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Advancements in Computer-Aided Drug Design: A Comprehensive Review

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ABSTRACT

In the last few years, the Computer-Aided Drug Design and Discovery is many successes rates. Computational drug design is used for drug lead discovery in various pharmaceutical industries and academic institutions. In the current era of medication research and discovery, structural data is crucial. Various docking programs have been created to visualize the three-dimensional structure of molecules. Drug design software that runs on computers is used to examine the docking score. It is a virtual screening technique for target molecule orientation, conformation, and position that is based on structure. The idea of ligand and protein docking is novel. Biological pathway analysis, de Novo drug design, and lead molecule optimization are the three complex aspects of the molecular docking approach.

Keywords: *Molecular docking; rigid; flexible; binding; receptor*

1. INTRODUCTION

One kind of computer modeling is molecular docking that makes it facilitate to predict the selected valid acclimatization of a ligand (or receptor) to another molecule (or other molecule) during them interact to form a reliable compound.[1] It is possible to anticipate the efficiency contour (such as confining free efficiency), durability, and reliable (such as binding affinity and binding constant) of complexes using information gleaned from the preferred orientation of bound molecules. The molecular docking scoring function can be used for this. In order to estimate the putative binding characteristics of tiny compounds, or therapeutic candidates, to their biomolecular targets, which include nucleic acids, proteins, and carbohydrates, molecular docking is widely used these days**.** This creates the raw data needed to rationally design new drugs with greater specificity and efficacy using structure-based drug development.[2]

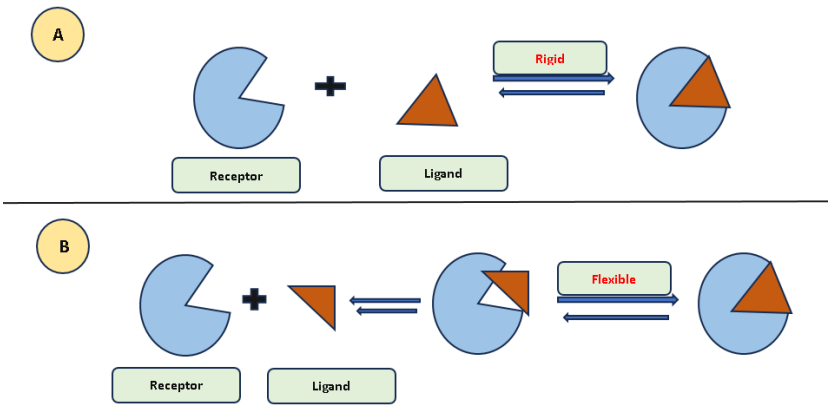


Figure 1: Two molecular docking models. Lock and key (A) and induced fit theory (B)

Achieving an ideal docked conformer of the two molecules in interaction is the primary goal of ligand and protein, which also aims to abate the system's overall free energy. Final anticipated dispersion and repulsion, hydrogen bonds, breakdown, electrostatic, torsional independent energy, final total internal energy, and unbound system's energy are all used to characterize binding free energy. So, full comprehension of the broad fundamentals a certain determined projected torsional independent energy gives additional details regarding molecule docking due to the nature of different types of interactions.[3]

A technique for ligand evaluation and a structural data bank for target discovery are required for the effective use of molecular docking. Many molecular docking techniques, along with technologies accessible to help with about. The below computer programs' potential ligands below can be ranked based on how well they interact with specific target candidates.

A creative sample of potential ligand poses in the designated target candidate pocket or groove is part of the molecular docking process, which aims to resolve the ideal binding geometry for small molecules bound to biological targets. The user-defined fitness or scoring function of the docking program can be used for this [1,4]. NMR spectroscopy and X-ray crystallography are the main methods used to investigate and establish three-dimensional structure data for biomolecular targets. However, homology modeling makes it easier to resolve the approximate structure of proteins (with unknown structures) whose sequences are highly similar to those of known structures. This offers an alternative method for establishing target structures, which serves as a starting point for the in-silico identification of high affinity drug candidates.

There are several databases accessible, which offer information on small ligand elements such as CSD (Cambridge Structural Database), ACD (accessible Chemical Directory), MDDR (MDL Drug Data Report) and NCI (National Cancer Institute Database). Different docked conformers, or poses, are created, graded, and compared with one another during molecular docking performance. A posture is either approved or denied based on the docking software's scoring feature. When a position is rejected, additional poses are created, and the search process repeats until it reaches the point where one pose is accepted. The processes of searching and scoring are closely related in molecular docking. Searching for the binding orientation of docked conformers appears to be easier than rating them based on their experimental binding affinities and binding free energy. Several scoring functions, including consensus scoring and applying multiple score functions to the same docked pose to reduce false positives, are used to get around this problem.[1-5]

It is important for computational approaches (In Silico methods) to be fast and reliable in order to have the most influence on target detection. For it, docking-based virtual screening protocols are used to assess the performance of various docking techniques in order to rank known active candidates among a number of inactive molecules from a database.[1-4] Numerous attempts have been made to build and establish effective scoring and docking protocols with this in mind. However, considerable advancements have been made in the computer prediction of docking mechanisms between ligands and receptors. Numerous study and review articles exist that outline the different new facts in this field. The types, applications, and recent computational docking techniques are the focus of this review study.

