A Review on In Silico molecular docking Studies

Minerva College of Pharmacy Indora
Sanket Singh[1] Happy[*],Dr Kapil Kumar Verma[1], Vinay

Coressponding Author
Happy
Contact No. 8894039608
Email: choudharyhappy15@gmail.com

ABSTARCT

Molecular docking is a pivotal computational technique in drug design, aimed at predicting the optimal binding orientation of ligands to target proteins. This process not only elucidates protein-ligand interactions but also facilitates virtual screening, which accelerates the identification of lead compounds from extensive chemical libraries. With advances in structural biology, including X-ray crystallography and NMR, the availability of three-dimensional protein structures has enhanced the accuracy of docking simulations. The technique can be classified into rigid and flexible docking, addressing molecular dynamics during binding. Additionally, it encompasses covalent docking methods to assess ligands that form permanent interactions with targets. As molecular modeling evolves, docking approaches continue to integrate machine learning and high-throughput methods, enhancing efficiency in drug discovery. This comprehensive exploration of molecular docking underscores its significance in unraveling complex biological interactions and fostering innovative therapeutic developments.

Key words:, Drug Designing, Molecular docking Docking Parameter, Approches of Molecular docking

INTRODUCTION

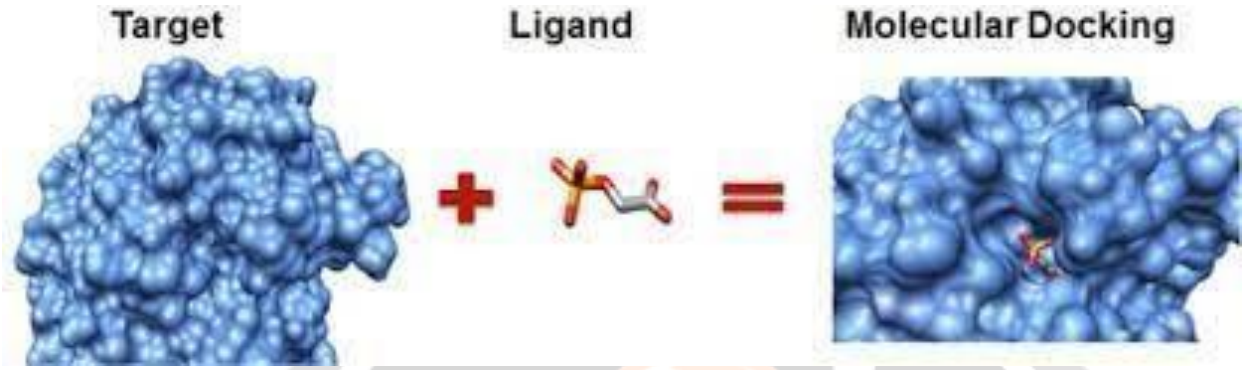
Molecular docking is an optimization problem that uses the "best-fit" orientation of a ligand that binds to a target protein to predict the structure of the intermolecular complex that will form between two or more molecules. Because of its applications in medicine, the protein-ligand interaction is the most fascinating example. A little chemical called a ligand interacts with protein binding sites. Mutual conformations can lead to binding in a variety of ways. Broadly speaking, these are called binding modalities [3]. One popular technique in modern drug design to understand how a drug interacts with its receptor is molecular docking. Predicting the binding orientation of small molecule therapeutic candidates to their target drug receptors is a typical use of molecular docking, which offers valuable insights into drug receptor interactions. Molecular docking is a popular technique to anticipate the binding orientation of small molecule therapy candidates to their protein targets, thereby providing insight into the small molecule's affinity and overall efficacy. It offers helpful information regarding how different drug receptors interact as well. (Source:)

These molecular-level interactions are generated and explored in computational chemistry through the use of docking. These techniques need the protein under study to have a three-dimensional (3D) structure. Fortunately, there is an abundance of structural target data available. We now have crucial three-dimensional information about enzymes and receptors thanks to recent advances in structural biology, mainly in the fields of nuclear magnetic resonance (NMR) and X-ray analysis. Protein-ligand interaction research requires the use of docking methods because they provide information about the molecular properties of both the protein targets and the interacting ligands.In [4]

