Principles and aspects of molecular docking: A bird's eye view

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Abstract

Molecular docking is an evolving and expanding *in-silico* structure-based method with multiple applications. It performs a search algorithm to create an optimum number of configurations and evaluates until the minimum energy convergence is reached. The docking strategy can vary according to the ligand/target flexibility. Various robust and dynamic molecular tools based on different algorithms are freely available. These tools exhibit a wide variety of applications including drug design, vaccine development, drug repositioning, and bioremediation. The results of molecular docking can be evaluated on the basis of scoring functions and root mean square deviation values and can be visualized using various software. Despite enormous advances in the field of computational biology over decades and the widespread applications of docking methods, several pitfalls still exist. This review presents a collaborative view of molecular docking where we have focussed on its algorithms and functions along with the applications and challenges. It also provides insights into the process of docking through an elaboration of AutoDock server and into various visualising software used for analyzing the results.

Keywords: Molecular docking, docking algorithms, docked structure visualisation, Auto Dock, applications of docking

Abbreviations: RMSD- Root mean square deviation; LGA- Lamarckian genetic algorithm; GA- Genetic algorithm; LS- Local search; PDB- Protein data bank

1. Introduction

In modern times as the need for better therapeutics is growing by leaps and bounds, molecular docking has emerged as an important tool in drug discovery and vaccine development. This is evident by the increasing level of sophistication of different docking aspects and growing number of users from both academia and pharmaceutical industry. Molecular docking is the *in-silico* method that anticipates the favoured orientation of ligand against receptor to make a stable complex and uses electrostatic, Van der waals, coulombic interactions and hydrogen bonds to quantify it (Chaudhary & Mishra, 2016). The sum of all these interactions is approximated by a docking score, which represents the potentiality of binding. Docking servers/tools are assisted by a search algorithm which inspects the various conformations of the ligands until the confluence to the minimum potential energy is reached and an affinity binding function is obtained which is meant to rank the various binding conformations as the sum of electrostatic and Vander waals energies (Pagadala et al., 2017). Three key ingredients of the docking are representation of the system, conformational space search and ranking of the potential solutions.

Docking essentially simulates the interaction of the protein surface. The surface can be described by mathematical models, for example by geometrical shape descriptors or by a grid, which is basically an experimentally appropriate site where the ligand is supposed to bind. Alternatively, it can involve static

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or dynamic treatment of the protein frame/receptor. Various algorithms like Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, distance geometry and many more are applied for analysis of the potential solutions (Halperin et al., 2002).

In this review we have tried to shed some light upon the various components of molecular docking, result visualisation and analysis, applications and challenges along with the elucidation of a highly used tool- AutoDock.

2. General aspects of molecular docking

2.1 Search Algorithms

Docking is a computationally difficult task because there are many ways of putting two molecules together owing to the three translational and three rotational degrees of freedom (degree of freedom signifies various ways in which a molecule can move or rotate). The number of possibilities grows exponentially with the size of the components (Halperin et al., 2002). A search algorithm is a means to create an optimum number of configurations on the basis of experimental methods of determining binding mode (Chaudhary & Mishra, 2016). The search for candidate solutions in the molecular docking is addressed in two essentially different approaches: (1) a full three-dimensional space search and, (2) a gradual guided progression through solution space. The former scans the entire solution space in a pre-defined systematic manner. In contrast, the latter either scans only a part of the solution space in a partially random and partially criteria-guided manner, or generates fitting solutions (Audie& Swanson, 2012).

2.2 Scoring function

A search algorithm may produce a large number of solutions inconceivable for any practical need. Here the scoring function comes into play which discriminates between the "correct" native solutions with low Root Mean Square Deviation (RMSD) within a reasonable computation time. RMSD is used to compare the docked conformation with the reference mode or with other docked complexes (Halperin et al., 2002). RMSD between the experimentally observed heavy-atom positions (subset of atoms for which RMSD is calculated) of the ligand and those predicted by the docking program is used as a scoring function when the experimentally known structure of the complex exists (Mih °an, 2012; Pedotti et al., 2011). Complexes with RMSD values <2 Å are considered a success, while RMSD values between 2 - 3 Å are only partially acceptable (Cole et al., 2005; Mih °an, 2012).

