INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Paper

Autodock & Autodock Vina: Development, Capabilities, & Applications in Molecular Docking

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ARTICLE INFO

Published: 18 May. 2025
Keywords:
AutoDock, AutoDock Vina, Molecular Docking, Computational Drug Delivery, AutoDock Tools, Structure-based drug design
DOI:
10.5281/zenodo.15458275

ABSTRACT

AutoDock and AutoDock Vina are popular molecular docking technologies that are essential to structure-based drug discovery because they can predict ligand-receptor interactions. Their theoretical underpinnings, methods of application, and comparative effectiveness across several biological targets are assessed in this study. Vina's multicore support and empirical scoring are compared to AutoDock4's semi-empirical scoring function and flexible docking strategy. Furthermore, the impact of developments like AutoGridFR and GPU-accelerated versions on computational efficiency is examined. The benefits of AutoDock Tools' (ADT) user interface in ligand and receptor synthesis are investigated. This research shows how advances in algorithm design and parallelization continue to improve the accuracy and accessibility of molecular docking, and it offers insights into optimizing docking procedures.

INTRODUCTION

Over 35 sites worldwide received the initial version of AutoDock, and as of right now, over 600 sites have the most recent versions. AutoDock 3.0, which has been greatly improved with the addition of a new empirical free energy function and powerful new search techniques, comes with this user manual for the first time. The AutoDock software was created to offer an automated process for forecasting how ligands will interact with biomacromolecular targets. Problems with the design of bioactive substances, and specifically

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

with computer-aided drug design, are the driving force behind this endeavor. Many significant protein and nucleic acid structures are still being revealed by advancements in biomolecular x-ray crystallography. These structures might serve as targets for bioactive substances that help regulate plant and animal illnesses, or they might just be essential to comprehending a basic biological concept. In the development phase, the exact way that these agents or candidate molecules interact is crucial. In fact, AutoDock can be a useful tool in the actual process of determining the x-ray structure: given the ligand's electron density, AutoDock can assist in reducing the number of possible configurations and assisting in the identification of a desirable structure. Our objective has been to help researchers identify biomolecular complexes by offering a computational tool. [1,2] The automated ligand-receptor docking program AutoDock has amassed a sizable user base and emerged as the most mentioned docking software during the last 20 years. AutoGrid computes affinity maps, which are three-dimensional (3D) rectilinear grids that AutoDock uses to represent the rigid portion of the receptor. [3] An affinity map is calculated for each type of atom in the ligand to be docked, as well as electrostatic and desolvation maps, for a certain receptor and docking box. Because trilinear interpolations in the maps enable the computation of interactions between a ligand atom and the complete set of atoms in the receptor, these maps significantly cut down on the runtimes required for docking calculations. Although AutoDockVina allows for the real-time computation of these maps, there are a number of intriguing benefits to precalculating them. In hydrated docking, which predicts water-mediated interactions between ligands and receptors as part of docking a ligand, custom water maps have been utilized. Using Attractor's maps, ligands with flexible macrocycles have been docked and covalent docking has been studied. [4] Additionally, binding pocket prediction technologies like AutoLigand and AutoSite use these maps. Examining them visually can reveal important information about ligand optimizations and binding modalities. Lastly, precalculating affinity maps avoids recalculating them for every ligand docked in virtual screening applications, where millions of ligands are docked at the same receptors in parallel. Only rudimentary support for locating and generating these affinity maps is offered by software tools, including those we have previously developed. These tools primarily enable the docking box to be placed and scaled visually. They are also using outdated graphical toolkits. The creation of a new software tool, AutoGridFR, or AGFR for short, was spurred by these factors. [5,6] The software was created to: [2] facilitate the creation of maps for advanced docking applications like covalent docking, hydrated docking, docking with flexible side chains, or creating maps for multiple binding sites; [3] enable the calculation of maps from a command line interface (CLI) or using a contemporary graphical user interface (GUI); [4] incorporate our most recent algorithms for pocket identification and post-processing maps; [5] support the creation of maps for advanced docking applications like covalent docking, hydrated docking, docking with flexible side chains, or creating maps for multiple binding sites; [6] facilitate map management and support data-provenance and reproducibility through the addition of meta data. For the latter, we created a file container (target file) that holds the AutoGrid-calculated affinity maps as well as information about the maps' creation. AutoDock4 is backward compatible with the maps that are contained in target files. In this article, we present AGFR, a new software application that makes it easier to manage AutoDock affinity maps by allowing them to be specified, calculated, visualized, and analyzed as

target files. AGFR simplifies the process of making and maintaining precomputed affinity maps while preserving all of its benefits. [7,8]

