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Review Article

A Review on Molecular Docking

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ABSTRACT

Molecular docking is a computational approach used to model the structural complexes that arise from the interactions between two or more molecules. Its main goal is to predict the three-dimensional configuration of the target molecule, making it a vital technique in the realm of drug development. The availability of molecular data and structural databases has become increasingly important in this area. Molecular docking provides a range of advanced tools for drug design and analysis, with the straightforward prediction of molecular interactions and easy access to structural databases serving as essential resources for medicinal chemists. One of the most prominent applications of molecular docking is virtual screening. Various docking programs have been created to visualize the three-dimensional structures of molecules, and the outcomes of docking can be assessed through different computational methods. This technique is a fundamental component of structural molecular biology and computer-aided drug design. It can be utilized to perform virtual screenings of large compound libraries, rank the results, and formulate structural hypotheses about ligand-target interactions, which is crucial for lead optimization. Many drug discovery projects have incorporated molecular modeling techniques into pharmaceutical research to explore complex chemical and biological systems. The integration of experimental and computational methods is vital for the discovery and development of new compounds. Molecular docking is extensively used in modern drug design to investigate the conformations of ligands within target binding sites, as well as to estimate the binding energy between ligands and receptors. This article offers essential insights into molecular docking, covering aspects such as molecular modeling, types of docking, docking models, key requirements, methodologies, applications, evaluations, and available software for molecular analysis.

INTRODUCTION

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The field of molecular docking has experienced a surge in demand over the past few decades, largely driven by the requirements of molecular biology structures and structure-based drug discovery. This growth has been significantly supported by advancements in computational power and accessibility, as well as the ease with which small chemical and protein libraries can now be obtained. [1] The discovery of a new medication is not only a resource-demanding endeavor but also an expensive one, given its lengthy, complex, and challenging nature. Fortunately, computational techniques have emerged as crucial tools in optimizing the drug development process. [2]

In the field of molecular modeling, docking is a method used to predict how one molecule will interact with another when they come together to create a stable compound. [3]. Information of the chosen direction in rotate may be worn to expect the strength of involvement or binding affinity linking two molecules with each, for example, score function. The interactions between important molecules like proteins, peptides, nucleic acids, carbohydrates, and lipids are crucial for how signals are transmitted in the body. Additionally, how these molecules are positioned relative to each other can determine the kind of signal that is generated, such as whether it acts as an agonist or antagonist. This is why docking is useful for predicting both the strength and type of signal that will be produced. Molecular docking is a widely used method in drug design because it can accurately predict how small molecule ligands will fit into their target binding sites. Understanding how these bindings work is essential for designing effective drugs and for explaining key biochemical processes. [4]

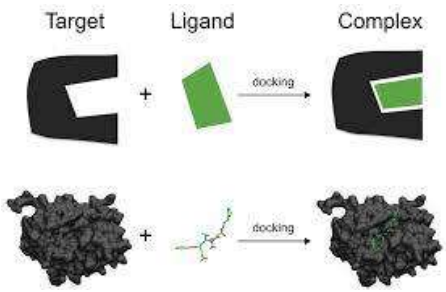

Fig.1, Schematic diagram of docking an undersized molecule ligand (green) to a protein target (black) produce a steady compound

Molecular docking aims to find the best shape for both the protein and the ligand, as well as the ideal interaction between them, in order to reduce the overall free energy of the system. [5]. Molecular recognition is really important for facilitating basic bimolecular processes, like how enzymes interact with substrates, as well as how drugs connect with proteins and nucleic acids. [6]. Understanding the basic principles that govern the interactions (like van der Waals forces, hydrogen bonds, and electrostatic attractions) between ligands and their protein or nucleic acid targets can help create a solid foundation for developing drugs that are both effective and specific for particular therapeutic targets. [7]. To effectively use this information, we need structural data to determine its importance and a way to assess potential ligands. [8]. There are many different computational docking methods available. [9]

Molecular docking

Docking is the process of arranging molecules in the most advantageous arrangements for interaction with a receptor. 2 Docking is a phenomenon observed within moments in a cell when molecules are bonded together to form a sustainable complex, , as seen in Figure 2.

