



Review on Computational Bioinformatics and Molecular Modelling: Novel Tool for Drug Discovery

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ABSTRACT

Advancement in science and technology has brought a remarkable change in the field of drug discovery. Earlier it was very difficult to predict the target for receptor but nowadays, it is easy and robust task to dock the target protein with ligand and binding affinity is calculated. Docking helps in the virtual screening of drug along with its hit identification. There are two approaches through which docking can be carried out, shape complementary and stimulation approach. There are many procedures involved in carrying out docking and all require different software's and algorithms. Molecular docking serves as a good platform to screen a large number of ligands and is useful in Drug-DNA studies. This review mainly focuses on the general idea of molecular docking and discusses its major applications, different types of interaction involved and types of docking.

KEY WORDS: *Molecular Modelling, Binding Affinities, Receptor, Ligand*

INTRODUCTION

Drug designing uses a new approach of the computational tool. This gives scientists a direction to find out new targets of drugs. Molecular docking is a branch of biology called as computational modelling, which facilitates the prediction of preferred and favoured binding orientation of one molecule (ligand) to another (receptor) in order to make a stable complex when both interact with each other as shown in fig. 1[1]. Information gained from the preferred orientation of bound molecules i.e.- scoring function may be employed to predict the energy profiling (such as binding free energy), strength and stability (like binding affinity and binding constant) of complexes. Now a day, it is often used to predict the binding orientation of small molecules (drug) to their bio molecular target (such as carbohydrate, protein and

nucleic acid) with the purpose of determining their binding energies. This provides fair data for rational drug designing (structure-based-drug development) of agents with better efficacy and more specificity [2]. The main objective of molecular docking is to attain a stable docked conformer for both the interacting molecules in a continuance of achieving the reduced free energy of the whole system. Final expected binding free energy (ΔG_{bind}) is displayed in terms of dispersion & repulsion (ΔG_{vdw}), electrostatic (ΔG_{elec}), torsional free energy (ΔG_{tor}), final total internal energy (ΔG_{total}), desolvation (ΔG_{desolv}), hydrogen bond (ΔG_{hbond}), and unbound system's energy (ΔG_{unb}). Therefore, predicted data of binding free energy (ΔG_{bind}) provides enough information about the nature of various kinds of interactions driving the docking of molecules [3].

Molecular docking requires structural data bank for finding the target of interest and ligand along with the methodology to evaluate it. To complete this, there are many methodologies and molecular docking tools are available. These tools provide the list of potential ligands based upon their ability to interact with given target candidates. In recent years, computer modelling has gained popularity.

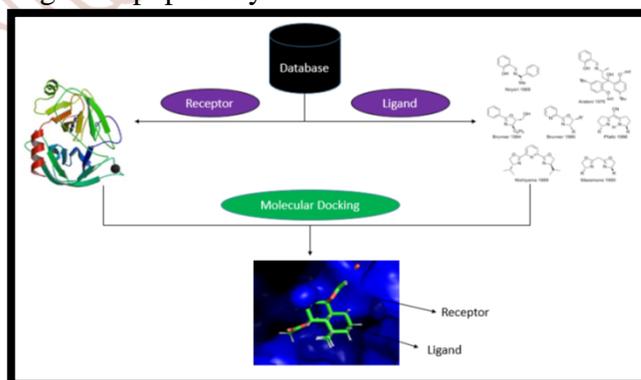


Fig. 1: Molecular docking flow chart

Molecular docking of small molecules to a biological target includes an imaginative sampling of possible conformation of ligands in the specified groove or pocket of target candidate in order to establish a stable optimal binding geometry. This can be performed using scoring function of docking software [1,4]. Homology modelling enables the prediction of tentative structure of those proteins (of unknown structure) which have high sequence homology or to know structure. This presents a substitute approach for target structure establishment and forms an initiation point for in silico discovery of high affinity drug candidates. Information on small ligand molecules can be extracted from online databases such as ACD (Available Chemical Directory), CSD (Cambridge Structural Database), NCI (National Cancer Institute Database) and MDDR (MDL Drug Data Report).