AutoDock is a popular software suite for molecular docking, a computational method that forecasts the interactions between biological macromolecules like proteins or enzymes and tiny molecules like ligands or medicines. AutoDock, which was created mainly for drug development, aids scientists in forecasting the preferred binding modes and binding affinities of compounds when they are docked into target protein active sites. This procedure is essential for comprehending molecular interactions, locating possible therapeutic candidates, and creating new treatments. [9] AutoDock's primary function is to model the three-dimensional binding of ligands to receptor molecules and determine the best docking arrangement using energy minimization techniques. Because of its flexible docking, which enables conformational changes in both the ligand and the receptor during the docking process; it is possible to predict molecular interactions with greater accuracy. A collection of scoring functions built into AutoDock assesses the stability and strength of ligand-receptor interactions, making it possible to determine the most likely binding positions. AutoDock has become an indispensable tool in computational biology, particularly in virtual screening and structure-based drug design, thanks to its user-friendly interface and robust computational capabilities. [10] Additionally, the software is compatible with a wide range of input formats and features interfaces such as AutoDockTools (ADT), which makes it easier to prepare molecular structures and analyze docking findings. AUTODOCK is a popular molecular docking application. Its single-threaded characteristic, which means it only uses one CPU core when running, is what distinguishes it from a computational perspective. Its effective adaptation to accelerators can lead to notable performance increases by taking use of the embarrassingly parallel nature of the underlying algorithms. Parallel programming frameworks can be used to express such parallelism in an appropriate way. Among these is the Open Computing Language, or OpenCL, which offers a universal standard that works with hybrid platforms including CPUs and GPUs. More sophisticated search techniques can be investigated from an algorithmic perspective and based on the possible benefits of an OpenCL implementation, without suffering the significant performance costs that would be associated with the single-threaded AUTODOCK version. [11] In this paper, we present our OpenCL version of AUTODOCK for GPUs. An enhanced AUTODOCK search method, which incorporates scoring-function gradients for translation, rotation, and torsion variables, serves as the foundation for this application. It continues to use a Lamarckian Genetic Algorithm (LGA) for global search, which is comparable to AUTODOCK's. In addition to the original random numerical optimizer Solis-Wets, we new add the gradient-based ADADELTA approach for the local search. We assessed the algorithmic and computational improvements our OpenCL implementation offered over the original AUTODOCK through a series of trials. [12]

1.1. AutodockVina& Autodock4

Two open-source, free programs, Autodock4 (AD4) and AutodockVina (Vina), can be used to rapidly determine the ligand-binding affinity. Over the past ten years, each of the two packages has received almost 6000 citations, demonstrating their widespread use. Vina has been accessible since 2010, whereas AD4 was first made available in 2009. [4] A Coulomb potential term, a Lennard-Jones potential term, desolvation linked to volume, and conformational entropy linked to the number of rotational bonds are all components of the semi-empirical AD4 scoring function. A number of strong inhibitors that attach to peptides, proteins,