To ensure that forecast the impact and compatibility of a smaller molecule, docking is widely utilized to anticipate the direction in which small molecule therapy candidates attach to their target proteins. Therefore, docking is essential to the rational structure of drugs.

Molecular docking is the process of positioning the ligand molecule over the receptor molecule in a way that creates a stable complex.[1–7] Using scoring functions, this orientation is used to forecast the affinity for binding and strength of the protein-ligand relationship. The affinity and activity of molecules are predicted by the drug-receptor interaction [8–17]. It is essential to the development and discovery of new drugs. It reduces the system's total free energy. Researching and generating novel drugs is a very ambitious task. The challenge researching and generating novel drugs extremely ambitious. New drugs are discovered with the aid of the In-silico approach [18–27]. Computer-based drug design should be employed to expedite the drug discovery process. It is helpful in computational drug design and the structural biology of molecules [28–35]. It is employed to predict a molecule's three-dimensional structure. Currently, candidates for documentation are ranked using a score method to conduct virtual screening for large libraries [36–42].

2. COMPUTER AIDED DRUG DESIGN

1) Drug Design assisted by a computer, it is a computer-based method participated computational chemistry to find, improve, on the other hand analyze drugs as well as corelated physiologically kinetic molecules.
2) It is especially helpful when designing new medications.
3) It offers information on the biological and chemical characteristics of targets and ligands.
4) It helps discover and develop new medications.
5) The development of In-silico filters to forecast undesired characteristics such as low activity, poor pharmacokinetics, and low toxicity in pharmacological molecules.
6) It is applied to the improvement of new therapeutic targets. CADD is employed to locate hits.
7) Virtual screening is used to find new therapeutic compounds by utilizing chemical scaffolds.

2.1 Structure-Based Drug Dseign

In order to determine the interaction energies for each tested molecule, drug design using computers and structure relies based on understanding the target protein's structure [43–46]. Target proteins that have crystallized are available in the structural database. Designing molecules that bind securely and selectively to a target with the least amount of energy required is called structure-based [47–57].

Virtual high-throughput screening, is a computer-based screening technique a certain enables the viewing of a sizable library of comparable chemical combination for a certain bioactive compound [58–65]. Chemical similarity searches, compound selection based on predicted biological activity using virtual docking of drugs versus quantitative structure-activity relationship (QSAR) models, pharmacophore mapping, and target polypeptides targets are a few examples of virtual high-throughput screening methods [66–74].

It is important and cost-beneficial to use computational techniques at the optimization of lead stage of drug discovery. Use of algorithm and problem solving techniques to optimize hit-to-lead while minimizing the amount of compounds requiring In vitro synthesis and testing [75–79].

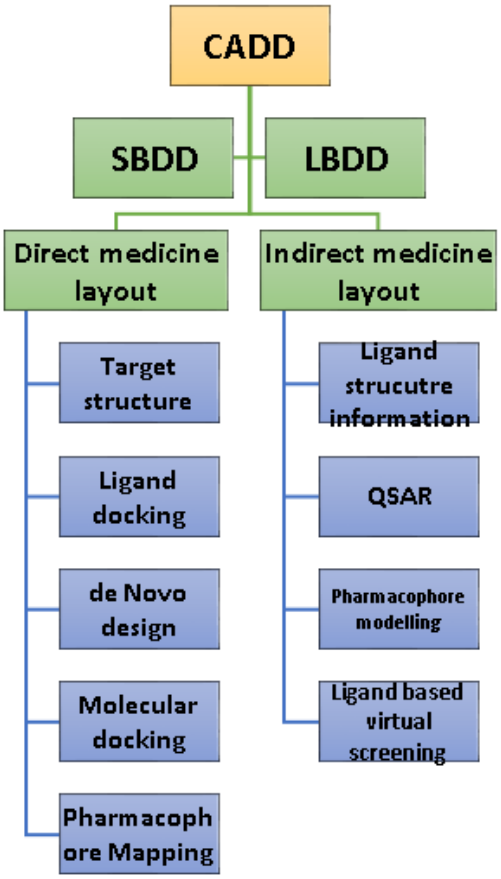


Figure 2: Drug Development Structure

2.2 Ligand-Based Drug Design

Ligand-based approaches use chemical similarity searches or quantitative structure-activity relation (QSAR) to take advantage of the knowledge of known active and inactive compounds. Ligand-based approaches are the best when the target proteins ' three-dimensional structures are unavailable.

Structural-Based Computer-Aided Drug Design:

Steps include:

1. To prepare the target peptide and chemical library for docking.
2. Ascertaining each compound’s ideal binding position.
3. Sorting the molecular docked structures.

