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Computational Methods in Drug Discovery and Development

S. Y. Ugurlu (1*)

(1) School of Computer Science, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom, s.yavuz.ugurlu@gmail.com

***Corresponding author:** s.yavuz.ugurlu@gmail.com

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Abstract: The rapid advancements in computational methods have revolutionized drug discovery and development. These methods, ranging from molecular modeling to machine learning algorithms, have drastically increased in number and sophistication. However, a comprehensive understanding of these diverse approaches is essential for researchers aiming to make significant contributions to this evolving field. This review aims to provide a detailed overview of the most prominent computational methods currently used in drug discovery. It will analyze their underlying principles, discuss their applications, and highlight their potential for future advancements in the field. Through this examination, we aim to equip researchers with the necessary insights to navigate and contribute to the rapidly expanding landscape of computational drug discovery.

Keywords: Computational drug discovery, Molecular modeling, Drug development, Computational methods, Drug design applications, and Machine learning algorithms.

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1. Introduction

Traditional methodologies for drug discovery can be classified according to the availability of target and ligand structures (Figure 1). The conventional drug categorization discovery methodologies encompass four primary groups ([3]): (i) Library design, (ii) Structure-based design, (iii) Ligand-based

design, (iv) De Novo Design (Figure 1). In addition to traditional classification, it is possible to introduce a novel category known as the quantum mechanical simulations and chemoinformatics approach, which can be considered novel classes.

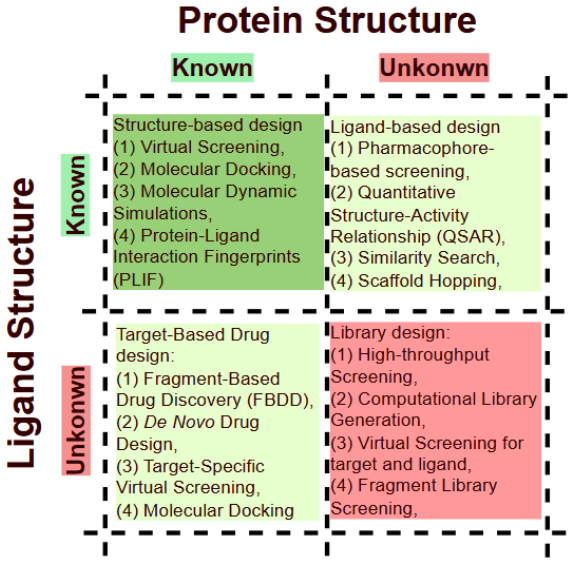

Figure 1: Overview of Conventional Approaches for Drug Discovery

The overview shows that target and ligand structures define the categorization of conventional approaches for drug Discovery. There are four conventional classes: (i) library design, (ii) structure-based drug discovery, (iii) ligand-based drug discovery, and (iv) target-based drug discovery. Besides these, quantum mechanical simulations and chemoinformatics can be used as modern approaches.

Commonly categorized based on the presence of target and ligand structures, traditional approaches to drug discovery each provide unique advantages and challenges. First, structure-based drug discovery, or SBDD, is the method of developing novel medications using knowledge of the three-dimensional form of the target protein to produce small molecules that can precisely bind to particular areas on the surface of the protein and alter its action. Often utilized to identify potential therapeutic candidates in the structure-based medicinal design process are techniques such as virtual screening, molecular dynamics simulations ([151]), and molecular docking ([108, 109, 166, 144, 219, 190, 237]). Second, ligand-based drug discovery (LBDD) is more concerned with investigating well-known ligands' chemical and structural characteristics that firmly bind to the target protein. By analyzing ligand similarities and differences, LBDD techniques—such as pharmacophore-based virtual screening and quantitative structure-activity relationship (QSAR) modeling ([187]), can forecast novel compounds with similar biological properties. Third, using either experimental or computational approaches, library design is essential for identifying molecules with specific pharmacological characteristics among vast collections of chemicals. The last, de novo design ([103, 226]), aims, in essence, to create new chemical entities not seen in the natural world before (Figure 1). Besides these four conventional approaches, cheminformatics, as the last group, uses computer methods to organize, analyze, and predict chemical data and attributes to identify drug candidates and optimize their efficacy and safety. It streamlines medication design by integrating chemistry and biology to uncover new medicinal molecules faster and more accurately.

With the accumulation of data and the development of advanced methods, the conventional approaches (Figure 1) have expanded, leading to a rapid increase in the number of main categories. However, in the review, the literature has been reviewed across six sections to present a comprehensive overview of conventional approaches in drug discovery: (i) Library design for drug screening; (ii) Structure-Based Drug Discovery, which delves into methods utilizing the 3D structure of target proteins; (iii) Ligand-Based Drug Discovery, focusing on approaches that rely on known ligands

to find new drugs; (iv) Target-based Drug Discovery; (v) Quantum Mechanical Simulations, which forecast atomic-level molecular behavior, revealing electronic structures, reaction mechanisms, and binding interactions, and (vi) Cheminformatics Approaches for Drug Discovery, highlighting computational techniques to analyze chemical data.

1.1 Library Design for Drug Screening

Library design for drug screening is one of the key steps in drug discovery (Figures 1 and 2). Library design is the most time-consuming process in drug discovery since there is no target or ligand at the beginning of the drug discovery. The most logical way to define a target library is since the possible target number is significantly lower than possible ligands and drug candidates. A library with a target-focused approach refers to a compilation of chemicals that have been intentionally created or constructed to target a protein or protein family specifically. The rationale behind screening such a library is based on the notion that a reduced number of compounds is required to identify hit compounds. Moreover, it is commonly observed that there is a higher rate of successful hits when comparing the screening of diverse sets. Additionally, the hit clusters resulting from a successful focused library screening campaign typically display transparent structure-activity relationships, which aid in the subsequent analysis and investigation of these hits ([80]).

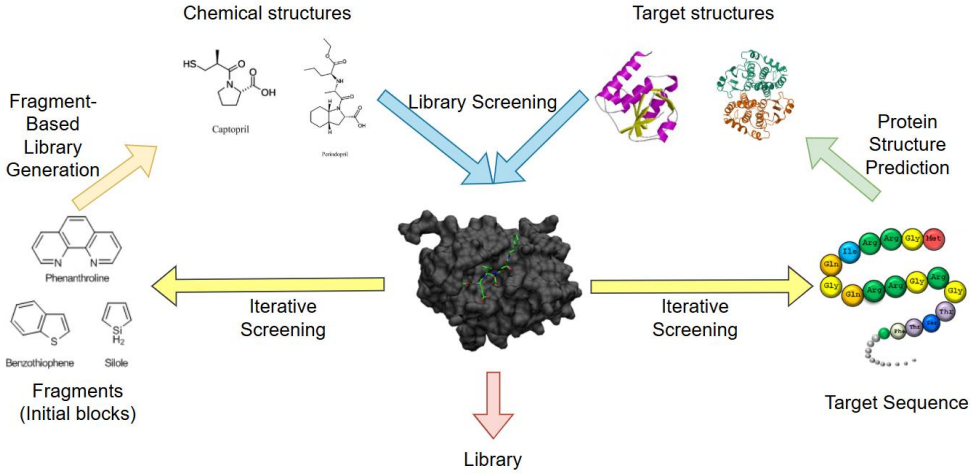

Figure 2: The schematic representation of the library design

The library design procedure for drug and target screening encompasses many crucial elements to guarantee the inclusion of a wide-ranging and all-encompassing assortment of probable therapeutic candidates. The process commences with the choice of primary constituents, which are diminutive, structurally diverse molecules employed as the fundamental basis for the collection. Subsequently, these fundamental components are merged in different ways during the phase of library formation, resulting in a wide range of chemical compounds. Subsequently, the library undergoes global propagation and the establishment of a collection of diverse species, wherein various molecular variations are methodically generated and organized. Subsequently, these species undergo testing to determine their capacity to attach to the designated receptor, thereby identifying potential candidates that show promise for subsequent advancement. The technique is recursive, where the successful binding species guide the selection of new building blocks, thus continuously improving and enlarging the library for succeeding screening cycles.

Target-oriented libraries usually have a single core or scaffold with one or more attachment points, usually two or three. Different substituents or side chains are added to get the desired molecules. If all conceivable combinations were considered, a scaffold that is diversified at two or three attachment locations of diversity would provide a library consisting of numerous chemicals. Generally, a subset of these compounds is often selected for synthesis, ranging from 100 to 500. The selection is made in order to effectively investigate the design hypothesis and ensure adherence to drug-like features with the help of systematic exploration ([80]).

The systematic exploration of the chemical space and the identification of prospective

therapeutic candidates are facilitated by constructing a library for drug screening, a critical element of drug development ([80]). Choosing molecules that demonstrate a diverse array of structural characteristics is imperative to enhance the probability of identifying active matches. Furthermore, the design approach frequently employs computational techniques to predict the pharmacokinetic and pharmacodynamic properties of the medications, thereby enhancing the efficacy of the screening process. Consequently, these libraries can be implemented in various drug discovery methodologies, including structure-based, ligand-based, de novo drug development, and cheminformatics.

1.2 Structure-based drug discovery

Utilizing three-dimensional structures of biological targets, such as proteins or nucleic acids, in the computational drug discovery approach known as structure-based design (SBDD), enables the formulation of novel therapies with high specificity and affinity. To put it differently, SBDD is crucial in contemporary drug development since it utilizes molecular knowledge about target-ligand interactions to inform the logical creation of small molecules or biologics. SBDD allows for identifying crucial chemical interactions and optimizing compound structures to improve binding affinity and selectivity by comprehending the spatial arrangement of atoms within the target binding site. This methodology encompasses diverse methods, such as molecular docking, virtual screening, fragment-based design, and molecular dynamics simulations. The primary objective is to leverage structural data in order to accelerate the process of drug exploration and advance the development of safer and more efficacious therapies for a multitude of diseases ([16]), such as using Molecular docking.

1.2.1 Molecular Docking in Drug Discovery

Molecular Docking (MD) is one of the most common methods to investigate drug-target correlation (Figure 3). Regrettably, conventional and ML-based docking methods have been plagued by a significant false-positive rate, leading to limited effectiveness ([2, 222]). ML models trained using the outcomes of molecular docking programs can effectively decrease the occurrence of false positives in MD and ML-based docking ([190]). Therefore, high false positives reduce the performance of MD. Initially, comprehending the concept of molecular docking is the primary prerequisite for constructing a proficient machine-learning model on molecular docking software.

The first use of molecular docking in drug discovery was in the early 1980s ([29]), with a simplified function based on “hard sphere repulsions” and “hydrogen bonding” ([2]). The research on docking has enhanced its streamlined functionality by considering different variables in the scoring function besides “hard sphere repulsions” and “hydrogen bonding”. The enhanced functionalities augmented the precision of docking and gradually introduced innovative phases. For example, the enhanced functionalities include data on the binding strength and the molecules’ shape. Consequently, the efficiency of MD has progressively increased due to the implementation of new features, including enhanced functionalities.

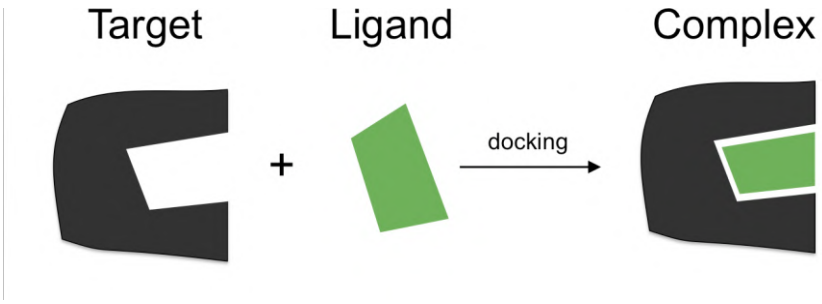

Figure 3: A fundamental component of molecular docking

The graphic shows the molecule bonding process. Fundamental to molecular docking is the computer prediction of the binding

mechanism and affinity of small molecules (ligands) within the active site of a target protein. This method helps to find possible therapeutic options by assessing the degree of interaction and complementarity between the ligand and the protein target ([148]).

