International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 6 Nov - Dec 2025, pp: 204-213 www.ijprajournal.com ISSN: 2456-4494

# A Review on Computational Prediction of Ligand Receptor Interactions Using Molecular Docking Approaches

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Date of Submission: 05-11-2025 Date of Acceptance: 15-11-2025

**ABSTRACT**
A computational method called "molecular docking" simulates intermolecular interaction order to forecast the complex's structure. Finding a ligand's three-dimensional shape and ideal binding orientation to its receptor is the primary context of molecular docking. This method is frequently used in the research and discovery of new drugs. The availability of sophisticated computational tools and molecular databases has made docking an essential part of contemporary medicinal chemistry. It offers time- and money-efficient methods for locating possible therapeutic agents and offers insightful information about drug design, molecular interactions, and binding mechanisms.

**Keyword:** computational, docking, algorithm, PDB

## I. INTRODUCTION

Docking is a computer technique in molecular modeling that predicts a molecule's preferred orientation in relation to another when it forms a stable complex [1]. By comprehending this orientation, it is feasible to estimate the strength of the interaction or binding affinity between molecules, frequently using scoring systems.

Biological signaling and molecular recognition depend heavily on the interactions between biomolecules, including proteins, peptides, organic acids, polysaccharides, and fatty substance. The kind of biological response (such as agonistic or antagonistic effects) can be determined by the relative orientation of these interacting molecules. As a result, molecular docking is an essential technique for forecasting ligand receptor complex binding affinity and functional behavior.

Because it can anticipate the binding conformation of low molecular weight compounds to specific target sites, molecular docking is one of the most widely utilized tools in structure-based drug design [2]. It improves knowledge of biochemical interactions and supports logical drug design [3].

Finding an optimal protein and ligand shape that minimizes the total binding free energy is the ultimate objective of molecular docking [4]. Many biological processes, such as interactions between drugs and proteins, enzymes and substrates, and nucleic acids, depend on molecular recognition [5]. Designing ligands with the best potency and specificity for therapeutic targets is made easier by an understanding of the fundamental forces (van der Waals, hydrogen bonding, and electrostatics) that control these interactions [6].

## II. THEORY OF DOCKING

The basic purpose of molecular docking is to use computational techniques to anticipate the structure of the ligand-receptor complex. Two interconnected steps can be used to accomplish docking: first, ligand conformations in the protein's active site are sampled, and then these conformations are ranked using a scoring function. The determined binding orientation should ideally be reproducible by sampling algorithms, and it should also be ranked maximum among all generated conformations by the scoring function. We provide a brief introduction to fundamental docking theory from these two viewpoints. [7]

By combining and optimizing factors such as steric, hydrophobic, and electrostatic complementarity, as well as measuring the association energy (scoring), docking algorithms fit a ligand into a binding site [8].

### 1. Sampling algorithm

As previously mentioned, there are a vast number of ways that two molecules can bind to one another, and even with the advancements in parallel computing and the faster clock speeds of contemporary computers, it would be costly and time-consuming to generate every mode that could exist. Algorithms that could separate the useful conformations from the useless ones were therefore required.

In this context, several algorithms were created, and they can be categorized based on how many degrees of freedom they disregard. The degree of freedom was reduced to just six (three

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translational and three rotational) by the most basic algorithm that was proposed, which regarded the molecules as two rigid entities. DOCK is a highly quoted example of a software that uses this algorithm [9]. The objective of this program was to identify molecules with a high degree of form resemblance to binding sites or pockets/grooves. It creates a picture of the protein's surface that shows possible binding locations. This image is made up of multiple overlapping spheres with different radii that only make two points of contact with the macromolecule's molecular surface. The ligand molecule is also thought of as a collection of spheres that roughly occupy the ligand's space. The pairing rule is used after the substrate and polypeptide surface representations in terms of spheres are finished. The pairing rule is predicated on the idea that if the internal distances of every sphere in the ligand set match those of every protein set, allowing for a user-specified tolerance, then a ligand sphere can be associated with a protein sphere. As a result, it enables the program to recognize clusters of spheres on the polypeptide region and the binding molecule that are geometrically similar. Many other programs, such as LibDock [8], LIDAEUS [10], PhDOCK [11], Ph4DOCK [12], Q-fit [13], SANDOCK [14], and others, were created later and use this matching algorithm (MA). All of these MA-based programs have the benefit of speed, but they also have a number of drawbacks, including the requirement for precise receptor geometry beforehand and a lack of molecular flexibility that makes it difficult to precisely define many facets of ligand-protein interactions.