Molecular docking, a structurally based computer simulation method, is used to predict the directions or conformation of a receptor-ligand complex. It is also utilized to forecast the molecules in the complex's binding affinities.

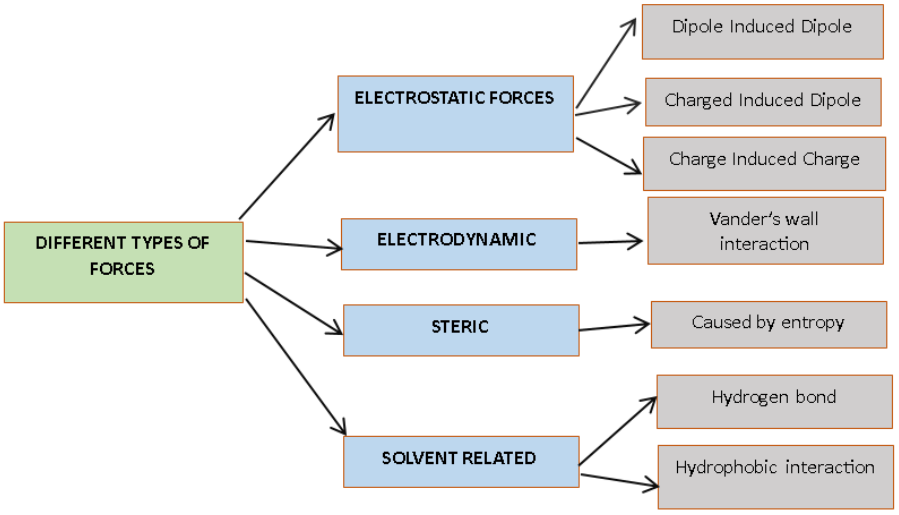


Figure 3: Different types of interaction

3. TYPES OF MOLECULAR DOCKING

1. Search Algorithm: The number of combinations and binding modes are found through experimentation. The Monte Carlo approach, qualitative along with fragment-based systematic investigations, are used for docking analysis.

a) Rigid Docking

b) Flexible Docking

2. Rigid Docking: In this type of docking, the ligand and receptor molecules are both fixed. Docking is carried out.

3. Flexible Docking: In this type of docking, both the receptor and the ligand can move. It is flexible in terms of conformance. Every spin has an associated energy. The cell occupancy on each conformation surface is computed. The most ideal binding position is then chosen.

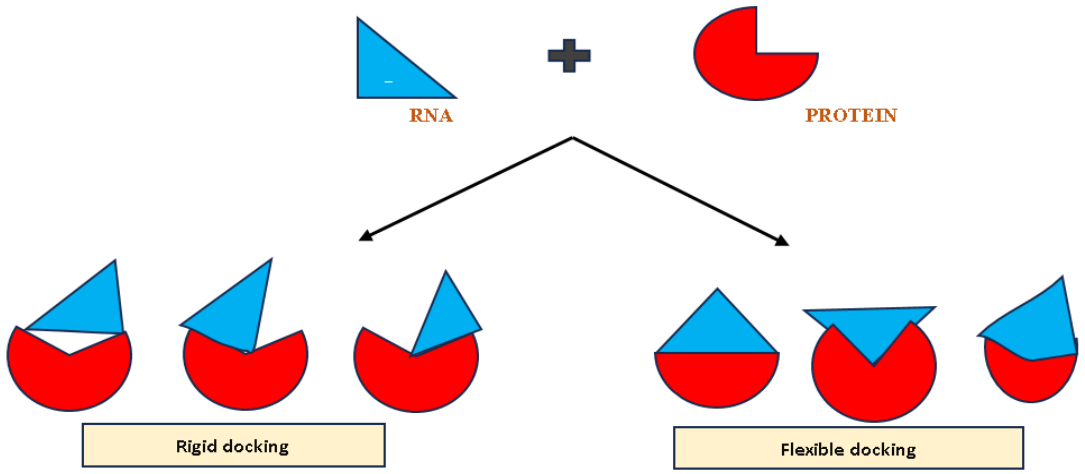


Figure 4: Types of molecular docking

4. Scoring Function: The binding affinity that openly correlates to the binding score is the scoring function. The highest rated ligands are the best binders. It may be knowledge-based, experimental, or based on molecular dynamics. Docking In the drug-design process, scoring is crucial:

a) Knowledge based scoring function

b) Energy component scoring method

- **Knowledge based scoring function**

A statistical analysis of the inter-contact frequencies recorded in a sizable database containing the protein-ligand complex crystal structures are used by the knowledge-based scoring system. High binding affinities are found in molecular interactions that are near to the maximum frequency of interactions in the database [80–85]. A low binding affinity molecular interaction in a database will have a low interaction frequency.

- **Energy component scoring method**

The energy component scoring method is predicated on the mathematical premise that the shift in free energy following ligand-protein binding (DG bind) is the total of the free energies for ligand interaction, ligand-protein and solvent interaction, ligand and protein conformational changes, and motion of the ligand and protein target during complex formation [86–90].

