

MOLECULAR DOCKING: AN ADVANCE BIOINFORMATICS STRATEGY FOR STRUCTURE- BASED DRUG DESIGNING

Abstract

The computational modeling of structural complexes created by two or more interacting molecules is known as molecular docking. Prediction of an interesting three-dimensional structure is the aim of molecular docking. Software for molecular docking is mainly employed in drug development. Molecules and simple access to structural databases have harmed a vital mechanism. Several pricey tools for drug design and research are provided by molecular docking. Simple molecular prediction and quick access to structure databases are now essential tools on the desktop of a medicinal chemist. The major application of molecular docking is virtual screening. Different computational techniques can be employed to analyze docking gain, and numerous docking programs were utilized to visualize the molecule's three-dimensional structure. In structural molecular biology and computer-aided drug design, molecular docking is crucial. Docking may be used to perform virtual screening on huge libraries of compounds, score the outcomes, and provide structural hypotheses for how the ligands reduce the target, all of which are beneficial for lead optimization.

Keyword: Molecular docking; molecular docking types; docking mechanism; docking assessment; application.

Authors

Poojaben M Prajapati

Department of Botany
Bioinformatics
Climate Change and Impact Management
School of Science, Gujarat University
Ahemdabad.

Komal G Lakhani

Department of Biotechnology
College of Agricultur
Junagadh Agricultural University
Junagadh, India.
komallakhani2706@gmail.com

Bharat Maitreya

Department of Botany
Bioinformatics
Climate Change and Impact Management
School of Science, Gujarat University
Ahemdabad, India.

G. V. Marviya

Krishi Vigyan Kendra
Junagadh Agricultural University
Targhadia (Rajkot)
India.

I. INTRODUCTION

Molecular docking is finding the best alignment between the ligand and receptor molecules to create a stable complex [1]. Applying the scoring function, this orientation predicts binding affinity and the bond strength between a ligand and a protein. Drug-receptor interaction reveals molecular affinities and activities [2]. It is essential for both drug discovery and drug design. The system's overall free energy has been reduced. Finding and developing new drugs is a complicated process. The In-Silico approach aids in the development of novel drugs [3]. Computer-based drug design should be used to accelerate the drug discovery process. It is helpful in computational drug design and the structural biology of molecules [4]. It's used to predict how molecules would look in three dimensions. The scoring approach is now used to execute the virtual screening for rank candidates docking for large libraries molecules [5].

II. IMPORTANCE OF MOLECULAR DOCKING

- Molecular docking has emerged as a key technique in the drug development toolbox, and academic institutions are increasingly embracing it due to its apparent ease of usage and minimal cost implications [35].
- One of the most fundamental and significant methods for drug discovery has been molecular docking studies. It makes it possible to anticipate the molecular interactions that keep a protein and a ligand bound [34].
- The most promising drug design and discovery method is computational molecular docking and scoring [33].
- It is a method that foretells a ligand's preferred orientation, affinity, and interaction inside a protein's binding site. Using scoring functions, it is possible to forecast the intensity of the binding affinity between a therapeutic target and ligand molecule using information on the preferred orientation [36].

III. COMPUTER-AIDED DRUG DESIGN

- The term "CADD Computer Aided Drug Design" describes a computer-based approach used in computational chemistry to discover, enhance, or investigate medicines and related physiologically active compounds. It is especially helpful when creating novel drugs.
- It reveals the chemical and biological characteristics of ligands and targets.
- It is employed to discover and enhance innovative medications.
- Development of in-silico filters to forecast unfavorable characteristics of pharmacological compounds, such as poor activity, poor pharmacokinetics, and toxicity.
- It is used for the optimization of novel drug targets.
- CADD is utilized to locate hits. Using chemical scaffolds, new use of virtual screening for novel drug compounds [6].

