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Molecular Docking vs. Molecular Dynamics: Comparative Approaches Driving Drug Discovery

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ABSTRACT :

Molecular docking and molecular dynamics (MD) are two essential computer-based methods that have changed how new drugs are discovered today. Both methods focus on understanding how biomolecules interact with possible drug molecules, but they work in different ways and offer useful information that complements each other. Molecular docking is popular because it quickly predicts how small molecules will bind, their arrangements, and their strengths at specific binding sites. It acts like a tool that helps scientists quickly reduce many compounds to find the most promising options. However, docking usually assumes that biomolecules are rigid and might overlook the flexible nature of how proteins and ligands interact. On the other hand, molecular dynamics simulations give detailed insights into how biomolecules can change shape, stay stable, and their energy changes over time. MD observes important processes, like how molecules fit together, how they are surrounded by solvent, and long-term changes in their structure, which docking alone cannot fully show. Together, these techniques create a strong partnership in systematic drug design: docking speeds up the process of finding possible drug candidates, while MD checks and improves docking results by examining the structure and energy details more closely. Despite improvements in algorithms and computing resources, both methods have some challenges, such as inaccuracies in scoring in docking and high computing expenses in MD. This review looks at molecular docking and molecular dynamics side by side, highlighting their basic ideas, uses, strengths, and weaknesses. By combining these different methods, researchers can gain a deeper understanding of how drugs interact with their targets, which can lead to better accuracy and success in drug discovery efforts.

Keywords: Molecular docking, Molecular dynamics, Drug discovery, Protein–ligand interactions, Computational chemistry, Structure-based drug design, In silico methods

Introduction:

While methods like molecular docking and molecular dynamics mainly assess how well a drug works by estimating how it binds and stays stable with its target, ADMET modeling is essential for determining whether a drug can succeed in clinical trials. The safety and effectiveness of drugs rely on a careful balance of various factors related to how the body processes the drugs, which include absorption, distribution, metabolism, excretion, and toxicity, collectively known as ADMET. Improving these mixed factors is still a big hurdle in drug research. As a result, there has been notable progress in creating computer tools that can predict ADMET outcomes during the early stages of drug development, from finding potential drug leads to refining those leads [1].

The skill to accurately simulate and forecast how molecules interact has significantly sped up the process of finding new drugs. This has helped in discovering new compounds and advancing treatments for various diseases, including serious infectious diseases. Molecular docking has become a very useful method in the drug development process, as it allows scientists to measure how well different substances bind, anticipate how they will fit together, and check how stable the pairs of molecules are. By lessening the need for expensive and lengthy lab experiments, docking makes it easier to prioritize and improve possible new medicines. In the end, this ability to predict helps in choosing which compounds should move forward for further testing in the lab and eventually in clinical trials [2,3,4,5,6]

Molecular docking is a popular computer-based method that is very important in finding and creating new drugs by figuring out how small molecules fit with certain target proteins. This process gives valuable information about how ligands and proteins work together, which helps in designing and making new treatments. Starting in the 1980s, this area has changed a lot thanks to improvements in algorithms, scoring methods, and computer power, making it much better at predicting how things will bind. Nowadays, molecular docking is a fundamental part of drug research, helping to find good medicine

candidates and improve how well they connect with their targets. It helps scientists to model and study drug-target combinations, guess where they might bind, and boost how strongly and specifically they connect. Additionally, molecular docking is widely used for quickly screening large collections of compounds, speeding up the discovery of potentially useful molecules [7,8,9].

The creation of new medicines is still one of the toughest tasks in today's science, needing teamwork from the pharmaceutical sector, biotechnology firms, regulatory bodies, university scientists, and both government and private organizations. This collaborative and demanding process has not only resulted in finding safer and more efficient treatment options but has also helped improve scientific understanding by encouraging the creation of advanced tools and methods for designing and refining drugs. A key achievement in this process was finishing the Human Genome Project, which was originally thought to provide many new targets for drugs. However, the roughly 30,000 genes discovered did not create a straightforward way to develop drugs because treatments usually target proteins instead of genes. The proteome is much larger and more complicated, adding extra difficulties since proteins go through modifications after translation, interact with other molecules and cofactors, and combine into larger complexes, making it harder for them to be used as targets for drug development [10].

The success of today's treatments for tuberculosis (TB) has been greatly affected by the rise of drug resistance. This resistance mainly happens due to changes in the genes that are targeted by medications, which makes the standard treatments less effective. The situation is made worse when TB occurs alongside human immunodeficiency virus (HIV), creating difficulties in treatment results and increasing the overall impact of the disease worldwide. In recent years, the worrisome growth of multidrug-resistant tuberculosis (MDR-TB), extensively drug-resistant tuberculosis (XDR-TB), and recently, totally drug-resistant tuberculosis (TDR-TB), has deepened the problem and represents a serious risk to global public health. These resistant strains greatly reduce the available treatment options, making it harder to manage TB and highlighting the urgent need for new medicines and effective treatment plans [11,12,13].

