ISSN: 2690- 912X

Research Article

Journal of Genetic Engineering and Biotechnology Research

Swiss Dock is a Novel Web Technology That Simplifies Molecular Docking

Imran Hossain*

Department of Chemistry, National University of Bangladesh, Dhaka, Bangladesh

***Corresponding Author**
Imran Hossain, Department of Chemistry, National University of Bangladesh, Dhaka, Bangladesh.
Email: imranhchem@gmail.com.

Submitted: 2024, Oct 01; **Accepted:** 2024, Oct 23; **Published:** 2024, Nov 13

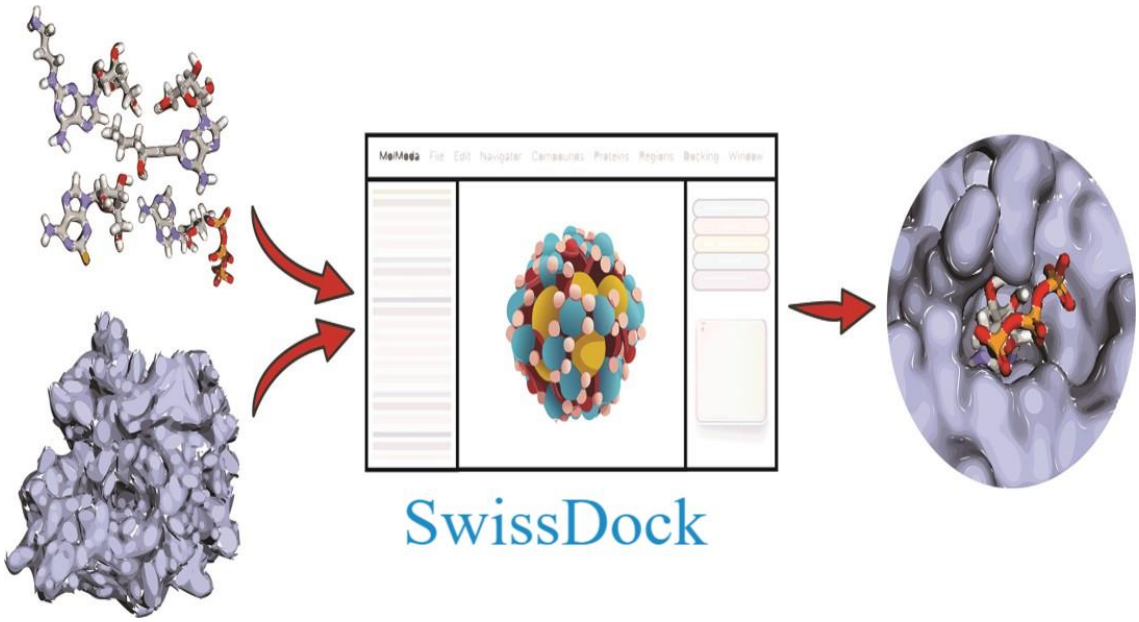
Citation: Hossain, I. (2024). Swiss Dock is a Novel Web Technology That Simplifies Molecular Docking. *J Gene Engg Bio Res, 6*(3), 01-07.

