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(REVIEW ARTICLE)

Swiss Dock 2025: Docking approaches comparison between attracting cavities and autodockvina

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Abstract

Molecular docking is a crucial computational tool in drug discovery enabling the prediction of ligand-target interactions and accelerating the screening of potential drug candidates. This study compares twowidely used docking algorithms AutodockVina and Attracting Cavities to evaluate their efficiency, accuracy and applicability in molecular docking studies. AutodockVina is known for its speed and computational efficiency making it suitable for high-throughput screening. In contrast, Attracting Cavities provides more accurate binding predictions particularly for covalent interactions but it requires significantly more computational time. The studies suggest that AutodockVina is preferable for rapid screening whereas Attracting Cavities is advantageous for detailed validation studies. Despite these advancements, molecular docking faces challenges in flexibility modelling, scoring function accuracy and solvation effects. Future directions involve integrating machine learning and quantum chemistry to improve predictive accuracy. This study highlights the importance of selecting docking algorithms based on study-specific requirements for drug discovery.

Keywords: Algorithms; Molecular Docking; Autodockvina; Attracting Cavities and Swiss dock

1. Introduction

Molecular docking is a computational technique used in the prediction of the preferred orientation of ligands when binding to a target macromolecule such as protein or DNA[1].Molecular docking is very significant in the drug discovery process as it helps to reduce the time required to screen different compounds that can be potential drug candidates[2]. Molecular docking helps to understand the interactions between ligands and targets thus facilitating the identification of potential drug candidates[3]. Molecular docking is widely used to predict ligand–target interactions, delineate structure-activity relationships and assist in the design of novel drugs without prior knowledge of the chemical structure of other target modulators[4].

By 2025, technology has improved significantly especially in molecular docking approaches[4]. Thus, it is important to select appropriate docking algorithms for successful drug discovery[5]. Various algorithms and approaches offer varying levels of speed, accuracy and computational efficiency[5]. Autodockvina and attacking cavities are widely used in molecular docking[6]. Studies show that molecular docking for prediction of the ligand-target interaction with Autodockvina offers faster predictions and attracts cavities providing more accurate results[7].Comparative assessments of molecular docking algorithms are important to highlight the importance of the selection algorithm that aligns with the specific needs of the study including accuracy in posing and computational efficiency. This article aimed to compare autodockvina and the attractive cavity approaches used in docking.

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2. Molecular docking and its role in drug discovery

Molecular docking is an essential technique in drug discovery and is utilized to estimate the optimal alignment of one molecule with another ensuring a stable complex formation[8]. This process is crucial for drug discovery and understanding of molecular interactions[8]. These studies suggest that molecular docking plays a major role in structure-based drug design allowing the prediction of ligand conformations and binding affinities[9]. Molecular docking parameters for accuracy and efficiency include correct pose prediction affinity scoring and the integration of computational advancements such as machine learning and protein flexibility considerations[10].

Molecular docking is an important tool in structure-based drug design, as it predicts the binding conformation of small-molecule ligands to target binding sites[11]. This prediction aids in the rational design of drugs and elucidates the fundamental biochemical processes[12]. This technique is widely used to explore ligand conformations within macromolecular targets, estimate ligand-receptor binding free energy and identify novel compounds of therapeutic interest[13]. It also assists in visualizing the 3D structures of molecules which is essential for understanding the interactions at the molecular level[14].

3. Docking algorithms

Docking algorithms are essential tools in molecular modelling, particularly in drug discovery in whichthey estimate the optimal orientation of a ligand when it binds to a protein target[15]. The primary goal of docking is to accurately predict the binding mode and affinity of a ligand for its target protein which is crucial for identifying potential drug candidates[16].