**2. Scoring functions**

In order to find a conformation that most closely resembles the receptor structure, sampling modifications among different degrees of freedom must be done accurately and quickly enough to evaluate millions of molecules in a predetermined amount of computational time. The range of algorithms covered above takes care of this. Scoring functions are an additional addition to algorithms.

A key component of VS is the assessment and ranking of anticipated ligand conformations. The scoring function must forecast the docked orientation that most closely resembles the "true" structure of the intermolecular complex when we are only interested in the way a single molecule attach to a biomolecule. However, in the event that we wish to assess more than one ligand, the scoring function must be capable of rank each ligand in relation to the others in addition to determining the "true" docking position. Consequently, it is crucial to build trustworthy scoring schemes and algorithms that can score various stances [15].

In order to get as near to the actual binding energy as feasible in the shortest amount of time, scoring functions typically analyze the binding energy of complexes utilizing a number of assumptions and simplifications. Well-liked scoring functions strike a suitable compromise between precise binding energy estimation and time-consuming computation. Numerous scoring functions have been developed over the years and fall into three primary categories: knowledge-based, force-field, and empirical [16].

## III. MECHANISM AND DIFFERENT STEPS OF MOLECULAR DOCKING

Understanding the mechanism of molecular docking begins with defining the structural framework of the target protein, which serves as the foundational element for any docking investigation. Docking algorithms utilize this three-dimensional (3D) protein structure along with a curated database of potential ligands as input parameters [17]. The overall performance and predictive reliability of a docking program depend primarily on two essential components the search algorithm, which explores possible binding conformations, and the scoring function, which quantifies binding affinity [18]. These two factors collectively determine the success of the docking simulation.

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Volume 10, Issue 6 Nov - Dec 2025, pp: 204-213 www.ijprajournal.com ISSN: 2456-4494