While performing molecular docking, different docked poses are created, scored and compared with each other. In docking- searching and scoring are tightly regulated with each other and ranking of docked conformers is given according to their experimental binding affinities.

Virtual screening:

Human genome project which was initiated in 1990 with an aim to determine the DNA sequence of eukaryotic genome. This was a 15 year long funded project [5]. By the end of human genome project, scientists were able to predict the target of many drugs and ligands but the drug discovery field lack many more gaps to cover up. At the same time:

- Protein purification,
- Crystallography,
- Nuclear magnetic resonance imaging,

And multiple techniques filled the gaps in drug discovery field and were able to predict the structure of protein. These experimental and high throughput screening methods were expensive, less efficient and time consuming to discover the ligand for variety of diseases like cancer, tuberculosis etc. More advancement takes place with time and computational method in a today scenario play important role in finding the target for diseases and their ligands[6]. This comprises two things based on the availability of structure information:

1. Structure based drug designing method: Molecular Docking.

2. Ligand based drug designing method: Quantitative structure activity relationship (QSAR) method and pharmacophore modelling [7].

Advantages of (VS) technique:

1. Low cost.
2. Effective screening

Types of molecular docking:

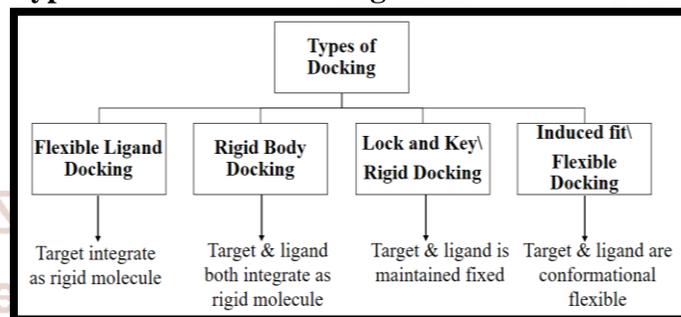


Fig. 2: Various type of molecular docking

Molecular docking is of 4 types

1. Flexible ligand docking: In this type of docking, the target is integrate as a rigid molecule. This is the most frequently used technique in docking as shown in fig. 2.
2. Rigid body docking: In this type of docking, the target and ligand molecules both are kept as rigid molecules [8].
3. Lock and Key Rigid Docking: In this type of docking, both the receptor and ligand are maintained fixed and docking is performed.
4. Induced fit Flexible docking: In this type of docking, both the ligand and the receptor are conformationally flexible and binding energy is calculated; later the most favourable conformation is selected [9].

Different types of interactions:

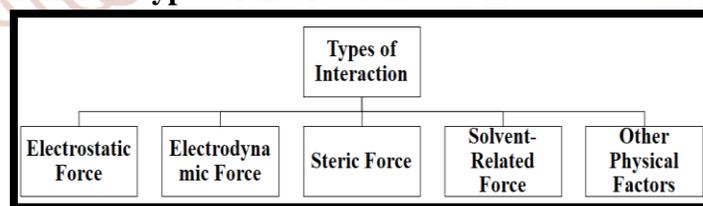


Fig. 3: Various kind of molecular interaction during docking

Interactions between atoms can be defined as a magnitude of forces between the molecules contained by the particles. These forces are divided mainly into four categories as shown in fig. 2.

1. Electrostatic forces: This category of force includes charge-charge, charge-dipole and dipole-dipole interaction forces with electrostatic origin due to the charges residing in the matter [10].
2. Electrodynamics forces: This includes Van der Waals interactions which are distance dependent interaction between atom or molecules. This disappear off at longer distances between two interacting molecule [11].
3. Steric forces: Steric forces are non-bonding interactions that effect the reactivity and conformation of ion and molecule. The resulting forces can affect chemical reactions and the free energy of a system [12].
4. Solvent-related forces: These forces generated due to chemical interaction between the solvent and the protein or ligand. Examples are Hydrogen bonds- hydrophilic interactions and hydrophobic interactions which ultimately effect the solubility of ligand or protein [13].
5. Other physical factors: There are many other forces and interactions which affect the solubility and binding energy of protein.

