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Problem Solving Protocol

Dockey: a modern integrated tool for large-scale molecular docking and virtual screening

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Abstract

Molecular docking is a structure-based and computer-aided drug design approach that plays a pivotal role in drug discovery and pharmaceutical research. AutoDock is the most widely used molecular docking tool for study of protein–ligand interactions and virtual screening. Although many tools have been developed to streamline and automate the AutoDock docking pipeline, some of them still use outdated graphical user interfaces and have not been updated for a long time. Meanwhile, some of them lack cross-platform compatibility and evaluation metrics for screening lead compound candidates. To overcome these limitations, we have developed Dockey, a flexible and intuitive graphical interface tool with seamless integration of several useful tools, which implements a complete docking pipeline covering molecular sanitization, molecular preparation, paralleled docking execution, interaction detection and conformation visualization. Specifically, Dockey can detect the non-covalent interactions between small molecules and proteins and perform cross-docking between multiple receptors and ligands. It has the capacity to automatically dock thousands of ligands to multiple receptors and analyze the corresponding docking results in parallel. All the generated data will be kept in a project file that can be shared between any systems and computers with the pre-installation of Dockey. We anticipate that these unique characteristics will make it attractive for researchers to conduct large-scale molecular docking without complicated operations, particularly for beginners. Dockey is implemented in Python and freely available at https://github.com/lmdu/dockey.

Keywords: molecular docking, virtual screening, parallel docking, drug design, protein–ligand interactions

Introduction

Drug discovery is a process that strives to identify a compound for comprehensive evaluation as a potential drug candidate and plays an important role in pharmaceutical industry [1, 2]. Unfortunately, the pipeline of discovery and development of drug has always been costly and time-consuming. Recent estimates show that the median capitalized research and development cost to bring a new drug to the market is about 985 million dollars [3], and the median clinical development time for FDA-approved drugs during the past decade is approximately 8.3 years [4]. Despite such immense investments, the attrition rates of drugs remain extreme high, even over 90% [5], leading it to be a critical issue and key challenge in drug discovery and development. With the rapid development of both computer and biological science, Computer-Aided Drug Design (CADD) has become one of the most efficient methods to greatly reduce the economic costs, time and attrition rates of drug development [6].

Molecular docking is a structure-based CADD approach that has been widely used within virtual screening to assist in streamlining and accelerating the overall drug discovery process [7]. Its procedure can be separated into two sections including search algorithm for generation of possible poses and scoring function for ranking candidate poses. The goal of molecular docking is to predict the preferred conformation, affinity and interaction of a ligand within the binding site of a macromolecular with the aid of computational tools [8]. In practice, ultra-large compound libraries are demanded and docked against a target for selecting the best-fitting molecule to discover novel lead compounds [9, 10]. Apart from new drug discovery, molecular docking is also broadly used in drug repurposing to explore new indications for approved drugs [11]. For instance, molecular docking has been recently applied to seek approved and clinical trial drugs for the treatment of COVID-19 caused by SARS-CoV-2 [12, 13].

In the past few decades, over 60 docking tools have been developed for both academic and commercial purposes [14]. Among these tools, AutoDock, representing AutoDock4 [15] and AutoDock Vina [16, 17], is the most popular docking tool with the highest

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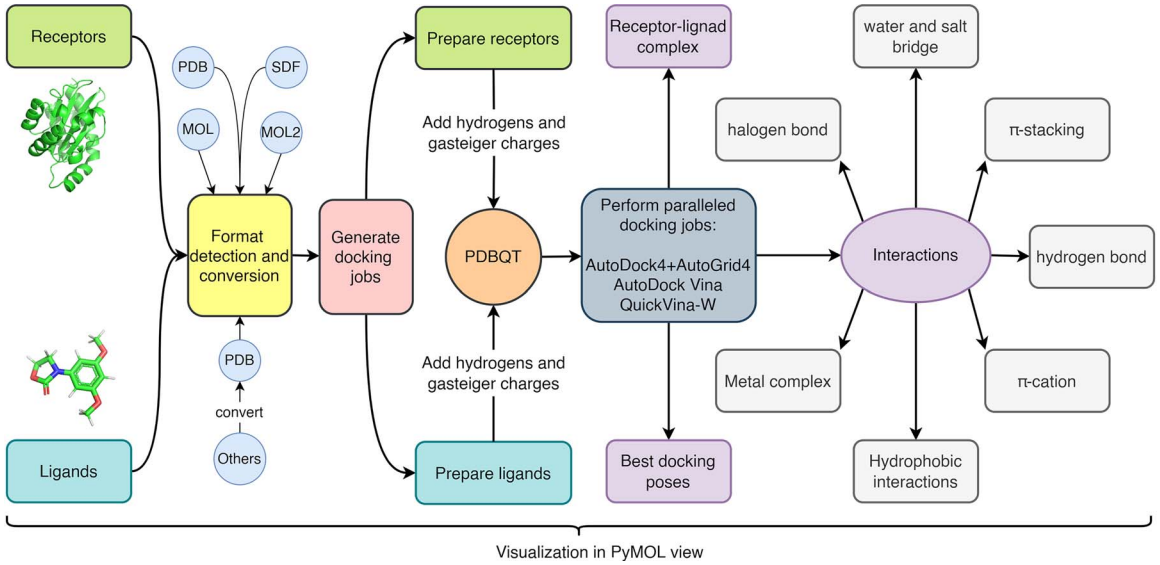

