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Review Article

Basics, types and applications of molecular docking: A review

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ABSTRACT

From hit discovery through lead optimization and beyond, computational methods have become an essential part of many drugs development processes. There are typically several steps in the docking process, and each one provides a new level of complexity. Docking methods are used to place small molecules in the active region of the enzyme. In addition to these methods, scoring functions are used to estimate a compound's biological activity by looking at how it interacts with prospective targets. Molecular docking is considered to be the most widely utilized computational phenomenon in the field of computer-aided drug design (CADD). It is being utilized at the academic level as well as in pharmaceutical companies for the lead discovery process. Molecular docking is mainly associated with two terms: ligand and protein. Protein is the target site where ligand may bind to give specific activity. Molecular docking provides information on the ability of the ligand to bind with protein which is known as binding affinity. Applications of molecular docking in drug development have evolved significantly since it was first created to aid in the study of molecular recognition processes between small and large compounds. This review emphasizes the basic features of molecular docking along with the types, approaches and applications.

1. Introduction

Molecular docking is a method to identify the architecture of compounds generated by two or more distinct molecules computationally. The objective of docking studies is to anticipate the desired three-dimensional structures. Docking, in and of itself, generates only suitable incentive structures.[1] These possibilities are sorted using scoring functions to determine which structures are most likely to be present in nature. The present study outlines the state of the art in several computational elements of molecular docking-based virtual screening of a library of small compounds.[1] This review discusses molecular docking methodologies, various search algorithms, and docking techniques' scoring functions, as well as their relevance to protein and nucleic acid therapeutic targets. Additionally, the limitations of existing technology are discussed, as well as future opportunities.

1.1. Basics of molecular docking

Docking is widely used to anticipate the alignment of small molecule therapeutic compounds concerning their protein targets in anticipating the small molecule's affinity and activity.[1] Docking plays a critical role in rational drug design. Considering the biological and pharmacological importance of docking studies, much effort has been made to improve the algorithms for docking prediction. Docking is a mathematical technique that anticipates the preferable orientation of one molecule relative to another when they are linked together to create a stable complex.[2] Using scoring functions, it is possible to estimate the strength of the connection or binding affinity across two compounds based on their preferential orientation. Signal transduction is

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dependent on the interactions of physiologically significant substances such as proteins, nucleic acids, carbohydrates, and lipids.[2] As a result, docking may be used to forecast both the intensity and type of signals generated. Docking is widely used to anticipate the alignment of drug candidates relative to specific target molecules to manage the small molecule's affinity and activity. As a result, docking is critical in the structural characterization of medications. The goal of docking studies is to optimize the shape of both the ligand and protein, as well as the relative orientation of the protein and ligand, to reduce the total system's free energy.[2]

1.2. 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 1.

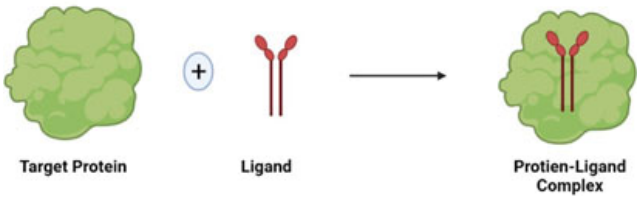

Fig. 1: Molecular docking

1.3. Molecular modelling

Molecular modelling is a tool for originating, describing, and modifying the configurations and interactions of compounds, as well as the attributes of these molecules that are reliant on their three-dimensional geometries.[2]

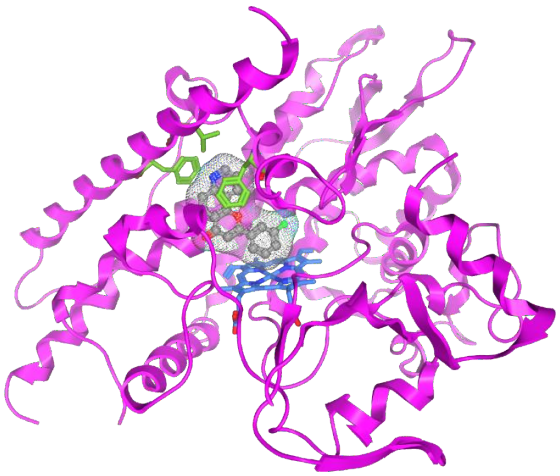

Fig. 2: Illustration of molecular modelling

1.4. Types of docking

There are two distinct forms of docking.

1. Rigid docking
2. Flexible docking

1.5. Rigid docking

Assuming the compounds are inflexible, we are seeking a rearrangement of one of the compounds in three-dimensional space that results in the best match to the other compounds in parameters of a scoring system.[3] The ligand's conformation can be formed with or without receptor binding activity.

1.6. Flexible docking

In conjunction with transformation, we evaluate molecular flexibility to identify confirmations for the receptor and ligand molecules as they exist in the complex in Figure 4.