Docking algorithms generally operate by exploring the conformational space between the ligand and protein to identify the optimal binding pose[17]. It consists of two key elements: search algorithms and scoring functions[18]. Search algorithms explore the possible orientations and conformations of the ligand within the binding site while scoring functions evaluate these positions to predict binding affinity[18]. This process often involves the use of force fields, energy calculations and solvent models to simulate the interaction between the ligand and protein[19]. Docking approaches can be broadly classified based on the flexibility of the molecules involved and the methods used such as rigid, flexible, fragment-based and consensus docking[20].

Table 1 Classification of docking approaches

Classification	Description
Rigid Docking	Both the ligand and the protein were treated as rigid bodies. This approach is computationally efficient but may not accurately capture the true binding mode due to the lack of flexibility.
Flexible Docking	The ligand, protein, or both are flexible. This approach is more accurate as it accounts for conformational changes upon binding but it is computationally more demanding.
Fragment-Based Docking	This method involves docking small fragments of the ligand separately and then assembling them at the binding site. It is particularly useful for large and complex ligands.
Consensus Docking	Recent advances incorporate machine learning algorithms to improve the prediction of binding poses and affinities leveraging large datasets to refine docking predictions.

4. Attracting cavities

The Attracting Cavities algorithm is a covalent docking procedure designed to predict interactions between covalent drugs and their biological targets[21].It resembles the two-step process of covalent ligand binding where the ligand initially interacts with the protein cavity via non-covalent forces followed by the establishment of a covalent bond through a chemical reaction[21]. This approach allows for a more accurate prediction of covalent interactions than traditional docking methods[21].

The Attracting Cavities algorithm has been applied to various drug discovery contextsparticularly in the study of covalent inhibitors[22]. For instance, it has been used to assess the binding of covalent complexes to the SARS-CoV-2

main protease demonstrating its utility in antiviral drug discovery. In this challenging test set, Attracting Cavities achieved success rates of 58% for re-docking and 28% for cross-docking highlighting its potential for identifying effective inhibitors against viral targets[23]. Additionally, its integration into Swiss Dock facilitates its application in broader drug discovery efforts by providing a streamlined process for docking predictions[24].

The Attracting Cavities algorithm has notable advantages and limitations[25]. Its accuracy stands out, demonstrating superior prediction of covalent interactions compared to docking codes such as GOLD and Auto Dock achieving a 78% success rate with a root mean square deviation (rmsd) ≤ 2 Å, outperforming GOLD (66%) and Auto Dock (35%)[26]. Furthermore, Attracting Cavities integration of Attracting Cavities into platforms such as Swiss Dock enhances its accessibility and usability for researchers offering both a user-friendly interface and command-line access for efficient docking predictions[27]. However, the complexity of the algorithm may require more computational resources than simpler docking methods potentially limiting its use in high-throughput screening scenarios. Additionally, while Attracting Cavities excels in covalent docking its performance in non-covalent scenarios or with highly solvent-exposed ligands may not be as robust, as indicated by the lower success rates in cross-docking tests[27].

5. Autodockvina

AutoDockVina is a molecular docking technique used to predict how proteins and ligands interact by determining their binding modes[28]. This is an improvement over its predecessor, AutoDock 4, offering enhanced speed and accuracy[28].Vina achieved a speed-up of approximately two orders of magnitude compared to AutoDock 4 primarily because of its efficient optimization and multithreading capabilities[28]. In addition,Vina autonomously generates grid maps and clusters results, enhancing user convenience[29]. Compared with AutoDock, Vina is noted for its superior docking power ranking in the top quarter of the methods tested in the CASF-2013 benchmark[30].

