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Molecular docking in drug design: Basic concepts and application spectrums

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ABSTRACT

Computational approaches have become essential throughout the drug development pipeline, from initial hit identification to lead optimization and subsequent stages. The molecular docking process comprises several steps, each introducing increasing complexity. Docking techniques are used to place small molecules into the active pockets of enzymes accurately. Complementing these techniques, scoring functions estimate the biological activity of compounds by analyzing their interactions with target molecules. Molecular docking stands as one of the most widely employed computational methods in computer-aided drug design. It is extensively utilized in both academic settings and the pharmaceutical industries during the discovery of lead compounds. Central to molecular docking are two primary components: The ligand and the protein. The protein acts as the binding site where the ligand attaches to trigger a specific biological response. Molecular docking offers valuable information about how effectively a ligand can bind to a protein, a measure known as binding affinity. Since its introduction, the role of molecular docking in drug development has grown considerably, particularly in helping to decode the molecular recognition between small ligands and larger biomolecules. This review focuses on the core principles of molecular docking, along with its classification, techniques, and various applications.

Keywords: Computational approaches, Ligand, Molecular docking, Protein, Techniques in molecular modeling

INTRODUCTION

Molecular docking is a computational approach used to predict how two or more molecules interact to form a stable complex. Its primary goal is to forecast the most likely three-dimensional conformations of these molecular assemblies. While docking provides potential binding orientations, these predicted structures are further evaluated using scoring functions to rank their likelihood of occurring in a biological setting. This study reviews current advancements in computational strategies for virtual screening through molecular docking, particularly focusing on libraries of small molecules. It explores various docking methodologies, search algorithms, and scoring techniques, emphasizing their application to therapeutic targets involving proteins and nucleic acids.

BASICS OF MOLECULAR DOCKING

Docking is a commonly employed computational approach used to predict how small therapeutic molecules interact with their protein targets, specifically focusing on estimating their binding strength and biological activity. It serves as a cornerstone in the field of rational drug design.

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Given its significance in both biological and pharmacological research, substantial efforts have been directed toward enhancing docking algorithms for more accurate predictions. Essentially, docking is a computational strategy used to determine the most favorable spatial arrangement between two interacting molecules to form a stable complex. Scoring functions are then applied to quantify the binding affinity based on this predicted orientation. Signal transduction relies on the interactions among biologically essential molecules such as proteins, lipids, carbohydrates, and nucleic acids. Accordingly, docking can be utilized to predict not only the strength of these molecular interactions but also the nature of the biological signals that might result from them.^[1]

In drug development, docking helps determine how potential drug compounds align with target biomolecules, guiding the assessment of their binding affinity and activity.

This technique is therefore vital in identifying and refining the structural features of candidate drugs. The overarching aim of docking studies is to fine-tune the shapes of both the ligand and the receptor protein, along with their relative orientation, to achieve the lowest possible free energy configuration of the resulting complex.^[1]

MOLECULAR DOCKING

Docking refers to the method of positioning molecules in optimal orientations to interact effectively with a receptor. It represents a process that naturally occurs within cells in a matter of moments, where molecules come together to create a stable and lasting complex, as seen in Figure 1.^[2]

MOLECULAR MODELING

Introduction to molecular modeling

Molecular modeling refers to a collection of computational techniques used to visualize, simulate, and predict the

behavior and interactions of molecules. It plays a fundamental role in various scientific disciplines such as chemistry, biology, and pharmaceutical research. Through molecular modeling, scientists can understand the structural and functional aspects of molecules, aiding in the development of new drugs, materials, and biochemical tools.^[2]

Core techniques in molecular modeling

Several methods are used in molecular modeling, each serving different purposes. Molecular mechanics uses classical physics and force fields to predict molecular energy and stability. Molecular dynamics (MD) simulates the time-dependent motion of molecules, offering insight into their flexibility and behavior in real-time. Quantum mechanical methods are more precise and calculate electronic structures, making them useful for studying chemical reactions at the atomic level.^[3]

Protein structure and interaction analysis

Homology modeling is a powerful tool in molecular modeling, used to predict the 3D structure of a protein based on the known structure of a similar protein. Docking studies are another essential technique, used to predict how small molecules, such as drugs, bind to protein targets. These methods are crucial in drug discovery, allowing researchers to identify and optimize compounds that can interact effectively with disease-related proteins.^[3]

