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"ADVANCES IN MOLECULAR DOCKING: A COMPREHENSIVE REVIEW OF TYPES, APPROACHES AND APPLICATIONS"

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ABSTRACT

A type of computational modelling known as "molecular docking" is used to represent the complexes produced when two or more molecules interact. It is a method for computing the architecture of compounds consisting of two or more distinct molecules. Molecular docking aims to predict an interesting three-dimensional structure. The words "ligand" and "protein" are mostly linked to the concept of molecular docking. The target site of a protein is where a ligand may bind to produce a particular activity. Based on the binding characteristics of the involved ligand and target molecules, molecular docking software is mostly employed in drug development. Computational approaches have become a key component of many drug development processes, from hit discovery to lead optimization and beyond. The docking procedure often consists of numerous steps, and each one provides another level of complexity. Small molecules are positioned in the enzyme's active site using docking techniques. Molecular Docking provide a collection of expensive tools for drug design and analysis. Molecular docking is anticipated to be the computational phenomenon that is used the most frequently in the area of computer-aided drug design (CADD). It is used for the lead discovery process in the

pharmaceutical industry and at the academic level. In this review, which mainly the highlights molecular docking along with its mechanism, types, approaches, and applications.

Key words: Molecular docking, Ligand, Receptor, Mechanism, Types, Approaches, Software.

1 INTRODUCTION

It is possible to anticipate the preferred binding orientation of a molecule (such as a ligand) to a different one (such as a receptor) when they interact to produce a stable complex through a type of computational modelling known as molecular docking [1]. It is a computational technique for determining the architecture of compounds made up of two or more different molecules. Predicting the desirable 3D structures is the objective of molecular docking studies. Only appropriate incentive structures are generated by docking in and of themselves [2]. By employing a scoring function, the orientation of the ligand and receptor molecules in a stable complex can be used to predict the binding affinities and the strength of the link between the ligand and the protein. [3]. In order to identify the structures that are most likely to exist in nature, these possibilities are ordered using scoring functions [2]. Candidates docking for huge libraries are now ranked with the aid of a scoring function. The affinity and activity of a compound are predicted by the drug receptor interaction. It is essential for both drug discovery and drug design. The system's overall free energy is minimized. It is quite difficult to discover the new drugs and develop them. New drugs are discovered with the aid of the in silico approach. Computer-based drug design should be employed for the quick advancement of the drug discovery process. In computational drug design and molecular structural biology, it is helpful. It is used to predict a molecule's three-dimensional structure. [3].

The goal of molecular docking is to achieve an optimal conformation for both the protein and the ligand as well as the fundamental direction between the protein and the ligand in order to reduce the overall method's free energy. The promotion of basic bimolecular processes, such as interactions between drugs and proteins, nucleic acids, and enzyme substrates, depends significantly on molecular recognition. Signal transduction depends extensively on the interactions between physically suitable compounds such peptides, proteins, carbohydrates, nucleic acids and lipids. Furthermore, the kind of signal created (such as agonist vs. antagonism) may affect the relative orientation of the two interact associates. Docking is therefore useful, in order to estimate the strength and type of signal that will be produced. Molecular docking is one of the most often utilized techniques in structure-based drug design. Because of its capacity to predict he binding-conformation of small molecule ligands to the appropriate target binding site. Both the rational design of medications and the explanation of basic biochemical processes depend heavily on the binding performance's characterization. [4]. There are numerous research and review publications that distinguish different developing facts in this field. In this review, we mainly discusses the basic requirement, mechanism, types, approaches, software’s and applications of molecular docking.

1.1 Basics of molecular docking

In order to predict the small molecule's affinity and activity, docking is frequently utilized to connect therapeutic small molecules with their protein targets. Docking plays an important role in the process of rational drug design and development. Many efforts have been made to enhance the docking prediction for algorithms in light of the biological and pharmacological significance of docking research. The preferred orientation of one molecule in relation to another when they are brought together to form a stable complex is predicted using a mathematical technique called docking. In order to control the small molecule's affinity and activity, docking is frequently utilized to anticipate the alignment of therapeutic candidates with regard to particular target molecules. Docking is therefore essential for characterizing the structural medications [2].

1.2 Basic Requirements for Molecular Docking

The target's and the ligand's structural details as well as computational support, are the fundamental requirements for docking research. When it comes to proteins, homology modelling plays crucial role if the structure is unknown. The detail information is provided with the help of NMR techniques or X-ray crystallography, if the structure is known. One option is to develop the ligands' structure; another is to employ a library of compounds. In most docking techniques, the ligand is typically regarded as flexible while the protein is typically considered rigid. Along with the conformational degree of freedom, the binding pose in the binding pocket of the receptor is taken into the consideration [5].