and genes were discovered thanks in part to AD4. The Vina scoring function, on the other hand, is entirely empirical and includes hydrophobic and torsion components, repulsion, hydrogen bonds, and Gaussian steric interactions. Vina is incredibly user-friendly and has parallel processing capabilities built into its architecture. According to the CASF-2013 benchmark, Vina was found to be more accurate than AD4 in determining the ligand-binding affinity. This explains why, in recent years, Vina has gained popularity over AD4. Because of its powerful computing capabilities, Vina has been used not only to ascertain the binding affinities of tiny compounds to biomolecular targets such as peptides, proteins, and genes, but also to forecast the binding positions of large substrates to protein targets. [13,14] At the Scripps Research Institute, Morris and colleagues created the popular docking tool AutoDock4. Due to its free availability to academic users, excellent accuracy, and demonstrated adaptability, AutoDock has become a popular first choice for new users and has helped to spread its use, as evidenced by its remarkably high number of citations. AutoDock4 provides a wide range of search techniques and a scoring function based on a huge collection of different protein–ligand complexes with known inhibition constants, the Assisted Model Building with Energy Refinement (AMBER) force field, and a linear regression analysis. [15] The application can be utilized with AutoDockTools (ADT), a visual interface that guarantees an effective study of the docking outcomes. Following the success of earlier AutoDock versions, Trott and Olson at the Scripps Research Institute in La Jolla, California, created the docking program AutoDockVina. Because Vina is open source, a lot of people can use it without any restrictions. While AutoDockVina is conceptually different from AutoDock4, it retains some of the concepts and methods of AutoDock 4. In addition to being up to two orders of magnitude faster than AutoDock4, it provides notable gains in the average accuracy of the binding mode predictions. It also has a hybrid scoring system that combines knowledge-based and empirical scoring, as well as a new search method. The huge number of citations for the original publication demonstrates how quickly it spread throughout the docking community thanks to its multicore capability, excellent performance and improved accuracy, ease of use, and free availability. This program is a competitive substitute for virtual screening due to its great computational efficiency and capacity to utilize multiple CPUs or CPU cores. [16,17] The well-known protein-ligand docking tool AutoDockVina was developed in the same research facility as the well-known AutoDock4 instrument. It uses a new search algorithm to forecast the likely binding modes and a new scoring function to estimate protein-ligand affinity to construct an effective optimization approach. To speed up the computation, it can also use several cores on a single system to do calculations in parallel. We use the following vocabulary (the italicized terms) in this paper. [18] The configuration parameter exhaustiveness determines how many times to repeat the calculations. In one execution, Vina attempts to predict where and how a putative ligand can best bind to a specific protein. Vina may repeat the computations using various randomizations. Known as the docking box, the coordinates of a cuboid define the region of the protein surface where the tool tries to bind. This is what the Vina instructions refer to as the "search space. [19] By default, the randomized seeding of the calculations can result in different binding modes when the same execution is repeated on the same ligand-protein combination. In order to replicate the docking results, Vina does, however, allow the user to manually select an initial randomization seed. [20] On a multi-core computer, Vina may do the repeated computations

in parallel since they are independent of one another. It accomplishes this by creating several threads, which the program's threads will execute in parallel whenever the cores are available. When the docking experiment begins, the command-line option cpu can be used to limit the maximum number of threads that can run simultaneously. Vina attempts by default to generate as many threads as there are cores available. [21]

1.2. AutoDockTools (ADT)

One crucial graphical user interface (GUI) element created to make the setup, running, and analysis of molecular docking simulations with the AutoDock suite easier is AutoDockTools (ADT). ADT is an intuitive environment that makes it easier to prepare ligands and receptors for docking research, especially for users who are not experienced with command-line procedures. The assignment of Gasteiger partial charges, the inclusion of hydrogen atoms, and the conversion of input files into the PDBQT format—the particular file format used by AutoDock—are among the molecular structure preparation modules offered by ADT. Additionally, it allows users to specify the docking grid box, which establishes the ligand binding search space and guarantees that computational resources are directed toward the biologically significant areas of the enzyme. [22,23] ADT provides strong visualization features for examining input and output files in addition to preparation. Researchers can examine docking poses and evaluate possible ligand–receptor interactions by using ADT to visualize binding conformations, interaction energies, and hydrogen bonding patterns once docking is finished. [24] The creation of grid parameter files (GPF) and docking parameter files (DPF), which are crucial parts of an AutoDock docking run, is also automated by ADT. These files manage the computational configuration, including the number of runs of the genetic algorithm, the search method, and the energy evaluation parameters. [25]

