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# A MAGICAL TOOL FOR DRUG DISCOVERY & THEIR DEVELOPMENT: MOLECULAR DOCKING

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## ABSTRACT

Molecular docking is a chief tool for the revelation of drug and their evolution. Initiation about molecular docking technique and their use in drug discovery is very useful. The principles of molecular docking incorporate sampling algorithm and scoring function. The distinction in accessibility and functioning of docking software are also described. The application of flexible docking is mainly that incorporate flexibility in receptor are a obstacles for available docking methods. For the drug discovery the utilization and example of molecular docking are provided.

**Keywords: Docking, Methods, Drug discovery**

## INTRODUCTION

The accomplishment of the human genome study arise a enlarge number of novel therapeutic areas for drug discovery. Simultaneously, NMR spectroscopy and crystallography technique have been establish and provide structural characteristic of protein as well as protein molecule complexes. These features permit

the computational approach for the discovery of drug using virtual screening technique for the recognition and methods for lead optimization. Virtual screening is more useful for the revelation of drug and also has the advantage of cheap and effective screening. When compared to high throughput screening technique. Virtual screening can be distinguished into a types first one is ligand-based and other one is structure based methods. When the characteristic features structure of the target are not available and potent ligand molecule is acknowledged so the ligand based methods is utilize like pharmacophore modeling and QSAR methods. In early 1980s molecular docking is most conventional method used as structure based drug design. To carry out docking study different algorithm were evolve in which molecular docking is a major tool in pharmaceutical research. Numerous exceptional reviews have been published previously on docking and numerous comparison study were govern to analyses the performance of the programs. The docking method can be utilize to give the relationship between a small molecule and a protein to specify the actions of molecule at the binding position of target protein and it also explain chief or important biochemical processes. The docking procedure incorporate two basics strategy:- Geometry of ligand as well its position and orientation and evaluation of the binding affinity. These two strategies are associated to methods of sampling and scoring schemes. Before the procedure of docking if the location of the binding site will be acknowledge then it remarkable increases the docking efficiency. In many occasion the binding site is noted or recognized before docking ligands into it. Also it procure details about the site by comparing with the family of proteins which share a homogenous function. In the lack of enlightenment about the binding sites the cavity detection servers are used to point out well known active sites within proteins. Ex- GRID (20, 21), Surf Net (23, 24), Pocket (22), Pass (25) and MMC(26).

Docking in the absence of any presumption about the binding position is called blind docking. Ligand receptors binding procedure is the lock and key postulate which is proposed by fischer where ligand attached with receptor similar to lock & key. The first describe docking method were based on this postulates and they both (ligand& receptor) were consider as unalterable bodies. Induce fit postulates given by Koshland which proclaim that the active site of the protein is frequently change by association with the ligands. This postulate proposes that the ligand and receptor should be flexible throughout the docking. Therefore it could express the binding events more precisely than the rigid

bodies. After think carefully about the drawback of computer resources, docking has been execute with a flexible ligand and a rigid receptor for a years and remains the considerably conventional method in used. At a recent time numerous attempt have been made to tackle with the flexile of the receptor mainly backbone pliability in receptors, yet existing a crucial challenge for accessible docking methods. In our research we suggest a Local Move Monte Carlo (LMMC) approach as a possible solution to flexile receptor docking complications.

**METHOD OF DOCKING**

In the docking analysis, protein is employed and these proteins huge acquire throughout homology modelingfor detecting the binding pocket of ASMT Dog site webserver was used. The good biological activity illustrates by seventy-three various ASMT inhibitors were chosen from the reports. The bi-dimensional shape of the melatoninergic inhibitors were withdrawn by utilizing chemical structure drawing package, chemoffice 2018. UCSF Chimera was utilize to minimum the conformational energy of inhibitors and these structures were then utilize for docking study **[31, 32]**.

**DOCKING PROTOCOL**

To predict the binding affinity of various ligands molecular docking protocols are used. Intention of work to explore the relationship amid docking score and experimental bioactivities of inhibitors. All the docking research was performed with default parameters to get an accurate result. About 1-2 minute time was taken to dock one ligand. The docking software used for docking are GOLD & FRED, Auto dock/Vina was run on a Linux workstation (Open SUSE 11.4) with 1 GB of RAM and Intel Pentium D processor (3.0GHZ).FlexX docking software was performed on Windows 7 equipped with an intel R Atom$^{TM}$Processor (1.67GHZ) and 1 GB of RAM **[29]**.