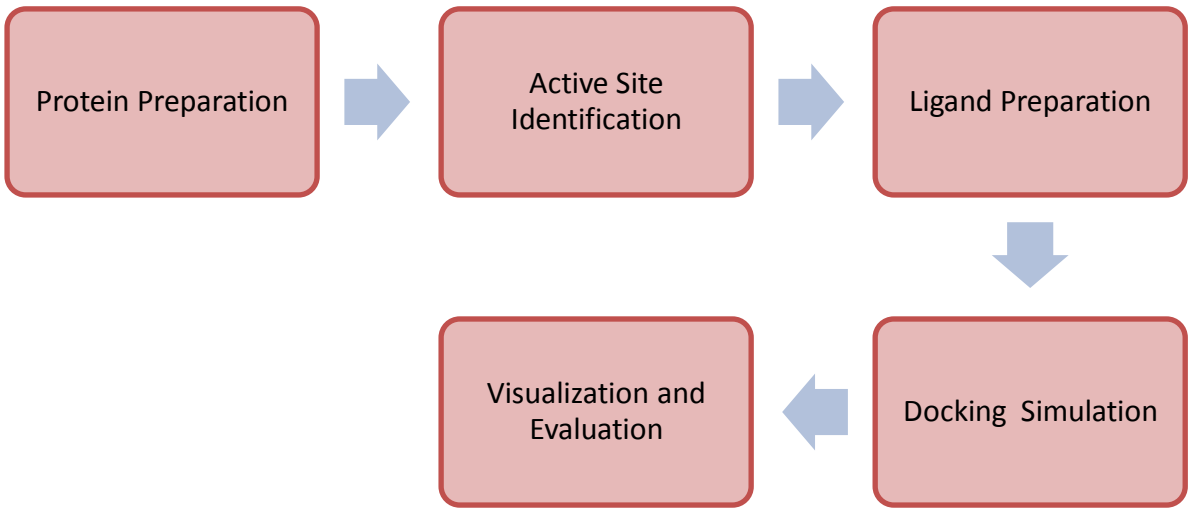


**Fig. II. Mechanistic Steps Involved in Molecular Docking.**

The search or conformational space encompasses all possible orientations, conformations, and binding modes that a ligand can adopt within a protein's active site [19]. Given the limitations of current computational technologies, it remains impractical to exhaustively explore this entire conformational landscape, as doing so would require evaluating every conceivable distortion of the protein and every potential translational and rotational arrangement of the ligand at the binding interface [20–21].

**Step 1: Protein Preparation**

The initial phase involves obtaining the 3D structure of the receptor protein, typically from the Protein Data Bank (PDB). Preprocessing is essential to ensure accuracy and stability of the protein model. This step includes adding missing residues or side chains, optimizing hydrogen atom positions, balancing charge distributions, and removing non-essential water molecules or heteroatoms from the binding cavity. Such refinements enhance the protein's structural integrity and ensure compatibility with docking algorithms [22, 23].

**Step 2: Active Site Identification**

Once the protein is properly refined, the binding or active site the region responsible for ligand interaction—must be accurately identified. Proteins may contain multiple potential binding sites; however, the biologically relevant site is selected for detailed study [24, 25]. Typically, water molecules and heteroatoms within the cavity are excluded from the docking process, as they rarely contribute meaningfully to receptor–ligand binding [26].

**Step 3: Ligand Preparation**

Ligands intended for docking can be constructed using molecular design tools such as ChemSketch or ChemDraw, or retrieved from public databases including ZINC and PubChem[27, 28]. The suitability of these ligands is commonly evaluated based on Lipinski's Rule of Five, which predicts the drug-likeness of a compound and helps distinguish pharmacologically viable molecules from non-drug-like entities [29, 30]. This stage is a critical component of Computer-Aided Drug Design (CADD), a process that facilitates rational compound selection and predicts the likelihood of success or failure in subsequent drug development steps [31–32].

**Step 4: Docking Simulation**

The docking phase involves computationally positioning the ligand within the receptor's active site to determine the most energetically favorable binding orientation. The docking algorithm explores various conformations and orientations, while the scoring function assesses the interaction energy between the two molecules to predict binding affinity and stability [33, 34].

**Step 5: Visualization and Evaluation**

Following the docking process, the results are analyzed and visualized using molecular graphics tools to assess the quality of the predicted complexes. The scoring function values generated by the software are examined to estimate binding

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strength wherein higher or lower scores may indicate stronger interactions, depending on the algorithm employed [35,36]. Additionally, score decomposition analysis is often performed to identify the contribution of individual energy components, such as hydrogen bonding, van der Waals interactions, and electrostatic forces, to the overall binding energy [37–38].

## IV. MOLECULAR DOCKING SOFTWARE

Molecular docking program design

Molecular docking has been essential in many drug development efforts, particularly for the virtual screening of phytochemicals or nutraceuticals as potential medicinal molecules. The earliest docking program was developed in the mid-1980s by Irwin Kuntz of the University of California, and efforts to improve docking computations are ongoing. In order to predict an enzyme's capability, recent advancements in docking techniques determine its natural substrates [39]. Protein structure can be effectively predicted by restricting the search for likely reactant and reaction mechanism to the region where the target protein is found to belong to a particular superfamily [40].

Framework for ranking docked molecules

A range of methods and systems are used to carefully rank the docked molecules. The frequently used are highlighted in this section.

### 4.1.DOCK 3.5.x

This program's premise is that refers to enzyme facillitating reaction through limiting the activating complex that the substrate prefers. Docking molecule designed to replicate the transition state also produce an enhanced signal relative to the docking substrates because amidohydrolase enzyme exhibit hydrolytic activity to maintain the structural stability [41].