Advanced modeling and applications

Additional modeling approaches include pharmacophore modeling, which identifies essential features responsible for biological activity, and coarse-grained modeling, which simplifies large systems to study broader dynamics such as protein folding or membrane behavior. Molecular modeling is widely applied in drug design, toxicology,

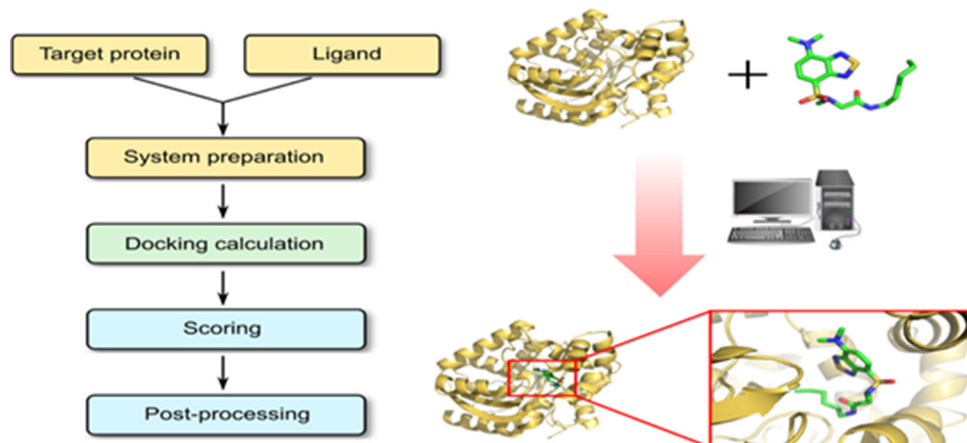


Figure 1: Molecular docking process. Red box signifies interaction between ligand and molecule. Red arrow denotes the next step in the process.

enzyme mechanism analysis, and materials science. It helps researchers test hypotheses and predict molecular behavior before conducting expensive or time-consuming experiments.^[3]

Benefits and Limitations

The advantages of molecular modeling include cost efficiency, speed, and the ability to study molecular systems that are difficult to observe experimentally. It provides atomic-level insights and supports rational drug design. However, it also has limitations, such as dependency on accurate input data and high computational demands for complex systems. Despite these challenges, molecular modeling remains an indispensable tool in modern scientific research.^[4]

Types of docking

Rigid docking

Rigid docking treats both the ligand (small molecule) and the receptor (target protein) as fixed, inflexible structures during the docking process. This method is the simplest and fastest form of docking because it assumes that neither the ligand nor the receptor undergoes any conformational changes upon binding. The process is based on the premise that the binding site remains static throughout the interaction. While computationally efficient and useful for quickly screening large libraries of compounds, rigid docking is less accurate since it ignores the natural flexibility of molecules. It is not ideal when the binding site is flexible or its structure is unknown.^[1]

Flexible docking

Flexible docking allows for movements and conformational changes either in the ligand, the receptor, or both. This category can be divided into three types: Ligand-flexible docking, where the ligand can adopt multiple conformations while the receptor stays rigid; receptor-flexible docking, where the receptor changes but the ligand remains rigid; and fully flexible docking, often called induced fit docking, where both molecules adapt their shapes during interaction. Flexible docking offers a more realistic and accurate prediction of molecular binding by capturing conformational adaptability, but it requires more sophisticated algorithms and computational resources.^[1]

Blind docking

Blind docking does not require prior knowledge of the receptor's active site. Instead, the entire surface of the protein is considered as a potential binding region, allowing the docking process to explore multiple possible pockets. This approach is particularly valuable when the location of the

active site is unknown or for newly discovered proteins. However, blind docking is computationally intensive and may generate many false positives because it explores vast regions of the protein surface without targeting specific sites.^[5]

Site-specific docking (targeted docking)

In contrast to blind docking, site-specific docking focuses on a predefined active or binding site within the receptor. This method requires prior knowledge of the binding pocket structure, allowing for a more targeted and efficient docking process. Site-specific docking is generally faster and more accurate than blind docking, as it narrows the search to biologically relevant regions. However, it is limited to cases where the active site is already known and does not allow the discovery of alternate or novel binding areas.^[5]