Two steps define docking primarily: (i) prediction of the binding site and (ii) prediction of a ligand conformation and binding affinity ([125]). Unfortunately, even with developments in molecular docking methods, accurate docking cannot be guaranteed. Consequently, the success percentage of docking ranges from 0% to 92.66% ([27]). Therefore, establishing successful docking—which directly affects our machine—learning model's efficacy—depends on understanding docking classifications and selecting the current approaches. Thus, building strong and very effective models depends on understanding the mechanism of molecule docking. Therefore, the fundamentals of molecular docking are discussed in the following seven sections, from the Molecular Mechanism of Docking to the Classification of Docking by Search Space.

Molecular Mechanism of Docking

In molecular docking simulations, evaluating the quality of contacts between ligands and receptors depends on scoring functions, so the molecular mechanism of docking mainly consists of their usage. By evaluating several elements, including intermolecular forces, steric conflicts, hydrogen bonding, and electrostatic interactions, scoring systems in docking algorithms evaluate and rank possible binding positions. Forecasting the binding affinity between a ligand and a receptor is one of these purposes; this is crucial for discovering potential drug candidates. Standard scoring systems are empirical, which uses pre-defined criteria, and physics-based, which uses computational models derived from basic physical principles. The dependability of docking predictions depends much on the precision of scoring systems, affecting structural biology and drug discovery research's decision-making. Maximizing docking protocols and improving the accuracy and efficiency of molecular docking simulations depend on a knowledge of the complexity of scoring systems.

The scoring functions in molecular docking programs are essential in computational drug discovery and the research of protein-ligand interactions ([100]). It is a mathematical model employed to evaluate and prioritize the strength of the interaction between a tiny chemical (a ligand) and a target protein receptor. The scoring function assesses the potency of the ligand-receptor interaction, forecasting the probability of a favorable binding position. This forecast is crucial for identifying therapeutic candidates or comprehending protein-ligand interaction mechanisms ([100, 58]). A comprehensive scoring function considers multiple aspects, including van der Waals contacts, electrostatic interactions, hydrogen bonding, solvation effects, and entropy variations. The comprehensive scoring function is significant in effectively sifting through extensive collections of chemical compounds, prioritizing those with the strongest binding affinity for subsequent experimental confirmation. An accurately calibrated scoring function can significantly expedite drug development by directing medicinal chemists toward molecules with the highest therapeutic potential. Accurate calibration minimizes the time and resources required for synthesizing and testing candidate compounds ([203]).

A scoring function is used to estimate the binding affinity of a tiny molecule, which is a crucial component of docking software. A scoring function typically consists of three main subclusters: (i) physical force field-based, (ii) empirical, and (iii) knowledge-based scoring functions ([105]) (Figure 4).

Scoring functions that utilize physical force fields (or force fields) are employed to analyze molecular interactions (Figure 4). The approach integrates molecular dynamics (MD), binding affinity, and free energy perturbation (FEP) methods. Medusa Score, for example, is one of the physical force field-based approaches. The research demonstrated that the Medusa Score success rate is around 82% ([223]). The success rate is better than various standard scoring functions, including DrugScore, F-Score, LigScore, ChemScore, PLP, LUDI, PMF, X-Score, G-Score, D-Score, and AutoDock. When the scoring method was hybridized with DrugScore, it became 85% ([223]). However, the drawbacks of techniques are speed and sampling limitations ([223]).

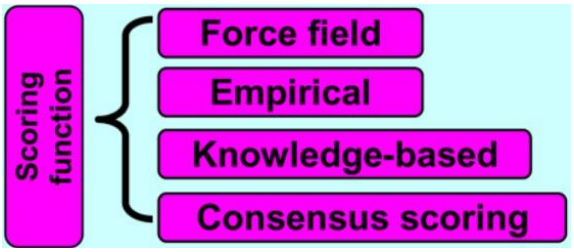

Figure 4: The scoring function classification of molecular docking programs

The diagram depicts three distinct categories of scoring functions that are frequently employed in molecular docking investigations: (i) scoring functions based on the force field, (ii) scoring functions based on empirical, (iii) scoring functions based on knowledge, and (iv) consensus scoring function. The scoring functions utilized in structure-based drug discovery employ unique approaches to assess the binding affinity between a ligand and its target protein.

Empirical scoring functions aim to calculate binding free energy by leveraging chemical interactions, such as hydrogen bonds ([67]). In essence, binding energy determination depends on the molecular interactions. Molecular interaction variables include Van der Waals, dipole-dipole interactions, London dispersion forces, and hydrogen bonds. Some examples of docking programs that utilize empirical scoring functions include DOCK 4.0 ([54]) and AutoDock ([125, 173]). Molecular docking programs using empirical scoring function examples have already demonstrated their efficacy in the field ([125, 173, 189]). Hence, empirical scoring functions are the most auspicious methodologies.

The other scoring method is knowledge-based scoring functions, which use statistical analysis of protein complex structures. These functions model uncommon atoms, such as sulphur-aromatic. They also work on the statistical analysis of the ligand-target 3D complex structure. For example, Bleep, DrugScore, PMF, and SMoG are the most common knowledge-based scoring functions ([75, 66, 197]). Knowledge-based scoring functions have demonstrated satisfactory performance in molecular docking programs.

Molecular docking programs that employ consensus scoring functions integrate the outcomes of various scoring methods to enhance the precision and dependability of forecasting ligand-receptor interactions ([185]). For example, CompScore utilizes a consensus scoring function in docking ([142]). The other example is CoBDock, which benefits molecular docking scoring function and cavity detection tools to build a consensus approach ([190]). The programs utilize consensus scoring to effectively balance the merits and drawbacks of individual scoring systems, thereby improving the overall accuracy of predictions ([21]). Consensus scoring offers a significant benefit by effectively decreasing the occurrence of incorrect positive results and enhancing the reliability of forecasts regarding binding affinity. Nevertheless, the drawback is that it frequently necessitates additional computer resources and time, as it involves many scoring calculations that must be done and combined. In addition, the intricacy of including many scoring algorithms might occasionally result in incongruous outcomes if the consensus approach is not optimized ([185, 99]). Consequently, our machine learning model underwent training using several scoring function outcomes in order to enhance its performance. Our ML model's method enhances molecular docking accuracy by mitigating false positives.

Bound vs. unbound molecular docking

A protein's conformation is categorized into bound (complex) and unbound (one outside of a complex) structures (Figure 5). The bound docking separates a complex and then redocks parts of the complex to build the original complex. While bound docking is essential for developing new docking programs, it does not hold much value in biology. When an unbound docking program predicts a new interaction between a ligand and target (where the ligand and target are not already bonded), it enhances our understanding and becomes highly beneficial.

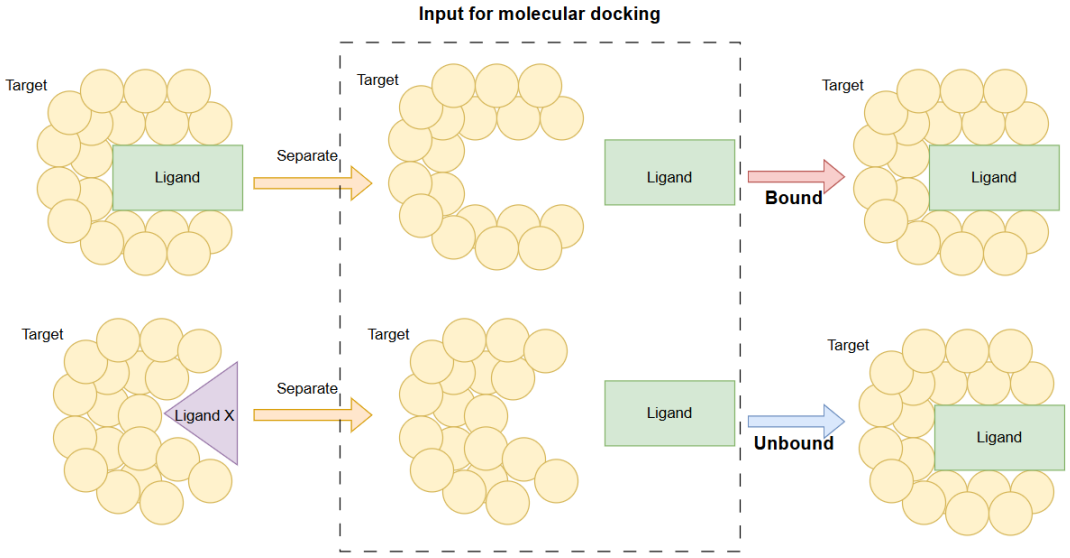

Figure 5: The representation of bound (up) and unbound (down) input for rigid and flexible docking

The bound docking process is similar to re-docking, where the ligand-protein complex is initially separated into its constituent components to perform docking. This approach aims to reproduce the original complex by predicting how the ligand binds to the target protein, often resulting in more accurate and reliable binding predictions. In contrast, unbound docking involves using different initial poses for both the ligand and protein, which helps prevent data leakage during the docking process. As a result, unbound docking typically performs less than bound docking due to the added complexity and uncertainty in predicting the correct binding mode without prior knowledge of the complex. However, unbound docking is critical in exploring novel interactions, particularly when investigating new or unknown targets, offering valuable insights into potential binding sites and ligand flexibility. While less precise, unbound docking is essential for discovering new drug-target interactions and for situations where the ligand-protein complex is not yet available or fully characterized.

Bound docking software cannot be significantly successful for an unknown compound because of limited performance in real-life cases. On the other hand, unbound docking provides vital information about unknown ligand-target complexes ([192]). Therefore, unbound docking is called “real-life docking” ([48]) because of the impact on research. Regrettably, the progress of unbound docking approaches has been hindered due to a lack of understanding of binding parameters. Hence, our machine-learning techniques and pipelines have been optimized for unbound docking, making them the superior choice for new drug discovery and development.

Template-Based (Homology) Docking

Using known protein structures (templates), template-based (homology) Docking is a computer method indispensable in structural biology and drug development that predicts the 3D structure of a target protein and performs molecular binding. This method depends on the idea that proteins with similar sequences usually show identical shapes and activity. Two main phases comprise the process: first, using a 3D model of the target protein derived from sequence comparison for template-based molecular docking, whereby possible ligands are assessed against the projected structure to identify potential drug candidates([38]).

Predicting 3D target model Approximately 6% of the protein correlations in the human interactome, predicted to be researched experimentally, have been examined ([182]). The scarcity of three-dimensional target models poses a significant obstacle in structural-based drug discovery and development. As a result, various techniques have been created to anticipate three-dimensional target models, one of which is template-based modeling (TBM). TBM uses the known structures to predict a protein model structure (Figure 6). Several TBMs exist in the literature, including MODELLER ([206]), SWISS-MODEL ([205]), and FoldX ([14]).