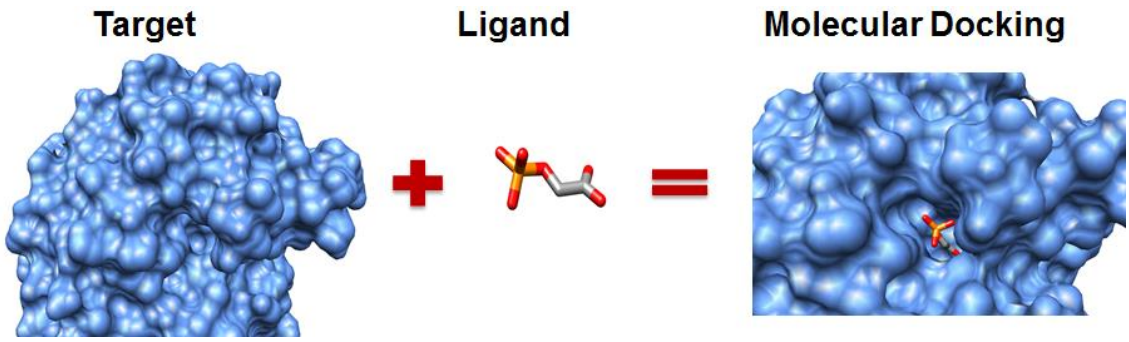
Abstract

Molecular docking techniques are essential for developing new medications by predicting how a ligand will bind, its affinity, and its position in the binding site of the target receptor. It has been demonstrated to be a rapid, uncomplicated, and economical method in both business and research settings. Swiss Dock, introduced in 2011 as part of the Swiss Drug Design project, provides a free internet-based tool for small-molecule docking that includes automated ligand and target setup. In this article, we present the latest version of Swiss Dock, in which EADock DSS is replaced by two newer docking software programs -Attracting Cavities and Auto Dock Vina. Auto Dock Vina provides faster docking predictions, while Attracting Cavities offer more accurate results. Ligands can be imported in using different methods, such as files, SMILES notation, or molecular sketches. Targets can either be imported in as PDB files or recognized based on their PDB ID. Users can utilize advanced search features to automatically access popular databases for both ligands and targets. The web interface has been completely redesigned to facilitate interactive submission and analysis of docking results. Swiss Dock provides a choice between command-line docking and covalent ligand docking, both of which include Attracting Cavities. Visit www.swissdock.ch for free access to Swiss Dock.

Keywords: Molecular Docking, Docking, Chemistry, Docking Server, Swiss Dock, Bioinformatics, Molecular Biology, Drug Discovery

Graphical Abstract





1. Introduction

Molecular docking is frequently used in structure-based drug design. It involves using computational methods to predict the ideal position, orientation, and conformation of a ligand in the binding site of a biological macromolecule. Docking is the process of generating different orientations of the small molecule on the surface of the target and determining the optimal position by considering the interactions between the ligand and target, as well as conformational and potentially desolvation energy. The docking program can forecast the binding free energy of small molecules to the target, assisting in identifying potential ligands. This predictive modeling technique speeds up drug discovery and reduces experimental costs. Molecular docking is based on the fundamental concepts of molecular recognition, which are mainly influenced by non-covalent interactions. The scoring functions used in molecular docking simulations strive to accurately represent these interactions, enabling the investigation of various chemical spaces and the discovery of ligands with optimal binding affinity. Multiple molecular docking techniques are accessible, including our proprietary EADock DSS and Attracting Cavities algorithms, as well as Auto Dock and Auto dock Vina. Various online tools offer docking algorithms, such as Docking Server, Webina, DOCK Blaster, Par DOCK, Seam Dock, and Proteins Plus. Swiss Dock, established in 2010, is a docking platform that is free to use and utilizes EADock DSS to forecast potential molecular interactions between a small molecule and a target protein. The goal is to reduce the complexity of using docking software and to expand the use of docking tools to a wider audience beyond the typical molecular modeling community. Swiss Dock automates the preparation of both the ligand and the target for docking. Calculations are conducted on a server without requiring the client to provide any computational resources. The engaging website displays docking outcomes, giving users a three-dimensional perspective of how ligands are positioned on the target's surface. Swiss Dock has been used by over 530,000 people from about 200 countries to perform over 710,000 docking procedures. According to Clarivate, Swiss Dock usage has been steadily growing, particularly throughout the SARS-CoV-2 pandemic, reaching around 1200 citations by January 2024. Swiss Dock provides the choice to make docking calculations using either our in-house method Attracting Cavities 2.0 or Auto Dock Vina. Auto Dock Vina provides fast docking predictions with accuracy, whereas Attracting Cavities delivers more dependable results but takes longer to compute. Both docking algorithms automate the preparation of the ligand and target, removing the necessity for user involvement. The web interface has been enhanced just like the rest of Swiss Drug Design's tools, such as Swiss Param, Swiss Sidechain, Swiss Dock, Swiss PARAM, Swiss Bioisostere, Swiss Target Prediction, Swiss Similarity, and Swiss ADME. The 2024 Swiss Dock online platform is easy to use and captivating. Ligands have the option to be imported in various formats. Targets can be imported as a Protein Data Bank (PDB) file or PDB ID. input data can be can be obtained from a variety of databases including ChEBI, PDBe, the Alpha Fold protein structure database, and SWISS-MODEL. Users can monitor the progress of their docking tasks and have the option to end them if needed. The interactive page displays result automatically with 3D visualizations of ligand poses. In the end, users have the ability to input, track, and access docking calculations via a visual interface. The new Swiss Dock 2024 can be found at https://www.swissdock.ch/, with the old version still accessible for six months at http://old.swissdock.ch/. Swiss Dock 2024 can be used without the need for logging in, and outcomes are shared under the CC BY 4.0 license.