- **Graphical User Interface (GUI)**

In order to help researchers, set up and analyze molecular docking simulations using the AutoDock suite, AutoDock Tools (ADT) offers a comprehensive and intuitive graphical user interface (GUI). By giving users the ability to carry out crucial operations such adding polar hydrogens, determining Gasteiger charges, defining torsional flexibility for ligands, and allocating suitable atom types, the GUI makes it easier to prepare the protein and ligand structures. ADT also makes it easier to define the grid box, which establishes the ligand binding search space. By enabling users to visually modify the grid center and size, the GUI guarantees accurate coverage of the intended binding site. The ability to display docked ligand conformations, rank results by binding energy, cluster comparable poses, and investigate important interactions like hydrogen bonds and hydrophobic contacts are just a few of the many visualization and analytical capabilities that ADT provides after docking. ADT is an essential part of structure-based drug discovery because of its integrated graphical environment, which improves the docking workflow, lowers human errors, and aids researchers in efficiently interpreting results. [26,27]

- **Preparing the Protein and Ligand**

The quality and dependability of docking results are directly impacted by the correct preparation of the ligand (small molecule) and the protein (receptor) in molecular docking studies. An organized and engaging environment is provided by AutoDockTools (ADT) to carry out this preparation effectively. [28]

- **Protein preparation**, ADT enables users to process the receptor structure for docking after loading it, usually in PDB format. In order to do this, the structure must be cleaned by eliminating extraneous molecules like ions, water, or co-crystallized ligands and fixing any structural problems. In order to accurately describe hydrogen bond interactions, ADT also helps with the addition of polar hydrogens and the assignment of Gasteiger charges, which are required for the computation of electrostatic interactions during docking. The protein is processed and then saved in PDBQT format, which is the input file type that AutoDock requires. This file type includes details on partial charges, atomic coordinates, and atom kinds that are unique to AutoDock. [29]

- **ligand preparation**, the ligand molecule can be loaded, all missing hydrogens can be added, Gasteiger charges can be assigned, and rotatable bonds can be identified using the GUI. ADT gives you the ability to specify which bonds will be flexible during the docking simulation, which enables the ligand to bind to the receptor in a variety of conformations. After the ligand is ready, it is saved in PDBQT format, which contains its charge information, torsion flexibility, and chemical structure. [30]

➢ **Defining the Grid Box**

The three-dimensional area surrounding the protein's binding site, where the ligand will be investigated during docking, is represented by the grid box, which can be graphically defined using the tools provided by the GUI. People can:

- To concentrate on the active site or other target areas, modify the grid center (X, Y, Z coordinates).
- Establish grid spacing and size to strike a balance between computational cost and accuracy.
- To guarantee precise covering of the binding pocket, visually verify the box's dimensions and placement within the 3D workspace. [31]

➢ **Analyzing Docking Results**

Once the docked ligand-protein complexes have been docked, ADT provides a range of tools for visual inspection and analysis. With the GUI, users are able:

- The 3D viewer may load and show docked ligand poses.
- Group related poses into clusters and sort docking data based on binding energy.
- Examine additional molecular contacts, such as hydrophobic interactions and hydrogen bonds.
- The flexibility and stability of binding modes can be understood by animating various ligand conformations. [32,33]

1.3. Theory of AutoDock

The purpose of the molecular docking program AutoDock is to forecast the binding conformation and affinity of ligands, or tiny molecules, to macromolecular targets, usually proteins. Concepts from molecular mechanics, thermodynamics, optimization techniques, and computational chemistry are all integrated into its theoretical framework.

1. Molecular Docking as a Search and Optimization Problem

According to AutoDock, docking is the process of determining a ligand's optimal binding location, orientation, and conformation inside the active region of a target receptor. The basic theoretical assumption is that the global minimum of the

binding free energy on the protein–ligand energy landscape represents the binding pose that is physiologically significant. [21]

2. Conformational Sampling (Search Algorithms)

To effectively search the enormous conformational space of ligand-receptor interactions, AutoDock uses a number of heuristic and stochastic search algorithms:

There are two main steps in the process:

A. LGA, or Lamarckian Genetic Algorithm

This is AutoDock's most effective and default search method. It blends:

- **Genetic Algorithms (GA):** a Darwinian evolution-inspired population-based worldwide search technique. We select, cross across, and mutate individuals (ligand poses).
- **Local Search (LS):** individual solutions are refined by a deterministic local optimizer (Solis-Wets algorithm).
- **Lamarckian Evolution Principle**: This principle mimics Lamarck's theory that learned qualities are inheritable, but in contrast to classical GA, the locally optimized (better) individual replaces the original.