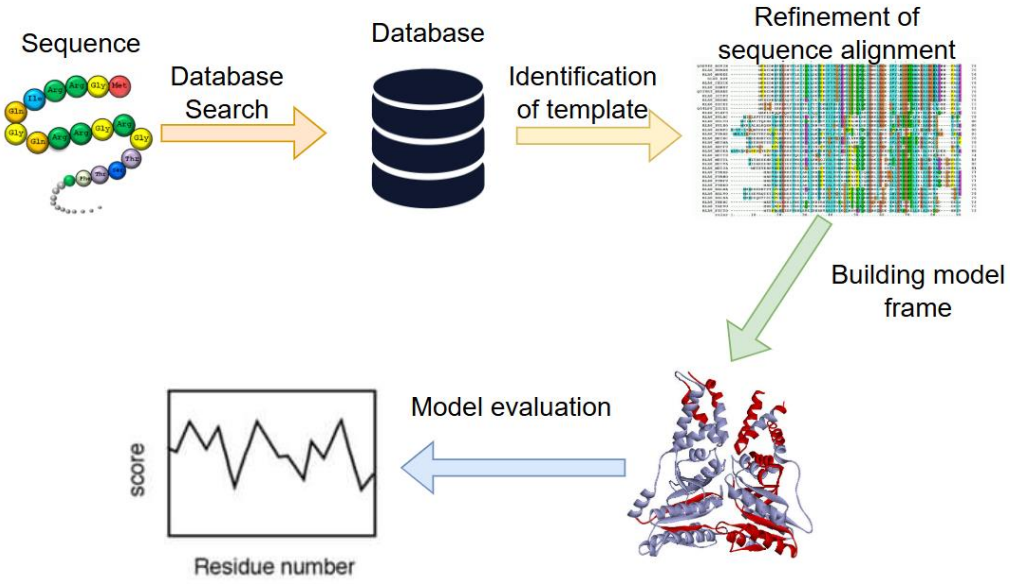

Figure 6: The figure illustrates the procedure for constructing a homology model based on a protein sequence.

The process entails aligning the sequence with homologous proteins with a known structure, selecting templates depending on the alignment quality, constructing a model using comparative modeling approaches, and refining the model to enhance its structural accuracy. Homology modeling allows for anticipating protein structures in three dimensions, helping develop structure-based drug design and other molecular investigations.

The main limitation of TBM is the lowered sequence similarity with known proteins, which significantly influences the prediction accuracy. Low sequence similarity compromises the structural model's dependability, leading to mistakes ([160]). Conversely, ab initio methods—which rely not on current protein structures—can provide answers in these contexts. Still, these methods are computationally demanding and labor-intensive; exact results often require significant resources. This double issue emphasizes the need for discoveries in both TBM and ab initio methods to improve the dependability and efficiency of protein structure prediction ([135]). However, TBMs are still practical for template-based molecular docking in drug discovery.

Template-based molecular docking Sometimes known as template-based or homology modeling, template-based docking is a computer technique used in molecular docking to predict the three-dimensional arrangement of a protein-ligand complex by using the established structure of a comparable protein-ligand complex ([65]). This method is predicated on the idea that proteins with similar sequences or structures often bind similarly to ligands. Matching the sequence or structure of the target protein with that of the template protein models the structure of the target protein in template-based docking. One uses computational methods to create the missing or variable elements, including side-chain prediction or loop modeling. Molecular docking techniques are applied to anticipate the binding shape and affinity of ligands within the target protein's binding site once a protein model is generated ([216, 146, 65]).

When the experimental structure of the target protein is not easily obtainable or accessible, template-based docking is quite beneficial for understanding the structure and using it in structure-based drug discovery and development. It substantially helps to identify new medications and provides essential new perspectives on the interactions between proteins and ligands. Still, it is imperative to confirm the accuracy and reliability of the expected models by rigorous computational analyses and experimental validation ([216, 146]). Understanding the classification of molecular docking can be beneficial for minimizing the need for experimental validation.

Classification of Docking by Molecule Type Different types of molecules used in the docking

process help to classify molecular docking, a fundamental computational tool used in structural biology and drug development. This classification distinguishes among several docking situations. Each is meant to address specific research hypotheses and objectives. Three varieties of molecular docking models are known to exist: small molecule-protein ([184]), peptide-protein ([234]), and protein-protein ([139]). Mostly in terms of the scoring systems, they have many parallels. The scoring system determines the strength of the contact between a target and a molecule. The three molecular docking techniques differ mainly in the molecules' dimensions and the search area's size.

Small molecule-protein docking

Small molecule-protein docking is an essential computational technique in structural biology and drug development. It aims to ascertain the binding modes and affinities inside the binding site of small compounds or ligands, thereby guiding their binding to a target protein([184, 56]) (Figure 7). Examples of small molecule docking programs are AutoDock ([49]), BetaDock ([89]), PLANTS ([55, 91]), and GalaxyDock3 ([219]). Also, rational drug design depends on this method since it provides essential knowledge on the molecular interactions between ligands and proteins. The data about interactions enhance the binding properties of potential drugs and helps to identify them.

Small molecule-protein docking systems also scan the conformational space of ligands and proteins using different scoring systems and search strategies in order to forecast energetically favorable binding locations ([211, 56, 229, 84]). By exposing the fundamental architecture of protein-ligand interactions, small molecule-protein docking helps to generate more selective and successful treatments.

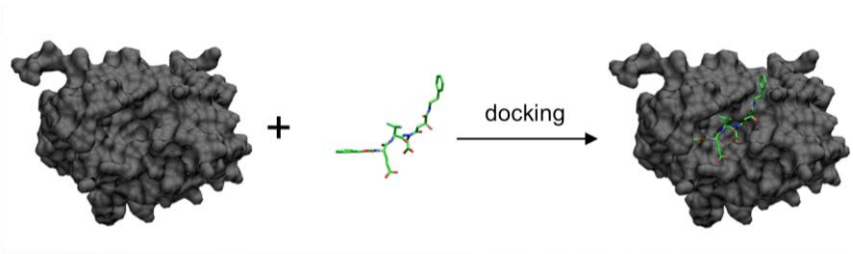

Figure 7: The figure depicts the process of small-molecule (ligand) docking into a protein target.

Molecular docking techniques computationally predict the binding mode and affinity of small molecules within the active site of the protein. The figure illustrates the exploration of ligand conformational space, docking pose generation, and scoring to identify potential drug candidates for further optimization in structure-based drug design studies.

The conformation of a ligand is one of the significant values to evaluate docking results, such as RMSD ([125]). RMSD calculates the average distance between the atoms of stacked proteins or ligands and assesses the similarity between the reference structure and the expected docked location. A known experimental structure is often used to determine the accuracy of docking predictions using docked conformation. Once the conformation of ligands approaches the natural structure, the RMSD of small ligands is close to zero.

Peptide-protein docking Peptides have vital roles in many biological processes, including cellular communication, control of enzymes, and modification of immune response ([119]). Also, targets for drug development are peptide-protein complexes since small peptides either act as inhibitors or modulators of protein activity. Furthermore, peptides derived from proteins can be the basis for developing peptide-based treatments such as peptide mimics or vaccinations ([121]). Therefore, it is essential to understand the binding topologies and strengths of peptide-protein complexes.

Molecular docking offers a vital tool for estimating peptide-protein complexes' binding topologies and strengths. Investigating the interactions between peptides and proteins is

accomplished by docking. This technique guarantees the prediction of the strength of the binding, finds the particular sites where these interactions occur, and helps to identify the relevant residues. Understanding peptide-protein interactions in biological systems ([119, 229, 121]) and developing peptide-based drugs depend on this knowledge. Finding the operational processes and possible therapeutic applications for peptides and proteins depends on understanding their interactions ([119]). Therefore, programs including pepATTRACT ([40]), FlexPepDock ([111]), HADDOCK2 ([193]), and PEP-SiteFinder ([162]) have been utilized to comprehend the binding topologies and strengths of peptide-protein complexes.

A comprehensive comprehension of the binding topologies and strengths of peptide-protein complexes is necessary to elucidate their functional functions and facilitate the development of therapies based on peptides. The process of peptide-protein docking generally consists of two primary stages using molecular docking ([234]): (1) the creation of peptide conformations and (2) the anticipation of their interaction with the protein target. The initial stage involves the utilization of diverse conformational sampling methodologies, such as Monte Carlo simulations or molecular dynamics simulations, to investigate the conformational space of the peptide ([150]). Docking algorithms are employed in the second stage to forecast the most favorable binding position and strength of the peptide within the binding site of the protein target. The algorithms frequently employ scoring functions to assess the compatibility between the peptide and protein, as well as to choose the binding mode that is most energetically advantageous (Figure 8).

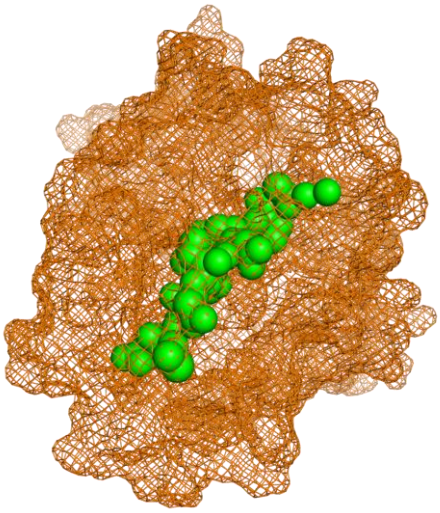

Figure 8: A sample of peptide (in green) and protein (in orange) complex after docking.

A peptide-protein docking program, such as Rosetta FlexPepDock, AutoDock, or HADDOCK, has been used to predict the binding pose of the peptide on the target protein. These tools evaluate peptide positioning by analyzing molecular interactions, including hydrogen bonds, hydrophobic contacts, and electrostatic forces. After docking, PyMOL was used to visualize the peptide (in green) bound to the target protein, highlighting the predicted binding pose and key interaction regions.

Protein-protein dockings

A computer method used to predict the three-dimensional shape of a complex resulting from the interaction of two or more proteins is protein-protein docking (Figure 9). Many biological functions, including enzyme activity and cellular signaling, depend critically on these relationships. Known examples of docking programs for protein-protein binding are HDOCK ([215]), MEGA DOCK ([174]), and ZDOCK ([144]) to investigate these interactions. Simulating the binding interaction between proteins using the protein docking program helps one to find the best orientation and position at which the two proteins bind. In the drug development framework, the given knowledge is quite valuable as it allows the creation of molecules that specifically target protein-protein interactions and inhibit pathogenic pathways. Due to the complex design of protein-protein interactions and the broad

spectrum of possible binding methods, protein docking remains challenging, even with significant advancement. Still, ongoing studies help to improve the accuracy and efficiency of docking methods, therefore transforming them into a powerful tool for understanding the intricate terrain of protein interactions.

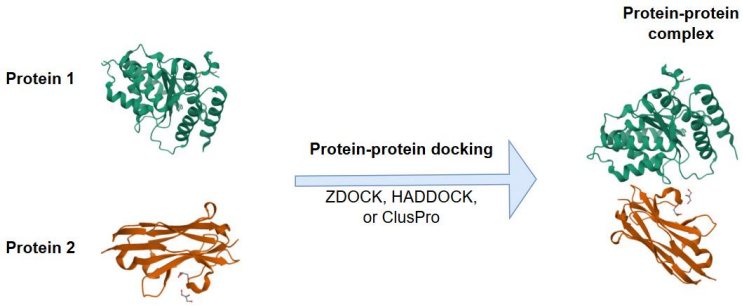

Figure 9: The figure shows an example of protein-protein docking, in which two protein molecules connect to form a complex.

A protein-protein docking approach predicts two proteins' most advantageous binding modes and affinity. The figure shows the study of conformational space, the generation of docking poses, and the scoring methods used to ascertain the binding configuration most energetically favorable among the proteins engaged in the interaction.

Classification of Docking by Flexibility

Molecular docking is a prevalent computational method in structural biology and drug development. It is used to forecast the binding interactions of molecules, such as proteins and ligands. The flexibility of molecules, specifically proteins, is vital in influencing their ability to bind and selectivity. Three primary methodologies are typically utilized in molecular docking research to accommodate protein flexibility: ([96]): (i) rigid docking, (ii) semi-flexible docking, and (iii) flexible docking (Figure 10). Each methodology presents unique benefits and constraints, and the method selection relies on the research goals and attributes of the studied biological system.