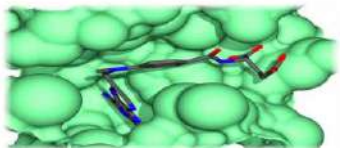

fig.2, molecular docking

Molecular Modelling

Molecular modeling is a method used to understand, visualize, and change the structures and reactions of molecules, as well as the properties that rely on these three-dimensional shapes.as seen in Figure 3. [10].

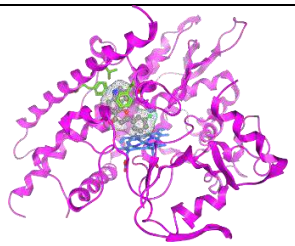

fig.3, illustration of molecular modeling

Types Of Docking

There are 2 types of docking

1. Rigid docking
2. Flexible docking

Flexibility can be approached in several ways. One method is flexible docking, which allows both the ligand and the receptor to move during the docking process. This can really boost the accuracy of molecular docking simulations. Flexibility can be achieved in two main ways: implicitly, by allowing the sidechains or backbone to be flexible, or explicitly, by running multiple docking simulations from various conformations, a technique called cross or ensemble docking. Moreover, soft docking techniques can help by smoothing out the protein surfaces or allowing some overlap to better account for flexibility and improve ligand binding. By keeping both the ligand and the receptor flexible in flexible docking, we get a more realistic view of how they interact, which increases the chances of finding the best binding positions..[11] . Daniel Koshland introduced the induced-fit theory in 1958, commonly known as "induced-fit docking." This theory involves calculating the binding energies of different shapes that a potential ligand can take when it interacts with a protein or receptor. [12].

FlexX-Pharm is an upgraded version of the flexible docking software FlexX. It's specifically made to include important details about how proteins and ligands bind together during the docking process. This improved version lets users add information from receptor-based pharmacophore features as constraints in the docking calculations. [13] .

Rigid docking

Rigid body docking refers to a type of molecular docking where both the protein and the ligand are considered to be stationary. In this approach, only the translational and rotational degrees of freedom are analyzed.[14 Rigid body docking is more computationally efficient compared to flexible or semi-flexible docking methods, which allow for variations in both the ligand and the protein. However, the rigid body assumption imposes limitations on the precision and reliability of the results. [15]. The fundamental concept of Rigid Docking is rooted in the Lock & Key theory introduced by Emil Fischer in 1898. [16,17] .

Molecular Docking Approaches

There are number of approaches exist for docking as follows

Monte Carlo Approach

i. It produces an initial configuration of a ligand within an energetic site, characterized by random conformation, transformation, and rotation.

ii. It score initial configuration. Then it generates new arrangement & score it.

iii. It employ Metropolis criterion to decide whether the new configuration is retain.

3.2 Metropolis Criterion

If the score of the new solution is better than that of the previous one, it is promptly accepted. In cases where the configuration is not novel, a Boltzmann-based prospect function proves beneficial. Should the solution meet the criteria of the possibility function test, it is deemed valid; otherwise, the configuration is considered undesirable. [18].

Fragment based method.

The fragment base methodology is characterized by the following steps: first, the fragments are docked, then they are combined, and finally, the ligand is separated into individual protons or fragments. Each piece is docked independently onto the receptors, and the results are used to create a framework of various potential docking conformations. This approach effectively circumvents the challenges associated with a high degree of freedom (DOF). [19] .

Distance geometry

You can show many different sequence features by using either intra- or intermolecular distances. These distances can be tailored, and we can figure out suitable three-dimensional structures through the distance geometry framework. A significant amount of effort has been put into building models of various molecules, including small molecules, peptides, and proteins, by applying distance geometry methods. [20] .

Matching approach

These strategies highlight how important it is for things to work well together. When a ligand atom is in the best spot at the site, it can be really important to adjust how the ligand and receptor interact. In a way, the protein and the ligand can be seen as surfaces that rely on each other and fit together. Talking about their complementarity in terms of how their shapes match helps us find the best way to connect the target and ligand molecules. [21] .

Ligand fit approach

Ligand fit is a quick and accurate way to place small molecule ligands into the active sites of proteins by focusing on how well their shapes match. The process of Ligand Fit involves two key steps: first, finding the cavities to identify and choose the part of the protein that will serve as the active site for docking, and second, actually docking the ligands into that selected site.. [22] .

Point complimentarily approach

This approach aims to evaluate how well the chemicals fit together and the shapes of the molecules that play a role in specific interactions. [23] .