Over the years, different scoring functions have been developed and grouped into three main categories: force field based, empirical function and knowledge based scoring function. There are three main applications of these scoring functions in docking (Bielska et al., 2011): a) identification of most favourable binding modes, b) accurate prediction of binding affinities and c) identification of potential binders from a ligand library. All three applications are related to each other and an ideal scoring function performs well for each of the applications (Huang et al., 2010).

2.3 Types of Molecular Docking

2.3.1 Lock and key/rigid docking: It is used to find complexes with high degree of shape complementarities between ligand and the receptor. In this approach the ligand and receptor remain as stiff structures and search space is very limited. In this case, ligand flexibility could be addressed by using a pre-computed set of ligand conformations, or by allowing for a degree of atom–atom overlap between the protein and ligand (Meng et al., 2011). The first docking program developed by Kuntz group named 'DOCK' was based on this mechanism. Other programs such as Patchdock and SymmDock also use similar mechanics.

2.3.2 Flexible ligand and rigid receptor docking: This method is based on induced-fit mechanics and considers the flexibilities of both the ligand and receptor as both change their conformations to form a minimum energy and perfect-fit complex. However, for better accuracy and computational time management the receptor is kept fixed while keeping the ligand flexible. Majority of the docking programmes like AutoDock and FlexXuse this mechanism (Meng et al., 2011).

2.3.3 Flexible ligand flexible receptor docking: This method is also based on induced fit mechanics but here the side chain flexibility plays a crucial role in the formation of the ligand-receptor complexes. These changes allow the receptor to alter its binding site according to the orientation of the ligand. This method has the advantage of computational efficiency as the receptor coordinates remain fixed and interactions are executed by adjusting Van der

waals parameters. GOLD and AutoDock3.0 involve this type of docking mechanism (Meng et al., 2011).

2.4 Approaches to molecular docking

2.4.1 Simulation approach: Here the ligand and target/receptor remain stable at some feasible physical distance and the ligand is allowed to bind in the groove of receptor after performing some definite movements in its conformational space. With every move in the conformational limit, ligand releases some of its potential energy. This approach is advantageous when docking is performed with the ligand of high flexibility. At present many grid-based tools like AutoDock utilizes this approach (Dar & Mir, 2017).

2.4.2 Shape complementarity approach: It emphasizes on surface structural features like lipophilicity and hydrophilicity of the ligand and receptor because of which Van der waals interactions play a major role. Here the surface of target is shown with respect to its solvent-accessible surface area and ligand's molecular surface is showed in terms of matching surface illustration with respect to receptor. For example, in protein target molecules, hydrophobicity is estimated by employing number of turns in the main-chain atoms. This approach is quick and involves scanning of numerous ligands for the binding possibilities to the target (Dar & Mir, 2017).

3. Steps involved in docking

Docking is basically the *in-silico* study of interaction between a macromolecule (receptor) and a micro molecule (ligand). For this purpose, both the molecules should undergo some pre docking preparatory phases before final analysis.

3.1 Preparation of receptor: The 3-D structure of the protein is retrieved from protein data bank (PDB) using online servers by providing entry code or by text search. After this as per the requirement, removal of water molecules, stabilization of charges, filling of the missing residues and side chain generation is performed.

3.2 Binding site prediction: Receptor protein may have many binding sites hence prediction of appropriate binding cavity is essential for a good docking outcome which is done by using the co-ordinates of a co-crystallized receptor-ligand structure.

3.3 Preparation of ligand: Ligands can be obtained from several databases like ZINC, PubChem or it can be designed using tools like Chem sketch. The ligand can be saved in several file formats like .mol, .pdband. and pdbqt for future references.

3.4 Docking: After the selection of receptor and ligand they are subjected to docking with some adjustments in the parameters like number of runs and number of cycles. This can be done by employment of several tools including AutoDock Vina, Hex and, many others (Table 1). At this stage interaction between ligand and receptor is analysed and the scoring function gives energy scores for the formed complexes on the basis of binding compatibility.