Major steps involved in mechanism of molecular docking

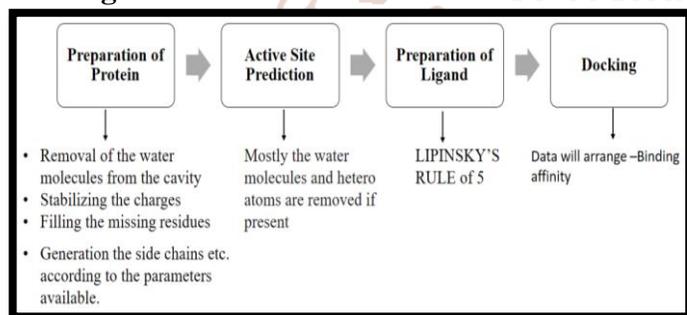


Fig. 4: Basic steps of molecular docking

Step I – Preparation of protein: From online database like Protein data bank (PDB), a pre-processed three dimensional structure of the protein would be retrieved[14]. This should undergo the following changes as shown in figure

Step II – Prediction of Active Site: The active site of protein should be predicted after completing the modification and preparation step of protein. The receptor might possess lot of active sites yet the one of concern should be picked out. Mostly the water molecules and hetero atoms are removed if present as shown in fig. 4 [15].

Step III – Preparation of ligand: Structure of ligands can be retrieved from several databases such as Pub Chem, ZINC or can be sketched by using Chem sketch tool. While picking out the ligand, the LIPINSKY'S RULE OF 5 should be used [16]. Lipinski rule of 5 assists in discriminating amongst non-drug like and drug like candidates. It promises high chance of success or failure due to drug likeness for molecules abiding by with 2 or more than of the complying rules.

For choice of a ligand allowing to the LIPINSKY'S RULE of 5:

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 LogP not over 5)
5. Molar refractivity should be between 40-130

Step IV- Docking: Ligand is docked against the target protein and the interactions are analysed. The docking software gives score and result on the basis of best docked ligand complex and data is analysed according to the binding affinity. In order to perform docking, various docking programs have been formulate.

Methods of molecular docking

For carrying out molecular docking, there are two approaches.

- One of the approaches uses computer simulations, in which binding energy is estimated for ligand target docked conformer.
- Second approach utilizes a method that analyses surface complementarity between ligand and target [17].

Simulation Approach

- In this approach, binding energy as per ligand-receptor pairs will be calculated.
- To achieve the best conformation and pose of ligand and receptor, minimum energy will be calculated [18].
- Performing molecular docking through this application, takes too much time as large energy profiling requires to be estimated.

Shape Complementarity Approach

- In this approach, complementary between ligand and drug will be estimated.

- To achieve the best conformation and pose of ligand and receptor, solvent accessible topographic features of ligand and receptor in terms of matching surface is described and followed by estimation of shape complementary between interacting molecules [18].
- Performing molecular docking through this way is quick and robust and takes few seconds for rapidly scanning large number of ligands.

Tools and software for docking study

In recent years, many docking software programme are available and formulated. Table1 summarized the detailed description of docking softwares which include the programme name, designer/company, algorithm along with its scoring term and its advantages as given in table 1.