IV. DESIGN OF DRUGS BASED ON STRUCTURE

To calculate the interaction energies of each tested chemical, structure-based computer-aided drug design requires knowledge of the target protein structure [7]. The structural database has information on crystallized target proteins. The structure-based design seeks to produce materials that bond tightly and specifically to the target while requiring the least energy [2]. Virtual high-throughput screening, a computer-based screening technique, enables the evaluation of a large number of chemical compounds that are similar to one another for a specific biological activity [8]. Quantitative structure-activity relationship (QSAR) models or pharmacophore mapping can be used to select compounds based on their predicted biological activity, and virtual docking of compounds against desired protein targets is another method of virtual high-throughput screening [9]. Using computational methods during the lead optimization phase of drug development is critical and practical. Utilizing computational techniques for hit-to-lead optimization, fewer compounds must be synthesized and tested in vitro [10].

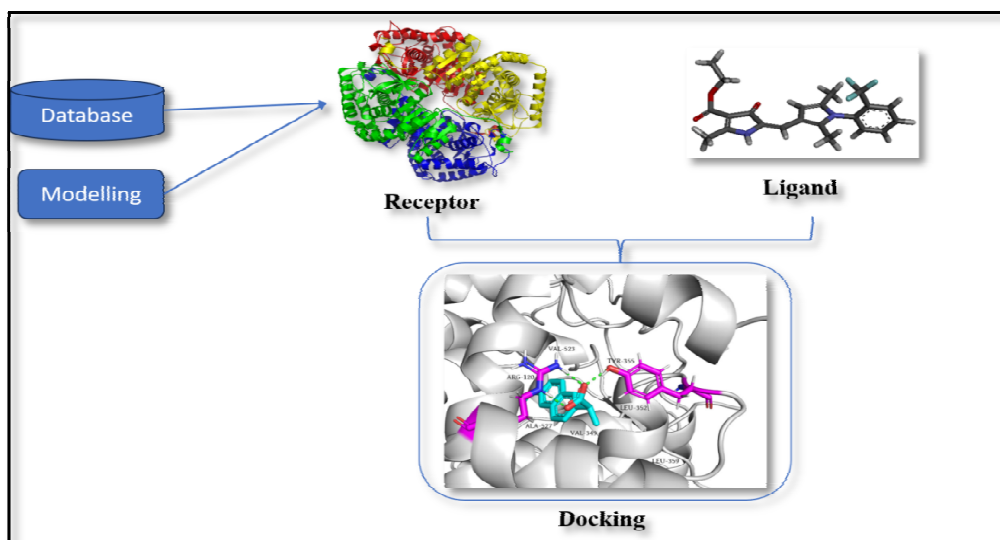


Figure 1: Model for Computer-Aided Drug Design

V. DRUG DESIGN BASED ON LIGAND

Ligand-based searches for chemical similarity or quantitative structure-activity relation (QSAR) are conducted using the knowledge of recognized active and inactive chemicals. Where the three-dimensional structure of the target proteins is unavailable, ligand-based techniques are ideal.

Computer-Aided Structural Drug Design:

The steps consist of:

- To prepare the target protein and chemical library for docking,
- Selecting a suitable binding position for each drug and ranking the docked molecule structures.

To forecast the orientations or conformations of a receptor-ligand combination, a structurally based computer simulation technique known as molecular docking is performed [11]. It also calculates the complex's molecules' estimated binding affinities.