Covalent docking

Covalent docking models the formation of a covalent bond between the ligand and the receptor, incorporating a chemical reaction into the docking process. This method is especially important for studying irreversible inhibitors or drugs designed to form permanent bonds with their targets. Covalent docking helps predict the mechanisms of irreversible binding and is useful in designing covalent inhibitors. However, it requires detailed knowledge of the chemical reaction involved and is more complex to simulate and validate compared to non-covalent docking.^[6]

Molecular Dynamics -assisted Docking

This method integrates molecular docking with MDs simulations to consider the flexibility and real-time movements of both the ligand and receptor. By simulating how molecules move and interact over time, MD-assisted docking refines predicted binding poses to reflect dynamic biological conditions more accurately. While this approach offers high precision and realistic modeling, it demands significant computational power and specialized hardware, making it resource-intensive.^[7]

Ensemble docking

Ensemble docking uses multiple receptor conformations instead of a single static structure. These conformations are often derived from MDs simulations or different crystal structures. By docking ligands to an ensemble of receptor shapes, this technique captures the dynamic nature of proteins more comprehensively than single-structure docking. Ensemble docking improves prediction accuracy but increases complexity and requires careful selection and management of receptor conformations.^[8]

Fragment-based docking

Fragment-based docking involves docking small molecular fragments rather than entire ligands into the binding site. These fragments can later be linked or grown into full-sized ligands during the drug discovery process. This approach is efficient for identifying novel chemical scaffolds and designing high-affinity compounds by combining multiple fragments. However, it relies on having a well-curated fragment library and can be challenging in terms of effectively linking fragments to create potent ligands.^[8]

Reverse docking

Reverse docking flips the typical approach by docking a single ligand against multiple protein targets. This method is useful for predicting off-target interactions, potential side effects, and drug repurposing opportunities. It aids in identifying alternative protein targets for a compound, which is valuable in designing multi-target drugs. The downside is that it requires access to large protein databases and can result in numerous low-affinity or irrelevant binding predictions, demanding careful analysis to identify meaningful results.^[9]

MODELS OF MOLECULAR DOCKING

The lock and key theory

The Lock and Key Model is a foundational concept used to explain how molecules, such as drugs and proteins, interact. In this model, the receptor (often a protein or enzyme) acts as a “lock” with a specific, rigid shape, while the ligand (a small molecule) acts as the “key” that fits precisely into the receptor’s binding site. This perfect fit between the ligand and receptor leads to the formation of a stable complex, which can trigger a biological response.^[1]

This model assumes that both the ligand and receptor are rigid structures and that no conformational changes occur during binding. The specificity of molecular interactions is explained by the complementarity in shape, size, and chemical properties between the ligand and its binding site. Because of this rigid fit, the Lock and Key Model has been widely used as a basis for rigid docking techniques in molecular docking studies, where both molecules are considered inflexible.^[1]

The lock and key model has its limitations. Many proteins and ligands are flexible and can adjust their shapes upon binding, a phenomenon not accounted for by this model. More advanced models, such as the induced fit model, address these dynamic changes by considering molecular flexibility. Despite its simplicity, the lock and key model remains important for understanding the initial concept of molecular recognition and is still relevant for certain docking scenarios.

The induced fit theory

The induced fit theory was first proposed by Daniel Koshland in 1958 as an improvement over the traditional lock and key model, which was introduced by Emil Fischer in 1894. While the lock and key model suggested that the enzyme’s active site and the ligand have complementary rigid shapes, Koshland observed that many enzymes and receptors undergo structural changes upon ligand binding. This insight led to the induced fit theory, which better explains the flexibility and adaptability seen in biological molecules.^[10]

According to the induced fit theory, the receptor’s binding site is not a fixed, rigid structure but rather flexible and capable of adjusting its shape when a ligand approaches. The initial contact between ligand and receptor triggers conformational changes in the receptor, allowing it to mold around the ligand for a tighter, more specific fit. This dynamic interaction enhances binding affinity and specificity, accommodating a wider range of molecules than a rigid model would allow.^[10]

Today, the induced fit theory is widely accepted and forms the basis for many modern molecular docking and drug design methods. It underpins flexible docking techniques where both ligand and receptor can change shape during interaction. This model provides a more accurate and realistic understanding of molecular recognition in complex biological systems, reflecting the dynamic nature of proteins and their interactions with ligands.^[10]

