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OPTIMIZING PERFORMANCE OF VIRTUAL SCREENING BY USING MOLECULAR DOCKING

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ABSTRACT

Molecular docking is a computer-based method that helps scientists understand how two molecules, such as a drug (ligand) and a protein (receptor), fit and interact with each other. It predicts the binding shape, binding strength, and how they work together inside the body. Docking is widely used in drug design, helping researchers create new medicines by studying molecular interactions. Recently, it has also been used in food science to study how nutrients, food components, and even harmful substances interact with biological molecules. This method is becoming popular because it can predict experimental results, save time, and reduce the need for early laboratory testing. This review explains the basic theory behind molecular docking, the software used, and its applications in food science and safety. It also summarizes how the docking process is performed.

KEYWORDS: Molecular docking; rigid body docking; Virtual screening; flexible body docking; Nutraceutical; Computational chemistry; Probiotics.

INTRODUCTION

In molecular modeling, docking is a method used to predict how one molecule fits and attaches to another molecule to form a stable complex. By studying how a molecule rotates

and positions itself during docking, we can estimate the strength of the interaction between two molecules. This interaction strength is often measured using a scoring function.[1]

Interactions between biological molecules, such as proteins, peptides, nucleic acids, carbohydrates, and lipids, are extremely important for processes such as cell signaling. The way in which two molecules fit together can even affect the type of signal produced (for example, whether a molecule activates or blocks a receptor).[2] Therefore, docking helps scientists predict both the strength of a molecule's effect and the type of signal it might trigger.[3]

Molecular docking is widely used in structure-based drug design because it can predict how a small molecule (drug) binds to its target site on a protein. Understanding how a drug interacts with its target is essential for designing effective medicines and understanding basic biochemical processes.[4]

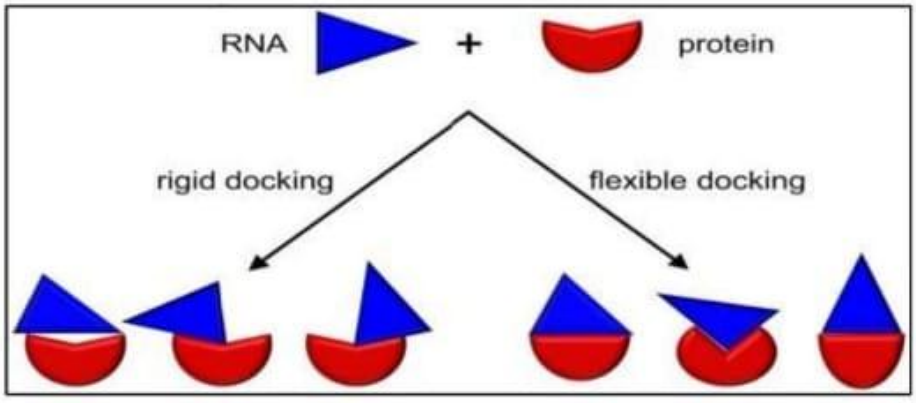

Fig. 1: Schematic diagram of docking a undersized molecule RNA (red) to a protein target (red) produce a steady compound.

Molecular docking is a computer-based method used to predict the fit of a small molecule, such as a drug, into a target protein in the body. It helps scientists understand how well a molecule can attach to a protein and the interactions that occur between them. This information is important because a drug must bind correctly to its target to function effectively. The concept of molecular docking was introduced in the 1980s. At that time, computers were slower, and the methods were simple. Over the years, as computers have become faster and algorithms have improved, docking has become more accurate and widely used. Today, it is one of the most important tools for drug discovery. Molecular docking allows researchers to simulate the binding process on a computer, instead of testing every

molecule in the laboratory. This saves time, money, and other resources By running these simulations, scientists can predict the molecules that are most likely to interact strongly with a protein.[5]