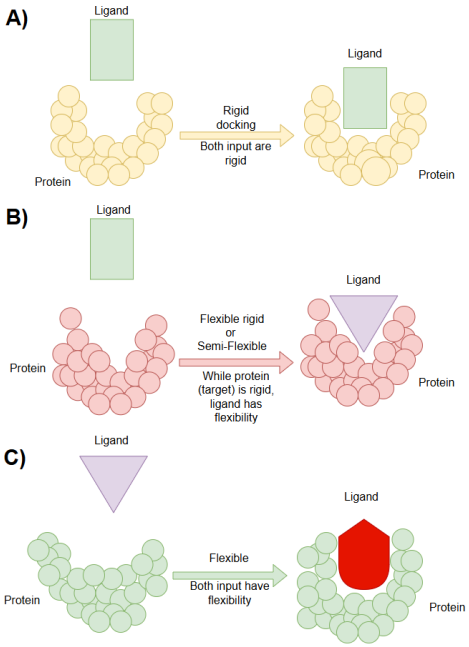

Figure 10: Three different protein docking techniques—rigid docking, flexible-rigid (semi-flexible) docking, and flexible docking—are shown in the diagram.

Every method forecasts the binding interactions among protein molecules using different approaches. While semi-flexible docking enables limited flexibility in some areas, rigid docking requires the absence of any changes in the shape of the protein

structures. Conversely, flexible docking considers significant conformational changes in proteins and ligands during binding.

Rigid docking

Rigid docking is a computational structural biology and drug development approach that predicts molecule-binding interactions. Here are several examples of grid docking programs that have been employed in drug discovery and development, including MS-DOCK ([167]), pyDock ([28]), and RDOCK ([101]). Such rigid docking programs assume that the ligand and receptor molecules have constant and unchanged shapes during the docking process ([4]). The technique helps determine the binding modes and affinities of molecular complexes. Rigid docking reduces the computational complexity by disregarding any changes in the shape or structure of the ligand or receptor when they bind together. It allows for a quick examination of the binding possibilities. Rigid docking methods utilize several algorithms and scoring functions to systematically explore energetically favorable binding positions, hence aiding in detecting potential interactions between ligands and receptors.

Although rigid docking may oversimplify the dynamic nature of molecular interactions, it continues to be a valuable tool for virtual screening, lead optimization, and structure-based drug design initiatives. Rigid docking is essential to drug discovery because of its computational efficiency and capability to handle massive datasets. It allows researchers to choose potential therapeutic candidates for further experimental validation and optimization ([167, 28, 4, 101]).

Semi-flexible docking (Flexible-rigid docking)

Semi-flexible docking (Figure 10) is a computational method that combines the features of rigid and completely flexible docking approaches. It aims to balance computational efficiency with the ability to ac- count for ligand flexibility during docking. Numerous molecular docking programs, such as DiffBind ([236]) and CANDOCK ([59]), have been documented in the literature and can be utilized to explore ligand-receptor interactions. Semi-flexible docking, such as DiffBind ([236]), involves keeping the receptor structure fixed while allowing the ligand to undergo limited conformational flexibility. This flexibility enables the ligand to make structural alterations to match the binding site better. The semi-flexible docking approach recognizes the significance of considering the flexibility of ligands in accurately forecasting binding modes and affinities, especially in situations where ligands can take on many conformations when binding to the receptor ([236]). Semi-flexible docking methods utilize algorithms and scoring functions that can effectively explore the flexibility of ligands while quickly sampling the space for binding. Semi-flexible docking is vital to enhance the reliability of virtual screening and drug design studies by effectively modeling ligand-receptor interactions while considering computing cost and accuracy ([183, 59]).

Flexible Docking

Flexible docking (Figure 10) is an advanced computational method used in molecular docking to consider the flexibility of both the ligand and receptor while performing docking ([152]). Flexible docking methods accommodate conformational changes in both the ligand and receptor, unlike rigid docking methods that assume constant conformations for both molecules. Flexible docking makes predictions more accurate and better than rigid and semi-flexible docking because it adds complete flexibility to the docking process ([158]). Therefore, there are plenty of flexible docking programs in the literature, such as CABS-dock ([94]), ATTRACT ([41]), DREAM++ ([120]), and SwarmDock ([188]). As a result, they provide a more thorough understanding of the landscape of interactions between ligands and receptors; therefore, it is a helpful tool in drug discovery, virtual screening, and structure-based drug design efforts ([158]).

Classification of Docking by Input Number

Classification of Docking by Input Number involves categorizing docking methods based on the number of input molecules or targets involved in the process. This classification helps in understanding the scope and application of different docking approaches. There are three main

groups under this classification: (i) Reverse (Inverse) Docking, which involves screening a single ligand against multiple protein targets to identify potential binding sites and off-target effects ([87]); (ii) Virtual Screening, where an extensive library of ligands is screened against a single protein target to identify potential drug candidates ([37]); and (iii) Cross-Docking, which involves docking multiple ligands against multiple protein targets to explore a wide range of possible interactions and binding affinities. Each group offers unique insights and advantages, making them valuable tools in computational drug discovery ([106]).

Reverse (inverse) docking

Reverse docking techniques utilize advanced algorithms and scoring functions to assess the binding affinity between the ligand and different protein targets ([214]) (Figure 11). Reverse docking allows for ranking candidate targets based on their projected interaction strength. It is a method that involves methodically analyzing protein structures to identify potential biological targets for small compounds. Therefore, reverse docking is a method that differs from typical docking approaches as it prioritizes the prediction of protein-ligand interactions. Instead of guessing how a ligand will interact with a protein, reverse docking looks through a library of protein structures to see which ones might interact with a specific ligand ([214]).

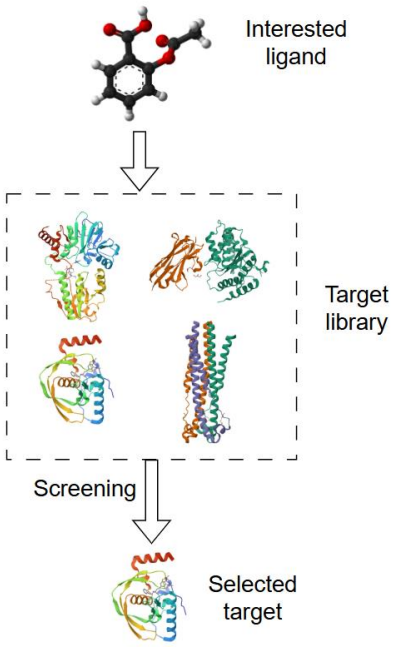

Figure 11: The representation of reverse docking for a small compound into a target database

The concept of reverse docking, a computer process used in drug discovery to identify possible protein targets for a given small molecule or ligand, is illustrated here. Reverse docking looks at the interactions between a ligand and a set of protein structures to identify likely binding partners, unlike traditional docking techniques that predict the binding mode of a ligand inside a specified protein target. In drug discovery research, the approach described has excellent relevance for target identification, lead optimization, and drug repurposing.

Reverse docking techniques are very beneficial in drug discovery, as they can assist in identifying targets, predicting off-target effects, and understanding the polypharmacol- ogy of small compounds ([96, 72]). The off-target bindings may be an option to design polypharmacological drugs, or they cause side effects. Distinguishing between two possibilities is critical to saving funds and time. For instance, Pfizer designed sunitinib, which is cardiotoxic. Off-target bindings on AMP-activated protein kinase (AMPK) families and the ribosomal S6 kinase (RSK) are the reasons for cardiotoxicity ([60]). The compound wasted significant time and funds of the pharmaceutical company ([60]). Therefore, reverse docking is promising to decide whether off-target binding is a reason for side-effect

or a polypharmacology opportunity.

Virtual Screening

Virtual screening (Figure 12), alternatively referred to as computational screening, is a robust computer methodology employed in the field of drug explo- ration to expeditiously assess extensive collections of chemical compounds and ascertain prospective drug contenders that exhibit a high probability of binding to a specific target protein of interest ([156]). The procedure involves docking several ligands, commonly of small size, into a target protein's binding site and then evaluating their interactions to determine the relative importance of compounds exhibiting the most significant binding affinity. Virtual screening is of utmost importance in the initial phases of drug development since it accelerates the identification of lead compounds with favorable pharmacological characteristics, including potency, selectivity, and drug-likeness ([37, 199, 177]).

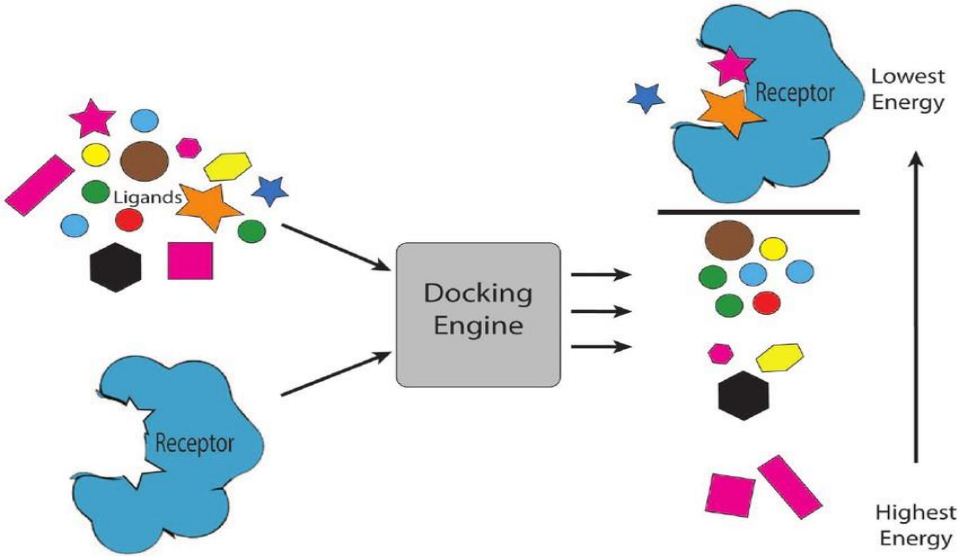

Figure 12: The schematic representation of virtual screening

The figure shows virtual screening, a computer technique used in drug research to precisely arrange multiple ligands into the binding area of a target protein. Virtual screening is a method that helps to quickly evaluate large chemical libraries in search of potential drug candidates with substantial pharmacological action and binding affinity. Since it speeds up the discovery of possible leads and improves the effectiveness of drug development pipelines ([77]), this method is essential in the first phase of drug research.

Cross-docking

Cross-docking is a complex computational technique for simultaneously binding several ligands into several target protein configurations ([106]) (Figure 13). Therefore, it provides an essential understanding of the selectivity and specificity of interactions between ligands and proteins. For example, it can be helpful to determine off-target binding, which indicates side effects. However, Cross-docking has a disadvantage in that, particularly for large-scale datasets, the considerable processing resources required to dock multiple ligands into several targets concurrently are a burden. Furthermore, cross-docking may have trouble with the precision of scoring systems and the complexity of ligand-protein interactions, which may lead to erroneous positive or negative forecasts of binding affinities. Also, it is limited to applying cross-docking outcomes to different protein families and structural modifications. Thus, careful analysis and result validation are much more critical. Cross-docking remains a valuable technique for examining the interactions between ligands and targets and for spotting new treatment candidates with diverse pharmacological profiles, even if there are challenges ([170]).