The conformational ensemble model

The conformational ensemble model emerged from advances in molecular biology and computational simulations in the late 20th century, as scientists recognized that proteins are not static structures. Early models, like lock and key and induced fit, could not fully explain the dynamic behavior observed in proteins. Research using techniques such as MDs simulations revealed that proteins exist in multiple conformations simultaneously, forming an ensemble of structures even before a ligand binds.^[10]

This model suggests that ligands bind by selecting and stabilizing one or more favorable conformations from this pre-existing ensemble, rather than inducing a shape change after binding. This explains how proteins can be highly specific yet flexible, accommodating diverse ligands and regulatory molecules.

MOLECULAR DOCKING APPROACHES

Monte Carlo approach

First, a random position and shape of the ligand are created inside the active site. This starting setup is given a score. Then, a new position and shape are made and scored again.

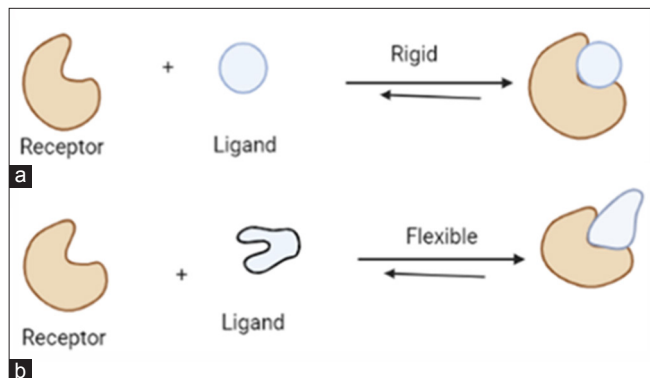


Figure 2: (a and b) Theory of rigid and flexible docking.

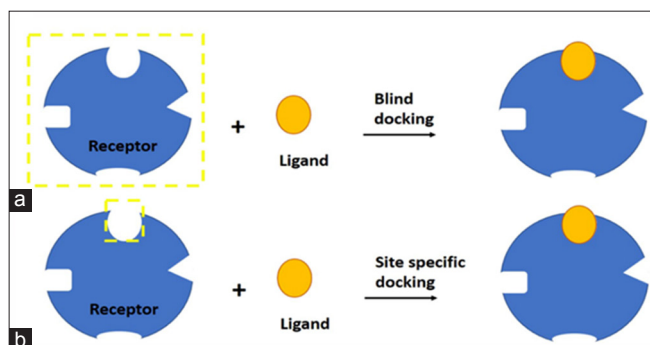


Figure 3: (a and b) Theory of blind and site specific docking.

Figure 2 illustrates the concepts of rigid and flexible docking approaches.^[1] Blind and site-specific docking strategies are depicted in Figure 3.^[5] If the new setup is better, it is accepted right away. If it is not better, it might still be accepted based on a probability that depends on how much worse it is. If the probability test passes, the new setup is kept; if not, it is rejected.^[11]

Matching approach

The matching approach is a molecular docking method where the shape and features of the ligand are matched to the binding site of the receptor. It works by comparing the geometric and chemical properties of both molecules to find the best fit. In this method, the ligand is positioned into the binding pocket in multiple orientations and conformations. The docking program looks for complementary shapes, electrostatic charges, and hydrophobic regions between the ligand and receptor. The best matches, which show the highest complementarity, are scored and ranked. This approach is generally faster and easier to implement because it focuses on matching surface features rather than simulating complete flexibility. However, it may be less accurate when the molecules undergo significant changes during binding.^[11]

Ligand fit approach

The ligand fit approach focuses on fitting the ligand into the receptor's binding site by exploring different shapes and positions of the ligand. It tries various conformations of the ligand to find the best fit inside the protein's active site. This approach helps identify how well a ligand can bind based on its shape and flexibility.^[11]

Point complementarity approach

This method focuses on comparing the shapes and chemical characteristics of different molecules to evaluate their compatibility.

Blind docking

Blind docking scans the entire surface of a target molecule to identify possible peptide ligand binding sites and understand their mechanisms of action, without prior knowledge of the binding location.

Fragment-based method

This approach breaks the ligand down into smaller fragments or particles, docks these pieces individually, and then connects them to reconstruct the full ligand.