B. Support for Additional Algorithms

- **Simulated Annealing (SA):** this method investigates the energy landscape by permitting upward motions according to a "temperature" parameter, then cooling down progressively to converge on minima.
- **Traditional Genetic Algorithm (GA):** relies only on evolutionary processes and does not use local search.
- Monte Carlo sampling, which generates random poses for quick first approximations. [34,35]

3. Scoring Function (Empirical Free Energy Function)

The scoring function of AutoDock is intended to simulate a ligand-receptor complex's binding free energy (ΔG_{bind}). The stronger the expected binding, the lower the value.

The semi-empirical scoring function is as follows:
$\Delta G_{bind} = \Delta G_{intermolecular} + \Delta G_{torsional} + \Delta G_{unbound}$
The most often used equation in AutoDock 4 is:
$\Delta G_{bind} = {}_{i,j}\sum(\Delta G_{vdW} + \Delta G_{electrostatic} + \Delta G_{hydrogen\text{-}bonding} + \Delta G_{desolvation}) + \Delta G_{torsion}$
Where;

Term	Description
ΔG_{vdW}	Van der Waals energy, is derived from a Lennard-Jones 12-6 potential.
$\Delta G_{Electrostatic}$	Coulomb's Law is used to explain electrostatic interactions using a dielectric constant that varies with distance.
$\Delta G_{hydrogen\text{-}bonding}$	Potential for directional hydrogen bonding that takes geometrical dependencies into consideration
$\Delta G_{desolvation}$	Desolvation energy using a pairwise solvation model based on atoms.
$\Delta G_{torsion}$	To compensate for the ligand's decreased flexibility upon binding, a torsional entropy penalty is used.

AutoDock is useful for virtual screening because of its scoring feature, which balances accuracy and processing speed. [36]

4. Energy Grid Maps (AutoGrid)

AutoDock uses AutoGrid to calculate grid-based energy maps prior to docking. The interaction energy between a single ligand atom type and the receptor at every location in three dimensions is represented by these precomputed grids.

Benefits:

- Prevents the need to recalculate receptor-ligand interactions each time.
- Significantly lowers the computational cost. [37]

5. Binding Pose Clustering

In order to determine the most likely binding modes, AutoDock clusters the generated poses based on the Root Mean Square Deviation (RMSD) after several docking runs are finished.

Clusters are arranged according to their frequency of occurrence and anticipated binding energy.

6. Underlying Assumptions

- **Rigid Receptor Model:** Unless flexible residues are specifically defined, the protein is regarded as static.
- **Flexible Ligand Model:** complete rotation of ligands around torsional bonds is permitted. Implicit Solvent: Instead of using explicit water molecules to describe solvent effects, the desolvation term is used in a simpler manner.
- **Binding Equilibrium:** The bound and unbound states are assumed to be in equilibrium for the simulation.

Mathematical Form of Scoring Terms

For a pair of atoms i and j:

$$E_{vdW}=A_{ij}/r^{12}_{ij}-B_{ij}/r^{6}_{ij}$$

$$E_{electrostatic}=q_iq_j/\epsilon(r_{ij})r_{ij}$$

$$E_{hydrogen}=E_{h-bond}\times f(\theta)$$

$$E_{desolvation}=S_iV_j+S_jV_i$$

where rij is the distance between atoms i and j, A and B are Lennard-Jones constants, q is atomic charge, ϵ\epsilonϵ is a distance-dependent dielectric, f(θ) accounts for hydrogen bond angular dependence, and S and V are solvation parameters. [38]

Scientific Impact

The philosophy behind AutoDock effectively strikes a balance between speed and precision, making it.