"Virtual screening," or in silico docking simulations, is the computational counterpart of high-throughput screening assays. The limits placed on the quantity or quality of the chemical compound library, as well as the practical challenges related to test automation, are absent from these simulations.[4] Developing novel compounds, selecting promising lead compounds from (internal) databases, and providing insight into the molecular properties that dictate a compound's binding and activity are the goals of in silico docking systems.[6]

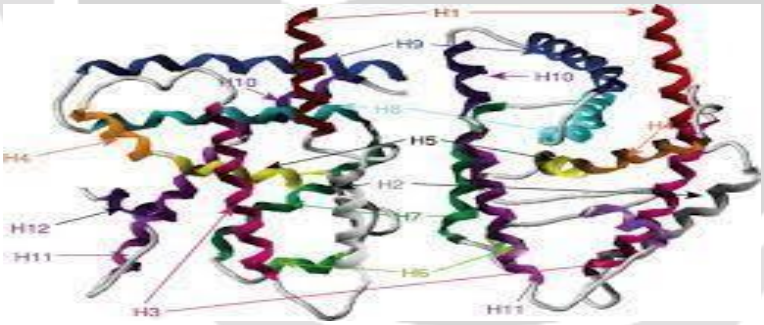
MOLECULAR DOCKING

Molecular docking is considered more beneficial in the design, assessment, and comparison of new drugs because it allows the investigation of molecule-to-molecule interactions in three-dimensional (3D) space while accounting for different molecule forms and identifies the factors that are important for pharmacological interactions [8]. Additional methods including in silico ADMET analysis, drug similarity prediction, and toxicity prediction are also employed to assess potential drugs from numerous databases. These computationally aided techniques cut down on the duration and cost of drug discovery experimentation.[7]



MOLECULAR MODELLING

Molecular modeling is a method for generating, describing, and modifying compound topologies and interactions as well as the properties of these compounds that rely on their three-dimensional geometries.



TYPES OF DOCKING
TWO DIFFERENT DOCKING FORMATS ARE AVAILABLE
RIGID DOCKING

If the compounds are stiff, we are trying to find a technique to reorganize one of them in three dimensions so that, in the context of a scoring system, it most closely resembles the other compounds [10]. Both with and without receptor binding activity, the ligand can take on its desired structure.

FLEXIBLE DOCKING

As the receptor and ligand molecules exist in the complex, we assess molecular flexibility in conjunction with transformation to find confirmations for them.