2. Materials and Methods

2.1 Docking Algorithms

The first Swiss Dock made use of the EADock DSS algorithm for molecular docking.

Swiss Dock 2024 incorporates the latest version of Attracting Cavities (AC) and offers users the ability to perform faster molecular docking with Auto Dock Vina. Swiss Dock is an online platform that forecasts the potential molecular interactions that may happen between a specific protein and a small compound. Two different docking methods are available on Swiss Dock 2.

• Attracting Cavities 2.0 (AC)

With AC, the jagged energy profile of the macromolecule is substituted with a continuous attractive energy profile formed by imaginary attracting points encircling the macromolecular surface. The sampling process for docking involves basic rotations, translations, and geometric optimizations of the ligand on the flat terrain. Optimizations in the "mold" are then accompanied by optimizations in the actual protein energy landscape as well as an implicit solvation treatment. The scoring function of AC consists of the CHARMM force field terms and the fast analytical continuum treatment of solvation (FACTS) model.

• Auto Dock Vina

The Vina scoring function includes a potential similar to van der Waals forces, a hydrogen bond component that is not directed,

a hydrophobic factor, and a penalty for conformational entropy. Vina uses trilinear interpolations of pre-calculated grid maps on the target structure to calculate interactions between molecules, and it employs the target structure for minimizing the docked poses during post-processing.

• Ligand Preparation

In Swiss Dock, the ligand can be uploaded in different ways: for docking with attracting cavities, you must provide a smiles or mole2 file, or use the sketcher option to convert 2D structure to SMILES using the Marvin JS chemical editor. A more sophisticated feature enables the search for small compounds based on their name, PDB ID, or InChI. We access information from the Protein Data Bank and the ChEBI database globally. When using auto dock vina for docking, the ligand must be provided in either mole2 format or as a PDBQT file, or you have the option to construct a 2D ligand. In order to attract Cavities 2.0, the ligand must be parameterized during preparation. Swiss PARAM performs the parameterization using the MMFF-based method. If the parameterization is successful, both the parameter file and the residue topology file will be generated. The target is ready for utilization with CHARMM. A file containing coordinates and a file containing the protein structure of the system are generated using the uploaded target file. In Auto Dock Vina, the ligand is changed into a pdbqt file by running the mk_prepare_ligand python script with the Meeko python package. The prepare receptor command tool from the ADFR Suite is used to convert the target into a pdbqt file.

• Target Preparation

The macromolecular target can be uploaded as a PDB (AC or Vina) or as a PDBQT file (Vina only). The PDB ID can also be used to retrieve it from PDBe directly. PDB files are analyzed in order to show details about chains and heteroatoms, allowing users to choose which elements to keep for the docking process through the Swiss Dock web interface. Swiss Dock 2024 also offers an enhanced target search feature in three distinct structural databases: PDBe, SWISS-MODEL, and the Alpha Fold protein structure database. Vina transforms the PDB file into a PDBQT file. CHARMM is used to fill in missing side chains and hydrogen atoms. Water molecules are eliminated automatically, and possible conflicts are identified and eliminated.

Force field parameters and topologies are sourced from the CHARMM36 force field for amino acids, nucleic acids, non-natural amino acids, post-translational modifications, and various ions. Cofactor parameters and topologies can be obtained from CHARMM36. By using the command line, targets can be readied for covalent docking. The web tool automatically alters the pre-reactive target structure. Both the target's pre- and post-reactive forms are readied for CHARMM. Furthermore, the command line offers a choice to preserve water molecules within the desired structure.

• Implementation

The frontend of the Swiss Dock 2024 website is implemented in HTML5, PHP 7.4.3, and JavaScript. In order to show ligands in the molecular sketcher with the correct protonation state for docking, PDBQT files are converted to SMILES notation using Open Babel (version 2.4.1) and Mol2 files are converted using RDKit (version 2022.9.1, http://rdkit.org/).On the submission and result pages, you can view the target protein's 3D structure and the ligand's calculated poses using the NGL Viewer (version 2.1.0) in Java Script. Molecular interactions can be shown for atoms chosen visually by the user. The user can choose to display hydrogen bonds, ionic interactions, hydrophobic contacts, as well as cation-π and aromatic interactions individually or collectively. The NGL viewer is also utilized for visually defining the search box. Dropdown selections are implemented with sumo select (version 3.4.9, http://hemantnegi.github.io/jquery.sumoselect). The 2D layout of the ligand on the outcome page is generated using the ChemAxon JChem Micro services. Our servers handle the calculations, so users do not need to use any computing power. The backend was developed utilizing the web.py (version 0.62) framework in Python 3.8. An arrangement for scheduling calculations was established using a queuing system that relies on Slurm (version 19.05.5). Users can keep track of their tasks and halt them if needed.