**DOCKING USING AUTO DOCK/VINNA**

Graphical user interface program Auto Dock Tools (ADT) is used for pdbqt files for the preparation of proteins and ligands as well as the creation of grid box. ADT allocates united atom Kollman charges, solvation parameters, polar hydrogen, and fragmental volume to the proteins. Prepared files are saved in PDBQT format by Auto Dock. A grid map is prepared by using a grid box with the help of the Auto grid. The grid spacing was set to 0.375A with a grid size of 60×60×60 xyz points and the grid center was formed at a measurable extent (x,y, and z): -1.095, -1.554 & 3.894. A scoring grid is determine from the ligand shape to reduce the arithmetic time. . Protein-ligand information and properties of grid box were used for the docking using

software Auto Dock/Vina. Protein and ligand are considered rigid during the procedure of docking. In positional root mean square deviation (RMSD) if the result will be less than showed by the outcome with the most affirmative free energy of binding. The pose with minimum energy of binding affinity was pull out and co-ordinate with the structure of the receptor for further analysis **[34, 35]**.

**DOCKING USING GOLD**

The Genetic algorithm employed in GOLD docking software to explore the spinning flexibility of receptor hydrogen & ligand configuration. Docking was accomplish by utilizing the wizard with default variable population size (100); a number of operation (10,000) selection pressure (1.1); number of island (1), operator weights for migrate(0), niche size (2), mutate(100) and cross over (100) were applied. The active sites selective on a residue of proteins with a 10A radius sphere for calculation genetic algorithm were used and the set of 10 solutions were saved for individual ligand. GOLD Docking software were used by a Gold score fitness function which is a scoring function for the determination of the binding position of ligand **[31-34]**.

Gold score fitness function calculated by following formula-

Fitness = S(hb_ext)+1.3750*S(vdw_ext)+S(hb_int)+1.0000*S(int)S(int)=S(vdw_int)+S(tors)

Where:

S(hb_ext): is referred as hydrogen bond.

S(vdw_ext): is referred as vanderwall score

S(hb_int): is referred as intramolecular hydrogen bond in the ligand.

S(vdw_int): is referred as intramolecular strain in the ligand.

**DOCKING USING FLEXX-**

FlexXis also docking software that is a part of a lead IT. Incremental construction algorithm (IC) employed in flexX. According to rotatable bonds, The Incremental construction (IC) algorithm first dissects an individual molecule in a fragment and then step-by-step gather the fragment all over the binding pocket. The pdb folders of ligands were convert into a SYBYL mol2 and a ligand collection was produced. A receptor illustration file was develop by the flexX graphic interface. The mobile sites was described by choosing the residue of the protein. The mobile site comprise protein residue about 10A radius sphere centralize on the ligand. On the basis of values of energy the top 10 ranked propose for individual ligands in the data set were sort out for further evaluation.

The binding energy of protein and ligand involved –

$\Delta G=\Delta G0+\Delta GrotxNrot+\Delta Ghb\sum neutralHbondsf(\Delta R,\Delta\alpha)+\Delta GioΣionicint.f(\Delta R,\Delta\alpha)+\Delta GarΣaroint.f(\Delta R,\Delta\alpha)+\Delta GlipoΣlipocont.f^*(\Delta)$

Where $f(\Delta R,\Delta\alpha)$ referred as a scaling function

$N_{rot}$ referred as a number of free rotational bonds.

The term $\Delta G_{io}$,$\Delta G_{hb}$,$\Delta G_0$,and $\Delta G_{ar}$ are referred as a adaptable parameters.

$\Delta G_{lipo}$ is referred as lipophilc energy.

**DOCKING WITH FRED**

Fred utilizes numerous conformers docking algorithm which individually create a set of low energy conformer as well as execute rigid docking for individual conformer. FRED required a precisely prepared ligand conformer library and also prepared receptor files. Make – receptor files were used to prepare a receptor file which is provided in FRED whereas Omega (Open Eye Scientific Software) 2.3.2 is used for the preparation of a ligand conformer library. The docking box focus on the receptor was extending in all directions till it was almost 31671 Å. The measurement of the box was 28.10 Å × 32.91 Å × 34.25 Å. To acquire a potent inhibitor against ASMT chemgauss4 was used to dock ASMT. The chemically identical positions throughout the ligand docked posed. These chemical position are compatible to the neighboring specific groups in the receptor. Mostly the interlink age are hydrogen bond or acceptors and an affirmative hydrogen bond score is acquire when a polar hydrogen spot on sole molecule overlap a lone pair spot on further molecule. The interlink age which can be obtained by chemgauss functions is – acceptor, stearic, coordinating group, donor, lone pair, metals polar hydrogen and chelator coordinating groups.