4. APPROACHES OF MOLECULAR DOCKING

There are two main methods utilized to carry out molecular docking. In one method, energy profiling for ligand-target docked conformers is determined by computer simulations. On the other hand, the second approach uses a technique to ascertain the target and ligand's surface complementarity. [1] The following is a quick description of both approaches, along with a summary of their primary characteristics. (Table 1).

4.1 Simulation Approach

In order for the ligand to connect into the target molecule's groove or pocket after a "definite time of moves" within its conformational space, the ligand and target molecules must be physically separated.

The movements include changes to the ligand structure on the outside (rigid body transformations like rotations and translations) or within (torsional angle rotations). The energy produced by each conformational change in the ligand is measured as the "Total Energy of the System." This strategy has an advantage over shape complementarity one since it is better suited to the molecular modeling tool's acceptance of ligand flexibility. Another benefit of this approach is that it increases the realism of the chemical recognition between the target molecule and the ligand. However, molecular docking using this method takes longer to assess the optimal docked conformer because large energy landscapes need to be computed for each position. Nevertheless, this disadvantage has been greatly mitigated by rapid optimization strategies and grid-based tools, which have made computer simulation approaches more accessible. [1,96]

4.2 Shape Complementarity Approach

This method uses the surface structure properties of the ligand and target to help with molecular docking. The goal of molecular docking is to explain the ligand's molecular surface in terms of matching surface illustrations, while the target's molecular surface is clarified in terms of its solvent-accessible surface area. Shape matching pictures are used to assess the complementarity between two molecular surfaces and help find the complementary groove or pocket on the target molecular surface where ligand docking may occur. The number of twists in the main-chain atoms is specifically used to evaluate hydrophobicity for protein target molecules. In order to determine the potential binding characteristics of ligand on the surface of the target molecule, the shape complementarity approach, which is relatively quick and robust, rapidly scans hundreds of ligands in a matter of seconds. [1,96]

Simulation Approach	Shape Complementarity Approach
This method calculates interaction energy for each pair of ligands and receptors.	This method suggests estimating the complementarity between the surface of the ligand and the receptor.
The ligand is permitted to fit into the receptor's groove in order to produce the optimal docked conformer of the ligand and receptor based on lowest energy evaluation.	Solvent accessible topographic properties of the ligand and receptor in terms of matching surface are specified in order to obtain the docked conformer via this approach. The calculation of shape complementarity between interacting molecules is then performed in order to identify the ideal groove or pocket for ligand binding on its target.
To choose the optimum docked conformer with the least amount of energy, the entire power of the structure is generated through each movement of the ligand into the receptor's pocket for optimal connection.	The steps in this process are surface representation (i.e., surface construction and smoothing) of the receptor and ligand, features/curvature computation, docking, and scoring based on geometric complementary criteria.
This method allows for more accurate evaluation of	Both flexible docking and stiff docking are permitted

molecular perception and the connection with ligand and receptor atoms since it is best suited for recognizing ligand adaptability in molecular simulation tools.	by the shape complementarity technique. In case of flexible or soft docking conformational changes may take place among bound and free interacting molecules. This is coupled with the penetration and overlaying of both interacting molecules on each other. Rigid docking, however, prevents spatial modification of the interacting molecules' structure during molecular modeling.
With this method, molecular modeling takes a lot longer to complete because extensive energy profiling needs to be estimated. Grid-based tools and quick optimization techniques, however, have greatly transformed this drawback.	This approach yields reliable and timely results since it quickly scans a large number of ligands for binding on its target in a matter of seconds.

Table: 1. Molecular Docking Approaches

5. MOLECULAR DOCKING SOFTWARE

The three primary categories of molecular docking software are listed in Figure 2. The usage of flexible-rigid docking is common. But in recent years, the relevant researchers have been less of a study spot because flexible docking is typically more precise. Table 1 enumerates the popular molecular docking software along with an overview of its features, algorithms, and application domains.