4. AutoDock: A promising docking tool

Auto Dock is open source software for computational based docking and virtual screening of small molecule to macromolecular receptors developed by Morris et. al. at the Scripps Research Institute (Morris et al., 2009; Huey, et al., 2009) It is based on Lamarckian genetic algorithm (LGA) which is a hybrid of genetic algorithm (GA) and local search (LS) (Fu et al., 2018). Due to its free-availability for academic users, high accuracy, efficient performance and easy usage, AutoDock has become a very popular choice as docking software which is well indicated by its high number of citations in recent years. It is a suite of several complementary tools, namely, AutoDock Vina, AutoDock 4, Raccoon, AutoDockTools, and AutoLigand, for computational docking and virtual screening (Forli et al., 2016). AutoDock 4 and AutoDock Vina are the two generations of the molecular docking software which differ on the grounds of automated grid map calculation, speed and accuracy (Morris et al., 2009; Huey, et al., 2009; Trott & Olson, 2009). AutoDockTools, a graphical user interface, has been developed to facilitate formatting of input molecule files to identify active sites and determine volume of search space, and to cluster, display and analyse the docking results (Morris et al., 2009; Huey, et al., 2009). On the other hand, Raccoon is a graphical interface used to virtually screen a library of ligands with a single receptor and also to process ligand libraries in different formats, automatically (Forli et al., 2016). As the docking of ligands to the entire protein surface is generally not practically feasible, it is essential to identify the optimal binding sites on receptors. This task can be performed in AutoDock using a program from the suite that is AutoLigand which predicts the binding sites on the basis of the free-energy force field (Harris et al., 2008).

Table 1: Description of some most-cited docking programs and servers.

Program/ Server	Developer /Creators	Licence terms	Docking features (Sousa et al., 2013)
Autodock (Morris, Ruth, et al., 2009; Trott & Olson, 2009)	Morris & co-workers, The Scripps Research Institute	Free availability to academic users	-Offers a variety of search algorithms -Can be used with a visual interface called autodocktools (ADT) for efficient analysis of the docking results
–GOLD (Jones et al., 1997)	Cambridge Crystallographic Data Centre (CCDC)	Commercially available	-Interactive docking set-up via Hermes -Genetic algorithm (GA) based search method
DOCK (Allen et al., 2015)	Irwin Kuntz University of California, San Francisco	Available free of charge for academic institutions	-AMBER molecular mechanics scoring function with implicit solvent, conjugate gradient minimization, and molecular dynamics simulation capabilities

FlexX (Rarey et al., 1996)	T.Lengauer and M.Rarey Biosolveit	Commercially available	-Robust incremental construction algorithm through which the ligand is decomposed into pieces and then flexibly built up in the
			-Allows both rigid body and flexible ligand docking
Glide (Friesner et al., 2004)	Schrodinger LLC	Commercially available	-Approximates a complete systematic search of the conformational, orientational and positional space of the docked ligand -Offers the full range of speed vs. Accuracy options

Patchdock (Schneidman-Duhovny et al., 2005)	Dina Schneidman-Duhovny, Yuval Inbar, Ruth Nussinov and Haim J. Wolfson	Freely available web server	-Input consists of two molecules: proteins, DNA, drugs, peptides -Geometry-based /rigid docking algorithm
CABS-dock (Kurcinski et al., 2015)	Mateusz Kurcinski, Michal Jamroz, MaciejBlaszczyk, Andrzej Kolinski, Sebastian Kmiecik	Freely available web server	-Does not require pre-defined knowledge of binding site -Uses highly efficient protocol for flexible docking of peptides to proteins