3. Results and Discussion

Results and outputs of docking are available under a CC-BY 4.0 International License. Swiss Dock web page we found tutorials docking a to z. FAQ page for additional info. Command-line operation tutorials, old version Swiss Dock, Swiss Dock suite tools. contact page for assistance and ligand-target examples page.

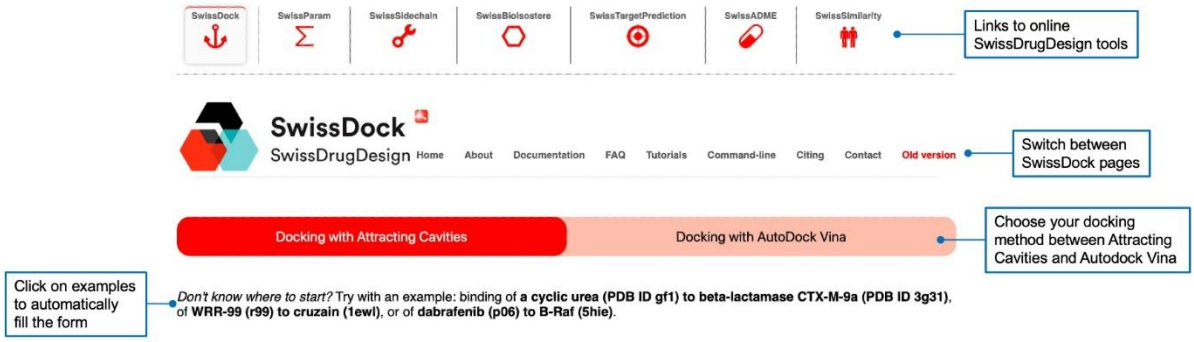
• Command-Line Access

Swiss Dock can now be easily accessed through a user-friendly command-line interface. The procedures for molecular docking are identical to those for the web interface. prepare the ligand and target ready, adjust the parameters, verify the session, and begin the docking process. In order to conduct a docking, one must have a ligand, a target, and a specified box center prepared. Once both are ready, you can establish your parameters and review your session. If your session can be submitted, you can start the docking. You have the option to upload your ligand in Mol2 format using the command, where it will undergo automated preparation with Swiss PARAM for docking with Attracting Cavities 2.0. The Swiss PARAM will prepare your SMILES for docking with Attracting Cavities. If everything checks out, you will be given a session number at random along with suggestions for different protonation states. You have the option to specify the pH for protonation of the SMILES directly, or the existing protonation state in your SMILES will be applied. After the target is uploaded and properly prepared, you can adjust the parameters for the docking process as you would for a noncovalent docking before initiating the docking using the commands. Additional information about the covalent docking preparation can also be found on the 'Command-line' webpage. In order to perform a docking using Swiss Dock, the first step is selecting the algorithm. There are two choices: Attracting Cavities 2.0 (AC) or Auto Dock Vina (Vina).

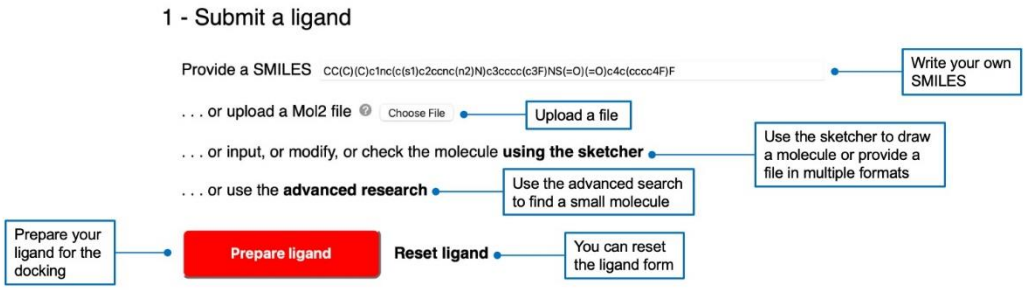
Next, you must 1) provide a ligand, 2) provide a target, 3) specify a search area, 4) choose your settings, and 5) initiate the docking process.

