteric binding locations can also be obtained by MD simulation research. The MD simulation makes the most multiple the force fields, such OPLS, GROMOS. Protein conformations are provided via the trajectories produced by simulation, which may be used in multiprotein conformation docking applications. The outcomes of molecular docking are validated by MD simulations' application. Docking, however, is a very flexible method that simulates the ligand-protein binding process under physiological conditions.

Post docking refinement

Improving docking poses using simulations of molecular dynamics (MD) & improvement. Binding estimate after refinement [BEAR] is post docking processing approach used for the refinement of ligand-binding modes predicted by tools [Auto Dock and Dock] and evaluates the binding-free energies performed with MM-PBSA and MM-GBSA algorithms. The docked molecules were first preprocessed by the BEAR tool's computational processing; next, using the MM-GBSA and MM-PBSA algorithms, the estimation of the free energy of binding of the docked complex was determined. Rescoring and post docking developing techniques in drug development lead to greater correlation with experimental results and increased hit rates in virtual screening.

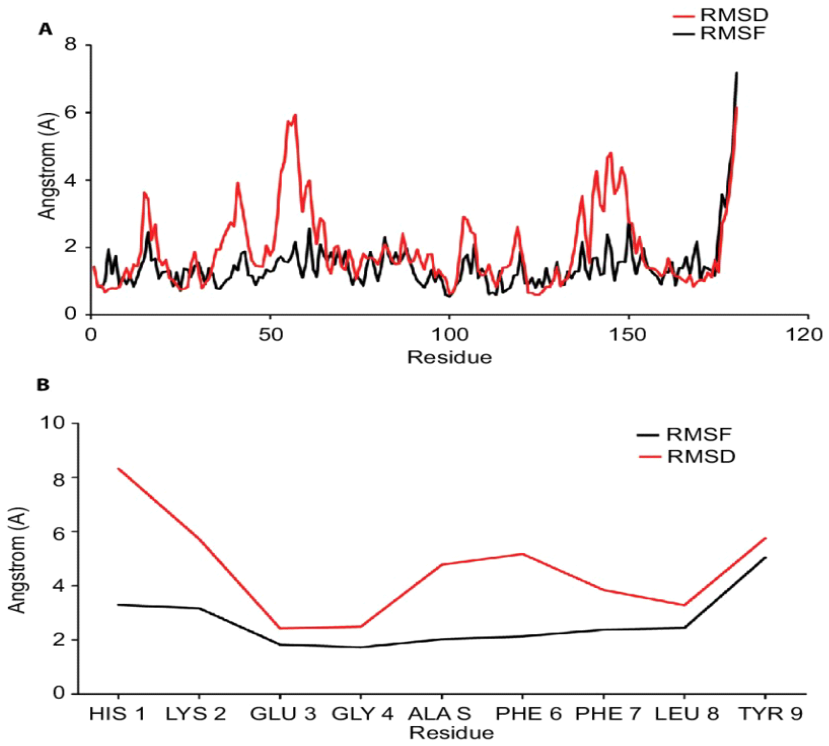

Figure 12**:** *(A) RMSD plot, (B) gyration plot, demonstrate the trajectory analysis of molecular dynamics simulation*

Calculations of binding free energy: MM-GBSA/MM-PBSA

An effectiveness of Docking of proteins with ligands, peptides, and other proteins is defined by binding affinity. The computation of absolute binding-free energy requires the use of many accurate methods and an effective computational system. The connections that are established in between statistics thermodynamics and models of end-point free energy determine the precision the MM-GBSA/MM-PBSA is. According to Geneden and Ryde (2015), the post analysis method for finding out the free binding energies of atomically organized complicated is called the MM-PBSA/MM-GBSA technique. The approach breaks down free energy into three categories: solvent entropy terms, mol specific mechanical energies, and continuum solving energies.[37]

