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Special Issue: Computational drug designing and molecular docking analyses

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Computer Aided Drug Designing (CADD): Tools used for structure-based drug designing

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Abstract

Traditional drug designing utilizing conventional methods is considered to be an exorbitant and time-consuming process. CADD was introduced as an effective method which has enormously increased and economized the drug designing and development process utilizing computational methodologies. CADD can be achieved by ligand-based drug designing (LBDD) and structure-based drug designing (SBDD). It has reduced the time required for a drug to move from its initial stages to the market by utilizing CADD process and its respective methodologies in comparison with the traditional drug designing. In this review, we've discussed the most cited computational tools for 3D structure prediction of target protein along with the tools and scoring techniques to scrutinize molecular docking of target and ligand complex, to achieve novel drugs centered on structure of biological target.

Introduction

Drug designing is the process of designing novel molecules relying on the concept of particular biological targets. It implicates to design a molecule having reciprocal charge as well as shape corresponding to a particular biological target to which the molecule will create an interaction and to perform its function after getting bound to it. The novel drug designing using conventional methods is a tiresome and cost exorbitant procedure.

The computational drug designing is an effective method to speed up and economize the drug designing and development process. To accelerate the process of antibiotic drug design, computational approaches are convenient tools to explain and experimentations [1]. Computer Aided Drug Designing (CADD) necessitates a wide range of computational methodologies including virtual screening, lead optimization, virtual library design, molecular docking and molecular dynamics simulations. The two general types of CADD includes structure-based drug designing (SBDD) and ligand-based drug designing (LBDD). LBDD depends on the available information of other molecules that bind to the biological targets. The molecules are utilized to acquire a pharmacophore model for virtual screening. Alternatively, Quantitative structure-activity relationship (QSAR) utilized to determine the inter-relationship between premeditated characteristics of the molecules and their experimentally ascertained biological activity acquired [2]. SBDD based on the comprehension of three dimensional (3D) structures of the biological targets which can be acquired from the techniques such as X-ray crystallography and NMR spectroscopy. SBDD consists of various steps including protein structure prediction, molecular docking, binding free energy, flexibility of the protein ligand complex and *de novo* evolution.

Protein Structure Determination

The most basic step of structure-based drug designing is to determine the structure of the target molecule. Numerous structures related to protein-ligand complex are present in RCSB Protein Data Bank, but many structures are still not known because of the certain restrictions in the X-ray and NMR. In case, if an experimental structure of the biological target is not available then automated computational procedures are used such as homology modeling and threading approaches[3]. For the prediction of the structures of proteins utilizing their sequences of amino acids, the robust approach is homology modeling. Homology modeling involves various efficient steps to predict the exact protein's structure[4]. These are comprised of template recognition, calibration with the template, model erection and several post-modeling procedures. There are number of tools used for homology modelling such as ROBETTA, ICM, MODELLER, I-Tasser, 3D-JIGSAW, 3D-JURY, PSIPRED, RaptorX, PHYRE2, SWISS-MODEL, Sybyl, and SCWRL4. A more detailed list of available software and tools for 3D structure prediction of protein is described in **Table 1**.

ROBETTA

Based on Rosetta standalone package, Robetta is a publicly available server of homology modeling for protein structure determination [5]. For structure predictions of protein, Robetta is a fully automated tool. Protein structural models can be generated by two possible methods as comparative modelling and *de novo* structure prediction through sequence in to Robetta server [6]. It is also able to predict the outcomes of mutational interactivity by scrutinizing the computational interface of alanine.

MODELLER

Modeller is an automated protein homology modelling tool that is broadly used for comparative modelling of protein 3D-strutures prediction [7]. It is utilized through command-line and in order to use it adroitly the fundamental concepts of python scripting is essential [8]. It is a standalone tool available for windows with modeller and python pre-installed, which assist in building tertiary and quaternary structures of proteins, their visualization and optimization. The prediction through modeller comprise of model building and model evaluation [9].

I-Tasser

I-Tasser is categorized as the leading techniques in the server list of community wide critical assessment of structure protein[10]. The algorithm of server is utilized to design the complete automated 3D structures of proteins where to assist the users scoring system is used for the simple evaluation of models in I-Tasser. The server is accessible free of cost, where first query threaded from PDB leads to uninterrupted threading of queries utilized to muster the 3D structures [11]. I-Tasser server predicting 3D structures can be either modeling deploying template or modeling without any template [12].

