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A REVIEW ON APPLICATIONS OF MOLECULAR DOCKING IN DRUG DESIGNING

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ABSTRACT

Molecular docking is a computational modelling of structure of complexes formed by two or more interacting molecules. In the field of molecular modelling, docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength of association or binding affinity between two molecules using scoring functions. Molecular docking is one of the most frequently used in structure based drug design due to its ability to predict the binding-conformation of small molecules ligands to the appropriate target binding site.

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INTRODUCTION

The three dimensional structures known may be represented to show different views of the structures. With complex molecular mechanics programs it is possible to superimpose one structure on another. The same approach is used to superimpose the three dimensional structure of a potential drug on its possible target site. This process, which is often automated, is known as docking. The small molecule called Ligand usually interacts with protein's binding sites. Binding sites are areas of protein known to be active in forming of complex with ligand. There are several possible mutual conformations in which binding may occur. These are commonly called binding modes. It also predicts the strength of the binding, the energy of the complex; the types of signal produced and calculate the binding affinity between two molecules using scoring functions. The most interesting case is the type protein-ligand interaction, which has its applications in medicine.The associations between biologically relevant molecules such as proteins, nucleic acids, carbohydrates and lipids play a central role in signal transduction. Furthermore, the relative orientation of the two interacting partners may affect the type of signal produced. Therefore, docking is useful for predicting both the strength and type of signal produced.

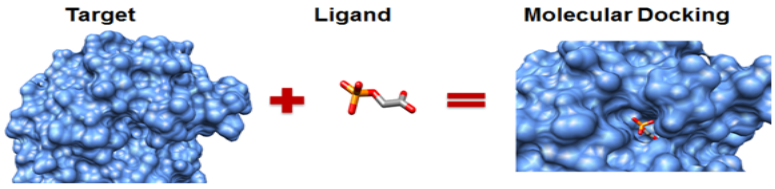


Figure 1: protein and ligand docked complex.

BASIC CONCEPT

Docking is the formation of protein ligand complex. Given the structures of a ligand and a protein, the task is to predict the structure of the resulting complex. This is so called docking problem. Because of the native geometry of complex can generally be assumed to reflect the global minimum of binding free energy, docking is the energy optimizing problem. Accordingly, heuristic approximations are frequently required to render the problem tractable within a reasonable time frame. The development of docking methods is therefore also concerned with making the right assumptions and finding acceptable simplifications that still provide a sufficiently accurate and predictive model for protein-ligand interactions.

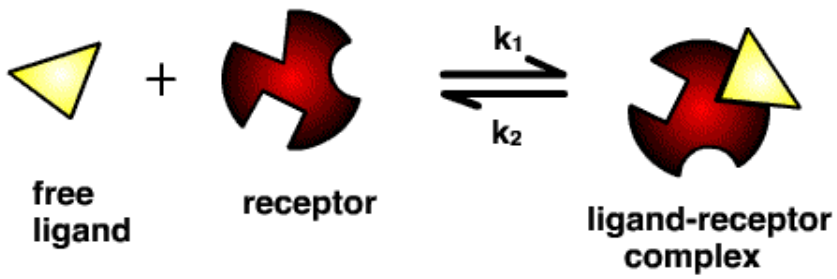


Figure 2: protein ligand complex.

MOLECULAR DOCKING APPROCHES

Two approaches are particularly popular within the molecular docking community. One approach uses a matching technique that describes the protein and the ligand as complementary surfaces. The second approach simulates the actual docking process in which the ligand-protein pairwise interaction energies are calculated. Both approaches have significant advantages.

