Review Article

Over View on Molecular Docking: A Powerful Approach for Structure Based Drug Discovery

[1]Dr.N.Astalakshmi,*[2] Gokul T, [3] Gowri Sankar K B, [4] Nandhini M, [5] Hari Hara Sudhan M R., [6] Gowtham S, [7]Dr.S.T.Latha, [8]Dr.M.Surendra Kumar

[1] M.Pharm., Ph.D.,Professor, Dept. of Pharmaceutical Chemistry, Senghundhar College of Pharmacy, Tamilnadu, India.
[2,3,4,5,6] B.Pharm Final Year, Senghundhar College of Pharmacy, Tamilnadu, India.
[7] M.Pharm., Ph.D., Hod, Dept. Of Pharmaceutical Chemistry, Senghundhar College of Pharmacy, Tamilnadu, India.
[8] M.Pharm., Ph.D., Principal, Senghundhar College of Pharmacy, Tamilnadu, India.
***Corresponding author's E-mail:** gokulmurugan855@gmail.com

Received: 18-08-2022; **Revised:** 23-11-2022; **Accepted:** 30-11-2022; **Published on:** 15-12-2022.

ABSTRACT

The process of search of a lead molecule is long and tiresome process. Luckily, computational tools have come to the emancipation and have doubtlessly played a crucial role in rationalization path to drug discovery. In this review article, we present a brief introduction of molecular docking methods, and their development and applications in drug discovery. The study of molecular docking and simulation deals with the intermolecular interaction between the drug targets like proteins, nucleic acid, lipids, and ligands. The focus of molecular docking is to obtain the optimized conformation for both ligand and protein and relative orientation between protein and ligand. The aim of the article is to clear-cut various aspects of molecular docking including basic steps of docking, type of interactions, software tools with their algorithms, scoring functions have been summarized. This review article will help the researchers and clinicians to make use of massive potential of computer aided drug design in designing and identification of drug molecules and thereby helping in the management of many lethal disease.

Keywords: Docking, Structure Based drug design, Ligand, Receptor, Scoring function, Algorithm, Protein-ligand interaction, Software and Hardwares.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2022.v77i02.029

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v77i02.029

INTRODUCTION

The completion of the human genome project has resulted in an increasing number of new therapeutic targets for drug discovery. At the same time, high-throughput protein purification, crystallography and nuclear magnetic resonance spectroscopy techniques have been developed and contributed to many structural details of proteins and protein-ligand complex.[1] Over the last couple of decades, many experimental and high-throughput screening methods have been used in drug designing. Traditional approaches were highly expensive, more time consuming and less efficient to discover novel therapeutic drugs. To overcome drawback of traditional methods, more effective and rational methods have been introduced which rely on virtual screening. Based on the availability of structural information, the method of virtual screening can be classified as structure based and ligand-based drug designing method. The structure-based drug designing approach describes molecular docking whereas ligand-based methods are dealing with quantitative structure activity relationship and pharmacophore modeling. A wide range of therapeutically important molecular targets are known due to availability of structural information of proteins and protein –ligand complexes through techniques of chemical synthesis, purification, X-ray crystallography and Nuclear Magnetic Resonance Spectroscopy (NMR).[2] When the three-dimensional structure of the target, even from experiments or computing, exists, a frequently used technique to design inhibitor molecules is structure-based drug design (SBDD). The most popular method in SBDD is molecular docking.[3] The molecular docking method determines interaction between ligand and target molecule. It predicts binding affinity of ligand to form a stable complex with protein by finding preferred orientation of minimum free binding energy.[4] In addition to pharmacodynamics data (e.g., potency, affinity, efficacy, selectivity), pharmacokinetic properties (ADMET: absorption, distribution, metabolism, excretion and toxicity) have also been studied through the application of these methodologies. The field has progressed hand in hand with advances in bio-molecular spectroscopic methods such as X-ray Crystallography and nuclear magnetic resonance (NMR), which have enabled striking progress in molecular and structural biology. These techniques have allowed the resolution of more than 100,000 Three-dimensional protein structures, providing vital structural information about key macromolecular drug targets. Efforts in storing, organizing and exploring such information have generated a growing demand for robust and sophisticated computational tools. Based on

this perspective, the accurate integration of in silico experimental methods has provided the up-to-date understanding of the intricate aspects of intermolecular recognition.[5] The research-based pharmaceutical industry has increasingly employed modern medicinal chemistry methods, including molecular modeling, as powerful tools for the study of structure-activity relationships (SAR). [6]

STRUCTURE BASED DRUG DISCOVERY

Structure based drug design in most powerful and efficient process in the Entire drug discovery paradigm. Computational resources serve as an efficient technology for accelerating the drug discovery process, which includes various screening procedures, combinatorial chemistry, and calculations of such properties as absorption, distribution, metabolism, excretion and toxicity (ADMET).[7] SBDD is an iterative process (Figure no: 1) and it proceeds through multiple cycles leading an optimized drug candidate to clinical trials. Generally, a drug discovery process consists of four steps:

- Discovery Phase
- Development Phase
- Clinical Trial Phase
- Register Phase

In Discovery Phase – a potential therapeutic target and active ligands are identified.

In Development Phase – the top hits are synthesized and optimized.

In Clinical Trial Phase – determine the 3D structure of the target protein in complex with the promising ligand obtained in the first phase. This phase includes clinical trials of the lead compounds.

In Registry Phase – those compounds that pass the clinical trials proceed to the fourth phase in which the drug is distributed in the market for clinical use.[8]

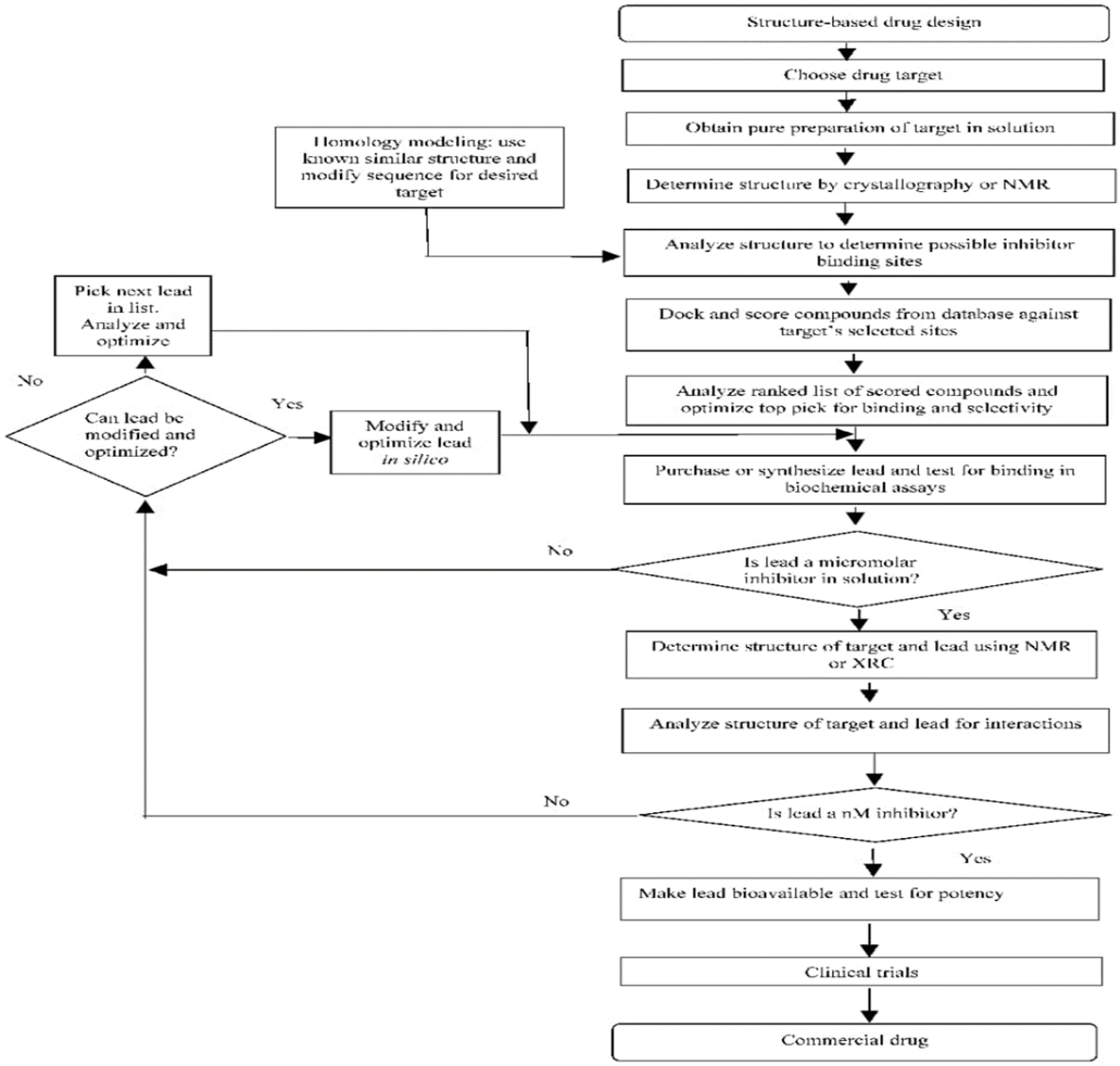

Figure 1: The iterative process of Structure-Based Drug Design.[1]

MOLECULAR DOCKING

Molecular docking is an essential in-silico structure-based method widely used in drug discovery.[9] Docking is a computational method, which facilitates the prediction of preferred binding orientation of one molecule (eg. Ligand) to another (eg. Receptor), when both interact each other in order to form a stable complex (figure 2).[10] The best way involved in explaining molecular docking is "Lock and Key System" the steps involve in this system is

- Finding the better orientation for the key which on the surface the key lock is present.
- On the surface the key lock is present.
- On which the direction to turn the lock is given.