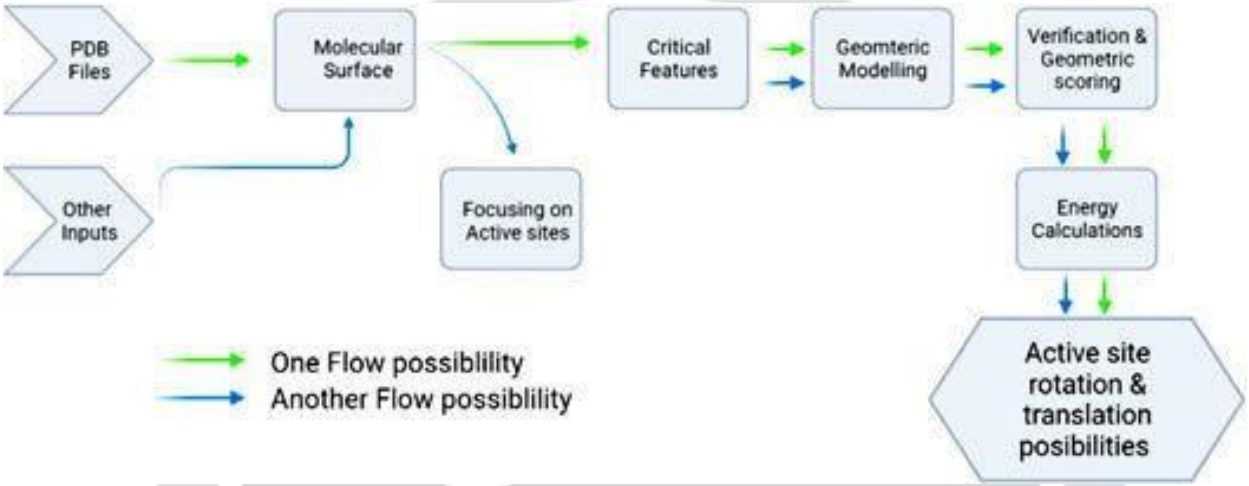


Fig. Rigid and flexible docking

THEORY OF DOCKING

The two main steps in the molecular docking process are the prediction of the conformation of the ligand, which is typically a tiny molecule, as well as its orientation and position within the protein binding site (referred to as pose). A scoring function is then used to evaluate the quality of the pose. The experimental binding mode should ideally be able to be replicated by the sampling process, and it should also be ranked top among all generated poses by the scoring function. Predictive docking, which involves giving active molecules a higher score than known inactives, is an additional task of the docking technique. This degree of accuracy is challenging to get, though, as it is typically impacted by a wide range of extrinsic factors unrelated to the protein.

METHODS

The user must get the necessary input files ready regardless of the docking technique chosen. This will be contingent upon the docking technique employed, specifically the molecular model employed in that technique. Auxiliary tools, scripts, and graphical user interfaces (GUI) are included with many docking systems to help the user with setup and post-docking analysis; Table 1 lists a few of these.

The atoms in the ligand and receptor molecules do not need to be partially charged in order to use docking techniques like FlexX and GOLD that do not need a force field. In contrast, partial atomic charges are needed by AutoDock and UCSF DOCK since they employ an AMBERderived force field. While AutoDock 4 utilized Gasteiger PEOE charges for both the ligand and the macromolecule, AutoDock 3 used Kollman united-atom partial charges on the macromolecule for its calibration. Noteworthy is the fact that additional AutoDock users

Table 1 Ligand input requirements for the most commonly cited docking software

Docking tools	Auxiliary tools	File format	Hydrogen atoms	Partial charges
AutoDock 4	AutoGrid, ADT, BDT	mol2, PDBQT	United atom	Gasteiger PEOE
DOCK 6	Chimera, Grid, Docktools, Nchemgrids, Sphgen, ANTECHAMBER	mol2	Explicit or united atom	AM1-BCC, Gasteiger
FlexX 2	FlexV	mol2, SD	United atom	Formal chargeonly
GOLD 3	GOLD Front End, SILVER	mol2, SD2	Explicit	None
ICM 3.4	ICM-Pro, ICM-VLS	mol2, SD	Explicit	MMFF, ICM

have looked into the use of different partial charges on the ligand. For example, Evans and Neidle derived their conclusion [14] [15] that the best charges for AutoDock 3's virtual screening of DNA minor groove binders came from AMSOL calculations using the AM1-CM2 Hamiltonian for nonpolar organic solvent [16].

3 DOCKING PARAMETERS

One of the main conformational search strategies used in AutoDock for molecular docking simulation is the Lamarckian genetic algorithm (LGA). For all potential conformations, a trail population is established. Subsequent generations of this process involve mutation, the interchange of conformational parameters, and competition akin to biological evolution, with the ultimate goal of selecting individuals with the lowest binding energy. The "Lamarckian" component is its added characteristic. It does the individual conformational search for its local conformational space, finding local minima and then continue with this information to later generations. Using the semi-empirical force field, the binding energy of small molecules to macromolecular targets is predicted By evaluating the energetics for both bound and unbound states using a thorough thermodynamic model, the force field enables the absorption of intramolecular energies into the projected binding energy [18].

4 COVALENT BONDS IN MOLECULAR DOCKING

Covalent medications have proven to be useful substitutes in a number of treatment domains, including diabetes, cancer, and gastrointestinal, neurological, cardiovascular, and infectious illnesses. According to recent statistics, covalent inhibitors make up around one-third of the enzyme modulators that are now on the market[20]. Because covalent ligands permanently deactivate their targets, re-synthesis of the target protein is required to restore the biological function that has been suppressed. Covalent inhibitors typically exhibit strong affinity for their molecular targets, resulting in a prolonged pharmacological response and a decreased need for frequent dosing [21]. Most R&D projects steer clear of covalent medicines due to their well-known side effects, which include toxicity, lack of selectivity, and high reactivity[22]. This idea has been reexamined, and new reports indicate that covalent inhibitors are becoming more and more popular. Consequently, a variety of approaches to the binding of covalent small-molecule inhibitors have been established. Covalent docking techniques are designed to assess the binding energetics of the interaction and investigate the energy landscape that the ligand has access to when it is covalently bound to the receptor[23]. Molecular modeling techniques created to tackle the issue of covalent docking are not as advanced as those devoted to noncovalent docking, even with the current revival of covalent drugs[24].

