Structure-based drug design: Understanding Dancing Bio-Molecules

Priyankal Sharma[1], Rupal Mishra[1], Aparna Patil Kose[1], Dr. Gaganjyot Kaur[1], Dr. Krupa Purandare[2] , Dr. Rupinder Kaur[3] , Dr. Kiran Mangaonkar[4]

[1]Guru Nanak Institute of Research and Development, Guru Nanak Khalsa College of Science, Arts and Commerce (Autonomous), Mumbai.

[2]Department of Microbiology, Guru Nanak Khalsa College of Science, Arts and Commerce (Autonomous), Mumbai.

[3]Department of Zoology, Guru Nanak Khalsa College of Science, Arts and Commerce (Autonomous), Mumbai.

[4]Department of Chemistry, Guru Nanak Khalsa College of Science, Arts and Commerce (Autonomous), Mumbai.

ABSTRACT

Structure-based drug design (SBDD) is a powerful approach that leverages the 3D structures of target proteins to guide the rational design of potential drug candidates. By identifying and optimizing ligands that specifically interact with the active sites of target proteins, SBDD aims to develop drugs with enhanced potency, selectivity, and reduced off-target effects. This review provides an overview of the key principles and methodologies involved in SBDD, including target selection, protein structure determination, active site identification, ligand docking, and scoring algorithms. We discuss the advantages and challenges of SBDD, such as addressing target flexibility, modeling membrane proteins, and incorporating water molecules in ligand-protein interactions. Furthermore, we explore emerging trends in SBDD, including the integration of artificial intelligence and machine learning techniques, multi-target drug design, and personalized medicine applications. The potential impact of SBDD on drug discovery for rare diseases and drug resistance is also highlighted. Despite its successes, future issues for SBDD, such as data management, reproducibility, ethical considerations, and regulatory adaptation, need to be addressed to maximize its potential in accelerating drug development. In conclusion, SBDD continues to be a critical component of the drug discovery pipeline, and its continued advancement promises to drive the development of innovative and targeted therapeutics for a wide range of diseases.

KEYWORDS: Structure based drug designing, SBDD, Drug discovery & design, Protein structure, Personalized medicine, Docking

I . INTRODUCTION

The pharmaceutical business faces a substantial issue with the process of developing new pharmaceuticals because it requires a big time and financial commitment to move through the various stages. A promising molecule must go through a long process of testing, development, and refinement before it may become a workable therapeutic option.

In the past ten years, advances in science and technology have significantly improved our understanding of the three-dimensional protein structures. This increase in knowledge is especially pertinent to the realm of drug discovery since it creates new opportunities for creating therapies that are more precise and effective. The innovative use of X-ray crystallography in the 1950s and 1960s, which represented the first steps toward solving the mysteries of protein architecture, is the origin of this trend of elucidating protein structures.

A key tool in the effort to speed up and optimize the drug discovery process is structure-based drug design, a methodology built on utilizing the complex intricacies of molecular structures. Structure-based drug design offers a streamlined and focused strategy in contrast to conventional techniques, which mainly relied on trial and error. Researchers can design possible medicine compounds to fit snugly and interact optimally by looking closely at the spatial arrangement of molecules within a biological target, improving the likelihood of therapeutic effectiveness. [2]

Due to its promise for rapid and economical lead discovery, this strategy has received a lot of traction. Researchers can model and anticipate how possible drug candidates will interact with their targeted targets because to the method's scientific underpinning and computational breakthroughs. By reducing the need for significant laboratory experimentation, this predictive skill lowers the time and money spent following dead-end leads.

The explosion of structural, functional, and genomic data in recent years has had a major impact on how drug development is conducted. Structure-based approaches can now be incorporated into the modern drug design pipeline because the vast majority of biological targets having three-dimensional structures that are known have been cataloged. By utilizing the plethora of information already available, this integration enables researchers to create molecules that are more likely to have the intended effects while limiting unfavorable interactions.

In essence, the combination of cutting-edge computational techniques and improved structural insights has made drug discovery a more effective and focused process. Structure-based drug design has developed into a crucial tool in the toolbox used by researchers in their search for innovative treatments that have the potential to significantly improve patient health and wellbeing.[1]