Blind Docking:

It was introduced for detection of possible binding sites & modes of peptide ligand by scanning the entire surface of protein targets.

Inverse Docking: A computer method is being used to identify the protein targets related to toxicity and side effects of a small molecule. By understanding these targets along with the pharmacokinetic profile from proteomics, we can better evaluate the possible toxicities and side effects of a drug candidate. One of these methods is chosen for docking studies of a specific ligand. [24]

Mechanism Of Docking

1.To create a docking screen, the initial requirement is the proper organization of the target protein. Generally, this structure has been stabilized through a biophysical technique such as X-ray crystallography, or, less frequently, NMR spectroscopy. The arrangement of this protein, along with a collection of ligands, provides the necessary input for a docking program. [25].

2. The effectiveness of a docking program relies on two key mechanisms: the search algorithm and the scoring function. The search space encompasses all potential orientations and conformations of the protein in conjunction with the ligand. [26]. With near computing possessions, it is Impossible to comprehensively discover the investigate space this would enumerate all potential distortion of each molecule and all probable rotational and translational Orientations of the ligand relation to the protein at an agreed level of granularity.

3. Many docking programs currently available take into consideration flexible ligands, and many are also working on creating models for flexible protein receptors. [27].

4.Molecular docking is a process where scientists examine how two molecules interact with each other using computer simulations. In this case, the larger molecule is a protein receptor, while the smaller one is a ligand, which can function as an inhibitor. [28].

Application Of Molecular Docking

binding communication between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonist or antagonism. Docking is mainly used in the field of drug design. Most drugs are small organic molecules, and Molecular docking has a wide range of applications, particularly in the field of drug discovery and development. Here are some key applications:

 Virtual **Screening**: Finding possible drug candidates from extensive collections of compounds by estimating how well they bind to specific target proteins. [29]

 Lead **Optimization:** Docking helps figure out how and where a ligand attaches to a protein, which is known as the binding mode or pose. This information can then be used to create more effective and targeted analogs. [30].

 Drug **Repurposing**: Finding new therapeutic uses for existing drugs by identifying additional targets they can bind to.[29]

 Protein-**Protein Interactions**: Researching how proteins interact helps us learn about biological processes and find possible targets for new treatments.[31]

 Structure-**Based Drug Design**: Creating new medications by analyzing the three-dimensional shape of the target protein and where it connects.[32]

 Toxicity **Prediction**: Predicting potential toxic effects of compounds by assessing their interactions with off-target proteins.[29]

Available Softwares For Docking

- DOCK (1982,2001)
- FleX (1996)
- Hammerhead (1996)
- Surflex (2003)
- SLIDE (2002)
- AutoDock (1990,1998)
- ICM (1994)
- MCDock (1999)
- GOLD (1997)
- GemDock (2004)
- Glide (2004)

AUTODOCK

- Grid for each atom type (e.g. C, H, O, N)
- A 3D grid made up of evenly spaced points that surrounds and focuses on a specific area within the macromolecule.
- Typical spacing is 0.375
- Probe atom placed at each

GOLD

- Genetic Optimisation and Ligand Docking, uses multiple subpopulations of ligand
- A scoring function that uses force fields consists of three components: the hydrogen bonding term, the potential for intermolecular dispersion, and the potential for intramolecular interactions.

- 71% success in identifying experimental binding mode in 100 protein complexes

FLEX-X

- Base fragment is picked up and docked using "poseclustering" algorithm
- A clustering algorithm is used to group similar ligand transformations into active site. Flexible fragments are gradually added using MIMUMBA and assessed with an overlap function, then energy calculations are performed until the ligand is fully constructed.
- The final assessment is done using Böhm's scoring function, which takes into account hydrogen bonds, ionic interactions, aromatic characteristics, and lipophilicity. [33,34].

CONCLUSION

Molecular docking is a cost-effective, safe, and user-friendly method that aids in exploring, understanding, and identifying molecular characteristics through three-dimensional structures. Since various models can produce different outcomes, it's important to have a limited set of standard models that can be applied to large systems. This technique is used to predict the structural interactions between two or more molecules. It's commonly utilized in computational chemistry and computational biology, dealing with molecular systems that range from small compounds to large biological entities and material assemblies. Currently, most studies focus on how a flexible ligand binds to a biological receptor.

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