1.3 Mechanism of Docking

The initial requirement is an organization of the attention protein in order to produce a docking screen. A biophysical technique, such as x-ray crystallography or, less frequently, NMR spectroscopy, has typically been used to maintain the structure. A docking agenda receives input from a folder containing ligands and information about protein organization [2, 4]. The two methods including scoring function and search algorithm that are used to determine the success of a docking program. The protein and ligand pair's potential orientations and conformations are included in the research space [2, 4]. Most currently used docking methods take flexible ligands to be considered, while others try to show a dynamic protein receptor [2]. The process used to study the intermolecular communication between two molecules in-silico is known as molecular docking. The macromolecule in this improvement serves as the protein receptor. Ligand refers to the tiny particle. A molecule that acts as an inhibitor [4].

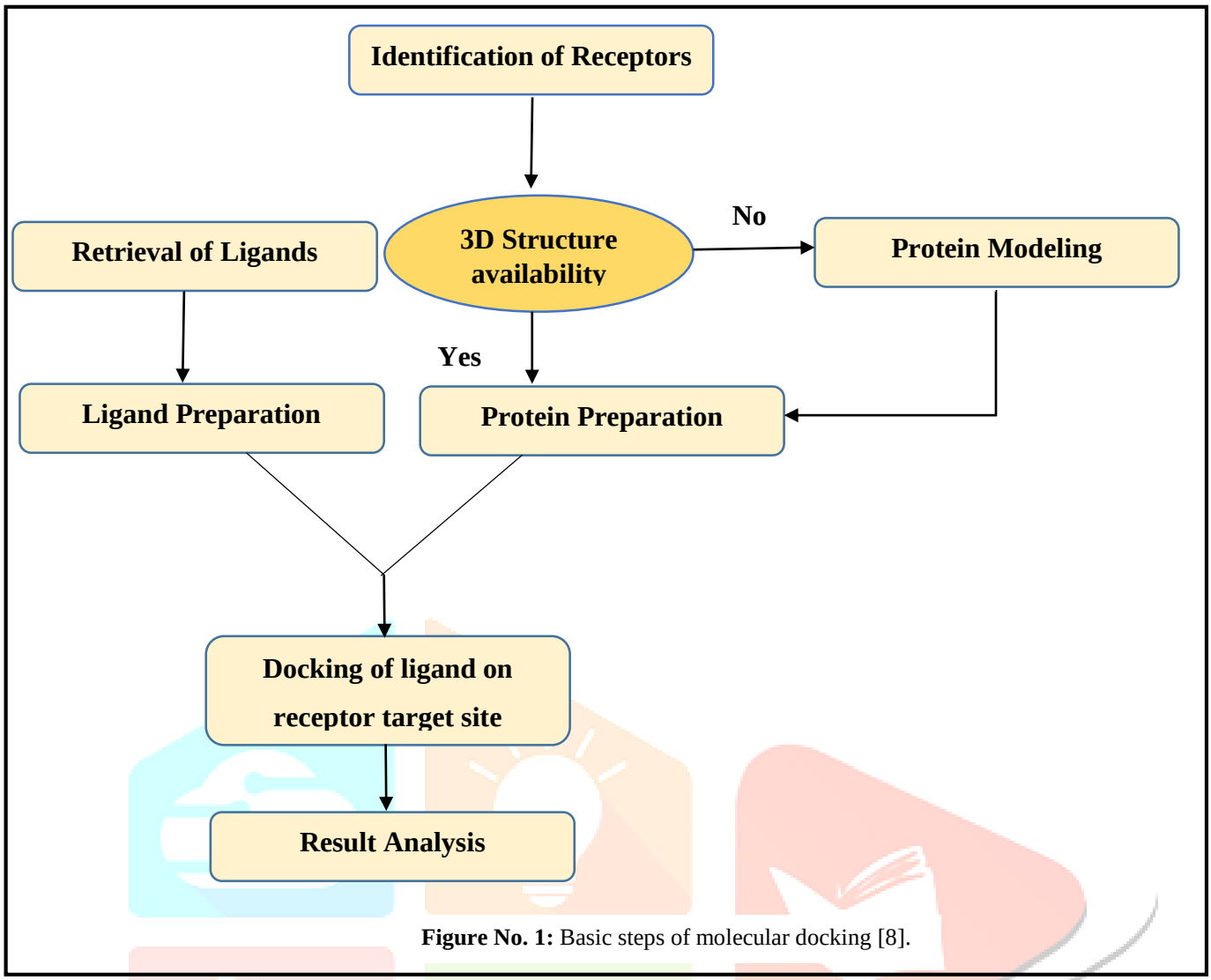

Figure No. 1: Basic steps of molecular docking [8].