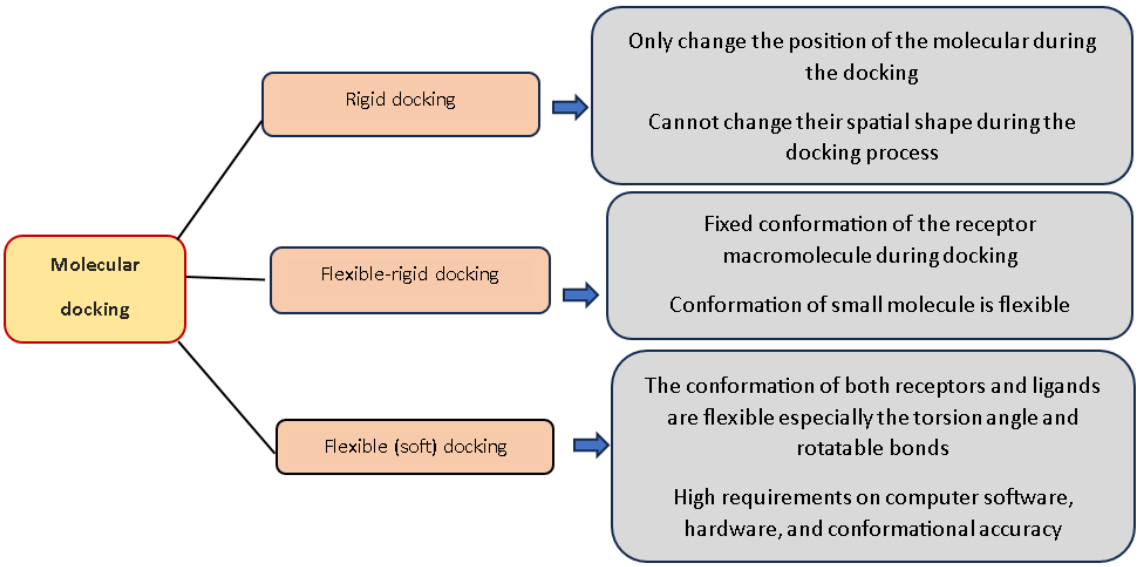
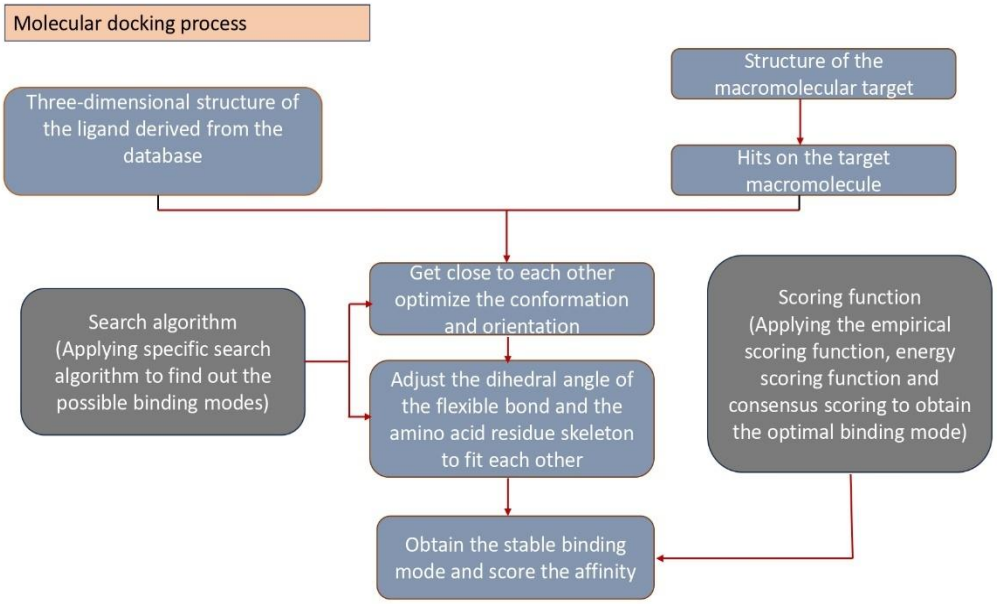


Figure 4. Molecular docking software classification.

5.1 Molecular docking databases

The public database Protein Data Bank (PDB) [97] is the most widely used database on protein structures. Also, the public databases such as PubChem Compound Database [98] and ZINC [99] are free to use. Besides, there are numerous notable commercial databases, such as compound Database (AcD), [100], Cambridge Structure Database (CSD) [101].

5.2 Process of Molecular docking



Name	Search algorithm	Evaluation method	Speed	Features and application areas
Flex X [33]	Fragmentation algorithm	Semi-empirical calculation on free energy	Fast	Flexible- rigid docking. It may be applied to incremental construction energy for virtual screening of small molecule database.
Gold [34]	GA (genetic algorithm)	Semi-empirical calculation on free energy	Fast	Flexible docking. The software is based on GA. This software's accuracy and dependability have received great reviews.
Glide [35]	Exhaustive systematic search	Semi-empirical calculation on free energy	Medium	Flexible docking. This program features high across virtual screen modes, XP (extra precision), and SP (standard precision) and leverages domain knowledge to restrict the searching range.
AutoDock [36]	GA (genetic algorithm) LGA (Lamarckian genetic algorithm)	Semi-empirical calculation on free energy	Medium	Flexible- rigid docking. This program is free for academic use and is always used in conjunction with Autodock-tools.
ZDock [37]	Geometric complement-arity and molecular dynamics	Molecular force field	Medium	Rigid docking. Chen et al. [37] Create the ZDOCK server and suggest a novel scoring system that combines pairwise shape complementarity (PSC) with electrostatic and desolvation techniques.
RDock [39]	GA (genetic algorithm) MC (montecarlo)	Molecular force field	Medium	Rigid docking. The refining and grading process based on CHARMm. In addition to its binding mode

	MIN (Simplex minimization)			prediction capabilities, it is specifically engineered for high throughput virtual screening (HTVS) programs.
LeDock [40]	SA (Simulated annealing) GA (genetic algorithm)	Molecular force field	Fast	Flexible docking. A new molecular docking software is called LeDock. According to the current study's findings, it is advised for the virtual screen work because of its speed and excellent accuracy.
Dock [42]	Fragmentation algorithm	Molecular force field	Fast	Flexible docking. The docking process between flexible proteins and ligands always uses it, and it has broad use.
Autodock Vina [6]	GA (genetic algorithm)	Semi-empirical calculation on free energy	Fast	Flexible- rigid docking. Using an iterated local search global optimizer, Autodock Vina operates more quickly than AutoDock 4.