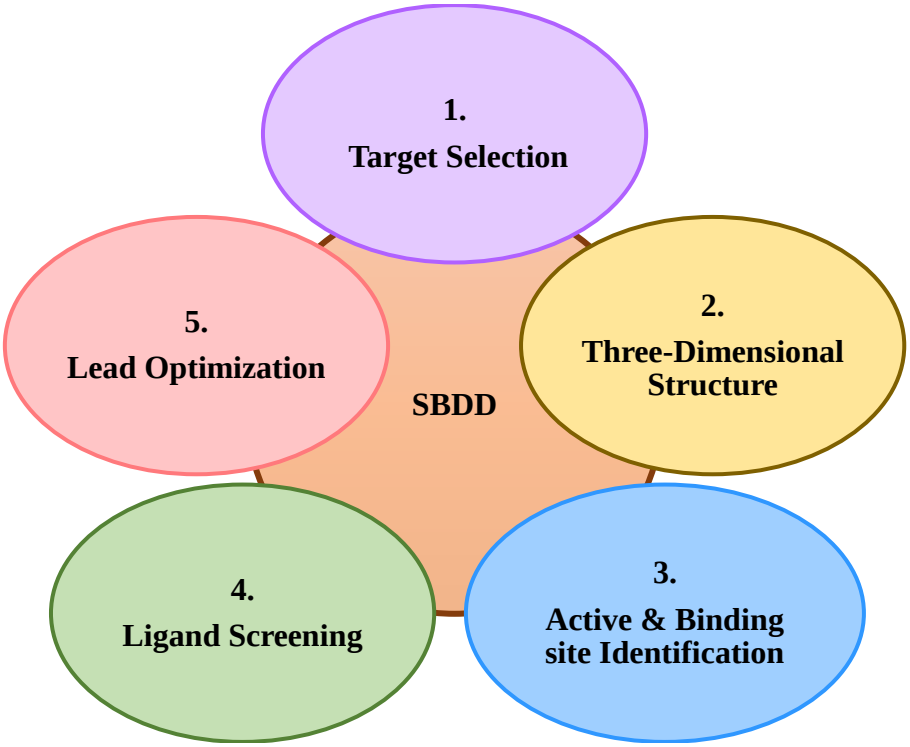


Figure 1: Structure Based Drug Designing Flowchart

The development of computing science becomes another driving force which makes it possible to use computational methods effectively in various phases of drug design and research. Structure-based drug design (SBDD) tools are widely used to help researchers to predict the position of small molecules within a three-dimensional representation of the protein structure and estimate the affinity of ligands to target protein with considerable accuracy and efficiency. [3] They also accelerate discovery speed of potent drugs and reduce the cost and times for drug research [2]. The availability of 3D structures of therapeutically important proteins favors identification of binding cavities and has laid the foundation for structure-based drug design (SBDD). This is becoming a fundamental part of industrial drug discovery projects and of academic research. SBDD is a more specific, efficient, and rapid process for lead discovery and optimization because it deals with the 3D structure of a target protein and knowledge about the disease at the molecular level. Among the relevant computational techniques, structure-based virtual screening (SBVS), molecular docking, and molecular dynamics (MD) simulations are the most common methods used in SBDD. These methods have numerous applications in the analysis of binding energetics, ligand–protein interactions, and evaluation of the conformational changes occurring during the docking process [1,2]. SBDD comprises several steps and they are as follows:

A. Protein Selection & Validation:

Protein selection and validation are crucial steps in structure-based drug design, which aims to identify, and design potential drug candidates based on the 3D structures of target proteins. Important steps involved in protein selection and validation:

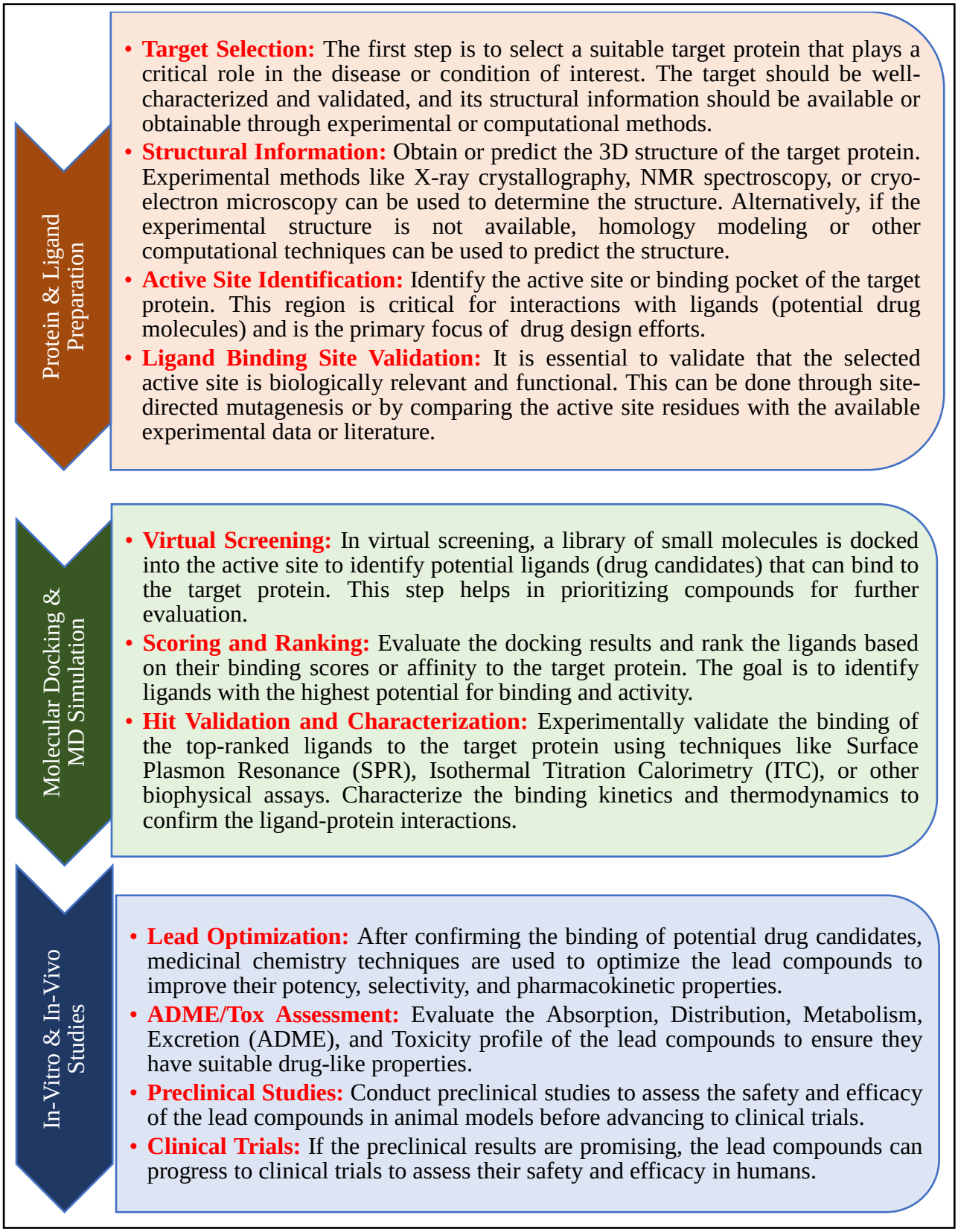
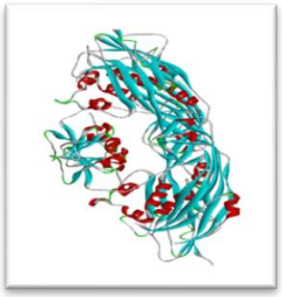
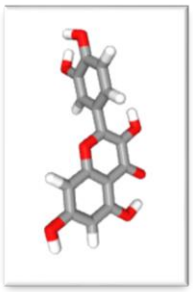