2 TYPES OF DOCKING

There are two types of the protein-ligand docking process: Rigid docking and Flexible docking.

2.1 Rigid Docking

The confirmation of the receptor and ligand molecules, as well as the complete docking system, are fixed for this kind of molecular docking. As a result, it is known as a rigid docking mode. In this system, only changes to the spatial position are permitted. Generally, in this docking techniques the simulation of proteins and nucleic acids are beneficial, often appropriate for large molecules and is extremely simple, since it just requires a few calculations and has a rapid calculating speed [6, 20]. The rigid body docking process is used as the initial stage in the majority of docking suites [7, 16].

2.2 Flexible Docking

Rigid molecule is included as a target in the flexible ligand docking. This is the docking technique that is most frequently utilized. Flexible docking with equally flexible interactions between the molecules [1, 20]. Although, protein flexibility would have to be considered in the ideal scenario, and various methods in regards to this have been established [7, 16].

3 APPROACHES OF MOLECULAR DOCKING

There are other methods that still work for docking, including methods are as described below:

3.1 Shape complementarity Approach

Complementarity is the fundamental idea of molecular recognition. The ligand and protein's molecular surface/complementary surface properties, which are used for docking, are utilized in shape complementarity/geometric matching techniques. In an illustration using solvent-accessible surface area, the ligand surface is compared to the receptor's molecular surface. Shape-matching descriptions helps to discover the complementary groove for the ligand on the receptor's surface by making it simpler to understand how two surfaces complement one another. Calculating the receptor molecule's hydrophobicity based on the number of twists in the main chain atoms is another area of interest in the topic of research. In order to determine the binding characteristics of the ligands on the molecular target surface, the shape complementarity approach is comparably faster and scans hundreds of ligands in a couple of seconds. This method can be useful for developing pharmacophores since they use geometric descriptors to determine the ideal binding energy of ligands [1, 5]. Using a search algorithm, determine the geometric complementarity of proteins and ligands. For predicting various ligand conformations, the search algorithms including Monte Carlo, Genetic Algorithms, and Exhaustive Methods are frequently utilized [8].

3.2 Simulation Approach

This method involves an apparently difficult processes. The ligand and receptor are physically separated from one another in the simulation approach, and the ligand is then permitted to connect to the active site of its receptor after a certain number of conformational space movements. These actions comprise diverse ligand structural modifications either through internally (torsional angle rotations) or externally (rotations and translations). The overall energetic cost of the system is induced with each movement of the ligand, as a result the total energy of the system is determined after each movement. In the technique, it has benefits above the complementarity since it also considers the flexibility of the ligand. Furthermore, to evaluate the molecular recognition between receptor and target is more correct. It takes more time to determine the ideal orientation because they must go through a wider energy landscape. In spite of this, modern methods, such as the rapid optimization method and grid-based techniques, have greatly aided in solving this particular problem [1, 5, 8, 9].

3.3 Monte Carlo Approach

A ligand in an active site is given a randomized conformation, translations, and rotation. It gives the configuration a starting value. Then a fresh configuration is created and scored. The Metropolis criterion is used to determine whether or not the new configuration should be retained [2, 4, 19].

3.4 Matching approach

These strategies emphasize complementarity. A ligand receptor is created when the ligand atom is in the "best" location at the site. Configuration with potential for optimizations [4].

3.5 Ligand fit approach

The term "ligand fit" describes a rapid and accurate method for docking small molecule ligands into protein active sites while taking form complementarity into consideration [2, 4].

3.6 Point complimentarily approach

These methods concentrate on contrasting the morphologies and/or chemical characteristics of several molecules [2, 4].

3.7 Fragment-based method

Fragment-based methods can be summed up as breaking down the ligand into individual photons or particles, joining the fragments, and finally linking the fragments [2, 4].

3.8 Distance Geometry Approach

With regards to intra- or intermolecular dimensions, a wide variety of sequence aspects can be expressed. These distances can be assembled and three-dimensional structures that work with them can be calculated using the distance geometry framework [2, 4, 19].

3.9 Inverse Docking Approach

The evaluation of a drug candidate's potential for toxicities and side effects can be aided by having a thorough understanding of all these targets in combination with a precise pharmacokinetic property. In order to conduct docking studies on a particular ligand, a special method is chosen [2, 4].

