Review on the use of Molecular Docking as the First Line Tool in Drug Discovery and Development

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Molecular docking has now become a novel approach for drug discovery in recent years. Computer-aided drug design is an area that is rapidly growing and has seen many successes. Many big pharmaceutical industries, academic resources and research personnel are using the tools for new drug development. In this review, we have discussed briefly different molecular docking methods, software used in the molecular docking process and their application in drug discovery. Molecular docking is a configuration-based virtual tryout in which computer-generated three dimensional structures of small molecules are given the freedom to interact with the target structure in assorted positions, orientation, and conformations.

Key words: Molecular docking, binding energy, drug discovery, docking programs

In recent years molecular docking has played a crucial task in *in silico* drug development. The decisive advantage of the tools is that they require less investment in resources and time in comparison to the *in vivo* lab studies[1-5]. The dry lab, approach predicts the ligand orientation in a complex formed by the ligand itself with proteins or enzymes[6]. The quantification of the interaction is based on the shape and electrostatic interaction of the docked complex. Many docking programs (more than 50) and tools are now in use in the field of drug research and academics[7-11]. The docking programs like AutoDock, AutoDock Vina, FlexX, DOCK, Surflex, GOLD, Glide, ICM, Cdcker, LigandFit, FRED, MCDock, MOE-Dock, LeDock, rDock and UCSF Dock are used. Among this software AutoDock vina, Glide and GOLD are the top-ranking choices with the best scores[12-14]. GOLD and LeDock are commonly preferred to identify the correct ligand binding site[15,16]. According to Wang *et al.*[17], 90 % of accuracy of the poses was predicted by Glide and GOLD. From literature, it has been found that the enrichment factor obtained from GOLD was higher as compared to Glide in a screening tryout against factor Xa and produced higher enrichment factors than Glide in a virtual screening trial against factor Xa[18]. Meanwhile, in a comparable tryout, the performance of Glide was superior while the same target (Factor Xa) was under consideration. Depending on the experimental poses, some of these programs were also found to be effective in forecasting the Root Mean Square Deviations (RMSDs) ranging from 1.5 to 2 Å. Still, the contemporary docking programs are facing challenges in handling matters of flexible receptor docking, to be specific receptor backbone flexibility[19,20]. The underlying objective of the docking study is to assess, screen and forecast the computational electrostatics associated with the ligand-receptor complex. A typical molecular docking trial involves two distinct steps. In the first step, ligand conformations are sampled following the protein's active site. In the second step, the ligand conformations are ranked based on a scoring function. Conceptually, reproduction of experimental binding modes should be performed by sampling algorithms and obtained confirmations should also be ranked as per scoring function. This review work has been focused on molecular docking concerning these two perspectives. Docking analysis is the *in silico* experimental method comprising the study of the interaction between two molecules. Generally, the larger molecule (receptor protein) is designated as a macromolecule and smaller ones are considered

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as ligands during the study. The following steps are involved in the docking process. In step 1, involves the retirement of Three Dimensional (3D) structure of receptor protein from the Protein Data Bank (PDB) (fig. 1). Afterward, the pre-processing of the obtained 3D structure should be carried out as per parametric availability. Following pre-processing attributes are performed depending on the need i.e filling the missing residues, removal of water molecules, stabilizing the charges and generation of the side chain. In step 2, the interaction site is predicted on the macromolecule (protein). Further, these sites are regarded as active sites (fig. 2). The receptor protein might have one or more than one active sites. Only one of the concerns should be chosen according to the hypothesis of the experiment[21,22]. In step 3, the structures of the ligands are either obtained or sketched. For retrieving purposes, a database like Pub Chem can be used. Tools like Marvin sketch, Chem sketch and Chem draw can be utilized to sketch the ligands followed by pre-processing. The selection criteria of the ligand should strictly adhere to Pfizer's rule of five proposed by Lipinsky. The rule is vital in the process of screening of lead structure which has to be optimized in a step-wise fashion to increase the activity and selectivity. The rule also ensures the maintenance of the drug-like physicochemical property of the molecule. For a successful discerning of molecules, adherence to two or more of the following rules is mandatory. The no. of hydrogen bond donors should not be more than 5; The no. of hydrogen bond acceptors should not be more than 10; A molecular mass should be less than 500 Dalton; LogP (Octanol-water partition co-efficient) not more than 5 and the range of molar refractivity to be within 35-125. Additional rules has been proposed by Veber with respect to the presence of number of rotatable bonds (should be <10)[23]. Step 4 is the final step of the docking process. The screened and pre-processed ligand molecule is processed in the software for docking against the receptor protein and the molecular interaction between ligand and receptor protein is analyzed (fig. 3). The best-docked ligand complex is characterized based on docking score which is generated by the tools. In the past twenty years, various molecular docking tools have been formulated (Table 1). (Source: Chaudhary KK, Mishra N (2016) A Review on Molecular Docking: Novel Tool for Drug Discovery, (JSM Chem 4 (3): 1029) represents the different molecular docking tools[24]. The resultant binding interaction between ligand and macromolecule in the docking approach may result in the activation or inhibition of the receptor enzyme. Meanwhile, in the case of the receptor proteins and ligand binding may lead to agonism or antagonism. The docking approach can be applied in the field of drug discovery related to target identification through virtual trials; development of potent and selective analogs through optimization; pollutant prediction, which can be combated by enzymes; biological activity prediction; prediction of the active binding site through the blind approach; protein de-orphanization; interaction analysis between protein-protein and protein-nucleic acid; structural and functional analysis; enzyme catalytic reactions and protein engineering. The molecular docking technique presents a significant approach in the area of drug discovery, optimization and analysis. The easy access of structural databases and simple visualization of