Hence, the protein can be taken as the lock the ligand can be thought as a key.[11] Information gained from the preferred orientation of bound molecules may be employed to predict the energy profiling (such as binding constant) of complexes. This can be done using scoring function of molecular docking. This establishes raw data for the structure-based drug development of new agents with better efficacy and more specificity.[12] The main objective of molecular docking is to attain an optimized docked conformer of both the interacting molecules in furtherance of achieving lessen free energy of the whole system. Final predicted binding free energy (ΔG_{bind}) is modeled in terms of

- Dispersion and Repulsion (Δ_{Gvdw})
- Hydrogen bond (Δ_{hbond})
- Desolvation (ΔG_{desolv})
- Electrostatic (ΔG_{elec})
- Torsional free energy (ΔG_{tor})
- Final total internal energy (ΔG_{total})
- Unbound system's energy (ΔG_{unb})

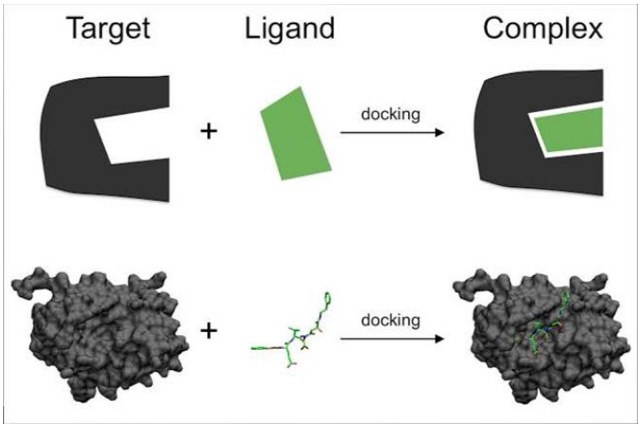

Figure 2: Molecular Docking.[2]

Therefore, detailed understanding of the general principles that govern predicted binding free energy (ΔGbind) provides auxillary information about the nature of various kinds of interaction driving the docking of molecules.[13]

Types of Docking:

The basic methodology of molecular docking can be categorized into three ways;

- Induced fit Docking
- Lock and key Docking
- Ensemble Docking

Induced fit Docking: In these both ligand and receptor are flexible. The ligands binds flexibly at the active site of receptor to maximize bonding forces between them.[2]

Lock and Key Docking: On the basis of lock and key theory, both ligand and receptor are rigid and show tight binding.[14] It defines the basic concept of three-dimensional complementary.[2]

Ensemble Docking: This approach explains flexibility and complexity of conformational states of proteins. Multiple protein structures utilized as an assemble for docking with ligand.[15, 16]

APPROACHES OF MOLECULAR DOCKING

For performing molecular docking, primarily two types of approaches are used.[2]

1. **Stimulation approach:** It is computer stimulations, in which energy profiling is estimated for ligand target docked conformer.
2. **Shape complementarity approach:** It is a technique that calculates surfaces complementarity between ligand and target.[2]

The main properties of both the approaches are described in below (table 1)

Table 1: Molecular Docking Approaches.

Simulation Approach	Shape Complementarity Approach
In this approach, interaction energy as per ligand-receptor pair are calculated.	This approach implies the estimation of complementarity between ligand and receptor surface.
To achieve the best docked conformer of ligand and receptor, ligand is allowed to fit into receptor's groove based upon minimum energy consideration.	To attain the docked conformer via this approach, solvent accessible topographic features of ligand and receptor in terms of matching surface is described. This is followed by the estimation of shape complementarity between interacting molecules for finding out optimal groove/pocket for ligand binding on its target.
Every move of ligand into receptor's pocket for best fitting generates an energy as total energy of system, which is compared to find out best docked conformer with minimum energy.	This method consists of surface representation of receptor and ligand (i.e. surface construction and smoothing), features/ curvature calculation followed by docking and scoring

	contingent to geometric complementary criteria.
This approach is more compatible to accept ligand flexibility in molecular modeling tool, which facilitates real assessment of molecular perception and interaction between ligand and receptor molecules.	Shape complementary approach allows both types of docking. In case of flexible or soft docking conformational changes may take place among bound and free interacting molecules. This is accompanied with the penetration and overlapping of both interacting molecules on each other. However, rigid docking does not let spatial alteration into shape of interacting molecules during molecular modeling.
Performing the molecular modeling through this approach, requires much longer time as large energy profiling needs to be estimated. However, grid-based tools and fast optimization methods have significantly transfigured this downside.	This method encompasses the rapid scanning of large number of ligands for the binding on its target in a few seconds and hence, provides quick and robust outcomes.

ALGORITHM

There are two key parts to any docking program, namely a search of the configurational and conformational degrees of freedom and the scoring or evaluation function. The search algorithm must search the potential energy landscape in enough detail to find the global energy minimum. In rigid docking this means that the search algorithm explores different position for the ligand in the receptor active site using the translational and rotational degrees of freedom. Flexible ligand docking adds exploration of torsional degrees of freedom of the ligand to this process.[17]

Fast Shape Matching (SM):

- Shape matching algorithms are approaches that take into account the geometrical overlap between two molecules.
- This approach may identify the possible binding sites of a protein by a macro-molecular surface search.
- SM specific algorithms establish possible conformations of predicted binding sites.[18]
- SM algorithm has been employed in several docking programs such as ZDOCK[19], SYDOC[20], EUDOC[21], DOCK[22], MSDOCK.[23]

Incremental Construction (IC):

This method split ligand into fragments that are docked separately in the receptor site. After the fragments are docked the parts are fused together. This fragmentation allows the algorithm to consider ligand flexibility. Rigid fragments that are docked initially work like "anchors" that are united secondarily by flexible parts of ligand which have rotatable bonds. In this way the ligand is gradually "constructed" inside the binding site of receptor.[18] IC algorithm has been employed in several docking programs such as DOCK[22], FLEXX[24], FLOG[25] and SURFLEX.[26]

Monte Carlo (MC) simulations:

- MC simulations were firstly introduced as a minimization procedure in molecular dynamics applications, such as implemented in GROMACS[27] and GROMOS.[28]
- Later it was adapted for flexible docking algorithms as MCDOCK[29] and ICM[30]
- Further, MC simulations have demonstrated to be able to determine accurate and precise relative binding constants for protein systems.[31]
- It is a good method to make analysis of bio-molecular systems in different thermodynamic conditions.[18]

Simulated Annealing (SA):

In SA a bio-molecular system is simulated by a specific kind of dynamic simulation. Every docking conformation is carried into a simulation where temperature is decreased gradually during regular intervals of time in each cycle of simulation. It may give a higher accuracy result when compared with MC, since it considers more detailed the conformational state and flexibility of both protein and ligand in different thermodynamics states during an interval of time.[18] The application of this method has been subject of several studies, such as

- ✓ Conformational-analysis[32]
- ✓ Protein-structure prediction studies[33]
- ✓ Molecular docking search methods[34]

Distance Geometry (DG):

This search method make use of information that can be expressed through intra- and intermolecular distance. These distance can be assembled, which enables the calculation of structure or conformations with them.[35]

Evolutionary Programming (EP):

EP algorithms use computational models of evolutionary natural processes as a tool to resolve problems. Despite having a large number of proposed computational models, all of them have one common concept: the concept of simulating species evolution through the processes of selection, mutation and reproduction, which depend on the "performance" of individuals (or "chromosomes") of the specie inside of an "environment".[18]

Genetic Algorithm (GA):

GAs belong to the class of EP algorithms with the purpose of finding or approximately solutions for search problems and, in molecular docking case, trying to find the exact or closet conformation of the global energy minimum.

In GA programming, crossover, which is a genetic operator that combines (mates) two chromosomes (parents) to

produce a new chromosome (offspring), is applied in order to generate new chromosome that may be better than both of the parents if it takes the best characteristics from each of the parents. This process that swaps large regions of the "parents" is permitted in genetic algorithms. In this process many complex scoring functions are used, taking into account a set of parameters, such as mutation rates, crossover rates and number of evolutionary rounds.[18] GA employed in several docking programs such as GOLD and DOCK.[22]

"Lamarckian" GA (LGA) is also implemented in docking algorithms. The LGA switches between "genotypic spaces" and "phenotypic space". Mutation and crossover occur in genotypic space, while phenotypic space is determined by the energy function to be optimized. Energy minimization (local sampling) is performed after genotypic changes have been made to the population (global sampling) in phenotypic space, which is conceptually similar to MC minimization. The phenotypic changes from the energy minimization are mapped back into the genes (by changing the ligand coordinates in the chromosome).[36] One of the most known molecular docking programs that use LGA is the program AUTODOCK.[37]

Tabu Search (TS):

- Tabu search (TS) is an iterative procedure designed for obtaining solution of optimization problems.
- It was developed and described by Glover and has been used to solve a large variety of hard optimization problems.
- This procedure can be defined as a Meta-Heuristic methodology that can move from a solution to another being able to save in memory the already visited solutions.
- TS algorithm is as extension of local search (LS) methods. Both methodologies share the same kind of search space, which is built from all possible solutions that can be considered (visited).
- For molecular docking algorithms the search space refers to all possible conformations between two molecules.
- TS differs from LS with use of a memory structure (tabu list) that avoids revisiting the already considered solutions and promotes the search for new solutions.[18]

SCORING FUNCTIONS

The Scoring functions play the role as poses selector, used to discriminate putative correct binding modes and binders from non-binders in the pool of poses generated by the sampling engine.[38] The scoring function is one of the most important components in structure-based drug design. Despite considerable success, accurate and rapid prediction of protein-ligand interactions is still a challenge in molecular docking.[39]

Different Type of Scoring Function

Some of the commonly-used scoring function are summarized in figure 3.