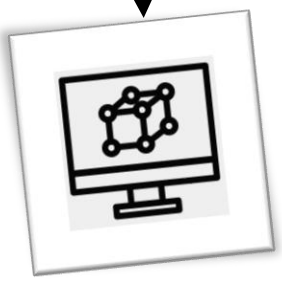
Figure 2: Overview of protein selection and validation



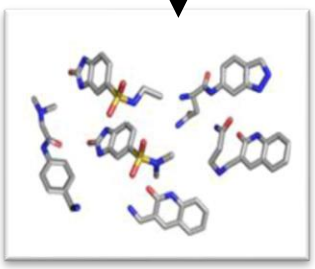
Protein Preparation



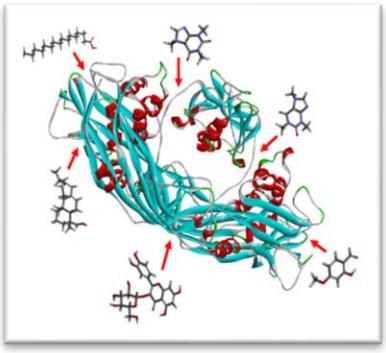
Ligand Preparation



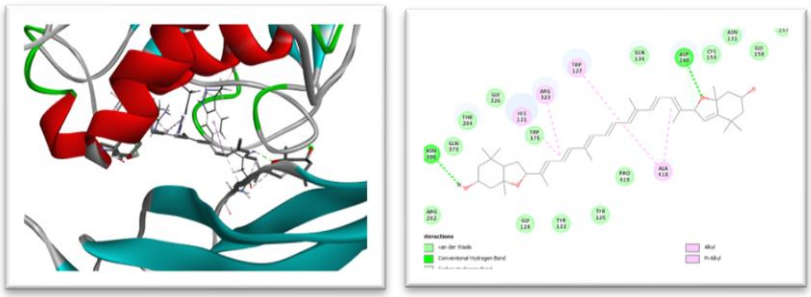
Validation & Energy Minimization



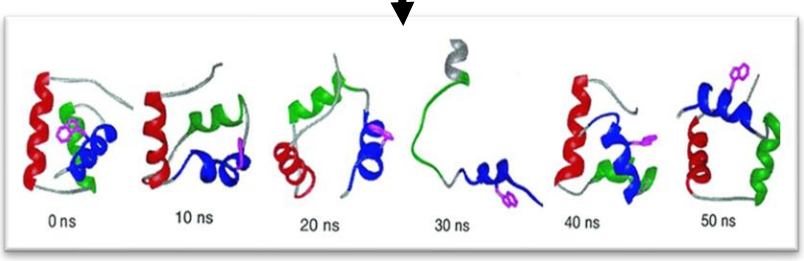
Energy Minimization



Molecular Docking



Visualization of Docked Structure



Simulation

Figure 3: Steps to perform Molecular Docking

In the journey of drug discovery, the progression through various stages is often characterized by an iterative process. This means that as researchers move forward, they continuously revisit and refine their previous steps based on new insights gained along the way. The knowledge obtained from one step serves as a guiding light for shaping decisions in earlier stages, creating a dynamic feedback loop. This iterative cycle persists until a potential drug candidate emerges as promising for further advancement. [4] Each iterative loop brings about a deeper understanding of the compound's properties, interactions, and potential efficacy. This continuous reevaluation allows researchers to optimize their strategies and tailor their approaches more effectively, ultimately increasing the likelihood of identifying a drug candidate that holds substantial therapeutic promise. Importantly, within the vast landscape of drug discovery, structure-based drug design stands as one approach among many. It involves using the three-dimensional structures of biological molecules to guide the design and optimization of potential drug compounds. This method capitalizes on the intricate understanding of how molecules interact at a molecular level, helping researchers to fine-tune the chemical properties of drug candidates for optimal binding and therapeutic effect. However, the field of drug discovery is multifaceted, and no single approach holds all the answers. Alongside structure-based methods, other techniques contribute significantly to the overall process such as ligand-based drug design and phenotypic screening, may also be employed in conjunction with structure-based methods. In practice, these various approaches often collaborate harmoniously. This multidimensional approach takes advantage of the strengths of each technique while compensating for their individual limitations, thus increasing the robustness and efficiency of the drug discovery process. [6]