Figure 1. Overview of the Dockey workflow.

frequency of usage [18]. Due to open-source and fast speed, AutoDock Vina is more highly cited than AutoDock4 and has many variations with new features, like QuickVina-W designed especially for blind docking [19]. In order to improve and simplify the usage of these docking tools, a lot of efforts have been made to provide user-friendly graphical user interfaces (GUIs), such as Windock [20], DOVIS [21], PaDEL-ADV [22], VSDocker [23], DockoMatic [24], MOLA [25], AUDocker LE [26], VSDK [27], PyRx [28], Raccoon [29], DockingApp/RF [30, 31], JADOPPT [32], AMDock [33], Webina [34], InstaDock [35]. However, the majority of these tools are not well suitable for modern computer systems with the outdated GUIs and does not support cross-platform operation. In addition, most of them have no capability of analyzing the docking results and visualizing the docking conformations. Moreover, none of them provide the ability to detect non-covalent protein–ligand interactions. Altogether, these limitations have led users to struggle with many different tools and enhanced the requirements of more specific computer skills for users, especially for novice users.

Here we present Dockey, a novel tool with flexible and intuitive GUI to aid in facilitating the accomplishment of molecular docking. We seamlessly integrate several external tools to implement the complete docking pipeline covering molecular sanitization, molecular preparation, paralleled docking execution, interaction detection and visualization. Dockey is developed to run on all operating systems without installation of other tools or libraries except for docking engines. Furthermore, the application saves all data into a project file that can be transferred and reused between different computers and systems. In conclusion, Dockey will dramatically lighten the workload of researchers for performing molecular docking experiments.

Materials and methods

Docking pipeline

Dockey is written in Python and can be run as a standalone desktop application on multiple systems without dependencies. The workflow of Dockey is shown in Figure 1. We employ OpenBabel [36] to convert non-supported formats to PDB format and extract molecule base information including number of atoms, number of rotatable bonds, molecular weight and calculated octanol–water partition coefficient (*logP*). The input file format of AutoDock must be PDBQT format that is similar to the PDB format with extra atomic partial charges and atom types. The ligands and receptors are preprocessed and converted to PDBQT format using AutoDockTools [15] that comes as part of MGLTools software. Instead of MGLTools, the coordinates of molecules are prepared by AutoDockTools_py3, which is a slightly modified version of AutoDockTools that has also been used by AMDock and is particularly applicable to Python3. We also integrate Meeko [37] with the dependencies of RDKit [38] and Numpy [39] to help users to prepare small molecules for AutoDock Vina. We adopt AutoDock4, AutoDock Vina and QuickVina-W as docking engines which require PDBQT formatted file as the input. The interaction patterns of a ligand and receptor are determined with Protein-Ligand Interaction Profiler (PLIP) [40, 41]. In addition, PyMOL [42] is utilized to visualize three-dimensional structures of molecules and docked conformations.

Metrics estimation

Dockey provides calculations of various metrics for users to guide the selection and optimization of candidate lead compound in virtual screening. Ligand efficiency (LE) is the first proposed metric that is widely used for evaluation of goodness of interaction between a ligand and receptor [43]. LE is calculated according to the following equation [44]:

$$LE = -\Delta G/N$$

where ΔG is the free energy of binding and N represents the number of heavy atoms (non-hydrogen atoms) of ligand. Subsequently, size-independent LE (SILE) and fit quality (FQ) have been proposed to overcome the size dependency of LE. SILE has evolved from LE, as shown in following equation [45]:

$$SILE = -\Delta G/N^{0.3}$$

FQ is scaled *LE* that can be estimated using the following equation [46]:

$$FQ = LE/\left(0.0715 + 7.5328/N + 25.7079/N^2 - 361.4722/N^3\right)$$

Apart from molecular size, lipophilicity is another important factor to be considered in drug discovery. Lipophilic ligand