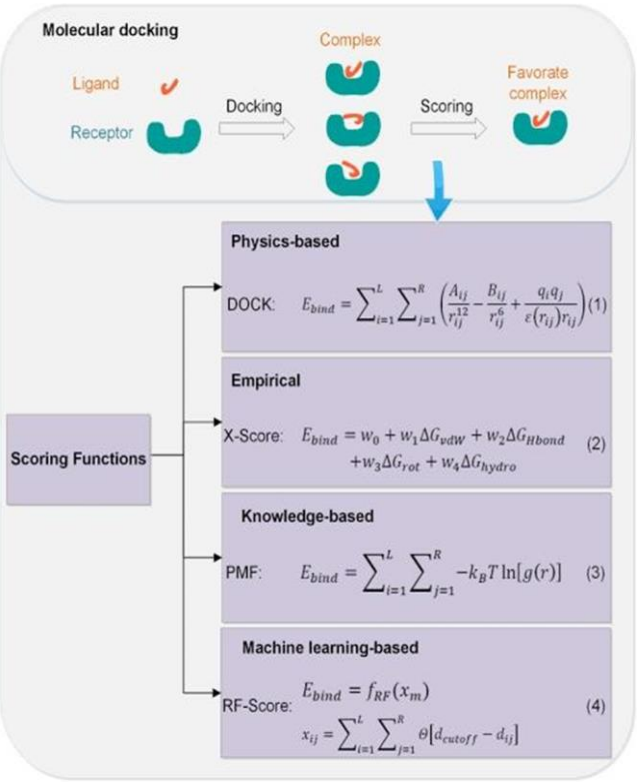

Figure 3: Commonly used Scoring Functions.[3]

PHYSICS –BASED SCORING FUNCTIONS:

Figure 4 describes the physics-based SFs including the scoring functions based on force field[40], solvation models[41,42] and quantum mechanics methods.[43,44]

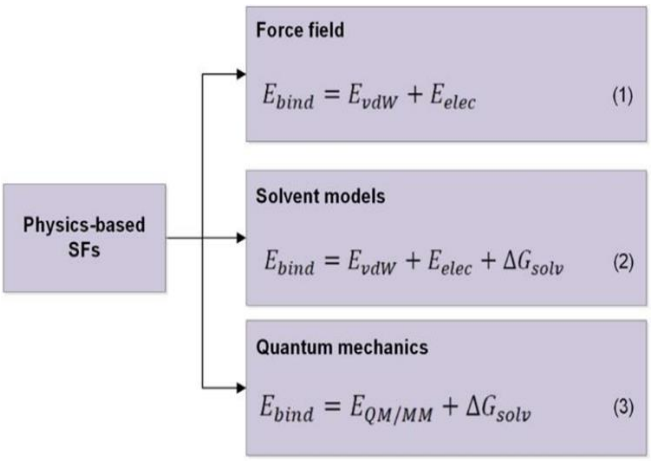

Figure 4: The description for physics-based Scoring Functions.[3]

Force Field Based Scoring Function:

Affinities are estimated by summing the strength of intermolecular van der waals and electrostatic interactions between all atoms of the two molecules in the complex using a force field (Eq.1 in Fig.4). The intra molecular energies (also referred to as strain energy) of the two

binding partners are also frequently included. Molecular mechanics force fields usually quantify the sum of two energies, the receptor-ligand interaction energy and internal ligand energy (such as steric strain induced by binding).[39]

Solvent Methods:

The force field-based SFs is improved by incorporating the torsion entropy of ligands and the solvation/desolvation effect described by explicit and implicit solvent methods (Eq.2 in Fig.4). However, the predictive accuracy for the binding energy is significantly subjected to the functional form of the potential energy and related parameters that are hard to locate because this type of scoring function is based on the force field.[45]

Quantum Mechanics:

Recent studies have developed the SF based on quantum mechanics (QM) to address the challenges of covalent interactions, polarization, and charge transfer in docking.[45] However, the QM-based SF has greater accuracy and computational cost than the force field-based SF. For this reason, a hybrid quantum mechanical/molecular mechanics (QM/MM) approach (Eq.3 in Fig.4)[46] was developed to compromise the computational cost and predictive accuracy.[43,44]

EMPIRICAL SCORING FUNCTIONS

These functions are the sum of various empirical energy terms such as van der Waals, electrostatic, hydrogen bond, desolvation, entropy, hydrophobicity, etc., which are weighted by coefficients optimized to reproduce binding affinity data of a training set by least squares fitting.[47]

An example of empirical SFs: X-score[48] can be written as Eq.2 in Fig 3.

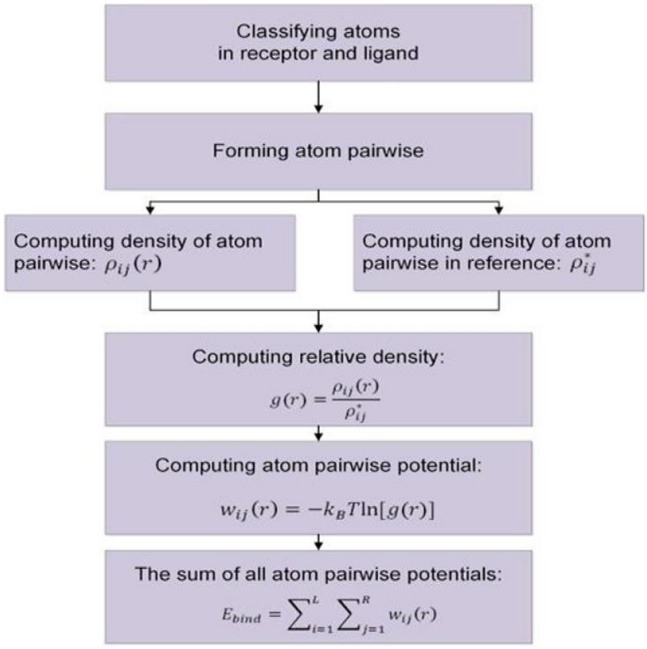

Figure 5: The computational processing of knowledge – based SFs.[3]

Knowledge-Based Scoring Functions:

Knowledge–based SFs derive the desired pairwise potentials from three-dimensional structure of a large set of protein-ligand complexes based on the inverse Boltzmann statistic principle. It is assumed that the frequency of different atom pairs in different distance is related to the interaction of two atoms and converts the frequency into the distance-dependent potential of mean force. The greatest advantages for knowledge–based SFs is compromising the computing cost and predictive accuracy compared with the physics-based and empirical SFs.[45] Figure 5 describes the computational flow for knowledge-based SF.

Machine-Learning-Based Scoring Functions:

Unlike the classical SFs (Fig.3) with assumed mathematical functional form, machine-learning –based SFs employ a variety of machine-learning algorithms, such as support vector machine, random forest, neural network, deep-learning etc, Figure 6 shows the common workflow to train a machine-learning-based SF. Although machine-learning-based SFs have outperformed classical SFs,[49,50,51] they are seldom directly incorporated into docking software but are usually used for rescoring.[52] The reason is machine-learning-based scoring function rely on the training dataset. If the protein and ligand are docked by classical docking software, and then the docked structure is rescored by machine-learning SFs, the accuracy will be improved.[45]

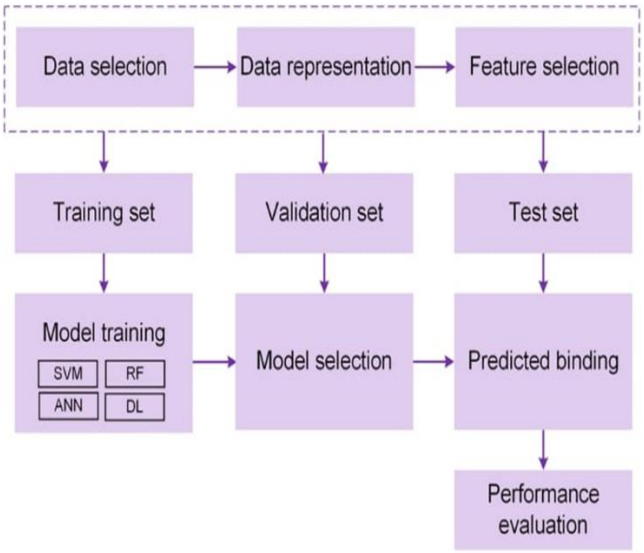

Figure 6: Workflow of training a machine-learning-based SFs.[3]

Software and Hardwares:

The Various Software Tools, Sources of Protein and Ligand Database Used in the Molecular Docking are shown in the following Table 2.

Table 2: Software Tools Used in the Molecular Docking

S.No	Software Tools	Novel features	Reference
1.	Glide (Grid-based Ligand Docking with Energetics)	Algorithm-Monte Carlo Scoring Term-Glide Score Advantages-Lead discovery and lead optimization Organization – Schrodinger Year of published -2004 Docking Speed – Medium Accuracy of Docking – 90 % Availability – Commercial Website - https://www.schrodinger.com/glide	53
2.	Autodock	Algorithm- Lamarkian genetic algorithm Scoring Term- Emperical free energy function Advantages-Adaptability to user defined input Organization – The Scripps Research Institute Year of Published – 1989 Docking Speed – Medium Accuracy of Docking – 53% Availability – Free (GNC License) Website – http://autodock.scripps.edu/	54
3.	Autodock Vinca	Algorithm – Broyden-Fletcher-Goldfab-Shannom (BFGS) Scoring Term – Semi-Empirical calculation on free energy. Advantages – It employs an iterated local search global optimizer and it is faster than AutoDock 4 Organization – The Scripps Research Institute Year of Published – 1989 Docking Speed – Fast Accuracy of Docking – 80% Availability – Free (Apache License) Website – http://autodock.scripps.edu/	55
4.	GOLD(Genetic optimization for ligand Docking)	Algorithm- Genetic algorithm Scoring Term - Gold score, Chemscore, ASP (Astex Statistical Potential), CHEMPLP (Piecewise Linear Potential), Used defined Advantages - Allows atomic overlapping between protein and ligand. Organization - University of Cambridge Docking Speed – Fast Accuracy of Docking – 90 % Availability – Commercial Website – https://doi.org/10.1002/prot.10465	56
5.	Surflex	Algorithm – Surflex-Dock search algorithm Scoring Term – Bohm's scoring function Advantages – High accuracy level by extending force-fields Organization – BioPharmics LLC Years of Published – 1998 Docking Speed – Fast Accuracy of Docking – 58% Availability – Commercial Website – https://pubmed.ncbi.nlm.nih.gov/12570372/	57
6.	LeDOCK	Algorithm – Stimulated annealing (SA), Genetic Algorithm (GA) Scoring Term – Molecular Force Field Advantages – Program for fast ana accurate flexible docking of small molecules into a protein Organization – Lephar Year of Published – 2016 Docking Speed – Fat Accuracy of Docking – 77% Availability – Free (for academic use) Website – http://www.lephar.com/download.htm	58