3D-JIGSAW

Based on the known structures of homologs, 3D-Jigsaw is a fully automated program for the 3D structure prediction of proteins. The basic aim of 3D-jigsaw system is to generate high resolution 3D image of protein structures utilizing radar sensor technology, techniques and systems [13]. This automated algorithm is utilized for comparative modeling to build and analyze fourteen models in CASPs technique [14]. The server observes the templates of homologues in the sequenced databases such as PDB or PFAM and split the sequences in inquiry to conserve domains. The optimization and precision of models can be authenticate using its 3D printing and mechanical testing [15].

3D-JURY

For the advancement in quality of structural annotation in novel proteins, 3D-Jury is introduced to design a simple however robust approach using variable methods for the construction of meta-predictions [16]. It is a protein structure prediction server that assemble predictions from various servers and construct the final model utilizing a consensus approach and a finer features of structure is based on 3D-Jury score and model quality measure [17]. It is highly sensitive and specific in contrast with other meta-servers because of the fact that it has a significant features of establishing high correlation between described 3D-Jury score and reliability of the model [18].

PSIPRED

The PSIPRED is a suite that has multiple protein structural prediction and annotation tools [19]. It is a simple and considered as an accurate secondary structure prediction approach having threading algorithms including GenTHREADER, pGenTHREADER, pDomTHREADER, Bioserf, MetSite, HSPred, MEMSAT-SVM, MEMPACK, FFPred, DomPred and DISOPRED2 [20]. The server incorporates two feed-forward neural networks which perform analyses on output obtained from PSI-BLAST (Position Specific iterated - Blast) and permit users to carry out structural prediction [21].

RaptorX

RaptorX server, which is highly utilized for the prediction of secondary structures of proteins, based on the modeling of template structures and evaluation of a standard alignment score [22]. It is the leading server in CASPs and differs from other homology modeling servers due to its assessment of calibration among target sequences and numerous protein template [23]. It is an automated server of threading approach utilized standard alignment for structure prediction [24]. RaptorX property prediction is a foremost web server in evaluation work utilized in protein structure property prediction together with secondary structure, solvent accessibility and disordered regions without using templates [25].

PHYRE2

Phyre2 is a suite comprising of various tools for the analysis and 3D structure prediction of proteins, their functions and mutational analyses [26]. Pyhre2 is a very robust tool which is capable to perceive exceedingly remote homology and utilized to generate unambiguous models of protein structures, though having >15% sequence identity [27]. It constructs a 3D structure acquired by the given protein sequences based on its respective modes such as normal mode, intensive mode and advanced functions.

SWISS-MODEL

It is an automated comparative modeling tool which provoke 3D structures of protein including template selection, alignment and model building [28]. The focus of this server is to keep its users up with the contemporary annotation of 3D protein models and with fairly simple interface. It also provides an approach to scrutinize the model quality, explore possible template structures and construct models mutually utilizing SWISS-MODEL workspace [29].

ICM

ICM is a software that provides a convenient environment to its users to reveal the structure of proteins and focused on protein structure prediction through comparative modeling and molecular docking [29]. The software has been utilized to generate five models through comparative modeling [30]. To generate a protein structure, ICM utilizes formerly organized biomolecular structures and required sequence identity covering from 25-77 %. The pliable

Table 1: Describe the salient attributes of the tools utilized for Binding site Prediction in Bioinformatics