Table 2: Representative software for molecular docking

6. MOLECULAR DOCKING MECHANICS STEPS

The intermolecular interactions between two drug molecules were investigated using the in-silico approach. The macromolecule is the protein receptor. It acted as an inhibitor. The docking process involves the following steps.

Step I: Preparation of protein and Ligand: The 3D structure of the protein can be downloaded from the Protein Data Bank (PDB) of the Research Collaboratory Structural Bioinformatics. The downloaded structure needs to be pre-processed after that. After the water molecules are removed from the cavity, the charges stabilize, the missing residues are filled, and side chains of hydrogen atoms are added.

Step II: Ligand Preparation: The Pub Chem Ligands molecule can be downloaded by using several databases, such as ZINC. In a Mol file, it can be drawn using the Chem Sketch Tool. Next, for this ligand molecule, use LIPINSKY'S RULE of 5. Both drug-like and drug-unlike compounds are employed with it. It increase the high success rate and low failure rate because of molecules' drug-like qualities.

Step III: Grid Generation: During this phase, all variables such as location, rotating group, and eliminated quantities, and rules are maintained at the same level. The amount of genetic the primary factor in determining is the operations carried out (crossover, migration, and mutation). It's necessary to do Binding Cavity Prediction.

Step IV: Active Site Prediction: It is necessary to estimate the protein molecule's active site. following that protein preparation, the water molecules and heteroatoms, if any, are extracted from the cavity.

Step V: Docking: Analysis of ligand-protein interactions is conducted. The best docking score ought to be chosen.

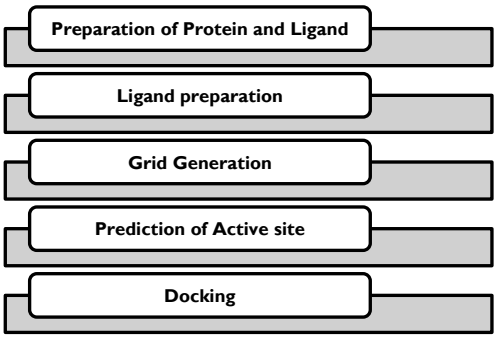


Fig:5 Molecular docking mechanism steps

Properties	Lipinsky's rule of 5	Muegge rule
Molecular weight	<500g/mol	780.94 g/mol
Log P	<5	3.92
H-bond donar	<5	6
H-bond acceptor	<10	14
Polar surface area	<140 A^0	203.06 A^0

Table:3 Difference between Lipinsky's rule and muegge rule.

Sr No.	Program	Docking Approach	Scoring Function	Advantages	Disadvantages	Licence Term
1	Auto Dock	Genetic algorithm and stimulated Annealing fitting of shape	force-field methods	Hydrophobic ligands were able to enter tiny cavities.	Polarized flexible protein	Free for usage in academic settings
2	Dock	Genetic algorithm and stimulated Annealing fitting of shape	Chem score	Identified binding location	Slowly action.	Free for usage in academic settings
3	Flex X	Construction Reduction	Flex Score	Hydrophobic ligands were able to enter tiny cavities.	More sensitive ligands	Commercial free evaluation (6 week)
4	FRED	Fitting of shape	Piece wise linear potential	Fast and spacious binding site	Polarized protein	Free for usage in academic settings
5	Glide	Sampling of Monte Carlo	Glide score, glide compound	Hydrophobic ligands that are flexible	Very sluggish ranking.	Economic
6	Gold	GA searching	Gold and Chem Score	diminutive hydrophobic ligands	Wide chamber binding score	Economic
7	Ligand fit	Sampling of Monte Carlo	Ligand score	Identified binding location	Slowly action	Economic

Table:4. Docking software with their approach, advantages and disadvantages.