Covalent drug binding differs from noncovalent molecular interactions in a few ways, most notably in the thermodynamics of binding. Present-day molecular mechanics (MM) algorithms has the ability to accurately forecast noncovalent binding occurrences. Nevertheless, these approaches do not adequately address the creation of covalent bonds [24]. Quantum

mechanical techniques (QM) are suitable for addressing the problem of covalent-bond formation because they may investigate the entire reaction mechanism [23].

Programs like DOCK [32], Auto Dock [34], and Gold [35] are popular molecular docking tools that focus on the challenge of simulating covalent bonds. Every one of these applications uses a different method to control covalent docking. For example, Gold defines one atom in the ligand and the receptor to act as a "link atom" in an attempt to imitate the creation of covalent bonds [25]. The ligand link atom is then superimposed on the protein link atom, and certain aspects of the scoring function—such as the collision, torsion, and valence-angle bending parameters—are used to assess the covalent bond's shape. Another program, called DOCKovalent, is a modification of DOCK3.6 designed to carry out covalent virtual screening on a wide scale [26]. The method methodically investigates the ligand conformational space surrounding the modeled covalent bond and establishes a covalent attachment point a priori. The DOCK3.6 default scoring mechanism is used to rank each conformation. A different strategy is a more current version of AutoDock4 that suggests the "two-point attractor method" for covalent docking [27]. As part of the standard AutoDock procedure, an interaction energy map is created by calculating the energies of several probe atoms. These maps are then used as reference tables in a conformational search to determine the binding energetics. The following is how the two-point attractor method functions: First, the residue's two terminal atoms that are covalently attached to the ligand are taken off.
Subsequently, this fragment is joined to the appropriate ligand atom and designated with two distinct atom types (A and B). After that, altered interaction maps for these atoms are produced using a Gaussian function, with the original location of the atoms in the covalently bound amino acid residue serving as the center. The ligand conformations where A or B are not correctly positioned in their original places are penalized by these interaction energy maps.

1. THE APPLICATIONS OF MOLECULAR DOCKING

Virtual screening to discover the lead compound and hit compound
Virtual screening has significantly increased screening efficiency over the classic screen approach by locating the lead and hit compounds from the chemical databases based on a scoring algorithm. Virtual screening applications are widely utilized. The integrated method is particularly successful because of the rapid advancements in high throughput, high-performance computing, machine learning, and deep learning techniques. As an illustration, consider the deep learning approach used in virtual screening, which generates distributed vector representations for protein-ligand complexes by identifying pertinent features from molecular docking data. Additionally, a virtual high throughput screening was suggested.

Prediction of potential targets
It should be emphasized that the aforementioned techniques are all general docking techniques that dock with the same receptor using various ligands from the database. But the reverse docking method that is now in use differs from them. In this case, we used to explain the reverse docking method. Reverse docking involves using a single small-molecule ligand as the probe to dock with several receptors in order to find possible binding holes. This process helps identify novel targets. It is possible to estimate the possible targets of drugs in this way. For instance, investigated the reverse docking software program Mdock to the putative target, PRIMA-1's oxidized squalene cyclase (OSC). Additionally, specific proteins of marine chemicals with anti-tumor activity were found using the reverse docking technique. also demonstrated that reverse docking is a useful target fishing technique that works well in conjunction with in vitro tests. Lastly, we thought that the novel drug design may be greatly aided by investigating pertinent mechanisms of action or side effect profiles using structural biology research, such as the pocket analysis.

APPROACHES OF MOLECULAR DOCKING

Molecular docking is mostly accomplished using two kinds of methods. Using computer simulations, one method estimates the energy profile of ligand targets coupled conformers. In contrast, the second strategy makes use of a method that determines the complementarity of surfaces between the ligand and the target [30].