7.	Flex X	Algorithm – Incremental reconstruction Scoring Term – Modified Bohm scoring function Advantages – Provides large number of conformations Organization – BioSolveIT Docking Speed – Fast Accuracy of Docking – 75% Availability – Commercial Website – https://www.biosolveit.de/FlexX/	59
8.	FlexAID(Flexible Artificial Intelligence Docking)	Algorithm – FlexAID (A Small - Molecule Docking Algorithm that accounts for Target Side - Chain Flexibility) Scoring Term – Soft Scoring Function (based on Surface Complementarity) Advantages – Support full ligand flexibility as well side-chain flexibility of the target Organization – University of Sherbrooke Year of Published – 2015 Availability – Free (Apache License) Website – http://biophys.umontreal.ca/nrg/resources.html	60
9.	ICM(Internal Coordinate Modelling)	Algorithm – Monte Carlo minimization Scoring Term -Virtual library screening scoring function Advantages – Allows side chain flexibility to find parallel arrangement of two rigid helixes Organization – MolSoft Years of Published – 1994 Docking Speed – Fast Availability – Commercial Website – http://www.molsoft.com/docking.html	61
10.	MVD (Molegro Virtual Docker)	Algorithm – Evolutionary Algorithm Scoring Term – MolDock score Advantages – High accuracy level of predicting binding mode Organization – Molexus Accuracy of Docking – 87% Availability – Commercial Website – http://molexus.io/molegro-virtual-docker/	62
11.	Fred(Fast Rigid Exhaustive Docking)	Algorithm – Exhaustive search algorithm Scoring Term – Gaussian scoring function Advantages – Nanostochastic approach to examine all possible poses within protein active site Organization – OMEGA (Open Eye Scientific Software) Availability – Commercial Website – https://www.eyesopen.com/oedocking-tk	63
12.	LigandFit	Algorithm – Monte Carlo Method Scoring Term – LigScore, Piecewise Linear Potential (PLP), Potential of Mean Force (PMF) Advantages – Generates good hit rates based on LigScore Docking Speed - Fast Accuracy of Docking - 46 Availability – Commercial Website- https://www.phenix-online.org/documentation/reference/ligandfit.html	64
13.	FITTED(Flexibility Induced Through Targeted Evolutionary Description)	Algorithm – Genetic algorithm Scoring Term – Potential of Mean Force (PMF), Drug Score Advantages – Analyzes effect of water molecules on protein ligand complexes Organization – SAMSON Availability – Commercial Website – http://mgltools.scripps.edu/documentation/links/fitted	65
14.	GlamDock	Algorithm – Monte Carlo method Scoring Term – ChillScore Advantages – Provides provision of two-dimensional analysis to screen ligands by targeting protein. Organization – Chil^2 Docking Speed - Fast Accuracy of Docking – 62% Availability – Free	66

		Website – http://www.chil2.de/Glamdock.html	
15.	vLifeDock	Algorithm – Genetic algorithm Scoring Term – PLP score, XCscore Advantages – Facilitates batch docking Organization – vLife Docking Speed - Fast Availability – Commercial Website – https://www.vlifesciences.com/products/Functional_products/VLifeDock.php	67
16.	iGEMDOCK	Algorithm – Genetic algorithm Scoring Term – Empirical scoring function Advantages – Highly significant in post-screening analysis Organization – BioXGEM Year of Published –2006 Accuracy of Docking – 78 % Availability – Free (for non-commercial researches) Website – http://gemdock.life.nctu.edu.tw/dock/igemdock.php	68
17.	GEMDOCK (Genetic Evolutionary Method for Molecular Docking)	Algorithm – Rotamer-Based Mutation Scoring Term – AMBER-based energy function Advantages – the accuracy of molecular docking and the screening utility were better than other docking methods Organization – Developed by Jinn-Moon Yang, a professor of the institute of bioinformatics, National Chiao Tung University Accuracy of Docking – 85% Availability – Free (For Non-commercial Researches) Website – http://gemdock.life.nctu.edu.tw/dock/igemdock.php	69
18.	SCIGRESS	Algorithm – Genetic Algorithm Scoring Term – Semi-empirical quantum methods Advantages – It is software suite for molecular modelling, computational chemistry, drug design and material science. Organization – Developed And Distributed by Fujitsu Year of Published – Stable Realease - 2020 Availability – Commercial Website – https://doi.org/10.11546/cicsj.26.122	70
19.	HomDock	Algorithm – Monte Carlo method Scoring Term – ChillScore Advantages – shows significantly higher accuracy than normal docking in cross docking benchmarks Organization – Chil^2 Docking Speed – Fast Availability – Free (open for general research) Website – http://www.chil2.de/HomDock.html	71
20.	Fleksy	Algorithm – CORINA Scoring Term – PLP Advantages – Consideration of protein flexibility during docking predictions with high accuracy. Organization – Provided by the centre for Molecular and Biomolecular Informatics, Radboud University Nijmegen Availability – Free (for academic users) Website – https://doi.org/10.1021/jm070593p	72
21.	CABS-dock	Algorithm – Monte Carlo Algorithm Scoring Term – knowledge-based and MM-GBSA scoring function Advantages – Stimulate significant backbone flexibility of the entire protein-peptide system in a reasonable computational time Organization – University of Warsaw Year of Published – 2015 Availability - Free (for academic users and non-profit users) Website – http://biocomp.chem.uw.edu.pl/CABSdock/tutorial	73
22.	Dock	Algorithm – Genetic Matching Algorithm Scoring Term – AMBER Score (Assisted Model Building with Energy Refinement)	74

		Advantages – Predict the binding modes of small molecules Organization –University of California-San Francisco Year of Published –1988 Availability – Free Website – https://dock.compbio.ucsf.edu/	
23.	EADock	Algorithm – Evolutionary Optimization Scoring Term – CHARMM (Chemistry at Harvard Macromolecular Mechanics) Advantages – Accurately predict binding modes Organization – Swiss Institute of Bioinformatics Year of Published – 2007 Docking Speed – Fast Availability – Free (for academic use) Website – http://www.swissdock.ch/	75
24.	GalaxyPepDock	Algorithm – GalaxyPepDock Algorithm Scoring Term – Galaxy Refine flexible refinement method Advantages – Protein-peptide docking based on interaction similarity Organization – Computational Biology Lab, Department of chemistry, Seoul National University Year of Published – 2018 Accuracy of Docking – 75.4% Availability – Free Website - http://galaxy.seoklab.org/pepdock	76
25.	GalaxyDock	Algorithm – CSA (Conformational Space Annealing) Scoring Term – AutoDock-Based Energy Function Advantages – Protein-ligand docking program that allows flexibility of pre-selected side chains of the ligand Organization – Computational Biology Lab, Department of chemistry, Seoul National University Accuracy of Docking – 10%-60% Availability – Free Website – http://galaxy.seoklab.org/softwares/galaxydock.html	77
26.	HADDOCK (High Ambiguity Driven Biomolecular Docking)	Algorithm – Hybrid Scoring Term – Score is a Weighted um of a variety of energy terms including van der Waals intermolecular energy, electrostatic intermolecular energy, radius of gyration energy, desolvation and restraint violation energies Advantages – Docks protein-protein based on biochemical or biophysical information Organization – Centre Bijvoet Center for Biomolecular Research Year of Published – 2003 Accuracy of Docking – 83% Availability – Free Website – https://wenmr.science.uu.nl/haddock2.4/	78
27.	HEX	Algorithm – Spherical polar Approach Scoring Term – CAPRI (Critical Assessment of PRedicted Interactions) Advantages – An interactive protein docking and molecular superposition program Organization – Written by Dave Ritchie Year of Published –2008 Docking Speed – Fast Availability – Free (for academic and governmental users) Website – http://hex.loria.fr/	79
28.	OEDOCKING	Algorithm – Shape Matching Scoring Term – Chemgauss4, Chemgauss3, Chemscore, PLP, Shapegauss Advantages – can utilize multiple crystallographic protein structures Organization – OpenEye Scientific (CADENCE MOLECULAR SCIENCES) Docking Speed – Fast Availability – Free (for academic use) Website – https://www.eyesopen.com/oedocking	80
29.	LightDock	Algorithm – Glowworm Swar Optimization (GSO) Algorithm Scoring Term – Gradient-Free Minimization	81

		Advantages – Optimizes the generated docking poses towards those energetically more favourable at every stimulation step Organization – Barcelona Supercomputing Center Year of Published – 2018 Availability – Free Website – https://github.com/brianjimenez/lightdock	
30.	MedusaDock	Algorithm – on-the-fly algorithm Scoring Term – Force-Field-Based Scoring Function Advantages – Rapid flexible docking using a stochastic rotamer library of ligands Organization – Dokholyan Laboratory Year of Published – 2019 Availability – Free Website – https://dokhlab.med.psu.edu/medusadock/#/NewTask	82
31.	MOE (Molecular Operating Environment)	Algorithm – Stochastic Search Scoring Term – Hybrid Advantages – An integrated computer-aided molecular design platform Organization – Chemical Computing Group Year of Published – 2008 Availability – Commercial Website – https://www.chemcomp.com/Products.htm	83
32.	ParaDockS (parallel docking suite)	Algorithm – Particle – Swarm Optimizer (PSO) Scoring Term – Empirical energy function p-Score Advantages – Molecular docking with population-based metaheuristics Organization – Martin Luther University of Halle-Wittenberg and Partner Institute for Computational Biology Year of Published – 2010 Accuracy of Docking – 73 % Availability – Commercial Website – https://doi.org/10.1021/ci900467x	84
33.	ParDock	Algorithm – Monte Carlo Algorithm Scoring Term – All atom energy based scoring function Advantages – Rigid protein ligand docking, implemented in a fully automated, parallel processing mode which Predicts the binding mode of the ligand in receptor target site Organization – Indian Institute of Technology Year of Published – 2007 Availability – Free Website – http://www.scfbio-iitd.res.in/pardock/	85
34.	PSI-DOCK (Pose-Sensitive Inclined)	Algorithm – Genetic Algorithm Scoring Term – Shape-Complementary scoring function Advantages – used for flexible ligand docking Organization – Peking University Year of Published – 2006 Accuracy of Docking – 77% Availability – Free (for academic) Website – https://doi.org/10.1002/prot.20790	86
35.	QXP	Algorithm – Monte Carlo Algorithm Scoring Term – Energy Minimization in Cartesian space Advantages – Reliable, Easy to use and Sufficiently Rapid for routine application in structure-based drug design Organization – Novartis Pharmaceuticals Corporation Year of Published – 1997 Docking Speed – Fast Availability – Commercial Website – https://doi.org/10.1023/A:1007907728892	87
36.	rDock	Algorithm – Genetic Algorithm (GA1,GA2,GA3), Monte Carlo (MC) and Simplex minimization (MIN) Scoring Term – Molecular Force Field.(S^{total}) is a weighted sum of intermolecular (S^{inter}), ligand intramolecular(S^{intra}), site intramolecular(S^{site}) and external restraint terms($S^{restraint}$) Advantages – A docking tool for small molecules against proteins and nucleic acids	88