Shape complementarity

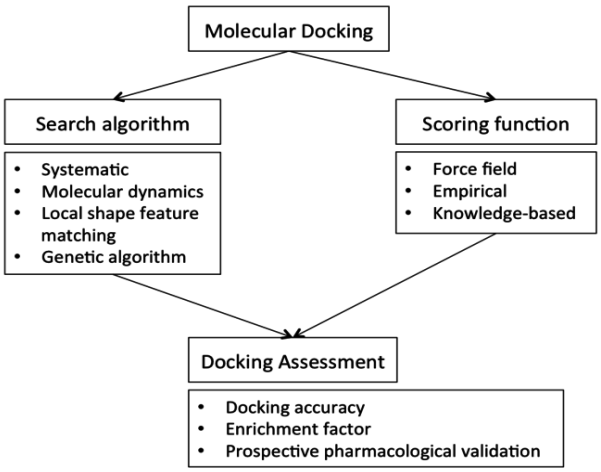
In this case, the receptor's molecular surface is described in terms of its solvent-accessible surface area and the ligand's molecular surface is described in terms of its matching surface description. The complementarity between the two surfaces amounts to the shape matching description that may help finding the complementary pose of docking the target and the ligand molecules. Shape complementarity methods can quickly scan through several thousand ligands in a matter of seconds and actually figure out whether they can bind at the protein's active site, and are usually scalable to even protein-protein interactions. They are also much more amenable to pharmacophore based approaches, since they use geometric descriptions of the ligands to find optimal binding.

Simulation

Simulating the docking process as such is much more complicated. In this approach, the protein and the ligand are separated by some physical distance, and the ligand finds its position into the protein's active site after a certain number of "moves" in its conformational space. The moves incorporate rigid body transformations such as translations and rotations, as well as internal changes to the ligand's structure including torsion angle rotations. Each of these moves in the conformation space of the ligand induces a total energetic cost of the system. Hence, the system's total energy is calculated after every move.The obvious advantage of docking simulation is that ligand flexibility is easily incorporated, whereas shape complementarity techniques must use ingenious methods to incorporate flexibility in ligands. Also, it more accurately models reality, whereas shape complimentary techniques are more of an abstraction.Clearly, simulation is computationally expensive, having to explore a large energy landscape. Grid-based techniques, optimization methods, and increased computer speed have made docking simulation more realistic.

MECHANICS OF DOCKING

The success of a docking program depends on two components: the search algorithm and the scoring function.



SEARCH ALGORITHM

The search space in theory consists of all possible orientations and conformations of the protein paired with the ligand. However, in practice with current computational resources, it is impossible to exhaustively explore the search space this would involve enumerating all possible distortions of each molecule (molecules are dynamic and exist in an ensemble of conformational states) and all possible rotational and translational orientations of the ligand relative to the protein at a given level of granularity. Most docking programs in use account for the whole conformational space of the ligand (flexible ligand), and several attempt to model a flexible protein receptor. Each "snapshot" of the pair is referred to as a pose**.**

A variety of conformational search strategies have been applied to the ligand and to the receptor. These include:

- Systematic or stochastic torsional searches about rotatable bonds
- Molecular dynamics simulations
- Genetic algorithms to "evolve" new low energy conformations and where the score of each pose acts as the fitness function used to select individuals for the next iteration

The algorithm should create an optimum number of configurations that admit by experimentation method determining binding modes. The following are the various algorithms applied for docking analysis such as Point complementary, Monte Carlo, Fragment-based, Genetic algorithms, Systematic searches, Distance geometry etc.

Molecular dynamics (MD) simulation

In this approach, proteins are typically held rigid, and the ligand is allowed to freely explore their conformational space. The generated conformations are then docked successively into the protein, and an MD simulation consisting of a simulated annealing protocol is performed. This is usually supplemented with short MD energy minimization steps, and the energies determined from the MD runs are used for ranking the overall scoring. Although this is a computer-expensive method (involving potentially hundreds of MD runs), it has some advantages: for example, no specialized energy/scoring functions are required. MD force fields can typically be used to find poses that are reasonable and can be compared with experimental structures.The Distance Constrained Essential Dynamics method (DCED) has been used to generate multiple structures for docking, called eigenstructures. This approach, although avoiding most of the costly MD calculations, can capture the essential motions involved in a flexible receptor, representing a form of coarse-grained dynamics.

Shape – complementarity methods

The most common technique used in many docking programs, shape-complementarity methods focus on the match between the receptor and the ligand in order to find an optimal pose. Programs include DOCK, FRED,[4] GLIDE,[5] SURFLEX, eHiTS and many more. Most methods describe the molecules in terms of a finite number of descriptors that include structural complementarity and binding complementarity. Structural complementarity is mostly a geometric description of the molecules, including solvent-accessible surface area, overall shape and geometric constraints between atoms in the protein and ligand. Binding complementarity takes into account features like hydrogen bonding interactions, hydrophobic contacts and van der Waals interactions to describe how well a particular ligand will bind to the protein. Both kinds of descriptors are conveniently represented in the form of structural templates which are then used to quickly match potential compounds (either from a database or from the user-given inputs) that will bind well at the active site of the protein. Compared to the all-atom molecular dynamics approaches, these methods are very efficient in finding optimal binding poses for the protein and ligand.