3.10 Point Complimentarily Approach

These methods are based on evaluating the form and/or chemical complementarity of molecules that interact [4].

3.11 Blind Docking Approach

By scanning the full surface of protein targets, it was developed to find potential binding sites and peptide ligand binding mechanisms [4].

3.12 Metropolis Criterion Approach

A new solution is immediately approved if its score is higher than the previous one. A Boltzmann-based prospect function is helpful if the configuration is not brand-new. The solution is confirmed if it passes the possibility function test; else, the arrangement is undesirable [4].

4 MAJOR STEPS INVOLVED IN MECHANICS OF MOLECULAR DOCKING

The procedure used to study the in silico intermolecular interaction between two molecules is called molecular docking. The macromolecule acts as the protein receptor in this process. A micromolecule called a ligand has the ability to function as an inhibitor. Thus, the following steps are involved in the docking process [10].

Step I – Preparation of Protein

Protein data bank (PDB) should be used to retrieve the three-dimensional structure of the protein; pre-processing should then be done on the returned structure. According to the parameters supplied, this should allow for the removal of water molecules from the cavity, formation of side chains, stabilization of charges, adding missing residues etc. [3, 4, 10].

Step III – Preparation of Ligand

Ligands may be downloaded from a variety of databases, including ZINC and Pub Chem, or they may be sketched using the Chem. sketch tool. The LIPINSKY'S RULE OF 5 should be applied while choosing the ligand. The Lipinski Rule of Five helps distinguish between drug-like and non-drug-like behaviours. Due to drug likeness for compounds that continue to meet two or more of the conforming rules, it ensures a strong chance of being successful or unsuccessful. For selecting a ligand that follows to the Lipinski Rule: [4, 10, 17].

(1) Hydrogen bond donors should be Less than five
(2) Hydrogen bond acceptors should be Less than ten
(3) Molecular mass less than 500 Da
(4) High lipophilicity (expressed as LogP not over 5)
(5) Molar refractivity should be between 40 -130

Step III – Active site prediction

Predicting the protein's active site is necessary after protein preparation. There are numerous active sites on the receptor, but just the one that is of concern should be selected. In general, the presence of water molecules and hetero atoms is unimportant [4, 10].

Step IV- Grid Generation: Constraints, excluded volumes, and rotatable groups were kept constant at this site. The most important factor in determining is the quantity of genetic operations (crossover, migration, and mutation) were carried out. Predictions for the Binding Cavity must be done [3].

Step V Docking:

After docking the ligand against the protein, the interactions are analyzed. The scoring function selects the best docked ligand complex and assigns a score based on their selection [3, 4, 10, 17].

5 AVAILABLE SOFTWARE FOR MOLECULAR DOCKING

The software's which are used in the Molecular docking are as shown in the Table No.1:

Table No. 1: Molecular Docking Software

Docking Software	Year Published	Designer / Company	Licence terms	Supported platforms	Docking Approach	Scoring function
Auto Dock [5, 6, 7, 8, 10, 11, 12, 13]	1990	D. S. Good sell and A. J. Olson The Scripps Research Institute	Free for Academic use	Unix, Mac OSX, Linux, SGI	Genetic algorithm Lamarckian genetic algorithm Simulated Annealing	Auto Dock (force-field methods)
DOCK [5, 6, 7, 10, 11, 13,14, 15, 18]	1988	I. Kuntz University of California, San Francisco	Free for Academic use	Unix, Linux, Sun, IBM AIX, Mac OSX, Windows	Shape fitting (sphere sets)	Chem Score, GB/SA solvation scoring, other
Auto Dock Vina [5, 10, 11, 13]	2010	Dr. Oleg Trott at The Scripps Research Institute.	Open source, no web server available	x86 and compatible 64-bit Linux systems	GA (genetic algorithm)	Empirical / Knowledge-Based
Flex X [5, 6, 8, 10, 11, 12, 13, 14, 15]	2001	T. Lengauer and M. Rarey Bio SolveIT	Commercial Free evaluation (6 weeks)	Unix, Linux, SGI, Sun Windows	Incremental Construction	FlexXScore, PLP, Screen Score, Drug Score
FRED [5, 8, 10, 11]	2003	Open Eye Scientific Software	Free for academic use	Unix, Linux, SGI, Mac OSX, IBM AIX, Windows	Shape fitting (Gaussian)	Screen Score, PLP, Gaussian shape score, user defined
Glide [5, 7, 8, 10, 11, 13, 15]	2004	Schrödinger Inc.	Commercial	Unix, Linux, SGI, IBM AIX	Monte Carlo Sampling	Glide Score, Glide Comp
GOLD [5, 7, 8, 10, 11, 13, 14]	1995	Cambridge Crystallographic Data Centre	Commercial Free evaluation (2 months)	Linux, SGI, Sun, IBM, Windows	Genetic Algorithm	Gold Score, Chem Score user defined