### 4.2.Glide

By enabling side chain flexibility and calibrating and re-ranking the docked structure through an enhanced material science driven scoring framework, the program allows for the precise positioning of predicted substrate and distinguishes the enzymes that belong to a particular enolase superfamily subgroup [42].

Notable functionalities of molecular docking software:

There are numerous docking programs available; this section covers several widely recognized ones.

### 4.3.Dock

A molecular docking program called Dock was created by the Chimera team at UCSF. It is an easy-to-use tool for docking small molecules into receptor-binding sites. Dock assesses ligand-receptor binding affinities using a grid-based methodology. In order to assess the poses produced throughout the docking procedure, it also has scoring mechanisms. PDB, MOL2, and SDF are among the input file types that the dock supports. You can access the dock at http://dock.compbio.ucsf.edu/.

### 4.4.Autodock

The Scripps Research Institute created the popular molecular docking program Autodock. Both stiff and flexible docking can be done using this free, open-source program. Autodock optimizes ligand distribution inside the receptor binding region using a Lamarckian genetic method. Additionally, it has a number of scoring features to assess ligand-receptor binding affinities. PDB, MOL2, and SDF are just a few of the input file types that Autodock supports. You may get Autodock from http://autodock.scripps.edu.

### 4.5.Argus lab 4.0.1

Mark Thomson of the Department of Energy at Pacific Northwest National Laboratory in the USA developed the molecular modeling program Argus Lab, which models solvent effects by combining algorithms from quantum theoretical and conventional modelling techniques. This software can do things like molecular modeling, drug design, and graphic production. You can access Argus Lab at http://www.arguslab.com.

### 4.6.Genetic optimization for ligand docking (GOLDTM)

GOLD, a protein-ligand docking software, contains several key characteristics. In order to account for side chain and spine chain flexibility in computations, it uses user-defined scoring functions. The energy functions are based on both structural and non-reinforced contact information. Among the several docking possibilities is the ability to remove crystallographic water molecules from the ligand binding site. Additionally, GOLD can handle metal atoms automatically if they are set up correctly in the protein data file. Lastly, the companion tools SILVERTM or GoldMineTM can

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be used to effectively examine and post-process the findings of virtual screening high-throughput screening.At http://www.ccdc.cam.ac.uk/products/lifesciences/gold, you can get this software.

**4.7.MolDock**

MolSoft LLC created the molecular docking program MolDock [43]. Small molecules can be docked into a receptor-binding site using this quick and effective docking program. MolDock assesses the ligand-receptor binding affinity using the fast Fourier transform (FFT) technique. Additionally, it incorporates a scoring algorithm designed to that considers the van der Waals forces, electrostatic interactions, and shape complementarity between the docking molecule and the target protein. MolDock is compatible with a number of input formats including, including as SDF, MOL2, and PDB.https://www.molsoft.com/about.html is where you may find it.

**4.8.Discovery studio**

Discovery Studio is a molecular modeling and simulation program developed by Dassault Systes BIOVIA. Included are numerous tools for molecular docking, virtual screening, protein modeling, and molecular dynamics simulation analysis. 1The molecular docking component is used to predict the binding mechanism and assess the strength of interaction between a ligand (small molecule) and a target protein. 2Discovery Studio generates a set of possible ligand binding poses and ranks them based on their expected binding energies using a variety of docking algorithms, such as CDOCKER, GOLD, and LibDock. The software also provides capabilities for viewing and analyzing the docking data, as well as for comparing the binding modalities of different ligands to the same protein target. https://discover.3ds.com/discovery-studio-visualizer-download is where you can get it.

**4.9.Chimera**

A program called Chimera was developed by the University of California, San Francisco to model, analyze, and visualize molecular structures. For molecular docking simulations and for visualizing the three-dimensional structures of proteins, nucleic acids, and small molecules, it provides a range of tools. The "Dock Prep" molecular docking component of Chimera is used to make the target protein and ligand ready for docking simulations. The ligand can be positioned in the protein binding site with the use of its capabilities for adding hydrogens, allocating charges, and creating molecular surfaces. Furthermore, Chimera provides tools for analyzing the docking data, such as the capacity to calculate binding energies, visualize the binding poses, and generate maps of interactions between the ligand and protein residues. Chimera may also link with other molecular docking software applications, such as AutoDock, to do more intricate docking simulations.

