Molecular Docking: A Highly efficient Method for Structure-Based Drug Designing

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ABSTRACT

With the introduction of innovative approaches in drug discovery, numerous techniques to structure-based drug design have been employed. Molecular docking is one of the most essential methods. Today, molecular docking is turning into a crucial tool for drug discovery and molecular modeling purposes. Molecular docking is a type of computational modeling of complexes that are generated by the intermolecular interaction of two or more molecules, such as proteins, nucleic acids, lipids, and ligands. By optimizing the shape of the protein and the ligand as well as their relative orientation, molecular docking seeks to reduce the free energy of the entire system. Based on the binding characteristics of the involved ligands and target molecules, it guesses the three-dimensional geometry of adducts. Molecular docking provides many alternative candidate structures, which are scored and grouped together using the scoring function in the molecular docking program software. Docking simulations estimate an optimum docked conformer depending on the system's total energy. Molecular docking research is important for predicting possible disease targets and generating successful medications for the pharmaceutical sector.

In this chapter, we provide a brief overview of various computational features associated with molecular docking, such as fundamental docking steps, docking types and interactions, software programs and their algorithms, scoring functions, and the available molecular docking methods, as well as their development and utilization in drug discovery. The binding mechanism and afinity of the complex generated are assessed via Molecular Docking, which aids in the Molecular Identification Process docking towards the development of novel leads for medicines.

Keywords— Molecular Docking, Receptor, Ligand, AutoDock Vina, PDB

I. INTRODUCTION

Computational chemistry is the utilization of computer calculations to tackle chemical problems. It employs theoretical chemistry methods, which are integrated in sophisticated computer programs for determining the structure and characteristics of molecules. Computational techniques are critical in the drug discovery process, particularly in taking use of the growing number of solved X-ray and NMR protein ligand structures [1].

Many experimental and high throughput screening approaches have been employed in drug development throughout the last few decades. Traditional ways of discovering innovative therapeutic medications were prohibitively costly, time-consuming, and inefficient. To address the limitations of old approaches, new effective and reasonable methods based on virtual screening have been devised. The virtual screening approach may be divided into structure-based and ligand-based drug developing methods based on the accessibility of structural data. The structure-based drug development technique is concerned with molecular docking, whereas ligand-based approaches are concerned with quantitative structure activity relationships and pharmacophore models.

II. Theoretical foundations of molecular docking (MD)

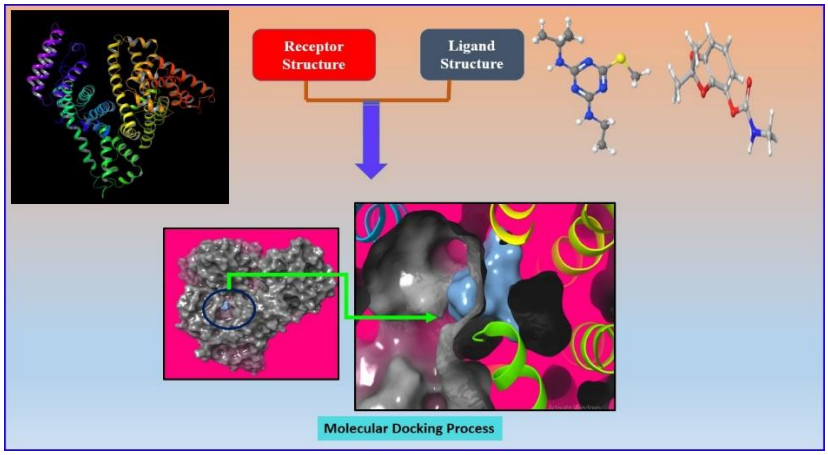

Fig.1 Molecular docking flow chart.

Since the molecular docking approach has been widely employed in recent years, it has substantially improved efficiency and reduced research costs. It has evolved into an important tool in computer-assisted drug design [2]. Molecular docking is a type of computational modeling that makes it easier to figure out the favored binding orientation of one molecule (such as a ligand) to another (such as a receptor) when they interact with one another to produce a stable complex and helps to choose effective molecules as a component of virtual screening of huge databases. The energy profile of a complex, such as the binding free energy, strength, and stability (such as binding affinity and binding constant), may be predicted using information on the favored orientation of bound molecules. This is possible using the molecular docking scoring function. It is critical to detect the optimum ligand poses and properly rate the relative docking propensity of multiple ligands [3,4].