On the flip side, simulations of molecular dynamics that include clear solvent molecules make it possible to closely look at how these solvents affect the shape of proteins, their ability to change form, and their general stability. These types of simulations give important information about the general features of biomolecular systems, such as their density, ability to conduct electricity, and dipole moment. Additionally, they allow for the assessment of key thermodynamic factors like interaction energies, shifts in free energy, and entropy, thus providing a thorough insight into how biomolecules act in conditions that are relevant to living organisms [14].

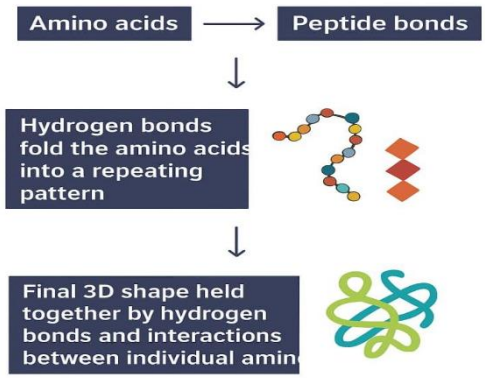
Over Review Molecular docking

Molecular docking is a computer-based method commonly used in the search for new drugs to simulate and forecast how small substances interact with biological receptors. This technique imitates a natural process in cells, where molecules quickly come together to create stable combinations in just a few seconds. Using sophisticated algorithms, molecular docking estimates how and where these small molecules, known as ligands, attach to their target proteins. This helps scientists understand the structural aspects of how molecules recognize each other and allows them to focus on compounds that show a good potential to become effective drugs. Typically, docking studies produce multiple ways the ligands can bind, which are then ranked using scoring functions that measure both the strength and stability of the interaction. For ligand docking tests, it is usually necessary to have a specific protein structure, a small molecule ligand, a database of virtual compounds, and a computer system that can effectively search through different shapes of the molecules. In many docking methods, the protein is generally treated as a stable structure, while ligands are seen as flexible, allowing them to take on various forms. Various computational techniques are used to make precise predictions, such as clique searching, geometric hashing, and clustering different poses. Additionally, special algorithms like point complementarity, Monte Carlo simulations, methods based on fragments, genetic algorithms, and distance geometry improve the accuracy and efficiency of docking, aiding in the thoughtful design of medications [15,16,17,18,19,20,21,22,23,24]

Molecular docking has three main goals: to screen large chemical collections, to predict how ligands will bind, and to estimate how strong the binding is. For docking to work well, it needs to tell apart real binding sites from areas where binding does not happen, while also describing the molecular interactions that hold the ligand and receptor together. Additionally, when used with large groups of compounds, strong docking methods should be able to identify which molecules are active and which are not and rank the active ones as the most promising candidates [25,26].

X-ray crystallography and nuclear magnetic resonance (NMR) spectroscopy are two of the most effective methods used to find out the precise three-dimensional shapes of biomolecules when they are functioning. These techniques give important information about key amino acids, how molecules interact with each other, the strength of weak bonds, the energy involved in binding, and how well the shapes of interacting molecules fit together. However, these methods face some difficulties, like problems with crystallizing certain proteins, restrictions on size, and the high cost and time it takes to gather data. Because of these challenges, the three-dimensional shapes of many proteins are still unknown and missing from the Protein Data Bank (PDB).To address these issues, bioinformatics-based methods like homology modeling have been created, helping scientists predict the structure of a target protein when there is no experimental data available. Homology modeling is based on the idea that proteins that have similar sequences of amino acids usually have similar shapes, showing their common evolutionary background. By using the structure of a known protein as a guide, researchers can model the three-dimensional shape of a related target quite accurately. One of the most popular online tools for homology modeling is the Swiss-Model Server. It offers automated steps for finding templates, aligning sequences, building models, and validating them, making it easy for both experts and beginners to use. These computer-based methods have become essential for current structural biology, discovering new drugs, and designing effective therapies [27]

Fig:1 3DStructure Of Molecular Docking in Amino Acid Sequence [28]



Types Of Molecular Docking and Its Methods

Rigid docking

In rigid docking, which is also known as rigid-body or geometric docking, the ligand, which is a small molecule, and the receptor, which is a target protein, are both considered unchanging during the docking process. This method is quick and works well for predicting how these substances bind at the atomic level, making it ideal for large virtual screening projects. However, because it does not account for the shape changes that can happen when a ligand attaches, rigid docking may overlook how proteins and ligands can move. As a result, even though it gives valuable initial information, it might not be as accurate as flexible docking methods [29,30].

Methods of rigid docking

Several computational algorithms and software tools have been developed for rigid docking. These methods generally involve the following steps

Preparation:

In molecular docking, it is important to carefully prepare the shapes of both the receptor and the ligand to make sure the results are precise. This usually means taking out water molecules that are part of the crystal structure, adding hydrogen atoms, giving correct partial charges, and adjusting the shapes of the molecules if needed. These steps before the actual docking are crucial for enhancing the trustworthiness and effectiveness of the predictions.