**DOCKING APPROACHES**

For molecular docking mainly to approaches properly used. The first one is the matching technique that expresses protein and ligand as matching surfaces. The second perspective is to stimulate the existing docking procedure in which the interaction energies are evaluated of ligand-protein interaction. These both approaches have a limitation as well as significant advantages they are enlisted below.

**SHAPE COMPLEMENTARITY**

Shape complementarity is a technique which defines the protein and ligand as a set of significant characteristic to make them dockable. These significant characteristic can involve molecular surface descriptors. Uppermost layer of the receptor molecule defined solvent-attainable surface area & the uppermost layer of the ligand molecule is defines as matching surface description. The matching in between the two surfaces and the detail of shape matching of ligand & target is very useful for the docking. The Hydrophobic feature of protein is also an essential features using turns in the main chain atoms. Yet other approach is to utilize a fourier shape descriptor method. Although the shape matching based approach are generally fast & strong. Whereas currently development allow these

method to analyse ligand flexibility. Shape complementary technique scan rapidly to thousands of ligands and detect whether these ligands bind to the active sites as well as they are generally adaptable to protein-protein interactions **[26, 28]**.

**SIMULATION**

Simulating the docking procedure is a lot more complex. Due to this complication the ligand and protein are detached by physical distance and the ligand find its spot within active sites of the protein after a definite number of movement in its conformational space. The movement includes rigid body transformation like rotation and translations. It also causes internal alteration to the ligands structure as well as torsion angle rotation. Ligand flexibility is the advantage of a docking simulation. Ligand flexibility is comfortably incorporated whereas the shape complementarity method is an inventive method to incorporate the flexibility of the ligand. Simulation is expensive it is a grid-based technique it increases the speed of computers which make docking simulation moreover genuine **[29]**.

**MECHANICS OF DOCKING**

The first condition to execute docking procedure is to determine the shape of protein of interest. The shape and the structure of the protein is found out by x-ray, Nmr, as well as homology modeling construction. The potential ligand and the protein structure serve as input to a docking program. The search algorithm and the scoring function are the two components on which the success of a docking program depends **[31, 32]**.

**SEARCH ALGORITHM**

The search space in thesis comprise of all configuration and orientation of protein couple with the ligand but using latest computational service or facility it is impossible to completely examine the search space which involves a summary of all possible distortion of an individual molecule as well as translational conformational search strategies have been applied such as.

1- Molecular dynamics simulations.
2- Stochastic torsional or systematic searches about rotatable bonds.
3- Genetic algorithms

**LIGAND FLEXIBILITY**

Configuration of the ligand may be formed in the absence of the receptor and afterwards docked may be formed on the fly in the existence of the receptor binding space or with full spinning flexibility of each dihedral angle by utilizing fragment based docking. Force field energy estimation are commonly used to choose energetically logical configuration however knowledge based procedure have also been used. Proteins are extremely flexible as well as big, size molecule which makes

modeling their flexibility a complicated task **[22-26]**.

**RECEPTOR FLEXIBILITY**

Over the last decade, computational role has risen dramatically over the last few decade which make possible the utilization of more advance and computationally intensive procedure in computer assisted drug design. The docking method dealing with receptor is still a difficult issue. The main cause behind this type of difficulty is the large number of degree of freedom during the calculation. If we ignore it may cause poor docking **[28-30]**.

**SCORING FUNCTION**

Docking program produces a mass of potential ligand from which some can be instantly decline due to collision with the protein. The rest are estimated using certain scoring function. Scoring functions are based on a molecular mechanics force field that evaluates the energy of the pose inside the binding site. The component comprises conformational changes in the ligand and protein, solvent effects, internal rotations, free energy due to protein-ligand interaction, the energy of ligand and receptor to the formation of a lone complex, and free energy due to alternate vibration modes. Stable system showed a negative energy and thus a likely binding interaction and another method is to acquire skill based statistical ability for interaction from a huge database of protein ligand complex like protein data bank and according to the inferred potential evaluate the fit of the pose. X-ray crystallography is used to determine the complex structure of amino acid and high-compatibility ligands, as compared to fewer low compatibility ligands, after this complexes undergo less stable and therefore more tough to crystallize. The high-affinity ligands correctly dock by the scoring function but they will also give reasonable docked conformation for the ligands that does not bind. This permit a huge number of false positive hits i.e when ligand and protein are placed together in a test tube they don't bind with each other. One way to decrease the number of false positives is to reevaluate the energy by using intensive technique like Boltzmann methods **[18-24]**.