It has been routinely and effectively utilized in pharmaceutical and medical research for the design, manufacturing, and discovery of therapeutically significant medicines and dyes. Molecular docking is used to investigate protein-ligand interactions and validate experimental interpretations in silico (Fig.1). Molecular docking is a promising approach that uses experimental information to theoretically anticipate the ideal position of a small molecule (ligand) in a macromolecule such as protein and DNA (target) to generate a stable complex; the interaction of ligand receptor demonstrates that the ligand and the receptor have particular complementary geometric shapes that fit completely into one another. Molecular docking studies can be done prior to wet-lab investigations to anticipate the manner of interaction of a ligand with a macromolecule. It can assist to confirm the findings of wet-lab investigations and to better understand the process of binding [5].

Automated software is used to do molecular docking studies, which aids in predicting the mechanism of binding, the affinity of binding, and the creation of an energetically advantageous conformation between a ligand and macromolecule. Additionally, it offers insightful information on how various ligands interact, including those that are therapeutically active [6].

III. Major steps involved in mechanics of Molecular Docking

The method of studying the intermolecular interaction between two molecules in-silico is known as molecular docking. The Macromolecule in this process is the protein or DNA receptor. The Ligand molecule is a tiny molecule that can serve as an inhibitor. As a result, the docking procedure includes the following phases and are shown in Fig.2.

A. Step I –Macromolecule preparation (Protein/DNA):

A three-dimensional Protein data bank (PDB) structure of a macromolecule ought to be downloaded from the RCSB protein database or other databases, and then pre-processed. According to the parameters given, this should allow for the elimination of water molecules from the cavity, the stabilization of charges, the filling of lacking residues, the formation of side chains, and so on.

B. Step II – Active site Identification:

The active site of the macromolecule (Protein/DNA) should be anticipated once it has been prepared. The receptor may have several active sites; nevertheless, just the one that is of concern should be chosen. Most of the time, if any, water molecules and hetero atoms are eliminated [7].

C. Step III –Ligand preparation:

A variety of databases, including ZINC, Pub Chem, and ChemSpider, may be used to access ligands. They can also be drawn using the Chem sketch tool.

D. Step IV- Docking Process:

Analysis of the interactions occurs when the ligand is docked against the protein. The scoring function assigns a score based on the best-chosen docked ligand complex.

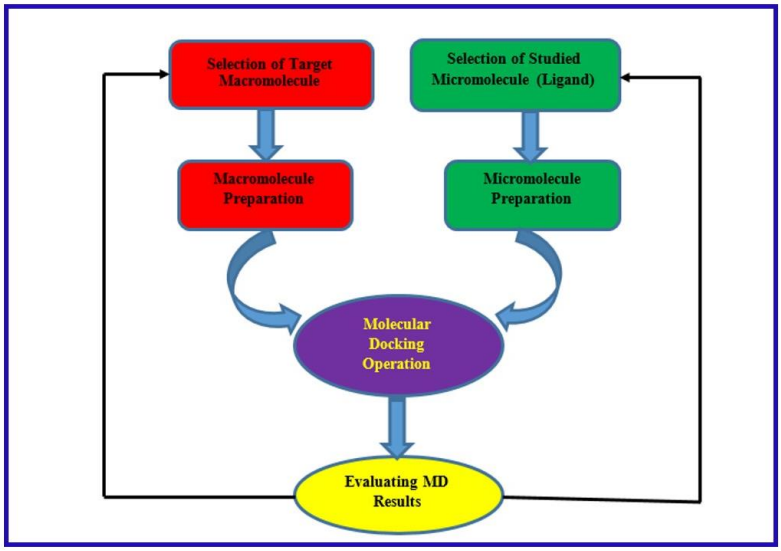

Fig. 2. A flow plan for analyzing docking

IV. Molecular docking software classification / Types of molecular docking

There are three forms of molecular docking, as seen in Fig.3.

