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# Review on Molecular Docking Computational Methods for the Molecular Dynamics and Simulations Research

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ABSTRACT

Molecular docking is a method for simulating molecule complexes. Docking predicts three-dimensional structures. Drug-improvement software based on docking. This critical mechanism allows access to molecular and structural databases. Molecular Docking provides tools for drug design and analysis. Simple molecular prediction and structural databases are required by medicinal chemists. The primary application of docking is virtual screening. Docking programmes visualise the molecule's 3-D structure, and docking gain can be computed. Molecular docking is used in structural molecular biology and drug design. Docking can be used to conduct virtual screening on large compound libraries, rank the results, and propose structural hypotheses for how ligands reduce the target. Computer-aided drug design and discovery has proven to be effective.

**Keywords:** - Computer aided drug design and discovery (CADDD), Molecular docking, ADMET, Binding, Conformations, ADMET: Absorption, Distribution, Metabolism, Excretion and Toxicity; PDB: Protein Data Bank; 3D: Three Dimensional; SBDD: Structure-Based Drug Design; SBVS: Structure-Based Virtual.

## I. INTRODUCTION

Academic institutions and pharmaceutical companies both use computerised drug lead discovery. Proteomics, genomics, and structure informatics are all used in contemporary drug discovery. A virtual screening method called molecular docking uses structure to place small molecules in a target structure. Docking has a wide range of uses. Structure-based drug design, lead optimization, and evaluation recognition are common strategies. There are drug docks. New molecular modelling methods have benefited computer-assisted drug design. Three docking applications are covered in this article. First, we use molecular and quantum mechanics to look into the enzymatic mechanism of a flavoprotein. We will then examine the synthesis of anti-infective agents with structural motivation. We conclude by talking about the implications of drug design for protein-

protein complexes. This review describes how to use solvent to investigate large drug discovery systems[1], [2].

Molecular docking is a methodology for determining the preferred orientation of a ligand against a receptor (Protein) in order to form a stable complex[2]. Using scoring functions, preferential orientation could be used to predict the strength of the bond or binding affinity between the ligand and protein. Docking is frequently used to predict the binding orientation of drug candidates against protein targets in order to forecast the affinity and activity of a drug (Figure a). Therefore, docking is crucial for the development of new drugs[3] . In order to lower the overall system's free energy, molecular docking's primary goals are to achieve an optimized conformation and computationally simulate the molecular identification process[4]–[6]. Discovering a new drug is a very difficult process. An in-silico-Chemico-biological approach is the main pillar of the contemporary drug discovery process. The use of computer-aided techniques in the drug discovery and development process is growing in acceptance, popularity and use[7], [8].

A. CADD Involves

a. Utilization of computation to speed up the drug discovery and development process.
b. Utilizing chemical and biological knowledge of ligands and/or targets to find and improve new drugs.
c. The creation of in-silico filters to eliminate chemical compounds with undesirable characteristics (poor activity and/or poor ADMET, or absorption, distribution, metabolism, excretion, and toxicity) and choose the most promising candidates.
d. Finding new drug targets and retrieving them from target protein structure databases, such as the Protein Data Bank (PDB) at www.pdb.org. To find hits (drug candidates), CADD (Figure-a ) is used.
e. By looking through databases, virtual screening is used to identify new drug candidates from a variety of chemical scaffolds[9], [10].

B. Different Kinds of Interactions: Interaction forces are classified into four types.:

a. Dipole-dipole, charge-dipole, and charge-charge electrostatic forces.
b. Forces of electrodynamics - Interaction of Van der Waals.
c. Steric forces –Due to entropy.
d. Forces associated with solvents - Interactions between hydrogen bonds and hydrophobic molecules[11], [12].

## II. MOLECULAR DOCKING

Molecular docking is divided into two categories.The algorithm should generate the greatest number of configurations that allow for the experimentation method of determining binding modes. Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry, and other algorithms are used for docking analysis [13], [14].Molecular docking is shown in following figure 1 as

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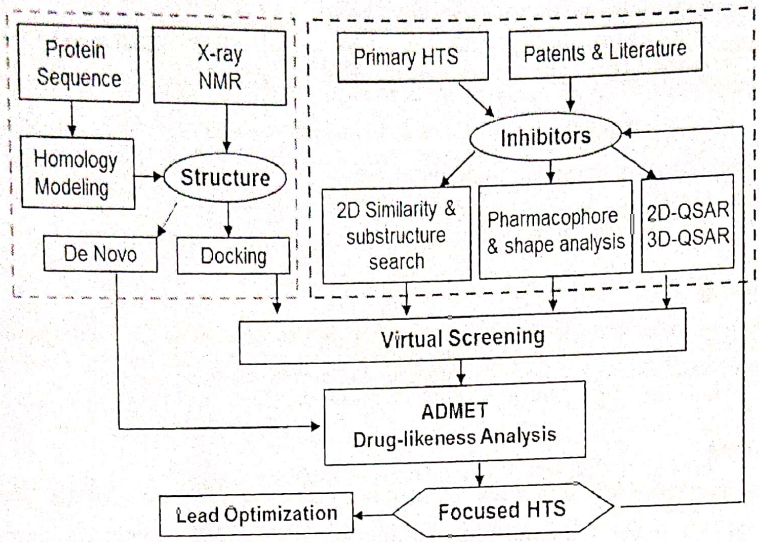