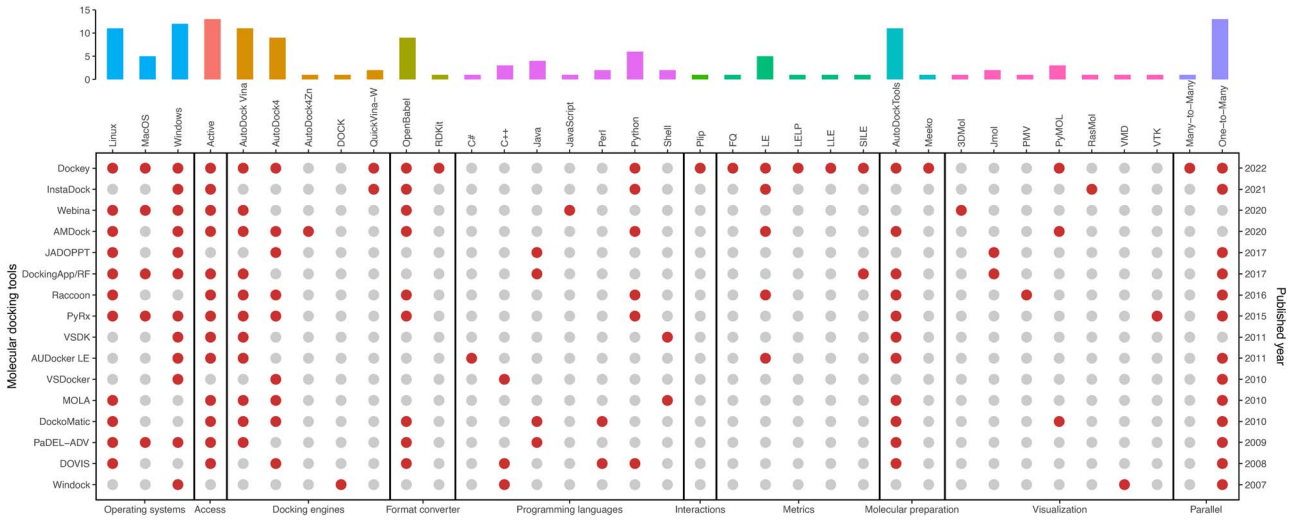

Figure 2. Comprehensive comparison of features between Dockey and other tools. The red dots indicate feature support. The bar plot shows the number of tools supporting that feature.

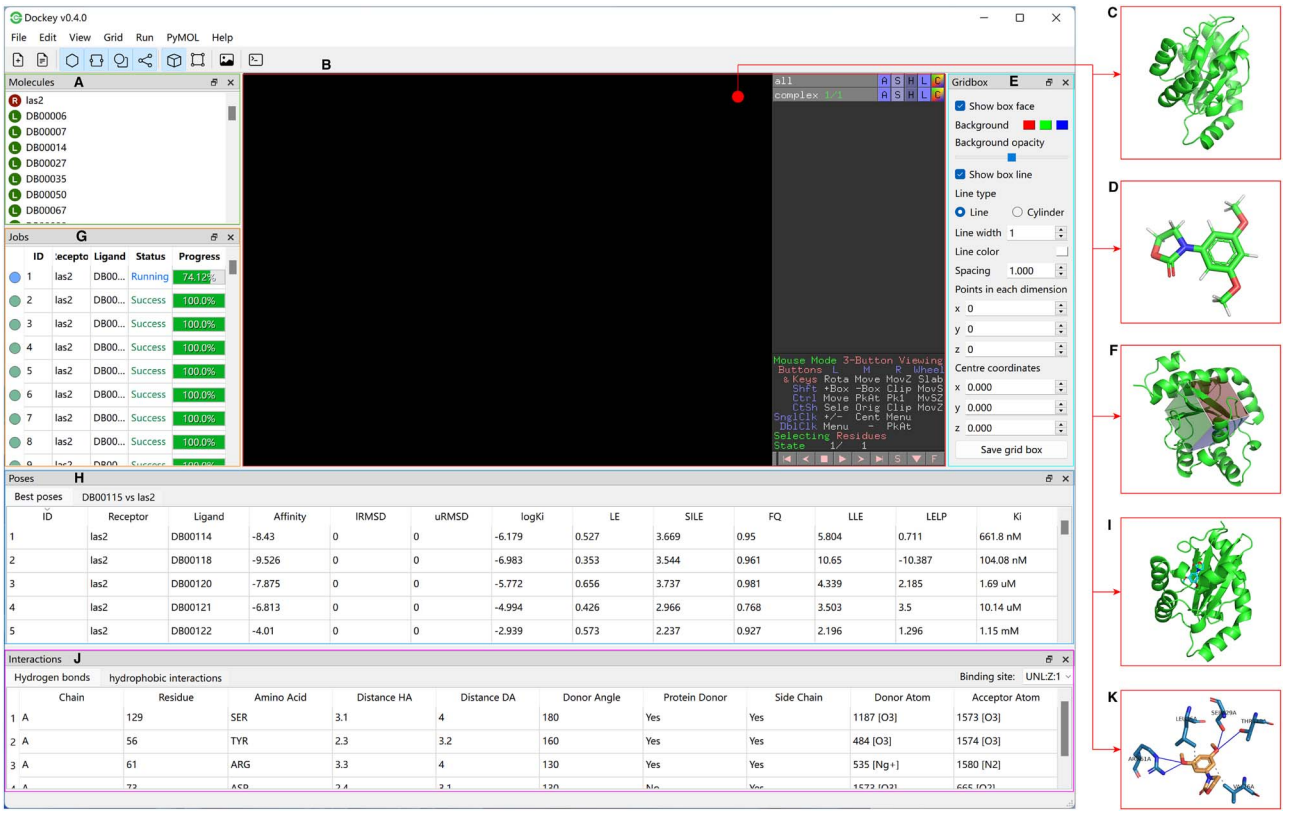

Figure 3. Main window of the Dockey. (**A**) Molecule list. (**B**) PyMOL view. (**C**) 3D structure view of receptor. (**D**) 3D structure view of ligand. (**E**) Grid box setting panel. (**F**) View of grid box in PyMOL. (**G**) Docking job table. (**H**) Docking poses for the best or a certain job. (**I**) 3D structure view of protein–ligand complex. (**J**) Protein–ligand interaction table. (**K**) View of detected various kinds of interactions in PyMOL.

