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Molecular Docking

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Abstract

Molecular docking is a key computational method in contemporary drug discovery, enabling the prediction of ligand–receptor interactions and providing information about binding affinity and stability. This study highlights the fundamental principles of docking algorithms and scoring functions, which form the basis for predicting optimal binding orientations and evaluating interaction strengths. Various types of docking approaches, such as rigid, flexible, inverse, and blind docking, are discussed to illustrate their applicability across different research contexts. Additionally, this study examines widely used molecular docking software, including Auto Dock Vina, Glide, GOLD, and MOE, emphasizing their unique features and performance characteristics. Molecular docking applications include lead discovery, virtual screening, structure-based drug design, and identification of potential therapeutic mechanisms. A notable example is its critical role during the COVID-19 pandemic, where docking was extensively used to screen antiviral compounds, target SARS-CoV-2 proteins, and accelerate the search for potential inhibitors of the disease. Overall, molecular docking remains a powerful and versatile tool that continues to advance drug discovery and biomedical research.

Keywords COVID-19, SARS-CoV-2, AutoDock, Vina, MOE, Flexible

Introduction

The aim of automated molecular docking software is to understand and forecast molecular recognition, both structurally by identifying probable binding modes and energetically by forecasting binding affinity. Typically, a small molecule and target macromolecule engage in molecular docking. Although protein–protein docking is becoming more popular, it is frequently referred to as ligand protein docking. This chapter will concentrate on ligand-protein docking, using the more general phrase molecular modeling of proteins. 443 Andreas Kukol, editor, Humana Press, Totowa, NJ 365 366 Morris, G.M., and Lim- The protein, DNA, or RNA macromolecule to which a much smaller molecule (or "ligand") is being docked is referred to as the Wilby "target."

Structure-activity studies, lead optimization, virtual screening to identify possible leads, binding hypotheses to help with predictions for mutagenesis studies, supporting X-ray crystallography in fitting substrates and inhibitors to electron density, chemical mechanism studies, and combinatorial library design are just a few of the many uses and applications of molecular docking in drug discovery. Finding hits and leads through library enrichment for screening is greatly aided by virtual screening based on the molecular descriptors and physical characteristics of in active ligands. (1) The preferred binding orientation of one molecule (such as a ligand) to another (such as a receptor) when the two combine to create a stable complex can be predicted more easily thanks to a kind of computational modeling known as "molecular docking."(2)

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Information on the preferred orientation of bound molecules can be used to predict the energy profile (such as binding free energy), strength, and stability (such as binding affinity and binding constant) of complexes. This can be accomplished using the molecular docking score function. Molecular docking is widely used to determine the approximate binding characteristics of small molecules (drug candidates) by predicting how they would bind to biomolecular targets (such as proteins, polysaccharides, and nucleic acids). For the rational drug design (structure-based drug development) of innovative medications with improved specificity and efficacy, this generates raw data.(3)

Widely used docking technologies employ search strategies such as genetic, fragment-based, Monte Carlo, and molecular dynamics algorithms. Furthermore, DOCK, GOLD, FlexX, and ICM are some tools that are mostly used for high-throughput docking simulations. Different kinds of molecular docking procedures utilize either flexible or rigid ligand/target, depending on the objectives of docking simulations. (3,4,5)

1)There are types of docking;

Flexible ligand docking, which incorporates target as rigid molecule. This is the most commonly used in docking.

Rigid body docking, where both the target and ligand molecules are kept as rigid molecules.

Flexible docking that involves both interacting molecules as flexible

2)Docking Algorithms and Scoring Functions

Currently, there are many different docking and scoring methods. Because there is currently no truly universal instrument that offers trustworthy and accurate solutions to the majority of varied docking challenges, it is often necessary to select an ideal combination for a particular target. The advantages and disadvantages of these methods, as well as the goals for which they are most effective, are significant and well-studied. Numerous studies have compared docking methods in terms of CPU time consumption, precise binding mode prediction, and virtual screening accuracy have been reported. (6,7) The authors compared the new docking tools FRED (OpenEye Scientific Software) and GLIDE (Schrödinger Inc.) with the results of previous studies using FLEXX (Tripos Inc.). The incremental construction process (FLEXX) and multiconformer docking (FRED, GLIDE), which separate a molecule's conformational search from its location in the binding site, are two widely used methods that are covered. The latter engages in tailored interactions with the protein by hooking a tiny, stiff piece at various positions inside the active region. These algorithms incorporate various scoring functions (empirical, knowledge-based, or molecular force field-based). "Soft" functions, including PMF, PLP, and DrugScore, do not contain directed terms and instead focus on lipophilic interactions and general sterical fit. "Hard" functions (ChemScore and FLEXX scoring functions) contain angular terms used to define hydrogen bonds. This study distinguishes between "objective" functions, which are used to estimate receptor-ligand interaction energy and minimize during docking, and "scoring" functions, which are used for ranking ligands. Docking studies for seven protein targets utilizing a portion of the Derwent World Drug Index (8)

3) Popular Molecular Docking Software

Table 1: List of software tools for docking and their algorithms.