		Organization	Venalis R&D	University of York	University of Barcelona	
		Year of Published	1988	2006	2012	
		Availability	Commercial	Academic	Open source	
		Docking Speed – Medium Accuracy of Docking – 99% (generation of correct pose) Website – http://rdock.sourceforge.net/				
37.	SEED (Solvation Energy for Exhaustive Docking)	Algorithm – Monte Carlo Stimulated Annealing Scoring Term – Force-field based evaluation Advantages – Automated docking of fragments with evaluation of free energy of binding including electrostatic solvation effects in the continuum dielectric approximation Organization – University of Zurich Year of Published – 1999 Availability – Open Source Website – http://www.biochem-caflisch.uzh.ch/download				89
38.	SwissDock	Algorithm – Evolutionary Optimization Scoring Term – CHARMM (Chemistry at Harvard Macromolecular Mechanics) Advantages – Predict interaction between a protein ana a small molecule ligand Organization – Swiss Institute of Bioinformatics Year of Published – 2011 Availability – Free (for academic use) Website – http://www.swissdock.ch/docking				90
39.	VirtualFlow	Algorithm – Artificial Intelligence Driven Docking Algorithm Advantages – VFLP (VirtualFlow for ligand preparation) is dedicated for the curation of libearies containing large numbers of small molecules. VFVS (VirtualFlow for Virtual Screening) is dedicated to carrying out the actual virtual screening procedures Organization – Harvard University Year of Published – 2020 Availability – Open Source Website – http://www.vls3d.com/10-links/bioinformatics/10-virtual-screening-docking				91
40.	ZDOCK	Algorithm – Geometric complementarity and molecular dynamics Scoring Term – Molecular force field Advantages – Propose a new scoring function which combines pairwise shape complementarity (PSC) with desolvation and electrostatic and develop the ZDOCK server Organization – University of Massachusetts Medical School Availability – Commercial Website – https://zdock.umassmed.edu/software/				92
41.	Molegro Virtual Docker	Algorithm – Differential Evoluation (Alternatively Simplex Evolution and Iterated Simplex) Scoring Term – Semiempirical Scoring Function Advantages – Handles all aspects of the docking process from preparation of the molecules to determination of the potential binding sites of the target protein and prediction of the binding modes of the ligands Organization – Molexus Year of Published – 87% Availability – Commercial Website – http://molexus.io/molegro-virtual-docker/				93
42.	Smina	Algorithm – Monte Carlo stochastic sampling + local optimisation Scoring Term – Empirical (customisable) Scoring Function Advantages – After docking, results will be analyzed for the deviation from the crystal structure Organization – Sourceforge Availability – Free Website – https://pypi.org/project/docking-py/				94

43.	PLANTS (Protein-ligand ANT system)	Algorithm – Ant Colony Optimisation Scoring Term – Empirical Scoring Function Advantages – Generate Lower-energy conformations with a higher probability. Organization – Konstanz University Accuracy of Docking – 80% Availability – Commercial Website – https://doi.org/10.1021/ci800298z	95
44.	Dock6	Algorithm – Anchor-and-grow incremental construction Scoring Term – Physical-based (several other options) Advantages – Additional Scoring Options During Minimization Organization – University of California San Francisco Accuracy of Docking – 56% Availability – Free (for academic use) Website – https://dock.compbio.ucsf.edu/DOCK_6/index.htm	96
45.	GAsDock	Algorithm – Entropy-based multi-population genetic algorithm Scoring Term – Physics-based Advantages – A rapid,accurate,and flexible docking program Organization – DNV Docking Speed – Fast Availability – Free (for academic use)	97
46.	DockThor	Algorithm – Steady-State Genetic Algorithm (with Dynamic Modified Restricted Tournament Selection method) Scoring Term – Physical-based + Empirical Advantages – Performs pose prediction on redocking studies Organization – GMMSB (Grupo de Modelagem Molecular de Sistemas Biologicos) Accuracy of Docking – 60% Availability – Free Website – https://dockthor.lncc.br/v2/	98
47.	DAIM-SEED-FFLD (Decomposition and identification of molecules)-(Solvation Energy for Exhaustive Docking)-(Fragment-based Flexible Ligand Docking)	About – Free open-source fragment-based docking suite. The docking is realized in three steps. DAIM decomposes the molecules into molecular fragments that are docked using SEED (program for docking libraries of fragments with solvation energy evaluation). Finally, the molecules are reconstructed 'In situ' from the docked fragments using the FFLD program. Organization – Computational Structural Biology of ETH, Zurich, Switzerland Availability – Free Website – http://www.biochem-caflisch.uzh.ch/movies/0003	99
48.	FlipDock	Algorithm – Genetic Algorithm, Coarse-grained molecular dynamics Scoring Term – Empirical, Knowledge based, Force Field based Advantages – It Predicts the binding mode between a flexible ligand and a flexible protein Organization – Developed by the Department of Molecular Biology at the Scripps Research Institute, La Jolla Published Year – 2005 Docking Speed – Fast Accuracy of Docking – 72% Availability – Free (for academic use) Website – http://flipdock.scripps.edu/	100
49.	HYBRID	Algorithm – Exhaustive search algorithm Scoring Term – Chemical Gaussian Overlay (CGO) Advantages – Significantly improves the performance in both binding affinity and binding mode predictions, compared to the sole mdock program Organization – OpenEye scientific software Docking Speed – Very Fast Ligand guided docking Availability – Commercial Website – https://doi.org/10.1021/acs.jcim.5b00275	101
50.	POSIT	About – Ligand-guided pose prediction. POSIT uses bound ligand information to improve pose prediction. Using a combination of several approaches, including structure generation, shape alignment and flexible fitting, it produces a predicted pose whose accuracy depends on similarity measures to known ligand poses. As such, it produces a reliability estimate for each prediction pose. In addition, it provided with a selection of	102

		receptors from a crystallographic series, POSIT will automatically determine which receptor is best suited for pose prediction. Organization – OpenEye scientific software Docking Speed – Fast knowledge guided pose prediction Availability – Free Website – https://docs.eyesopen.com/applications/oedocking/posit/posit_overview.html	
51.	Rosetta Ligand (ROSIE)	Algorithm – Monte Carlo Minimization Scoring Term – Electrostatics model, an explicit orientation-dependent hydrogen bonding potential, an implicit solvation model and van der waals interactions Advantages – Provides the 3D structure prediction and high-resolution design of natural and non-natural polymers Organization – Developed by Sergey Lyskov at GrayLab at JHU. Rosetta Commons Member Institutions. Published Year – 2006 Accuracy of Docking – 64% Availability – Free (for academic and non-profit users) Website – https://rosie.rosettacommons.org/	103
52.	CDocker	Algorithm – Molecular dynamics (MD) Stimulated Annealing-based Algorithm Scoring Term – CHARMM (Chemistry at Harvard Macromolecular Mechanics) Advantages – Produce highly accurate docking results Organization – CD ComputaBio Accuracy of Docking – 66-76% Availability – Free Website – https://doi.org/10.1002/jcc.10306	104
53.	YASARA Structure	About – Adds support for small-molecule docking to YASARA View/Model/Dynamics using AutoDock and Fleksy Advantages – a molecular-graphics-modeling and simulation program Organization – YASARA Availability – Free Website – http://www.yasara.org/products.htm	105
54.	FINDSITE-LHM (Ligand Homology Modeling)	Algorithm – Evolutionary related templates Scoring Term – Similarity based ligand binding pose prediction Advantages – Homology modeling approach to flexible ligand docking Organization – Skolnick Research Group Availability – Free (for academic and non-profit users) Website - http://www.mybiosoftware.com/findsite-lhm-1-0-homology-modeling-approach-flexible-ligand-docking.html	106
55.	BetaDock	Algorithm – Genetic Algorithm Advantages – A molecular docking simulation software based on the theory of Beta-complex Organization – Voronoi Diagram Research Center Published Year - 2011 Availability – Free Website – http://voronoi.hanyang.ac.kr/software.htm	107
56.	ADAM	Algorithm – Systematic Search Advantages – Predict the stable binding mode of flexible ligand molecule to target molecule Organization – IMMD Inc Docking Speed – Fast Availability – Commercial Website – http://adam.vbi.vt.edu	108
57.	DockVision	Algorithm – Monte Carlo Algorithm, Genetic Algorithm, Database Screening docking Algorithm Advantages – Increases capability to generate laudable results Organization – DockVision Published Year – 1999 Availability – Free Website – http://dockvision.sness.net/overview/overview.html	109

58.	FLOG	Algorithm – Systemic Search Scoring Term – van der waals, electrostatics, hydrogen bonding and hydrophobic interactions Advantages – Rigid body docking program using database of pre-generated conformations Organization – Developed by the Mark Research Laboratories Published Year – 1994 Availability – Commercial Website – https://doi.org/10.1007/BF00119865	110
59.	GriDock	About – GriDock Designed to perform the molecular docking of a large number ligands stored in a single database (SDF or Zip format) in a lowest possible time. It takes full advantage of all local and remote CPUs through the MPICH2 technology, balancing the computational load between processors/grid nodes. Organization – Drug design Laboratory,University of Milano Availability – Free Website – https://www.ddl.unimi.it/cms/index.php?Software_projects:GriDock	111
60.	BDT	About – Graphic front-end application which controls the conditions of AutoGrid and AutoDock runs, Advantages – Using receptor flexibility during docking using a large library of ligands onto one or more receptors without defining one a priori ligand-binding site on them Organization – Maintained by the Universitat Rovira I Virgili Availability -Free Website – http://www.quimica.urv.cat/~pujadas/BDT/	112
61.	DockoMatic	About – GUI application that is intended to ease and automate the creation and management of AutoDock jobs for high-throughput screening of ligand/receptor interactions Organization – SOURCEFORGE Availability – Free Website – https://doi.org/10.1186/1756-0500-3-289	113
62.	Hammerhead	Algorithm – Systemic Search Scoring Term – Empirical Scoring Function Advantages – Fast, fully automated docking of flexible ligands to protein binding sites Availability – Commercial	114
63.	EUDOC	About – Program for the identification of drug interaction sites in macromolecules and drug leads from chemical databases Availability – Commercial Website – https://doi.org/10.1002/jcc.1129	115
64.	hint! (hydropathic interactions)	About – Estimate LogP for modeled molecules or data files; numerically and graphically evaluates binding of drugs or inhibitors into protein structures and scores DOCK orientations, constructs hydropathic (LOCK and KEY) complementarity maps that can be used to predict a substrate from a known receptor or protein structure or to propose the hydropathic structure from known agonists or antagonists and evaluates/predicts the effects of site-directed mutagenesis on protein structure and stability. Advantages – An empirical molecular modelling system with new methods for de novo drug design and protein or nucleic acid structural analysis Availability – Commercial Website – https://doi.org/10.1007/BF00135313	116
65.	MS-Dock	About – Free multiple-conformation generator and rigid docking protocol for multi-step virtual ligand screening Advantages – All multiple conformations are rigidly docked Availability – Commercial Website – https://doi.org/10.1186/1471-2105-9-184	23
66.	eHiTS	Algorithm – Systemic search Scoring Term – Empirical And Statistical approaches Organization – Developed by SimBioSys Inc.Canada Advantages – Easy to use, fully automated program including automatic pocket detection on the protein surface, automatic assignment of partial charges to atoms and more Availability – Free (for academic use)	117
67.	Lead Finder	About – Program for molecular docking, virtual screening and quantitative evaluation of ligand binding and biological activity. Distributed by Moltech. For Windows and linux.	118