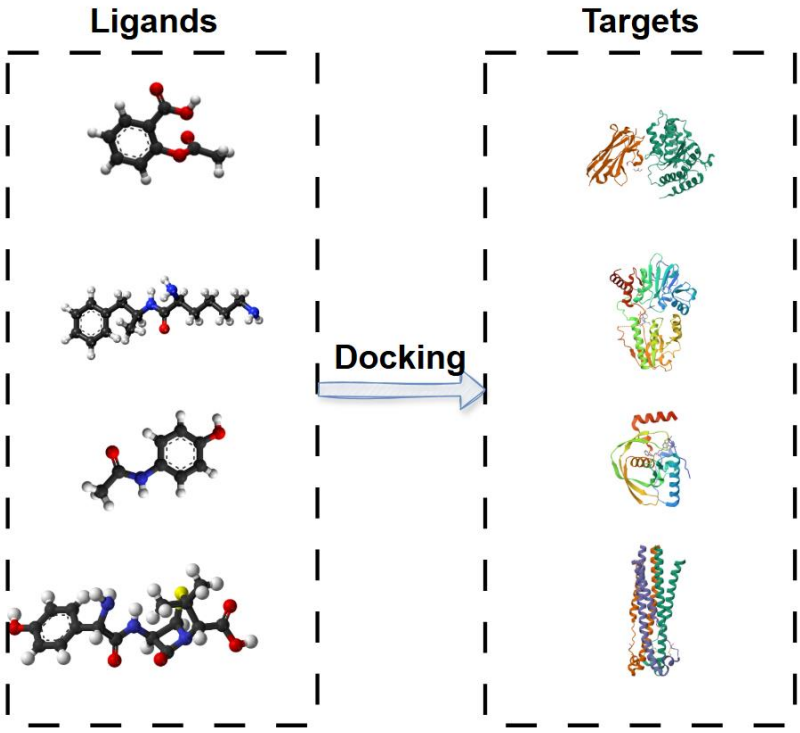

Figure 13: The overview of cross-docking for multiple ligands into multiple targets

A computational method applied in structural biology and drug development to dock many ligands into a binding region of a target protein. Cross-docking is unlike conventional docking, which concentrates on a single ligand-target complex in that it allows the evaluation of ligand binding modes and interactions across several ligand-target combinations by docking a varied range of ligands into a single protein structure. This method improves the development of structure-based drug design techniques by helping to comprehend protein-ligand recognition patterns and pointing up shared binding motifs.

Classification of Docking by Search Space The classification of docking by search space is the grouping of docking techniques depending on the extent of the search area taken into account during the docking procedure. Understanding the attention and computing needs of several docking techniques depends on this classification. This classification has two main categories: (i) Local Docking, which limits the search area to a particular region or binding site on the protein, and (ii) Global Docking, which looks over the whole surface of the protein to find possible binding sites and binding poses ([218]) (Figure 14).

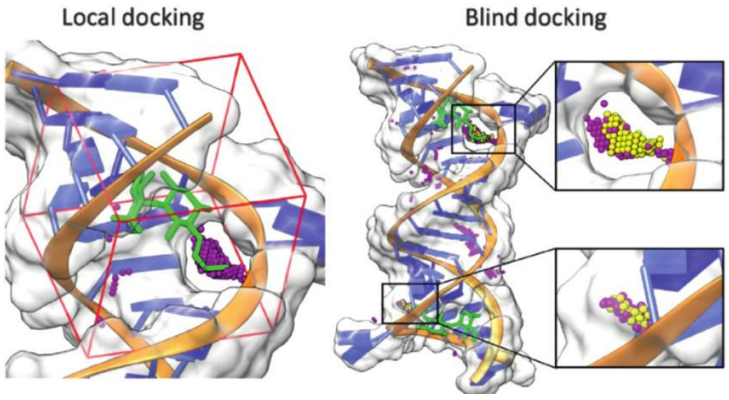

Figure 14: The representation of local and blind (global) docking

Local and global docking simulations of the aminoglycoside antibiotic Gentamicin (shown in green) with bacterial ribosome's 16S rRNA A-site. RLDOCK ([181]) predicts binding locations in the image in pink and yellow. The red cup shows that local docking concentrates especially on a limited area. Therefore, it optimizes the search for possible binding sites inside a

particular target molecule. Global docking, on the other hand, searches the whole protein surface, looking for several likely binding sites where the ligand might engage. This all-encompassing strategy lets one broadly investigate binding options around the target structure. Understanding molecular recognition and creating effective antibiotics depends on knowledge of the different intensities and orientations of ligand interactions ([97]).

Local docking:

Local docking requires a binding site and search space from a user-defined one (Figure 14). There are two main approaches to defining a location for local docking: (i) experimental ligand binding sites and (ii) theoretical predictions. (i) Experimental techniques capture the location of small natural molecules on targets as a binding site. Small natural molecule binding sites are called ligand binding sites (LBSs) ([230]). Most natural LBSs are located on the surface of a protein because of the high affinity obtained by large interfaces. By utilizing the coordinates of LBSs, a molecular docking program can be employed to identify the potential positions of ligands on the coordinates. (ii) Also, theoretical approaches have been developed to identify potential binding regions. For example, Deep-learning cavity finders are the most effective method ([230]), but they suffer from interoperability and extended training time. Recently, the quantum algorithm increased the predictive power of machine learning in a short time ([164]). The research provided Polar+, the first biological modeling, and it was tested on quantum computers ([164]). However, it has significantly higher training costs than classical machine learning approaches ([230]).

Regrettably, the prediction methods used by LBSs are inadequate for fully resolving the issue of detecting LBSs due to factors such as protein flexibility, the limited efficacy of computational approaches, the intricate nature of molecular interactions, and the difficulties in accounting for solvent effects ([76]). Also, cryptic sites become clear when proteins are in a complex (bounded form). There are some studies to determine LBSs successfully. For example, molecular dynamics simulation is a popular method to assess LBSs since it analyses the physical movements of atoms and molecules. Also, machine learning or deep learning integrated with molecular dynamics is promising ([230]). Finally, although combining computational predictions and experimental data is currently the best solution ([44, 171, 186, 70]), performing global (blind) docking is another option to overcome the limitation of identification of binding sites.

Global(blind) docking

Global docking—also known as blind docking—involves the thorough study of the whole surface of the protein to identify likely binding sites and project the ligand binding mechanisms without first understanding the exact location of the binding site ([180, 159, 237]) (Figure 14). Unlike local docking, global docking does not necessitate prior knowledge of specific binding cavities, enabling an impartial evaluation of the binding affinity between the target and ligand ([43]). Global docking comprehensive technique facilitates the identification of previously unnoticed binding sites that more targeted methods may disregard. Hence, global docking is especially advantageous during the initial phases of drug development since it facilitates the creation of novel pharmaceuticals by offering a comprehensive perspective of potential interaction sites throughout the complete target protein. Global docking can potentially uncover previously undiscovered binding sites, which can be used to create more potent and groundbreaking medicinal medicines. The most cited global docking programs are ZDOCK ([25]), FlexX ([92]), GOLD ([196]) and MEGA DOCK 4.0 ([136]).

Global docking offers several advantages in molecular docking, such as exploring all potential binding sites on a target protein. This comprehensive approach ensures that no potential binding region is overlooked, providing a complete understanding of possible ligand interactions. One significant advantage is its utility in predicting side effects, as it examines every cavity on the target protein, identifying off-target binding sites that might lead to adverse impacts. The therapeutic effect or side-effect of a ligand depends on where and how it binds to a target ([74]). Any cavity on a target may be a reason for side effects. Therefore, cavities should be considered to predict side effects ([161]). These requirements make global docking more suitable to investigate side effects. A unique

consensus-global docking method can destroy the limitations of global dockings, such as high false-positive and low accuracy ([220]). Despite the advantages of global docking programs, they have been plagued by lower performance than local docking methods.

A global docking program has been suffering from a lack of critical location features for binding. Binding location helps local docking focus on the correct location, while global docking should define that position first before increasing performance in ligand pose ([35]). Therefore, global docking's performance is lower than that of local docking. As a result, hybrid molecular docking has been published to improve global docking performance ([73]).

Hybrid molecular docking combines the strengths of both global and local docking approaches. It initially employs global docking to explore potential binding sites across the target surface. Then, it refines the search using local docking techniques to focus on the most promising regions, enhancing the accuracy and efficiency of the docking process ([73]). For example, the hybrid global docking example is LigDockCSA ([175]), which combines conformational space annealing (CSA) with AutoDock's energy function. It has an 84.7% success rate, compared to 80.5% for GOLD and 81.7% for AutoDock. Also, the success rate of LigDockCSA becomes 89.4% with the help of conformational entropy ([175]).

1.2.2 Molecular Dynamics Simulations in Drug Discovery

The classical molecular dynamics (MD) methodology is a computationally taxing technique enabling quantitative study of molecular events. Classical all-atom MD is a modeling method that precisely simulates all atoms in a given system, including the solvent. Considering interatomic forces, it uses classical bonded and nonbonded potentials (Fi ure 15). Its better performance has resulted in significant developments and has been efficiently applied to handle conformational changes, folding binding penetration, and many other problems ([107]).

MD has faced two main challenges: first, the computation of interatomic potential tables, sometimes known as force fields, has historically been a laborious process requiring excellent refinement; second, it is computationally demanding despite reasonable efforts and developments in expediting molecular dynamics codes ([124, 45]). To overcome these challenges of conventional MD, machine learning (ML) techniques in MD simulations have been enhanced in terms of their value and efficiency in drug development ([18]). Machine learning methods can analyze large amounts of simulation data to identify trends and project molecular behaviors. Using ML-driven MD so accelerates the process of spotting possible drug candidates with promise. ML-driven MD simulations offer a potent mix of accuracy and efficiency by improving force fields, anticipating binding affinities, and maximizing sample efficiency. MD simulations and ML streamline the drug development process and allow logical synthesis of more specific drugs ([18, 163]).

1.2.3 Binding Site Identification in Drug Discovery

Medications' effects are manifested by their interactions with distinct binding sites on target proteins. These binding sites can be categorized into groups according to their respective mechanisms and locations. The binding sites can be classified into three primary groups: (i) orthosteric, (ii) allosteric, and (iii) cryptic binding sites ([191]).

Orthosteric binding site: Orthosteric drugs bind to a protein's active site, competing with the natural substrate or ligand (Figure 15). Their effects are exerted by outcompeting the native substrate and obstructing the active site when they possess a strong affinity for the site. Most drugs available in the market are traditionally orthosteric ([210, 141]). Also, the orthosteric active sites within a protein family exhibit a high degree of conservation, implying that a drug designed to target the active site of one protein can also interact with the active sites of other proteins belonging to the same family ([115]).

Although extensively employed, orthosteric binding sites and pharmaceuticals have specific drawbacks in drug design and therapeutic use ([50]). A notable constraint is the possibility of off-target effects caused by the extensive similarity of active sites throughout protein families ([213]). Off-target binding can result in unintentional interactions with proteins that have similar structures, leading to adverse effects and diminishing the selectivity of the medicine. Furthermore, orthosteric medications frequently compete with endogenous ligands or substrates for binding, which might restrict their effectiveness in specific physiological situations or disease states characterized by fluctuating substrate concentrations ([50, 213, 194]). Also, the total suppression of protein function by orthosteric medications may not always be preferable, as it can interfere with regular cellular processes that depend on regulated enzyme activity ([34]). The significance of taking into account alternative drug design techniques, such as allosteric modulation, is emphasized by these aspects. These strategies aim to obtain more accurate and specific therapeutic results while reducing the possible disadvantages associated with orthosteric binding.

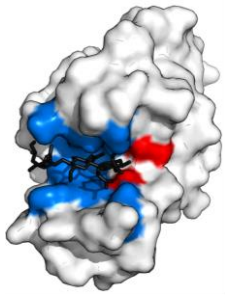

Figure 15: The representation of the Orthosteric binding site (in blue) on the target protein

The orthosteric binding site (in blue) is the primary binding site on targets such as proteins, where the ligand directly interacts with the target to exert its biological effect. These binding sites are typically located on the surface of the protein, which allows for a larger interaction area with the ligand, facilitating more substantial and more efficient binding. The surface localization of orthosteric sites is crucial for many biological processes, enabling the target to interact with various molecules. However, orthosteric binding sites may also be found inside the protein, often called inner binding sites. These internal sites can regulate the protein's activity by affecting its conformational state or function. Both surface and inner orthosteric binding sites are critical for drug discovery, as they represent potential targets for therapeutic intervention, with the ability to either enhance or inhibit the biological activity of the target.

