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Molecular Docking: a decision-making tool for drug discovery

Sonakshi Tandon, Anna Balaji, Shaheen Sultana*
IIMT College of Pharmacy, Greater Noida

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ABSTRACT
Molecular in-silico docking of the protein influenza virus using the docking software with some of the drugs to study the drug target interaction. The encouraging approach is to identify the drug molecules through virtual screening via molecular docking. Molecular docking has been recognized as a fast and inexpensive technique which analyses the conformation and orientation of the atoms or molecules into the binding site of macromolecular target. For so many years biochemists have been developed various models to get the key elements of the molecular process. Docking methods are classified in terms of the degrees of flexibility of the molecules under investigation. Interaction between the small molecular such as ligand and protein which may be an enzyme can predict the activation or inhibition of the target enzyme, the main theories has been followed in this review are lock and key, induced-fit, conformation ensemble. There are three main types of scoring functions used in molecular docking those are: force-field-based scoring functions, empirical scoring functions, and knowledge-based scoring functions. Expanding the pharmacodynamics information, such as strength, viability, selectivity, pharmacokinetic properties, absorption, distribution, metabolism, excretion and toxicity (ADMET) have been concentrated using docking software. In this review we are going to learn about how molecular docking can optimized the drug design by finding out the best target site of the protein for the ligand before developing the drug which will enhance the ligand-receptor binding.
Key words: molecular docking, influenza virus, force-field, ligand, receptor, lock and key, conformation ensemble, induced-fit.

I. MOLECULAR DOCKING

The molecular docking is the approach that can be used to model the interaction which is between small molecule and a protein at the atomic or molecular level. It helps us to characterize the behavior of the small molecules in binding site of target proteins [1]. The docking process includes both, the prediction of ligand conformation and orientation which shows the posing within a binding site. Molecular docking studies has been done with the two most important aims, namely, are accurate structural modeling and the correct prediction of activity [2]. Molecular in-silico docking of the protein influenza virus using the docking software with some of the antiviral herbal drugs to study the drug target interaction [3]. The discovery of an antiviral drug is an important aspect in the excessive spread of flu. The emergence of new circulating viral strains, novel effective antivirals are needed urgently and with less side effects, resulting the computational molecular docking of the antiviral drugs to enhance the drug-target interaction, will provide the new antiviral drug with high efficacy towards the virus [4]. The encouraging approach is to identify the drug molecules through virtual screening via molecular docking [5]. Molecular docking has been recognized as a fast and inexpensive technique which analyses the conformation and orientation of the atoms or molecules into the binding site of macromolecular target [6]. The docking process includes both, the prediction of ligand conformation and orientation which shows the posing within a binding site. Molecular docking studies has been done with the two most important aims, namely, are accurate structural modeling and the correct prediction of activity [7]. Molecular in-silico docking of the protein influenza virus using the docking software with some of the antiviral herbal drugs to study the drug target interaction [8].

Knowing the location of the binding site before processing the docking process helps in increasing the docking efficacy, In most cases the bin ding site is known before docking ligands into it. The lock and key theory by Fischer is helpful in the mechanism for the early elucidation for the ligand-receptor binding [9, 10], which shows how the ligand fits into the receptor like lock and key and both the ligand and receptor were treated as rigid bodies.

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The active site of the protein continuously reshaped itself by interactions with the ligands as, and this theory is known as induced-fit which was proposed by Koshland followed by the lock and key theory, which suggests to treat ligand and receptor as flexible during docking [11, 12]. Docking allows the understanding of the relationship between the different molecular targets that are involved in a given disease which is of high relevance of modern drug discovery in general [13].