Tools	Type	Features	Links
ROBETTA	Web Server	Based on Rosetta fragment-insertion method, Robetta is a standalone, highly automated server utilized for protein structure prediction purpose [32].	http://www.robetta.org/ [6]
ICM	Program	ICM is suite of software which provide a fairly simple interface for the prediction of low energy structures of bio-molecules [33].	www.molsoft.com [34]
MODELLER	Program	Modeller is highly utilized program for comparative modeling to generate comparative models of protein using unknown structure [35].	https://salilab.org/modeller/ [36]
I-TASSER	Program/Web server	I-Tasser is a fully automated and integrated we server utilized for the prediction of 3D structures of proteins and their functionality [36].	https://zhanglab.ccmb.med.umich.edu/I-TASSER/ [37]
3D-JIGSAW	Web server	3D-Jigsaw is a web-based homology modeling server utilized to generate three dimensional protein structure based on homologues of investigated structures [38].	http://bmm.crick.ac.uk/~3djigsaw/ [39]
3D-JURY	Web server	3D-Jury is the meta prediction server for structure prediction of proteins and consider to be chief server because of exploring high correlation between confidence score and predicted models [40].	http://meta.bioinfo.pl/submit_wizard.pl [41]
PSIPRED	Program/Web server	PSIPRED is homology modeling program that is utilized for the prediction of secondary structure of proteins and remarkably attain accurate models [42].	http://bioinf.cs.ucl.ac.uk/psipred/ [43]
RaptorX	Web server	Leading server in CASPs utilized for theh prediction of secondary and tertiary structures of protein alog with the binding site and annotation [44].	http://raptorx.uchicago.edu/ [45]
PHYRE2	Web server	Advanced version of phyre, Phyre2 is a web-based modeling tool utilized for three dimensional structure prediction [46].	http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index [47]
SWISS-MODEL	Web server	Eliminating the use of costly softwares to construct the models, SWISS-MODEL is the highly automated, adaptable server for homology modeling [48].	https://swissmodel.expasy.org/ [49]
WHAT IF	Program	A flexible web-based program which is highly utilized in molecular modeling and drug designing to work with proteins and its likewise components such as ligands or nucleic acid [50].	https://swift.cmbi.umcn.nl/whatif/[51]
SYBYL	Program	SYBYL is a suite of computational software utilized for homology modeling to improve the process of drug designing based on its good scoring function [52].	http://tripos.com [53]
DRAGON	Program	DRAGON is the geometry based program for homology modeling utilized to generate low resolution models of protein [54].	http://www.nimr.mrc.ac.uk/~mathbio/aaszodi/dragon.html [55]
SCWRL4	Program/Web server	Based on new algorithm and with appropriate speed, SCWRL4 is utilized for side-chain conformation prediction and demand reduced computational assay as compare to other servers [56].	http://dunbrack.fccc.edu/scwrl4/ [57]

molecular docking and scoring techniques are standardized for ligand binding prediction and modeling methodology comprises of side-chain prediction and loop prediction [31].

Molecular Docking

Molecular docking is an approach for detecting molecular interactions to create virtual simulations based on their molecular interactional information. Molecular docking is an approach of SBDD as it predicts the ligand-protein binding and their conformation with great precision [58]. In computer-aided drug redirecting pipelines, molecular docking approaches can be applicable in various ways as by filtering a compound against the collection of protein structures in order to predict new drug-target interactions [59]. In addition, docking tools are based on such algorithms for ranking the ligands and for the predictions of binding affinities by using different

scoring functions [58]. Molecular docking is the frequently used approach in bioinformatics for SBDD which utilizes the structures and ligand-target interactions to predict the lead compound and to reposition the drug for medicinal use [60]. There are two main factors on which the conformation of ligand-binding complex depends as the possible binding positions defined by large conformational spaces and prediction of definite binding affinities associated with each conformation.

To attain minimum energy state, a series of iterations are carried out in which different scoring functions are utilized to evaluate the ligand-binding conformations [58].

Types of Docking

Molecular docking has been classified into different types on the basis of conformational changes in the structures of the ligand and target due to ligand-target interaction:

- **Rigid Docking** is a docking process carried out through static both the target and the ligand [60, 61].
- **Flexible Docking** has both the target and ligand as flexible [60, 61].
- **Flexible ligand and rigid target docking** have the target molecule rigid while the ligand as flexible.
- **Ensemble Docking** utilized different structures of rigid protein to dock against a ligand and results are generated as a combination based on the method of selection.
- **Hybrid method** approach utilizes the flexible receptor and uses different methods of docking [60].

Forces to induce target-ligand interactions

Various forces involve in the interaction of the target and ligand as electrodynamic forces and Van der Waals forces are weak and short-range forces. Electrostatic forces include Dipole-Dipole interactions, charge-dipole interactions and charge-charge interactions. Steric forces create the interactions through entropy. Hydrogen bonding and hydrophobic/hydrophilic interactions are considered as the strongest ones [60, 61]. Other substantial elements that brings conformational changes in ligand and target structures may prove significant for the study of molecular docking [60, 62].

Mechanism of Docking

Molecular docking is an approach in which a ligand is 'Docked' against a particular biological target and a specific 'Docking score' is assigned to each ligand-target conformation in the binding site of the target protein. This score is utilized to calculate the possibility of ligand-target binding for the prediction of biological efficacy of a ligand against the specific target [2]. Different mechanisms and approaches involved in molecular docking are explained in Fig. 1.