Table 3: Sources of crystallographic structure of proteins

S. No	Source	Website Link
1.	wwPDB: worldwide Protein Data Bank	https://www.wwpdb.org/
	wwPDB has four members: 1. Research Collaboratory for Structural Bioinformatics Protein Database (RSCB)	www.rcsb.org
	2. Protein Data Bank in Europe (PDBe)	http://www.pdbe.org
	3. Protein Data Bank Japan (PDBj)	http://www.pdbj.org
	4. Biological Magnetic Resonance Data Bank (BMRB)	http://www.bmrb.wisc.edu
2.	BINDINGDB	https://www.bindingdb.org/
3.	BindingMOAD-Mother of All Databases	https://bindingmoad.org/
4.	PDBbind	http://www.pdbbind-cn.org/
5.	ModBase: Database of Comparative Protein Structure Models	https://modbase.compbio.ucsf.edu/
6.	PDB-REDO databank	https://pdb-redo.eu/
7.	EBI: The European Bioinformatics Institute	https://www.ebi.ac.uk/services/structures

Table 4: List of Available Ligand Databases

S. No	Database	Website Link
1.	Zinc	https://zinc.docking.org/
2.	Enamine	https://enamine.net/11-databases
3.	NCI Open Database	https://cactus.nci.nih.gov/download/nci/
4.	ChEMBL	https://www.ebi.ac.uk/chembl/
5.	DrugBank	https://www.drugbank.com/
6.	ASINEX	http://www.asinex.com/
7.	Cambridge Structural Database (CSD)	https://www.ccdc.cam.ac.uk/solutions/csd-system/components/csd/
8.	PubChem	https://pubchem.ncbi.nlm.nih.gov/
9.	SPECS Database	https://www.specs.net/
10.	AYBRIDGE Database	https://maybridge.com/
11.	Life chemicals Database	https://lifechemicals.com/
12.	HEMBRIDGE Database	https://www.chembridge.com/

SUMMARY AND CONCLUSION

Molecular docking has been established as a pivotal technique among the computational tools for structure-based drug discovery. Successful molecular docking protocols require a solid knowledge of the fundamentals of the applied methods. Here we addressed key aspects of the methodology and discussed recent trends in the literature for advancing and employing the technique for successful drug design. The principles and methods discussed in this review highlight the strategies by which molecular docking and SBDD approaches have been applied in the identification of novel bioactive compounds. The scoring function is one of the most important components in structure-based drug design. We review the scoring functions used for protein-ligand interactions of molecular docking by classifying them into physics-based, empirical, knowledge-based, machine-learning-based scoring function. Understanding these principles is essential in the production of meaningful results. The docking methodologies were developing day after day gets more better result for drug designing. A number of protein-ligand docking programs currently available is high and has been steadily increasing over the last decades. Despite considerable success, accurate and rapid prediction of protein-ligand interactions is still a challenge in molecular docking, so that many companies producing newer software to overcome the challenges observed in old one. Molecular docking could be more powerful approach to increase innovation in the pharmaceutical industry and to discovery novel threapies for unmet medical needs.

REFERENCES

1. Xuan-Yu Meng, Hong-Xing Zhang, Mihaly Mezei, Meng Cui. Molecular Docking: A powerful approach for structure-based drug discovery. Current Computer-Aided Drug Design, 2011;7(2):24-31.
2. Anushree Tripathi, Krishna Misra. Molecular Docking: A Structure-Based Drug Designing Approach,JSM Chemistry.2017;18(1):50-56.
3. Jerome de Ruyck, Guillaume Brysbaert, Ralf Blossey, Marc F Lensink. Molecular docking as a popular tool in drug Design, an in silico travel. Advances and Applications in Bioinformatics and Chemistry.2016;08(2):33-39.
4. Ferreira LG, Dos Santos RN, Oliva G, Andricopulo AD. Molecular docking and structure-based drug design strategies. Molecules. 2015; 2: 13384-13421.
5. Leonardo G. Ferreira, Ricardo N. dos Santos, Glaucius Oliva and Adriano D. Andricopulo. Molecular Docking and Structure-Based Drug Design Strategies.Molecules, 22 July 2015.
6. Hughes, J.P. Rees, S. Kalindjian, S.B.Philpott, K.L. Principles of early drug discovery. Br. J.Pharmacol. 2011;162:1239–1249.
7. Batool M. Choi, S. Identification of drug able genome in staphylococcus aureus multidrug resistant strain. In Proceedings of the 2017 IEEE Life Sciences Conference (LSC), Sydney, NSW, Australia,2017; pp. 270–273.
8. Maria Batool, Bilal Ahmad, Sangdun Choi. A Structure-Based Drug Discovery Paradigm. International Journal Sciences. 6 June 2019.
9. Luca Pinzi, Giulio Rastelli. Molecular docking: shifting paradigms in drug discovery. International journal of molecular sciences.2019;20(18):4331.
10. B Mukesh, K Rakesh. Molecular docking: a review. IJRAP. 2011; 2:1746-1751.
11. Bhawna Poudyal. Molecular Docking Technique. National Journal of Pharmaceutical Sciences.2020.