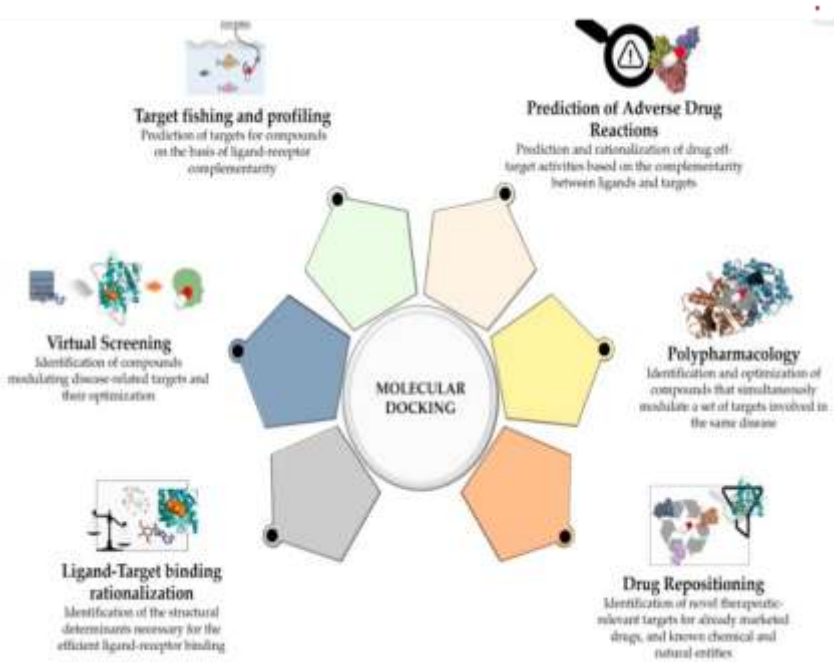

Fig1: various applications of molecular docking in current drug discovery. Molecular docking helps in rationalizing ligands activity towards a target of interest, perform structure based virtual screening, it can be used to identify series of targets for which the ligands present good complementarity. Docking is being employed for identification of ligands that bind to selected targets of interest. Successful docking methods search high-dimensional spaces effectively and use a scoring function that correctly ranks candidate dockings. Docking can be used to perform virtual screening on large libraries of compounds, rank the results, and propose structural hypotheses of how the ligands inhibit the target, which is invaluable in lead optimization [14].

Molecular docking models

For so many years biochemists have been developed various models to get the key elements of the molecular process[15,16] Although it is very simplified, these models have proven to have highly useful properties for the scientific community, different models have developed in different years by numerous authors [17].

AUTHOR	MODEL	YEAR
Emil Fischer	Lock and key	1894
Daniel Koshland	Induced-fit	1958
Buyong Ma et al.	Conformation ensemble	2003

Table1

Lock and key theory

In 1894, Emil Fischer proposed that specificity of an enzyme towards its substrate can be based on two components exhibiting complementary geometric shapes fit perfectly like a 'key in a lock'. This simple 'lock and key' analogy

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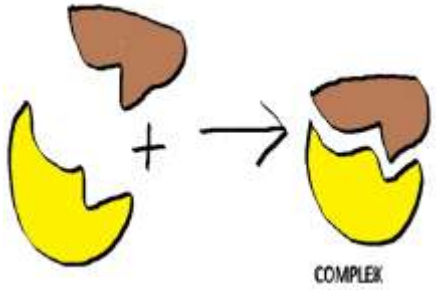
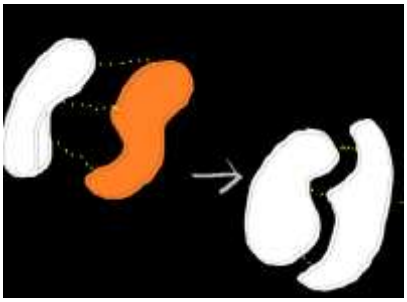
where the lock describes the 'enzyme' and the key describes the 'substrate' or ligand. It is a requirement that the 'key' (substrate) fit appropriately into the keyhole (active site) of the 'lock' (enzyme/receptor). Keys that are too small, too large, or withincorrectly positioned, will not be fit into the lock [18,19].