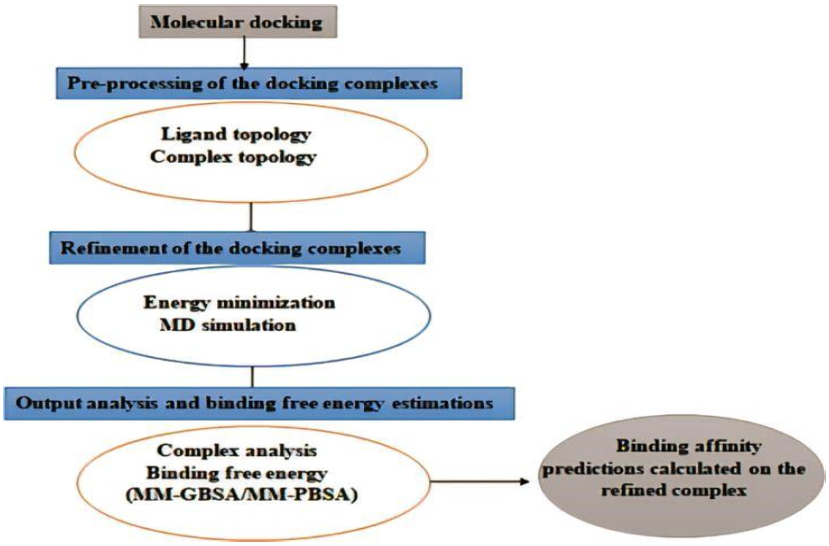

Figure 13**:** *The binding affinity estimation computational workflow following refinement*

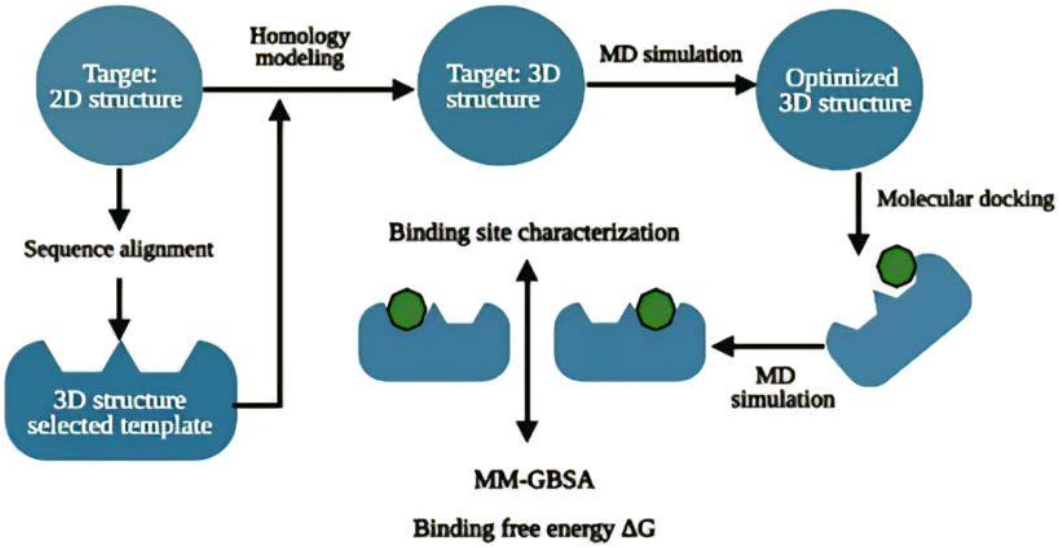

***Figure 14*:** *An outline of the procedures for calculating binding-free energy that come from modeling, docking, and molecular dynamics simulation*

CONCLUSION

Molecular docking provides a strong foundation for ligand-receptor interaction prediction, which has made it an important strategy in the disciplines of drug and molecular biology discovery. Docking offers important insights into the mechanisms of action and the structural basis of therapeutic efficacy by imitating tiny molecules attaching themselves to specific proteins. The accuracy and dependability of docking predictions have increased due to ongoing developments in computer algorithms and scoring functions, which have made it possible for researchers to quickly screen huge compound libraries and find viable therapeutic options. Molecular docking remains an essential tool in the contemporary drug development process, despite its drawbacks like its reliance on the accuracy of structural data and the underlying assumptions in scoring techniques.

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