Figure (1): Computer Added Drug Discovery

A. Function of Scoring

The scoring function provides a way to rank the positioning of ligands in relation to one another. To ensure that the highest scoring ligands are also the highest binders, the score should, in theory, directly reflect the ligand's binding affinity for the protein. Scoring criteria can be based on molecular mechanics, knowledge, or empirical methods. Scoring is made up of three different expressions that are relevant to docking and drug design.

a. Ranking of generated configurations based on docking search.
b. Comparing various ligands to proteins (virtual screening).
c. A ligand or ligands ranked by their affinity for binding to various proteins (selectivity and specificity)[15]–[18]

B. Different kinds of docking

The following are the most common docking techniques.

a. Key and Lock Rigid Docking: The receptor and ligand are both kept stationary while docking is done.
b. In induced fit flexible docking, the ligand and the receptor are both conformationally flexible.The surface cell occupancy and energy are calculated for each rotation, and the best pose is then chosen[19].

## III. THE PRIMARY STEPS IN THE MECHANICS OF MOLECULAR DOCKING

In order to have a stable complex, Molecular Docking predicts the preferred orientation of the ligand against the receptor (Protein)[20]. Favored orientation possibly utilized to predict the strength of connection or binding affinity among ligand and protein by utilizing scoring functions. Docking is frequently used to

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forecast how drug candidates will bind to protein targets in order to forecast their affinities and activities. Consequently, docking is essential to the process of developing new drugs[3]. The main aim of molecular docking is to computationally simulate the molecular identification process and accomplish an optimized conformation so that the free energy of overall system is minimized. The process of discovery of a new drug is a very difficult task. Modern drug discovery is mainly based In-silico–chemico biological approach. The acceptance, use, and popularity of computer-aided techniques in the drug discovery and development process are rising quickly. There are 2 types of docking; 1. Flexible docking 2.Rigid docking

A. Adjustable Docking

Our goal is to find the confirmations of the receptor and ligand molecules as they emerge in complex systems by first considering molecule flexibility and then adding transformation[21], [21].

B. Inflexible Docking

If we assume that the molecules are rigid, then we search for a conversion of one of the molecules into three-dimensional space that will make it the most compatible fit with the other molecules according to a scoring function. In the presence of receptor binding activity or in the absence of a receptor, the ligand may generate a particular conformation.

## IV. DIFFERENT MOLECULAR DOCKING APPROACHES

There are number of approach survive for docking as follows –

A. Method of Convergence

These strategies emphasise complementarity. The site's "best" position for the ligand atom results in the creation of a ligand receptor. An optimization-related configuration.

B. Ligand-Fit Methodology

Small molecule ligand docking into protein active sites using the ligand robust term provides a quick, accurate protocol that takes shape complementarity between the ligand and protein active sites into consideration.

C. Complementary PointApproach

These techniques are based on evaluating the shape and/or chemical complementarity of molecules that interact.

D. Blind Docking

It was developed to scan the entire surface of protein targets to find potential binding sites and peptide ligand binding modes.

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E. Inverse Docking

a. In this application of a computer technique for decision-making, a small molecule's protein targets are toxicities and side effects.

b. Understanding these targets and proteomics' pharmacokinetic profile can help with the evaluation of potential toxicities and side effects of drug candidates.

c. For docking studies of a specific ligand, one of these protocols is chosen[22].

F. Monte Carlo Approach

a. It creates a ligand's initial configuration in an energetic site, which consists of random conformation, conversion, and rotation.Initial configuration gets a score. Then a new arrangement is generated and scored.

b. It decides whether to keep the new configuration using the Metropolis criterion.

G. Metropolis Criterion

A new solution is instantly accepted if it receives a higher score than the previous one. If the configuration is not new, a Boltzmann-based prospect function is useful. If the possibility function test is passed, the solution is determined; if not, the configuration is undesirable [2], [4].

H. Method Based on Fragments

Fragment base method can be described as separating the ligand into divide protons or fragments, docking the fragments & finally connecting these fragments together.

I. Measurement of Distant Objects

There are many different kinds of structural sequences that can be described as intra- or intermolecular distances. These detachments can be assembled using the distance geometry formalism, and 3D structures dependent on them can be taken into consideration.