Genetics algorithm

Two of the most used docking programs belong to this class: GOLD and AutoDock Genetic algorithms allow the exploration of a large conformational space – which is basically spanned by the protein and ligand jointly in this case – by representing each spatial arrangement of the pair as a "gene" with a particular energy. The entire genome thus represents the complete energy landscape which is to be explored. The simulation of the evolution of the genome is carried out by cross-over techniques similar to biological evolution, where random pairs of individuals (conformations) are "mated" with the possibility for a random mutation in the offspring. These methods have proven very useful in sampling the vast state-space while maintaining closeness to the actual process involved.

Although genetic algorithms are quite successful in sampling the large conformational space, many docking programs require the protein to remain fixed, while allowing only the ligand to flex and adjust to the active site of the protein. Genetic algorithms also require multiple runs to obtain reliable answers regarding ligands that may bind to the protein. The time it takes to typically run a genetic algorithm in order to allow a proper pose may be longer, hence these methods may not be as efficient as shape complementarity-based approaches in screening large databases of compounds. Recent improvements in using grid-based evaluation of energies, limiting the exploration of the conformational changes at only local areas (active sites) of interest, and improved tabling methods have significantly enhanced the performance of genetic algorithms and made them suitable for virtual screening applications.

SCORING FUNCTION

In the fields of computational chemistry and molecular modelling, scoring functions are fast approximate mathematical methods used to predict the strength of the non-covalent interaction (also referred to as binding affinity) between two molecules after they have been docked. Most commonly one of the molecules is a small organic compound such as a drug and the second is the drug's biological target such as a protein receptor. Scoring functions have also been developed to predict the strength of other types of intermolecular interactions, for example between two proteins or between protein and DNA**.**

Force field

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. The intramolecular energies (also referred to as strain energy) of the two binding partners are also frequently included. Finally since the binding normally takes place in the presence of water, the desolvation energies of the ligand and of the protein are sometimes taken into account using implicit salvation methods such as GBSA or PBSA.

Empirical

Based on counting the number of various types of interactions between the two binding partners.[6] Counting may be based on the number of ligand and receptor atoms in contact with each other or by calculating the change in solvent accessible surface area (ΔSASA) in the complex compared to the uncomplexed ligand and protein. The coefficients of the scoring function are usually fit using multiple linear regression methods. These interactions terms of the function may include for example:

- Hydrophobic — hydrophobic contacts (favorable).
- Hydrophobic — hydrophilic contacts (unfavorable) (Accounts for unmet hydrogen bonds, which are an important enthalpic contribution to binding.[] One lost hydrogen bond can account for 1–2 orders of magnitude in binding affinity.[].
- Number of hydrogen bonds (favorable contribution to affinity, especially if shielded from solvent, if solvent exposed no contribution).
- Number of rotatable bonds immobilized in complex formation (unfavourable conformational entropy contribution).

Knowledge-based (also known as statistical potentials) – based on statistical observations of intermolecular close contacts in large 3D databases (such as the Cambridge Structural Database or Protein Data Bank) which are used to derive "potentials of mean force". This method is founded on the assumption that close intermolecular interactions between certain types of atoms or functional groups that occur more frequently than one would expect by a random distribution are likely to be energetically favourable and therefore contribute favourably to binding affinity.

Machine-learning

Unlike these classical scoring functions, machine-learning scoring functions are characterized by not assuming a predetermined functional form for the relationship between binding affinity and the structural features describing the protein-ligand complex. In this way, the functional form is inferred directly from the data. Machine-learning scoring functions have consistently been found to outperform classical scoring functions at binding affinity prediction of diverse protein-ligand complexes. This has also been the case for target-specific complexes, although the advantage is target-dependent and mainly depends on the volume of relevant data available. When appropriate care is taken, machine-learning scoring functions perform at least as well as classical scoring functions at the related problem of structure-based virtual screening.