efficiency (LLE) and ligand efficiency dependent lipophilicity (LELP) enable us to evaluate the lipophilicity. *LLE* can be derived from the following equation [47]:

$$LLE = -logKi - logP$$

where *Ki* indicates the estimated inhibition constant and *logP* denotes the calculated octanol–water partition coefficient. *LELP* is defined as the following equation [48]:

$$LELP = logP/LE$$

Results and discussion

Feature comparison

We have performed comprehensive comparison between the Dockey and other 15 existing tools in various aspects of features. The comparison results are illustrated in Figure 2. Most tools can

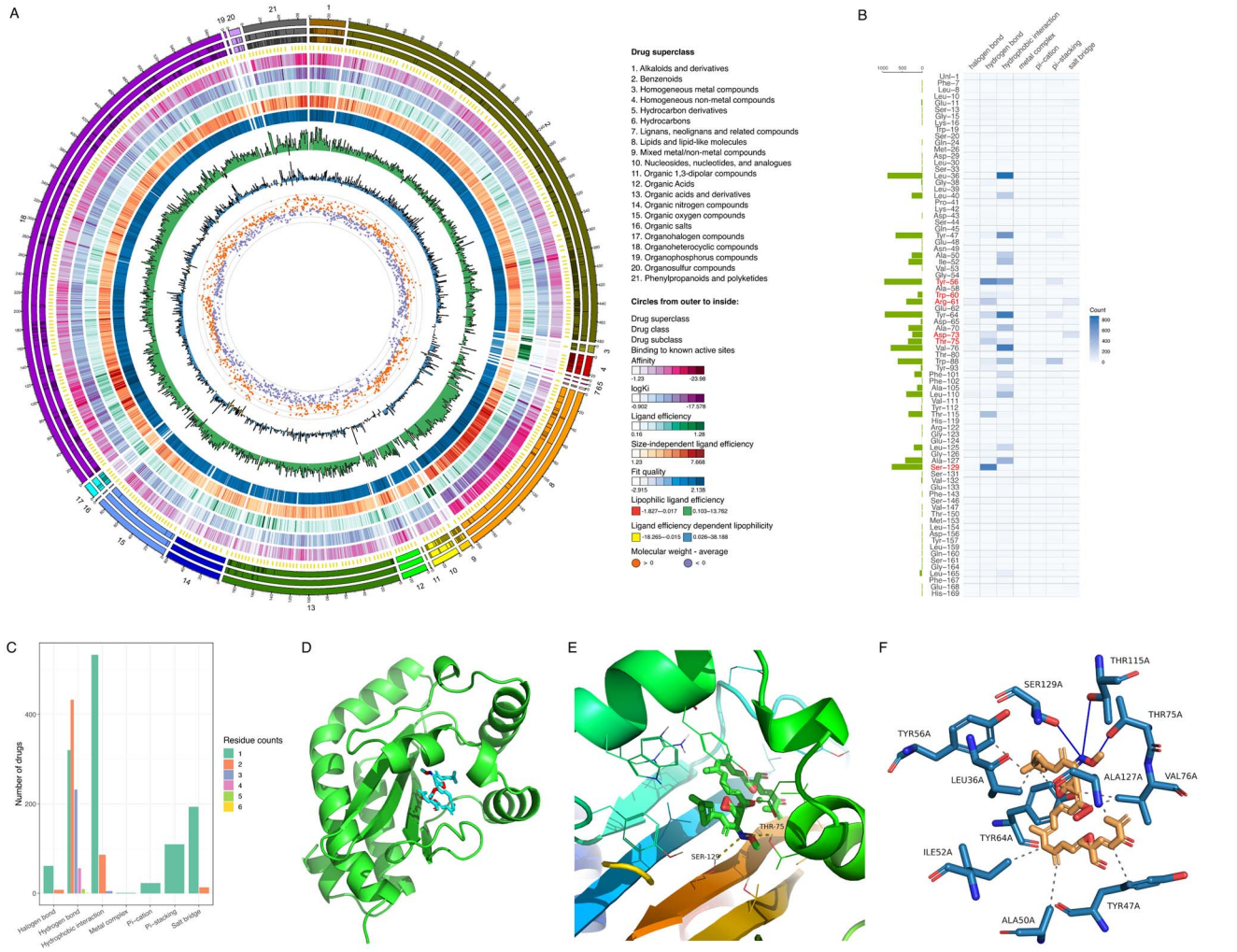

Figure 4. Prediction of potential repurposing of FDA-approved drugs to *P. aeruginosa* by docking with LasR protein. (**A**) Circos plot depicting the docking results of all drugs. From the outer to inner of the Circos plot: drug superclass; drug class; drug subclass; whether drug binding to known active sites; heatmap for binding affinity; heatmap for logKi; heatmap for LE; heatmap for SILE; heatmap for FQ; line plot for LLE; line plot for LELP; point plot for deviation from average molecular weight. (**B**) The heatmap indicates the abundance of all binding sites within each type of interaction. The bar plot shows the number of drugs interacting with that binding site. The red colored label indicates known active binding sites. (**C**) The number of drugs that can interact with multiple active binding sites within each type of interaction. (**D**) The best docking pose as an example for protein–ligand complex. (**E**) Hydrogen bonds of the best docking pose detected and displayed by PyMOL. (**F**) Various kinds of interactions of the best docking pose detected by PLIP and displayed in PyMOL.