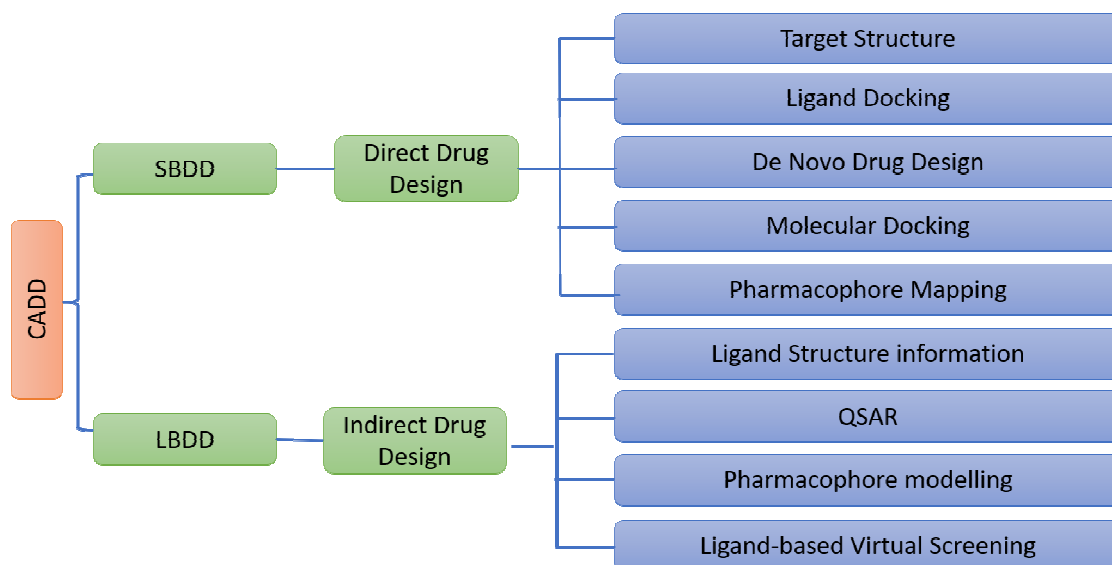


Figure 2: Drug Design Structure

VI. MOLECULAR DOCKING TYPES

1. **Search Technique:** The number of configurations created and the binding modes are determined via experimentation. The Monte Carlo approach, fragment-based genetic searches, and systemic searches are used for docking analysis.
 - Rigid Docking
 - Flexible Docking
2. **Rigid Docking:** The ligand and receptor molecules are fixed during this docking. Docking occurs [12].
3. **Flexible Docking:** Both the ligand and the receptor are mobile during this docking. It is flexible in conformation. The energy is determined for each rotation. Calculations are made for each conformation surface cell occupancy. The best possible binding stance is then chosen.
4. **Scoring Function:** The binding affinity that the binding score directly corresponds to. The highest-rated ligands are the best binders. It may be experimental, based on information, or based on molecular mechanics. Docking A critical component of medication design is scoring.
 - Knowledge-based and
 - Energy component methods

Statistics of the observed inter contact frequencies in a sizable database of protein complex crystal structures using a knowledge-based scoring system. High binding

affinities are expected for molecular interactions near the maximum frequency of interactions in the database. Low-binding affinity molecular interactions in databases will have low interaction rates [29].

Energy component scoring method based on the mathematical assumption that the free energy change that takes place when a ligand binds to a protein target (DG bind) is the sum of the free energies for the interaction between the protein and the ligand, the solvent, the conformational changes in the protein, and the motion of the ligand and protein target during complex formation [13].

VII. DOCKING MECHANICS FOR MOLECULES

Steps: The intermolecular interaction between two drug molecules was examined using an in silico approach. The macromolecule is the protein receptor. It had an inhibiting effect. The steps in the docking procedure are as follows.

- **Step I – Preparation of protein and Ligand:**
They obtain the protein's three-dimensional (3D) structure from the Protein Data Bank (PDB) of the Research Collaboratory for Structural Bioinformatics. After that, pre-processing should be applied to the downloaded structure. Hydrogen atoms are added to stabilize charges, fill residue spaces, create side chains, and remove water molecules.
- **Step II –Ligand Preparation:**
You can obtain molecules from PubChem Ligands using several databases, including ZINC. The Chem sketch tool in the Mol file can be used to design it. The ligand molecule was then evaluated using LIPINSKY'S RULE OF 5. The drug's like and unlike compounds are used with it. Due to the molecules' drug-like characteristics, it raises the success rate and lowers failure rates.
- **Step III- Grid Generation:**
The location, rotating group, excluded volumes, and restrictions did not change. The primary influencing factor is the nature of the mathematical processes (crossover, migration, mutation). Predictions for the binding cavity must be made.
- **Step IV –Prediction of Active site:**
Predictions should be made about the protein's active site. Following protein preparation, water molecules and the cavity is cleared of heteroatoms.
- **Step V- Docking:** Ligand and protein interactions are analyzed. The optimal docking result should be chosen [14].