Methods to assign scores in Docking

The most important constituent of docking tools is to assign different scores to the ligand-target complex utilizing the scoring function. Using different scoring methods, molecular docking tools assign different values to different ligand-target conformations based on the scoring methods. Force field-based method has the aim to comprehensively pattern out different types of ligand-target interactions by using different parameters and constants obtained from different experiments quantum mechanical simulation (QMS). DOCK, GOLD and AutoDock molecular docking tools provide such scoring methods. Empirical methods use machine learning and regression methods to calculate and to predict the binding affinities of ligand-target complexes and also their general features including the number of hydrogen-bonded pairs. LUDI, PLP and ChemScore use the said scoring methods. Statistical approaches assign score to the ligand-target complex based on the frequency by which the structural features of the ligand-target complex take place in the training set of ligand-target complex. The molecular docking tools using such scoring methods include PMF, DrugScore, SMoG, and Bleep [63].

Softwares/Tools for molecular docking

In bioinformatics, there are number of tools and databases available for molecular docking analyses.

The detailed list of available computational tools and programs for molecular docking analysis is given in Table 2.

AutoDock Vina

AutoDock Vina is publically available molecular docking program planted on uncomplicated scoring capacity and fast configuration search. It was multifaceted tool which accomplish the need for a publically available docking methods [64]. It has the ability to execute molecular docking analyses by using default approaches. AutoDock Vina does not need to select the molecular types and pre-figuring grid maps. Rather, it measures the grids intrinsic for the required atom types. AutoDock Vina has an upgraded local search pattern. Moreover, AutoDock Vina can exploit various central processing systems to consequently reduces the running span [64]. AutoDock tools and AutoDock Vina have the same PDBQT sub-atomic structure record group for the input and output. AutoDock Vina has been noted for running consequently quick under 64-bit Linux operating system in various global society grid projects [65].

AutoDock Tools

The team of AutoDock launched AutoDock Tools (ADT) which is a graphical user interface to analyze the result of AutoDock and visualize the result in 3D [66]. There are many new adaptations taken in which support are provided for the new arrangements utilized *via* AutoGrid4 and Autodock4 [66]. By using ADT, various functions can be performed including visualizing molecules in 3D, attachment of only Hydrogen atom or hydrogen ions, allocate hydrogen ions to the large size molecules or ligands, homogenize non-charged dissociated hydrogen and their charges, scan the conclusions of an autodock work and visualize graphically (http://mgltools.scripps.edu/downloads).

PatchDock

It is a computational tool for two or more combination of atoms [67] and to find docking alternation for atomic structures. PatchDock is performed by taking increment of two molecules having peptide bonds including proteins, DNA, peptides, drugs and the result have potential networks aligned by structure complementarity criteria [68]. The PatchDock tool divides the molecules into inward, raise and level patches. PatchDock method was demonstrated on enzyme-inhibitor and antibody-antigen nexus from benchmark 0.0 [69] and is effective method for protein-ligands and protein-protein docking analyses [67].

SymmDock

SymmDock is a free domain server for molecular docking. This technique elucidate the shape of a multimeric protein consisting of two or more identical components with periodic symmetry [70]. The process utilizes the server allowing wide range of docking experiments. It is much simpler method because it uses one molecule as input with symmetry order [71]. SymmDock estimates only periodic arrangement and symmetry is not in its local form than SymmDock does not accomplish its task.

MolDock

MolDock utilizes proficient method and is capable of prophesying the active site of the target molecules to attach against ligands [72]. The addition of hydrogen bonds and adhesive forces, the steric complementarity between the protein and ligand becomes prolonged due to MolDock capacity function [73]. MolDock can presage active sites of 87% of complexes. According to the tentative observation all computational docking project arithmetically estimate the 3D structure of a protein and a ligand [74]. The piecewise linear potential (PLP) act as a base for docking scoring function of Mol-Dock [75]. The MolDock software is much more accurate as compare to other softwares [76].

ZDOCK

ZDOCK is easy to understand protein docking web server utilized for estimating the biochemistry of protein-protein docking and align supplementary group of monomers. ZDOCK is a solid body protein-protein docking program [77]. A combination of two

proteins and 3D Fast Fourier Transform (FFT) is used by ZDOCK to analyze the space of docking position [78]. ZDOCK has multiple features incorporates structure supplementary, interactive forces and nuclear measurable potential developed utilizing content inclinations of transient protein [79]. ZDOCK has high predictive ability for protein-protein docking and >70% of success chances [80]. Due to pairwise statistical potential technique, ZDOCK is highly improved and has increased the efficiently [81].