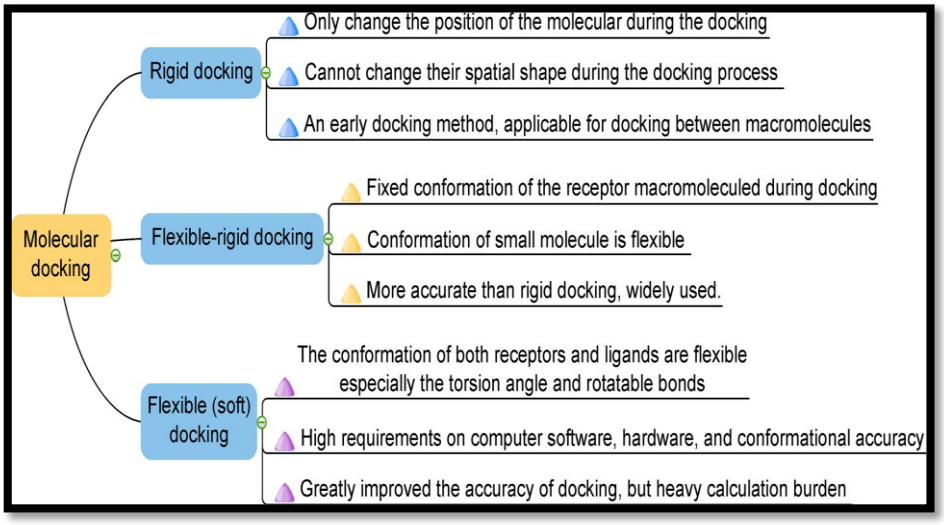

Fig.3 Categorization of Molecular Docking Software [2]

A. Rigid Docking/ Lock and Key:

According to Lock and key hypothesis, both the ligand and the receptor are stiff and exhibit tight binding. It establishes the fundamental idea of three-dimensional complementarity. It only calculates six transitional degrees of freedom and rotational freedom. ZDOCK [8] and RDOCK [9] is an outstanding example of a stiff docking approach that employs superimposing the ligand at the appropriate binding groove.

B. Flexible-rigid docking/Semi-flexible Docking:

In the semi-flexible technique, one of the molecules (the ligand) is regarded flexible, while the target is deemed stiff. Only one of two molecules (usually the ligand) is exposed to the theoretical process, while the protein is rigid. Docking procedures are used to stabilize the protein conformation that may correlate with the ligands to be docked. Flexible-rigid docking is commonly utilized. Flex X [10], AutoDock [11], and AutoDock Vina [12] are outstanding examples of flexible-rigid docking methods.

C. Flexible Docking/ Induced fit Docking:

Receptor and ligand both have some flexibility. To increase the bonding forces between the ligand and receptor, it binds flexibly at their active site. It carries forth the idea of complementarity between ligands and proteins or DNA.

Flexible docking computational approaches are commonly used to investigate the intermolecular interaction of superposition between a flexible macromolecule (receptor) and a tiny molecule (ligand). To optimize bonding forces between both, the ligand binds flexibly at the active site of the receptor. It enacts the idea of protein-ligand complementarity. Docking software such as Gold [13], and Glide [14], is commonly utilized in the automated process between a flexible ligand and an ensemble of flexible receptor conformations generated using experimental or particular computational techniques. Fischer [15] presented a lock-and-key explanation for the ligand-receptor binding process, in which the ligand fits into the receptor like a lock and key. The earliest documented docking approaches were based on this principle, and both the ligand and receptor were considered as rigid entities as a result [16]. The "induced-fit" hypothesis [17] developed by Koshland extends the lock-and-key theory by claiming that the active site of the protein is constantly altered by interactions with the ligands as the ligands interact with the protein. This idea proposes that the ligand and receptor be viewed as flexible during docking. As a result, it may be able to represent binding events more correctly than the rigid treatment.

The most prevalent docking algorithms utilize GA (genetic algorithm), LGA (Lamarckian genetic algorithm), and the rigid-receptor/flexible-ligand model to visualize the interaction between ligands and proteins/DNAs [2]. AutoDock 4.0, AutoDock 4.2, AutoDock vina, Hex 8.0, BSP SLIM online, and more tools are available to do docking between protein/DNA and ligand. AutoDock is the most often used docking software.

V. Methods of Molecular Docking

Based on the prediction of probable targets, molecular docking may be separated into two methods: general docking and reverse docking.

A. Reverse Docking Method:

A tiny ligand of interest is docked into the binding site of several protein/DNA (many receptors) structures, which may be downloaded from the protein database to obtain a suitable protein, in the reverse docking approach. Thus, prospective ligand/drug targets can be anticipated.

B. General Docking methods:

To get an appropriate ligand, a protein/DNA (receptor) of interest is docked into several tiny ligand structures retrieved from the chemical library. Figure 1 depicts a comparison of these two paradigms.

VI. Molecular Docking Databases

The Protein Data Bank (PDB) is the most widely used protein structural database. Furthermore, public databases such as PubChem Compound Database and ZINC are available for free [2].

VII. Various Types of Interactions

Interaction forces are classified into four types:

(1) Steric forces - Caused by entropy.
(2) Electrodynamics forces- Van der Waals interaction.
(3) Electrostatic forces - dipole-dipole, charge-dipole and charge-charge
(4) Solvent-related forces - Hydrogen bond and hydrophobic interactions [4].