Search algorithm:

Docking methods use different searching techniques to carefully examine the shape and arrangement of ligands and find the best fitting positions within the active site of a target. The goal of these techniques is to find a good balance between speed and correctness in predicting where the ligand will fit. Frequently used strategies consist of geometric hashing, Monte Carlo methods, methodical grid searches, and evolutionary approaches like genetic algorithms, each providing unique benefits in tackling the challenges of ligand-receptor interactions and improving binding efficiency.

Scoring function:

After creating several possible positions for the ligand, docking software uses scoring methods to assess and rank these shapes based on expected binding strength. These methods look at how stable the ligand-receptor combination is by examining important physical and chemical factors, such as shape matching, electrical attractions, van der Waals forces, and the energy involved in removing water molecules. By measuring these connections, scoring methods assist in finding the most likely ways the ligand can bind and aid in choosing ligands for additional testing and development of new drugs.

Post-processing and analysis:

Finally, techniques for post-processing are used to enhance the suggested binding arrangements and give a clearer evaluation of how ligands and receptors interact. These techniques usually include reducing energy, re-evaluating scores, or using molecular dynamics simulations to enhance the accuracy of shapes. Moreover, advanced visual tools allow scientists to closely study the linked complexes, making it easier to find important binding sites, hydrogen bonds, hydrophobic connections, and other essential interactions that help maintain ligand stability and specificity in the active site [31,32,33]

Flexible docking

Flexible docking gives room for movement in either the ligand, the receptor, or sometimes when they connect. This helps to recognize changes in shape and can lead to better guesses about how they fit together. Flexible docking, which can also be called flexible ligand docking or induced-fit docking, is a computer method used in molecular modeling. It helps to estimate how a ligand will bind to a receptor and how strong that bond will be while considering that both the ligand and the receptor can change shape. Unlike rigid docking, which assumes that the ligand and receptor stay stiff and unchanging when they connect, flexible docking looks at how both the ligand and receptor might change shape when they latch onto each other [34].

Methods of flexible docking

Methods typically involve the following steps:

Conformational Sampling:

Unlike fixed docking methods, flexible docking allows for different shapes by examining various structural forms of both the ligand and the receptor while they connect. This method provides a better understanding of the different shapes that can occur, helping to find binding positions that are both energetically stable and biologically important. Flexibility is achieved through computer-based methods like molecular dynamics simulations, which track how atoms move over time, normal mode analysis, which looks at how structures change collectively, or systematic search algorithms that test many different angles and shapes to improve the interactions between the ligand and the receptor more effectively[35].

Docking algorithm:

Docking algorithms used in flexible docking combine the exploration of different shapes with traditional searching methods to better determine the best fitting position of a ligand in a flexible receptor binding area. These approaches create several shapes of the ligand and receptor, which are then evaluated using scoring tools that measure how well they stick together and how stable they are. By analyzing how well each shape fits, the algorithms effectively steer the search towards the most advantageous binding positions, enhancing prediction accuracy in comparison to fixed docking techniques [36].

Scoring function:

In flexible docking, scoring functions are very important for measuring how the ligand and receptor interact with each other and for ordering predicted binding positions based on their stability and attraction. These functions usually include various factors, such as the shape fit, electrical interactions, van der Waals forces, the effects of being surrounded by solvents, and the changes in shape of the ligand or receptor. By bringing all these elements together, scoring functions assist in finding the best binding arrangements and aid in choosing possible drug options [37].

Induced-Fit modeling:

In some adaptable docking methods, techniques for induced-fit modeling are used to clearly show the shape changes in the receptor when a ligand attaches. These techniques can involve adjusting flexible side chains, refining loops, or, in more sophisticated instances, allowing for complete backbone flexibility. By considering structural changes at various levels of the receptor, induced-fit docking offers a more accurate depiction of how molecules recognize each other and enhances the reliability of predicted binding arrangements, especially in cases where the ability to change shape is very important [38].

Post-processing and analysis:

After creating several possible positions for the ligands, additional processes are used to improve the predicted docking results and give a clearer picture of ligand-receptor interactions. These processes might involve reducing energy, re-evaluating scores, or running brief molecular dynamics simulations to enhance shapes. Furthermore, sophisticated visualization tools help scientists take a closer look at the docked complexes, making it easier to find important binding sites, hydrogen bond connections, non-polar interactions, and changes in shape that are crucial for grasping molecular recognition and enhancing binding predictions [39].