Distance geometry

Various sequence features can be expressed as distances within or between molecules. The distance geometry technique uses these distances to build three-dimensional structures that fit these spatial constraints.

Inverse docking

By analyzing multiple potential targets along with accurate pharmacokinetic data, inverse docking helps predict a drug candidate's likelihood of causing toxicity or side effects. A specialized docking procedure is chosen for studying a particular ligand.

REQUIREMENTS FOR MOLECULAR DOCKING

A ligand docking approach requires several key components: A well-defined target protein structure, a set of compounds of interest or a database containing existing or virtual molecules for docking, and a computational platform capable of performing the docking and scoring procedures accurately. Most docking methods treat the protein as rigid, while allowing flexibility in the ligand. In addition to accounting for the ligand's structural flexibility, it is important to consider the protein's binding site and how the ligand fits within it. Docking of molecules or molecular fragments into

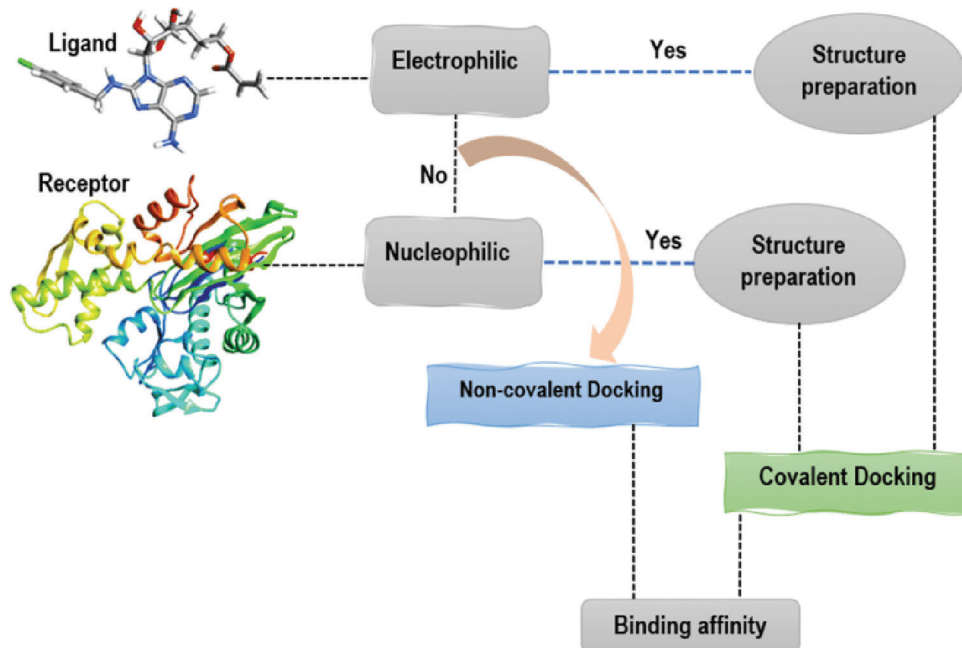


Figure 4: Scheme describing the workflow of covalent docking in drug discovery.

