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Review Article

Molecular Docking: A Powerful Tool In Modern Drug Discovery And Its Approaches

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ABSTRACT

The field of computer-aided drug design and discovery (CADD) has been growing rapidly in recent years, with many successes. Both large pharmaceutical companies and academia use CADD for drug lead discovery. Advances in structural informatics, genomics, and proteomics have been vital in modern drug discovery and development. Research over the past two decades has focused on studying different docking algorithms to predict the active site of a molecule. Various docking programs have been developed to visualize the 3D structure of a molecule, and docking scores can be analysed using different computational methods. Molecular Docking is a structure-based virtual screening (SBVS) technique used to position computer-generated three-dimensional structures of small molecules into a target structure in various positions, conformations, and orientations. Protein-ligand docking is a new concept that has various applications and is significant in structure-based drug design (SBDD), Lead Optimization, and Evaluation of Biochemical pathways, as well as in De Novo drug design. This review provides a comprehensive explanation of Molecular Docking and how it helps in the Molecular Recognition Process towards the discovery of new drug leads by estimating the binding mode and affinity of the complex formed.

INTRODUCTION

Discovering new drugs is a difficult task, and finding the appropriate lead compound plays a crucial role in the success of the project. According to the Tufts Centre for the Study of Drug Development in 2016, the cost of developing and introducing a new drug to the market has risen by nearly 145% in the past decade. In addition, although it now takes less time to bring a drug to clinical trials, the rate of drugs that are approved by the US Food and Drug Administration (FDA) has fallen to just 12%. Thankfully, computer-aided

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drug design (CADD) has provided a solution by allowing researchers to more quickly and cost-effectively identify the most promising compounds to pursue. Techniques like molecular docking and virtual screening (VS) are particularly useful within CADD, as they provide a valuable alternative to the laborious and expensive process of high-throughput screening (HTS).[1]

Molecular Docking is a method used to predict the best orientation for a ligand against a receptor (protein) in order to form a stable complex.[2] This can be used to determine the strength of the bond or binding affinity between the ligand and protein by utilizing scoring functions. Docking is often used to predict the binding orientation of potential drug candidates against protein targets to determine their affinity and activity, which is important in drug design and discovery.[3] The main goal of molecular docking is to simulate the molecular identification process computationally and achieve an optimized conformation that minimizes the overall system's free energy. Discovering new drugs is a challenging task, and modern drug discovery mainly relies on the in-silico-chemical biological approach. The use of computer-aided techniques is rapidly gaining popularity in drug discovery and development.

MOLECULAR DOCKING

Computational structure-based drug design (SBDD) commonly involves molecular docking, which has been in use since the early 1980s. [4] This method is particularly useful when the three-dimensional (3D) structure of the protein target is known. The popularity of molecular docking has surged due to the significant advancements in computer technology, as well as the growing accessibility of small molecule and protein structures. The primary objective of molecular docking is to comprehend and anticipate molecular recognition, encompassing both structural aspects (such as identifying potential binding modes) and energetic aspects (including predicting binding affinity). Initially, molecular docking was intended to be conducted between a small molecule (ligand) and a target macromolecule (protein). However, over the past decade, there has been an increased focus on protein-protein docking, nucleic acid (DNA and RNA)-ligand docking, and nucleic acid-protein-ligand docking. There are several applications of molecular docking in drug discovery. These include conducting structure-activity studies, optimizing leads, identifying potential leads through virtual screening, generating binding hypotheses to aid in predicting mutagenesis studies, and assisting in fitting substrates and inhibitors to electron density in X-ray and cryogenic electron microscopy (cryo-EM) crystallography.