These strong interactions are important because they often lead to better drug effects. Docking also helps researchers identify the best binding site on the protein for a drug. These is known as binding sites.[6] Knowing the binding site makes it easier to design a drug that fits perfectly, similar to a key fitting into a lock. Another advantage of docking is that it allows scientists to test thousands or even millions of compounds quickly.[7] This process is known as virtual screening (VS). This helps narrow down large libraries of molecules to a smaller group of promising drug candidates. Once promising molecules are identified, docking can also help improve them.[8] Researchers can adjust the shape or chemical features of the molecule to strengthen or enhance the specificity of binding. Thus, docking helps guide the optimization of new drugs. Overall, molecular docking has become an essential component of modern pharmaceutical research.[9] It helps scientists understand molecular interactions, discover new drug candidates, and design better medicines more efficiently.[10]

Types of Docking

There are two main types:

1. **Rigid Docking**
2. **Flexible Docking**

Rigid Docking

In rigid docking, we assume that both the ligand and receptor are solid and cannot change their shape.

The goal is to move and rotate the ligand in 3D space until it fits the receptor in the best possible way, according to a scoring function.

The ligand shape (conformation) can be generated with or without considering the receptor.

Principle of Rigid Docking

The principle of rigid docking is based on the lock-and-key model, where both the receptor (usually a protein) and ligand are treated as completely rigid structures with no flexibility allowed during the docking process. In this method, the active site of the protein and the ligand maintain fixed conformations, and only the position and orientation of the ligand are

altered to find the best possible fit. The algorithm rotates and translates the ligand in different directions to identify the optimal binding pose, where the maximum interaction occurs. The binding affinity between the receptor and ligand is then calculated using a scoring function that considers interactions such as hydrogen bonding, van der Waals forces, and electrostatic interactions. Because no conformational changes are allowed, rigid docking is computationally fast, making it useful for the initial screening of large compound databases. However, because biological molecules are naturally flexible, the lack of molecular adaptation limits the accuracy of this approach. Despite this drawback, rigid docking remains important in early drug discovery, virtual screening, and the study of fundamental protein–ligand interactions.

Flexible Docking

In flexible docking, we assume that the molecules can bend and change shape. Therefore, along with moving the ligand around, we also tried to find the best shapes (conformations) of both the ligand and receptor as they would appear when they bind together.[11,12]

Principle

Flexible docking is an advanced molecular docking approach that considers the conformational flexibility of both the ligand and, in many cases, the receptor (protein). Unlike rigid docking, which keeps structures fixed, flexible docking allows for rotations, torsions, and conformational changes in the ligand, enabling the exploration of different binding poses within the active site of the target protein. Some methods also incorporate partial protein flexibility, especially in the side chains of amino acids in the binding pocket, to mimic the actual biological conditions. Energy minimization and scoring functions were applied to evaluate and rank the best binding conformations based on their affinity and stability. Algorithms such as genetic algorithms, Monte Carlo simulations, and molecular dynamics simulations are commonly used to explore conformational space. Flexible docking improves the accuracy of binding predictions and is particularly useful when dealing with large ligands, induced-fit mechanisms, and proteins with adaptable-binding sites. It plays a key role in structure-based drug design by providing realistic models of ligand–receptor interactions.

Application

1. It is used in lead optimization to evaluate how structural changes in ligands influence the binding affinity.
2. This allows a detailed study of protein–ligand interactions, such as hydrogen bonding,

hydrophobic interactions, and conformational changes.

3. It enables the virtual screening of large compound libraries with higher accuracy than rigid docking.

Approches of molecular docking

Several methods are used to perform molecular docking. These methods help predict how a ligand fits into a receptor

1. Monte Carlo Approach

The computer randomly moves and changes the shape of the ligand It checks if the new position fits better.

If it's better, it keeps it.

If it's worse, it may still keep it with a small probability (to explore more options). Repeats many times until the best fit is found.

2. Matching Approach

The program looks for matching points between the ligand and the receptor's active site. It tries to place the ligand so its atoms match the shape or key positions in the active site. Helps quickly find the best position.

3. Ligand Fit Approach

Focuses on how well the ligand shape fits into the protein pocket. It places the ligand inside the pocket and checks how well it fills the space. Fast and useful for small molecules.

4. Point Complementarity Approach

Compares chemical and physical properties at many points (charge, shape, hydrophobicity). Tries to find positions where ligand and receptor points "match" well.

Used in blind docking, where the whole protein surface is searched for possible binding sites.