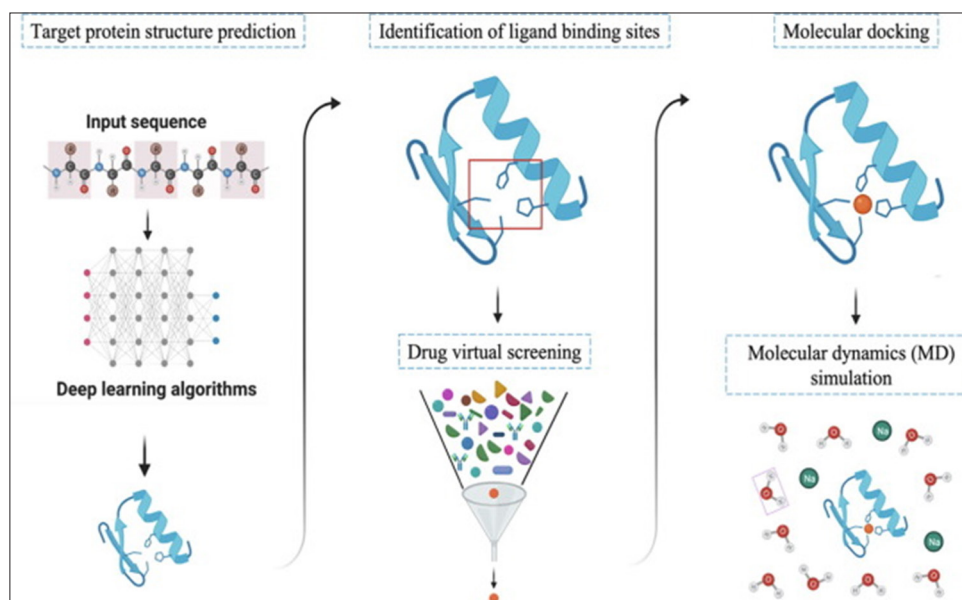


Figure 5: The basic steps involved in the molecular dynamics method.

the protein's active site can be carried out using techniques such as consensus search, geometric hashing, and pose clustering.^[12] The covalent docking workflow is summarized in Figure 4.^[6] Figure 5 outlines the fundamental steps of molecular dynamic simulations.^[7]

Ligand representation

In most cases, the molecular structure that is most likely to dominate under specific conditions is selected for further

refinement. This refinement involves the careful addition or removal of hydrogen atoms to accurately estimate the molecule's pKa values, which indicate how it will behave in different pH environments. During this process, it is essential to ensure that the atomic-level details are represented with high precision, as any inaccuracies can lead to incorrect predictions of chemical behavior and binding interactions.^[12]

Receptor representation

The quality of the receptor structure plays a vital role in ensuring reliable docking results. In general, higher-resolution crystal structures lead to more accurate docking outcomes. A recent evaluation of ligand–protein complex refinement methods offers a detailed review of the reliability, limitations, and potential risks associated with currently available structural data.^[12]

MECHANISM OF DOCKING

To start a docking study, the first requirement is the amino acid sequence of the target protein. The 3D structure of the protein is usually obtained using biophysical methods such as X-ray crystallography, and sometimes through nuclear magnetic resonance (NMR) spectroscopy. Docking software uses this protein structure, along with a database of chemical compounds, to predict how ligands will interact with the protein.

The success of a docking program mainly depends on three key parts: How it searches for possible fits (the search algorithm),

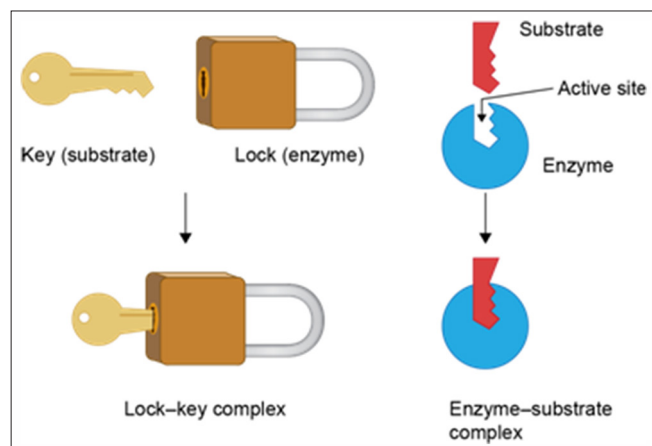


Figure 6: The lock and key hypothesis of enzyme–substrate binding.

how it evaluates those fits (the scoring function), and how it handles the input data. During docking, the software explores many different shapes and positions the ligand might take when binding to the protein. However, due to limited computing power, it's not possible to test every possible movement, rotation, or shape change of the ligand and protein in full detail. The lock and key hypothesis is illustrated in Figure 6.^[10]

Most docking tools assume that the ligand is flexible, meaning it can change shape during binding. Some advanced programs also try to model proteins as flexible or dynamic to make the results more accurate.^[11]

APPLICATION OF MOLECULAR DOCKING

Drug discovery and design

Molecular docking is a key technique in early drug discovery, where it predicts how small molecules (potential drugs) fit into the binding sites of disease-related proteins. This helps researchers identify promising compounds that can interact strongly and specifically with these targets, speeding up the identification of new medicines.^[12,13]

Lead optimization

Once initial drug candidates are found, molecular docking helps scientists refine these molecules by exploring different chemical modifications. This process improves how tightly the molecule binds (binding affinity), enhances its selectivity for the target protein, and reduces unwanted interactions, ultimately producing more effective drugs.^[12,13]