AutoDockVina utilizes an empirical scoring function to assess binding affinities which has been enhanced through multiple studies to optimize its accuracy and effectiveness[31]. For instance, the Vinardo scoring function based on Vina enhances docking and virtual screening capabilities by optimizing the correlation between predicted and experimental binding affinities[32]. Vina uses an iterated local search global optimizer which significantly improves the speed and accuracy of binding mode predictions compared with AutoDock[32]. The software also supports the AutoDock4.2 scoring function and allows simultaneous docking of multiple ligands[33]

AutoDockVina represents a significant advancement over AutoDock 4 offering improved speed and accuracy for molecular docking. Its strengths include speed and efficiency which are significantly faster owing to multithreading and efficient optimization[34]. Vina provides more accurate binding pose predictions and is more user-friendly with automatic grid map calculations and result clustering[35]. Flexibility is also a key strength supporting enhancements such as the Vinardo scoring function and halogen bonding parameters in VinaXB to improve docking accuracy[36]. However, Vina has weaknesses notably a lower correlation coefficient for binding affinity predictions, which can affect ligand ranking[37]. Earlier versions had limited feature support such as for macrocycles or explicit water molecules, although later updates have addressed this[37]. However, efficient large-scale virtual screening with Vina can still be resource-intensive, although GPU acceleration methods such as Vina GPU mitigate this[38]. In general, its strengths lie in its efficiency and user-friendliness while its weaknesses include challenges in binding affinity correlation and resource demands for large-scale screening[38].

6. Limitations and future direction

Molecular docking is a computational technique used to predict the interaction between two molecules, often applied in drug discovery[39]. Despite its utility there are several challenges in current docking algorithms that affect accuracy and efficiency[40]. One major challenge is conformational flexibility as both ligands and proteins undergo structural changes that need to be accurately modelled[41]. Scoring functions which predict binding affinities often lack precision due to oversimplified models and incomplete molecular structures[42]. Additionally, docking methods struggle with protein-protein interactions particularly when significant mobility or weak interactions are involved[43]. Another critical issue is properly accounting for solvation effects which significantly impact the accuracy of docking predictions[44].

To address these challenges, several improvements in docking techniques are being explored[45]. The integration of big data into scoring functions can enhance prediction accuracy by incorporating vast biological datasets[46]. Advanced algorithms, including deep learning and machine learning, are being developed to improve pose prediction and affinity scoring[47]. Furthermore, quantum chemistry methods are gaining attention for their ability to provide more precise

energy calculations, leading to better docking accuracy[48].These improvements have the potential to refine molecular docking techniques, making them more reliable and effective[49].

Emerging trends in molecular docking focus on leveraging advanced computational approaches to enhance accuracy and applicability[50]. Machine learning algorithms are increasingly being used to improve docking efficiency and prediction reliability[50]. Fragment-based approaches are also gaining traction, enabling a more detailed exploration of binding sites[51]. Additionally, there is a growing emphasis on realistic modelling considering protein interactions in vivo within crowded cellular environments[52]. As these advancements continue to evolve they are expected to significantly enhance the role of molecular docking in drug discovery and other biomedical applications[52].

7. Conclusion

Molecular docking plays a pivotal role in drug discovery by predicting ligand-target interactions aiding in structure-based drug design and facilitating the identification of potential drug candidates. This study compared two widely used molecular docking algorithmsAutoDockVina and Attracting Cavities highlighting their respective strengths and limitations. AutoDockVina demonstrated superior speed and efficiency making it an ideal tool for high-throughput screening applications where rapid predictions are essential. On the other hand, Attracting Cavities exhibited higher accuracy in binding score predictions particularly in covalent docking scenarios making it a valuable approach for validating target-ligand interactions.The comparative analysis revealed that while AutoDockVina is more computationally efficient Attracting Cavities offers greater precision in ligand-binding predictions. The case study using the leptin receptor and orlistat as a ligand further reinforced these findings with Attracting Cavities achieving a more accurate binding score, albeit at the cost of significantly increased computational time. These findings indicate that selecting a docking algorithm should depend on the study's specific needs whether emphasizing speed for large-scale screening or accuracy for target validation. Despite the advancements in molecular docking, challenges such as protein flexibility, solvation effects and scoring function limitations persist. Future developments integrating machine learning, quantum chemistry and big data analytics hold promise for enhancing the accuracy and efficiency of docking algorithms. As computational techniques evolve molecular docking will continue to be a cornerstone of drug discovery enabling the development of novel therapeutics with improved precision and reliability.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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