Induced-fit

The induced fit model accurately predicts ligand binding modes and structural changes into the receptor. A Python script automates the induced fit design (IFD) protocol and specify receptor and ligand structures [20]. Standard virtual docking studies assume a rigid receptor, but in reality, many receptors alter their binding site to conform to the shape and binding mode of the ligand. This is often referred to as induced fit and is one of the main complicating factors in structure-based drug design [21,22]. The ability to model induced fit docking has two main applications:

- Generation of an accurate complex structure for a ligand known to be active but that cannot be docked in an existing (rigid) structure of the receptor.
- Rescue of false negatives (poorly scored true binders) in virtual screening experiments, where instead of screening against a single conformation of the receptor, [23] additional conformations obtained from the IFD protocol are used.



Conformation ensemble model

In addition to small induced-fit adaptation, it has been observed that proteins can undergo much larger conformational changes. A recent model describes proteins as a pre-existing ensemble of conformational states. The plasticity of the protein allows it to switch from one state to another [24,25]. Therefore, these three models are not contradictory as each one of them focuses on a particular aspect of the recognition process, which is

-the lock-and-key model introduces the ''principle of 3D complementarity'',
-the induced-fit model explains ''how complementarity is achieved'',
-and the ensemble model ''depicts the conformational complexity of proteins ''

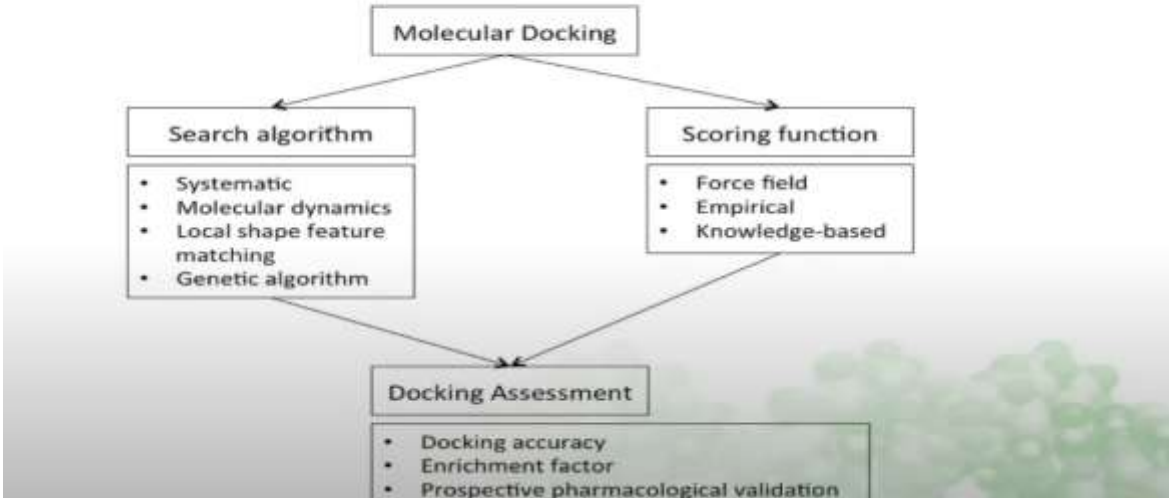


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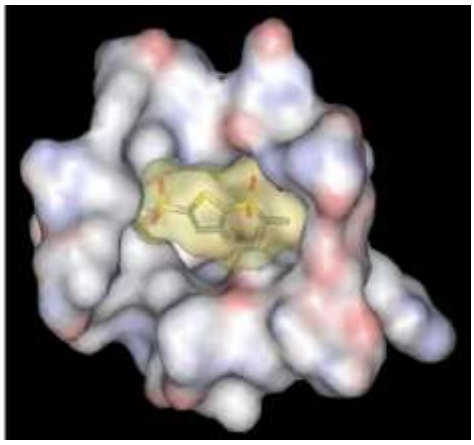
Fig 2: for the molecular docking process we have two parts that are search algorithm and scoring function. In the scoring function it has force field (auto dock 4), empirical (auto dock vina) and knowledge-based (involves machine learning), while in search algorithm we can decide how it can go for search and it includes systemic, molecular dynamics, local shape feature matching and also genetic algorithm [26], and then after processing these steps is moves forward to the docking assessment where the docking accuracy, enrichment factor and prospective pharmacological validation would be done and get the optimized results [27,28].