Simulation Approach
This method involves physically separating the ligand and target molecules, after which the ligand is permitted to bind into the target molecule's groove or pocket following a "definite times of moves" throughout its conformational space. The movements include changes to the ligand structure on the outside (rigid body transformations like rotations and translations) or within (torsional angle rotations).
The energy produced by each conformational change in the ligand is measured as the "Total Energy of the System." This strategy has an advantage over shape complementarity one since it is better suited to the molecular modeling tool's acceptance

of ligand flexibility. This method also has the advantage of making the chemical recognition between the ligand and the target molecule more realistic. However, because extensive energy landscapes must be computed for every pose, molecular docking employing this method takes longer to evaluate the ideal docked conformer. However, quick optimization techniques and grid-based tools have significantly changed this limitation to improve the usability of computer simulation approaches [30, 31].

Shape Complementarity Approach

This method uses the surface structure properties of the ligand and target to help with molecular docking. The molecular surface of the ligand is characterized in terms of matching surface illustration, whilst the molecular surface of the target is clarified in terms of its solvent-accessible surface area in order to perform molecular docking. Shape matching illustrations are used to assess the complementarity between two molecular surfaces and help find the complementary groove or pocket where ligand docking is most likely to occur on the target molecular surface. The number of twists in the main-chain atoms is specifically used to evaluate hydrophobicity for protein target molecules. In order to determine the potential three binding qualities of ligand on the target molecular surface, the shape complementarity approach, which is relatively quick and robust, rapidly scans hundreds of ligands in a matter of seconds [30, 31].