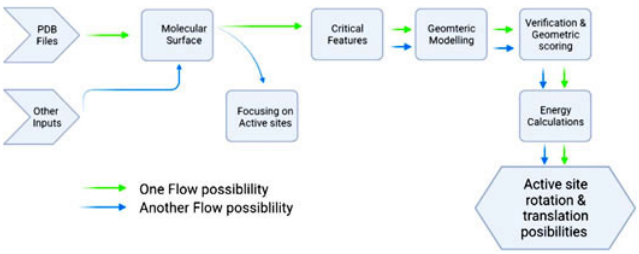

Fig. 3: Rigid and flexible docking

1.7. Models of molecular docking

1.7.1. The lock and key theory

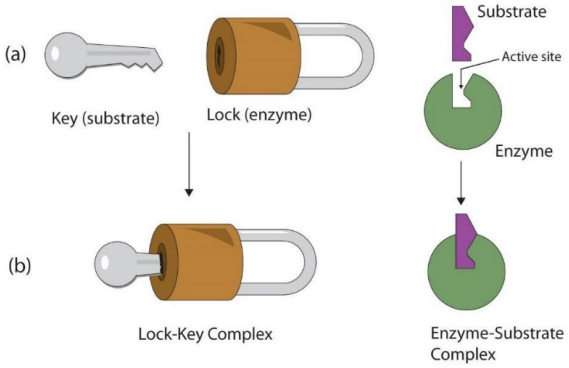

Fig. 4: Thelock and key theory

Emil Fischer created a concept termed the "lock-and-key model" in 1890, as seen in figure 4, to describe how biological processes operate.[4] A substrate is inserted into the active site of a macromolecule in the same way as a key

is inserted into a lock. In figure 4, biological locks exhibit distinct stereochemical properties that are required for their operation.[4]

1.7.2. The induced-fit theory

Daniel Koshland proposed the "induced fit theory" in 1958. The fundamental concept is that throughout the character recognition, both the ligand and target, as seen in figure 5, adapt to one another by modest conformational changes until an ideal match is reached.[4]

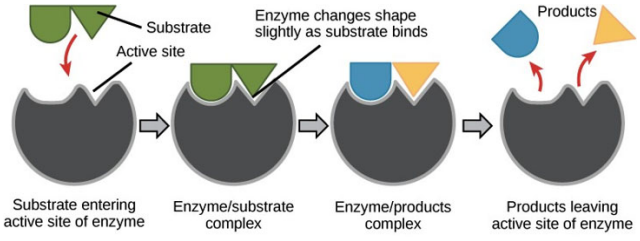

Fig. 5: Induced fit model

1.7.3. The conformation ensemble model

Apart from minor induced-fit modifications, proteins have been discovered to undergo significantly greater conformational changes. According to a new concept, proteins are composed of a pre-existing ensemble of conformational states. The protein's flexibility enables it to transition between states.[4]

2. Molecular docking approaches

2.1. Monte carlo approach

It creates a randomized conformation, translations, and rotation of a ligand in an active site. It assigns an initial configuration value.[5] Then it develops and scores a new configuration. It determines if the new configuration is kept using the Metropolis criterion. (Metropolis criterion- If a new approach outperforms the prior one, it is approved instantly.[5] If the arrangement is not novel, a likelihood study aimed at Boltzmann's law is employed. The resolution is acceptable if it satisfies the probability function test; otherwise, the arrangement is rejected).

2.2. Matching approach

This strategy emphasizes redundancy, the optimal location of the ligand atom in the site is determined, resulting in a ligand-receptor arrangement that might also need improvement.[5]

2.3. Ligand fit approach

Ligand fit is a word that refers to a quick and precise methodology for docking small molecules ligands into protein active sites while taking shape complementarity8 into account.[5]

2.4. Point complimentarily approach

These techniques are focused on comparing the shapes and/or chemical properties of different molecules. Blind Docking: This technique was developed to identify potential peptide ligand binding sites and mechanisms of action by scanning the full interface of target molecules.[5]

2.5. Fragment-based method

Fragment-based approaches may be summarized as dissolving the ligand into individual photons or particles, attaching the fragments, and lastly connecting the fragments.[5]

2.6. Distance geometry

Numerous sorts of sequence features can be represented in terms of intra- or intermolecular dimensions. The distance geometry framework enables the assembly of these distances and the calculation of three-dimensional structures that are compatible with them.[5]

2.7. Inverse docking

Understanding all these targets, when paired with a precise pharmacokinetic property, can aid in the evaluation of a drug candidate's potential for toxicities and side effects. A unique procedure is chosen for docking research on a certain ligand.[5]

3. Requirements for molecular docking

A ligand docking strategy involves the following elements: a target protein design, the compounds of interest or a database comprising existent or virtual compounds for the docking process, and a computational foundation that enables the appropriate docking and scoring methods to be implemented.[6] The majority of docking algorithms consider the protein to be stiff, whereas the ligand is often considered to be flexible. Apart from the structural degree of freedom, the bonding position of the protein in its binding pocket must be considered.[6] Docking of solid molecules or segments onto the active site of a protein can be accomplished in a variety of ways, including consensus search, geometric hashing, and pose clustering.[6]

3.1. Ligand representation

Commonly, the configuration with the highest probability of becoming predominant is further tweaked by adding or deleting hydrogen atoms to obtain estimated pKa values.[7] It is critical that precise atomic coding transpires.