Triggering the Computational Docking

The difficulties in obtaining structural data of the macromolecular complexes must have triggered the development of the computational predictive procedures [29]. Computational molecular docking is a computational science which aims at predicting the optimal binding orientation and conformation of interacting molecules in space, and helps to estimate the stability of their complex. Molecular docking predicts whether the two molecules interact or not, the binding affinity and the 3D structure of the complex [30, 31].



Classification of molecular docking:

Docking methods are classified in terms of the degrees of flexibility of the molecules under investigation. There are three classifications:

Molecule Based
Flexibility Based

- Protein-Protein Docking
Rigid Receptor-Ligand Docking
- Protein-Peptide Docking
Rigid Receptor-Flexible Ligand Docking
- Protein-Ligand Docking
Flexible Receptor-Ligand Docking
- Protein-DNA Docking
- DNA-ligand Docking

Rigid docking is where the ligand and target are both classified as rigid and just three translational and rotational degrees of freedom are considered in the sampling phase. This model is most commonly used for protein to protein docking and reflects the “lock and key” model of binding [32]. In semi-flexible method, the ligand is considered flexible, and the target is considered as rigid. The conformational degrees of freedom of the flexible molecule are sampled, and six translational plus rotational degrees of freedom are also added. Semi-flexible methods assume that a fixed conformation of a target might correspond to the one able to recognize the docking ligands [33]. The final method of flexible docking assumes that a protein does not behave passively during the binding phase and, therefore, it considers the target protein to be flexible as well as the ligand. There are numerous methods for flexible docking that have developed over the years with some focusing on model of induced fit binding and others focusing on conformational selection [34,35].

Popular Docking Algorithms:

Various molecular docking software are being employed currently those are

Protein Ligand Docking

Free: AutoDock, AutoDock Vina, DOCK, ArgusLab, SwissDock
Commercial: ICM, Glide, GOLD, FlexX, Molegro

Protein- Protein Docking

ClisPro, Hex, HADDOCK, ZDock

Each one of them are having differences in treating the hydrogen bonds, form of the energy functions and many more, and further the results of docking with force-field based functions can be refined with other techniques [36,37,38].

AutoDock Vina

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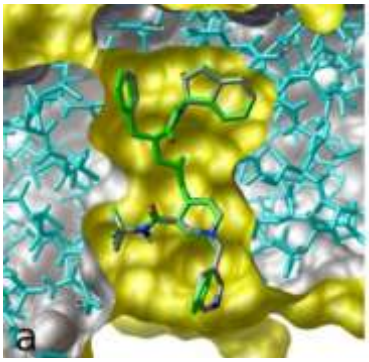

It is a program for molecular docking, it designed and implemented by Dr. Oleg Trott at the Scripps Research Institute.AutoDock Vina improves the average accuracy of the binding mode predictions as compared to AutoDock 4, the AutoDock Vina has been tested against virtual screening benchmark called as Directory of useful Decoys and it is found to be the strong competitor against many other software programs [39].

Compatibility: For its input and output, Vina uses the same PDBQT molecular structure file format used by AutoDock. PDBQT files can be generated and viewed using MGLTools [40].

Implementation Quality

- By design, the results should not have a statistical bias related to the conformation of the input structure.
- Attention is paid to checking the syntactic correctness of the input and reporting errors to the user in a lucid manner.
- The invariance of the covalent bond lengths is automatically verified in the output structures.
- Vina avoids imposing artificial restrictions, such as the number of atoms in the input, the number of torsions, the size of the search space, the exhaustiveness of the search and more [41,42].

An interesting application of docking to investigate enzymes that bind their substrates covalently is presented by DOCKovalent [43]. Is invented for enzymes, the method could be useful also in the field of GPCRs, e.g., for in silico experimental results [44]. Some new algorithms have been introduced and their huge flexibility was also reported. These reports could affect the GPCR field directly or indirectly, since there are a number of these receptors binding peptides as native ligands. The most characteristic feature of one of such new algorithms, AnchorDock, is incorporation of ligand recognition mechanisms into the docking process [45].