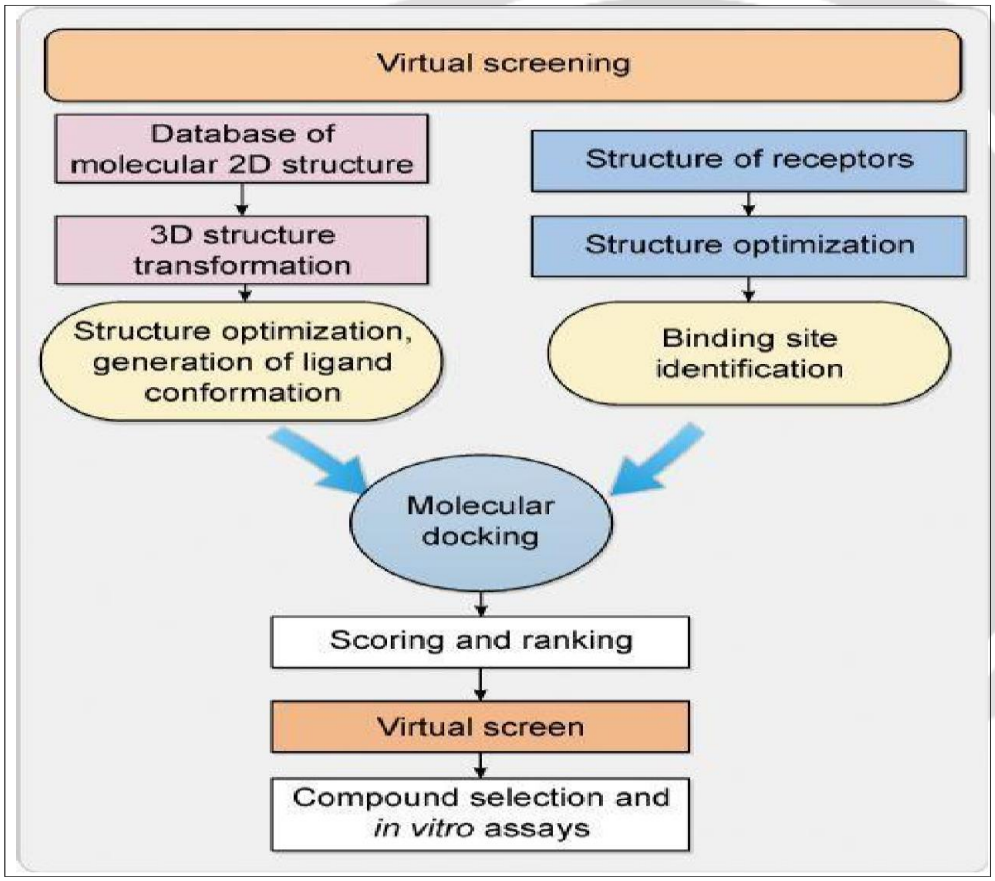


Figure: The process of virtual screen

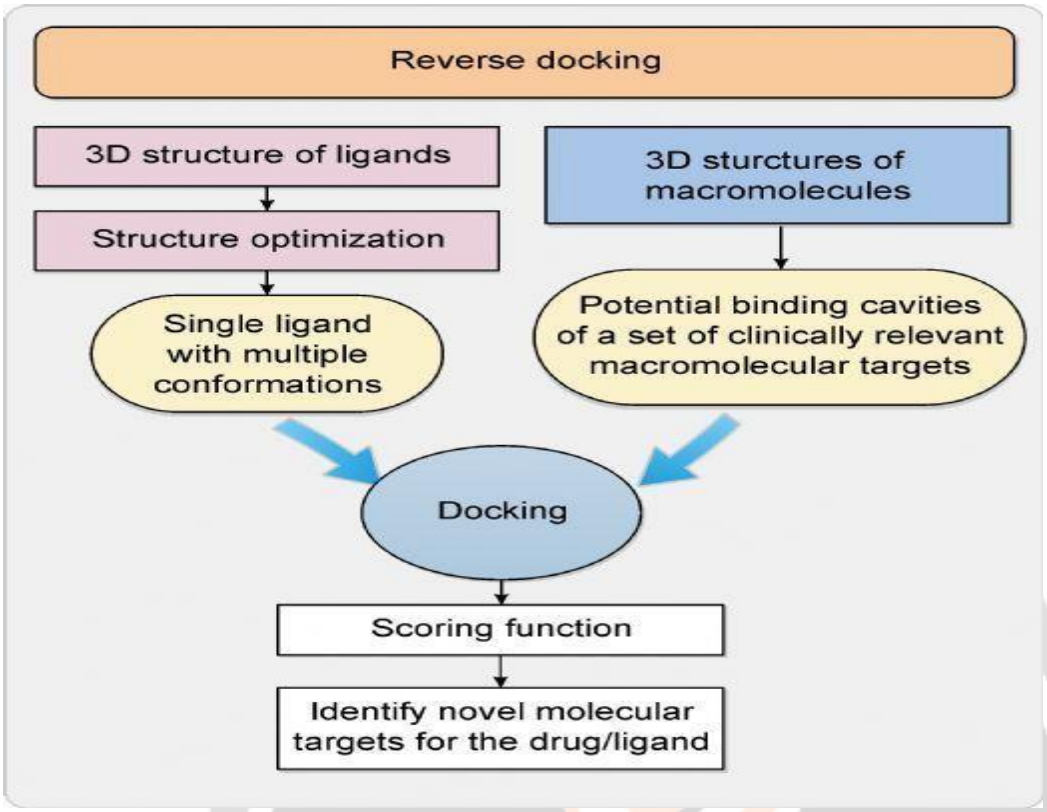


Figure: The reverse docking technique

2. GOALS OF MOLECULAR DOCKING

The goal of molecular docking for drug development is to search through a database of substances for ligands that take advantage of a feature of complementarity with the target receptor. For ligands that the receptor has never "seen," an effort is made to promote molecular recognition. This is something that needs to be explained. The receptor structure that is to be docked has been seen in both an unbound and bound condition by experimental observation or homology modeling. As a result, the receptor is in a predetermined conformation that may have been shaped to fit a specific ligand. Allowing the receptor to react to each potential ligand might be beneficial for docking studies. A more accurate indicator of the compound's potential as a real ligand would be provided by the receptor's flexibility, which would allow for the development of better connections. We wonder if it is conceivable to exhibit some aspects of conformational flexibility in the docking methods, without having to include explicit flexibility and incur a heavy performance penalty.

EVALUATING DOCKING RESULTS

There are two primary factors to take into account when assessing the outcomes of dockings: 1) How well did the docking anticipate the binding mode and, where available, how well did it match known structural data? 2) How well did the docking rank the ligands? How well does the technique match experimental binding data if its scoring function is meant to predict binding affinities?