VIII. APPLICATION OF MOLECULAR DOCKING

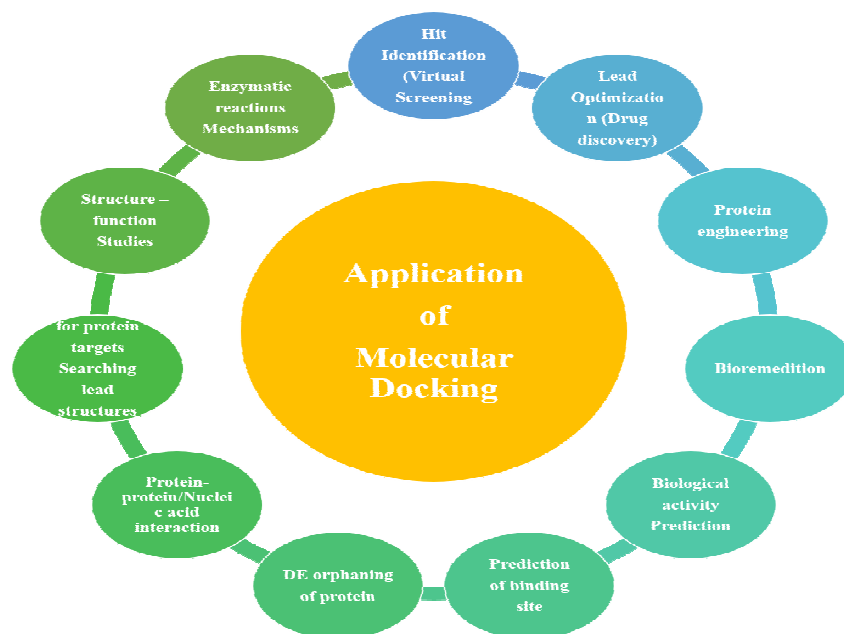


Figure 3: Application of Molecular Docking

Application of Molecular Docking in Plants:

Sr. No.	Plant Name	Diseases		Reference
1	Geranium wallichianum D.	antimicrobial activity.	elatine, kaempferol, and germacrene	[37]
2	Parkia timoriana	antioxidant and antimicrobial	Methyl beta-L-arabinopyranoside 3-n-Hexylthiolane, S,S-dioxide, L-(+)-Ascorbic acid, 2,6-Dihexadecanoate, 1H-Imidazole, 2-(Diethoxy methyl), Oleic acid, Cyclohexane butanoic acid	[38]
3	Neuropeltis racemosa	antidiabetic	Acarbose, Scopoletin	[39]
4	Withania somnifera	COVID-19	Withanoside V, Somniferine	[40]
5	Tinospora cordifolia	COVID-19	Tinocordiside	
6	Ocimum sanctum	COVID-19	Vicenin, Isorientin 4'-O-glucoside 2''-O-p-hydroxybenzoagte , Ursolic acid	
7	Amaranthus	anti-bacterial	Gallic acid and phytol	[41]

	lividus	and anti-proliferative		
8	Ficus carica L	Anti-cancer	β -Bourbonene	[42]
9	Amomum nilgiricum	antibacterial, antifungal, antiviral, antioxidant and antidiabetic	([3,12-diacetyloxy-10,14-dimethyl-13-oxo-15-(5-oxo-2H-furan-3-yl)-2-oxapentacyclo[9.7.0.01,3.05,10.014,18]octadecan-7-yl] acetate)	[43]
10	Helichrysum petiolare	Antidiabetic	sinocrassosideA1, engeletin, 4-feruloylquinic acid, 3-O-caffeoyl-4-O-methylquinic acid, protocatechuic acid, 3-caffeoylquinic acid, and arbutin	[44]

IX. APPROACHES OF MOLECULAR DOCKING

There are two techniques utilised for molecular docking.