5. Fragment-Based Approach

Breaks the ligand into small fragments. Finds where each fragment fits on the protein. Then joins the fragments together to form the final ligand pose. Very useful when the ligand is large or flexible.[13]

6. Simulation Approach

The ligand and the protein are kept apart at first. Then the ligand is allowed to move step-by-step toward the protein pocket.[14]

These steps include

Internal movements (changes in bond angles, twisting = torsion).

External movement (moving and rotating the entire ligand.)

Every movement creates a new shape.[15]

7. Point Complementarity Approach

Point Complementarity Approach: This approach compares the shape and chemical features of the two molecules to determine how well they match.

8. Blind docking

Scans the entire surface of a protein to identify all possible binding sites and binding modes without prior knowledge of the site.

9. Inverse Docking

This method uses computer tools to identify the proteins to which a small molecule binds. Combining this with proteomics and pharmacokinetic data helps identify the possible toxicities or side effects of drugs. One of these methods was chosen to perform docking with a specific ligand.

IMPROVING VIRTUAL SCREENING AS MULTI-STEP PROCEDURE

The success of virtual screening (finding good drug-like molecules by computer) depends not only on how well a program can place a molecule into a protein's binding site but also on several other steps**.**

One of the first important steps is to pre-process the library (the collection of molecules).

If we know enough about the protein's binding site, such as how it binds to its natural substrate or which amino acids are important, we can create a more specific and focused library. This is accomplished by filtering a large collection of molecules and retaining only those with features likely to bind well to the target protein.

To choose good molecules, the concept of similarity is used: molecules that look similar

often show similar biological activity. Therefore, to cover as many possible activities as possible, we selected diverse molecules that are structurally different from each other. This reduces the number of "redundant" molecules (those that look and behave the same).[13]

After the first filtering, the library can be filtered again. A quick rigid-body docking step is used to remove molecules that do not fit well into the protein's shape. For example, the MS-DOCK tool uses shape matching to eliminate molecules that obviously will not fit.

Post-processing is also important. Once rigid docking is performed, the remaining molecules can be tested using flexible docking (which allows movement) and then scored to determine how well they might bind. Using multiple scoring methods helps improve accuracy.

Application and Examples of Molecular Docking

Molecular docking is a primary tool used in drug discovery.

It helps scientists predict how a drug molecule fits into the target protein.

Docking is usually used together with other computer methods and laboratory experiments. It is very helpful for:

Finding new drug candidates.

Improving scoring functions (better prediction of binding).

Metabolism studies how drugs interact with enzymes, such as cytochrome P45. Below are three examples of how docking has been successfully used.

Example 1: Finding New Inhibitors for DNA Gyrase (Antibacterial Target)

DNA gyrase is a bacterial enzyme that is a target of antibiotics.

Traditional experimental screening (HTS) has failed to identify new inhibitors.

Researchers have analyzed the 3D structure of DNA gyrase using two known drugs (ciprofloxacin and novobiocin).

They observed a common binding pattern:

One hydrogen bond was donated to Asp73.

One hydrogen bond acceptance from a water molecule, Some lipophilic (greasy) parts needed for binding, Using this information, two programs (LUDI and CATALYST) searched the

chemical databases. Approximately 3000 potential compounds were selected and tested.

From these, 150 hits were found and grouped into 14 classes of compounds. Seven classes were identified as novel inhibitors.

Docking and 3D structure knowledge helped optimize these hits into powerful inhibitors.

Example 2: Docking in Cytochrome P450 and Heme Proteins

Cytochrome P450 enzymes help metabolize drugs in the body. Docking is difficult for these proteins because:

Ligands often bind to heme iron, which requires special scoring rules. The active site is highly hydrophobic (oily), making scoring difficult.

Example 3: Comparison of virtual screening (VS) and High-Throughput Screening (HTS) for PTP-1B

PTP-1B is a target of diabetes and obesity drugs. High-Throughput Screening (HTS):

We tested 400,000 compounds in the laboratory. Only 85 hits were found (hit rate = 0.021).