MAJOR STEPS INVOLVED IN MECHANICS OF DOCKING

Molecular Docking is the process in which the intermolecular interaction between 2 molecules was studied in In-silico. In this process, the Macromolecule is the protein receptor. The micro molecule is the Ligand molecule which can be acted as an inhibitor. So, the Docking process involves the following steps:

Step I –

Preparation of protein: Three dimensional structure of the Protein should be retrieved from Protein data bank (PDB); afterward the retrieved structure should be pre-processed. This should admit removal of the water molecules from the cavity, stabilizing the charges, filling the missing residues, generation the side chains etc. according to the parameters available.

Step II –

Active site prediction: After the preparation of protein, the active site of protein should be predicted. The receptor might possess lots of active sites merely the one of the concern should be picked out. Mostly the water molecules and hetero atoms are removed if present.

Step III –

Preparation of ligand: Ligands can be retrieved from several databases such as ZINC, Pub Chem or can be sketched applying Chem sketch tool. While picking out the ligand, the LIPINSKY'S RULE OF 5 should be utilized. Lipinski rule of 5 assists in discerning amongst non-drug like and drug like candidates. It promises high chance of success or failure due to drug likeness for molecules abiding by with 2 or more than of the complying rules. For choice of a ligand allowing to the

LIPINSKY'SRULE:

Step IV-

Docking: Ligand is docked against the protein and the interactions are analyzed. The scoring function gives score on the basis of the best docked ligand basis is picked out.

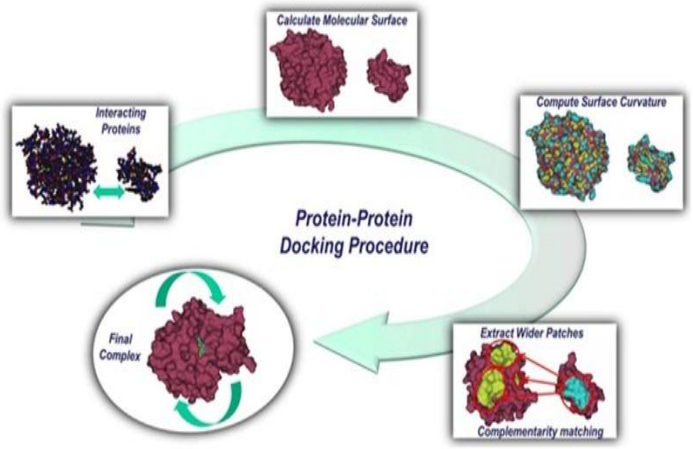
TYPES OF DOCKING

Molecular docking is the technique that is used to study molecular binding and how molecules bind. The term "docking" is mostly related to protein molecule interactions. There are several types of molecular docking for protein interactions:

Advantages:

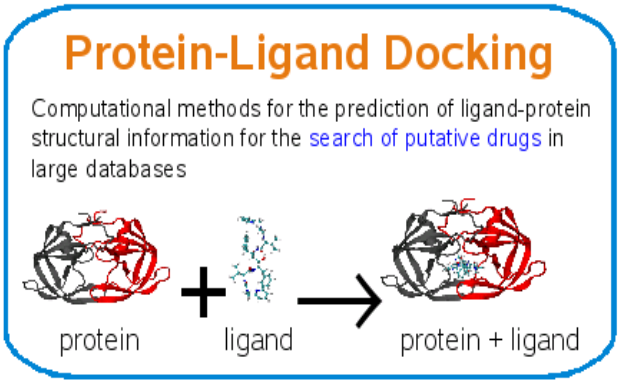
One of the major advantages conferred by docking is that it allows researchers to quickly screen large databases of potential drugs which would otherwise require tedious and prolonged work in the lab using traditional drug discovery procedures.

protein- protein docking interaction



Protein-protein interactions occur between two proteins that are similar in size. The interface between the two molecules tend to be flatter and smoother than those in protein-ligand interactions. Protein-protein interactions are usually more rigid; the interfaces of these interactions do not have the ability to alter their conformation in order to improve binding and ease movement. Conformational changes are limited by steric constraints and thus are said to be rigid.