Understanding molecular interactions

Docking reveals detailed insights into the types of forces that hold a drug and protein together, such as hydrogen bonding, electrostatic forces, and hydrophobic interactions. Understanding these at an atomic level allows researchers to design molecules that form optimal contacts, increasing drug efficacy.^[12,13]

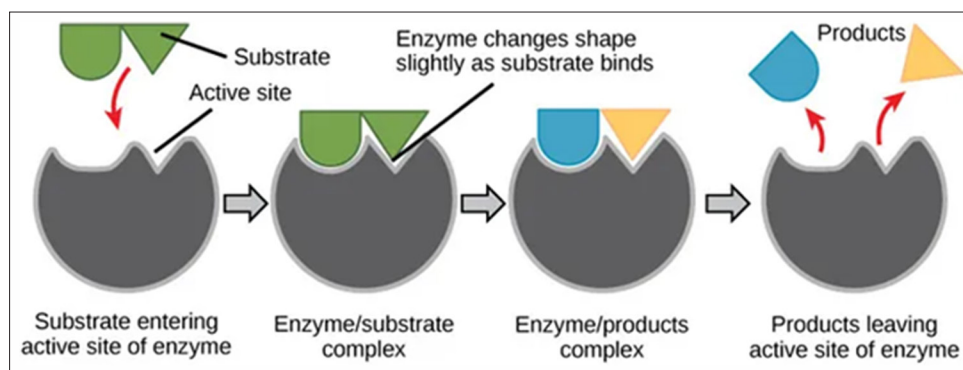


Figure 7: The induced fit theory.

Predicting binding modes and affinity

A key goal of docking is to predict the exact orientation (binding mode) of a ligand inside a protein's active site. It also estimates the strength of this interaction (binding affinity). These predictions help prioritize compounds likely to have strong biological effects for further experimental testing.^[12,13] The induced fit theory is depicted in Figure 7.^[10]

Virtual screening

Docking is used to rapidly screen large libraries containing millions of compounds against a protein target computationally. This process narrows down the list to the most promising candidates, saving time and cost compared to traditional laboratory-based screening methods.^[12,13]

Enzyme inhibitor design

Many diseases involve enzymes that malfunction or become overactive. Docking aids in designing molecules that fit into the enzyme's active site and block its activity. This strategy is widely used for developing drugs for conditions such as cancer, viral infections, and bacterial diseases.^[12,13]

Studying protein-protein or protein-DNA interactions

Beyond small molecules, docking can model how proteins interact with other proteins or DNA. These interactions are crucial in many cellular processes such as gene regulation and signal transduction. Understanding these helps in designing molecules that can modulate these interactions for therapeutic purposes.^[12,13]

Drug repurposing

Docking can screen existing drugs against new protein targets to find alternative therapeutic uses. This repurposing approach can shorten drug development timelines and reduce costs because the safety profiles of these drugs are already known.^[12,13]

Toxicity prediction

By docking drugs against a wide range of proteins, scientists can predict possible off-target interactions that may cause side effects or toxicity. Early identification of such risks helps in designing safer drugs and reducing late-stage failures.

Antibody-antigen interaction studies

In immunology, docking is used to study how antibodies recognize and bind to antigens such as viral proteins. This helps in vaccine design and the development of antibody-based therapies by identifying the key binding sites.^[12,13]

Understanding resistance mechanisms

Drug resistance often arises when mutations alter a protein's structure, weakening drug binding. Docking studies can simulate these mutations and predict how they affect binding affinity, guiding the design of new drugs that overcome resistance.^[12,13]

Personalized medicine

Since genetic differences cause variations in protein structure among individuals, docking can help tailor drugs that fit the patient's unique protein variants. This personalized approach aims to maximize treatment effectiveness and minimize side effects.^[12,13]

Nanotechnology and drug delivery

Docking supports the design of nanomaterials and drug carriers by modeling how these materials interact with biological molecules. This improves targeted delivery of drugs to specific tissues or cells, enhancing efficacy and reducing toxicity.^[12,13]

Environmental chemistry

Docking is used to study how environmental pollutants or chemicals bind to biological targets, which helps assess their potential harmful effects on humans, animals, and ecosystems. This information is valuable for environmental safety and regulatory decisions.^[12,13]