only run on one or two systems, whereas Dockey and other four tools can operate on Windows, Linux, MacOS systems. Besides the ability of invoking AutoDock4 or AutoDock Vina like other tools, Dockey can also use QuickVina-W as its docking engine. Although AMDock can utilize AutoDock4Zn [49] for ligand docking to zinc metalloproteins, AutoDock4Zn is now obsolete and has been integrated into the latest version of AutoDock Vina. As shown in Figure 2, only few tools provide metrics for ligand assessment and mainly focus on LE. In addition to commonly used LE, Dockey also offers size-independent ligand efficiency metrics including FQ and SILE and lipophilicity-related metrics comprising LLE and LELP. It is worth noting that Dockey is the unique tool that allows users to directly detect interactions between ligands and receptors. Specifically, the application of PLIP makes Dockey convenient for detecting various interactions such as hydrogen bonds, hydrophobic contacts, π-stacking, π-cation interactions, salt bridges, water bridges, metal complexes and halogen bonds. Additionally, the integration of PyMOL not only facilitates users to visualize docking conformations and binding interactions but also helps users to preprocess molecules involving removal of water, solvent, organic or chains. Obviously, almost all the currently released tools enable multiple ligands to be automatically docked against one target, except AMDock and Webina (Figure 2). We have extended this functionality in Dockey, allowing large numbers of ligands to be simultaneously docked to multiple target proteins, which drastically reduces the execution time of docking process.

Application overview and usage

The main window of Dockey consists of one visual view and five removable panels which can be detached from the main window and floated as an independent window (Figure 3). All the imported ligands and receptors will be separately listed in molecule panel (Figure 3A). Dockey allows users to obtain detailed information of molecule by using the right-click menu on the selected molecule and visualize its three-dimensional structure in

Table 1. The top 10 drugs with the lowest binding affinity and the interaction type of hydrogen bonds

Accession	Name	Affinity (kcal/mol)	logKi	LE	SILE	FQ	LLE	LELP	Binding residues
DB11431	Moxidectin	−23.98	−17.578	0.521	7.604	2.138	10.799	13.012	Thr-75, Thr-115, Ser-129[a]
DB01199	Tubocurarine	−20.56	−15.071	0.457	6.562	1.846	9.921	11.268	Arg-61, Ser-129[a],
DB00762	Irinotecan	−19.23	−14.096	0.447	6.222	1.746	10.737	7.514	Trp-60[a]
DB00872	Conivaptan	−19.21	−14.081	0.506	6.45	1.801	8.378	11.271	Tyr-56[a], Trp-60[a], Tyr-64, Ser-129[a]
DB13063	Parthenolide	−18.25	−13.377	1.014	7.668	1.999	10.553	2.785	Thr-115, Ser-129[a]
DB00320	Dihydroergotamine	−18.19	−13.333	0.423	5.886	1.652	13.553	−0.521	Arg-61[a]
DB12457	Rimegepant	−18.19	−13.333	0.466	6.061	1.692	8.496	10.38	Tyr-56[a], Trp-88, Thr-115, Ser-129[a]
DB01126	Dutasteride	−18.06	−13.238	0.488	6.113	1.702	8.385	9.944	Tyr-56[a], Ser-129[a]
DB01092	Ouabain	−18.02	−13.209	0.44	5.915	1.659	12.912	0.675	Tyr-56[a], Arg-61[a], Trp-88, Thr-115, Ser-129[a]
DB06786	Halcinonide	−18.01	−13.202	0.581	6.428	1.765	11.197	3.45	Tyr-56[a], Ser-129[a]

LE: ligand efficiency, SILE: size-independent ligand efficiency, FQ: fit quality, LLE: lipophilic ligand efficiency, LELP: ligand efficiency dependent lipophilicity.
[a]The known active binding sites.

PyMOL view (Figure 3B) through clicking the receptor (Figure 3C) or ligand (Figure 3D). Prior to molecular docking execution, the users can manually specify search space for each receptor in the grid panel (Figure 3E) by changing the size and central position of grid box that can be viewed in PyMOL view (Figure 3F); otherwise, the whole space of receptor will be calculated and used as default search space. Then, the users need to select a docking engine with the adjusted or default corresponding parameters to generate a docking task queue where each receptor will be docked to all prepared ligands. The generated docking tasks will be listed in a job table panel (Figure 3G) in which the users are allowed to view the running status and progress of each job. After docking is finished, the users can view the best docking poses with binding energy and scores as well as evaluation metrics in the pose table panel (Figure 3H). The users can click a successfully docked task in the job table to examine the docking results for that job. When the users click a pose in the pose table, the three-dimensional structure of receptor-ligand complex of that pose will be displayed in PyMOL view (Figure 3I). Simultaneously, the corresponding ligand–protein interactions will be listed in the interaction table panel (Figure 3J). Subsequently, the users can click an interaction to show its three-dimensional structure in PyMOL view (Figure 3K).