- Beneficial for chemical library virtual screening.
- Widely used in medication design that is based on structure.
- With modifications, it can be extended for protein-protein docking.
- A standard for predicting free energy in pharma and academics. [39,40]

METHODOLOGY

AutoDock is a popular molecular docking program for ligand-receptor interaction prediction. It uses the Lamarckian Genetic Algorithm (LGA), which combines local search and evolutionary optimization, for conformational searches. Key steps in the docking procedure include the following: [12,21]

1. Preparation of Macromolecule (Receptor) and Ligand

- Obtain the target receptor's three-dimensional structure from the Protein Data Bank (PDB).
- Use AutoDock Tools (ADT) to eliminate water molecules and non-essential heteroatoms.
- To take hydrogen bonding interactions into consideration, include polar hydrogens.
- Give the receptor a Gasteiger charge and save it in PDBQT format. [44]

2. Ligand Preparation

- The ligand structure can be obtained or constructed using PyMOL, Open Babel, or ChemDraw.
- Reduce the energy consumption with Open Babel or AutoDock Tools.
- The ligand file should be converted to PDBQT format.[45]

3. Generation of Grid Boxes

- Using AutoGrid, define a grid box surrounding the active site.
- Set the dimensions and grid spacing to cover the binding site, which is typically 0.375 Å.

4. Simulating Docking

- Use the Lamarckian Genetic Algorithm (LGA) to run AutoDock4.
- Specify the population size, energy evaluations, mutation rates, and the number of GA runs (often 10–100).
- Create a variety of ligand-receptor conformations by performing docking. [46]

5. Results of Docking Analysis

- Analyze AutoDock log (.dlg) files for binding energy scores (kcal/mol).
- Use LigPlot+, PyMOL, or Discovery Studio to visualize interactions.
- Choose the optimal position by considering hydrogen bonding interactions and binding energy.

6. Docking Validation

- Examine the position of the docked ligand in relation to known crystal structures.
- Determine the root-mean-square deviation **(RMSD)** in order to verify the accuracy of the docking.[47]

RESULT & DISCUSSION

AutoDock4 and AutoDock Vina's performance, flexibility, and computing efficiency differ significantly when compared to a variety of benchmark studies. Flexible ligand binding was successfully modeled by AutoDock4, which used a Lamarckian Genetic Algorithm. This was particularly useful in complicated systems that required in-depth torsional and conformational exploration. AutoDock4 accurately predicted postures with RMSD values under 2 Å in more than 75% of redocking experiments including 188 protein-ligand complexes, especially when lengthy GA runs were used. But because it was single-threaded, it took longer to execute, particularly when working with bigger ligand libraries. [48,49] On the other hand, AutoDock Vina showed better docking throughput. It was able to outperform AutoDock4 by up to 100 times because of its multithreaded architecture. Using the CASF-2013 dataset as a benchmark, Vina outperformed AutoDock4 in polar and charged receptor settings, correctly placing native-like poses in the top three results in more than 93% of situations. GPU-accelerated variants, as Vina-GPU, reported speed improvements of up to 403x while keeping consistent accuracy, greatly improving performance. [50] In addition to supporting sophisticated docking circumstances like covalent and hydrated docking, other tools like AutoGridFR enhanced the creation and viewing of energy grid maps. With its user-friendly graphical user interface (GUI), ADT significantly reduced setup time and human error while facilitating ligand and receptor preparation. AutoDock's adaptability to new scoring functions and optimization techniques, such as gradient-based ADADELTA in OpenCL-based modifications, further increased its usefulness for a variety of docking protocols. [51] The differences between AutoDock4 and AutoDock Vina highlight how crucial it is to use docking tools according to certain research requirements.

AutoDock4 is a good fit for investigations that need accurate interaction profiling and energetic interpretation because of its thorough modeling of ligand flexibility, incorporation of hydrogen bonding patterns, and dependence on empirically calibrated scoring methods. By using a genetic algorithm to simulate Lamarckian evolution, it provides a hybrid search mechanism that blends local and global optimization techniques. When combined with its adjustable docking settings, this capability allows for a thorough investigation of intricate binding modes, which is especially useful when dealing with flexible sidechains or macrocyclic ligands. [52] Despite these advantages, AutoDock4's limited capabilities in large-scale virtual screening are severely hampered by its single-core processing speed. AutoDock Vina, which was created to provide better performance through effective empirical scoring and multicore support, has substantially closed this gap. Vina's gradient-based local search improves posture convergence while using a manageable amount of computing power. In high-throughput scenarios like screening drug libraries against well-defined binding sites, benchmarking studies have continuously shown its higher predictive power in discovering native poses. [53]