## V. MECHANISM OF DOCKING

A. The first requirement is an organisation of the attention protein in order to produce a docking screen. Typically, a biophysical technique such as x-ray crystallography or, less frequently, NMR spectroscopy has been used to maintain the structure A docking agenda receives this protein organization and a collection of ligands as input[2], [23].

B. A docking program's success is dependent on two mechanisms, including the search algorithm and scoring function. All potential protein orientations and conformations are included in the study space. together with ligand[1], [24], [20]. With current computing capabilities, it is impossible to fully identify the research domain that would list every possible molecule distortion as well as every possible

rotational and translational orientation of the ligand relative to the protein at a predetermined level of granularity.

C. The majority of docking programmes currently in use take bendable ligands into account, and many are attempting to model a flexible protein receptor[1].

D. The process used in Insilica to study the intermolecular announcement between two molecules is known as molecular docking. The macromolecule in this improvement is the protein receptor.The ligand molecule, which is the small particle, can act as an inhibitor[3].

The process used to study the in-silico intermolecular interaction between two molecules is called molecular docking. The macromolecule serves as the protein receptor in this process. The ligand molecule, which can function as an inhibitor, is a micromolecule. Thus, the following are theMajor Steps Involved in Mechanics of Molecular Docking:

Step I – ProteinPreparation for docking: Protein data bank (PDB) should be used to retrieve the three-dimensional structure of molecules from the cavity, stabilising charges, adding missing residues, generating side chains, etc.

Step II – Prediction of active site : The protein's active site needs to be predicted after it has been prepared. Even though the receptor may have numerous active sites, only the one that is of concern should be chosen. When present, hetero atoms and most water molecules are removed[25], [26].

Step III – Ligand Preparation : Ligands can be found in a number of databases, including Zinc and Pub Chem, or they can be sketched using the Chem sketch tool. The Lipinsky's rule should be applied when selecting the ligand. The Lipinski rule of five helps distinguish between candidates who don't use drugs and those who do these already well discussed by earlier researchers[27]. Due to drug similarity, it promises a high chance of success or failure for molecules that follow two or more of the rules. For selecting a ligand that adheres to Lipinsky's Rule:

a. Less than five hydrogen bond donors
b. Less than ten hydrogen bond acceptors
c. Molecular mass less than 500 Da
d. High lipophilicity (expressed as LogP not over 5)
e. Molar refractivity should be between 40-130

Step IV- docking: The ligand is docked to the protein, and the interactions are investigated. The scoring function assigns a score based on the best docked ligand complex that is selected.

## VI. VARIOUS DOCKING SOFTWARES

Various docking programmes have been developed over the last two decades. Table (1summarises the key characteristics of the docking tools currently in use, including endorsed platforms, licence terms, algorithms, and scoring features.

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| Sr.No. | Tool Name | Docking Method | Scoring function |
|---|---|---|---|
| 1 | Auto Dock Vina | Genetic algorithm, Lamarckian genetical agorithm, Simulated Annealing | Auto Dock (force-field methods) |
| 2 | DOCK | Shape fitting (sphere sets) | Chem Score, GB/SA solvation scoring, other |
| 3 | Flex X | Incremental Construction | FlexXScore, PLP, Screen Score, Drug Score |
| 4 | FRED | Shape fitting (Gaussian) | Screen Score, PLP, Gaussian shape score, user defined |
| 5 | Glide | Monte Carlo Sampling | Glide Score, Glide Comp |
| 6 | GOLD | Genetic Algorithm | Gold Score, Chem Score user defined |
| 7 | LigandFit | Monte Carlo Sampling | Lig Score, PLP, PMF |

**Table (1): Basic features of currently available docking tools.**

## VII. MOLECULAR DOCKING APPLICATIONS

Molecular docking interactions can cause protein activation or inhibition, whereas ligand binding can cause agonism or antagonism. Molecular Docking could be used to:

A. Hit attribution(Virtual Screening)
B. Lead Optimization (Drug discovery)
C. Bioremediation
D. KA prediction (Biological activity)
E. Binding site prediction (Blind docking)
F. Protein de-orphaning
G. Interactions between proteins and nucleic acids.
H. Looking for potential protein targets' lead structures
I. Structure-function studies
J. Enzymatic catalytic reaction mechanisms
K. Modifying proteins

## VIII. DISCUSSION & CONCLUSION

Molecular Docking offers a variety of useful tools for drug design and analysis. The desktop of a medicinal chemist now must have easy access to structural databases and simple molecule visualization. The core user interface of commercial software programmes is constantly evolving. Variousabove mentioned docking software programmes for studying molecular docking patterns of drugs and complexes.New algorithms developed in industry and academia are quickly integrated into high-end packages. Public domain software is

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becoming more stable and functional, rivalling some commercial offerings. Every year and a half, computer speed doubles, while graphic displays become more sophisticated and intuitive. All of these factors combine to make molecular docking an essential component of drug design. It's becoming increasingly important in cutting-edge fields like computational enzymology, genomics, and proteomic search engines.

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