B. MD Simulations:

Directly viewing and manipulating every atom in biomolecule is difficult and time-consuming. Atomic-level computer simulations (Molecular Dynamics (MD) simulations) provide a potent substitute. These simulations offer insightful information on the behavior of bio-molecular systems by precisely describing the position and mobility of every atom. MD simulations, which take advantage of computer capacity to examine the complex dynamics and interactions of atoms, have helped researchers make ground-breaking findings in the disciplines of pharmacology, biochemistry and structural biology. MD simulations provide temporal resolution at femtoseconds making predictions of biomolecular events, such as ligand binding, conformational changes, and protein folding. Furthermore, by predicting how biomolecules would react to different perturbations at the atomic level, these simulations in better understanding of how perturbations may affect molecular structure and function. The simulations accomplish this by determining forces acting on each atom in accordance with Newton's equations of motion and updating its positions and velocities across successive time steps. Researchers may study the consequences of various molecular disturbances when conditions are precisely controlled. This analysis has profound significance for comprehending biological processes and furthering scientific understanding. [5]

To determine the forces acting on the atoms in biomolecules, molecular dynamics (MD) simulations use a force field based on quantum mechanical calculations and experimental data. Force fields are still approximate despite advancements, necessitating careful consideration when analyzing results. MD simulations require a lot of computing because they have many steps and short time steps to capture biological activities. However, longer and cheaper simulations are now possible thanks to improvements in technology and algorithms, including GPUs. To formulate research questions, create simulations, and analyze outcomes from intricate trajectory data, expertise is required. Given that they evaluate mobility and flexibility inside biomolecules and reveal structural variations that are difficult for experimental techniques to detect, MD simulations are an important tool for the study of biomolecular activity. The dynamic behavior of components like water and salt ions, which are vital for protein activity and ligand binding, is also clarified by simulations.

The improvement of structural models is another practical beneficial application. Simulations validate ligand binding poses and correct crystal structure aberrations. From low-resolution cryo-EM density maps, they successfully refine X-ray crystal structures and produce atomic-level models. MD simulations are essential for comprehending how biomolecules react to modifications. In order to investigate impacts on ligand binding, conformational alterations, post-translational modifications, and more, researchers manipulate systems. To find consistent difference in outcomes, several MD simulations are run. MD simulations are frequently used to research functional biomolecular processes including protein folding and ligand binding. They contribute to the study of allosteric mechanisms and ion transport across membranes, among other complex topics with insights that are difficult to obtain from experiments. [7,8]

MD simulations offer useful information for drug discovery, particularly in ligand-protein interactions, whether they capture whole processes or use better sampling strategies. MD simulations are useful tools for examining biomolecular behavior because they provide rich insights and advance scientific knowledge across a range of research fields. In structural biology, MD simulations have transformed drug discovery by enhancing experimental efforts. They are essential in considering protein's dynamic features, which has fueled the development of structure-based drug design for important therapeutic targets.