4.1 Work flow of docking experiment with Auto Dock Suite

A general docking experiment with AutoDock requires various steps including preparation of coordinate file, docking simulation, and analysis:

i. **Preparation of coordinate file:** Coordinate files for receptor and ligand are required for a successful docking and are prepared using AutoDockTools in a variety of common formats. AutoDockTools defines docking parameters and specifies PDBQT (Protein Data Bank, partial Charge Q and atom type T) files for ligand and receptor (Seeliger & de Groot, 2010) PDBQT is extended PDB format, used for coordinate files, which includes atomic partial charge, atom type, and polar hydrogen atom along with the information of torsional degree of freedom (Morris et al., 2009; Forli et al., 2016).

ii. **Docking simulation:** After preparation of the coordinate files, the user can go for various docking simulation such as single docking with AutoDock/AutoDock Vina, docking with explicit water and virtual screening with Raccoon and Vina, depending on the requirements. Initially, the center and size of the search space are defined using a grid whose coordinates are mentioned in the configuration file. Finally, the AutoDock/AutoDock Vina is run at the command line with the path of directory containing the coordinates and configuration files (Forli et al., 2016; Goodsell et al., 1996; Morris et al., 2009; Huey, et al., 2009).

iii. **Analysis:** The final analysis of the result is performed using AutoDockTools to visualize the coordinates of docked results and the interactions between the receptor and the ligand (Morris et al., 2009; Forli et al., 2016)

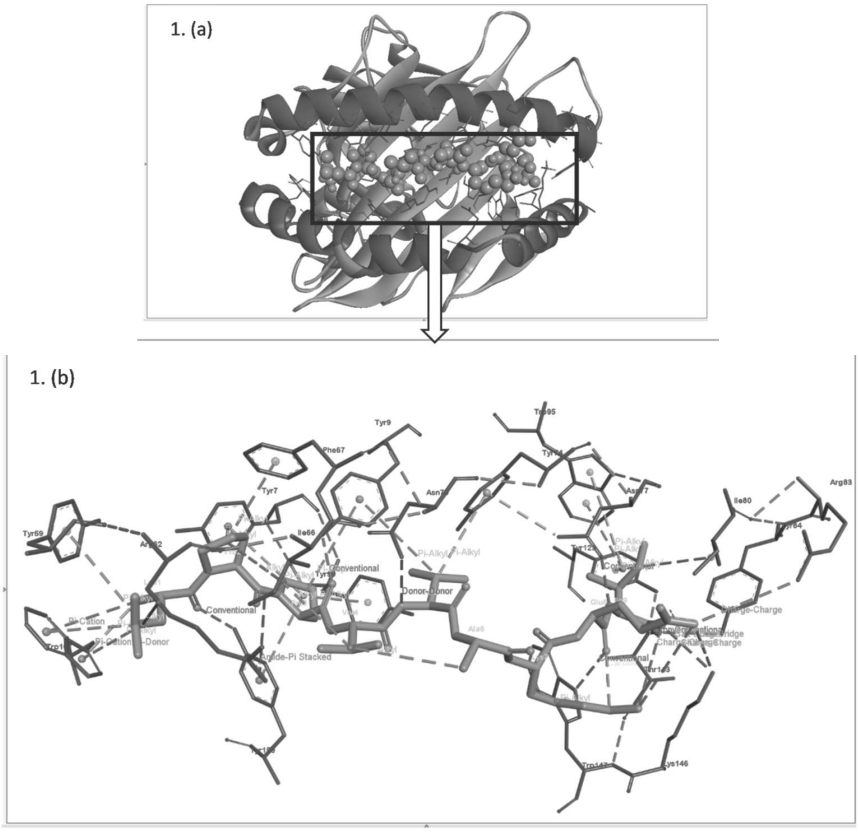

Figure 1: Docking result of HLA B*5101 with its control peptide. The receptor structure was obtained using the PDB database (PDB ID: 1E27). HEX server was used for docking and the figure was generated using Discovery Studio Visualizer. (a) Control peptide "LPPVVAKEI" in yellow colour docked into the peptide binding groove of HLA B*5101. (b) A zoomed in figure showing the different non-covalent interactions between the peptide (in yellow colour) and the HLA molecule (in blue colour).