To calculate the RMSD between the ligand's docked and "reference" crystallographic binding modes—which is usually used to evaluate success (RMSD less than 2 A)—it is necessary to know the crystal structure of the complex to which the ligand has attached. To answer the second condition, inhibition ���^ constants, or Ki values, for the ligands and the target system, must be found.

How frequently a certain binding mode was predicted across all of the dockings that were done is a crucial consideration when using a stochastic search strategy. In order to accomplish this, conformational clustering is typically used, which builds families of related conformations by determining if two conformations are similar enough to be in the same cluster by applying RMSD tolerances.

CONCULISON :

In silico molecular docking studies have emerged as an essential tool in drug discovery and design, offering a cost-effective and time-efficient alternative to experimental methods. These computational techniques enable the prediction of molecular interactions, helping to identify promising drug candidates by simulating their binding affinity to target proteins. Over the years, advancements in software algorithms, computational power, and available biological data have greatly enhanced the accuracy and reliability of molecular docking.

However, despite these developments, docking studies are not without limitations. Challenges such as receptor flexibility, solvation effects, and the accuracy of scoring functions can affect the precision of predictions. Therefore, it is crucial to complement docking studies with experimental validation and integrate them with other computational methods, such as molecular dynamics simulations, to provide a more comprehensive understanding of ligand-receptor interactions.

As computational techniques continue to evolve, molecular docking will remain a powerful and indispensable tool in the early stages of drug development, aiding in the efficient design of novel therapeutics. Future improvements in software precision and computational resources will further enhance its applications, making it even more integral to the fields of pharmacology, medicinal chemistry, and biophysics.

REFERENCES

1. Suzuki, F., Kuroda, T., Tamura, T., Sato, S., Ohmori, K., Ichikawa, S., 1992.New anti-inflammatory agents.
2. 5-Phenyl-3H-imidazo[4,5- c][1,8]naphthyridin-4(5H)-ones: a new class of nonsteroidal anti-inflammatory agents with potent activity like glucocorticoids. J. Med. chem. 35, 2863–2870.

2. A.M. Vijesh [a] , Arun M. Isloor[b] , *, Sandeep Telkar[c] , T. Arulmoli[d] , Hoong- Kun Fun[e] Molecular docking studies of some new imidazole derivatives for antimicrobial properties.

3. Sharma, N.K., Jha, K.K., Priyanka, 2010. Molecular docking: an overview. J. Adv. Sci. Res. 1, 67–72.

4. Hou T, Xu X. Recent development and application of virtual screening in drug discovery: an overview. Current pharmaceutical design. 2004 Apr 1;10(9):1011- 33.

5. Aldo Jongejan, Chris de Graaf, Nico P. E. Vermeulen, Rob Leurs, and Iwan J. P.de Esch The Role and Application of In Silico Docking in Chemical Genomics Research.

6. Taylor, R. D., Jewsbury, P. J., and Essex, J. W. (2002) A review of protein-smallmolecule docking methods. J. Comput. Aided Mol. Des. 16, 151–166.

7. S. Vardhan, S.K. Sahoo, arXiv preprint arXiv:2005.07955 (2020).

8. N. Mohammadi, N. Shaghaghi, Preprint. https://doi/. org/10.26434/chemrxiv 11987475 (2020) v1.

9. Shabbir Muhammad , Sayyeda Hira Hassan, Abdullah G. Al-Sehemi , Hafiz Abdullah Shakir , Muhammad Khan , Muhammad Irfan , Javed Iqbal g Exploring the new potential antiviral constituents of Moringa oliefera for SARS-COV-2pathogenesis: An in silico molecular docking and dynamic studies.

10. Huang N, Shoichet BK, Irwin JJ. Benchmarking sets for Molecular Docking. JMed Chem. 2006;49(23):6789–801. doi:10.1021/jm0608356.

11. Shoichet BK, Mcgovern SL, Wei B, Irwin JJ. Lead discovery using moleculardocking. Curr Opin Chem Biol . 2002;6(4):439–85. doi:10.1016/s1367- 5931(02)00339-3.

