NAVIGATING THE MOLECULAR MAZE: A PYTHON-POWERED APPROACH TO VIRTUAL DRUG SCREENING

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Globus Labs, University of Chicago

ABOUT ME

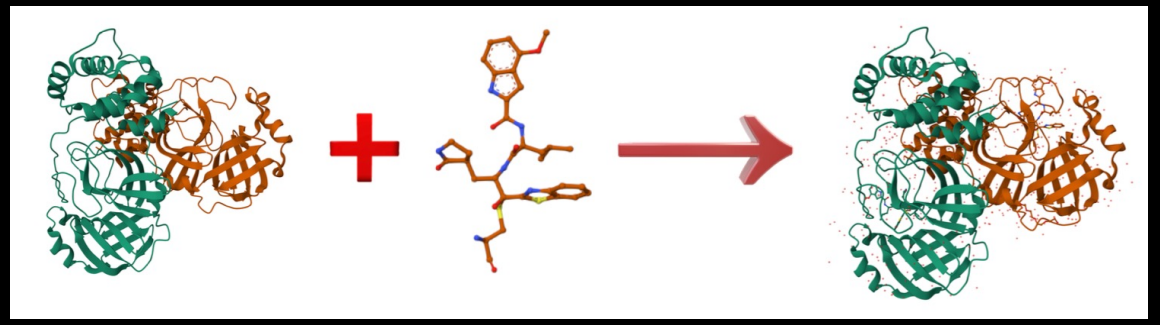
- Rising Senior at Glenbrook South
- Excited about the intersection of medicine and computing
- 10 Week Summer Internship in Globus Labs
- Advisors: Kyle Chard, Valerie Hayot

OVERVIEW

- COVID-19 pandemic brings urgency to accelerating virtual drug screening
- Brute force molecular search space is enormous
  - Finding the optimal drug candidates involves millions of Monte Carlo simulations that typically run for hundreds of seconds each ➔ thousands of years of computing on a single core
- Lightweight machine learning surrogate models can reduce the search space between 10x and 100x while maintaining high accuracy

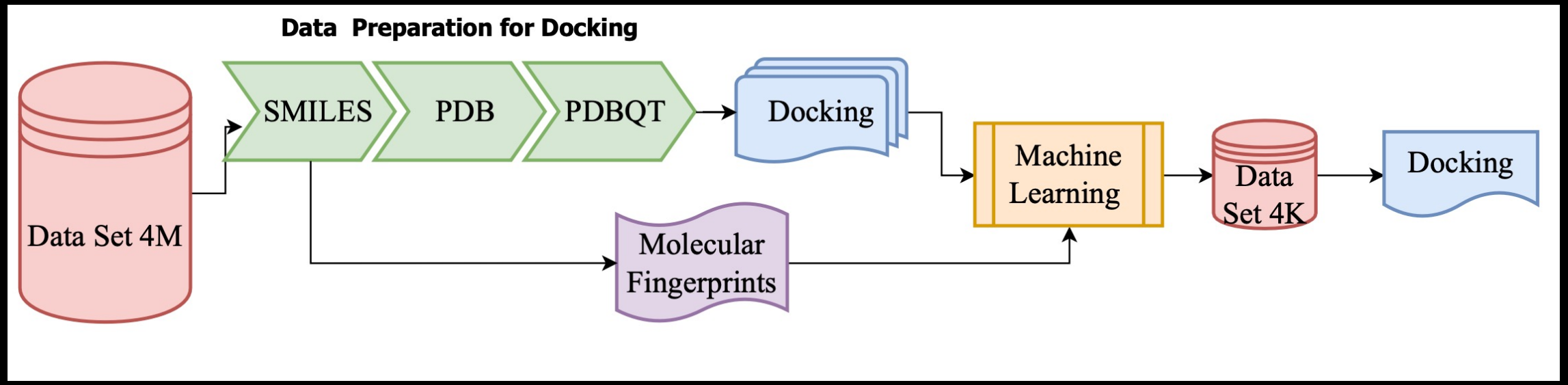
PROBLEM STATEMENT

- What is the problem?
  - Identifying the "best" ligands from a dataset of molecules by combining simulation and ML algorithms on HPC resources



- What are the challenges?
  - Machine learning model accuracy
  - Sampling efficiency
  - Computational cost
  - Complexity of docking workflow