5. Evaluation and visualization of docking results

The evaluation of the docking results relies mainly on a scoring function that ranks the different binding modes on the basis of calculated binding energies/affinities and other criteria, and usually only a small number of top-ranked complexes are chosen as candidates for further studies such as experimental assays (Cheng et al., 2012). Despite a number of scoring functions that have been developed, none of them are perfect in terms of accuracy and the compounds can exhibit poses with imperfect hydrogen-bonding, poor interactions with the binding pocket, poses based purely on hydrophobic interactions and shape complementarity or generation of poses outside the binding pocket (Bielska et al., 2011). Thus, selection of most favourable ligand solely based on binding affinities scores is not sufficient and visual inspection is often necessary for a thorough understanding of the structural principles that determine the strength and interactions of a protein-ligand complex. Protein–protein interactions play a central role in many biological processes, such as ligand mediated signal transmission making the understanding of protein–ligand recognition and binding of great importance for the discovery and design of new drugs (Dunn, 2010). Interactions are generally categorised into 5 types: a) hydrogen bond with ligand acceptor, b) hydrogen bond with ligand donor, c) ionic interactions, d) hydrophobic interactions and e) Pi stacking. These weak non-covalent interactions are key players in stabilizing a ligand energetically at the interface of a protein structure (Patil et al., 2010) .

Several software are available specifically for the structural analysis and for studying interactions between proteins and ligands. Protein-ligand complexes can be visualized and inspected using the tools such as Pymol, Discovery Studio, UCSF ChimeraX, Ligplot+ etc.

Pymol (Delano, 2002) is an open source molecular visualization system created by Warren

Lyford Delano and currently developed and maintained by Schrödinger Inc (Chan et al., 2017). Presently, Pymol is one of the most widely used macromolecular visualization tools that can produce high-quality movies and images of macromolecules in different representations including ribbons, cartoons, dots, surfaces, spheres, sticks, and lines. Pymol is particularly widely used since it is written in Python and can be extended to Python plugins easily (Chan et al., 2017). The Autodock/Vina-plugin for Pymol represents an interface between these programs and allows to carry out molecular docking, virtual screening and binding site analysis with Pymol (Seeliger& De Groot, 2010).

Discovery Studio (Biovia, 2017)is a suite of software developed and distributed by Dassault SystemesBiovia for analyzing and modelling molecular structures, sequences, and other data of relevance to researchers. The Discovery Studio Visualizer is a free viewer with features such as advanced molecular visualizations, displaying and editing ligand binding sites, display of a range of molecular surface properties including H-bonds, charge, ionizability, lipophilicity, aromaticity and solvent accessibility, monitoring non-bond interactions including favourable, unfavourable and unsatisfied interactions (Biovia, 2017). It also provides a rich set of viewers for displaying plots and other graphical representations of data. The application runs on Windows and Linux and is a fully integrated desktop environment that provides access to standard operating system features such as the file system, clipboard, and printing services. Figure 1 shows the result of a docking experiment performed using Hex program and visualized in Discovery Studio Visualizer.