S.No.	Software tools	Algorithm	Scoring term	Advantages	Reference
1.	Glide (Grid-based Ligand Docking with Energetics)	Monte Carlo	Glide score	Lead discovery and lead optimization	[9]
2.	AutoDock	Lamarkian genetic algorithm	Empirical free energy function	Adaptability to user defined input	[10]
3.	GOLD (Genetic Optimization for Ligand Docking)	Genetic algorithm	GoldScore, ChemScore, ASP (Astex Statistical Potential), CHEMPLP (Piecewise Linear Potential), User defined	Allows atomic overlapping between protein and ligand	[11]
4.	Surflex	Surflex-Dock search algorithm	Bohm's scoring function	High accuracy level by extending force-fields	[12]
5.	FlexX	Incremental reconstruction	Modified Bohm scoring function	Provides large number of conformations	[13]
6.	ICM (Internal Coordinate Modelling)	Monte Carlo minimization	Virtual library screening scoring function	Allows side chain flexibility to find parallel arrangement of two rigid helixes	[14]
7.	MVD (Molegro Virtual Docker)	Evolutionary algorithm	MolDock score	High accuracy level of predicting binding mode	[15]
8.	Fred (Fast Rigid Exhaustive Docking)	Exhaustive search algorithm	Gaussian scoring function	Nonstochastic approach to examine all possible poses within protein active site	[16]
9.	LigandFit	Monte Carlo method	LigScore, Piecewise Linear Potential (PLP), Potential of Mean Force (PMF)	Generates good hit rates based on LigScore	[17]
10.	FITTED (Flexibility Induced Through Targeted Evolutionary Description)	Genetic algorithm	Potential of Mean Force (PMF), Drug Score	Analyzes effect of water molecules on protein-ligand complexes	[18]

11.	GlamDock	Monte Carlo method	ChillScore	Provides provision of twodimensional analysis to screen ligands by targeting protein	[19]
12.	vLifeDock	Genetic algorithm	PLP score, XCscore	Facilitates batch docking	[20]
14.	iGEMDOCK	Genetic algorithm	Empirical scoring function	Highly significant in post-screening analysis	[21]

4) Molecular docking applications

Nonetheless, this docking was utilized to show the feasibility of any biochemical procedure that has already been completed for any known experimental component. Molecular docking has been used in several diverse fields. The interaction between proteins and micromolecules may be the primary predictor of nucleic acid activation or drug-binding properties. (22) because this element establishes a connection between a drug's molecular structure and cytotoxicity. This remark illustrates the ongoing efforts of medicinal chemists to characterize the molecular mechanism of drugs used in anticancer treatment by examining how drugs interact with nucleic acids when copper is present.(23). A medicinal chemist working in silico analyzed the main findings to predict whether the drug interacts with DNA or proteins. Furthermore, the mechanism of a complex can be ascertained from experimental results if a docking algorithm predicts the interaction of a drug with macromolecules. This will lead to the development of a new anticancer drug. The identification of therapeutic alterations that may lead to a structural or sequence relationship with its target can therefore be greatly aided by this clarity.(24)

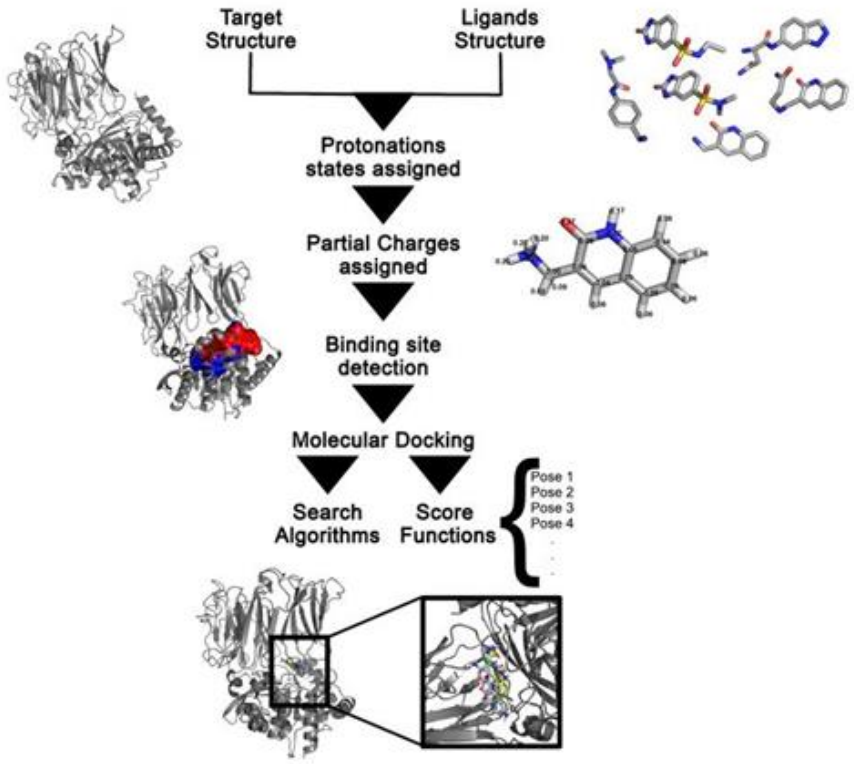

Figure 1Molecular docking calculations in general. Typically, the methods begin with the acquisition of target and ligand 3D structures. Partial charges and protonation states are then allocated. The target binding site is found if it is unknown beforehand, else a blind docking simulation could be carried out.