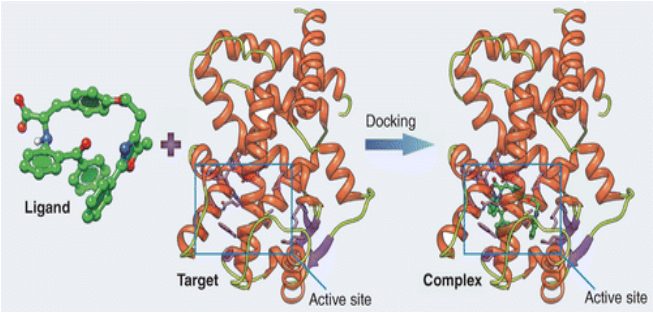

Figure 1: Elements in molecular docking

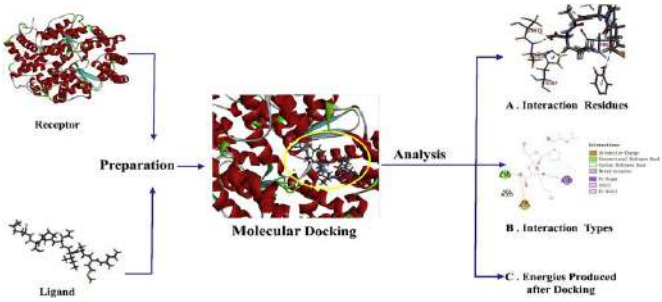

Figure 2: A Typical Workflow of Molecular Docking

2.1 Theory of docking

The process of molecular docking involves two main steps. Firstly, the prediction of the ligand's conformation, position, and orientation within the protein's binding site, known as the "pose". Secondly, the assessment of the pose's quality through a scoring function. The ideal sampling algorithm should be able to replicate the experimental binding mode, and the scoring

function should rank the pose highest. Another aspect of the docking procedure is to score active compounds higher than inactive ones, although this level of accuracy is challenging to achieve due to external factors. Therefore, the primary goal of the docking algorithm is to predict the ligand pose and assess the quality of the pose accurately, with active/inactive ranking as a secondary consideration for some scoring functions.[5]

2.2 Search algorithm

To determine binding modes, the algorithm must generate an optimal number of configurations in line with the experimentation method. Several algorithms are used for docking analysis, including Point Complementary, Monte Carlo, Fragment-Based, Genetic Algorithms, Systematic Searches, and Distance Geometry. [6,7]

2.3 Scoring Function

The scoring function is used to rank the placement of ligands in comparison to others. The score should ideally match the binding strength of the ligand to the protein, meaning that the highest-scoring ligands are the best binders. Scoring functions can be empirical, knowledge-based, or molecular mechanics-based. Scoring is made up of three different expressions that are used in docking and drug design.

(1) Generated configurations ranking by the docking search.

(2) Ranking different ligands against the protein (virtual screening).

(3) One or more ligands ranking against different proteins by their binding affinity (selectivity and specificity). [8,9]

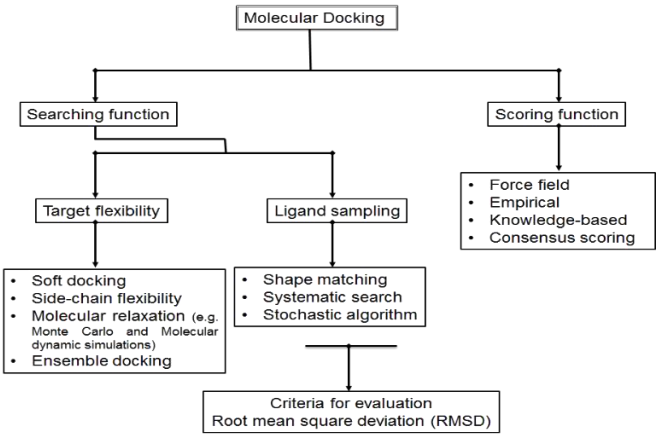

Figure 3: Methods used for protein-ligand docking

2.4 Various types of docking

The following are primarily applied methods for docking.

(1) Rigid Docking

The receptor and ligand are kept in place while the docking process is carried out. We are trying to rearrange one of the compounds in three-dimensional space to best match the other compounds in a scoring system, assuming that the compounds are inflexible. The ligand's conformation can be formed with or without receptor binding activity.[10] In this approximation, the ligand and receptor are considered rigid, with only six degrees of translational and rotational freedom explored, therefore flexibility is not taken into account. Many docking suites use a rigid body docking procedure as the initial step.[11]

(2) Flexible Docking

In flexible docking, both the ligand and receptor are flexible in conformation. For each rotation, the surface cell occupancy and energy are computed, and the optimal pose is then chosen. As part of the transformation process, we assess the flexibility of molecules to determine confirmations for both the receptor and ligand molecules within the complex.[12]

2.5 Major steps involved in the mechanics of molecular docking

Molecular Docking is a method used to study the interaction between two molecules in a computer simulation. During this process, a protein receptor

called a macromolecule and an inhibitor called a ligand molecule are examined. The docking process includes several steps to analyze their intermolecular interactions.