Table:1 Tools And Software in Molecular Docking Drug Design [40,41,42]

Tool / Software	Application in Drug Design
Auto Dock / Auto Dock Vina	Widely used for predicting ligand–receptor binding modes and affinities; supports flexible ligand and receptor docking.
Glide (Schrödinger)	High-accuracy docking and scoring; widely applied in lead optimization and structure-based drug design.
GOLD (Genetic Optimization for Ligand Docking)	Employs genetic algorithms, effective for flexible docking and screening compound libraries.
MOE (Molecular Operating Environment)	Integrates molecular docking with QSAR, pharmacophore modelling, and visualization, useful for drug discovery pipelines.

Swiss Dock	Web-based, user-friendly docking server for virtual screening in early drug discovery.
DOCK (DOCK6)	One of the earliest docking programs; applies fragment-based and flexible [docking] approaches for ligand screening.
Py Rx	GUI-based virtual screening tool integrating Auto Dock and Vina; suitable for large compound libraries.
Le Dock	Lightweight, fast, and accurate docking tool; useful in high throughput drug design studies.
Flex X	Fragment-based incremental construction approach; effective for structure-based drug design.
R Dock	Open source docking program; optimized for both protein and nucleic acid targets.

Over Review of Molecular Dynamics

Molecular dynamics (MD) simulations have significantly improved many areas of science, such as chemical physics, materials science, and biophysics. This computer-based approach has proven useful for deeply understanding biomolecular systems. It works well alongside experimental data, helps optimize experimental designs, and predicts important characteristics of chemical systems that are hard or costly to study in labs. One of the many uses includes examining how diseases develop and supporting the early phases of creating and developing medicines. MD simulations can be applied in various ways, including studying the structure and arrangement of membranes, how membranes allow substances to pass through, interactions between lipids and proteins, interactions between lipids and drugs, connections between proteins and ligands, and the structure and movement of proteins. The articles in this Special Issue demonstrate how adaptable MD simulations can be in this field. In this Special Issue, Cardoso et al. investigated how kojic acid (KA) derivatives made from aromatic aldehydes and malononitrile affect the activity of tyrosinase, an enzyme [43]. Tyrosinases are a group of proteins that contain copper and can cause issues in skin cancer when their functions are not normal. MD simulations showed that these derivatives interact well with tyrosinase, indicating that they might serve as strong competitors against the natural substances the enzyme usually works with. Hernández-Ochoa et al. examined 55 different compounds to explore their potential as new drugs that inhibit the activity of Helicobacter pylori glucose-6-phosphate dehydrogenase (HpG6PD) [44].

Fig:2 Molecualr Dynamics of Simulation [45]

Types And Methods of Molecular Dynamics

Accelerated Molecular Dynamics (aMD)

Accelerated Molecular Dynamics, or aMD, is a special technique that helps lengthen simulation periods by changing the potential energy landscape of a system. In aMD, a positive boost is added to areas with low energy, which helps reduce energy barriers that usually keep the system stuck in certain states. This change allows the system to move past rare transitions more often, making it easier to explore different shapes and arrangements. Unlike methods such as Replica Exchange or Meta dynamics, aMD does not need multiple copies of the system or set collective variables, which makes it easier to use. This method has proven helpful for exploring how proteins change shape, how ligands attach, and for observing large molecular movements. However, since aMD modifies the basic potential, careful adjustments are needed to ensure accurate thermodynamic properties, which can be tough to handle for very complex systems [46].

Methods Of Acceralated Molecular Dynamics

Accelerated Molecular Dynamics, or aMD, is an advanced method that improves the sampling of molecular shapes by changing the potential energy landscape to lower energy obstacles. The main idea is to introduce a boost in potential energy whenever the system's energy dips below a certain level, which speeds up the transition over barriers and helps in exploring shapes that would usually be hard to reach. This method has been used in different molecular dynamics software like AMBER and NAMD to examine intricate biological molecular systems [47].

- **Dual-Boost aMD**

The most common method used in fast molecular dynamics is to apply extra forces separately to the dihedral energy and the overall potential energy. This two-way boosting technique successfully manages to increase local twisting movements while also encouraging larger shape changes, allowing for a better investigation of the different shapes that biomolecules can take. By supporting small side-chain movements as well as bigger structural shifts, this method has been especially useful for examining proteins, nucleic acids, and various other complex biological systems.

- **Dihedral-Boost aMD**

In these fast molecular dynamics method, the added energy is only used for the twisting (dihedral) energy parts, specifically improving the sampling of how things can rotate. This focused method is really helpful for studying changes in shape of proteins and nucleic acids, where the ability to twist is the main factor in how the structure behaves. By concentrating on twisting movements, this technique allows for a smarter searching of shape states that don't often get explored, giving important information about how biomolecules work, their folding routes, and changing structures.

- **Total Potential-Boost aMD**

In these fast molecular dynamic's methods, a boost potential affects the whole potential energy surface, leading to a significant speedup of local and global movements. Although this overall technique allows for a wide range of shape sampling, using too high of a boost can create errors or change the natural energy landscape, making it necessary to fine-tune parameters carefully.