Input and output

Due to the integration of OpenBabel and RDKit for format conversion, the Dockey supports molecule files in various formats, such as pdb, mol, mol2 and sdf. The other formats will be converted into a pdb format after imported. Ultimately, these formats will be converted to PDBQT format by AutoDockTools or Meeko for molecular docking. In addition to importing molecules from local files, Dockey can automatically download and import molecules from PDB [50] and Zinc databases [51, 52] by the given identifiers. The docked pose of ligand and ligand-receptor complex can be exported to pdb formatted files. The three-dimensional structure and interactions of complex can be saved to PNG image files. Moreover, all the data in Dockey containing molecules, job queue, docking results and interactions can be saved to a project file with .dock extension that can be shared by any other computers and systems with the installation of Dockey.

Case study

Pseudomonas aeruginosa is a prevalent opportunistic Gram-negative pathogen responsible for acute and chronic nosocomial infections in immune-compromised patients, leading to high morbidity and mortality due to multi-drug resistance to antibiotics [53, 54]. LasR protein is reported as the most promising therapeutic target for treating *P. aeruginosa* infections by blocking quorum sensing system to reduce the secretion of virulence factors [55]. In order to identify drug repurposing candidates capable of interacting with LasR, we have carried out molecular docking calculations between LasR and large numbers of small molecules. First, we have downloaded LasR protein from the PDB database (Entry ID: 3IX3) and only chain A was retained to perform molecular docking. Then, we have extracted 2348 FDA-approved drugs belonging to 21 superclasses from DrugBank [56] database. After the removal of drugs with molecular mass > 700 Da and rotatable bonds >15, the remaining 2119 drugs were then prepared using Meeko and docked against LasR using Dockey with AutoDock Vina. Finally, 1867 drugs were successfully docked to LasR with binding affinity varying from −0.81 to −23.98 kcal/mol (mean ± SD, −9.74 ± 3.36). Among these drugs, 1276 drugs can interact with the known active binding sites Tyr-56, Trp-60, Arg-61, Asp-73, Thr-75, Ser-129 [57], 1036 of which have binding affinity less than −7.5 kcal/mol.

The docking results including drug class, molecular weight, binding affinity and evaluation metrics are depicted in Figure 4A. On aggregate, drugs in the lipids and lipid-like molecules class exhibit significantly lower binding affinity. The hydrogen bond and hydrophobic interactions were detected as the most abundant interactions between these drugs and LasR (Figure 4B). The hydrogen bonds mainly occur between drugs and the known active binding residues that mainly enriched in Tyr-56, followed by Ser-129. Moreover, more than 730 (69.19%) drugs can simultaneously bind to more than two active sites (Figure 4C). The top 10 drugs with the interaction type of hydrogen bond and the lowest binding affinity are listed in Table 1, and the best one is Moxidectin (DB11431) with an affinity of −23.98 kcal/mol. Taking Moxidectin for example, the Dockey allows users to view its conformation within the formed complex in PyMOL view (Figure 4D). In addition, the Dockey also enables users to detect its hydrogen bonds by using PyMOL (Figure 4E) or view all kinds of interactions detected by PLIP (Figure 4F).

Conclusions

In this study, we developed a robust and highly usable GUI tool named Dockey for conducting molecular docking and virtual screening experiments based on AutoDock and its variants. To our knowledge, Dockey is the first tool covering the whole streamlined pipeline of molecular docking that involves molecular sanitization, molecular preparation, docking execution, interaction detection and conformation visualization. In addition, Dockey is very competent to automatically dock thousands of ligands to multiple receptors in parallel accompanying with detection of various kinds of interactions. Due to its cross-platform compatibility, the generated project file can be shared between any systems and computers with the installation of Dockey. These unique features make Dockey easy to use for both novices and experts to greatly reduce cumbersome operations during performing molecular docking. Dockey is freely available at https://github.com/lmdu/dockey.

Key Points

- Dockey is a cross-platform integrated tool with a user-friendly and intuitive graphical interface for simplifying molecular docking for both novices and experts.
- Dockey has implemented the whole pipeline of molecular docking covering molecular sanitization, molecular preparation, docking execution, interaction detection and conformation visualization.
- Dockey has capability to automatically dock thousands of ligands to multiple receptors and analyze the corresponding docking results in parallel.
- Dockey can generate a project file with molecules information and docking results for sharing between any systems and computers.