Step I – preparation of protein: To obtain the three-dimensional structure of the protein, it is necessary to retrieve it from the Protein Data Bank (PDB). Once retrieved, the structure must undergo pre-processing, which involves removing water molecules from the cavity, stabilizing charges, filling in missing residues, and generating side chains, among other parameters available.

Step II – active site prediction: After preparing a protein, it is important to predict its active site. The receptor may have multiple active sites, but only one should be selected. Typically, any water molecules and hetero atoms are removed if present.[13]

Step III – preparation of ligand: There are several databases, such as ZINC and Pub Chem, where ligands can be retrieved. Alternatively, the Chem sketch tool can be used to sketch a ligand. When selecting a ligand, Lipinski's Rule of 5 should be applied. This rule helps distinguish between drug-like and non-drug-like candidates. It predicts a higher chance of success or failure based on drug-likeness for molecules that follow two or more of these rules. Therefore, when choosing a ligand, it is essential to ensure that it complies with Lipinski's Rule.

(1) Less than five hydrogen bond donors
(2) Less than ten hydrogen bond acceptors
(3) Molecular mass less than 500 Da
(4) High lipophilicity (expressed as Log P not over 5)
(5) Molar refractivity should be between 40-130

Step IV- docking: The protein-ligand complex is analyzed using a scoring function that gives a score based on the best-docked ligand.[14]

2.6 Types of Interactions

Interactions between a ligand and a receptor molecule can be explained by four main types of forces between particles:

1. **Electrostatic forces:** charged entities in matter create forces, such as dipole-dipole, charge-dipole, and charge-charge interactions.
2. **Electrodynamics forces:** The interactions involved here are mainly Van der Waals.
3. **Steric forces:** When atoms from different particles get close to each other, they create interactions that can impact their reactivity. These interactions affect the free energy system and chemical reactions through resulting forces, which are often caused by entropy.
4. **Solvent-related forces:** The forces between a receptor protein or ligand and solvent due to chemical reactions are called solvent-related forces. Examples of these forces include hydrophobic and hydrophilic interactions (such as hydrogen bonds).
5. **Other physical factors:** other changes that cause additional conformational changes in both the ligand and protein are often considered significant in docking studies.[15]

Recent studies have shown that irreversible protein inhibitors form covalent bonds with nucleophiles (proteins) and electrophiles (ligands), resulting in high selectivity and potency.[16] Covalent inhibitors exhibit a strong affinity for their targets, leading to prolonged pharmacological effects.[17] Examples of FDA-approved covalent drugs include warfarin, isoniazid, aspirin, azacitidine, and rivastigmine. The concept of covalent bonding can be applied to lead optimization, virtual screening, pharmacophore studies, and molecular dynamics simulations.[18] Most pharmaceutical companies avoid covalent drugs due to their lack of specificity, high reactivity, and toxicity.[19]

MODELS OF MOLECULAR DOCKING

3.1 The lock and key theory

In 1890, Emil Fischer introduced the "lock-and-key model" concept to explain biological

processes, as depicted in Figure 4. This model compares the insertion of a substrate into the active site of a macromolecule with the insertion of a key into a lock. The biological locks shown in Figure 4 possess unique stereochemical properties that are essential for their proper functioning.[20]

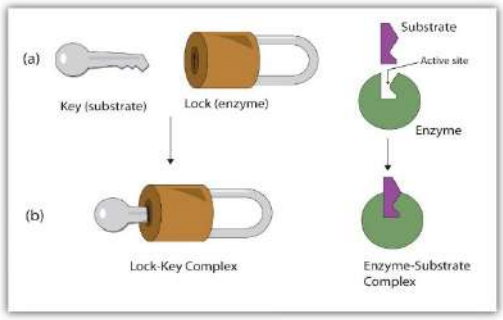

Figure 4: The lock and key theory

3.2 The induced-fit theory

In 1958, Daniel Koshland introduced the "induced fit theory." This theory suggests that during character recognition, both the ligand and target (as shown in Figure 5) adjust to each other through small conformational changes until they reach an optimal match.[20]

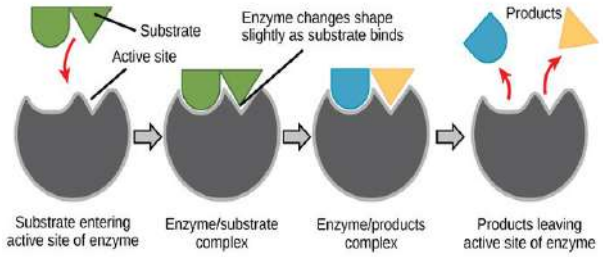

Figure 5: Induced- fit theory

3.3 The conformation ensemble model

A new concept suggests that proteins are composed of pre-existing conformational states, allowing for significant changes in flexibility and transitions between states with minor modifications.[20]