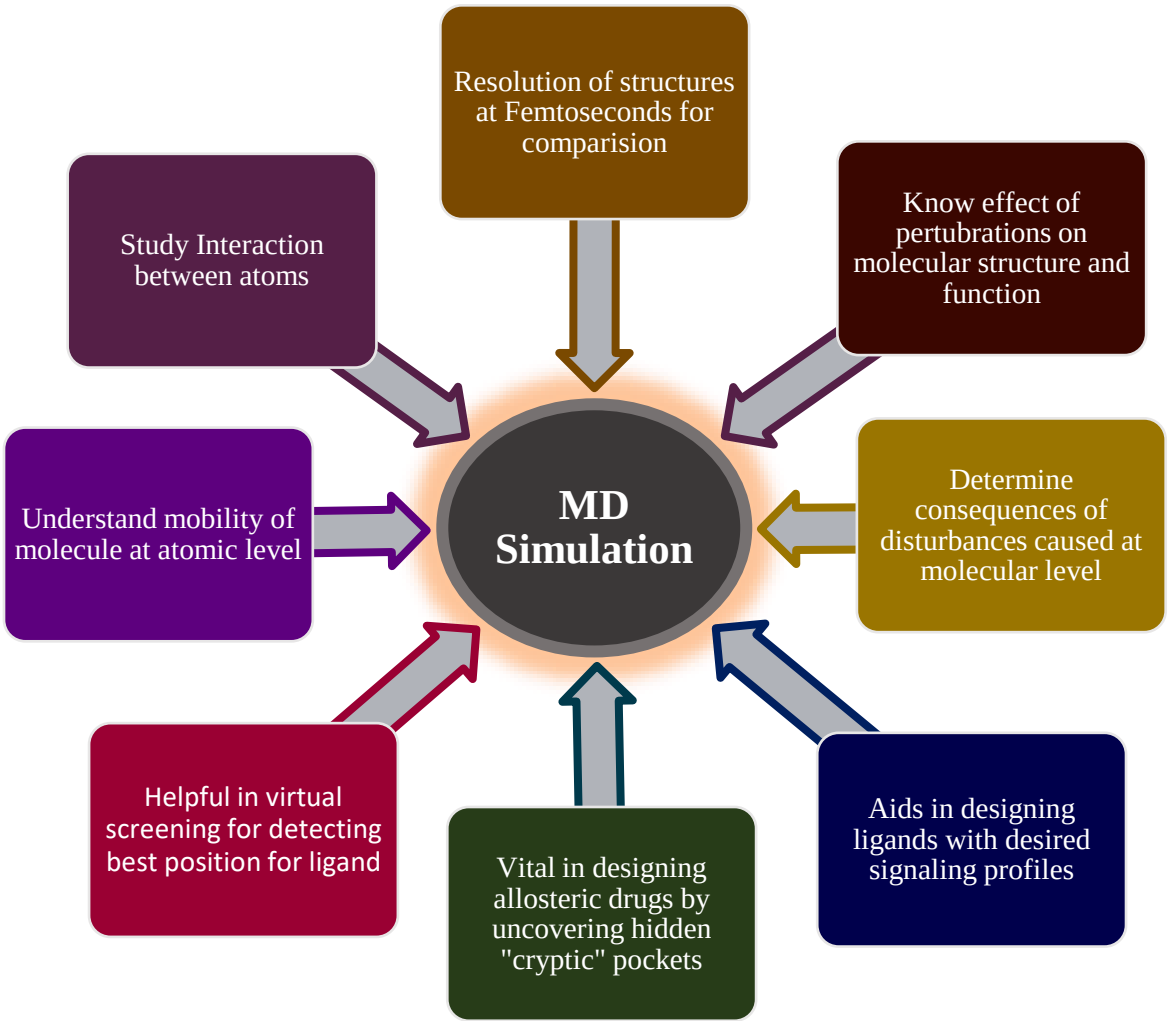


Figure 4: Why should we use MD Simulations

MD simulations provide quantitative and qualitative insights into the interactions and binding processes of ligands in lead optimization. They refine ligand poses, identify important interactions and arrangement changes in the binding pocket. In comparison to other computational methods, simulation-based techniques offer precise estimations of ligand binding affinities. MM/GBSA and MM/PBSA methods rely on the continuum solvent models to provide faster estimations. Additionally, helpful in virtual screening, MD simulations consider various protein structures to increase the variety of detected ligand binders. MD simulations aid to comprehend conformational variations in the binding pocket that result signaling outcomes for drug design aimed at signaling receptors. As a result, it is easier to create ligands that have the required signaling characteristics, such as complete agonists, inverse agonists, neutral antagonists, and partial agonists. It is possible to more efficiently identify and optimize prospective drug candidates, especially those that target signaling pathways, by combining simulations with experimental methods. [9]

To create allosteric medications that bind to different locations on target proteins than natural ligands, simulations are essential. Because of their ability to improve selectivity, alter signaling pathways, and target previously difficult areas, these medications are in high demand. Simulations can find hidden "cryptic" pockets and pinpoint the binding sites of well-known allosteric modulators, allowing the development of novel medications even when experimental structures fail to disclose allosteric binding sites. Chemical alterations that drastically change an allosteric ligand's actions at a GPCR have been made thanks to simulation-based methods. Simulations are helpful in the drug design process for achieving precise binding and dissociation kinetics, which are essential for medication efficacy and safety. For some targets, binding affinity loses importance in favor of ligand residence time.

The parameters governing binding kinetics have been clarified by simulation studies, enabling the logical design of ligands with desired kinetics. Simulations are helpful in determining the kinetic properties of ligands, as shown by the ability of MD-based approaches to rank related ligands according to dissociation rates. Considering on simulation software, force fields, and hardware is necessary for running an MD simulation. GPUs are used over force fields like AMBER, CHARMM, or OPLS because of their advantages in terms of speed and cost-effectiveness. Numerous force fields and features are supported by simulation programs as GROMACS, AMBER, Desmond, NAMD, CHARMM or OpenMM.

The molecular system must be ready before the simulation begins, including the addition of solvent molecules, missing atoms and force field parameters. System preparation tools are frequently included in software packages, simplifying the procedure. Choosing which simulations to perform, including any necessary better sampling strategies, and interpreting the enormous amount of data produced pose as the main challenges in MD Simulations. It can be challenging to glean pertinent and biologically important information from the data, particularly when dealing with complicated and random events related to functioning systems. While certain situations call for precise amounts, others include complex procedures that are challenging to plan ahead for. Simulations must be interpreted in conjunction with experimental data from the researched molecular system and related systems in order to provide useful insights. This requires a combination of visual and quantitative analysis, with the option to employ specially created analysis programs or scripts, made possible by frameworks for analysis software.