• Input: Choose a Docking Method

The docking algorithm can be selected by clicking on the relevant tab for your desired choice. You also have the option to select one of the three examples by clicking on the bold text that matches. This will complete the form with the ligand, target, and search space you want.

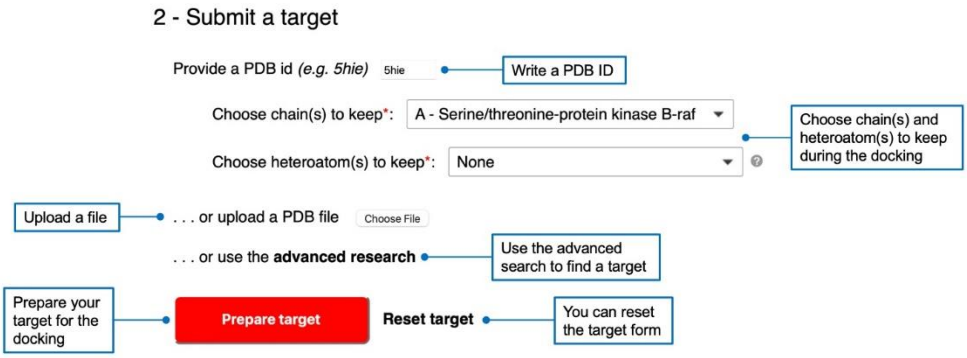


• Submit a Ligand



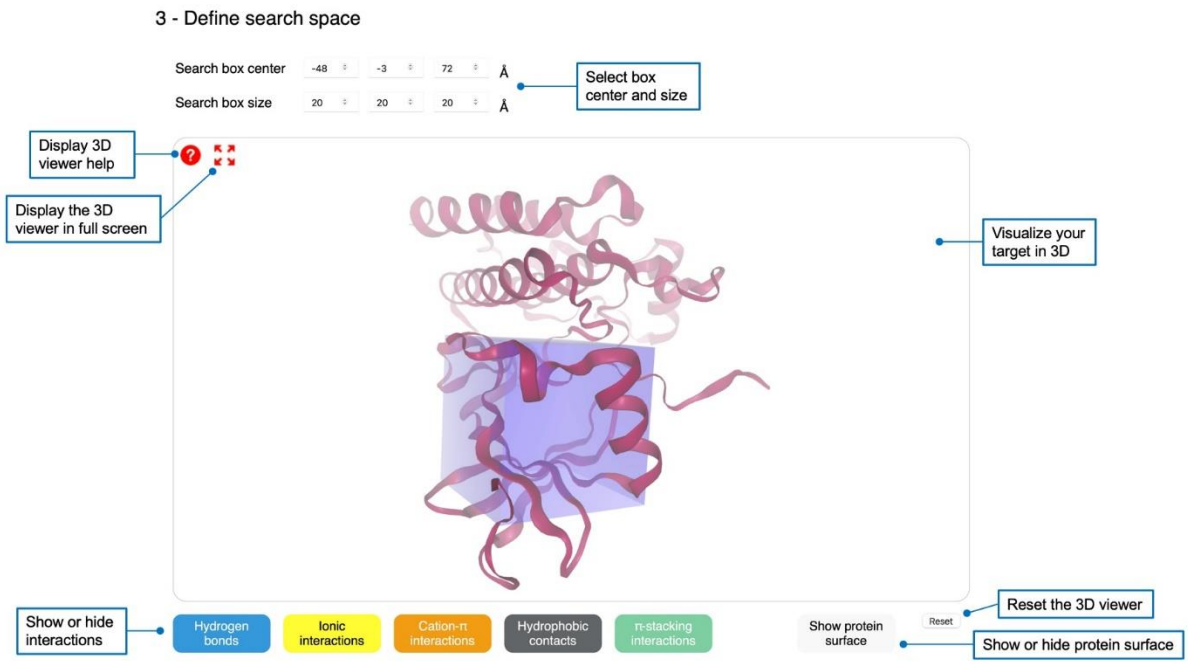
There are multiple methods available for submitting a ligand, such as entering a SMILES code, uploading a Mol2 file (and a PDBQT file for Vina), utilizing the sketcher tool, or accessing the advanced search option. The sketcher allows for the importation of various file formats. The SMILES notation will display your molecule in the text box. notation will be depicted in the molecular sketcher. After choosing a ligand, the "Prepare ligand" button will turn red and become clickable. If the preparation was successful, a tick mark will be displayed beside the button.