ClusPro

The most widely used tool for protein-protein docking and template-based modelling is ClusPro server (https://cluspro.org). It requires two files in PDB format for protein-protein docking [82]. The user can enter the accession number to download the PDB file automatically from PDB. The server predicts maximum of 30 conformations and generate 10 best predictions. It allows to customize the parameters including radius clustering, number of best hits utilized by free binding energies filtering and the number predictions [83]. ClusPro uses template based approach which helps in solving major issue of docking small ligands to the target proteins [84].

SwissDock

SwissDock (http://www.swissdock.ch) is utilized for fully automated docking functions having systematic Simple Object Access Protocol (SOAP) interface arranged to download the template files in Python, PHP and Perl. Moreover, it provides a gateway to the databases of experimentally determined protein-ligand complexes [85]. SwissDock has been programmed upon EADock DSS for target-ligand binding affinities prediction and utilizes simple integrated user interface[86]. The alternative sets of parameters are also provided by SwissDock web server utilizes cumbersome syntax for docking engine present behind a fair web interface [85].

EADock DSS

EADock DSS (Dihideral Space Sampling) has been made up on the two most effective traits of EADock2 include multipurpose scoring methods and engine sampling using hybrid methods. It has the ability to achieve the low processing time [87]. The accomplishment rate is 75% and 65% for local and blind docking respectively [88].

GEMDOCK

Generic Evolutionary Method for docking molecules, is used to identify the ligand structure and position with respect to the binding site of the target protein[89]. GEMDOCK is a developmental methodology for adaptable docking which is also an essential component of development of medication on the basis of structures and functions of the target molecules. This technique combines both evolutionary and neighbourhood search strategy [90]. It identifies molecular compound by limiting their energy of association. GEMDOCK is a programmed framework and can run as both adaptable or crossbreed docking approach and produces all docking factors such as target position [91].

RosettaDock

The structure of protein-protein docking can be determined by RosettaDock by enhancing the rigid body arrangement. The space between the rigid body and side chain of two interacting proteins can be estimated by RosettaDock to find free minimum energy complexes [92]. It estimated the structure of complexes and two protein structures used as input and beginning orientation by the RosettaDock server [93]. RosettaDock develops 100 free structures and for 10 high ranking scoring models [94].

TarFisDock

It is used for studying interactions between small molecules and the target proteins [95]. Goal of Fishing Dock (TarFisDock) is to search for potential binding proteins for a certain ligand [96]. The basis for the establishment of TarFisDock is wide use of docking programs[95]. It docks the intermolecular energies of proteins and those proteins are calculated and recorded. It also docks given molecule into possible binding sites of protein. It results in reverse docking, examined by TarFisDock. It provides the output of the top 2 to 10% best hits of the ranking list, out of which

protein entries are picked out by user for further biological studies [95]. The input file must be in mol2 format for the test molecules. For sketching 2D structure of molecule, ISIS/Draw (MDL Informations System) or ChemDraw are used [97]. One can access TarFisDock and PDTD at http://www.dddc.ac.cn/tarfisdock/ [96].

RDOCK

RDOCK is a program for docking ligands to proteins and nucleic acids. RDOCK originated from the program RiboDock, that was first developed for the virtual screening (VS) of RNA. This platform is an assemblage of command-line programs and scripts. The main functions that can be performed by this program includes rbcavity (cavity generation) as well as rbdock (docking). The receptor has to be provided in the Tripos MOL2 format. The ligands to be docked are accepted in the MDL SD File format (SDF). Accurate topology as well as bond orders are significant [98].

INVDOCK

It is a web server that is being utilized for finding a biological receptor for a particular ligand having a huge amount of receptors using reverse docking mechanism[99]. using a docking tool a small molecule (ligand) is docked against the binding pockets of each and every protein that is present in the database. The docking tools then assigns a binding score to each receptor-ligand complex using some scoring functions and rank them accordingly. The whole process has been integrated in the online web sever of INVDOCK [100]. The user can access INVDOCK web server at https://omictools.com/invdock-tool.