Small changes in the initial conditions and the chaotic character of molecular systems in simulations and reality can produce wildly divergent trajectory outcomes. This is addressed by doing several simulations with randomized initial velocities under each

circumstance to ensure statistical significance of the outcomes. Both the design and the interpretation of MD simulations should consider their limitations. Despite advancements, MD force fields are still approximations, and covalent bond forms or breaks don't happen in most MD simulations. Protonation states and disulfide bonds must therefore be carefully built up at the start of the simulation. Furthermore, the design of simulation studies based on existing experimental data is greatly influenced by the availability of correct experimental protein structures or trustworthy homology models as the beginning condition.

In order to examine biomolecular processes like conformational changes and ligand binding, MD simulations are useful tools; yet these processes frequently take place over longer timeframes than are supported by classical simulations. To access longer durations, specialized technology, Markov state modeling, and improved sampling strategies such targeted molecular dynamics and Meta dynamics are used. Additionally, greatly extending accessible timelines are coarse-grained MD simulations. Effective use of MD simulations necessitates an all-encompassing strategy. It entails developing pertinent biological questions, creating suitable simulations, carefully configuring simulations with regard to experimental data, and performing painstaking analysis while taking any mistakes and fluctuations into account. It is crucial to validate results by contrasting them with experimental data and running additional tests. [10]

It is essential to have a firm grasp of both the biological system and the theoretical underpinnings of MD simulations. Iteration is a common part of the process, as each simulation and analysis cycle feeds following research. Utilizing MD simulations for significant scientific discoveries requires a careful and iterative approach that combines biological knowledge with computational competence.

C. Ligand Selection & MD Simulation:

Molecular Docking - A Key Tool in Drug Discovery

Biomolecular interactions, which were previously studied mainly through experimental techniques, have become an important source of knowledge since the emergence of computational tools such as molecular modelling, docking, simulations, and so on. In fact, the static model of structural biology developed to represent the time-dependent structural and functional dynamics of biomolecules at the atomic scale. The introduction of the molecular docking technique further simplified our knowledge of biomolecular sensing mechanisms, with a focus on the sorts of interactions that regulate complex formation1. Molecular docking is now widely used in structural molecular biology and computer-aided drug development. Its use in drug design has proved critical in the development of potential medication candidates. Molecular docking is a critical computational tool used in drug development to anticipate the interactions of a small molecule ligand with a target protein.6 The procedure is critical in determining the binding affinity and manner of interaction of prospective drug candidates with their targeted targets. Researchers can forecast the most favorable configuration of the ligand within the protein's binding site by modelling the docking process, assisting in the rational design of novel medications and speeding the drug development process.

D. Molecular Docking Principles:

Molecular docking uses multiple methods and scoring functions to study the alternative orientations and conformations of a ligand within a protein's active site. The objective is to find the most stable ligand complex with the protein, resulting in favorable binding interactions and high affinity. [8]

The process involves several essential steps:

1. **Protein and Ligand Preparation:** The first stage in molecular docking is to get the target protein and ligand ready for simulation. The structure of the protein is acquired from experimental databases or predicted using homology modelling. The three-dimensional structure of the ligand is taken from a chemical database or produced computationally.
2. **Search Algorithms:** Docking algorithms search the ligand's wide conformational space within the protein's binding site for the most favorable docking poses. Genetic Algorithms, Monte Carlo methods, and molecular dynamics-based approaches are examples of frequent search algorithms.
3. **Scoring Functions**: Scoring functions rank docking postures based on their projected binding affinity. These functions consider a number of parameters, including van der Waals interactions, hydrogen bonding, electrostatic interactions, and desolvation energies. For determining the most likely binding stance, accurate scoring functions are critical.