7. APPLICATIONS OF MOLECULAR DOCKING

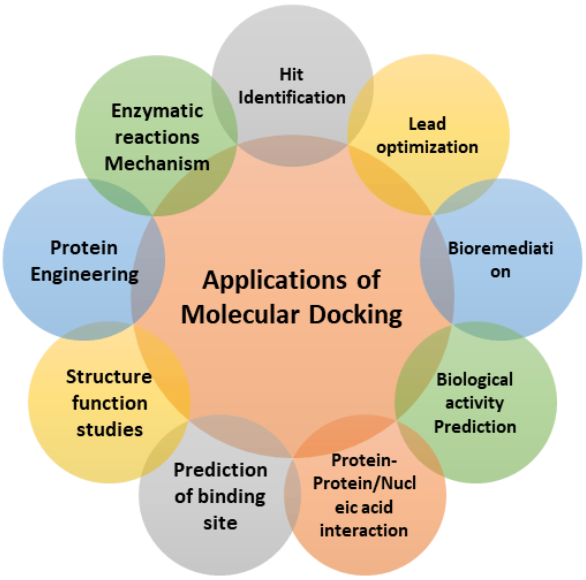


Figure 6: Applications of Molecular Docking

7.1 Virtual screening to discover the lead compound and hit compound

Virtual screening [102] has significantly increased screening efficiency over the conventional screen approach (figure) by locating the lead and hit compounds from the molecular databases based on the scoring function.

Virtual screening has many frequent applications. Notably, the integrated approach takes off rapidly due to the exponential rise of high-throughput [103], high-performance computing [104], machine learning [105], and deep learning [106] approaches. Pereira et al. [107], for instance, used a deep learning approach in virtual screening to generate distributed vector representations for protein-ligand complexes by extracting pertinent features from molecular docking data. Furthermore, the virtual high through-out screening was suggested by Pyzerknaap et al. [108].

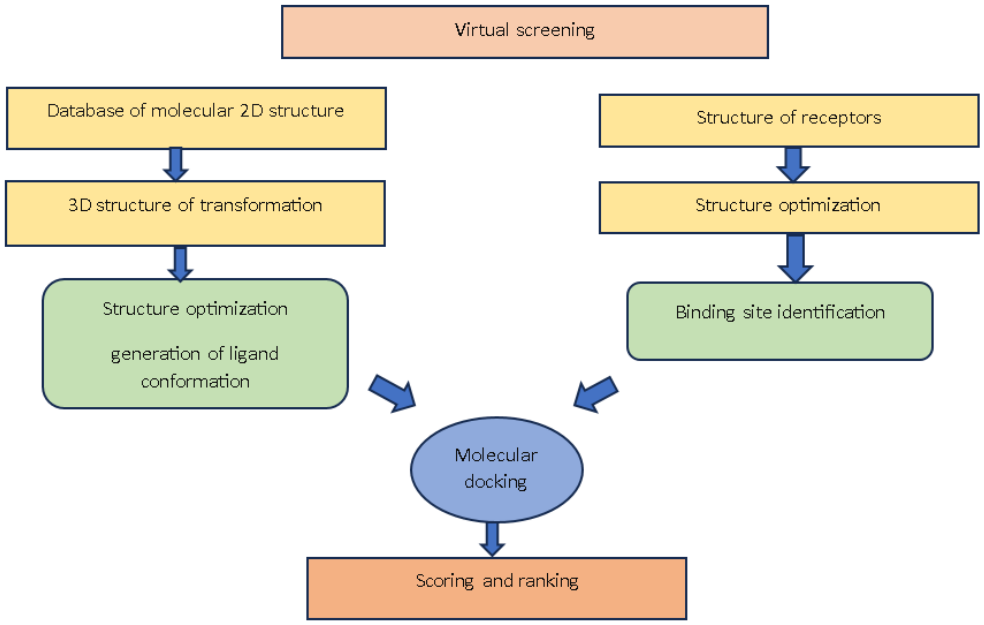


Figure 7: The process of virtual screen

Today's study requires molecular docking. If it is conducted prior to the hypothetical phase of any investigation, it can show that any task is feasible. Molecular docking has transformed the findings in certain domains. Studies on the interchange connecting small atom (ligands) and protein targets (which could be enzymes) in particular able be used to forecast when an enzyme will activate or become inhibited. Information of this kind could serve as a basis for logical drug design. The following is a description of some of the main uses for molecular docking:

7.2 Lead optimization

Small molecules or ligands can be optimally oriented on their target by using molecular docking. It has the ability to forecast various ligand binding strategies within the target molecule's groove. The information gathered from these kinds of studies can be used to create analogues that are more effective, selective, and powerful [5,109].

7.3 Hit Identifications

A vast collection may be screened using docking-based arrangements with scoring functions to find strong potential medicines in silico that can specific the molecules being targeted.