- **Selective aMD**

A new improvement in fast molecular dynamics includes intentionally using boost potentials in certain parts of the system, like enzyme active sites or the places where proteins and ligands meet. This aimed acceleration helps improve the sampling of shapes in important areas while keeping other parts of the biomolecule less disturbed. By focusing computing resources where they are most required, this method lowers the total expense of simulations and decreases the risk of artifacts, leading to better understanding of biomolecular dynamics [48,49,50].

Steered Molecular Dynamics (SMD)

Steered Molecular Dynamics (SMD) adds outside forces to molecular dynamics simulations to explore how biomolecules react mechanically. In this method, a fake "spring" or a steady speed force is applied to chosen atoms, simulating conditions like what is used in atomic force microscopy (AFM). By "pulling" or "pushing" molecules in a certain direction, SMD can show the processes of unfolding, unbinding, or moving that would be hard to see on normal timescales. The force-extension results obtained can be directly compared to what is measured in experiments, giving valuable insights into how stable molecules are and how they interact. SMD has been used extensively to examine protein unfolding, DNA stretching, and the breaking apart of receptor and ligand pairs. However, a major drawback of this technique is that the outcomes are heavily influenced by the speed of pulling and the force constant, which means that choosing the right parameters is crucial to prevent errors. Even so, SMD is still a strong method to study the mechanics and energy landscapes of biomolecules under outside pressure [51].

Methods of Steered Molecular Dynamics (SMD)

Steered Molecular Dynamics (SMD) is a computational technique in which external mechanical forces are applied to specific atoms or molecular groups to investigate structural transitions, binding interactions, and mechanical properties of biomolecules. By simulating the effects of controlled forces, SMD effectively mimics experimental single-molecule force spectroscopy methods, including atomic force microscopy (AFM) and optical tweezers. This approach provides detailed mechanistic insights into molecular processes and is implemented through several commonly used SMD methodologies

- **Constant Velocity SMD (cv-SMD)**

In the method of steered molecular dynamics, a virtual spring is attached to a specific atom or group of molecules, and its reference point is shifted at a steady speed. As the molecule undergoes mechanical stretching or tension, the force–extension relationship that emerges can be observed and studied. This technique is commonly used to explore essential biomolecular processes, such as the unfolding of proteins, the stretching of DNA and RNA strands, and the detachment of ligands from their receptor sites, offering in-depth insights into molecular mechanics.

- **Constant Force SMD (cf-SMD)**

In the constant-force steered molecular dynamics (cf-SMD) method, an ongoing external force is exerted on the system, unlike constant-velocity SMD (cv-SMD), which emulates the action of a moving cantilever. By applying a persistent mechanical load, cf-SMD allows for an in-depth analysis of how molecules respond to consistent stress. This technique is especially useful for examining rupture forces, assessing structural stability, and defining the mechanical strength of proteins, nucleic acids, and protein–ligand complexes.

- **Adaptive or Targeted SMD**

In adaptive steered molecular dynamics (ASMD), the direction of the pull and the strength of the applied force are continuously modified according to the system's reactions or to guide the molecule toward a specific target conformation or binding site. This flexible method enables more effective exploration of important conformational pathways, minimizes the chances of creating artifacts, and is especially beneficial for simulating intricate structural changes, investigating folding and unfolding processes, or precisely directing ligands to their binding locations.

- **Jarzynski's Equality in SMD**

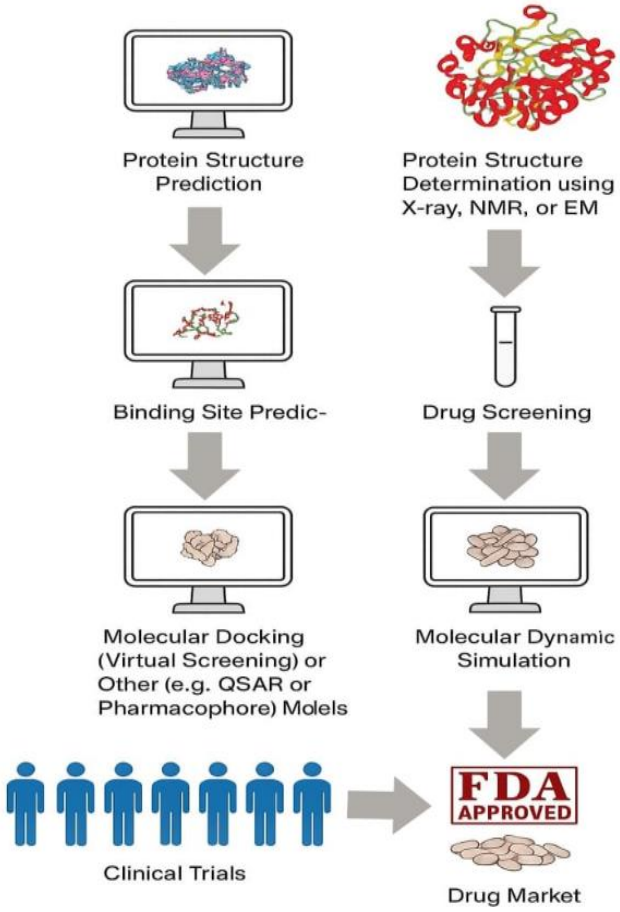
Using the Jarzynski equality, one can reweight non-equilibrium steered molecular dynamics (SMD) trajectories to determine differences in equilibrium free energy. This method successfully connects non-equilibrium pulling simulations with equilibrium thermodynamics, allowing for the precise calculation of binding affinities, stability of conformations, and other important molecular properties related to energy [52,53,54].