• Submit a Target



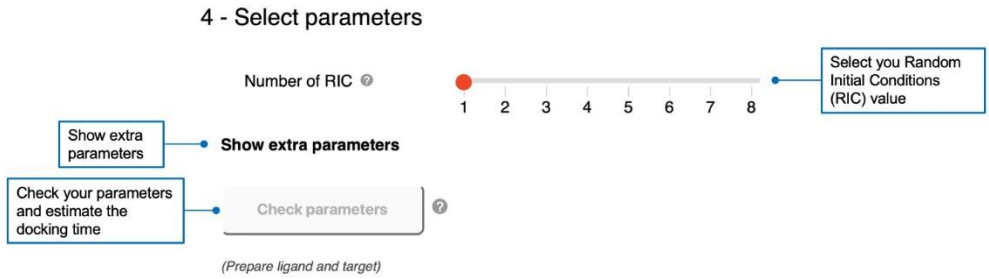
One way to submit a target is by writing a PDB ID, uploading a PDB file (along with a PDBQT file for Vina), or utilizing the advanced search link. The object you are focusing on will be visible in the three-dimensional display underneath. If you choose a PDB ID or utilize the advanced search, you must choose which chain(s) and heteroatom(s) to retain for the docking process. After choosing a target, the "Prepare target" button will turn red and be enabled. If the preparation is successful, a check mark will be visible beside the button.

• Define Search Space



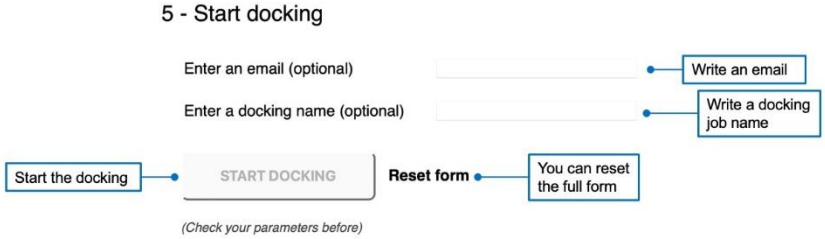
You have to establish an orthorhombic search area for docking the ligand. You have the option to set center and size values either through the boxes or by selecting an atom in the 3D viewer. You have the option to show multiple interactions by using buttons located underneath the viewer, in addition to the protein surface.

• Select Parameters



You have the option to define the Random Initial Conditions (RIC) parameter as 1, by default, for AC. You can also display additional parameters and: 1) specify the sampling thoroughly as low (180°), medium (default - 90°), or high (60°) values, 2) specify the cavity prioritization as buried (default - 70), medium (60), or shallow (50) values. Kindly consult the AC 2.0 reference for the definitions of these parameters. Vina allows for exhaustive sampling definition from 1 to 64, with a default value of 4 for Vina. After preparing a ligand and a target and choosing your parameters, you can click the "Check parameters" button to activate it and turn it red. If you want to review your settings, you can select the "Check parameters" button which will turn red and be enabled. This process will verify the adequacy of your docking input and predict the expected calculation duration. You may complete your docking task if the computation takes under 2 hours for AC, and 10 minutes for Vina. A tick will show up if your task is approved for execution.