FireDock

It is a web sever for tensile purification in molecular docking. It takes in development of the conformational changes in the side-chain as well as perform rigid-body alignment and permits a high-efficiency purification. Two main steps for purification are: (a) interface side-chains rearrangement, and (b) refinement of the relative alignment of molecules [101]. The user can access the web server page of FireDock at http://bioinfo3d.cs.tau.ac.il/FireDock/. It provides the facilities such as user-friendly graphical interface as well as 3D visualization of the resulting ligand-target complex [102]. A docking procedure includes a global exploration by PatchDock and refining steps by FireDock. This procedure is cooperative in refining and scoring the docking solutions for cases that have been taken from standard docking criterion [103]. Input for the FireDock consists of complexes, which is derived from an algorithm. Every complex comprises of two proteins molecules, out of which one acts as a receptor while the other acts as a ligand. The protocol of FireDock purifies each and every complex and lists the complexes in accordance to their binding affinities [102].

Conclusion

This review article determines various precedents from the literature and the substantial variety of computational tools utilized in CADD proposes that there are no radically supercilious approaches. In conclusion, the I-Tasser, Robetta and AutoDock are the more robust and efficient tools for threading, homology modeling and for molecular docking analyses respectively among the rest of the computational tools. The production and efficiency of these tools fluctuates to a great extent depending upon the target protein and available data and resources. Computational tools have been recommended to evolve to extricate such information from the massive amount of ligand binding data.

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Conflict of interest

The authors declare no conflict of interests.

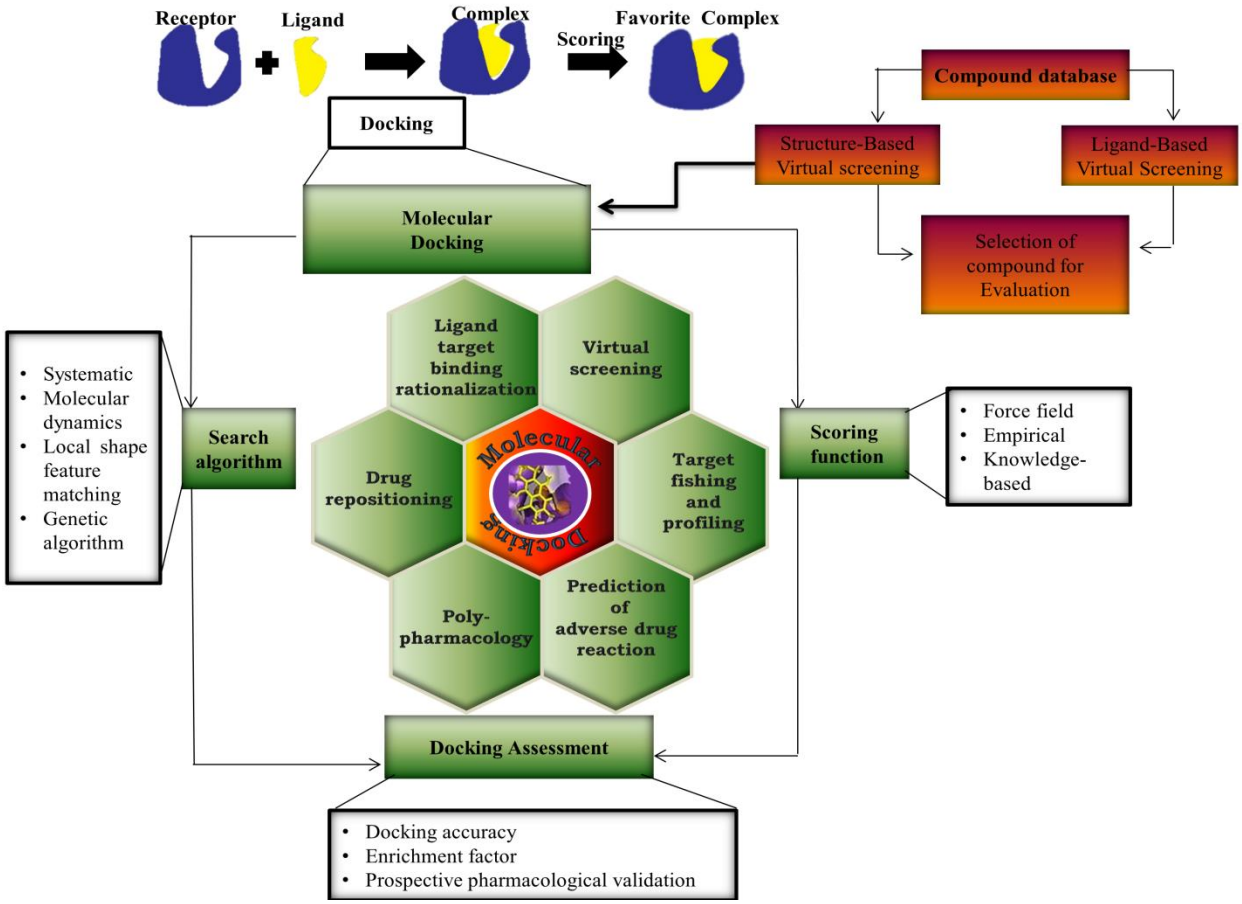

Fig. 1: Different mechanisms and approaches involved in Molecular Docking.