Table: 2 Comparative Aspects of Molecular Docking and Molecular Dynamics [55,56,57]

Aspect	Molecular Docking	Molecular Dynamics (MD)
Purpose / Role	Predicts binding pose, orientation, and rough binding affinity of small molecules to a target; used for high throughput screening.	Simulates time-dependent behaviour of molecular systems; provides insights into stability, binding pathways, kinetics, and thermodynamics.
Flexibility Consideration	Often treats protein as rigid; some methods allow limited side-chain flexibility or ensemble docking.	Simulates both ligand and receptor flexibility (including solvent) explicitly over time.
Throughput and Speed	Fast and inexpensive; suitable for screening large libraries (e.g. millions of compounds).	Computationally intensive; best for detailed analysis of a few selected complexes.

Accuracy of Binding Prediction	Provides approximate ranking; scoring functions have limitations and approximations.	Offers improved accuracy—accounts for induced fit, solvent, dynamic flexibility; can refine docking results and compute more accurate binding energies.
Typical Usage Strategy	First pass: quickly narrows down potential hits.	Used after docking to refine, validate, and analyse details of shortlisted molecules.
Limitations	May miss important conformational effects; static nature; scoring can mis-rank poses.	Requires significant computational resources; longer timescales; complex setup and analysis. *(inferred general knowledge)*

Fig:3 A Comparative Drug Discovery Structure of Molecular Docking and Molecular Dynamics [58]



Conclusion

Molecular docking and molecular dynamics (MD) serve as complementary computational techniques frequently used in drug discovery, each bringing its own advantages and drawbacks. Docking creates fast, high-volume predictions regarding ligand–receptor binding configurations and initial binding strengths, making it ideal for virtual screening and identifying potential leads. On the other hand, MD simulations grant in-depth, time-based views of the dynamic nature of biomolecular systems. They capture the flexibility of receptors, the effects of induced fit, and interactions influenced by solvents, aspects that docking cannot completely address. By combining docking with MD, the accuracy of binding predictions is improved, providing a better evaluation of ligand stability, binding rates, and the ability to adapt conformationally. These two methods together speed up rational drug development by merging efficiency with an understanding of mechanisms, not only enhancing the discovery but also the refinement of effective therapeutic candidates.

REFERENCE

1. Cheng F, Li W, Liu G, Tang Y. In silico ADMET prediction: recent advances, current challenges and future trends. Curr Top Med Chem 2013; 13(11): 1273 - 89.
2. Vasant OK, Chandrakant MA, Chandrashekhar KV, Babasaheb GV, Dnyandev KM A review on molecular docking.Int Res J Pure Appl Chem 2021; 22(3): 60 - 68.
3. Al-Karmalawy AA, Dahab MA, Metwaly AM, Elhady SS, Elkaeed EB, Eissa IH, Darwish KM. Molecular docking and dynamics simulation revealed the potential inhibitory activity of ACEIs against SARS-CoV-2 targeting the h ACE2 receptor. Front Chem. 2021; 4(9): 661230.