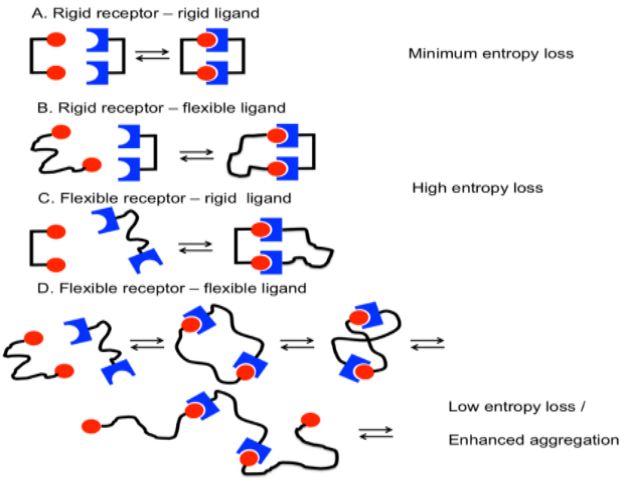
Protein receptor - ligand docking.



Also known as the molecular docking technique, protein receptor -ligand docking is used to check the structure, position and orientation of a protein when it interacts with small molecules like ligands. Protein receptor-ligand motifs fit together tightly, and are often referred to as a lock and key mechanism. There is both high specificity and induced fit within these interfaces with specificity increasing with rigidity. Protein receptor-ligand can either have a rigid ligand and a flexible receptor, or a flexible ligand with a rigid receptor.

Rigid ligand with a flexible receptor

The native structure of the rigid ligand flexible receptor often maximizes the interface area between the molecules. They move within respect to one another in a perpendicular direction in respect to the interface. This allows for binding of a receptor with a larger than usual ligand. Normally when there is ligand overlap in the docking interface, energy penalties incur. If the van der Waals forces can be decreased, energy loss in the system will be minimized. This can be accomplished by allowing flexibility in the receptor. Flexible receptors allow for docking of a larger ligand than would be allowed for with a rigid receptor.



Flexible ligand with a rigid receptor

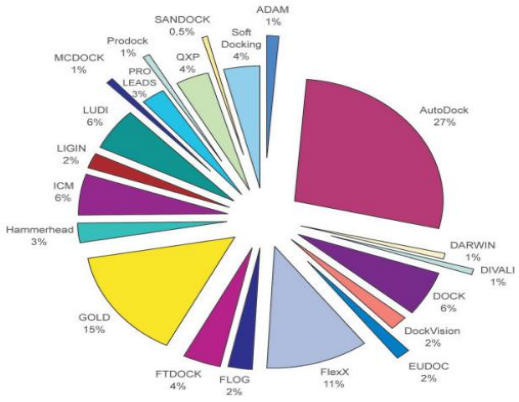
When the fit between the ligand and receptor does not need to be induced, the receptor can retain its rigidity while maintaining the free energy of thesystem. For successful docking, the parameters of the ligand need to be constant and the ligand must be slightly smaller in size than that of the receptor interface. No docking is completely rigid though; there is intrinsic movement which allows for small conformational adaptation for ligand binding. When the six degrees of freedom for protein movement are taken into consideration (three rotational, three translational), the amount of inherent flexibility allowed by the receptor is even greater. This further offsets any energy penalty between the receptor and ligand, allowing for easier, more energetically favorable binding between the two.

APPLICATION

- ✓ A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. If the protein is a receptor, ligand binding may result in agonism or antagonism.
- ✓ Docking is most commonly used in the field of drug design— most drugs are small organicmolecules, and docking may be applied to
  - hit identification – docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silicoto identify molecules that are likely to bind to protein target of interest
  - lead optimization – docking can be used to predict in where and in which relative orientation a ligand binds to a protein (also referred to as the binding mode or pose). This information may in turn be used to design more potent and selective analogs.6
  - Bioremediation – Protein ligand docking can also be used to predict pollutants that can be degraded by enzymes

LIST OF PROTEIN LIGAND DOCKING SOWTWARE

The number of docking programs currently available is high and has been steadily increasing over the last decades. The following list presents an overview of the most common protein-ligand docking programs, listed alphabetically, with indication of the corresponding year of publication, involved organisation or institution, short description, availability of a web service and the license. This table is comprehensive but not complete.