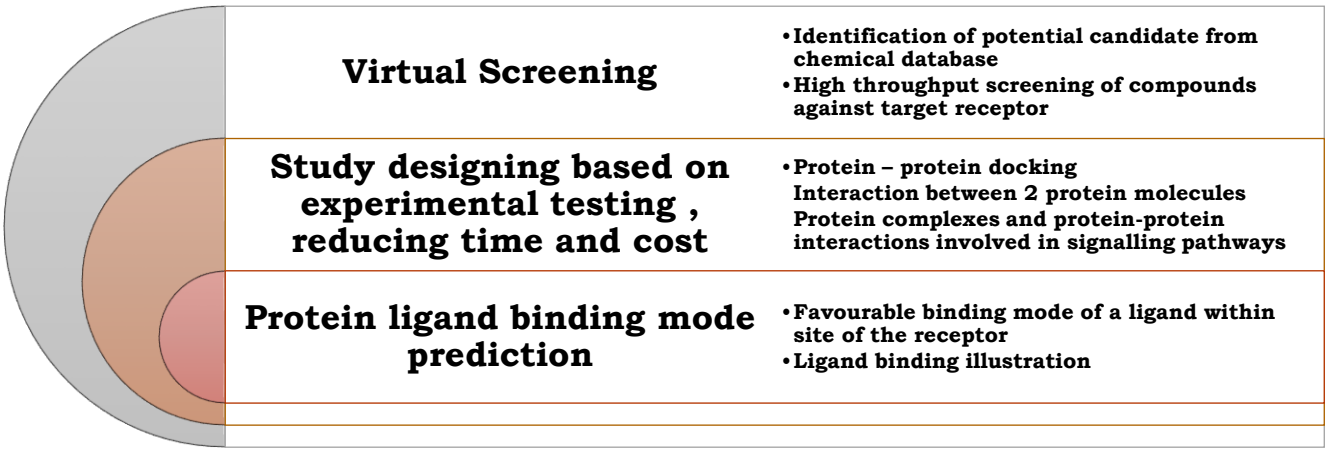


Figure 5: Types of Molecular Docking Techniques

Rigid body docking

- Most basic and widely utilized type of molecular docking.
- Both the ligand and the target protein are treated as rigid entities in this technique
- No conformational changes are permitted throughout the docking process.
- Objective is to find optimum match between the ligand and the binding site of the protein.
- Rigid body docking is a computationally efficient method that is well suited for large-scale virtual screening investigations

Flexible ligand docking

- For the ligand's flexibility while maintaining the protein rigidity.
- To obtain the optimal match within the protein's binding site.
- Useful when ligands can adopt multiple conformations during binding.

Flexible receptor docking

- It takes into account the target protein's flexibility while maintaining the ligand rigid.
- The protein's active site undergoes conformational changes to accommodate the ligand, allowing for a more accurate representation of the binding interaction.
- Suitable for cases where the protein undergoes significant structural changes upon ligand binding.

Induced fit docking

- Induced fit docking requires both the ligand and the protein to be flexible at the same time.
- The method investigates different ligand and protein conformations and takes into account the caused conformational changes that occur during binding.
- Useful method for predicting ligand-induced protein conformational changes.

Ensemble docking

- Involves the use of multiple protein conformations or models during the docking process.
- This approach accounts for the inherent flexibility of the protein and increases the accuracy of docking predictions.
- Useful when experimental protein structures are not available or when dealing with protein dynamics.

Blind docking

- The ligand is docked across the entire surface of the protein to explore potential binding sites.
- Useful method when the binding site is not well-defined or when looking for novel binding pockets.

Figure 6: Different types of docking methods with their uses

Visualizing the docked complex allows researchers to,

- Interpret Binding Interactions: Visualization allows for the investigation of hydrogen bonds, hydrophobic interactions, and other non-covalent interactions between the ligand and the receptor. This aids in the comprehension of binding affinity and the fundamental factors of ligand binding.
- Validation of Docking Results: A visual inspection aids in determining the dependability of docking predictions. Researchers can see possible steric conflicts or unrealistic binding postures that need to be improved.
- Structure-Based Drug Design: The visual analysis of the docked complex aids in the rational design of novel medications by highlighting potential modifications to improve ligand-receptor interactions.
- Selectivity and Specificity: Visualization assists in ligand selectivity research by evaluating interactions with various amino acids in the binding sites of closely similar proteins.
- Interaction Mapping: Visualization tools can provide interaction maps that highlight critical interactions between the ligand and the receptor, leading further ligand optimization.

E. Molecular Simulation in Molecular Docking

Molecular simulation is an important part of molecular docking because it provides useful insights into the dynamic behavior of ligand-receptor interactions. While docking predicts a ligand's most likely binding pose within a protein's active site, molecular modelling techniques like molecular dynamics (MD) allow researchers to analyze the complex's conformational changes, stability, and dynamic interactions over time. This chapter investigates the relevance of molecular simulation in molecular docking and the numerous parts of the drug development process that it improves. [10]

Setting up a molecular simulation of a docked complex, running the simulation, and analyzing the findings are all phases in the process. The following are the general steps for performing a docked complex simulation. [11]

Step 1: Molecular Docking is the first step: Before beginning the simulation, the docked complex must be created using molecular docking software such as Autodock Vina, Glide, or any other docking programme. Based on scoring systems and search algorithms, docking software predicts the ligand's binding position within the protein's active region.

Step 2: Structure Preparation: Using molecular modelling tools such as PyMOL or UCSF Chimaera, prepare the docked complex for simulation by inserting missing atoms, assigning charges, and specifying bond ordering. Remove any water or other solvent molecules that may have been present during the docking process.

Step 3: System Solvation: To generate a solvated simulation box, surround the docked complex with an appropriate solvent model (typically water molecules). The simulation box should be large enough to avoid false interactions between complicated periodic pictures.
Step 4: Ionisation and Neutralisation of the System: If necessary, add counterions (e.g., sodium or chloride ions) to neutralise the system's charge. Ascertain that the system's overall charge is zero or set to the desired physiological value.
Step 5: Parameterization of the system: In the simulation system, assign suitable force field parameters and partial charges to the ligand, protein, and solvent molecules. For accurate depiction of molecular interactions, use standard force fields such as AMBER, CHARMM, or OPLS.
Step 6: Energy Minimization: To relax any steric conflicts and eliminate unfavorable connections, do an energy reduction of the solvated system. Use energy reduction strategies such as steepest descent or conjugate gradient to reduce the energy to a minimum.
Step 7: Equilibration: Equilibrate the system by running a series of simulations at progressively higher temperatures and/or pressures. This procedure helps the system to stabilise before the production simulation.
Step 8: Manufacturing Simulation: Run the real molecular dynamics simulation for the necessary time period, which is commonly measured in nanoseconds or microseconds depending on the study objectives and system size. To do the production simulation, use molecular simulation software such as GROMACS, AMBER, NAMD, or CHARMM.
Step 9: Data analysis: Analyze the simulation trajectory to learn more about the ligand-receptor interactions. To visualize and analyses the simulation findings, use molecular simulation analysis tools like as VMD, PyMOL, or UCSF Chimaera. Examine critical metrics including RMSD, RMSF, binding free energy, hydrogen bonding, and other non-covalent interactions.