4. Taidi L, Maurady A, Britel MR. Molecular docking study and molecular dynamic simulation of human cyclooxygenase-2 [COX-2] with selected eutypoids. J Biomol Struct Dyn. 2022; 40(3): 1189 - 1204.
5. Nivatya et al. Leelananda SP, Lindert. Computational methods in drug discovery. Beilstein J Org Chem 2017; 12(1): 2694 - 2718.
6. Lohning E, Anna, et al., A practical guide to molecular docking and homology modelling for medicinal chemists. Current Topics Med Chem.2017; 17(18): 2023 - 2040.
7. Muhammed MT, Aki-Yalcin E. Molecular docking: Principles, advances, and its applications in drug discovery. Lett Drug Des Discov. 2024; 21(3): 480 - 95.
8. Asiamah I, Obiri SA, Tamekloe W, Armah FA, Borquaye LS. Applications of molecular docking in natural products-based drug discovery. Sci Afr. 2023; 20: e01593.
9. Vidal-Limon A, Aguilar-Toalá JE, Liceaga AM. Integration of molecular docking analysis and molecular dynamics simulations for studying food proteins and bioactive peptides. J Agric Food Chem. 2022; 70(4): 934.
10. Persidis A. Proteomics. Nat Biotechnol 1998; 16: 393 - 394.
11. Somvanshi P, Singh V, Seth PK. In silico prediction of epitopes in virulence proteins of Mycobacterium tuberculosis H37Rv for diagnostic and subunit vaccine design. J Proteomics Bioinform 2008; 1(3): 143 - 53.
12. Mbelele PM, Mohamed SY, Sauli E, Mpolya EA, Mfinanga SG, Addo KK, et al. Metanarrative review of molecular methods for diagnosis and monitoring of multidrug-resistant tuberculosis treatment in adults. Int J Mycobacteriol 2018; 7(4): 299 - 309.
13. Charlie L, Saidi B, Getachew E, Wanjiru CL, Abebe M, Tesfahunei HA, et al. Programmatic challenges in managing multidrug-resistant tuberculosis in Malawi. Int J Mycobacteriol 2021; 10(3): 255 - 259.
14. Alonso H, Bliznyuk AA, Gready JE. Combining docking and molecular dynamic simulations in drug design. Med Res Rev 2006; 26(5): 531 - 68.
15. Raval K, Ganatra T. Basics, types and applications of molecular docking: a review. IP Int J Comprehensive Adv Pharmacol. 2022; 7(1): 12 - 16.
16. Li J, Fu A, Zhang L. An overview of scoring functions used for protein– ligand interactions in molecular docking. Int Sci: Computat Life Sci. 2019; 11(2): 320 - 328.
17. Kuntz ID, Blaney JM, Oatley SJ, Langridge R, Ferrin TE. A geometric approach to macromolecule-ligand interactions. J Mol Biol. 1982; 161(2): 269 - 288.
18. Nicholls A, McGaughey GB, Sheridan RP, Good AC, Warren G, Mathieu M, Muchmore SW, Brown SP, Grant JA, Haigh JA, Nevins N. Molecular shape and medicinal chemistry: a perspective. J Med Chem. 2010; 53(10): 3862 - 3886.
19. Precup's A, Sandu R, Leonties AR, Anghel DF, Popa V. Complex interaction of caffeic acid with bovine serum albumin: calorimetric, spectroscopic and molecular docking evidence. New J Chem. 2017 41(24): 1 - 14.
20. Ruppert J, Welch W, Jain AN. Automatic identification and representation of protein binding sites for molecular docking. Protein Sci. 1997; 6(3): 524 - 533.
21. Wang R, Lu Y, Wang S. Comparative evaluation of 11 scoring functions for molecular docking. J Med Chem. 2003; 46(12): 2287 - 2303.
22. Chen T, Shu X, Zhou H, Beckford FA, Misir M. Algorithm selection for protein–ligand docking: strategies and analysis on ACE. Sci Rep. 2023; 13(1): 8219.
23. Guo J. Improving structure-based protein-ligand affinity prediction by graph representation learning and ensemble learning. PLoSONE;. 2024; 19(1): e0296676.
24. Kolb P, Irwin JJ. Docking screens: right for the right reasons? CurrTopMedChem. 2009; 9(9): 755 - 70.
25. Arnold K, Bordoli L, Kopp J, Schwede T. The SWISS-MODEL workspace: a web-based environment for protein structure homology modelling. Bioinformatics. 2006; 22(2): 195 - 201.
26. Stollar EJ. Uncovering protein structure. Essays in Biochemistry. 2020; 65(2): 203 - 22.
27. Lin R, Zhang J, Xu R, Yuan C, Guo L, Liu P, et al. Developments in molecular docking technologies for application of polysaccharide-based materials: A review. Crit Rev Food Sci Nutr. 2023; 1 - 13.
28. Liang L, Zhou C, Zhang J, Huang Y, Zhao J, Sun B, et al. Characteristics of umami peptides identified from porcine bone soup and molecular docking to the taste receptor T1R1/T1R3. Food Chem. 2022; 387: 132870.
29. Raval K, Ganatra T. Basics, types and applications of molecular docking: A review. IP Int J Compr Adv Pharmacol. 2022; 7(1): 12 - 6.
30. Azad I. Molecular docking in the study of ligand-protein recognition: An overview.Molecular DockingRecent Advances. 2023; 106583.
31. Luo H, Zhang K, Su Y, Zhong K, Li Z, Guo J, et al. Monocular vision pose determination-based large rigidbody docking method. Measurement. 2022; 204(4): 112049.
32. Jin Z, Wei Z. Molecular simulation for food protein-ligand interactions: A comprehensive review on principles, current applications, and emerging trends. Compr Rev Food Sci Food Saf. 2024; 23(1): 1 - 29.
33. Sahu, M. K., & Sahu, M. K. Exploring recent updates on molecular docking. International Journal of Pharmaceutical Research & Allied Sciences, 2024; 13(2), 24 - 40.
34. Huang, S.-Y., & Zou, X. Advances and challenges in protein–ligand docking. Frontiers in Biology, 2010; 5(5): 323 - 334.
35. Guedes, I. A., et al. New Machine Learning and Physics-Based Scoring Functions for Drug Discovery. Scientific Reports, 2021; 11(1): 82410.
36. Chaudhury, S., Lyskov, S., & Gray, J. J. Conformer selection and induced fit in flexible backbone docking. Proteins: Structure, Function, and Bioinformatics,2008; 73(2): 208 - 220.
37. Lin R, Zhang J, Xu R, Yuan C, Guo L, Liu P, et al. Developments in molecular docking technologies for application of polysaccharide-based materials: A review. Crit Rev Food Sci Nutr. 2023;1 - 13.

38. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. J Comput Chem. 2009; 30(16): 2785 - 91.

39. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: A new approach for rapid, accurate docking and scoring. 1. Method and assessment of docking accuracy. J Med Chem. 2004; 47(7): 1739 - 49.

40. Jones G, Willett P, Glen RC, Leach AR, Taylor R. Development and validation of a genetic algorithm for flexible docking. J Mol Biol. 1997; 267(3): 727 - 48.

41. Cardoso, R.; Valente, R.; da Costa, C.H.S.; da S. Gonçalves Vianez, J.L., Jr.; da Costa, K.S.; de Molfetta, F.A.; Alves, C.N. Analysis of Kojic Acid Derivatives as Competitive Inhibitors of Tyrosinase: A Molecular Modeling Approach. Molecules 2021; 26: 2875.

42. Hernández-Ochoa, B., Navarrete-Vázquez, G., Aguayo-Ortiz, R., Ortiz-Ramírez, P., Morales-Luna, L., Martínez-Rosas, V., González-Valdez, A., Gómez-Chávez, F., Enríquez-Flores, S., Wong-Baeza, C., et al. Identification and in silico characterization of novel Helicobacter pylori glucose-6-phosphate dehydrogenase inhibitors. Molecules, 2021; 26(16), 4955.

43. Ribeiro, J. V., Bernardi, R. C., Rudack, T., et al. QwikMD—Integrative molecular dynamics toolkit for novices and experts. Biophysical Journal, 2016; 110(8): 1526 - 1532.

44. Hamelberg D, Mongan J, McCammon JA. Accelerated molecular dynamics: A promising and efficient simulation method for biomolecules. J Chem Phys. 2004; 120(24): 11919 - 29.

45. Wang Y, et al. Implementation of Accelerated Molecular Dynamics in NAMD. Comput Phys Commun. 2011; 182(8): 1965 - 1971.

46. Pierce LCT, Salomon-Ferrer R, Augusto F de Oliveira C, McCammon JA, Walker RC. Routine access to millisecond time scale events with accelerated molecular dynamics. J Chem Theory Comput. 2012; 8(9): 2997 - 3002.

47. Miao Y, McCammon JA. Unconstrained enhanced sampling for free energy calculations of biomolecules: A review. Mol Simul. 2016; 42(13): 1046 - 55.

48. Markwick PRL, McCammon JA. Studying functional dynamics in biomolecules using accelerated molecular dynamics. Phys Chem Chem Phys. 2011; 13(45): 20053 - 65.

49. Isralewitz B, Gao M, Schulten K. Steered molecular dynamics and mechanical functions of proteins. Curr Opin Struct Biol. 2001; 11(2): 224 - 30.

50. Park S, Schulten K. Calculating potentials of mean force from steered molecular dynamics simulations. J Chem Phys. 2004; 120(13): 5946 - 61.

51. Grubmüller H, Heymann B, Tavan P. Ligand binding: Molecular mechanics calculation of the streptavidin–biotin rupture force. Science. 1996; 271(5251): 997 - 9.

52. Cuendet MA, Zoete V, Michielin O. How to extract thermodynamic information from steered molecular dynamics simulations. J Chem Theory Comput. 2011; 7(1): 276 - 85.

53. Salo-Ahen OMH, Alanko I, Bouvier G, et al. Molecular dynamics simulations in drug discovery and pharmaceutical development. Processes. 2020; 9(1): 71.

54. Ivanova A, Singh A, Leveille J, et al. StreaMD: the toolkit for high-throughput molecular dynamics simulations. J Cheminform. 2024; 16: 66.

55. De Vivo M, Masetti M, Bottegoni G, Cavalli A. Role of molecular dynamics and related methods in drug discovery. J Med Chem. 2016; 59(9): 4035 - 4061.

56. Śledź P, Caflisch A. Protein structure-based drug design: from docking to molecular dynamics. Curr Opin Struct Biol. 2018; 48: 93 - 102.

57. Santos, L. H. S.; Ferreira, R. S.; Caffarena, E. R. Integrating molecular docking and molecular dynamics simulations. In Docking Screens for Drug Discovery; Methods Mol. Biol.Springer; 2019; 2053; 13 - 34.

58. Alonso, H.; Bliznyuk, A. A.; Gready, J. E. Combining docking and molecular dynamic simulations in drug design. Med. Res. Rev. 2006; 26: 531 - 568.