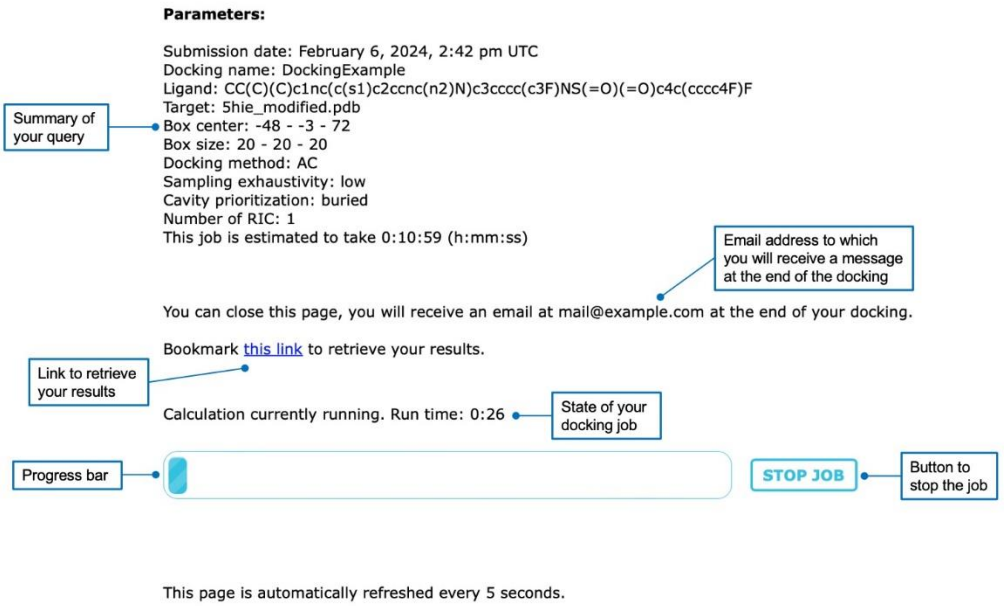
• Start Docking



Prior to commencing a docking assignment, you have the option to input your email address in order to receive a notification upon completion of the calculation. You can also provide a name for differentiation purposes between various tasks. After you have reviewed and confirmed your task, the "START DOCKING" button will turn red and be ready for use. You have the option to

click on it in order to begin your task.

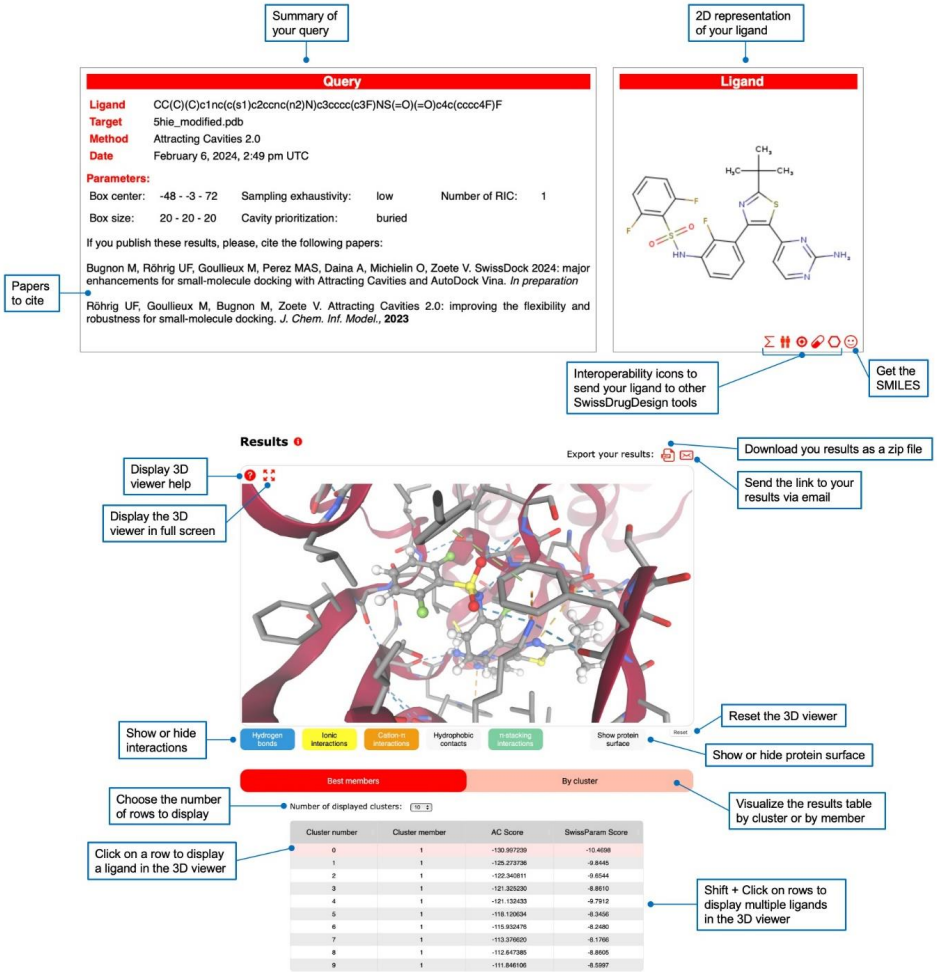
• Docking



As soon as you initiate a docking task, you will be directed to a waiting page without any further action required. You will find a summary of your query, the estimated time for execution, the calculation status, and a progress bar in this location.

If you wish to cancel your docking job, simply click on the "STOP JOB" button. If you entered an email address, feel free to exit the page; if not, please keep it open or save the results link. The page refreshes itself to provide updates on the progress of your job.