Allosteric binding site: Allostery, often called allosteric control, is a crucial biological phenomenon involved in signal transduction pathways, metabolic processes, and genomic transcription ([20, 51]). It arises from a rapid shift in the conformational ensemble balance at an allosteric site, leading to localized conformational changes at the active site ([82, 129]). These changes may result from interactions with small molecules, ions, or localized chemical modifications ([36, 63]). Consequently, allostery serves as a central mechanism for regulating the functions of biological macromolecules (Figure 16).

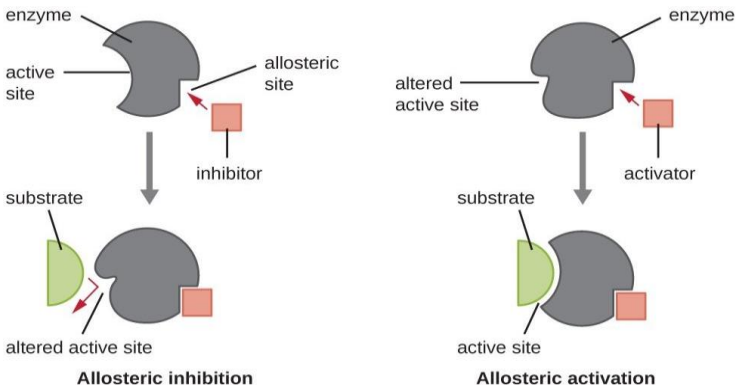

Figure 16: The representation of how allosteric activation and deactivation work.

Controlling protein activity is done by attaching parts of the protein that are not in the active site, the “orthosteric” site. The

figure shows allosteric inhibition, which happens when a ligand binds to an allosteric site and causes a conformational change on the protein's orthosteric side to inhibit binding. In contrast, allosteric activation (right) occurs when a ligand attaches to an allosteric site, rearranging the protein's orthosteric site structure that enhances its activity. Allosteric regulatory mechanisms are of utmost importance in the context of cellular signaling and the regulation of enzymes.

Knowing allostery can give critical new perspectives for the progress of allosteric drug discovery and development ([133, 30]). Among the essential roles allostery plays in many biological processes are those of enzyme catalysis, signal transmission, and gene regulation. Allostery is the phenomenon wherein activity occurs at a distance when a disruption at one point inside a macromolecule causes functional changes at another. Several processes can lead to the modulation of protein activity by allosteric mechanisms: effector-binding interactions involving small molecules, liquids, DNA/RNA, or proteins; covalent modifications including phosphorylation; and photoabsorption ([118, 20, 82, 129]).

Allosteric pharmaceuticals exhibit binding affinities or catalytic efficiency of biological macromolecules using a perturbation signal propagation but at a place distinct from the active site. Allosteric medications have various advantages compared to orthosteric drugs ([30, 134]). Based on sequence conservation analysis, it has been observed that allosteric sites exhibit a lower degree of conservation compared to orthosteric sites ([217, 117]). The lower degree of conservation of allostery enables allosteric modulators to effectively target specific subtypes within receptor families, leading to enhanced selectivity and reduced occurrence of adverse effects compared to orthosteric drugs ([22]). Also, allosteric medicines can regulate protein activity without directly competing with natural ligands, decreasing the probability of adverse effects related to unintended interactions ([132]). They offer more refined regulation of protein activity, enabling partial activation or inhibition instead of complete blockade ([143]). Partial activation or inhibition can be advantageous for preserving regular cellular processes. Furthermore, allosteric pharmaceuticals do not impede the interactions between substrates and proteins; a maximum limit exists to allosteric regulation ([143]). In addition, Allosteric pharmaceuticals are beneficial due to two primary factors: firstly, they can provide a less disruptive method to modulate the activity of a pathway, and secondly, they are more likely to have a reduced incidence of adverse effects ([42, 68, 86]). The other advantage of allostery is that the utilization of techniques that combine allosteric modulators with orthosteric medications can offer advantages due to the issue of drug resistance, which arises from mutations in the protein target that surpass the inhibitory effects of both orthosteric and allosteric pharmaceuticals ([127, 68, 86, 46, 224]).

Using allosteric modulators could help orthosteric treatments become even more effective. GNF-2 is one instance of an allosteric modulator; it shows binding affinity to T315I human Bcr-Abl's myristate-binding sites. On the mutant Bcr-Abl protein, GNF-2 and the substrate-competitive inhibitor imatinib show synergistic inhibitory effects ([227]). As such, the co-administration of these two drugs offers a possible approach to overcoming drug resistance in patients with chronic myelogenous leukemia (CML). Also, the US FDA has so approved several allosteric medicines. For example, developed by Genzyme ([131, 113]), plerixafor is one example of an allosteric blocker of the C-X-C chemokine receptor type 4 (CXCR4) that helps hematopoietic stem cells (HSCs) be mobilized. The debate mentioned above on the benefits of allostery, and the proof of successful allosteric drugs underlines the great possibilities of allostery. It is crucial to recognize its constraints, including the unknown positions of allosteric binding sites on target molecules, to overcome the restrictions of allostery.

Allosteric pharmaceuticals have various restrictions, even if they offer some encouraging benefits. The critical difficulty is that, for most pharmaceutical targets, the exact areas of allosteric activity are yet unknown ([112]). This ambiguity about the allosteric areas makes designing and developing medications that can attach to these locations efficiently challenging. Moreover, several obstacles hinder the identification of allosteric modulators, including restricted binding strengths and the usually unknown structural properties of putative tiny allosteric compounds ([102, 202]). Furthermore, allosteric sites show less conservation than orthosteric sites, which causes differences

in the therapeutic efficacy of several protein targets ([209]). Furthermore, the inherent adaptability of allosteric sites complicates the search for medications, which may only show themselves under particular structural states of the protein ([198]). These constraints hinder allosteric pharmaceutical development and call for more studies to grasp better and use allosteric pathways for therapeutic uses.

Cryptic binding site: Cryptic binding sites are hidden or transient regions that are not evident when the protein is inactive or not bound ([78]). However, these cryptic sites either arise or become accessible when a ligand hooks to the protein or when its form changes (Figure 17). These cryptic sites depend on particular conditions or the presence of specialist ligands for their visibility, so they are often invisible using typical structural research techniques such as X-ray crystallography or NMR spectroscopy ([157]). Since they offer fresh drug discovery and development opportunities, especially for targets that have been difficult to control using conventional orthosteric or allosteric sites, identifying and understanding hidden binding sites is vital. Thus, various compotation strategies have been designed to investigate cryptic binding sites and understand their mechanisms.

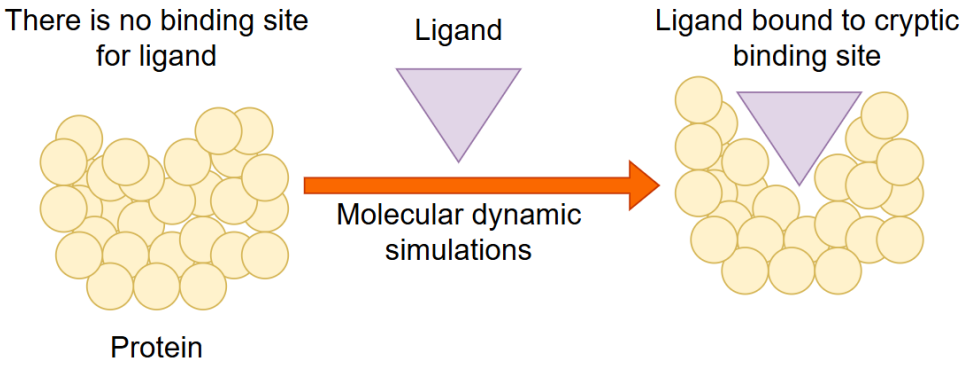

Figure 17: Initially lacking a pocket structure until the ligand binds, the concept of a cryptic binding site exposes the hidden binding site.

Often concealed within proteins, cryptic binding sites become accessible for ligand binding via conformational changes brought about by ligand binding or protein-protein interactions. Understanding and focusing on mysterious binding sites offer interesting chances for investigating drugs and applying therapeutic actions. These cases show how the MD technique is the accepted method for locating hidden places ([137]).

Various computational strategies have been employed to detect cryptic or ”transient” locations, considering protein dynamics ([5, 95]). For example, Markov state models on molecular dynamics simulations detect cryptic sites that effectively reveal the hidden locations of two β-lactamases ([61]). In their study, Gao et al. successfully produced bound conformations in lengthy microsecond molecular dynamics (MD) simulations employing unbound initial structures for a mere 8 out of the 39 systems under investigation ([61]). Also, Oleinkovas et al. did not identify hidden locations for three systems using microsecond-length molecular dynamics simulations. As a result, they devised a method to improve sampling by utilizing scaled Hamiltonians to sample water interfaces based on replica exchange molecular dynamics ([137]). Moreover, Cimermancic et al. ([32]) uncovered a set of proteins with cryptic sites for their web server, Cryptosite, which predicts binding sites. The term ”cryptic” was used to describe a site that could not be identified using FPocket ([98]) when utilizing the unbound structure.

Drug discovery depends on identifying cryptic binding sites, yet traditional computational and experimental approaches are somewhat limited. The always-shifting properties of cryptic sites, which usually go undetectable in the frozen protein structures obtained by crystallography or cryo-electron microscopy, provide a significant challenge. Furthermore, complicating the identification process is the natural flexibility of proteins ([6]) and the limited resolution of experimental instruments. Potential approaches to effectively overcome these limitations and find cryptic binding locations ([233]) come

from machine learning (ML). Using large databases of protein structures and binding interactions, ML models could forecast hidden sites that are not readily apparent with conventional methods. Combining molecular dynamics simulations with machine learning techniques allows one to precisely find hidden spots on proteins by recording their transient shapes ([204]). Furthermore, machine learning can help to analyze large amounts of experimental data by identifying relationships and traits that would point to the presence of latent binding sites, therefore accelerating the process of developing drugs.

1.3 Ligand-based Drug Discovery Approaches

Ligand-based drug discovery strategies are fundamental in contemporary pharmaceutical research. They concentrate on comprehending and enhancing the chemical characteristics of drug molecules to attain specific therapeutic outcomes. These approaches utilize ideas based on molecular interactions and physical features of ligands, which are small ligands that preferentially attach to biological targets like proteins or nucleic acids. Standard methodologies include Lipinski Rule of Five ([104]), LogP ([93]), Biophar- maceutics Classification System ([17]), and In-vitro in-vivo correlation (IVIVC) ([114]). While these methodologies are essential in drug discovery and development, the ”key” and ”lock” ideas have drastically impacted new tools and approaches ([33]).

The idea of ”key” and ”lock” in drug discovery is that “similar ligands bind similar targets”, so the molecular similarity is one of the target identification methods ([33]). Similarity methods require a representation method for compounds, such as the Simplified Molecular Input Line Entry System (SMILES). SMILES is the most common method to represent and compare the compounds in 1D ([208, 207]). It converts a compound into a string, using symbols such as C, c, N, O for atoms and =, # for bonds (www.daylight.com/dayhtml/doc/theory/theory.smiles.html). SMILES are available in quantity structure-activity (QSAR), virtual screening, and toxicity prediction. An example of a similarity search algorithm is the fingerprint Similarity Search Algorithm (MuS- SeL), which can provide IC50 or Ki values for ligands ([228]). Finally, other compound similarity methods exist in the literature, such as 2D-based compound similarity kernels (Figure 18).