Ligplot+ (Laskowski & Swindells, 2011) is a

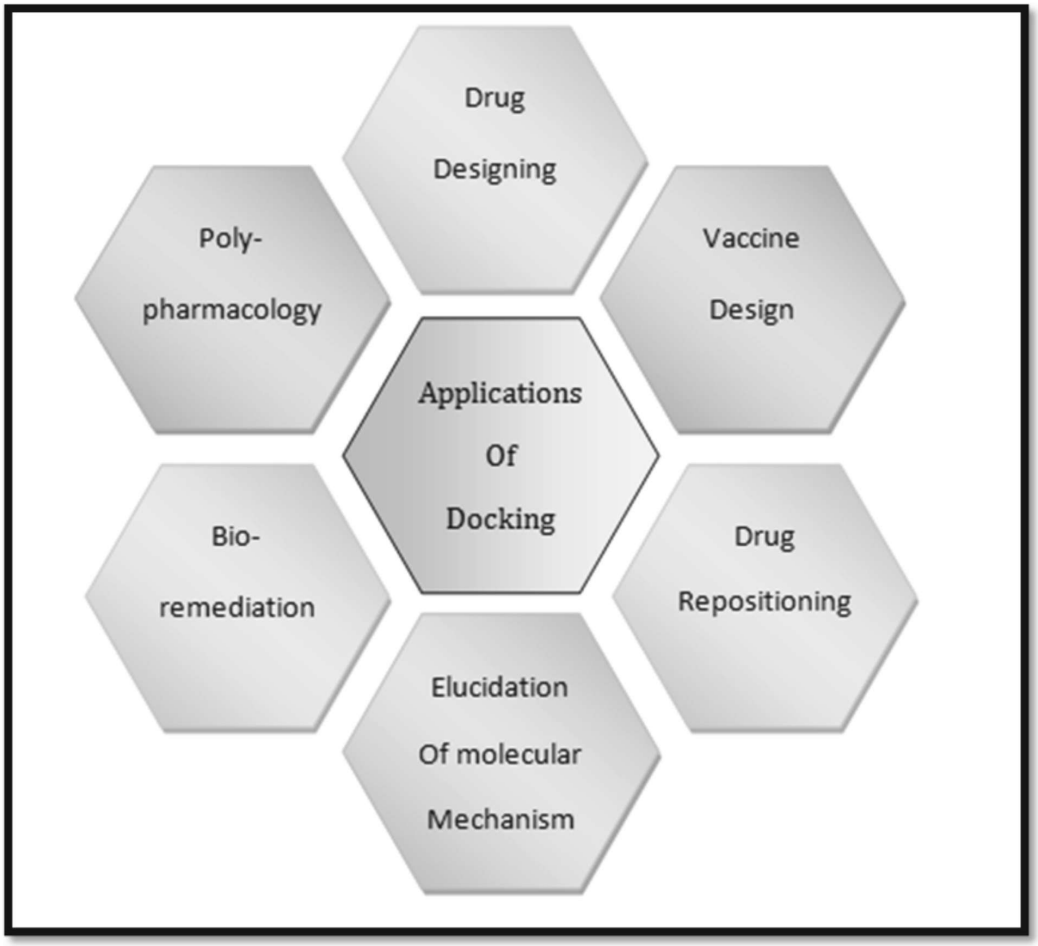

Figure 2: Applications of molecular docking: Various applications of molecular docking includes drug designing, vaccine design through the immunoinformatics approach, drug repositioning of the already approved drugs, elucidation of molecular mechanisms to have deeper understanding of the life processes, bioremediation to combat pollution, and polypharmacology to identify ligands which can bind to variety of therapeutic targets.

successor to the original Ligplot program developed by European Bioinformatics Institute. The Ligplot+ program automatically generates schematic 2-D representations of protein-ligand complexes from standard Protein Data Bank file input (Laskowski & Swindells, 2011). It runs from an intuitive java interface which allows on-screen editing of the plots via mouse click-and-drag operations. It provides an alternative to visualization of 3-D structures which is often difficult to quickly investigate with (Laskowski & Swindells, 2011). The 2-D representation diagrams portray the hydrogen-bond interaction patterns and hydrophobic contacts between the ligand and the main-chain or side-chain elements of the protein.

UCSF Chimerax (Goddard et al., 2018) is one of the most powerful 3D molecular visualization program developed by the Resource for Biocomputing, Visualization and Informatics . UCSF Chimerax is built over the original UCSF Chimera visualization system with the main goal to provide an integrated multiscale modelling environment that enables researchers to interactively access, visualize, and analyze structural data (Goddard et al., 2018).

6. Applications of molecular docking

Molecular docking exhibits a wide array of applications in today's world where bioinformatics is strengthening its grip onto the research based literature. An ever increasing computational power coupled with improvised algorithms has added to the list of molecular docking applications which includes drug discovery, prediction of toxicity and side effect targets, epitope prediction for epitope-based vaccine, drug repositioning, biological mechanism elucidation, bioremediation, and library building among many other (Figure 2) (Bielska et al., 2011; Dar & Mir, 2017; Goodsell et al., 1996).