Another new fully blind docking approach, called MDockPeP, first generates peptide structures on the basis of the template fragments and then performs modeling of the protein-peptide complex, which resembles classical docking [46]. In turn, knowledge-based strategy was implemented in GalaxyPepDock [47]. The program gathers information from databases of known protein-peptide interactions,

Certainly, these new algorithms can improve the quality of docking results which require less computational resources than others. However, a recent benchmark prepared by Hauser and Windshügel suggests that some of the more established algorithms like Surflex [48] or AutoDock Vina [49] can also perform well in docking of peptides longer than five aminoacids [50].

Applications of Molecular Docking

❖ Molecular docking can demonstrate the feasibility of biochemical reaction as it is carried out before the experiment. Interaction between the small molecular such as ligand and protein which may be an enzyme can predict the activation or inhibition of the target enzyme [51]. Some major applications of molecular docking are as follows:

Optimization

Molecular docking can predict optimized orientation of the ligand on its target. Can find the optimized structure and binding site for the ligand on the target enzyme, can helps to predict different binding modes of the ligand for the structure of the target molecule, which can helps in developing more potent, selective and efficient drug candidates [52,53].

Hit the identification

Molecular docking in combination with the scoring function can be used to evaluate large databases for finding out potent drug candidate virtually which can help to target the molecule of interest [54]

Drug-DNA interaction

Docking plays an important role in the initial prediction of the drug's binding properties to the target protein.This information forms the correlation between drug's molecular structure [55]. Medical chemists are doing in silico

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observations where they predict whether the drug is interacting with the protein. This knowledge would be useful in the detection of those structural modifications in a drug that could results in structure specific binding to their target [56,57].

Remediation

Protein-ligand interaction docking may be utilized to show which substances are degradable by enzymes. It can also be utilized for the findings of the desired location, collection of the most effective medication [58].

Molecular docking can be used to identify enzymes and their mechanism**.** It is utilized to determine relationships between the proteins**.** Molecules are screened virtually by using the remediation method [59].

- Modeling the structure of the protein–ligand complex is important for understanding the interaction between a potential compound (the ligand) and its objective (the protein).
- The motion space of the protein–ligand complex can be explored by using computer-aided docking to compute a steady configuration which can models the structure of the coupling complex [60,61].
- In expanding the pharmacodynamics information, such as strength, viability, selectivity, pharmacokinetic properties, absorption, distribution, metabolism, excretion and toxicity (ADMET) have been concentrated using docking software [62].

Working of Molecular Docking

The molecular docking method seeks to identify the binding mode of a given ligand that best matches with a target, such as a protein. The process involves generating multiple possible conformations and orientations of the ligand with the binding site of the target. Access to the three-dimensional structure of the target is, therefore, vital for this process [63,64]. The process of molecular docking involves two steps. The one is the generation and sampling of conformations, and the second step is the allocation of a score to each predicted pose to determine the likeliness of the molecule that binds to the target with the high affinity [65]. As a result, the process can select molecules that show favorable behavior and a high likelihood for binding to a target with high affinity [66]. There are three main types of scoring functions used in molecular docking those are: 1) force-field-based scoring functions, 2) empirical scoring functions, and 3) knowledge-based scoring functions.

Steps involved in Docking:

Step1: preparation of ligands

- Draw ligands using Java applet; draw chemical structures by MarvinSketch which is a Java based program.
- Upload a ligand in MOL, MOL2, MDL, PDB format; and upload multiple ligands in SDF format.
- Various parameters can be set accordingly during the simulation such as pH, structure optimization, charge calculations and many more.
- Various bonds and atoms can be modify manually.
- Download the attached files in the format of mol, pdb, mol2 and pdbqt
- Save your ligands can be saved and organized for the further docking process.