You can access Chimera at https://www.cgl.ucsf.edu/chimera/.2.4

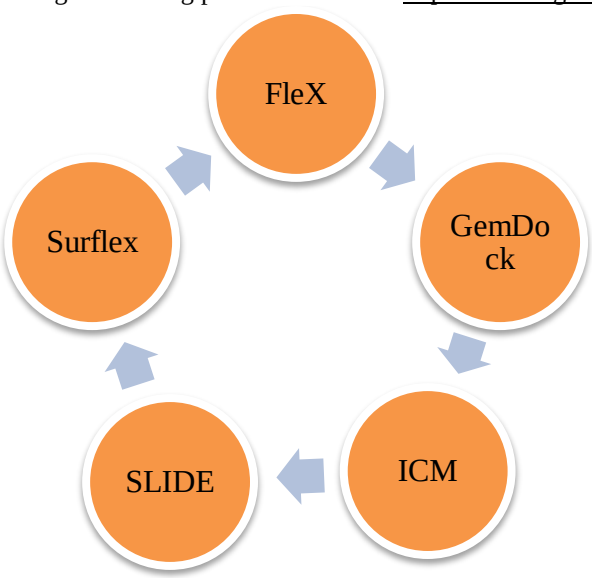


**Fig.II. Commonly Utilized Tools for Molecular Docking.**

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## V. DOCKING TYPES

There are two broad types of molecular docking:

### 5.1.Rigid Docking

In rigid docking, the receptor and the ligand are both considered to be stiff entities. Finding the spatial orientation that best matches the two molecules is the goal of using scoring functions. The ligand conformation can be built with or without the receptor.

### 5.2.Flexible Docking

Flexible docking takes into account the ligands (and sometimes the receptor's) conformational flexibility. This technique aims to identify the conformations of the two molecules that are most energetically beneficial when they join to create a complex [44].