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References

1. Hughes JP, Rees S, Kalindjian SB, *et al.* Principles of early drug discovery. *Br J Pharmacol* 2011;**162**(6):1239–49.
2. Zhou SF, Zhong WZ. Drug design and discovery: principles and applications. *Molecules* 2017;**22**(2):279.
3. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009-2018. *JAMA* 2020;**323**(9):844–53.
4. Brown DG, Wobst HJ, Kapoor A, *et al.* Clinical development times for innovative drugs. *Nat Rev Drug Discov* 2022;**21**(11):793–4.
5. Sun D, Gao W, Hu H, *et al.* Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sin B* 2022;**12**(7):3049–62.
6. Yasuo N, Ishida T, Sekijima M. Computer aided drug discovery review for infectious diseases with case study of anti-Chagas project. *Parasitol Int* 2021;**83**:102366.
7. Meng XY, Zhang HX, Mezei M, *et al.* Molecular docking: a powerful approach for structure-based drug discovery. *Curr Comput Aided Drug Des* 2011;**7**(2):146–57.
8. Morris GM, Lim-Wilby M. Molecular docking. *Methods Mol Biol* 2008;**443**:365–82.
9. Bender BJ, Gahbauer S, Luttens A, *et al.* A practical guide to large-scale docking. *Nat Protoc* 2021;**16**(10):4799–832.
10. Lyu J, Wang S, Balius TE, *et al.* Ultra-large library docking for discovering new chemotypes. *Nature* 2019;**566**(7743):224–9.
11. Luo H, Mattes W, Mendrick DL, *et al.* Molecular docking for identification of potential targets for drug repurposing. *Curr Top Med Chem* 2016;**16**(30):3636–45.
12. Jang WD, Jeon S, Kim S, *et al.* Drugs repurposed for COVID-19 by virtual screening of 6,218 drugs and cell-based assay. *Proc Natl Acad Sci USA* 2021;**118**(30):e2024302118.
13. Hosseini M, Chen W, Xiao D, *et al.* Computational molecular docking and virtual screening revealed promising SARS-CoV-2 drugs. *Precis Clin Med* 2021;**4**(1):1–16.
14. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: a review. *Biophys Rev* 2017;**9**(2):91–102.
15. Morris GM, Huey R, Lindstrom W, *et al.* AutoDock4 and AutoDockTools4: automated docking with selective receptor flexibility. *J Comput Chem* 2009;**30**(16):2785–91.
16. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem* 2010;**31**(2):455–61.
17. Eberhardt J, Santos-Martins D, Tillack AF, *et al.* AutoDock Vina 1.2.0: new docking methods, expanded force field, and Python bindings. *J Chem Inf Model* 2021;**61**(8):3891–8.
18. Sabe VT, Ntombela T, Jhamba LA, *et al.* Current trends in computer aided drug design and a highlight of drugs discovered via computational techniques: a review. *Eur J Med Chem* 2021;**224**:113705.
19. Hassan NM, Alhossary AA, Mu Y, *et al.* Protein-ligand blind docking using QuickVina-W with inter-process spatio-temporal integration. *Sci Rep* 2017;**7**(1):15451.
20. Hu Z, Southerland W. WinDock: structure-based drug discovery on windows-based PCs. *J Comput Chem* 2007;**28**(14):2347–51.
21. Jiang X, Kumar K, Hu X, *et al.* DOVIS 2.0: an efficient and easy to use parallel virtual screening tool based on AutoDock 4.0. *Chem Cent J* 2008;**2**:18.
22. Pharmaceutical Data Exploration Laboratory. PaDEL-ADV: a software to perform virtual screening using AutoDock Vina. 2009. Available from: http://www.yapcwsoft.com/dd/padeladv.
23. Prakhov ND, Chernorudskiy AL, Gainullin MR. VSDocker: a tool for parallel high-throughput virtual screening using AutoDock on Windows-based computer clusters. *Bioinformatics* 2010;**26**(10):1374–5.
24. Bullock C, Cornia N, Jacob R, *et al.* DockoMatic 2.0: high throughput inverse virtual screening and homology modeling. *J Chem Inf Model* 2013;**53**(8):2161–70.
25. Abreu RM, Froufe HJ, Queiroz MJ, *et al.* MOLA: a bootable, self-configuring system for virtual screening using AutoDock4/Vina on computer clusters. *J Chem* 2010;**2**(1):10.
26. Sandeep G, Nagasree KP, Hanisha M, *et al.* AUDocker LE: a GUI for virtual screening with AUTODOCK Vina. *BMC Res Notes* 2011;**4**:445.
27. Baba N, Akaho E. VSDK: virtual screening of small molecules using AutoDock Vina on Windows platform. *Bioinformation* 2011;**6**(10):387–8.
28. Dallakyan S, Olson AJ. Small-molecule library screening by docking with PyRx. *Methods Mol Biol* 2015;**1263**:243–50.
29. Forli S, Huey R, Pique ME, *et al.* Computational protein-ligand docking and virtual drug screening with the AutoDock suite. *Nat Protoc* 2016;**11**(5):905–19.