Step2: Preparation of proteins

- Protein structures can be uploaded or downloaded from the Protein Data Bank by using Docking server by providing entry code or text search.
- Select protein chain, heteroatoms, ligands and water molecules present in protein pdb file.
- Now setup the simulation box by

Selecting known binding site through a co-crystallized ligand
Selecting the center of mass of protein
Selecting the coordinates of box center
Selecting amino acid residues that defines the binding sites.

- Molecular docking server will calculate the necessary map files for each of the atom type and helps in preparing the input files for docking calculations.

Step3: Setup ligand protein docking calculations

- Select the ligand and protein from the library.
- Modify the parameters during simulation, such as no. of runs, evaluations etc.

Step4: Evaluation of the results

- Choose image from image gallery and put it in Molecular Docking Server.
- Now analyze the secondary interactions between protein and ligand.
- Create a method section for the reports automatically.

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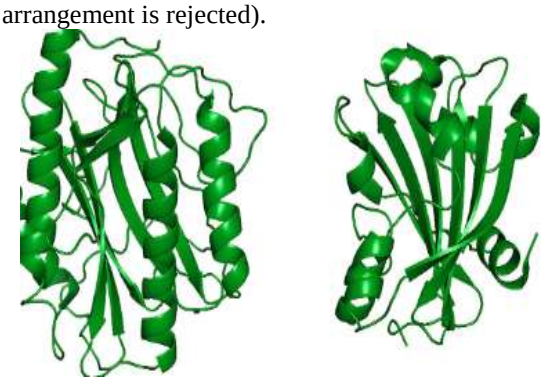
Molecular docking approaches:

Monte Carlo – creates randomized conformation, translations, rotation of ligand on active site [67]. Develops and scores a new configuration. This technique employs random or pseudo random modifications of bond rotations [68]. It determines if the new configuration is still using Metropolis criterion (in which Boltzmann's law is employed, the resolution is acceptable if it satisfies probability function test; otherwise arrangement is rejected).



Matching:

The optimal location of the ligand in site is determined, the accurate location for the ligand atom has been determined which results in a ligand-receptor arrangement which might also need improvement [69].

Point complimentarily:

It is focused on comparing the shapes and/or chemical properties of different molecules. Blind Docking is a technique that was developed to identify potential peptide ligand binding sites and mode of action of target molecules.

Distance geometry

Numerous features can be represented in terms of intramolecular or intermolecular dimensions. The distance geometry framework enables the assembly of these distances and the calculation of 3-D structures that must be compatible with them [70].

Inverse docking

When all these targets are paired with pharmacokinetic property, can get the evaluation of a drug's potential for toxicities and side effects.

Ligand representation

The configuration with the highest probability of becoming predominant by adding or deleting hydrogen atoms to obtain estimated pKa values [71]. It is critical that precise atomic coding transpires and represents the accurate and optimized ligand structure.

Receptor representation

The receptor structure used is significant for the effectiveness of docking simulations. The greater the resolution of the crystal lattice used, the greater the docking findings seen [72]. A recent study of the accuracy, limits, and hazards of ligand-protein complex structure refinement techniques, in general, provides a rigorous analysis of the known structures [73].

II. CONCLUSION

Molecular docking has become an important component of the drug discovery process, being developed in the 1980s [74].Molecular docking has beenthe most basic and important strategy for the drug discovery. It allows prediction of molecular interactions that hold together a protein and a ligand in the bound state [75].Considering the significance of application of such tools and strategies, a solved practical exercise along with a detailed outline of the protocol to follow. molecular dynamics methods have been used that emphasize the application of quantum chemistry, statistical mechanics, and the features of the electrical potential (force field) [76]. Several docking tools, such as AutoDock, AutoDock Vina, Gilde, DOCK, GOLD, FlexX, and Surflex, and many docking servers, such as ZDOCK, HDOCK, ClusPro, and SwissDock, are available for molecular docking purposes. Molecular docking is used for virtual screening, binding affinity, and binding free energy calculations and also for tracing out and visualizing various types of bonded and nonbonded interaction between the ligand and amino acid residues of a protein.

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