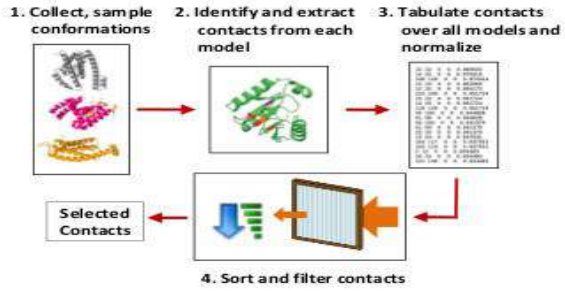

Figure 6: Conformation ensemble model

APPROACHES OF MOLECULAR DOCKING

4.1. Monte Carlo approach

The program generates a random arrangement, including the position and rotation of a molecule in a particular area. It then assigns an initial value to the arrangement and proceeds to evaluate and score a new configuration. The program uses the Metropolis criterion to determine whether the new arrangement should be kept or not. This criterion states that if the new arrangement performs better than the previous one, it will be approved immediately. If the arrangement is not new, a probability study based on Boltzmann's law is used. The arrangement will be accepted if it passes this test, and if not, it will be rejected.

4.2. Matching approach

This strategy focuses on optimizing the location of the ligand atom in the receptor site, resulting in a potential need for further improvements.

4.3. Ligand fit approach

Small molecule ligands may be docked into protein active sites quickly and precisely using the Ligand Fit approach, which also takes form complementarity into account.

4.4. Point complimentarily approach

These methods concentrate on contrasting the physical or chemical characteristics of several substances. Blind docking is a method for screening the whole interface of target molecules to find probable peptide ligand binding sites and mechanisms of action.

4.5. Fragment-based method

The three steps involved in fragment-based methods include breaking down the ligand into individual photons or particles, joining the fragments, and linking the fragments.

4.6. Distance Geometry

The representation of sequence properties in terms of intra- or intermolecular dimensions is very diverse. The assembling of these distances and the calculation of three-dimensional structures that work with them are made possible by the distance geometry framework.

4.7. Inverse docking

When combined with a precise pharmacokinetic property, knowledge of all these targets can help assess the likelihood of toxicities and side effects in a drug candidate. In order to conduct docking research on a certain ligand, a special method is chosen.[21]

4.8 Simulation Approach

This method involves a rather difficult procedure. In the simulation approach, the ligand and receptor are separated by a physical distance, and after a certain number of movements in the conformational space of the receptor, the ligand is permitted to attach to its active site. These actions comprise diverse ligand structural modifications either through internal (torsional angle rotations) or exterior (rotations and translations) means. The overall energetic cost of the system is induced with each movement of the ligand, hence the total energy of the system is determined following each movement. This method has advantages over shape complementarity since it also considers the flexibility of the ligand.[22]

AVAILABLE SOFTWARE FOR DOCKING

Over the past 20 years, numerous docking programs have been developed. Table No.1 lists the essential characteristics of the docking tools that are currently on the market, including endorsed platforms, license terms, algorithms, and scoring features.

Table 1: Basic characteristics of current protein-ligand docking tools

Sr. No.	Docking Software/ Reference	Inventor / Company/ Published year	License Conditions	Facilitated Platforms	Approach Docking	Function Scoring
1	Auto Dock [23]	D. S. Good sell and A. J. Olson The Scripps Research Institute (1990)	Free to use in Academics	Linux, Mac OS X, Unix, and SGI	genetic programming Simulated annealing using the Lamarckian genetic algorithm	Auto Dock (force-field methods)
2	DOCK [24]	I. Kuntz University of California, San Francisco (1998)	free to use in academia	Windows, Mac OS X, Linux, IBM AIX, and Unix	fitting the shape (sphere sets)	GB/SA solvation score, Chem Score, and additional
3	Flex X [6]	T. Lengauer and M. Rarey Bio Solve IT (2001)	Commercial Software Free assessment (6 weeks)	Sun Windows, SGI, Linux, and Unix	Incremental Construction	Scores for Flex X, PLP, Screen, and Drug
4	FRED [7]	Open Eye Scientific Software (2003)	free to use in academia	Windows, Mac OS X, Linux, and Unix	fitting the shape (Gaussian)	Gaussian form score, screen score, PLP, and user-defined
5	Glide [8]	Schrödinger Inc. Commercial	Commercial software	Linux, SGI, IBM	Samples from Monte Carlo	Glide Comp and Score