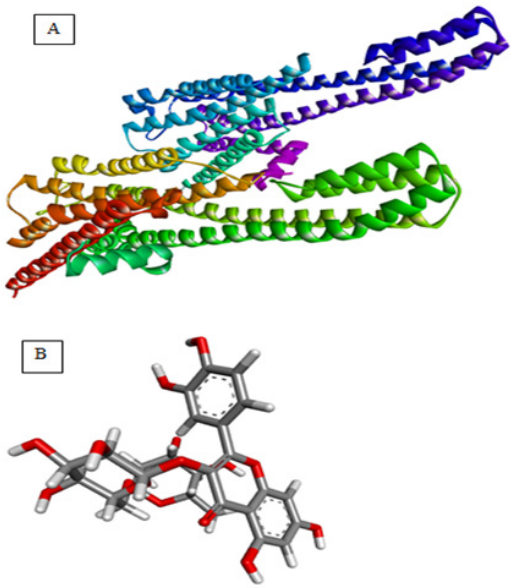

Fig. 1: (A): 3D structure of receptor protein (6A93) and (B): 3D structure of ligand (Rutin)

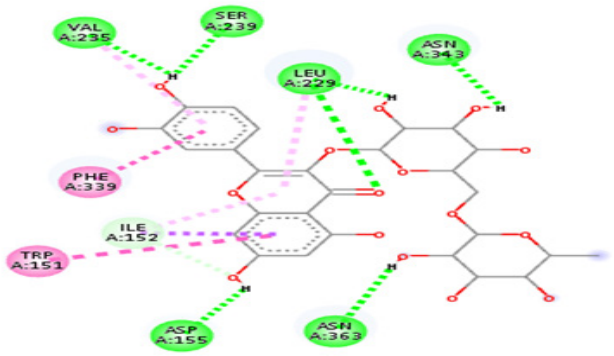

Fig. 2: Visualization of 2D models of docked complexes depicted by Discovery Studio Visualizer 3.5, depicting interactions of 5HT2A receptor (6A93) with phyto compound
Note: ( ) Conventional Hydrogen Bond; ( ) Carbon Hydrogen Bond; ( ) Pi-Sigma; ( ) Pi-Pi T shaped and ( ) Pi-Alkyl

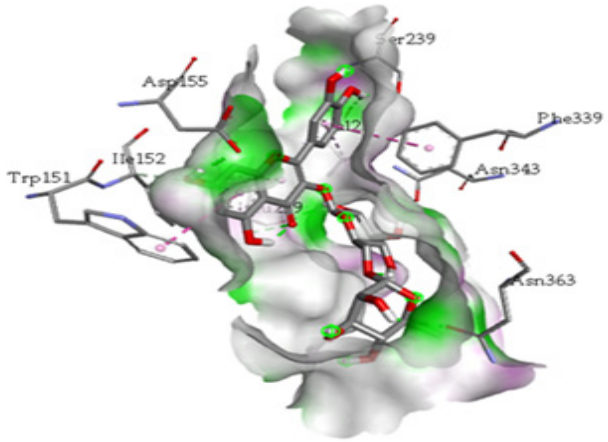

Fig. 3: Visualization of 3D models of docked complexes depicted by Discovery Studio Visualizer 3.5, depicting interactions of 5HT2A receptor (6A93) with phyto compound
Note: ( ) H-Bonds Donor and ( ) Acceptor

TABLE 1: LIST OF PROTEIN-LIGAND MOLECULAR MODELLING TOOLS

Software	Company/Designer	Licence terms	Supported platforms	Docking approaches	Scoring function
Auto Dock	D. S. Good sell and A. J. Olson The Scripps Research Institute	Free for academic use	Unix, Mac OSX, Linux, SGI	Genetic algorithm Lamarckian genetic algorithm simulated annealing	Auto dock (force-field methods)
Dock	I. kuntz university of California, san francisco	Free for academic use	Unix, Linux, Sun, IBM AIX, Mac OSX, Windows	Shape fitting (sphere sets)	Chem score GB/SA salvation scoring, other
Flex X	T. Lengauer and M. Rarey Bio SolveIT	Commercial Free evaluation (6 w)	Unix, Linux, SGI, Sun Windows	Incremental construction	FlexXscore, PLP, Screen Score, Drug Score
FRED	Open eye scientific software	Free for academic use	Unix, Linux, SGI, Mac OSX, IBM AIX, Windows	Shape fitting (Gaussian)	Screen Score, PLP, Gaussian shape score, user defined
Glide	Schrodinger Inc.	Commercial	Unix, Linux, SGI, IBM Aix	Monte Carlo Sampling	Glide Score Glide comp
GOLD	Cambridge crystallographic data centre	Commercial Free evaluation (2 mo)	Linux, SGI, Sun, IBM, Windows	Genetic algorithm	Gold Score, Chem Score user defined
LigandFit	Accelrys Inc.	Commercial	Linux, SGI, IBM AIX	Monte carlo sampling	Lig Score, PLP, PMF

molecules has now become essential components of the process. Nowadays the rapid expansion of docking software programs (commercial) among the user interfaces has paved the way for easy accessibility. Molecular docking is a computer-aided drug designing tool that relies on software programs[25]. The instance of logic, algorithms is the backbone of the designing tool. With increased input with respect to algorithms from the experts of the field, the method is gaining acceptance in terms of accuracy, sophistication, sensitiveness and perception. Even public domain programs are now equipped with at par functionality with that of the commercial ones. The flawless input commands and crispy graphical representations have improved the aesthetics of the tools, making it an elegant and effective way of drug design. Other than drug discovery, the *in silico* approach has been employed in formulation development, solubility analysis and drug complex stability study. Now also the technique has been adopted in the field of genomics, proteomics, and computational enzymology.

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Conflict of interest:

The authors declare no conflict of interest.

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