**DOCKING ASSESSMENT**

The co-relation between the sample & scoring function influence the docking ability in imagine binding affinities for newer compounds therefore the evaluation of a docking protocol is mostly required (When practical data is available) to calculate its predictive capability **[26, 28]**.

Different strategies are performed for docking assessment such as –

1- Docking precise calculation (DA)
2- The relationship between a docking score and the practical response or estimation of the enrichment factor (EF)

3- the interval between an ion-binding moiety & the ions in active site.
4- The existence of induced fit models.

**DOCKING ACCURACY**

Docking reliability illustrate one measure to evaluate the fitness of a docking program by justify the potential to forecast the correct pose of a ligand with experimentally observed. **[16]**.

**ENRICHMENT FACTOR**

Docking screen can too estimate by the enhancement of annotated ligands of familiar binder out of huge database of assuming non-binding "decoy" molecules. In such a way the triumph of a docking screen is estimated by its capability to enhance the few number of familiar active compounds in the high ranking of a screen out of much higher quantity of decoy molecules in the database. To estimate the performance area beneath the (ROC) curve is mostly used. Where ROC is termed as Receiver Operating Characteristic **[19, 20]**.

**PROSPECTIVE**

Resulting hits among docking screens are assigned to pharmacological evidence: (ex $IC_{50}$, affinity or potency measurement). This study can give a convincing proof of the appropriate technique for a specific target **[21]**.

**BENCH MARKING**

X-ray crystallography is used to determine the binding modes that can be evaluate by a range of docking benchmark sets. Several benchmark data sets for docking and virtual screening exist for small molecules such as –Astex Diverse Set comprise of good-quality protein ligand X-ray crystal structure or the Directory of Useful Decoys (DUD) for the assessment of virtual screening performance. An estimation of docking program for their capability to copy peptide binding modes can be evaluate by lessons for Efficiency Assessment of Docking and Scoring (LEAD-PEP) **[22]**.

**APPLICATIONS**

- A binding relations connecting a small molecule ligand and an enzyme protein may outcome in activation or inhibition of the enzyme. If the protein is a receptor ligand binding may outcome in agonist or antagonist. Docking is mostly employed in the arena of drug design. The maximum drugs are small organic molecules and docking may be implement to -
- Hit identification - Docking merge with a scoring function can be used to rapidly screen the molecules that are likely to bind to the protein target of interest **[20]**.
- Lead optimization – Docking can be utilize to forecast the relative orientation of a ligand and bind to a

protein which help to design more potent and selective analogs. **[21]**.

- Bioremediation – Docking can also be used for the prediction of pollutants that can be deteriorate by enzymes **[22]**.

## CONCLUSION

Docking and scoring becomes a valuable tool in the drug discovery process. This study was done to examine the four types of docking approaches (Auto Dock/Vina, GOLD, FRED, and FlexX) for our selected ASMT and to discover the lead compound by comparing them with each docking and scoring function. Auto Dock/ Vina was found to be more useful as compared to the other in bind docking pose prediction and also due to their consistent performance. Survey of the docked ligand with the protein brought into priority some major relations operating at the molecular level. The outcome of the ligand docking appear that the binding pocket include the amino acid residues Ser213, Ser98, Val97, Thr100, Val211, Ser227, Arg210, Arg280, Phe212, Leu198, Ile198, Ser104, Thr195, Leu160, Tyr327, Tyr108, Trp117, Leu326, Phe29, Phe19, Gln334, Asn330, Trp117,and Tyr327.As a result, we uncover a exceptionally potent lead compound which will be helpful for the outline of novel less toxic and highly effective drug for the cure of bipolar disorder and PPTs.

## CONFLICT OF INTEREST

The authors have no conflict of interest.

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## AUTHOR CONTRIBUTIONS

Conduct of the study, data collection (Pathak Manish., Shuklavivek); Manuscript preparation, design and review (Kumar Amit, Singh Lubhan).

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