		(2004)		AIX, and Unix		
6	GOLD [9]	Cambridge CrystallographicData Centre (1995)	Commercial Software Free assessment (2 months)	SGI, Sun, IBM, Linux, and Windows	Genetic Algorithm	User-defined Gold Score and Chem Score
7	Ligand Fit [25]	Accelrys Inc. Commercial (2003)	Commercial software	SGI, Linux, and IBM AIX	Monte Carlo Sampling	Score Lig, PLP, and PM

Table No. 2 Based on their codes, lists the benefits and drawbacks of the protein-ligand docking software currently available.[26]

Table 2: Benefits and Drawbacks of Docking Tools

Sr. No.	Docking software	Benefits	Drawbacks
1	DOCK	limited binding sites Unclosed cavities miniaturized hydrophobic ligands	Highly polar ligands are flexible ligands.
2	FLEXX	tiny hydrophobic ligands with small binding sites	highly adaptable ligands
3	FRED	substantial binding sites Adaptable ligands small, quick-acting hydrophobic ligands	Polar small hidden ligands
4	GLIDE	Adaptable ligands miniaturized hydrophobic ligands	Ranking extremely polar ligands slowly
5	GOLD	limited binding sites Miniature hydrophobic ligands	Sorting out the most polar ligands putting ligands in order in huge cavities
6	SLIDE	Flexibility of the side chain	sensitivity to coordinate input
7	SURFLEX	large cavities that are open limited binding sites highly adaptable ligands	For big ligands, low speed
8	QXP	enhancing established binding modes	sensitivity to coordinate input

LIMITATIONS OF MOLECULAR DOCKING

Molecular docking has made several notable advancements, but its full potential has not yet been realized. The difficulties now facing molecular docking investigations are:[27]

- ➢ There must be a better scoring mechanism.
- ➢ There is a trade-off between accuracy and efficiency
- ➢ A better model of flexibility is needed.

CURRENT CHALLENGES IN MOLECULAR DOCKING

The development of docking is currently advanced, however, it is still far from ideal. The majority of existing docking tools typically have success rates of between 70 and 80 percent with average accuracy ranges of 1.5 to 2A when predicting known binding poses. However, one of the main drawbacks of molecular docking is the computation of precise binding energies, which is closely tied to all the approximations made throughout a docking session (e.g. the treatment of solvent and the flexibility of the macromolecular system)

Perhaps the most harmful weakness of docking is the lack of a proper scoring function and searching algorithm that can effectively combine accuracy and speed, which has been extensively covered elsewhere in the article.

The results of a docking experiment should therefore not be viewed as the final product but rather as a good starting point or as part of a workflow for a deeper and more accurate analysis, despite their invaluable contribution to

understanding target ligand interactions in support of drug discovery projects.

7.1 Blind docking

Blind docking is the process of attaching a ligand to the whole surface of a protein without being aware of the target pocket beforehand. In blind docking, the entire protein is taken into account as a potential site for ligand binding, resulting in a substantially wider search area and an associated increase in running time. Additionally, the use of blind docking is severely constrained in practice due to the exponential growth in complexity of potential binding sites. For completely automated computational approaches for in silico drug design, however, blind docking algorithms that can forecast bound conformations without requiring prior knowledge of binding site locations would be necessary.[28]

7.2 Covalent docking

Due to the toxicity and probable off-target consequences of irreversible covalent medicines, non-covalent pharmaceuticals have historically received the majority of attention in drug discovery. However, we have seen a revival of covalent medicines in recent years, along with the Covid-19 pandemic.[29] Since covalent pharmaceuticals are more competitive than non-covalent endogenous substrates, they may offer additional benefits over non-covalent medications, such as improved efficacy. Due to smaller and less frequent dosages as well as enhanced target specificity provided by meticulous designs that focus on certain protein residues, they also offer a lower patient burden and less drug resistance.[30]

The covalent bond formation, bond breaking, and bond rearrangements are quantum mechanical (QM) phenomena that cannot be adequately handled by the force fields or empirical approaches typically used for non-covalent protein-ligand interactions, which presents unique challenges for the rational design of covalent ligands. [31]