Table 2: Commonly used Tools for Molecular Docking in Bioinformatics and their salient features.

Sr. No.	Tools	Type	Features	Links
	AutoDock Vina	Program	A tool utilized for docking as well as virtual screening. AutoDock Vina attains degree roughly two orders of extent relates with the Autodock-4 [104].	http://vina.scripps.edu/
	AutoDockTools	Program	It is a graphical user interface to analyze result of Autodock and visualize result in 3D [104].	http://autodock.scripps.edu/resources/adt
	PatchDock	Program	It helps in the structural prediction of proteins with other proteins as well as with compact molecular sized complexes [105].	http://bioinfo3d.cs.tau.ac.il .
	SymmDock	Web server	Structures of a homomultimers having cyclic consonance can be predicted using this tool which is specified by the structure of monomeric entity [105].	http://bioinfo3d.cs.tau.ac.il/SymmDock/
	AutoDock	Program/Web server	It ia a computerized software which is used to foresee how micromolecules hitch with target of known structure [104].	http://autodock.scripps.edu/
	ZDOCK	Web server	It is utilized to estimating the biochemistry of protein-protein docking and align supplementary group of monomers [106].	http://zdock.umassmed.edu/
	ClusPro	Web server	It utilizes fast algorithm for the selection of docked conformations having acceptable complementary surfaces, and depending upon the clustering characteristics ranks them [83].	https://cluspro.bu.edu/login.php
	EADock	Program/Web server	It is used for curating common concerns, DSS engine has been attached with configuration scripts and also for making ready the input files of ligand and targeted protein [85].	https://aurelien.latitude77.org/projects/eadock/index.html
	SwissDock	Web server	The algorithm behind SissDock is based upon the DSS engine of EADock with which the configurations scripts has been attached for the curation of general concerns as well as,	http://www.swissdock.ch/

		the prepration of input files for both ligand compound and the targeted protein [85].	
GEMDOCK	Program	It is refferred as Generic Evolutionary method which is used to identify the ligand structure and position on the target.[75].	http://gemdock.life.nctu.edu.tw/dock/
RosettaDock	Web server	It recognizes conformations having relatively low binding energies within protein interactions that are closed to specified initial arrangement by enhancing the orientations and conformations of both rigid-body and side-chains, respectively [94].	https://bio.tools/rosettadock_server
FireDock	Web server	It is used for elastic modification and assigning scores to protein–protein docking results. It comprises of algorithms to enhance the conformations of side-chain, and rigid-body alignment [102].	http://bioinfo3d.cs.tau.ac.il/FireDock/.
INVDOCK	Program/Web server	It is a docking process which is used to recognized possible receptor target for the micromolecules[107].	https://omictools.com/invdock-tool
RDOCK	Program	It is a technique used for the docking of micromolecules against protein, nucleic acids.It also determines how ligands attached to target [98, 108].	http://rdock.sourceforge.net/
TarFisDock	Web server	It is a method which is used for scanning of microprotein association over an large accumulation of protein structures and it requires a proper software to operate [95].	http://www. dddc.ac.cn/tarfisdock/
pyDock	Program	It is a technique which used to estimate the solid body docking of protein-protein structure [109].	https://life.bsc.es/pid/pydock/
FlexPepDock	Web server	The gap between peptide bond arrangement, structure and solid body position along with intial sample can be used by this technique productively and alternatively [110].	http://flexpepdock.furmanlab.cs.huji.ac.il/
FlexDock	Program	This tool has the ability to control all these hinges in adaptable molecular structure without effect on its operation time [111].	http://bioinfo3d.cs.tau.ac.il/FlexDock/
DOCK Blaster	Program	This technique will able to inaugurate a huge libraries by using a PDB code along with a ligand structure [112].	http://blaster.docking.org/
MCDOCK	Program/Web server	It is created to complete the atomic docking activity consequently [113, 114].	https://m.twitch.tv/mcdock/profile
FiberDock	Web server	This tool can sync 100 of alternation like PDB files, receptor and ligands and also modify 100 of solid docking solutions [115, 116].	https://bioinfo3d.cs.tau.ac.il/FiberDock/
PRODOCK	Program	PRODOCK used information of the collection remaining particles which makes molecular adaptation and programming efficient [117].	https://www.prodock.nl/
iGemdock	Program	This tool can give biological awareness by analysing the drug interaction without performing an experiment [118].	http://gemdock.life.nctu.edu.tw/dock/igemdock.php
SODOCK	Program	It is used the technique by which two solution are compared to obtain a satisfactory solution to resolve protein ligand docking disturbances [119].	https://omictools.com/sodock-tool
RiboDock	Program	The technique which identified the structure which are more easily bind to a drug target and direct the process of adaptable docking [120].	https://omictools.com/rdock-tool
SwarmDock	Web server	This tool is used to display the protein-protein complex structure in 3 dimensional array [121].	https://bmm.crick.ac.uk/~svc-bmm-swarmdock/
FRODOCK	Program	This stands for Fast rotational docking tool.It performs 6D docking and estimates how protein associate with each other [122].	http://frodock.chaconlab.org/
FLIPDock	Program	It is based on FRM (Fast Rotational Method) to perform protein-protein docking [123].	http://flipdock.scripps.edu/
MEDock	Web server	The maximum randomness in the Gussian probability distribution can be achieved by including complete pursuing scenario along with MeDock [124].	https://omictools.com/medock-tool
DOCKovalent	Program	It is used to analyse large collection electron loving micromolecules and alsodetermine the compounds which are able to form covalent bond with target protein that attack on nucleus loving protein [125].	http://covalent.docking.org/
SnugDock	Program	It is used to estimate antibody and antigen complexes with high resolution. It is used for the optimization of antibodies and antigens and their stiff body positions, and for the modifications of light and heavy chains [126].	https://www.rosettacommons.org/docs/latest/application_documentation/antibody/snugdock
DOCKGROUND	Web server	It is a database designed for complexes of proteins that are bound in relational database of annotation [127].	http://dockground.compbio.ku.edu/
DockDE	Program	It gives best output for merging speed and strength regardless of solution [128].	https://github.com/DocKDE