30. Di Muzio E, Toti D, Polticelli F. DockingApp: a user friendly interface for facilitated docking simulations with AutoDock Vina. *J Comput Aided Mol Des* 2017;**31**(2):213–8.
31. Macari G, Toti D, Pasquadibisceglie A, *et al.* DockingApp RF: a state-of-the-art novel scoring function for molecular docking in a user-friendly interface to AutoDock Vina. *Int J Mol Sci* 2020;**21**(24):9548.
32. García-Pérez C, Peláez R, Therón R, *et al.* JADOPPT: java based AutoDock preparing and processing tool. *Bioinformatics* 2017;**33**(4):583–5.
33. Valdés-Tresanco MS, Valdés-Tresanco ME, Valiente PA, *et al.* AMDock: a versatile graphical tool for assisting molecular docking with Autodock Vina and Autodock4. *Biol Direct* 2020;**15**(1):12.
34. Kochnev Y, Hellemann E, Cassidy KC, *et al.* Webina: an open-source library and web app that runs AutoDock Vina entirely in the web browser. *Bioinformatics* 2020;**36**(16):4513–5.
35. Mohammad T, Mathur Y, Hassan MI. InstaDock: a single-click graphical user interface for molecular docking-based virtual high-throughput screening. *Brief Bioinform* 2021;**22**(4):bbaa279.
36. O'Boyle NM, Banck M, James CA, *et al.* Open babel: an open chemical toolbox. *J Chem* 2011;**3**:33.
37. Meeko: preparation of small molecules for AutoDock. 2022. Available from: https://github.com/forlilab/Meeko.
38. RDKit: Open-Source Cheminformatics Software. 2022. Available from: https://www.rdkit.org.
39. Harris CR, Millman KJ, van der Walt SJ, *et al.* Array programming with NumPy. *Nature* 2020;**585**(7825):357–62.
40. Salentin S, Schreiber S, Haupt VJ, *et al.* PLIP: fully automated protein-ligand interaction profiler. *Nucleic Acids Res* 2015;**43**(W1):W443–7.
41. Adasme MF, Linnemann KL, Bolz SN, *et al.* PLIP 2021: expanding the scope of the protein-ligand interaction profiler to DNA and RNA. *Nucleic Acids Res* 2021;**49**(W1):W530–4.
42. Schrödinger, LLC. The PyMOL Molecular Graphics System, Version 2.0. 2015. Available from: https://pymol.org.
43. Hopkins AL, Keserü GM, Leeson PD, *et al.* The role of ligand efficiency metrics in drug discovery. *Nat Rev Drug Discov* 2014;**13**(2):105–21.
44. Hopkins AL, Groom CR, Alex A. Ligand efficiency: a useful metric for lead selection. *Drug Discov Today* 2004;**9**(10):430–1.
45. Nissink JW. Simple size-independent measure of ligand efficiency. *J Chem Inf Model* 2009;**49**(6):1617–22.
46. Reynolds CH, Tounge BA, Bembenek SD. Ligand binding efficiency: trends, physical basis, and implications. *J Med Chem* 2008;**51**(8):2432–8.
47. Leeson PD, Springthorpe B. The influence of drug-like concepts on decision-making in medicinal chemistry. *Nat Rev Drug Discov* 2007;**6**(11):881–90.
48. Keserü GM, Makara GM. The influence of lead discovery strategies on the properties of drug candidates. *Nat Rev Drug Discov* 2009;**8**(3):203–12.
49. Santos-Martins D, Forli S, Ramos MJ, *et al.* AutoDock4(Zn): an improved AutoDock force field for small-molecule docking to zinc metalloproteins. *J Chem Inf Model* 2014;**54**(8):2371–9.
50. Burley SK, Bhikadiya C, Bi C, *et al.* RCSB Protein Data Bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. *Nucleic Acids Res* 2021;**49**(D1):D437–51.
51. Sterling T, Irwin JJ. ZINC 15—ligand discovery for everyone. *J Chem Inf Model* 2015;**55**(11):2324–37.
52. Irwin JJ, Tang KG, Young J, *et al.* ZINC20—a free ultralarge-scale chemical database for ligand discovery. *J Chem Inf Model* 2020;**60**(12):6065–73.
53. Zhao K, Yuan Y, Li J, *et al.* Phenotypic and genetic characterization of Pseudomonas aeruginosa isolate COP2 from the lungs of COPD patients in China. *Pathog Dis* 2019;**77**(4):ftz038.
54. Yuan Y, Yang X, Zeng Q, *et al.* Repurposing dimetridazole and ribavirin to disarm Pseudomonas aeruginosa virulence by targeting the quorum sensing system. *Front Microbiol* 2022;**13**:978502.
55. Sadiq S, Rana NF, Zahid MA, *et al.* Virtual screening of FDA-approved drugs against LasR of Pseudomonas aeruginosa for antibiofilm potential. *Molecules* 2020;**25**(16):3723.
56. Wishart DS, Feunang YD, Guo AC, *et al.* DrugBank 5.0: a major update to the DrugBank database for 2018. *Nucleic Acids Res* 2018;**46**(D1):D1074–82.
57. Bottomley MJ, Muraglia E, Bazzo R, *et al.* Molecular insights into quorum sensing in the human pathogen Pseudomonas aeruginosa from the structure of the virulence regulator LasR bound to its autoinducer. *J Biol Chem* 2007;**282**(18):13592–600.