Table 1: List of software tools for docking

S. No.	Docking Software	Designer/company	Algorithm	Scoring Term	Advantages	Reference
1.	Fred (Fast Rigid Exhaustive Docking)	Open Eye Scientific Software	Exhaustive search algorithm	Gaussian Scoring Function	Nonstochastic approach to examine all possible poses within receptor active site	[19]
2.	Auto Dock	D. S. Good sell and A. J. Olson The Scripps Research Institute	Lamarckian genetic algorithm	Empirical free energy function	Flexibility to user distinct input	[20]
3.	Ligand Fit	Accelrys Inc.	Monte Carlo method	LigScore, Piecewise Linear Potential (PLP), Potential of Mean Force (PMF)	Produces good success rates based on LigScore	[21]
4.	FlexX	T. Lengauer and M. Rarey Bio SolveIT	Incremental reconstruction	Modified Bohm scoring function	Provides large number of conformations	[22]
5.	GOLD (Genetic Optimization for Ligand Docking)	Cambridge Crystallographic Data Centre	Genetic algorithm	GoldScore, ChemScore, ASP (Astex Statistical Potential), CHEMPLP (Piecewise Linear Potential), User defined	Allows atomic coinciding between protein and ligand	[23]
6.	Glide (Grid-based Ligand Docking with Energetics)	Schrödinger Inc	Monte Carlo	Glide score	Lead discovery and lead optimization	[24]

Application and significance of molecular docking

Molecular docking study is tremendously useful in computer aided drug designing as shown in fig. 5.

- A binding interaction between a ligand and an enzyme- protein may consequence in activation or inhibition of the enzyme.
- Ligand binding may consequence in agonism (initiate a physiological response) or antagonism(block the biological response).

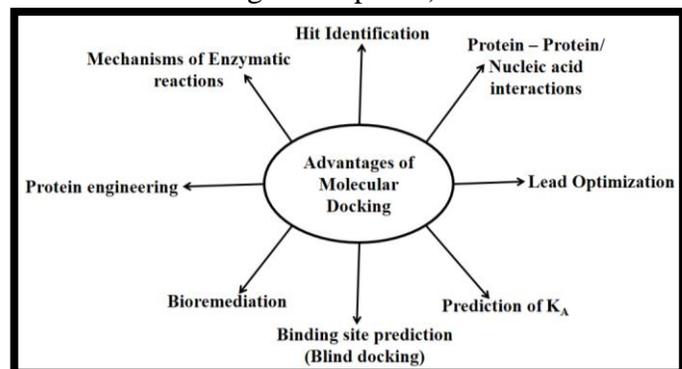


Fig. 5: Applications of molecular docking

1. Lead optimization

Docking can be used in finding and analysing the comparative orientation of a ligand binding to a protein, which is also referred as the binding mode or pose in order to design more potent, effective and selective analogs this information is very useful. [25, 26].

2. Bioremediation

Molecular docking can also be helpful in predicting pollutants that can be degraded by enzymes. It leads to discovery of therapeutic drugs through multiple ways that include:

- Finding of potential target
- Synthesis of chemical compounds with less time consumption
- Screening of effective drugs as activators/inhibitors against certain diseases
- Prediction of binding mode and nature of active site

3. Hit Identifications

Molecular docking in association with scoring function can be used to monitor huge databases for finding out potent drug candidates in silico, which can target the molecule of interest [27].

4. Drug-DNA Interactions Studies

Molecular docking is useful to study Drug-DNA interaction, which means it has significant role in preliminary prediction of drug's binding properties to

nucleic acid and this data is useful to find the correlation between drug molecular structure and its cytotoxicity. This understanding can be exploited in the synthesis of new drugs, possessing better efficacy and having less side effects, since; non-specific binding restricts drug dose and regularity in cancer treatment [26, 28].

CONCLUSION

Form the above study; we can conclude that recent methods of molecular modelling have enriched the field of In-silico Drug Discovery. It provides a collection of important tools for drug design and analysis. Docking is quite fast, robust and takes less time. It provides the scientist with a new approach to target the receptor. This field helps the drug industry to target new proteins and to cure diseases. Its role is extended in new techniques such as genomics, computational enzymology and proteomics search engines. Widely accepted and validated test data should be established to facilitate the comparisons needed to explain the new frontiers of research in this field.

CONFLICT OF INTERESTS

The author declare that no conflict of interest occur during the work.

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