• Results



After the docking task is completed, you will be automatically sent to the results page. Above, you'll see a brief overview of your search and a 2D depiction of your ligand that can be shared with other Swiss Drug Design tools through interoperability icons. You can additionally access the SMILES representation of the ligand. Underneath the query and ligand boxes, there is a 3D viewer showing your target and the ligand poses that have been calculated. Icons located above the 3D viewer enable users to either download their results as a zip file or share a link to the page via email. Displayed under the 3D viewer is a table showing ligand poses ranked according to their score. To sort poses in AC, you have the option to arrange them either by their AC score or by their Swiss PARAM score by clicking on the corresponding header. Refer to the FAQ to grasp the distinction between the two scores. You can also choose to show a table that highlights the top members of each cluster, or have a separate table for each cluster. By clicking on a row in the table, you can view the matching ligand pose in the 3D viewer. The 3D shape will become visible, and a zomm feature will display connections between the position and the goal. You have the option to display various interactions by clicking on the interaction buttons located below the viewer. You also have the option to show the protein surface. One can view several ligand poses by pressing shift and selecting multiple rows.

4. Conclusions

Swiss Dock 2024 is the only online tool available that gives users the ability to use two advanced docking algorithms, one for accuracy and one for speed. It also enables the binding of small molecules to biological targets such as proteins, nucleic acids, and cofactors through non-covalent and covalent interactions without requiring any prior preparation. Users have the option to choose from different input formats for both ligands and targets, which includes an advanced search function for accessing several popular databases. Unlike other online docking tools, Swiss Dock conducts calculations on its server, removing the requirement for users to provide computational resources. Swiss Dock is tightly integrated into the Swiss Drug Design suite of online tools. By simply pressing a button, users can conveniently retrieve ADME parameters for a ligand via Swiss ADME, identify related small molecules using Swiss Similarity and forecast potential targets through Swiss Target Prediction. On the other hand, Swiss Dock has the ability to accept input ligands from these tools [1-8]. We believe that Swiss Dock is still essential for the scientific community and drug discovery, particularly due to its recent notable improvements. The user-friendly interface, coupled with effective docking algorithms, simplifies the prediction of ligand-target interactions, ultimately saving time. One can easily access Swiss Dock 2024 without needing to log in by using the user-friendly new command-line available at https://www.swissdock.ch/. Swiss Dock is a component of the Swiss Drug Design collection, overseen by the Molecular Modeling Group at the SIB Swiss Institute of Bioinformatics located at Lausanne University.

Conflict of Interest

The authors declare that they have no conflicts of interest

References

1. Kuntz, I. D., Blaney, J. M., Oatley, S. J., Langridge, R., & Ferrin, T. E. (1982). A geometric approach to macromolecule-ligand interactions. *Journal of molecular biology, 161*(2), 269-288.
2. Stanzione, F., Giangreco, I., & Cole, J. C. (2021). Use of molecular docking computational tools in drug discovery. *Progress in medicinal chemistry, 60*, 273-343.
3. Ferreira, L. G., Dos Santos, R. N., Oliva, G., & Andricopulo, A. D. (2015). Molecular docking and structure-based drug design strategies. *Molecules, 20*(7), 13384-13421.
4. Boike, L., Henning, N. J., & Nomura, D. K. (2022). Advances in covalent drug discovery. *Nature Reviews Drug Discovery, 21*(12), 881-898.
5. Grosdidier, A., Zoete, V., & Michielin, O. (2011). Fast docking using the CHARMM force field with EADock DSS. *Journal of computational chemistry, 32*(10), 2149-2159.
6. Zoete, V., Schuepbach, T., Bovigny, C., Chaskar, P., Daina, A., Röhrig, U. F., & Michielin, O. (2016). Attracting cavities for docking. Replacing the rough energy landscape of the protein by a smooth attracting landscape. *Journal of computational chemistry, 37*(4), 437-447.
7. Röhrig, U. F., Goullieux, M., Bugnon, M., & Zoete, V. (2023). Attracting cavities 2.0: improving the flexibility and robustness for small-molecule docking. *Journal of Chemical Information and Modeling, 63*(12), 3925-3940.
8. Morris, G. M., Huey, R., Lindstrom, W., Sanner, M. F., Belew, R. K., Goodsell, D. S., & Olson, A. J. (2009). AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of computational chemistry, 30*(16), 2785-2791.