Program	Year Published	Organisation	Description	Webservice	License
1-Click Docking	2011	Mcule	Docking predicts the binding orientation and affinity of a ligand to a target	Available →	Basic free version
AADS	2011	Indian Institute of Technology	Automated active site detection, docking, and scoring(AADS) protocol for proteins with known structures based on Monte Carlo Method	Available →	Free to use Webservice
ADAM	1994	IMMD Inc.	Prediction of stable binding mode of flexible ligand molecule to target macromolecule	No	Commercial
AutoDock	1990	The Scripps Research Institute	Automated docking of ligand to macromolecule by Lamarckian Genetic Algorithm and Empirical Free Energy Scoring Function	No	Freeware →
AutoDock Vina	2010	The Scripps Research Institute	New generation of AutoDock	No	Open source →
BetaDock	2011	Hanyang University	Based on Voronoi Diagram	No	Freeware →
Blaster	2009	University of California San Francisco	Combines ZINC databases with DOCK to find ligand for target protein	Available →	Freeware
BSP-SLIM	2012	University of Michigan	A new method for ligand-protein blind docking using low-resolution protein structures	Available →	Freeware
DARWIN	2000	The Wistar Institute	Prediction of the interaction between a protein and another biological molecule by genetic algorithm	No	Freeware
DIVALI	1995	University of California-San Francisco	Based on AMBER-type potential function and genetic algorithm	No	Freeware
DOCK	1988	University of California-San Francisco	Based on Geometric Matching Algorithm	No	Freeware for academic use →
DockingServer	2009	Virtua Drug Ltd	Integrates a number of computational chemistry software	Available →	Commercial
DockVision	1992	DockVision	Based on Monte Carlo, genetic algorithm, and database screening docking algorithms	No	Commercial →
DOLINA	2013	University of Basel	Combinatorial solution to local induced fit	No	Academic
EADock	2007	Swiss Institute of Bioinformatics	Based on evolutionary algorithms	Available →	Freeware →
eHiTS	2006	SymBioSys Inc	Exhausted search algorithm	No	Commercial →
EUDOC	2001	Mayo Clinic Cancer Center	Program for identification of drug interaction sites in macromolecules and drug leads from chemical databases	No	Academic
FDS	2003	University of Southampton	Flexible ligand and receptor docking with a continuum solvent model and soft-core energy function	No	Academic
FlexX	2001	BioSolveIT	Incremental build based docking program	No	Commercial →
FlexAID	2015	University of	Target side-chain flexibility and soft scoring	No	Open source →

		Sherbrooke	function, based on surface complementarity		
FlexPepDock	2010	The Hebrew University	Modeling of peptide-protein complexes, implemented within the Rosetta framework	Available →	Freeware
FLIPDock	2007	Scripps Research Institute	Genetic algorithm based docking program using FlexTree data structures to represent a protein-ligand complex	No	Free for academic use →
FLOG	1994	Merck Research Laboratories	Rigid body docking program using databases of pregenerated conformations	No	Academic
FRED	2003	OpenEye Scientific	Systematic, exhaustive, nonstochastic examination of all possible poses within the protein active site combined with scoring Function	No	Free for academic use →
FTDOCK	1997	Biomolecular Modelling Laboratory	Based on Katchalski-Katzir algorithm. It discretises the two molecules onto orthogonal grids and performs a global scan of translational and rotational space	No	Freeware →
GEMDOCK	2004	National Chiao Tung University	Generic Evolutionary Method for molecular docking	No	Freeware →
Glide	2004	Schrödinger	Exhaustive search based docking program	No	Commercial →
GOLD	1995	Collaboration between the University of Sheffield, GlaxoSmithKline plc and CCDC	Genetic algorithm based, flexible ligand, partial flexibility for protein	No	Commercial
GPCRautomodel	2012	INRA	Automates the homology modeling of mammalian olfactory receptors (ORs) based on the six three-dimensional (3D) structures of G protein-coupled receptors (GPCRs) available so far and performs the docking of odorants on these models	Available →	Free for academic use
HADDOCK	2003	Centre Bijvoet Center for Biomolecular Research	Makes use of biochemical and/or biophysical interaction data such as chemical shift perturbation data resulting from NMR titration experiments, mutagenesis data or bioinformatic predictions. Developed for protein-protein docking, but can also be applied to protein-ligand docking.	Available →	Freeware →
Hammerhead	1996	Arris Pharmaceutical Corporation	Fast, fully automated docking of flexible ligands to protein binding sites	No	Academic
ICM-Dock	1997	MolSoft	Docking program based on pseudo-Brownian sampling and local minimization	No	Commercial →
idTarget	2012	National Taiwan University	Predicts possible binding targets of a small chemical molecule via a divide-and-conquer docking approach	Available →	Freeware
iScreen	2011	China Medical University	Based on a cloud-computing system for TCM intelligent screening system	Available →	Freeware
Lead finder	2008	MolTech	Program for molecular docking, virtual screening and quantitative evaluation of ligand binding and biological activity	No	Commercial →
LigandFit	2003	BioVia	CHARMm based docking program	No	Commercial
LigDockCS	2011	Seoul National	Protein-ligand docking using	No	Academic