The best compound had an IC_{50} value of 4.2 μM. Virtual Screening (VS):

A total of 235,000 molecules were docked into the crystal structure of PTP-1B. The docking program DOCK3.5 was used.[16-22]

Concept of nutraceutical

Nutraceuticals Functional Foods: Isolated from food, whole foods (normal food items), taken as supplements, Enriched/fortified with extra nutrients, Example: Vitamin C capsule, Example: Calcium-fortified milk. Governed by different laws in many countries, it is regulated as a food product. Cardiologists prefer nutraceuticals that reduce heart disease (e.g., omega-3 fatty acids, phytosterols, and grape flavonoids). Oncologists focus on nutraceuticals that may help prevent cancer (e.g., antioxidants and detox compounds).[31-36]

Concept of Nutraceuticals in Virtual Screeninig

In virtual screening, a nutraceutical refers to any bioactive compound derived from food sources, such as plants, herbs, fruits, vegetables, or other natural products, that is evaluated using computational methods to predict its potential health benefits or therapeutic effects. These compounds include vitamins, minerals, phytochemicals, flavonoids, alkaloids, and other naturally occurring molecules with potential medicinal properties. In this context, virtual screening uses tools such as molecular docking to assess the effectiveness of

nutraceutical compounds in interacting with specific biological targets, helping researchers identify the most promising natural molecules for disease prevention or health enhancement.

Role of nutraceutical in virtual screening

Virtual screening plays a crucial role in nutraceutical research by enabling the rapid identification of bioactive compounds using computational tools, such as molecular docking. Through virtual screening, large libraries of phytochemicals or food-derived molecules can be evaluated against specific biological targets to predict their binding affinities, interaction patterns, and therapeutic potentials. Molecular docking helps simulate how these nutraceutical compounds fit into the active sites of enzymes or receptors related to various diseases, providing insights into their mechanisms of action even before laboratory studies begin. This approach significantly reduces the time, cost, and experimental effort required to discover promising nutraceutical candidates. By prioritizing the most effective compounds for further in vitro and in vivo testing, virtual screening enhances the efficiency of nutraceutical development and supports the evidence-based selection of functional food ingredients**.**

Classification of Nutraceuticals

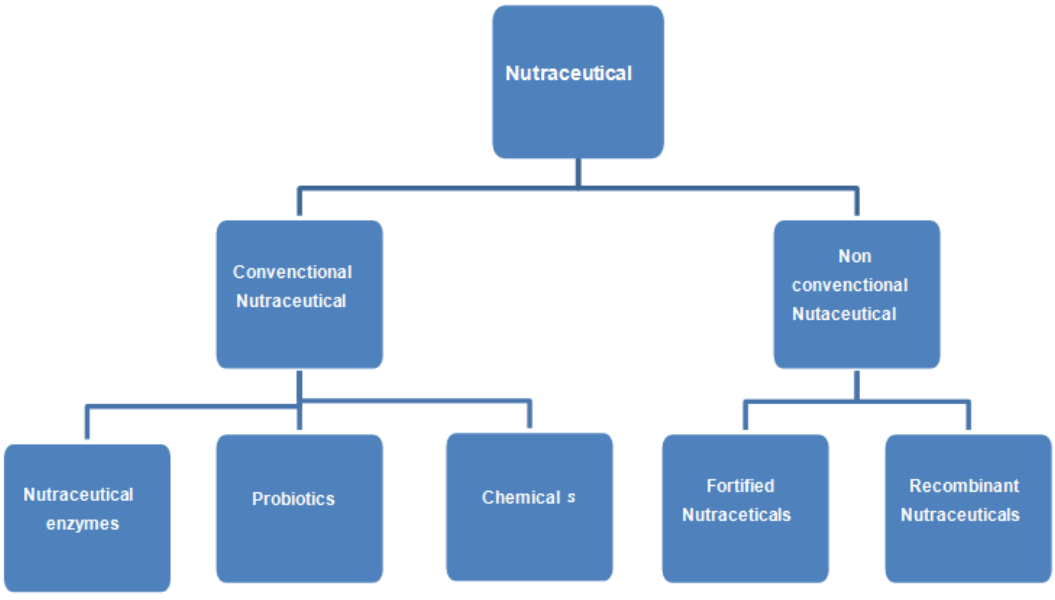

Fig. Classification of Nutraceuticals.