VIII. Scoring Function

The scoring function provides a way to rank the location of ligands in relation to one another. The score is supposed to correspond precisely to the ligand's binding affinity for the protein/DNA, such that the highest scoring ligands are also the best binders. Scoring functions may be concrete, knowledge-driven, or they might be centered on molecular mechanics. Scoring is made up of three distinct expressions that are relevant to docking and ligand design [4].

The docking analysis is performed on the most energetically advantageous conformer, i.e. the run with the lowest binding energy. This method allows for flexibility within the ligand to be docked as well as the use of sophisticated molecular mechanics to compute the ligand's energy in the context of the ostensibly active region. After docking, a 2D plot may be created, which can offer a graphical depiction of the various forces and residues of amino acids participate in the binding mechanism by utilizing software such as 'Discovery Studio,' LigPlot, and so on. It also includes details on the force and amino acid residues associated in the binding process [18].

The collected data, alone or in combination with molecular modeling tools, might be used to investigate the toxicity of manufactured drugs and aid in the clarification of the molecular processes of in vivo toxicity.

IX. Advantages of molecular docking Techniques

The molecular docking approach offers numerous benefits over other drug discovery strategies such as High-Throughput Screening (HTS).

a) The molecular docking approach is significantly quicker and less expensive for assessing binding affinity of ligands from a vast chemical library.
b) It shortens the processing time required to examine the complexity of protein-ligand interactions.
c) Accurate scoring functions with little computational cost
d) Computational techniques (In Silico methods) should be fast and resilient.

X. Applications of molecular docking

Molecular docking research is particularly important in an extensive variety of applications in computer-aided drug development. Molecular docking is essential in modern research. If performed before to the experimental portion of any inquiry, it can illustrate the practicability of any task. There are various domains where molecular docking has transformed research. Interaction studies between tiny compounds (ligands) and protein targets (which might be enzymes) in particular can predict enzyme activation or inhibition. Such data might be used as a starting point for rational medication design. In computational chemistry research, molecular docking is an essential technique. The importance of molecular docking is well acknowledged and established in the pharmaceutical industry. Docking is mostly utilized in drugs design. The majority of medicines are tiny organic compounds, and docking may be used on them:

a) Hit Recognition (Virtual Screening)
b) Lead Optimization (Drug Development)
c) Bioremediation
d) Anticipation of KA (Biological activity)
e) Binding site prediction (Blind docking)
f) De-orphaning of protein
g) Protein – Protein/ Nucleic acid interactions
h) Looking for lead structures for protein targets
i) Studies of Structure – function
j) Mechanisms of Enzymatic reactions
k) Protein engineering
l) Bioremediation: Protein ligand docking may additionally be employed to predict contaminants that enzymes can breakdown.
m) Research on Drug-DNA Interactions: Identification of drug binding characteristics to nucleic acid.
n) By creating and discovering innovative medications, this technique may be utilized to treat a wide range of chronic conditions.
o) The molecular docking approach was used to anticipate effective therapeutic compounds that would limit the proliferation of cancer stem cells. It might demonstrate the viability of any role or feature of the investigated substances before they are employed in the experimental phase of any inquiry. The accuracy forecast of molecular docking yields great results, especially when analyzing the interaction between a tiny molecule and a macromolecule, which provides a wealth of knowledge about its vital function (activation or inhibition). Obtaining this sort of details prior to doing any experimental investigation may assist researchers in designing novel medications with different properties.
p) Its involvement in intriguing new approaches such as computational enzymology, genomics, and proteomic search engines continues to grow [4,19].

XI. Conclusions

Simple molecular visualization as well as easy access to structural databases have become crucial components of the medicinal chemist's workspace. Molecular docking offers a variety of useful methods for drug creation and research. In particular, for protein-ligand docking, induced-fit movements and protein flexibility will be used in the next years to find and create novel chemotherapeutic drugs. Computational docking simulations are now widely used at various phases of drug development and rational drug design processes. As the field of molecular docking-based virtual screening expands, its awareness will rise dramatically. Several software tools have been published that investigate ligand binding affinity against different receptors. However, more advancements are required to incorporate thermodynamic characteristics like as desolvation energies, real-time

energy changes owing to conformational alterations in both the receptor and the ligand, i.e. dynamic simulations. The application of molecular docking methods may be utilized to cure a number of chronic diseases through synthesizing, designing, optimizing, discovering, and developing new therapeutic medicines, as well as studying the molecular interactions of various enzyme activities. Accurate and low-cost scoring functions may propel docking applications to new heights. In conclusion, we expect that the molecular docking approach will become a trustworthy drug-design tool by refining the scoring system and updating the relevant search algorithms.

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