Ligand Fit [5, 8, 10]	2003	Accelrys Inc.	Commercial	Linux, SGI, IBM AIX	Monte Carlo Sampling	Lig Score, PLP, PMF

6 APPLICATIONS OF MOLECULAR DOCKING

In several fields, where the discoveries have been revolutionized by molecular docking. Today's research demands the use of molecular docking. It is possible to estimate whether an enzyme will be activated or inhibited by analyzing the interactions between tiny molecules (ligands) and protein targets (may be an enzyme) [1]. Agonism or antagonism may come from the protein's receptor being bound by a ligand [8]. The basic materials for rational drugs design may be found in this kind of information. Following are some of the main applications for molecular docking [1, 4, 5].

6.1 Lead optimization

An ideal position for a tiny molecule or ligand to bind to its target can be estimated through molecular docking. Different ligand binding modalities in the groove of the target molecule can be estimated. The information gathered from these kinds of investigations could be used to create analogues that are more powerful, discriminating, and effective [1, 2, 4, 5, 7, 8].

6.2 Hit Identifications

In order to search through enormous databases to identify the potential drug candidates that can target the desired molecule, molecular docking can be utilized in connection with a scoring function [1, 2, 4, 5, 7, 8].

6.3 Remediation

Protein-ligand docking can also be used to predict which pollutants are enzyme-degradable. It can be used to find the ideal location and gather the most potent drugs. Molecular docking can be used to identify enzymes and their mode of action. The relationships between proteins can also be established using it. By employing the remediation method, molecules are virtually screened [2].

6.4 Bioremediation

It is possible to estimate which pollutants can be destroyed by enzymes using protein ligand docking [4, 7]. The discovery of therapeutic medicines is facilitated by molecular docking in a variety of ways, including [8]:

a. Identification of potential target [8].
b. Screening of potent drugs as activators/inhibitors against certain diseases [8].
c. New drug development through lead optimization [8].
d. Prediction of the nature of the active site and the binding mode [8].
e. Less a time-consuming chemical compound synthesis [8].
f. Drug-DNA interactions [5].
g. Protein de-orphaning [5].
h. Nucleic acid and protein interactions [5].

i. Structure-function studies [5].
j. Discovering the lead structures of potential protein [5, 7].
k. Enzymatic reaction mechanisms [5].
l. Protein modification [5].

7 DISCUSSION & CONCLUSION

Different tools for drug design and discovery are provided by molecular docking. The structural databases of molecules are simple to visualize for medicinal chemists. It effectively anticipates how ligands will bind to receptors. These medications use molecular docking technique as part of their drug design. It is economical and saving time [3]. The approach is employed in molecular systems ranging from small molecules to enormous bio molecules and material assemblies in computational chemistry and computer-aided biology. Most docking research now concentrates on the interaction of a flexible ligand to a physiological receptor [2]. It is employed in the developing of new drugs. Finding out about the novel drug design and novel drug development process is quite helpful for future medicinal chemists. Optimizing the lead molecule, assessing biological pathways, and developing new drugs are difficulties with the molecular docking process.

In the current review include all relevant information about molecular docking. We have mainly concentrate the key aspects on basic requirement, mechanism, types, approaches, applications of molecular docking, although demands for flexibility and flourishing scoring remain key challenges. The development of scoring functions with high accuracy and minimal computing expense may advance docking applications to a new stage. High end programmes are quick to include the new algorithms from academia and industry. It keeps expanding its involvement in cutting-edge new technologies like genomics, computational enzymology, and proteomics search engines. Finding a new indication for an existing drug and using that drug to treat a disease with the newly discovered drug. Computational drug design technique is an established and trustworthy substitute for the costly and time-consuming conventional method of drug discovery, and also it is a process that is both cost-effective and less time-consuming. There are numerous software programmes that have been reported for investigating ligand binding affinity against numerous receptors. Utilizing molecular docking techniques makes it easier to create new therapeutic medications and understand the molecular interactions involved in a variety of enzymatic activities. Using this strategy, new medications can be designed and discovered to treat a variety of chronic conditions. With the use of computer-aided drug design (CADD), it has become a potent alternate technique to find and generate innovative medications from current drugs.

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