(Based on the Food Availability Framework (Bairagi & Patel).

1. Conventional Nutraceuticals

These have been well-known and used since ancient times. Examples include vitamins (C, D), minerals, Omega-3 fatty acids, and probiotics.[40]

They are divided into three types

a) Chemical

- Nutrients: vitamins and minerals (e.g., Vitamin D and iron).
- Herbals – plant-based (e.g., ginger, turmeric, and ginseng).
- Phytocompounds: active chemicals from plants (e.g., flavonoids and carotenoids).

Probiotic

- Live microorganisms (good bacteria) are found in yogurt, kefir, and sauerkraut.
- It helps improve gut health and immunity.

(c) Nutraceutical Enzymes

- Enzymes taken as supplements
- Digestive enzymes → help digestion
- Proteolytic enzymes → reduce inflammation

2. Nonconventional Nutraceuticals

- These come from new or unusual sources.
- Algae, fungi, insects, and animal by-products.
- Examples include Spirulina, Chlorella, mushroom extracts, and insect-based proteins.
- These are still under research for safety and effectiveness.
- Types of Non-Conventional Nutraceuticals

(a) Fortified Nutraceuticals

These foods are enriched with additional vitamins and minerals.

Example: Fortified With Purpose: Orange juice calcium + vitamin D, bone health, breakfast cereals, iron, vitamin B, prevent anemia. Milk Vitamin D, better calcium absorption, energy drinks, vitamins, and improved energy metabolism.

(b) Recombinant Nutraceuticals

These are genetically engineered using recombinant DNA technology to produce specific, beneficial substances.

Examples

1. Recombinant antibodies are used in cancer and autoimmune disease treatment.
2. Recombinant vitamins, such as Vitamin B12, for deficiency.
3. Recombinant proteins, such as insulin for diabetes.[41-46]

Abbreviation

1. MD – Molecular Docking
2. VS – Virtual Screening
3. HTVS – High-Throughput Virtual Screening
4. SBVS – Structure-Based Virtual Screening
5. LBVS – Ligand-Based Virtual Screening
6. Docking Algorithms / Software
7. AD – AutoDock
8. ADV – AutoDock Vina
9. GOLD – Genetic Optimization for Ligand Docking
10. DOCK – (Original docking program, often referred simply as DOCK)
11. MDock – (Molecular Docking tool name)
12. Smina – (Modified version of AutoDock Vina
13. Glide – (Schrödinger docking software)
14. Flexx– Fragment-based docking method
15. FRED – Fast Rigid Exhaustive Docking
16. HADDOCK – High Ambiguity Driven protein-protein DOCKing
17. ICM – Internal Coordinate Mechanics (MolSoft)
18. CDOCKER – CHARMm DOCKER (used in Discovery Studio)
19. Scoring Functions
20. SF – Scoring Function
21. PSF – Physics-based Scoring Function
22. ESF – Empirical Scoring Function
23. KSF – Knowledge-based Scoring Function

CONCLUSION

Molecular docking is a powerful tool for drug design and analysis. It helps scientists visualize molecules and easily access structural databases, which are important tools for medicinal chemists. Commercial software is also improving and is becoming easier to use.

Before performing docking, researchers carefully study the target protein and ligand (drug molecule) and select the best docking method. The flexibility of ligands is usually easy to handle, but the flexibility of proteins is more difficult and requires better techniques.

Water molecules should be included during docking because they help form hydrogen bonds, which play an important role in the interactions between the drug and the protein.

Molecular docking has developed significantly, and this review mainly discusses its types, approaches, and applications. However, challenges remain, particularly in terms of handling flexibility and improving scoring functions. Scoring functions are important because they measure how well a drug binds to a protein; however, they still require improvement.

Computer methods have successfully identified useful molecules from large databases and have aided in the design of new small drug molecules. However, the real interactions between drugs and receptors still need to be confirmed using experimental methods.

In the future, more accurate and low-cost scoring functions may enhance the power of docking. New algorithms from research and industry are being added to advanced software packages.

Molecular docking is now being used in modern fields like computational enzymology, genomics, and proteomics.

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