CovalentDock	Program	It utilizes computational algorithm to Model the phenomenon of chemical bonding and extending it to the server [129].	https://omictools.com/covalentdock-tool
BDOCK	Program	It is an algorithm based on FFT docking system. It comprises of particular scoring functions that are used for complexes of different types [130].	https://bio.tools/bdock
NPDock	Web server	It is used to estimate about complexes of structures of proteins and nucleic acids that are used for implementing a workflow. This workflow comprises of docking, pose scoring, gathering the best scored models and cataloging the best solution [131].	http://genesilico.pl/NPDock
GalaxyPepDock	Web server	Docking that is similarity based is the basis of this program. It is used to find templates from a certain database from structures that arises by experimentation. It also involves in building different models for structures elasticity with the help of energy based optimization [132].	http://galaxy.seoklab.org/pepdock
CombDock	Program	It is a docking algorithm that gives heuristic solutions for the problems related to assemblage of structural units in the form of NPC [133].	http://bioinfo3d.cs.tau.ac.il/CombDock/download/
FastDock	Program	This program is based upon structure. It involves docking of ligands into proteins. This step is followed by the implementation of PMF scoring function that give access to the ligand to bind with protein [134].	https://pypi.org/project/fastdock/
GlamDock	Program	It is used for the comparison of hybrid interaction matching and search space of internal coordinate [135].	http://www.chil2.de/Glamdock.html
PostDOCK	Program	It is designed for distinguishing docking artifacts that were formed by DOCK version 4.0.1 from binding of true ligands and proteins [136].	https://omictools.com/postdock-2-tool
ParaDockS	Program/Web server	It is developed for optimization of many algorithms and for other objectives [137].	http://www.paradocks.at/
AUDocker LE	Program	It is designed to form a software tool as a front end graphical interface that uses C language for experimentation in PCs that are windows based [138].	https://sourceforge.net/projects/audocker/files/AUDOcker%20LE/
MEGADOCK	Web server	Protein-protein docking software package which samples an extremely large number of protein dockings at high speed [139].	https://www.bi.cs.titech.ac.jp/megadock/
MTiOpenScreen	Program	It helpsful for docking of micromolecules and also used in drug discovery to search libraries of small molecules There are two services which are available, namelyMTiAutoDock and MTiOpenScreen [140].	https://bioserv.rpbs.univ-paris-diderot.fr/services/MTiOpenScreen/

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