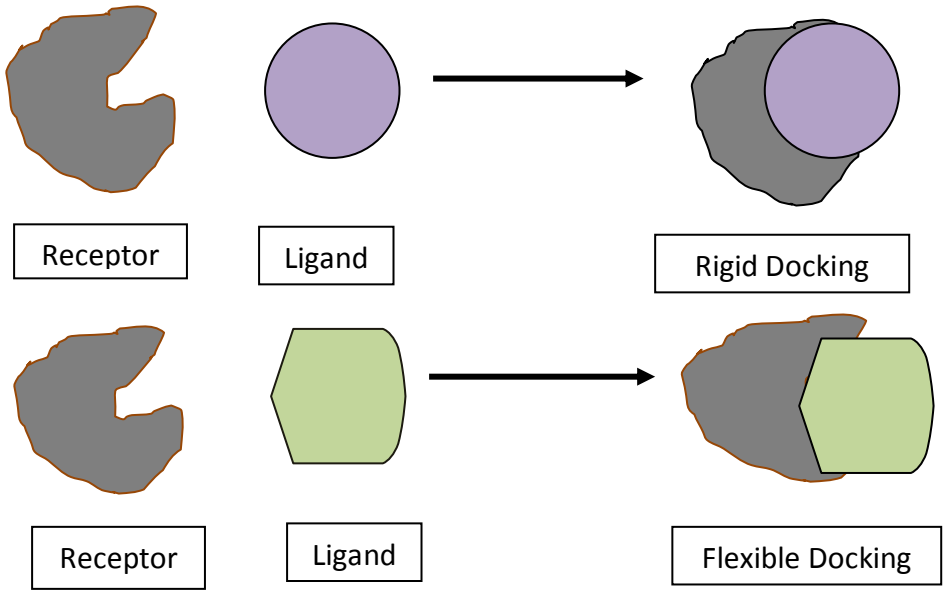


**Fig.III ligand-Receptor Intraction in different Docking Types**

## VI. REQUIREMENTS FOR MOLECULAR DOCKING

Molecular docking involves three essential components: the target protein, the ligand(s) or compound library (including existing or virtual molecules), and a computational platform capable of performing docking and scoring. Most docking algorithms treat the protein as relatively rigid, whereas the ligand is typically considered flexible to explore possible conformations. Beyond conformational flexibility, the binding orientation and position of the ligand within the protein's active site must also be taken into account. Docking of rigid molecules or molecular fragments into protein active sites can be performed using approaches such as consensus searching, geometric hashing and pose clustering.[45]

### 6.1.Ligand Representation

The ligand's most likely conformation is generally refined by adding or removing hydrogen atoms to estimate its pKa values[46]. Accurate atomic representation is crucial, as errors in the ligand's structure can significantly affect docking results.

### 6.2.Receptor Representation

The quality and accuracy of the receptor structure are critical for successful docking simulations. Higher resolution crystallographic structures tend to produce more reliable docking predictions. Recent studies evaluating the accuracy, limitations, and risks of ligand–protein complex refinement methods emphasize the importance of using well-validated receptor structures to ensure meaningful docking outcomes.[45]

## VII. MOLECULAR DOCKING APPROACHES

Molecular docking employs a number of computational techniques, such as:

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**7.1.Monte Carlo Approach**

By using random conformations, rotations, and translations, this technique creates ligand configurations that are unpredictable inside the binding region. Iteratively, new configurations are created after each one is scored. New configurations are either accepted or rejected based on the Metropolis criterion [47].

**7.2.Metropolis Criterion**

A new configuration is approved if it produces a higher score than the old one. Otherwise, it is accepted based on a probability function derived from the Boltzmann distribution, ensuring that energetically favorable conformations are more likely to be selected.

**7.3.Fragment-Based Method**

This method splits the ligand into smaller pieces, each of which docks onto the active site on its own. The entire ligand structure is then rebuilt by joining these pieces.

**7.4.Distance Geometry**

This technique builds three-dimensional structures that are compatible with these measurements by using geometric constraints, such as intra- or intermolecular distances.

**7.5.Matching Approach**

This strategy optimizes the ligand's location occupying the binding region for the optimal match by concentrating on the geometric and chemical complementarity at the ligand-receptor interface.

**7.6.Ligand Fit Approach**

This method for docking tiny compounds into protein active sites is quick and effective. It assesses how well the ligand and binding pocket complement each other in shape.

**7.7.Point Complementarity Approach**

This method predicts the best binding orientations by evaluating the geometric and electrostatic complementarity of interacting molecules.

**7.8.Blind Docking**

Without knowing the active site beforehand, blind docking looks across the receptor's whole surface to find possible binding sites and interaction pathways.

**7.9.Inverse Docking**

For a given small molecule, inverse docking suggests possible protein targets. It is helpful in assessing a drug candidate's possible toxicity, adverse effects, and off-target interactions [48].

## VIII. APPLICATIONS

There are numerous uses for molecular docking in the environmental and biological sciences:

**8.1.Hit Identification**

In order to compounds with potential to interact a target protein efficiently, docking and scoring methods allow for the molecular docking-based screening of huge compound libraries [48].

**8.2.Lead Optimization**

It aids in figuring out how ligands interact with target proteins and how they bind. Designing more effective and selective analogues requires this knowledge [48].

**8.3.Bioremediation**

In order to help with environmental cleanup studies, docking may also serve to predict possible contaminants that can be broken down by particular enzymes.

## IX. CONCLUSION

Molecular docking that was recognized as a significant tool in structural biology and contemporary drug discovery. A key component of computational drug design, it can predict binding affinities and show ligand-receptor interactions. Problems including precise scoring functions, protein flexibility, and solvent modeling still exist despite tremendous advancements. Molecular docking will remain essential in genomics, proteomics, and enzyme design as long as computer based approaches and laboratory based approaches validation continue to progress, which will result in the creation of safer and more efficient treatments.

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