5)Molecular docking in COVID-19

There is currently no known treatment for COVID-19. Molecular precursors that could serve as potent antiviral drugs to treat any disease have been developed as a result of ongoing study. Many studies have been carried out to develop natural substances that might act as strong antiviral agents and reduce the pathogenicity of the SARS-CoV-2 Mpro virus. because more than 100 powerful natural antiviral drugs have already been identified and documented in databases. MetaPocket 2.0 was used to identify the active location of the protease enzyme. (25) The docking was done using AutoDock 4, a supporting application that explains the ligand-Mpro interaction. It was discovered that a few of the many chemicals that were docked had high bonding energies. Strong protease inhibitors include rutin, hypericin, robustaflavone, solenoid, and aflavin 3-30 digallate. Furthermore, it was discovered that darunavir, saquinavir, and atazanavir interacted more successfully than any other natural compounds and were potent protease inhibitors. The pharmacokinetics, toxicity, and productivity of drugs that are currently being used and repurposed against COVID-19 were also revealed by the investigations using docking. It was discovered that there were fewer H-bonds produced with Mpro than with the natural material utilized in the investigation. and the approved drugs have large binding energies as well. Naturally occurring plant metabolites that are neither carcinogenic nor mutagenic include flavonoids, terpenoids, alkaloids, phenolics, tannins, and sapon. Natural compounds have not yet resulted in any adverse effects. Molecular dynamics was run fifty times using Schrodinger and the Desmond package to evaluate the stability and flexibility. The outcomes demonstrated that the ligand and the protein remained stable during the stimulation. Our diet is mostly composed of phytocompounds, which have developed into powerful antiviral agents. in opposition to COVID-19, and anyone might use it to prevent contracting the virus. (26)

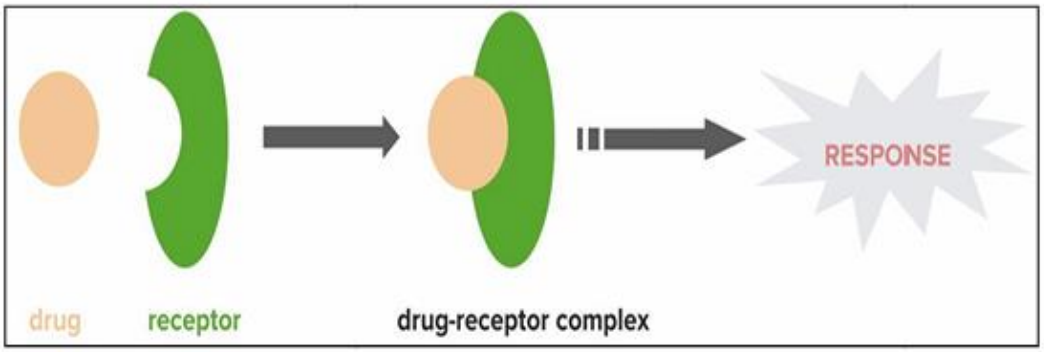

Fig. 2. Drug receptor response

6)Conclusion, limitation and future research

The two primary applications of molecular docking technology in food in recent years, which have substantially helped humans, are the screening of receptor proteins or target molecules and the exploitation of intermolecular interactions. Examining the relationship between digestive enzymes and nutrients may improve food availability and aid in the development of diets suitable for specific populations. Simulating the binding mode between harmful substances and receptors allows for a deeper understanding of the action mechanism. It is possible to screen for safe and nontoxic enzyme inhibitors to regulate the absorption of hazardous medications and cut costs. In conclusion, it is likely that molecular docking technology will be used in food science. It is crucial to keep in mind that molecular docking can be used to validate experimental findings and provide guidance for further research, but it cannot fully replace actual experiments. Many docking operations are performed in a vacuum since natural conditions such as pH, temperature, and solvent cannot be accurately replicated. Additionally, because the range of molecular changes during the docking process is restricted, molecular docking is frequently employed when proteins are involved. Furthermore, evaluating the accuracy of docking data depends on the known stable structures of the ligand and receptor. Consequently, the proteins found in the Protein Data Bank (PDB) are commonly utilized as research subjects. There are several restrictions because it is necessary to represent chemicals that cannot build the crystal structure. Therefore, molecular docking technology should concentrate more on algorithm development to ensure the effectiveness of docking results. Furthermore, the characteristics of the ligand and receptor must be taken into consideration when designing and developing docking software. This may make molecular docking more useful in the realm of food science.

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