Crucially, the emergence of GPU-compatible implementations, such Vina-GPU and OpenCL-enhanced AutoDock, has made it possible for these platforms to scale well on contemporary hardware, cutting down on time-to-result for large datasets. Even on consumer-grade systems and cloud infrastructures, real-time docking simulations are now possible thanks to these modifications and the usage of external parallelization frameworks. [54]

Graphical tools like AutoGridFR and AutoDock Tools (ADT) have made the docking pipeline much simpler. For creating grid boxes, preparing proteins and ligands, and analyzing results, ADT offers a visual interface. AutoGridFR, on the other hand, facilitates reproducibility by controlling affinity map metadata and permitting map reuse, which is crucial for uniformity in virtual screening campaigns. [55] However, there are still difficulties. The performance of both instruments varies according to the physicochemical characteristics of the target. In general, AutoDock performs well in hydrophobic conditions, whereas Vina prefers polar binding sites. The necessity of meticulous preprocessing and validation is further highlighted by the fact that subtle structural variations in receptor models can result in disparities in pose prediction. Both technologies' flexibility modeling for receptors is still restricted, while AutoDock4's flexible sidechain docking provides some respite. To sum up, AutoDock4 is still useful for its extensive configurability and dynamic insights, even while Vina offers quick and typically correct predictions for the majority of cases. Together, they create a complementary toolkit that, when appropriately matched with research objectives and computational capabilities, can tackle a wide variety of computational docking problems. [56,57]

❖ APPLICATIONS

When AutoDock was first released in FORTRAN, it was tested on several protein-substrate complexes that had been described using x-ray crystallography. N-formyltryptophan binding to chymotrypsin, N-acetylglucosamine binding to Lysozyme, and phosphocholine binding in an antibody combining site were among these assays. The crystallographic compounds were functionally recreated in nearly every instance by the AutoDock simulation results. AutoDockwas utilized in subsequent applications to forecast substrate-aconitase interactions before complex crystallographic structures were determined. Not only did we forecast the isocitrate binding mode in this work, but we also showed how useful AutoDock is for creating substrate models in the

preliminary phases of crystallographic protein structure resolution. One of the two binding modes identified by citrate docking studies closely matched the experimental electron density found for an aconitase-nitrocitrate complex. Information about the enzyme's suggested reaction mechanism was revealed by the docking simulation results. [58] According to Koshland's lab, the program was used in one unique and fascinating way. According to the diagram below, these researchers predicted the structure of the receptor-protein complex by utilizing the known structures of the aspartate receptor's ligand binding domain and the maltose-binding protein (MBP). The two octapeptides on the protein that are known to be involved in binding to the aspartate receptor were chosen using information from mutational studies on MBP. They then used our automated docking code to independently dock these peptides to the receptor model (the backbones of the peptides were fixed, but the side-chain conformations and overall orientations were unrestrained). The protein-receptor complex could be reasonably predicted because the two peptides' orientation and distance when bound to the receptor matched those of the intact MBP. When data on multi-site interactions are available, this method may be usually helpful. [59,60]

CONCLUSION

AutoDock and AutoDock Vina's open-source status, proven accuracy, and ongoing innovation keep them at the forefront of molecular docking. While AutoDock4 is still useful for its versatile docking capabilities and in-depth energetic analysis, Vina is favored for high-throughput applications due to its speed and predictive performance. ADT and AutoGridFR are two examples of tools that improve the docking workflow by making structure preparation and energy map creation easier. Better algorithms and GPU acceleration are quickly making virtual screening more widely available to scientific groups. Improved receptor flexibility modeling, improved cloud platform integration, and uniform benchmarking standards should be the main goals of future developments to promote structure-based drug discovery.

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HOW TO CITE: Sarthak Pal, Meenu Chaudhary*, Kanishak Kala, Autodock & Autodock Vina: Development, Capabilities, & Applications in Molecular Docking, Int. J. of Pharm. Sci., 2025, Vol 3, Issue 5, 3005-3019. https://doi.org/10.5281/zenodo.15458275