3.2. Receptor representation

The integrity of the receptor structure used is critical for the effectiveness of docking simulations. Overall, the greater the resolution of the crystal lattice used, the greater the docking findings seen.[7] A recent study of the accuracy, limits, and hazards of ligand-protein complex structure refinement techniques, in general, provides a rigorous analysis of the known structures.[7]

3.3. Mechanism of docking

The initial condition for conducting a docking screen is the sequence of the specific protein. The structure is often discovered using a biophysical approach like x-ray crystallography or, less frequently, NMR spectroscopy.[7] A docking tool uses this protein function and a database of compounds as inputs. A docking program's success is contingent upon three sections: the search algorithm and the scoring mechanism]. When searching the conformational space of a protein bound to a ligand, the search space encompasses all potential directions and conformations of the protein. With current processing resources, it is difficult to exhaustively traverse the search space, which would include enumerating all potential molecular distortions and all potential translational and rotational configurations of the ligand reference to the protein at a moderate criterion of resolution.[7] The majority of docking systems in use consider flexible ligands, and others attempt to represent a dynamic protein receptor.

3.4. Applications of molecular docking

3.4.1. Applications of molecular docking in drug development

Docking is most often employed for drug discovery, as the majority of medications are composed of tiny organic compounds. Docking may be used to:

3.4.2. Hit identification

Docking in conjunction with a score function enables rapid screening of vast databases of possible medications in silico to find compounds that are capable of binding to a particular target of interest.[7]

3.4.3. Lead optimization

Docking can be used to anticipate the location and relative position of a ligand's interaction to a protein (also referred to as the binding mode or pose).[7] This data can be utilized to develop more powerful and selective analogues.

3.4.4. Remediation

Additionally, protein-ligand docking may be utilized to forecast which contaminants are degradable by enzymes. It can be utilized for the determination of the desired location, collection of the most effective medication.[7] Molecular docking can be used to identify enzymes and their mode of action**.** It can also be utilized to determine relationships between proteins**.** Molecules are screened virtually by using the remediation method.[7]

3.5. Application of molecular modeling in modern drug development

It is used to evaluate for potential harms produced by relationships with other proteins, such as proteases, cytochrome P450, and others. Docking can also be used to determine the specificity of a proposed medication against homologous proteins. Additionally, docking is a frequently utilized technique for identifying protein-protein interactions.[8] Comprehension of cellular connections helps in the comprehension of a range of processes occurring in live organisms and the identification of potential pharmaceutical targets.

3.6. Receptor preparation

It depends upon the docking software utilized. It can be used for the Selection of a structure and binding sites.[8] Frequently, hydrogens must be added, with some programmed being more position-sensitive than others.

3.7. Ligand preparation

It can Predict the pKa values for each charged atom — Implement programs for each possible charge arrangement within a specified pH range (e. g., 5-9).[8] Typically, through the use of a quantum mechanical force field, it can be used to reduce chemical structure.

3.8. Software available for docking

3.9. Gold

Genetic Enhancement and Receptor Docking make use of numerous ligand subgroups. Three terms comprise the force-field-based scoring function: The phrase "H-bonding" refers to the potential for intermolecular dispersion.[8] The word "intramolecular potential" refers to the potential for intramolecular dispersion. 71% success rate in determining the experimental binding mode for 100 protein complexes.

3.10. Autodock

Consists of a three-dimensional lattice of regularly spaced points encircling and cantered about the macromolecule's region of interest.

3.11. Flex-X

Using the "position clustering" technique, the base fragment is picked up and docked. A clustering approach is

used to combine related ligand changes into active site modifications.[8] Flexible fragments are sequentially added using MIMUMBA and assessed using the overlap function, followed by energy calculations to finish the ligand construction.[8] Final assessment using Böhm's scoring system, which incorporates hydrogen bonds, ionic, aromatic, and lipophilic terms.[8]

There is several other software are available for docking such as Hammerhead, ICM, MCDock, GOLD, GemDock, Glide and Yucca.

4. Conclusion

Molecular docking is a low-cost, safe, and simple-to-use technique that aids in the investigation, interpretation, explanation, and discovery of molecular features through the use of three-dimensional structures. Since diverse models provide inconsistent outcomes, it is vital to have a limited number of specific models that apply to extremely vast systems. Docking is a technique used to anticipate the structural interactions of two or more chemical molecules. The methodology is used in computational chemistry, computer-aided biology, and molecular systems ranging from tiny molecules to huge bio molecules and material assemblies. The majority of docking research is now focused on the interaction of a flexible ligand to a physiological receptor.

5. Source of Funding

None.

6. Conflict of Interest

The author declares that there is no Conflict of interest.

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