- 1. Simulation Approach:** This process physically separates the ligand and target before allowing the ligand to bind into the target groove after "definite times of moves" in its conformational space. Internal (torsional angle rotations) and outward (rotations and translations) alterations to the ligand's structure are also possible. "Total Energy" is released each time the ligand moves inside the conformational limit. This method is better since it allows for ligand flexibility and It is also more accurate to assess the molecular recognition between the ligand and the target. This approach takes longer to determine which conformation is best docked because each conformation dissipates a substantial amount of energy. This shortcoming has recently been revolutionized to make simulation approaches more approachable through fast optimization algorithms and grid-based tools [24].
- 2. Shape Complementarity Approach:** This method uses the surface structure characteristics of the ligand and target to offer their molecular interaction. The molecular surface of the ligand is illustrated in terms of the surface area of the target that is accessible to solvents. Searching the complementary groove for a ligand on the target surface is made easier by the complementarity between two surfaces based on the shape-matching illustration. For instance, the hydrophobicity of protein target molecules depends on the number of twists in the main chain. Our approach rapidly scans thousands of ligands in seconds to assess a ligand's potential binding capabilities on the target molecular surface [25].

X. FUNDAMENTAL CHALLENGES IN MOLECULAR DOCKING

Under the following headings, several fundamental docking and scoring difficulties are covered.

- 1. Ligand Chemistry:** How the ligand is prepared significantly affects the docking results because any biomolecule must recognize the ligand in three dimensions and through electrostatic contact. This illustrates the importance of ligand production and ligand structure. When preserving approximate pKa values, the structure was optimised by removing or adding hydrogens. However, there was still a significant gap between the tautomeric and protomeric states of the molecules that needed to be docked. Almost all databases store molecules in their neutral states, even though they are ionized in a physiological setting. As a result, ionizing them before docking is required. However, several programs make it simple to obtain standard ionisation. The question of which tautomer to employ or whether to use all available tautomers still exists in the topic of tautomers [26].
- 2. Receptor Flexibility:** An important hurdle in docking is the management of flexible proteins. Depending on the ligand it binds to, the conformation of a biomolecule or protein can change. This illustrates that docking with a stiff receptor may produce just one receptor shape. However, the ligands might need to bind to many receptor conformations if a flexible receptor is employed for docking. The various protein conformational states are frequently the aspect of molecular docking research that is most ignored. Protein flexibility is important because it increases affinities between a drug and a target. Active site water molecules also influence target flexibility. Water molecules must be adjusted to avoid using artefact waters during docking [27].
- 3. Scoring Function:** Another challenge for docking is imperfections in the scoring mechanism. A scoring system should be able to discriminate between genuine binding modes and all other parallel modes, much like a search approach may yield the optimal conformation. The analysis of different binding methods would suffer because a hypothetical scoring algorithm would be computationally far more efficacious [30]. When accuracy is present, several recommendations for determining ligand affinity are made via scoring functions. Systems for calculating scores disregard important concepts like entropy and electrostatic interactions. As a result, the need for an accurate and rapid scoring function is the main bottleneck in molecular docking programming [28].

XI. MOLECULAR DOCKING:

Figure 4: An ordinary docking process. The essential processes shared by all docking procedures are shown in this flowchart. The target macromolecule and the small molecule's 3D structures must be selected first, and each structure must then be built according to the docking method employed. The docking results must be examined, and the best-scoring binding modes must be chosen.