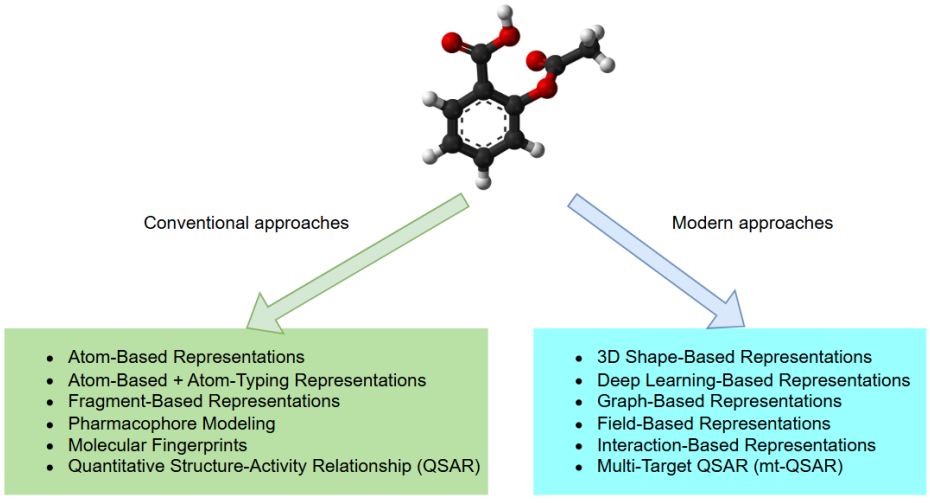

Figure 18: The representation of ligand-based drug discovery approaches

Atom-based representations focus on modeling molecules by their atoms, capturing basic structural features. Atom-Based + Atom-Typing Representations extend this by categorizing atoms based on their chemical environment, enhancing the structural detail. Fragment-based representations break molecules into smaller, functional fragments, which can be analyzed for their activity and interaction potential. Pharmacophore Modeling identifies the essential chemical features required for a ligand to bind to its target. Molecular Fingerprints encode molecular structures into bit-strings, enabling efficient compound comparison. Quantitative Structure-Activity Relationship (QSAR) correlates molecular structure with biological activity, providing insights into the effects of structural modifications. In novel and advanced approaches, 3D Shape-Based Representations model molecules in three-dimensional space, highlighting their shape and flexibility for target binding. Deep Learning-Based

Representations leverage machine learning models to accurately predict ligand-target interactions. Graph-based representations represent molecules as graphs, facilitating the application of graph theory for interaction prediction. Field-Based Representations focus on molecular fields, such as electrostatic and hydrophobic interactions, which are crucial for understanding binding affinity. Interaction-Based Representations model the interactions between ligands and targets to refine drug design. Lastly, Multi-Target QSAR (mt-QSAR) extends traditional QSAR to predict activity across multiple targets, aiding in developing multi-target drugs.

Generally, 2D-based compound similarity kernels, such as SIMCOMP ([138]), are preferred to predict drug-target prediction. Here are some examples of 2D-based compound similarity techniques to indicate their success. One of the 2D-based compound similarities is TargetHunter, a web-based tool ([201]). TargetHunter was trained on ChEMBL data, and PubChem bioassay was utilized as test data ([201]). Compared to 2D and 1D representation, SMILES-based similarity may be computationally more efficient than 2D-based approaches ([138]). Consequently, the ligand-based drug discovery approach can be more successful with other techniques, such as De Novo Drug Discovery.

1.4 Target-based Drug Discovery

Target-based drug discovery (TBDD) is a strategic approach to developing therapeutic agents that focuses on identifying and modulating a specific biological target associated with a disease. Typically, these targets are proteins, such as enzymes, receptors, or ion channels, whose activity can be influenced to achieve a desired therapeutic effect. The process begins with a deep understanding of the target's structure, function, and role in disease pathology. This enables researchers to design or identify molecules that interact specifically with the target to alter its behavior.

The importance of TBDD lies in its precision and rationality. Focusing on a well-defined biological target allows for the systematic design of drugs with high specificity and efficacy. Unlike phenotypic approaches, which often rely on observing general biological effects, TBDD provides a clear mechanistic pathway from the molecular interaction to the therapeutic outcome. This precision reduces the likelihood of off-target effects and toxicity, making TBDD a cornerstone of modern drug discovery and development. Moreover, advancements in structural biology, computational modeling, and high-throughput screening have significantly enhanced the efficiency and success rate of TBDD, making it a critical tool in addressing complex diseases such as cancer, neurodegenerative disorders, and infectious diseases. In order to investigate target-based drug discovery, there are two groups: (i) High-Throughput screening (HTS) and (ii) De Novo Drug Discovery.

1.4.1 High-throughput Screening (HTS)

High-throughput screening (HTS) is a widely used method in drug discovery that enables the rapid testing of large chemical libraries to identify compounds with potential biological activity against a specific target. By leveraging automated systems, robotics, and advanced data processing, HTS can evaluate thousands to millions of compounds relatively quickly. This approach is beneficial in the early stages of drug discovery for identifying initial "hits" that can be further optimized into lead compounds.

The importance of HTS lies in its ability to significantly accelerate the drug discovery process. Traditional methods of testing compounds were labor-intensive and time-consuming, limiting the pace of innovation. HTS overcomes these limitations by integrating automation and miniaturization, allowing researchers to screen vast libraries efficiently. The method is crucial for identifying promising candidates in areas like enzyme inhibition, receptor binding, or other target-specific interactions. Furthermore, HTS has applications beyond drug discovery, including toxicology, material science, and functional genomics.

Key concepts in HTS include assay design, which ensures the screening process is robust, reproducible, and relevant to the target of interest. Another critical element is using sophisticated data analysis tools to interpret the results and identify "hits" with statistically significant activity. Additionally, integrating diverse chemical libraries is essential to maximize the chances of identifying active compounds. Recent advancements, such as using artificial intelligence for hit prioritization and incorporating high-content screening for more complex biological readouts, have further enhanced the scope and effectiveness of HTS.

1.4.2 *De Novo* Drug Discovery

The concept of de novo drug design (DNDD) pertains to creating new chemical entities that adhere to a predetermined set of limitations through computational growth algorithms ([168]). The term ”de novo” denotes the process of creating new molecular entities without the need for a starting template, as it involves starting from scratch ([47]). *De Novo* drug design can be classified into four main groups: (i) structure-based, (ii) atom-based, (iii) ligand-based, and (iv) fragment-based (Figure 19). Also, the next frontiers for machine-learning-enabled de novo drug creation, as a new group, include future directions such as toxicogenomics integration and vaccine development opportunities.

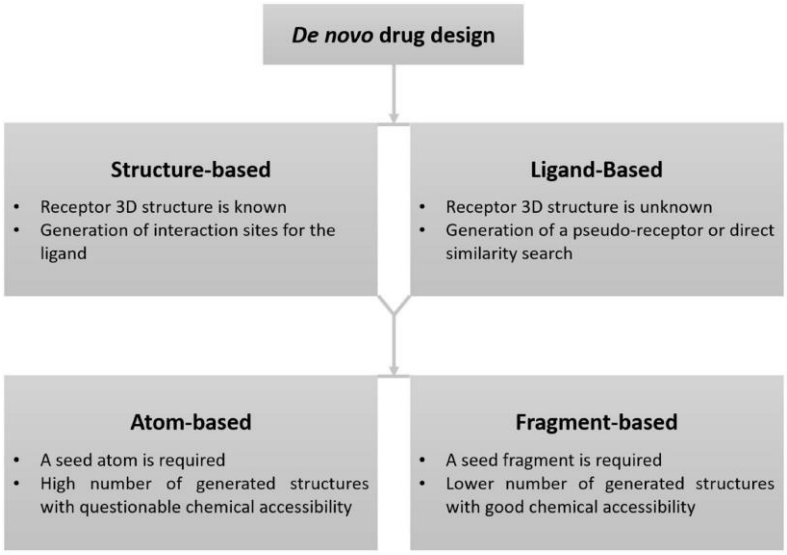

Figure 19: Classification of De novo drug design methods

The de novo drug-design process calls for several cutting-edge technologies, each of which uniquely helps to produce new medicinal molecules. Structure-based drug design uses the complex 3D structure of the target protein to produce molecules that exactly suit its active site, hence improving binding interactions for best efficacy. Second, ligand-based drug design uses information from known ligands interacting with the target to generate new molecules with similar or improved potency. This approach often uses computer models to predict how changes to the ligand can increase binding affinity and specificity. To guarantee the best interaction with the binding site of the target protein, atom-based drug design gives spatial configuration and atom composition top priority. This degree of precision helps maximize the molecular interactions, producing the best possible therapeutic effect. Fragment-based drug design involves the identification of small chemical fragments attaching to different parts of the target protein. These then are chemically linked or amplified to create a potent and targeted pharmacological molecule. Combining these four techniques allows de novo drug design to effectively generate novel compounds with a high probability of therapeutic efficacy ([130]).

De novo drug design offers several benefits, such as the ability to explore a broader range of chemical possibilities, the creation of compounds that represent innovative intellectual property, the possibility of developing new and enhanced therapies, and the efficient development of drug candidates in terms of cost and time. One of the primary obstacles encountered in de novo drug design is the synthetic inaccessibility of the molecular structures produced ([69]). Although de novo drug design benefits, it has limitations that encompass several desired properties or chemical

characteristics, such as a predetermined range of solubility, toxicity below a certain threshold, and the inclusion of specified chemical groups in the structure ([39]). Fortunately, machine learning applications in De Novo Drug discovery have the potential to overcome limitations such as computational intensity and limited performance ([122]).

The section provides supporting terms to explain the terms and increase understanding of the research. The supporting literature review is divided into three sections: (i) How do drugs work based on binding site classifications? (ii) Quantum Mechanical Simulations in Drug Discovery and (iii) Cheminformatics Approaches for Drug Discovery

1.5 Quantum Mechanical Simulations

Quantum mechanics operates on the domain of electrons and nuclei, disregarding the influence of chemical bonds. Solving the Schrodinger equation offers a valuable means of understanding systems at the atomic level ([13, 238]). The equation's answer interprets the spatial arrangement of electrons and their respective energy levels. Furthermore, it offers insight into molecule structure, chemical bonding, and molecular interactions ([7, 238]). Nevertheless, the Schro¨dinger equation can only be solved for the Hydrogen atom. Therefore, approximations of the equation's outcomes are used for the remaining atoms.

Density functional theory is a computer tool for determining the ideal molecule arrangement, vibrational frequencies, free energy shift during a chemical process, and dipole moments (DFT ([11, 238])). Furthermore, DFT is quite important in determining the affinities of protein-ligand interaction, a fundamental feature in the discipline of drug development ([52, 238]). By providing in-depth knowledge of the electronic structure of molecules, density functional theory (DFT) allows exact predictions of the interactions between possible drug candidates and their target proteins ([88]). DFT's properties make it a vital tool for the logical development of new drugs since they help to find exciting compounds and improve their binding capacity. This computational approach increases the efficiency and output of the drug development process, hence producing more strong and targeted drugs ([53]).

Quantum Mechanics (QM) approaches show promise but have encountered limitations such as computational power constraints, the absence of atoms and residues on proteins, and inadequate entropic methods. Rather than imposing restrictions on quantum mechanics (QM), QM possesses significant predictive capabilities in binding free energy ([19]). Machine learning techniques in the context of quantum mechanisms can yield distinctive attributes for drug design and development by overcoming the limitations of conventional QM ([128]).

1.6 Cheminformatics Approaches for Drug Discovery

Cheminformatics methods use computational and informational tools to solve chemical problems and enhance the discovery process of new drugs. Combining chemistry, biology, pharmacology, and cheminformatics approaches helps efficiently handle, examine, and present large datasets ([24]). Accelerating the identification of potential pharmacolog- ical candidates, improving their features, and predicting their performance in biological systems depend on this multidisciplinary field ([123]). Cheminformatics offers several advantages, including the rapid analysis of large chemical databases, reduced cost and duration of experimental procedures, and enhanced accuracy in target identification and lead optimization. Ultimately, these approaches enable drug research and development procedures' success and efficiency, generating fresh and creative treatments. Three chemogenomic techniques include (i) machine learning-based, (ii) graph methods, and (iii) network model approaches ([212]).