A		University	conformational space annealing		
LIGIN	1996	Weizmann Institute of Science	Molecular docking using surface complementarity	No	Commercial
LPCCSU	1999	Weizmann Institute of Science	Based on a detailed analysis of interatomic contacts and interface complementarity	Available →	Freeware
MCDOCK	1999	Georgetown University Medical Center	Based on a non-conventional Monte Carlo simulation technique	No	Academic
MEDock	2007	SIGMBI	Maximum-Entropy based Docking web server is aimed at providing an efficient utility for prediction of ligand binding site	Available →	Freeware
MOE	2005	Chemical Computing Group	Supply a database of conformations or generate conformations on the fly. Choose between various scoring functions[30] and optionally constrain the generated poses to satisfy a pharmacophore query to bias the search towards known important interactions. Refine the poses using a forcefield based method with MM/GBVI[31] scoring or a fast grid based method.	No	Commercial
MolDock	2006	Molegro ApS	Based on a new heuristic search algorithm that combines differential evolution with a cavity prediction algorithm	No	Academic
MS-DOCK	2008	INSERM	Multi-stage docking/scoring protocol	No	Academic
ParDOCK	2007	Indian Institute of Technology	All-atom energy based Monte Carlo, rigid protein ligand docking	Available →	Freeware
PatchDock	2002	Tel Aviv University	The algorithm carries out rigid docking, with surface variability/flexibility implicitly addressed through liberal intermolecular penetration	Available →	Freeware
PLANTS	2006	University of Konstanz	Based on a class of stochastic optimization algorithms (ant colony optimization)	No	Free for academic use
PLATINUM	2008	Moscow Institute of Physics and Technology (State University)	Analysis and visualization of hydrophobic/hydrophilic properties of biomolecules supplied as 3D-structures	Available →	Freeware
PRODOCK	1999	Cornell University	Based on Monte Carlo method plus energy minimization	No	Academic
PSI-DOCK	2006	Peking University	Pose-Sensitive Inclined (PSI)-DOCK	No	Academic
PSO@AUTODOCK	2007	University of Leipzig	Particle Swarm Optimization (PSO) algorithms varCPSO and varCPSO-ls are suited for rapid docking of highly flexible ligands	No	Academic
PythDock	2011	Hanyang University	Heuristic docking program that uses Python programming language with a simple scoring function and a population based search engine; source codes available (Jaeyoon Chung; jychung@bu.edu)	Available	Academic
Q-Dock	2008	Georgia Institute of Technology	Low-resolution flexible ligand docking with pocket-specific threading restraints	No	Freeware
QXP	1997	Novartis	Monte Carlo perturbation with energy	No	Academic