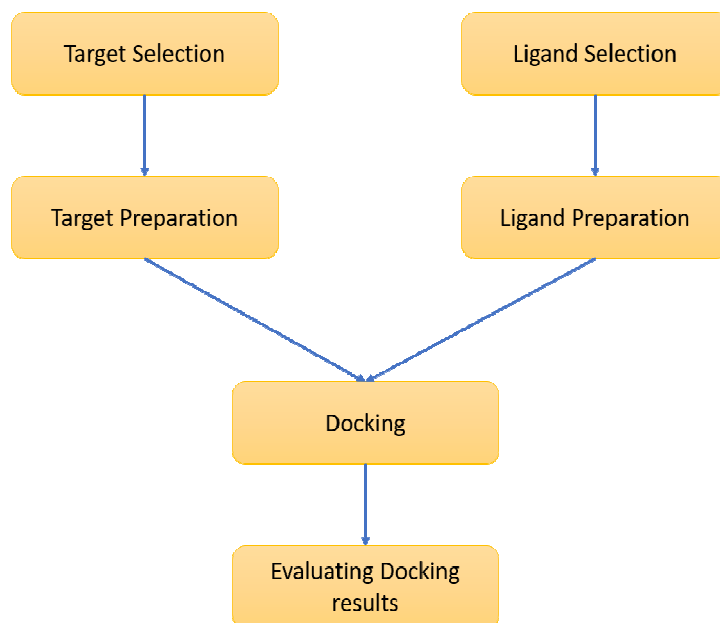


Figure 4 depicts the fundamental docking operations that all techniques share. Finding the most beneficial binding mode(s) of a ligand to the target of interest is docking. The binding mode of a ligand to a particular receptor can be determined using the state variables of the ligand. There are three of these: the ligand's position (represented by the x, y, and z translations), orientation (represented by the axis-angle, the Euler angle, or a quaternion), and if the ligand is flexible, its conformation (expressed by the torsion angles for each rotatable bond) [31]. In a multidimensional search space, each state variable determines one degree of freedom, and its bounds define the scope of the search. The search area is significantly less when using rigid body docking instead of treating the ligand as flexible. Even yet, the chances of discovering a complementary match are reduced if the ligand's shape needs to be altered.

All docking strategies require a scoring system to evaluate the numerous binding modes that could be used and a search method to look into the state variables [32]. Systematic and stochastic search techniques fall into two broad types, while empirical, force field-based, or knowledge-based scoring systems might be used. Deterministic systematic search methods sample the search space at regular intervals. The search results may vary because dynamic search methods randomly update the state variables throughout each iteration until a user-defined termination criterion is reached [15]. Sousa et al. study these families of algorithms in more detail. Additionally, each search method's breadth of the search space can be classified as local or global. Local search methods frequently find the nearest or local minimum energy to the existing conformation, while global search methods hunt for the best or global minimum energy over the preset search space. Compared to global methods, hybrid global-local search approaches are more productive and capable of locating lower energies [16].

For instance, Solis and Wets [17] and Pattern Search [18] are two local search approaches; Monte Carlo (MC) simulated annealing [19] and the genetic algorithm [20] are global search techniques; and the Lamarckian GA (LGA) is a hybrid global-local search strategy. All of these search methods are included in AutoDock 4. To compare the ligand's

chemical characteristics and the binding site's inverse model, DOCK conducts a methodical search. FlexX couples ligand properties with complimentary interaction sites. The GOLD technique for global search makes advantage of GA. The search method used by ICM combines a biased MC methodology with a local energy reduction strategy.