12. IA Guedes, CS de Magalhães, LE Dardenne. Receptor–ligand molecular Docking, Biophysical Reviews. 2014; 6: 75-87.
13. Shweta Agarwal, Ranjana Mehrotra. An overview of Molecular Docking. JSM Chemistry. 2016;4(2): 1024.
14. Agarwal S, Mehrotra R. An overview of Molecular Docking. JSM Chem.2016; 4: 1024.
15. Lorber DM, Shoichet BK. Flexible ligand docking using conformational Ensembles. Protein Sci. 1998; 7: 938-950.
16. Huang SY, Zou X. Ensemble docking of multiple protein structures: Considering protein structural variations in molecular docking. Proteins. 2007; 66: 399-421.
17. Natasja Brooijmans, Irwin D. Kuntz. Molecular Recognition And Docking Algorithms.Annu. Rev. Biophys. Biomol. Struct. 2003;32:335–73.Doi: 10.1146/annurev.biophys.32.110601.142532.
18. Raquel Dias Walter Filgueira de Azevedo Jr.Molecular Docking Algorithms.Current Drug Targets, 2008;9:1040-1047.
19. Chen, R. Li, L. and Weng, Z.Proteins, IJRPS. 2003;52(1):80-87.
20. Pang, Y.P. and Kozikowski, A.P.J. Comput. Aided Mol.Des.,1994;8(6):683-693.
21. Perola, E.; Xu, K.; Kollmeyer, T.M.; Kaufmann, S.H.; Prendergast, F.G. and Pang, Y.P. J. Med. Chem.,2000;43(3):401-408.
22. Ewing, T.J.; Makino, S.; Skillman, A.G. and Kuntz, I.D.J.Comput. Aided Mol. Des., 2001;15(5):411-428.
23. Nicolas Sauton, David Lagorce, Bruno O Villoutreix, Maria A Miteva.MS-DOCK: accurate multiple conformation generator and rigid docking protocol for multi-step virtual ligand screening.BMC bioinformatics, 2008;9(1):1-12.
24. Rarey, M.; Kramer, B.; Lengauer, T. and Klebe, G. J. Mol.Biol.,1996;261(3):470-489.
25. Miller, M.D.; Kearsley, S.K.; Underwood, D.J. and Sheridan, R.P. J. Comput. Aided Mol. Des.,1994;8:153-174.
26. Jain, A.N.J. Molecular docking, Med. Chem.,2003;46(4):499-511.
27. Spoel, D.V.D. Lindahl, E.; Hess, B.; Groenholf, G.; Mark, A.E.and Berendsen, H.J.C.J. Comput. Chem.,2005;26(16):1701-1718.
28. Christen,M.; Hunenberger,P.H.; Bakowies,D.; Baron,R.; Burgi,R.; Geerke, D.P.; Heinz, T.N.; Kastenholz, M.A.; Krautler, V.;Oostenbrink, C.; Peter, C.; Trzesniak, D. and van Gunsteren, W.F.J. Comput. Chem.2005;26(16):1719-1751.
29. Liu, M. and Wang, S.J. Comput. Aided Mol. Des.,1999;13(5):435-451.
30. Totrov, R. and Abagyan, R. Proteins,1997;1:215-220.
31. Essex, J.W.; Severance, D.L.; TiradoRives, J. and Jorgensen, W.L.J. Phys. Chem., 1997;101(46):9663-9669.
32. Salvino, J.M.; Seoane, P.R. and Dolle, R.E.J. Comput.Chem.,1993;14:438-444.
33. Laughton, C.A. Molecular docking, Protein Eng.,1994;7:235-241.
34. Goodsell, D.S. and Olson, A.J. Proteins-Struct. Funct. Ge-net.,1990;8(3):195-202.
35. Moré, J.J. and Wu, Z. J. Global Optimization, 1999;15(3):219-234.
36. Brooijmans, N. and Kuntz, I.D. Annu. Rev. Biophys. Biomol. Struct., 2003;32:335-373.
37. Morris, G.M.; Goodsell, D.S.; Halliday, R.S.; Huey, R.; Hart, W.E.; Belew, R.K. and Olson, A.J. J. Comput. Chem.1998;19(14):1639-1662.
38. Veronica Salmaso, Stefano Moro.Bridging Molecular Docking to Molecular Dynamics in Exploring Ligand-Protein Recognition Process: An Overview. Frontiers. August 2018.https://doi.org/10.3389/fphar.2018.00923.
39. Rahul H, Mukti M, Md Maidul I. Molecular Docking an Important Tool for Drug Designing. Mod Appro Drug Des.2018;1(4):18-22. MADD.000518.DOI: 10.31031/MADD.2018.01.000518.
40. Meng EC, Shoichet BK, Kuntz ID. Automated docking with grid-based energy evaluation,1992;vol 13. Wiley, New York.
41. Jorgensen WL, Chandrasekhar J, Madura JD, Impey RW, Klein ML(1983) Comparison of simple potential functions for simulating liquid water. J Chem Phys.1983;79(2):926–935.
42. Pullman B Intermolecular forces. D. Reidel Publishing Company,Dordrecht.1981.
43. Raha K, Peters MB, Wang B, Yu N, Wollacott AM, Westerhoff LM, Merz KM Jr. The role of quantum mechanics in structure-based drug design. Drug Discov Today. 2007;12(17–18):725–731. https://doi.org/10.1016/j.drudis.2007.07.006.
44. Senn HM, Thiel W.QM/MM methods for biomolecular systems. Angew Chem (Int Edn Engl).2009;48(7):1198–1229. https://doi.org/10.1002/anie.200802019.
45. Jin Li,Ailing Fu,Le Zhang. An Overview of Scoring Functions Used for Protein–Ligand Interactions in Molecular Docking. Interdisciplinary Sciences: Computational Life Sciences. March 2019. https://doi.org/10.1007/s12539-019-00327.
46. Chaskar P, Zoete V, Rohrig UF. Toward on-the-fly quantum mechanical/molecular mechanical (QM/MM) docking: development and benchmark of a scoring function. J Chem Inf Model.2014;54(11):3137–3152. https://doi.org/10.1021/ci5004152.
47. Huang, S.-Y, Zou, X. Advances and challenges in protein-ligand docking. Int. J. Mol. Sci.2010;11:3016–3034. Doi: 10.3390/ijms11083016.
48. Murray CW, Auton TR, Eldridge MD. Empirical scoring functions. II. The testing of an empirical scoring function for the prediction of ligand-receptor binding affinities and the use of Bayesian regression to improve the quality of the model. J Comput Aided Mol Design.1998;12(5):503–519.
49. Khamis MA, Gomaa W, Ahmed WF .Machine learning in computational docking. Artif Intell Med.2015;63(3):135–152. https://Doi.org/10.1016/j.artmed.2015.02.002.
50. Ma DL, Chan DS, Leung CH.Drug repositioning by structure-based virtual screening. Chem Society Rev.2013;42(5):2130–2141.https://doi.org/10.1039c2cs35357a.
51. Cheng T, Li Q, Zhou Z, Wang Y, Bryant SH (2012) Structure-based virtual screening for drug discovery: a problem-centric review. AAPS J. 14(1):133–141. https://doi.org/10.1208/s12248-012-9322-0.
52. Zhang L, Ai HX, Li SM, Qi MY, Zhao J, Zhao Q, Liu HS. Virtual screening approach to identifying influenza virus neuraminidase inhibitors using molecular docking combined with machine-learning-based scoring function. Oncotarget. 2017;8(47):83142–83154. https://doi.org/10.18632/oncotarget.20915.
53. Shivani Kumar, Suman Chowdhury,Suresh Kumar.In silico repurposing of antipsychotic drugs for Alzheimer's disease. BMC Neuroscience. 2017;18:76. DOI 10.1186/s12868-017-0394-8.
54. Kiranpreet Kaur, Paranjeet Kaur, Amit Mittal, Surendra Kumar Nayak, Gopal L Khatik.Design and Molecular Docking Studies of Novel Antimicrobial Peptides Using Autodock Molecular Docking Software. Asian Journal Of Pharmaceutical And Clinical Research. July 2017.DOI: http://dx.doi.org/10.22159/ajpcr.2017.v10s4.21332.
55. Maria Kadukova, Sergei Grudinin. Docking of small molecules to farnesoid X receptors using AutoDock Vina with the Convex-PL potential: lessons learned from D3R Grand Challenge 2. Journal Of Computer-Aided Molecular Design, Springer Verlag, 2018;32 (1):pp.151-162. Ff10.1007/s10822-017-0062-1ff.ffhal-01591157ff.
56. Sugunadevi Sakkiah, Sundarapandian Thangapandian, Shalini John, Keun Woo Lee. Pharmacophore based virtual screening, molecular docking studies to design Potent heat shock protein 90 inhibitors. European Journal of Medicinal Chemistry.2011;46: 2937e2947.
57. Ajay N Jain.Surflex: Fully Automatic Flexible Molecular Docking Using a Molecular Similarity-Based Search Engine. Journal of Medicinal Chemistry. 2020;46(4):499-511.DOI:46(4):499-511.
58. Ni Liu, Zhibin Xu. Using LeDock as a docking tool for computational drug design. IOP Conf. Series: Earth and Environmental Science,2019;218:012143. doi:10.1088/1755-1315/218/1/012143.
59. A. K. Chakraborti and R. Thilagavathi, Computer–Aided Design of Selective COX–2 Inhibitors: Molecular Docking of Structurally Diverse Cyclooxygenase–2 Inhibitors using FlexX, Internet Electron. J. Mol. Des. 2004;3:704–719, http://www.biochempress.com.
60. Louis-Philippe Morency, Francis Gaudreault,Rafael Najmanovich.Applications of the NRGsuite and the Molecular Docking Software FlexAID in Computational Drug Discovery And Design.

Methods in Molecular Biology, vol. 1762,https://doi.org/10.1007/978-1-4939-7756-7.

61. Chimaobi J. Ononamadu, Aminu Ibrahim. Molecular docking and prediction of ADME/drug-likeness Properties of potentially active antidiabetic compounds Isolated from aqueous-methanol extracts Of Gymnema sylvestre and Combretum micranthum. BioTechnologia, 2021;vol. 102 (1) C: pp. 85–99 C.
62. Mohammadi N, Shaghaghi N. Inhibitory Effect of Eight Secondary Metabolites from Conventional Medicinal Plants on COVID_19 Virus Protease by Molecular Docking Analysis. ChemRxiv. Cambridge: Cambridge Open Engage; 2020. 26434/chemrxiv.11987475.v1.DOI:10.26434/chemrxiv.11987475.v1.
63. McGann M. FRED and HYBRID docking performance on standardized datasets. J Comput Aided Mol Des. 2012 Aug;26(8):897-906. Doi: 10.1007/s10822-012-9584-8. Epub 2012 Jun 5. PMID: 22669221.
64. C.M.Venkatachalam, X.Jiang,T.Oldfield, M.Waldman.LigandFit: a novel method for the shape-directed rapid docking of ligands to protein active sites. Journal of Molecular Graphics and Modelling. January 2003;21(4):289-307.
65. Pedro J Ballester, John BO Mitchell. A machine learning approach to predicting protein–ligand binding affinity with applications to molecular docking.Bioinformatics.2010;26(9):1169-1175.
66. Simon Tietze,Joannis Apostolakis. GlamDock: Development and Validation of a New Docking Tool on Several Thousand Protein−Ligand Complexes. J. Chem. Inf. Model. 2007;47(4):1657–1672.https://doi.org/10.1021/ci7001236.
67. Sunil Jawla and Yatendra Kumar.Molecular Docking Interaction of Pinitol (Ligand) with Dipeptidyl Peptidase-4 Receptor (PDB 3C45).World Applied Sciences Journal. 2013;24 (12):1629-1634. DOI: 10.5829/idosi.wasj.2013.24.12.7653.
68. V. Balavignesh, E. Srinivasan, N. G. Ramesh Babu,N. Saravanan.Molecular docking study ON NS5B polymerase of hepatitis c virus by screening of volatile compounds from Acacia concinna and ADMET prediction. April: 2013;4(4):2548-2558.
69. Bitencourt-Ferreira G, de Azevedo WF Jr. Docking with GemDock. Methods Mol Biol. 2019;2053:169-188. Doi: 10.1007/978-1-4939-9752-7_11. PMID: 31452105.
70. El Kayal WM, Shtrygol SY, Zalevskyi SV, Shark AA, Tsyvunin VV, Kovalenko SM, Bunyatyan ND, Perekhoda LO, Severina HI, Georgiyants VA. Synthesis, in vivo and in silico anticonvulsant activity studies of new derivatives of 2-(2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)acetamide. Eur J Med Chem. 2019 Oct 15;180:134-142. Doi: 10.1016/j.ejmech.2019.06.085. Epub 2019 Jul 2. PMID: 31302446.
71. Nilesh Gajanan Bajad,Swetha Rayala, Gopich and Gutti, Anjali Sharma, Meenakshi Singh, Ashok Kumar, Sushil Kumar Singh.Systematic review on role of structure based drug design (SBDD) in the identification of anti-viral leads against SARS-Cov-2.Current Research in Pharmacology and Drug Discovery, 2021; 2:100026.
72. Markus Wagener, Jacob de Vlieg, Sander B Nabuurs.Flexible protein-ligand docking using the Fleksy protocol. Journal of Computational Chemistry 2012;33(12):1215-1217.
73. Mateusz Kurcinski, Aleksandra Badaczewska-Dawid, Michal Kolinski, Andrzej Kolinski, Sebastian Kmiecik.Flexible docking of peptides to proteins using CABS-dock.Protein Science 2020;29(1):211-222.
74. Todd JA Ewing, Shingo Makino, A Geoffrey Skillman, Irwin D Kuntz. DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. Journal of computer-aided molecular design, 2001;15(5):411-428.
75. Aurelien Grosdidier, Vincent Zoete, Olivier Michielin. Fast docking using the CHARMM force field with EADock DSS. Journal of computational chemistry, 2011;32(10):2149-2159.
76. Hasup Lee, Lim Heo, Myeong Sup Lee, Chaok Seok. GalaxyPepDock: a protein–peptide docking tool based on interaction similarity and energy optimization.Nucleic acids research, 2015;43 (W1): W431-W435.
77. Minkyung Baek, Woong-Hee Shin, Hwan Won Chung, Chaok Seok.GalaxyDock BP2 score: a hybrid scoring function for accurate protein–ligand docking.Journal of Computer-Aided Molecular Design, 2017;31(7):653-666,.
78. Cunliang Geng, Siddarth Narasimhan, Joao PGLM Rodrigues, Alexandre MJJ Bonvin.Information-driven, ensemble flexible peptide docking using HADDOCK.Modeling Peptide-Protein Interactions, 2017;109-138.
79. Vaithiyalingam Jagannathan Vishnuvarthan, Karunanidhi Santhanam Lakshmi, Ammayappan Rajam Srividya.In-silico screening of flavonoids targeted for death receptors in cancer by using Hex molecular docking.Journal of Young Pharmacists, 2017; 9 (2):168.
80. WF Vaz, JMF Custodio, GDC D'Oliveira, BJ Neves, PSC Junior, CH Andrade, CN Perez, EP Silveira-Lacerda, HB Napolitano.Dihydroquinoline derivative as a potential anticancer agent: synthesis, crystal structure, and molecular modeling studies. Molecular Diversity , 2021;25(1):55-66.
81. Brian Jimenez-Garcia, Jorge Roel-Touris, Miguel Romero-Durana, Miquel Vidal, Daniel Jimenez-Gonzalez, Juan Fernandez-Recio. LightDock: a new multi-scale approach to protein–protein docking. Bioinformatics, 2018;34(1):49-55.
82. Mengran Fan, Jian Wang, Huaipan Jiang, Yilin Feng, Mehrdad Mahdavi, Kamesh Madduri, Mahmut T Kandemir, Nikolay V Dokholyan. Gpu-accelerated flexible molecular docking.The Journal of Physical Chemistry, 2021;B125(4):1049-1060.
83. Noor Rahman, Ijaz Muhammad, Haroon Khan, Michael Aschner, Rosanna Filosa, Maria Daglia.Molecular docking of isolated alkaloids for possible α-glucosidase inhibition. Biomolecules, 2019;9(10):544.
84. Rene Meier, Martin Pippel, Frank Brandt, Wolfgang Sippl, Carsten Baldauf.ParaDockS: A Framework for Molecular Docking with Population-Based Metaheuristics. Journal of chemical information and modeling, 2010;50(5):879-889.
85. A Gupta, A Gandhimathi, P Sharma, B Jayaram.ParDOCK: an all atom energy based Monte Carlo docking protocol for protein-ligand complexes.Protein and peptide letters, 2007;14 (7):632-646.
86. Jianfeng Pei, Qi Wang, Zhenming Liu, Qingliang Li, Kun Yang, Luhua Lai.PSI-DOCK: Towards highly efficient and accurate flexible ligand docking. Proteins: Structure, Function, and Bioinformatics, 2006;62(4):934-946.
87. Laleh Alisaraie, Lars A Haller, Gregor Fels.A QXP-based multistep docking procedure for accurate prediction of protein− ligand complexes. Journal of chemical information and modeling, 2006;46(3):1174-1187.
88. Daniel Soler, Yvonne Westermaier, Robert Soliva.Extensive benchmark of rDock as a peptide-protein docking tool.Journal of Computer-Aided Molecular Design, 2019;33(7): 613-626.
89. Nicolas Majeux, Marco Scarsi, Joannis Apostolakis, Claus Ehrhardt, Amedeo Caflisch.Exhaustive docking of molecular fragments with electrostatic solvation.Proteins: Structure, Function, and Bioinformatics, 1999;37(1):88-105.
90. Gabriela Bitencourt-Ferreira, Walter Filgueira de Azevedo.Docking with SwissDock. Docking Screens for Drug Discovery, 2019;189-202.
91. Christoph Gorgulla, Konstantin Fackeldey, Gerhard Wagner, Haribabu Arthanari. Accounting of receptor flexibility in ultra-large virtual screens with VirtualFlow using a grey wolf optimization method.Supercomputing frontiers and innovations, 2020;7(3):4.
92. Brian G Pierce, Kevin Wiehe, Howook Hwang, Bong-Hyun Kim, Thom Vreven, Zhiping Weng.ZDOCK server: interactive docking prediction of protein–protein complexes and symmetric multimers.Bioinformatics, 2014;30(12):1771-1773.
93. Gabriela Bitencourt-Ferreira, Walter Filgueira de Azevedo.Molegro virtual docker for docking.Docking screens for drug discovery, 2019;149-167.
94. Sekhar Talluri.Molecular docking and virtual screening based prediction of drugs for COVID-19.Combinatorial Chemistry & High Throughput Screening, 2021;24(5):716-728.
95. Oliver Korb, Thomas Stutzle, Thomas E Exner.Empirical scoring functions for advanced protein− ligand docking with PLANTS.Journal of chemical information and modeling, 2009;49(1):84-96.