In molecular simulations, this involves analyzing the simulation time scale and extracting relevant information from a collection of atomic coordinates across time. Researchers can acquire useful insights into the dynamic behavior, stability, and interactions of ligand-receptor complexes by using diverse analytical approaches, contributing to a better understanding of biological processes.[13]
Nanoseconds (ns): In molecular simulations, "nanoseconds" (ns) are a unit of time used to calculate the simulation's duration. One billionth of a second (10-9 seconds) is equal to one nanosecond. Molecular dynamics simulations generally last several nanoseconds to microseconds, depending on the study aims and system complexity.
Interpretation: For investigating the dynamic behavior of a biomolecular system, the length of a molecular simulation is critical. Short simulations (e.g., nanoseconds) can be used to investigate quick conformational changes, ligand binding/unbinding kinetics, and early events in protein-ligand interactions.
Longer simulations (e.g., microseconds) are necessary to capture slower conformational changes, protein dynamics, and to reach free energy calculation convergence.
A "trajectory" is a collection of atomic coordinates (positions) of the simulated system across time in the context of molecular simulations. The coordinates of each atom in the system are recorded at regular intervals during a molecular dynamics simulation, providing a trajectory that reflects the system's mobility and behavior during the simulation.[17]
Interpretation: Trajectories include useful information about the biomolecular system's dynamic behavior, such as protein conformational changes, ligand binding interactions, and solvent fluctuations.
Trajectories may be examined by researchers to evaluate many features of the simulation, such as protein-ligand interactions, binding posture stability, and solvent effects.
Calculating root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), hydrogen bond analysis, and contact mapping are all common trajectory assessments.[15]
Trajectory Interpretation: To extract relevant insights from the simulation, the trajectory data must be interpreted using a variety of analysis tools and approaches.

Important steps in understanding trajectories:

1. RMSD Calculation: The RMSD analysis calculates the time-dependent variation of protein or ligand atomic locations from their original structures. It aids in determining the complex's stability and identifying conformational changes.
2. RMSF Evaluation: RMSF analysis computes the atomic position variation of residues or ligands during simulation. It sheds light on the adaptability of various sections within the complex.
3. Analysis of Hydrogen Bonds: During the simulation, hydrogen bond analysis assesses the creation and stability of hydrogen bonds between protein and ligand or protein residues. It aids in understanding the main interactions that contribute to ligand binding. [13]

In drug development and structural biology, molecular docking and simulation are essential methods. Docking models ligand-receptor interactions, whereas simulations investigate complicated dynamics. They contribute to our understanding of biomolecular system binding processes, stability, and conformational changes. These approaches speed treatment discovery and optimization by uncovering crucial interactions and validating promising medication candidates. Molecular docking and simulation continue to increase our understanding of biological processes, assisting in the discovery of new medications and advancing precision medicine techniques. [10,12]

II. DISCUSSION & CONCLUSION:

Structure-based drug design (SBDD) has revolutionized the drug discovery process by enabling a rational and targeted approach to identify potential drug candidates. This method utilizes the 3D structures of target proteins, often obtained through X-ray crystallography, NMR spectroscopy, or computational modeling, to design ligands that can specifically interact with the target and modulate its activity. Structure-based drug design has emerged as a powerful tool in modern drug discovery and has significantly impacted the development of new therapeutic agents. By leveraging the 3D structures of target proteins, SBDD enables the design of ligands that specifically interact with their targets, leading to increased potency and reduced off-target effects. However, SBDD is not without its challenges. Obtaining accurate and relevant target structures can be difficult, especially for novel or difficult-to-crystallize proteins. Docking and scoring algorithms still face limitations in accuracy, especially when dealing with protein flexibility and accounting for water molecules. Despite these challenges, structure-based drug design continues to be an indispensable component of the drug discovery pipeline. When integrated with other approaches, such as ligand-based methods and phenotypic screening, SBDD

can greatly improve the efficiency and success rate of drug discovery projects. As computational power and modeling techniques continue to advance, structure-based drug design is expected to become even more effective and play an increasingly critical role in the development of novel and more targeted therapeutics for a wide range of diseases. [11]

III. FUTURE ASPECTS

As structure-based drug design (SBDD) continues to evolve, several future issues and challenges are likely to arise. Addressing these challenges will be crucial to maximizing the potential of SBDD in drug discovery.
Key issues which are need to take into consideration:

Figure 7: Possible future advancements

In conclusion, structure-based drug design has come a long way and has significantly impacted drug discovery. However, future advancements in computational methods, data availability, and integration with experimental techniques will be essential to tackle the challenges and unlock the full potential of SBDD in developing safer, more effective, and personalized therapeutics. Collaboration between researchers, computational experts, and experimentalists will be crucial to address these future issues successfully.

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