There are numerous compounds in nature which exhibit biological effects on humans which can be a result of a long-term co-evolution (Ji et al., 2009). The computational screening of large libraries of natural compounds against the molecular targets reduces time, effort and cost for finding the desired drug target. Molecular docking is one of the most successful and popular *in-silico* methods which helps in predicting interactions between the molecules and biological target. Along with structure-based virtual screening, it is also employed to identify targets for which the ligands exhibit good complementarity, also known as target fishing and profiling. Moreover, it is also utilized to identify ligands that show simultaneous binding with a variety of therapeutic relevant targets of interest; a process known as polypharmocology (Pinzi& Rastelli, 2019). Given the extensive evaluation and safety measures required for a new molecule to be approved as a drug, it is always preferable to repurpose an established and approved drug towards novel therapeutic targets. For example, a docking-based study has discovered that mebendazole, which is an anti-parasitic drug, is also found to be an anti-angiogenic inhibitor (vascular endothelial growth factor receptor 2) (Dakshanamurthy et al., 2012). This strategy of drug repositioning using the computational approach of molecular docking also involves the screening of structural complementarity. Several computational approaches including molecular docking are also used to identify or indicate side effects of drugs by analyzing the existing databases of drug-adverse drug reaction (drug-ADR)pairs (Xu et al., 2018). For instance, Ma. et. al, in an *in-silico* study using a docking based program predicted the toxicity related target protein for melamine and its metabolite, cyanuric acid (Ma et al., 2011). Along with the extensive use of molecular docking in drug designing and its related aspects, it is also being used worldwide as a part of immunoinformatic approach to find a probable epitope-based vaccine candidate. In these studies, epitopes selected after numerous screening methods are docked with various HLA molecules in order to validate their ability to be presented by antigen presenting cells to cytotoxic T-cell or helper T-cell (De Groot et al., 2002). Recently, there has been a spike in the utilization of molecular docking tools for the immunoinformatics and drug design approaches in an attempt to recognize vaccigenic epitopes and inhibitory molecules against SARS-CoV-2 (Sarkar et al., 2020). A docking strategy with novel methods of analysis also makes it possible to understand the deeper insights of various delicate molecular mechanisms (Bartuzi et al., 2017). Apart from the wide array of applications of molecular docking in life science and pharmacology, it has also been successfully employed in environmental remediation. In this case, active sites of various enzymes are analysed for their biodegradative properties and ability to accommodate the pollutant molecules (Liu et al., 2018).

7. Challenges in docking

It is evident from docking literature that it is in a mature stage of development but significant challenges still remain. Though important advances are being made in all aspects of docking programs, flexibility and successful scoring are still far from perfect (Huang & Zou, 2010). Opting for a docking program that will suit best according to the needs

and will give the best results is also not simple and straight forward (Akhter, 2016). Along with this, unlike the ligand flexibility, the protein flexibility is still in infancy and requires improvement (Huang & Zou, 2010). Various studies have also reported that due to major biochemical and physical differences in charges, binding pockets, and solvation, existing docking programs which have been developed for proteins, face difficulties when employed directly for nucleic acids (Luo et al., 2019). Despite all these challenges the *in-silico* docking procedures offer a great deal of insights into protein interactions.

8. Conclusion

In the present study, we have reviewed the basic aspects of molecular docking by explaining the workflow using the key docking tools and the various modern-day applications of docking. Molecular docking method has seen increased usage and is currently seen as a key player in early stage drug-discovery and vaccine development. Many protein-ligand docking programs and web-based servers are currently available and new alternatives are being developed every year. Despite such advances, docking studies are far from being perfect and involve a number of drawbacks. Treatment of receptor flexibility and lack of a perfect current scoring function appear as major hurdles in docking. Nevertheless, despite the drawbacks of each docking strategy, docking based virtual screening remains a useful and promising *in-silico* tool for developing new therapeutics. This is especially evident from the number of studies using molecular docking approaches to screen for both natural and synthetic medications to treat COVID-19.

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