96. Paula Jofily, Pedro G Pascutti, Pedro HM Torres.Improving blind docking in DOCK6 through an automated preliminary fragment probing strategy. Molecules, 2021;26(5): 1224.

97. Igor Jose dos Santos Nascimento, Thiago Mendonca de Aquino, Paulo Fernando da Silva Santos-Junior, Joao Xavier de Araujo-Junior, Edeildo Ferreira da Silva-Junior.Molecular Modeling Applied to Design of Cysteine Protease Inhibitors–A Powerful Tool for the Identification of Hit Compounds Against Neglected Tropical Diseases. Front.Comput, Chem.2020; 5:63-110.

98. Karina B Santos, Isabella A Guedes, Ana LM Karl, Laurent E Dardenne. Highly flexible ligand docking: benchmarking of the DockThor program on the LEADS-PEP protein–peptide data set. Journal of Chemical Information and Modeling, 2020;60(2):667-683.

99. Peter Kolb, Amedeo Caflisch. Automatic and efficient decomposition of two-dimensional structures of small molecules for fragment-based high-throughput docking.Journal of medicinal chemistry, 2006;49(25):7384-7392.

100. Guilin Chen, Armel Jackson Seukep, Mingquan Guo. Recent advances in molecular docking for the research and discovery of potential marine drugs. Marine drugs, 2020;18 (11):545.

101. Vsevolod Yu Tanchuk, Volodymyr O Tanin, Andriy I Vovk, Gennady Poda.A new, improved hybrid scoring function for molecular docking and scoring based on AutoDock and AutoDock Vina. Chemical biology & drug design, 2016;87(4):618-625.

102. Brian P Kelley, Scott P Brown, Gregory L Warren, Steven W Muchmore.POSIT: flexible shape-guided docking for pose prediction. Journal of Chemical Information and Modeling, 2015;55(8):1771-1780.

103. Samuel DeLuca, Karen Khar, Jens Meiler. Fully flexible docking of medium sized ligand libraries with RosettaLigand. PLOS one,2015;10 (7):e0132508.

104. Jessica K Gagnon, Sean M Law, Charles L Brooks III.Flexible CDOCKER: Development and application of a pseudo-explicit structure-based docking method within CHARMM. Journal of computational chemistry, 2016;37(8):753-762.

105. Henrik Land, Maria Svedendahl Humble. YASARA: a tool to obtain structural guidance in biocatalytic investigations. Protein Engineering, 2018; 43-67.

106. Michal Brylinski, Jeffrey Skolnick.FINDSITELHM: A Threading-Based Approach to Ligand Homology Modeling.PLoS computational biology,2009;5(6):e1000405.

107. Deok-Soo Kim, Chong-Min Kim, Chung-In Won, Jae-Kwan Kim, Joonghyun Ryu, Youngsong Cho, Changhee Lee, Jong Bhak.BetaDock: shape-priority docking method based on beta-complex. Journal of Biomolecular Structure and Dynamics, 2011;29(1): 219-242.

108. Mizutani M. Y., TomiokaNItaia. Rational automatic search method for stable docking models of protein and ligand. J. Mol. Biol. 1994;243:310-326.

109. Hart, T.N. and Read, R.J. A multiple-start Monte Carlo Docking method. Proteins Struct. Funct. Bioinform.1992; 13: 206–222.

110. Simon K Kearsley, Dennis J Underwood, Robert P Sheridan, Michael D Miller.Flexibases: a way to enhance the use of molecular docking methods.Journal of computer-aided molecular design, 1994;8(5): 565-582.

111. Giulio Vistoli, Alessandro Pedretti, Angelica Mazzolari, Bernard Testa.Homology modeling and metabolism prediction of human carboxylesterase-2 using docking analyses by GriDock: a parallelized tool based on AutoDock 4.0.Journal of computer-aided molecular design, 2010, 24 (9), 771-787.

112. Reed B Jacob, Tim Andersen, Owen M McDougal.Accessible high-throughput virtual screening molecular docking software for students and educators.PLoS computational biology, 2012;8 (5):e1002499.

113. Casey Bullock, Nic Cornia, Reed Jacob, Andrew Remm, Thomas Peavey, Ken Weekes, Chris Mallory, Julia T Oxford, Owen M McDougal, Timothy L Andersen. DockoMatic 2.0: high throughput inverse virtual screening and homology modeling. Journal of chemical information and modeling, 2013;53(8):2161-2170.

114. William Welch, Jim Ruppert, Ajay N Jain. Hammerhead: fast, fully automated docking of flexible ligands to protein binding sites. Chemistry & biology, 1996;3(6):449-462.

115. Suzanne M Tomlinson, Robert D Malmstrom, Andrew Russo, Niklaus Mueller, Yuan-Ping Pang, Stanley J Watowich. Structure-based discovery of dengue virus protease inhibitors. Antiviral research, 2009;82(3):110-114.

116. Elaine C Meng, Irwin D Kuntz, Donald J Abraham, Glen E Kellogg. Evaluating docked complexes with the HINT exponential function and empirical atomic hydrophobicities. Journal of computer-aided molecular design,1994;8(3):299-306.

117. Orr Ravitz, Zsolt Zsoldos, Aniko Simon. Improving molecular docking through eHiTS' tunable scoring function. Journal of computer-aided molecular design, 2011;25 (11):1033-1051.

118. Fedor N Novikov, Viktor S Stroylov, Alexey A Zeifman, Oleg V Stroganov, Val Kulkov, Ghermes G Chilov.Lead Finder docking and virtual screening evaluation with Astex and DUD test sets.Journal of computer-aided molecular design.26(6):725-735.

Image Courtesy

1. Amy C. Anderson. The Process of Structure-Based Drug Design. Chemistry & Biology, September, 2003;10:787–797.

2. Bhawna Poudyal, Molecular Docking Technique. National Journal of Pharmaceutical Sciences.2020;15:41-46.

3. Jin Li, Ailing Fu, Le Zhang. An Overview of Scoring Functions Used for Protein–Ligand Interactions in Molecular Docking. Interdisciplinary Sciences: Computational Life Sciences. March 2019;10:60-66.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.