7.3 Reverse docking

Reverse docking (RD), also known as inverse docking, is the process of docking a collection of one or more ligands against a variety of protein families in order to determine a prospective target's affinity for binding or poly pharmacology profile (Fig. 7). Furthermore, RD can make a significant contribution to drug repositioning, drug repurposing, and drug rescue. It may also discover therapeutic targets for mechanisms that have been previously unknown, and it can help to rationally design less toxic or multitarget medications. [32] As a result, medications that have received clinical approval may be used to treat conditions other than those for which they were initially developed. One well-known example of this is the phosphodiesterase-5 (PDE5) inhibitor sildenafil, which is now used to treat erectile dysfunction but was originally created to treat angina.[33]

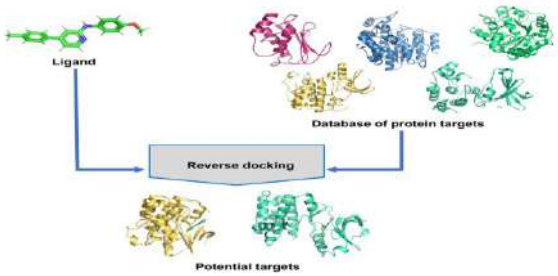

Fig 7: A flowchart of reverse docking

LOOKING FORWARD

Over time, docking's methods for assisting with various drug discovery activities have evolved. Despite being created and utilized initially as a stand-alone method, docking is now frequently used in conjunction with other computational techniques inside integrated workflows to get beyond some of the most important inherent restrictions that are unique to molecular docking.

Docking applications have been investigated to help with various activities involved in drug discovery. In order to help with target fishing, drug repurposing, and the prediction of adverse drug reactions (ADR), docking has been utilized in conjunction with ligand-based, binding free

energy calculations and AI/ML techniques to improve prediction performances in de novo virtual screening. Similarly, many strategies can be used at various stages of the screening pipeline to enhance docking predictions. For instance, to find appropriate receptor conformations for docking, MD and AI-based techniques could be coupled. The predicted docking poses could then be rescored using ligand-based techniques.

Even with the abundance of in silico tools and methods currently on the market, docking still has a tonne of potential applications in integrated workflows. Furthermore, ongoing advances in hardware and software engineering have made it easier to integrate them. For instance, the parallelization of molecular docking has made it possible to efficiently screen millions of molecules in silico by employing distributed computing infrastructures to conduct the computationally intensive operation (the energy calculation step) across numerous CPUs (DCIs).[34]

APPLICATIONS OF MOLECULAR DOCKING

Since molecular docking studies may determine if an enzyme reaction is feasible, they are crucial in many in-silico drug design applications. Small molecule binding interactions lead to the inhibition or activation of enzymes. The following are some examples of molecular docking applications:

➢ **Hit identification**

A scoring method is used to evaluate large databases utilizing docking to find prospective drug candidates in silico against the target of interest.[35]

➢ **Lead optimization**

Docking studies can forecast a ligand's optimal orientation. More discerning, effective, and potent therapeutic candidates are created as a result of the prediction of the many binding mechanisms of a ligand in the protein's binding pocket.[36]

➢ **Bioremediation**

Ligand-protein complex can be used to predict enzymes degrading pollutants.

➢ DNA-drug interactions

➢ Binding site prediction

➢ De-orphaning of protein

➢ Protein-protein/nucleic acid interactions

➢ Studies of structure-function

➢ Searching for lead structures for protein targets

➢ Mechanisms of enzymatic reactions

➢ Protein engineering.

➢ Application of molecular modeling in modern drug development

It is employed to determine whether interactions with other proteins, such as proteases, cytochrome P450, and others, may cause any possible harm. A suggested medication's specificity against homologous proteins can also be assessed using docking. Furthermore, docking is a widely used method for determining protein-protein interactions. Understanding cellular connections aids in understanding a variety of processes taking place in living things and the identification of prospective drug targets.[37]

CONCLUSION

For the creation and analysis of pharmaceuticals, molecular docking offers a wide range of useful techniques. Simple molecular visualization and quick access to structural databases are now necessary tools on the medicinal chemist's desktop. The fundamental user interface is still being improved upon by commercial software products. High-end packages quickly include new algorithms from businesses and academics. Public domain software is improving and now competes with some commercial products in terms of functionality. Every year and a half, the speed of computers doubles while the sophistication and usability of graphic displays increase. These factors collectively make molecular docking an essential component of drug design. It keeps expanding its involvement in innovative new

methods including computational enzymology, genomics, and proteomics.

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