		Pharmaceuticals Corporation	minimization in Cartesian space		
rDock	2013	University of York/ Open source project	HTVS of small molecules against proteins and nucleic acids	No	Open source →
SANDOCK	1998	University of Edinburgh	Guided matching algorithm	No	Academic
Score	2004	Alessandro Pedretti & Giulio Vistoli	The Score service allows to calculate some different docking scores of ligand-receptor complex	Available →	Freeware
smina	2013	University of Pittsburgh	Fork of AutoDock Vina optimized for scoring and minimization	No	Open Source
SODOCK	2007	Feng Chia University (Taiwan)	Swarm optimization for highly flexible protein-ligand docking	No	Academic
SOFTDocking	1991	University of California, Berkeley	Matching of molecular surface cubes	No	Academic
Surflex-Dock	2003	Tripos	Based on an idealized active site ligand (a protomol)	No	Commercial →
SwissDock	2011	Swiss Institute of Bioinformatics	Webservice to predict interaction between a protein and a small molecule ligand	Available →	Free webservice for academic use
VoteDock	2011	University of Warsaw	Consensus docking method for prediction of protein-ligand interactions	No	Academic
YUCCA	2005	Virginia Tech	Rigid protein-small-molecule docking	No	Academic
MOLS 2.0	2016	University of Madras	Software package for peptide modeling and protein-ligand docking		

CONCLUSION

Molecular docking is easy and helps in investigating, interpreting, explaining and identification of molecular properties using three dimensional structures. molecular docking tries to predict the structure of the intermolecular complex formed between two or more constituent molecules. It continues to extend its role in exciting new techniques such as computational enzymology, genomics and proteomic search engines. Molecular docking has been able to identify promising compounds that might represent future solutions in critical areas of human health.

REFERENCES

1. Atkins PW (1997): Physical Chemistry, 6th edn. New York: W. H. Freeman & Co.
2. Nadendla Rama Rao, molecular modelling: A powerfull tool for drug design and molecular docking, Resonance. 2004; 51-60
3. Molecular modelling from Wikipedia, the free encyclopedia [update 22 Nov 2011.] Available from http://en.wikipedia .org/wiki/molecular_modelling.
4. Lengauer T, Rarey M. Computational methods for bimolecular docking. Curr Opin Struct Biol. 1996; 6: 402-406.
5. Kitchen DB, Decornez H, Furr JR, Bajorath J. Docking and scoring in virtual screening for drug discovery: methods and applications. Nat Rev Drug Discov. 2004; 3: 935-949.
6. Pozzan A. Molecular descriptors and methods for ligand based virtual high throughput screening in drug discovery. Curr Pharm Des. 2006;
7. Schulz-Gasch T, Stahl M. Binding Site Characteristics in Structure-based Virtual Screening: Evaluation of Current Docking Tools. J Mol Model. 2003; 9: 47-57.
8. Friesner RA, Banks JL, Murphy RB, Halgren TA, Klicic JJ, Mainz DT, et al. Glide: A New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking acuracy. J Med Chem. 2004; 47: 1739-1749.
9. Jones G, Wilett P, Glein RC, Leach AR, Taylor R. Development and Validation of Genetic Algorithm and an Empirical Binding Free Energy Function. J Mol Biol. 1997; 267: 727-748.
10. Venkatachalam CM, Jiang X, Oldfield T, Waldman M. LigandFit: A Novel Method for the Shape-directed Rapid Docking of Ligands to Protein Active Sites. J Mol Graphics Modell. 2003; 21: 289-307
11. Molecular docking using VLifeMDS: VLife product documentation, tutorial: Biopredicta, VLife sciences Technologies Pvt.ltd.2011; 1-17.
12. Schapira M, Abagyan R, Totrov M. Nuclear hormone receptor targeted virtual screening. J Med Chem 2003;46: 3045-59.
13. Davis AM, Teague SJ, Kleywegt GJ. Application and Limitations of X-ray Crystallographic Data in Structure- Based Ligand and Drug Design. Angew Chem Int Ed Engl 2003; 42: 2718-36.
14. Jorgensen WL. Rusting of the lock and key model for protein Anderson AC, O'Neil RH, Surti TS, Stroud RM. Approaches to solving the rigid receptor problem by identifying a minimal set of flexible residues during ligand docking. Chem Biol 2001; 8: 445- 57.
15. Nakajima N, Higo J, Kidera A, Nakamura H. Flexible docking of a ligand peptide to a receptor protein by multicanonical molecular dynamics simulation. Chem Phys Lett 1997; 278: 297-301.)
16. Abseher R, Horstink L, Hilbers CW, Nilges M. Essential spaces defined by NMR structure ensembles and molecular dynamics simulation show significant overlap. Proteins 1998; 31: 370-82.