12. Keval Raval1,*, Tejas Ganatra Basics, types and applications of moleculardocking: A review.

13. Francesca Stanzione*, Ilenia Giangreco, and Jason C. Cole Use of moleculardocking computational tools in drug discovery.

14. Cramer, C.J. and Truhlar, D.G. (1992) AM1-SM2 and PM3-SM3 parameterized SCF solvation models for free energies in aqueous solution. J Comput Aided Mol Des, 6(6): 629–666.

15. Hawkins, G.D., Giesen, D.J., Lynch, G.C., Chambers, C.C., Rossi, I., Storer, J.W., Li, J., Zhu, T., Thompson, J.D., Winget, P., Lynch, B.J., Rinaldi, D., Liotard, D.A., Cramer, C.J., and Truhlar, D.G. (2007) AMSOL 7.1, Department of Chemistry and Supercomputer Institute, University of Minnesota: Minneapolis, Minnesota,

16. 4. Evans, D.A. and Neidle, S. (2006) Virtual screening of DNA minor groove binders. J Med Chem, 49(14): 4232–4238.

17. Garrett M. Morris and Marguerita Lim-Wilby ,Molecular Docking.

18. Mujwar S, Pardasani KR: Prediction of Riboswitch as a potential drug target for infectious diseases: an in silico case study of anthrax. J Med Imaging Health Inform 2015;5:7–16.

19. Kamal Shah,1 Somdutt Mujwar,1 Jeetendra Kumar Gupta,1 Sushant K. Shrivastava,2 and Pradeep Mishra1 Molecular Docking and In Silico Cogitation Validate Mefenamic Acid Prodrugs as Human Cyclooxygenase-2 Inhibitor.

20. Kumalo, H.M.; Bhakat, S.; Soliman, M.E. Theory and applications of covalent docking in drug discovery: Merits and pitfalls. Molecules 2015, 20, 1984–2000.

21. Singh, J.; Petter, R.C.; Baillie, T.A.; Whitty, A. The resurgence of covalent drugs. Nat. Rev. Drug Discov. 2011, 10, 307–317.

22. Ouyang, X.; Zhou, S.; Su, C.T.T.; Ge, Z.; Li, R.; Kwoh, C.K. CovalentDock: Automated covalent docking with parameterized covalent linkage energy estimation and molecular geometry constraints. J. Comput. Chem. 2013, 34, 326– 336.

23. Moitessier, N.; Englebienne, P.; Lee, D.; Lawandi, J.; Corbeil, C.R. Towards the development of universal, fast and highly accurate docking/scoring methods: Along way to go. Br. J. Pharmacol. 2008, 153, S7–S26.

24. Verdonk, M.L.; Cole, J.C.; Hartshorn, M.J.; Murray, C.W.; Taylor, R.D. Improved protein-ligand docking using GOLD. Proteins 2003, 52, 609–623.

25. London, N.; Miller, R.M.; Krishnan, S.; Uchida, K.; Irwin, J.J.; Eidam, O.; Cimermančič, P.; Gibold, L.; Bonnet, R.; Shoichet, B.K.; et al. Covalent dockingof large libraries for the discovery of chemical probes. Nat. Chem. Biol. 2014, 10, 1066–1072.

26. Bianco, G.; Forli, S.; Goodsell, D.S.; Olson, A.J. Covalent docking using Autodock: Two-point attractor and flexible sidechain methods. Protein Sci. 2015, Epub ahead of print.

27. Xu, M.; Lill, M.A. Induced fit docking, and the use of QM/MM methods in docking. Drug Discov. Today Technol. 2013, 10, e411–e418.

28. Menikarachchi, L.C.; Gascón, J.A. QM/MM approaches in medicinalchemistry research. Curr. Top. Med. Chem. 2010, 10, 46–54.

29. Molecular Docking and Structure-Based Drug Design Strategies Leonardo G. Ferreira *, Ricardo N. dos Santos, Glaucius Oliva and Adriano D. Andricopulo *.

30. B Mukesh, K Rakesh. Molecular docking: a review. IJRAP. 2011; 2: 1746- 1751.

31. Lamb ML, Jorgensen WL. Computational approaches to molecular recognition.Curr Opin Chem Biol. 1997; 1: 449-457.