Agricultural and pesticide development

In agriculture, docking helps design pesticides that specifically bind to proteins unique to pests, minimizing harm to beneficial organisms and humans. This selectivity improves pesticide safety and effectiveness.^[12,13]

Allosteric modulator design

Not all drugs bind at the active site; some bind to allosteric sites, which regulate protein activity indirectly. Docking helps identify and design such allosteric modulators that can fine-tune protein functions, offering new therapeutic strategies.^[12,13]

Synthetic biology and enzyme engineering

Docking aids in designing new or modified enzymes with improved or novel functions. This is useful in industrial applications such as biofuel production, food processing, and pharmaceuticals by predicting how substrates interact with engineered enzymes.^[12,13]

SOFTWARES AVAILABLE FOR DOCKING

AutoDock

AutoDock is widely used free software that helps scientists predict how small molecules, called ligands, fit into proteins. It allows the ligand to move and change shape (flexible ligand), while usually keeping the protein rigid. This flexibility helps find the best way the ligand can bind to the protein, which is important for drug design. AutoDock uses a scoring system to estimate how strong the interaction is.^[14]

AutoDockVina

AutoDockVina is an improved version of AutoDock. It works faster and often provides more accurate results. The software is also easier to use and requires less manual setup. AutoDockVina uses a better algorithm that searches the possible binding positions more efficiently, making it great for screening many compounds quickly.^[14]

DOCK

DOCK is one of the first docking programs developed. It usually treats the protein as a rigid structure and places the ligand into the protein's active site based on shape complementarity. Although this makes DOCK less flexible compared to newer programs, it is still valuable for quick initial docking and when the binding site is well known.^[14]

Glide

Glide is a commercial software popular in pharmaceutical companies due to its high accuracy. Unlike rigid docking, Glide allows both the protein and the ligand to adjust their shapes slightly during the docking process (flexible docking). This flexibility helps capture how molecules truly interact in the body. Glide also uses advanced scoring functions to predict how tightly a drug will bind.^[14]

Genetic optimization for ligand docking (GOLD)

GOLD uses a genetic algorithm, which mimics natural selection to find the best docking poses. It generates many different binding possibilities and evolves them to optimize fit and interaction energy. Both ligand and protein flexibility are considered, which improves the prediction of realistic binding modes.^[14]

FlexX

FlexX speeds up the docking process by breaking the ligand into small fragments. It docks these fragments into the protein's binding site one by one and then reconstructs the full ligand inside the site. This piece-by-piece approach

allows FlexX to quickly explore many ligand conformations, making it useful for screening large compound libraries.^[14]

Molecular operating environment (MOE)

MOE is an all-in-one software suite that includes docking tools, molecular modeling, simulations, and visualization. It is user-friendly, designed for both beginners and experts, and supports flexible docking with customizable options. MOE also integrates other drug discovery workflows, making it a popular choice for research labs.^[14]

SwissDock

SwissDock is a web-based docking tool, meaning you don't have to install anything on your computer. You upload your protein and ligand files online, and the docking runs on their servers. It is easy to use, making it great for students and researchers who want quick docking results without technical setup.^[14]

PatchDock

PatchDock specializes in shape-based docking, focusing on how the surfaces of two molecules fit together, like puzzle pieces. It is widely used for docking large molecules such as protein-protein complexes, protein-DNA, or protein-RNA interactions. PatchDock scores solutions based on surface complementarity and geometry.^[14]

High Ambiguity Driven DOCKing (HADDOCK)

HADDOCK is designed for docking larger biomolecules and can use experimental data (such as NMR or mutagenesis data) to guide the docking. This data-driven approach helps improve the accuracy when docking proteins with other proteins or nucleic acids, making it ideal for studying complex biological systems.^[14]

CONCLUSION

Molecular docking is an economical, safe, and straightforward technique that assists in analyzing and interpreting molecular characteristics using 3D structures. Since different models can produce varied results, it is important to choose a limited set of specific models suitable for very large systems. Docking is used to predict how two or more chemical molecules will interact structurally. This method is applied in fields such as computational chemistry, computer-aided biology, and studies of molecules ranging from small compounds to large biomolecules and material complexes. Most current docking studies focus on the interaction between a flexible ligand and a biological receptor.

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