1.6.1 Machine Learning-based Methods in Cheminformatics

Machine learning techniques in cheminformatics transform drug development pro- cess by utilizing sophisticated algorithms to analyze intricate chemical and biological data ([110]). These techniques utilize patterns and correlations in data to forecast the characteristics and behaviors of possible drug candidates, expediting the process of identifying and refining new therapeutic substances. The significance of machine learning in drug discovery is its capacity to manage extensive information, reveal concealed insights, and enhance the precision of predictions in contrast to conventional methods. The benefits encompass improved efficacy in analyzing extensive chemical libraries, the capability to simulate complex biological interactions, and the possibility to decrease expenses and durations linked to medication development ([110]).

With the help of ML techniques in cheminformatics, several successful cheminformatics studies have been reported in the scientific literature ([155]). The preferable ML model is a supervised model used to study DTIs. For example, the PaDEL descriptor utilized the 1287-dimensional target descriptor and the 1024-dimensional drug descriptor from these datasets to predict DTIs ([200]). The standard classification models used in DTI research are random forest, random walk with restart, support vector machines (SVM), and decision trees ([200]). In another example, Yu et al. designed a method to indicate drug-target interactions from heterogeneous biological data using Random Forest and SVM ([225]). Also, several machine learning models have been built on structure-activity relationships (SAR) and structure-property relationships (SPR) ([232, 221]). An instance of the SAR model application is TargetNet ([221]). TargetNet, containing 623 SAR models, is a web service working with Naıve bayes based multi-target SAR models to predict DTIs ([221]). The last example of the QSAR model is that Bender et al. ([12]) benefit from the Bayesian-based method to build QSAR models. Finally, deep-learning algorithms in chemoinformatics also promise to identify targets for a compound ([110]).

Deep learning in cheminformatics is an advanced method that utilizes artificial neural networks with numerous layers to analyze and simulate intricate chemical data ([110]). Deep learning approaches can improve drug discovery by allowing more precise forecasts of drug-target interactions, molecular characteristics, and potential adverse effects ([15, 62, 231]). For example, the chemogenomics neural network (CN) is the formulation of chemogenomics with deep learning. The deep learning CN approach is superior to novel shallow methods ([145]). In addition, a deep-learning model has been designed to predict retrosynthetic pathways ([169]). Also, Feng et al. ([57]) proposed a Deep-Belief Network (DBN) to foresee DTIs, and DBN has 8420-dimensional Protein Sequence Com- position (PSC) of target proteins and 6144-dimensional Extended-Connectivity Fingerprints (ECFP) of drugs ([57]). The last example is that Rayhan et al. ([153]) designed FRnet-Encode to distinguish 4096 features. FRnet-Encode is constructed on a deep convolutional neural network ([153]). These accomplished researches indicate that the impact of the deep-learning algorithm on hit identification will increase over time.

Deep-learning models in cheminformatics face significant challenges in accurately identifying targets due to their complexity and the limitations of analyzing extensive training datasets ([154]). These models often struggle to discern meaningful patterns within large datasets, leading to biases in target selection rather than providing new insights ([154]). An effective strategy to address these deep-learning model issues involves developing integrated models that combine ligand and target data to build comprehensive machine-learning frameworks ([154]). In line with this approach, our methodology constructs a robust machine-learning model by integrating molecular docking techniques with advanced chemogenomic models.

1.6.2 Graph-based Method in Cheminformatics

In cheminformatics, graph-based methods use graph representations to show molecule

structures and interactions, offering a flexible means of understanding and predicting chemical properties and behavior ([154]) (Figure 20). These techniques use graph representations to explain molecules using atoms as nodes and bonds as edges. These techniques allow for relational as well as structural elements. This approach is significant in drug development since it can effectively control complex chemical structures and their interactions, surpassing more traditional techniques. Graph theory and algorithms let researchers rapidly examine molecular fingerprints, predict biological activity, and optimize lead compounds ([179]). Therefore, graph-based methods are crucial for the advancement of computational chemistry as well as for the quick identification of new therapeutic compounds.

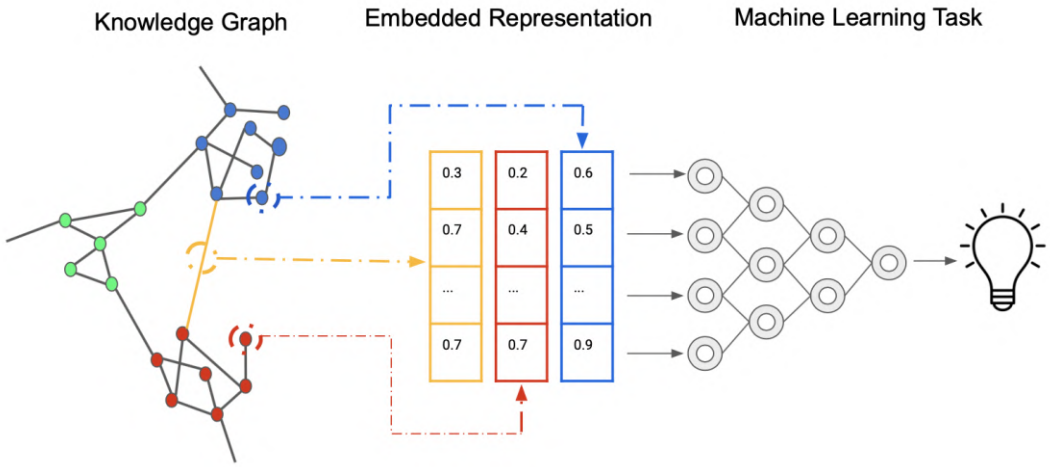

Figure 20: Embedding of a knowledge graph

The vector representation of the entities and relations within the knowledge graph allows for the transformation of complex, structured data into a more suitable format for machine learning models. This representation captures the semantic relationships between entities, enabling the application of advanced algorithms for tasks such as link prediction, classification, clustering, and recommendation. By leveraging these embeddings, machine learning applications can make more accurate predictions and uncover hidden patterns within the data, providing valuable insights across domains such as natural language processing, drug discovery, and social network analysis.

Graph-based methods in cheminformatics encompass diverse applications, such as molecular fingerprinting, molecular similarity assessment, and predictive modeling of biological activities ([110]). These methods leverage graph representations to capture intricate structural details and relational data within molecular structures, offering powerful tools for drug discovery and computational chemistry. Here are examples of graph embedding methods ([64]) based on knowledge graphs that boost DTI prediction performance with the help of ML or DL-based models constructed on low-dimensional feature representation. The graph-based method uses correlations between correlation drug-drug, target-target, and similar matrices, such as DASPfind ([10]). DASPfind ranks correlations by their path scores to identify the top 1%. The DASPfind approach is superior to most network-based models ([10]). Also, DTINET ([116]) uses graph embedding approaches and matrix factorization to foresee novel DTIs from a heterogeneous graph. DTINET integrates several types of correlation knowledge, such as protein-protein interaction, drug-drug similarity, drug-disease association, drug-drug interactions, protein-protein similarities, drug-side effect associations, and protein-disease association ([26]). The DTINET protocol builds a full heterogeneous graph and then learns a low- dimensional feature using matrix factorization ([116]). These approaches make DTINET outperform others; however, DTINET cannot predict the interaction of new compounds or targets ([116]). Although they still have drawbacks, the example studies indicate that graph-based methods are competitive strategies to identify DTIs.

1.6.3 Network-based Models in Cheminformatics

Network-based cheminformatics models use network science ideas to represent molecular structures, interactions, and biological data as networks or graphs ([147]). Network-based cheminformatics models offer a methodical technique to investigate and grasp complex interactions within biological and chemical systems. Network-based models provide essential insights into network pharmacology, interactions between medications and their targets, and the operation of molecules. Network-based models are significant in fitting several data kinds—including chemical structures, biological pathways, and protein-protein interactions—into a coherent framework ([147, 85]). This integration helps to investigate network properties, identify critical molecular players, and project new therapeutic targets or cooperative drug combinations. Using linked data benefits finding emergent properties, improving knowledge of pharmacological activities at a systems level, and creating logical drug design methods emphasizing network-level interactions ([85, 176]). Improving our understanding of complex biological systems and accelerating drug discovery depends critically on network-based models.

Network pharmacology models are still the bottleneck of modern drug discovery, especially target identification ([85, 200]). Network pharmacology is to study the mechanism of a drug candidate at a metabolic level ([71]). It needs network analysis, bioinformatics, and integration of multiple knowledge sources ([140]). Several databases are employed in network-based methods, including Gene Ontology (GO) ([8]) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) ([81]). The databases have information about a drug–target–pathway network, which is essential for network pharmacology. For instance, Yamanishi et al. utilized data extracted from the KEGG BRITE, BRENDA, SuperTarget, and DrugBank databases ([138]). Although network-based models have achieved significant breakthroughs, their application is still restricted by the complex intricacies of human metabolism ([83]). The complexity originates from the extensive interconnection of biochemical events and regulatory mechanisms that govern metabolic pathways ([195]). Existing models frequently encounter difficulties in comprehensively capturing the dynamic interactions and metabolic fluxes within this intricate system, which presents obstacles to precisely forecasting drug metabolism, toxicity, and efficacy ([235]). Continuous progress in data integration, modeling approaches, and computational resources is necessary to overcome these restrictions and attain more extensive and dependable forecasts in drug development and personalized medicine.

2. Future Direction

Developing state-of-the-art artificial intelligence and machine learning algorithms has the potential to enhance the precision and effectiveness of structural-based drug development. By incorporating these models with detailed protein structures, the accuracy of predicting protein-ligand interactions can be improved, which expedites the discovery of promising pharmaceutical candidates. Moreover, these models aid in predicting alterations in protein structure and their impact on the strength of molecular interactions. Consequently, the current accuracy of computational methods can be improved.

Another future direction is utilizing deep learning techniques, such as geometric deep learning ([9]), to analyze complex ligand-binding data and generate prediction models to create novel medications. Deep learning enhances virtual screening by identifying novel ligand binding patterns and improving chemical libraries based on known ligands. This approach may aid in discovering compounds that exhibit reduced off-target effects and enhanced efficacy. However, deep learning can mitigate the interpretability of the model, making understanding how the model works harder ([190]). Nevertheless, deep learning has critical potential to improve the performance of currently available computational methods.

Hybrid methods are promising to enhance the performance of the current method without

losing interoperability ([190]). For example, a conventional molecular docking program, Vina ([49]), can be executed to produce ligand poses. Then, an ML model can only order the outputs to improve the overall performance of molecular docking. As a result, such a method improves the performance without losing interpretability.

While computer power and ML techniques are drastically improving, more accurate but computationally intense methods, such as Density Functional Theory simulation ([11]), will quickly provide higher performance and dominate computational drug discovery and development methods.

3. Conclusion

Integrating sophisticated computer techniques has fundamentally changed the terrain of drug discovery and development. From molecular modeling and structure-based approaches to ligand-based strategies and creative de novo design techniques, these computational tools have greatly improved our capacity to find and create new therapeutic medicines. Constant improvement and integration of these techniques promise to propel more discoveries as the area develops.

This review clarifies the fundamental ideas and uses of several computational techniques, giving a whole picture of their contributions to drug development. Future developments have great promise from high-resolution structural data, advanced algorithms, and developing technologies, including artificial intelligence. However, the intricacy and variety of these approaches call for sophisticated knowledge and ongoing adaptation to match the fast developments in the area.

Overcoming obstacles and opening new possibilities will depend critically on developing more accurate predictive models, integrating multi-dimensional biological data, and optimizing computational procedures. Staying current with these developments and using the insights offered in this review can help researchers shape the direction of drug discovery and development, therefore hastening the introduction of fresh and potent treatments to meet unmet medical needs.

Copyright and Conflict of Interest Statement

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