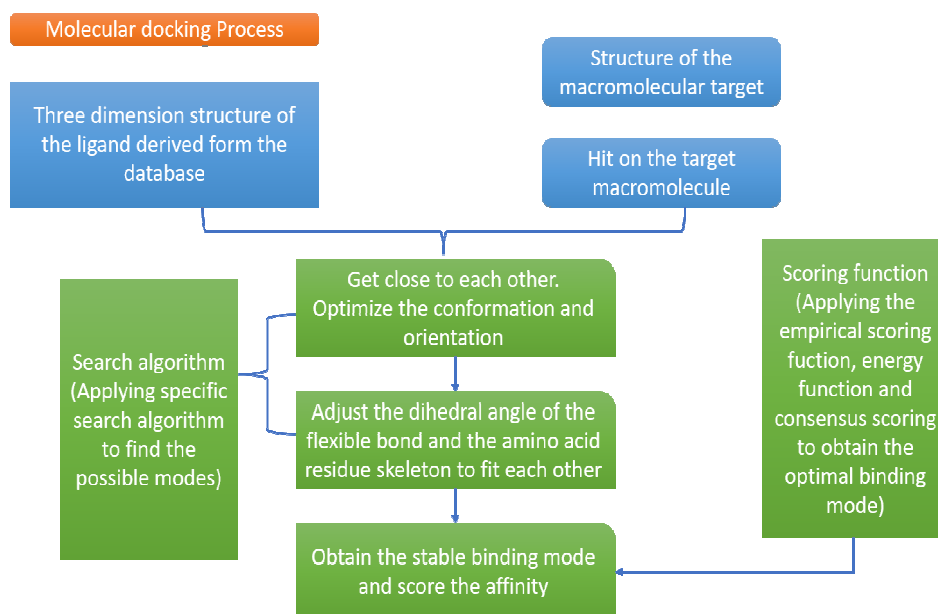


Figure 5: Molecular docking process.

- 1. Molecular Docking Software:** The three primary categories of molecular docking software. The usage of flexible-rigid docking is common. Flexible docking is typically more precise, however. Therefore recent years have seen a surge in research into this area. The frequently used molecular docking software is included in Table 1, along with its algorithms, evaluation techniques, features, and application domains.
- 2. Molecular Docking Databases:** The public database Protein Data Bank (PDB) is the most widely used protein structural database. Additionally, it is free to use public databases like ZINC and the PubChem Compound Database. The Compound Database (AcD) and Cambridge Structural Database (CSD) are only examples of the numerous significant commercial databases available.

Table 1: Representative Molecular Docking Software

Name	Search algorithm	Evaluation method	Speed	Features & Application areas
Flex X	Fragmentation algorithm	Semi-empirical calculation on free energy	Fast	Flexible-rigid docking. It can be used for the virtual screening of small molecule databases using an incremental construction strategy.
Glide	Exhaustive	Semi-	Medium	flexible docking. This software

	systematic search	empirical calculation on free energy		has XP (extra precision), SP (standard precision), and high throughput virtual screen modes and leverages domain knowledge to restrict the search range.
AutoDock	GA (genetic algorithm) LGA (Lamarckian genetic algorithm)	Semi-empirical calculation on free energy	Medium	rigid-flexible docking. This programme is free for academic use and is always used with Autodock-tools.
ZDOCK	Geometric complementarity and molecular dynamics	Molecular force field	Medium	Rigid docking. Chen et al. [21] propose a new scoring function that combines pairwise shape complementarity (PSC) with desolvation and electrostatic and develop the ZDOCK server [22]
Autodock Vina	GA (genetic algorithm)	Semi-empirical calculation on free energy	Fast	Flexible-rigid docking. AutoDock Vina employs an iterated local search global optimizer and it is faster than AutoDock 4 [23]

XII. CONCLUSION

Molecular docking has emerged as a sophisticated and powerful strategy in the realm of bioinformatics for structure-based drug design. Through intricate computational algorithms, it enables the prediction of how small molecules, like potential drug candidates, interact with target proteins, offering invaluable insights into their binding affinities and modes of action. This method has revolutionized the drug discovery process, facilitating the identification and optimization of lead compounds with enhanced specificity and efficacy. Its ability to rapidly screen vast chemical libraries against target proteins accelerates the discovery of novel therapeutics, holding immense promise for addressing complex diseases. With its continuous advancements in accuracy and efficiency, molecular docking stands at the forefront of modern pharmaceutical research, driving innovation and precision in drug development.

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