7.4 Drug-DNA Interaction Studies

Nowadays, chemotherapy is a common component of most cancer treatment regimens and techniques. The cytotoxic mechanism of several chemotherapeutic drugs is incomprehensible, despite the chemotherapy's absolutely essential function in the care, therapy administration and supervision of cancer. The primary biological targets of many of these anticancer chemotherapeutic medications are nucleic acid and related activities. In light of this, scientists are continuously working to clarify the molecular basis of pharmaceuticals' anticancer activity by examining the manner in which medicines and nucleic acids interact. [111-115]. Here, the initial prediction of the drug's nucleic acid binding characteristics is greatly aided by molecular docking. The data acquired from the results of these studies is useful in establishing a relationship between the cytotoxicity of a medicine and its molecular structure. Moreover, this information would be helpful in identifying any structural alterations in a medication that would cause a sequence- or structure-specific binding to its target (a nucleic acid). This understanding can be utilized in the logical formulation and creation of novel medications with enhanced effectiveness and fewer adverse effects, as non-specific binding limits the dosage and consistency of pharmaceuticals used in the treatment of cancer. [109,110,116]

7.5 Prediction of potential targets

It should be emphasized that the aforementioned techniques are all general docking techniques that dock with the same receptor using various ligands from the database. However, the current reverse docking approach varies from those used previously. We utilized figure [117] to describe the reverse docking process. In reverse docking, a single small-molecule ligand is used as a probe to dock with several receptors in order to identify potential binding gaps. This process helps identify novel targets. It is possible to estimate the possible targets of drugs in this way.

For instance, Grinter et al. [118] used the reverse docking software program Mdock to investigate the possible target, oxidized squalene cyclase (OSC) of PRIMA-1. Reverse docking was also used by Chen et al. [119] to identify the targeted proteins of marine chemicals with anti-tumor action. Additionally, Chen et al. [119] suggested that reverse docking is a useful target fishing technique that may be used in conjunction with in vitro tests. Lastly, we thought that the novel drug design may be greatly aided by investigating pertinent mechanisms of action or side effect profiles using structural biology research [120], such as the pocket analysis [121].

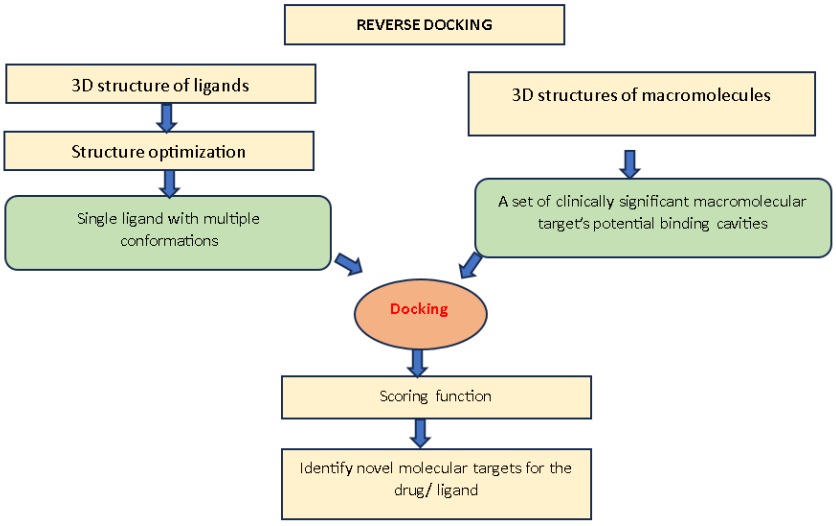


Figure 8: The reverse docking technique

8. CONCLUSION

For the purpose of designing and discovering new drugs, Molecular Docking offers many techniques. Chemical databases are easily seen by medicinal chemists. The prediction of ligand binding within the receptor is accomplished with success. Molecular docking is a procedure used in drug design that these medications facilitate. Both money and time are saved by it. Novel drug development is the usage of it [91–95].

Learning about the Novel Drug Design and Development Process Is Very Helpful for Future Medicinal Chemists. The complexity of the molecular docking method lies in lead molecule optimization, evaluation of the biological route, and de Novo drug creation. This review covers every detail there is to know about molecular docking. Due to the development of strains resistant to drugs, infectious diseases such as malaria, heart failure, cancer, and others pose a threat to public health in most countries, demanding the development of novel and effective treatments [96–100]. Finding a new use for an existing medication and using that newly discovered medication to treat a condition. An established and trustworthy substitute for the costly and taking a lot of time traditional method of drug discovery is computational drug design, which is a less time-consuming and cost-effective approach.

Due to the growth of drug resistance strains, infectious diseases such as malaria, heart failure, cancer, and others pose a threat to public health in most nations, demanding the development of novel and effective treatments. discovering new uses for an already-approved medication and using that medication to treat illness. A verified and dependable substitute for the costly and taking a lot of time traditional the process of finding new drugs is computational medication design, which is a less time-consuming and cost-effective strategy using the aid of computer-aided drug design, it has grown into a potent alternate method for finding and creating new medications from those that already exist (CADD).

9. ACKNOWLEDGEMENT

We sincerely acknowledge the Honorable Vice-Chancellor of CSJM University, Kanpur for the resources and substantial support.

Abbreviations: **CADD** Computer Aided Drug Design, **CSD** Cambridge Structural Database, **ACD** Accessible Chemical Directory, **MDDR** MDL Drug Data Report and **NCI** National Cancer Institute Database, QSAR Quantitative Structure-Activity Relationship.

10. CONFLICT OF INTEREST

The author declare that there is no conflict of interest.

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