PROPOSED SOLUTION



EXPERIMENTAL SETUP

- **Programming Tools**
  - Python 3.8.3, Parsl 1.3.0.dev0
- **Libraries**
  - AutoDock Vina 1.2.3, Visual Molecular Dynamics 1.9.3, Scikit-learn 1.3.0, NumPy 1.24.3, Pandas 1.5.3
- **Hardware**
  - 8c-laptop: 8-core Intel Core i9 CPU, 2.4GHz, 64GB DDR4, 8TB NVMe, MacOS 12.6.3
  - 192c-server: 8x 24-core x86 Intel Xeon CPU, 2.1GHz, 786GB DDR4, 16TB SSD, Ubuntu Linux 22.04
- **Dataset**
  - 0.9 GB file containing four million ligands stored as SMILES strings

SMILES ➔ PDB ➔ PDBQT

- **DB03048 SMILES**: c1c([nH]c(=O)[nH]c1=O)CC(=O)[O-]
- **DB03048 PDBQT**:

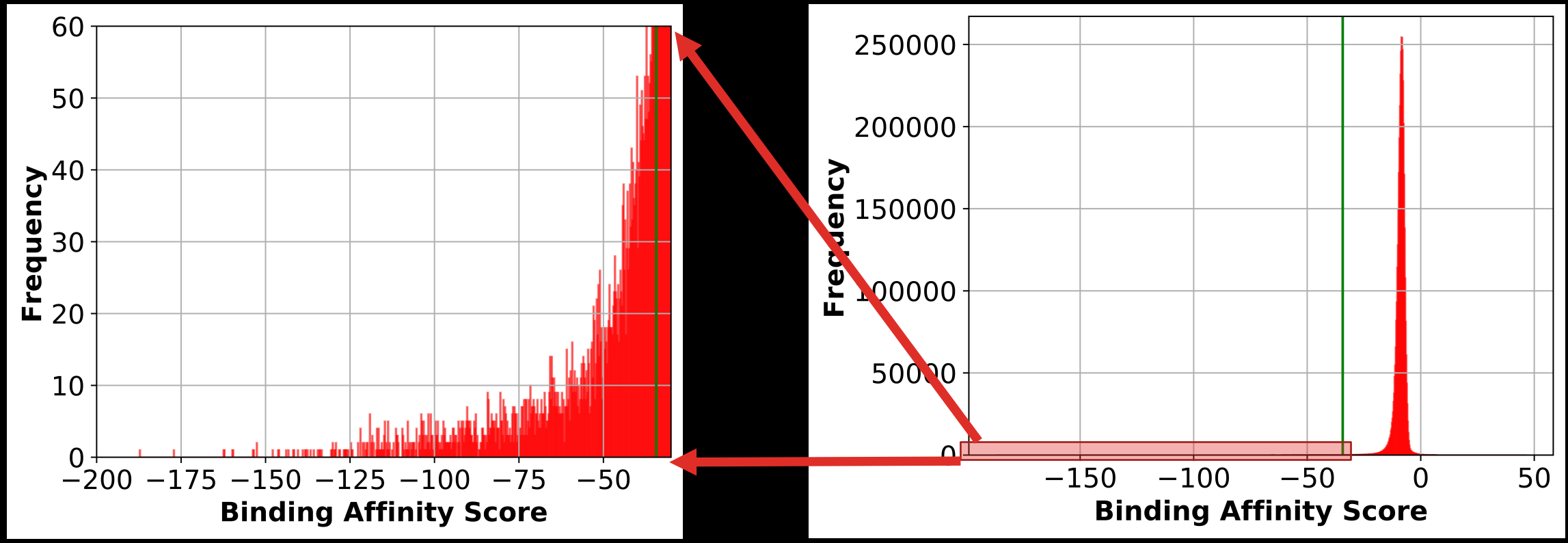
```
REMARK  2 active torsions:
REMARK  status: ('A' for Active; 'I' for Inactive)
REMARK    1  A    between atoms: C2_2  and  C5_9
REMARK    2  A    between atoms: C5_9  and  C6_10
ROOT
ATOM      1  C1  UNL X   1      -0.335   1.388  -0.190  1.00  0.00     0.100 A
ATOM      2  C2  UNL X   1       0.260   0.195  -0.322  1.00  0.00     0.029 A
ATOM      3  N1  UNL X   1      -0.405  -0.944   0.070  1.00  0.00    -0.312 N
ATOM      4  C3  UNL X   1      -1.656  -0.960   0.616  1.00  0.00     0.327 A
ATOM      5  O1  UNL X   1      -2.225  -1.982   0.991  1.00  0.00    -0.247 OA
ATOM      6  N2  UNL X   1      -2.264   0.262   0.718  1.00  0.00    -0.275 N
ATOM      7  C4  UNL X   1      -1.696   1.454   0.373  1.00  0.00     0.251 A
ATOM      8  O2  UNL X   1      -2.276   2.528   0.510  1.00  0.00    -0.268 OA
ATOM      9  H2  UNL X   1       0.132  -1.821   0.056  1.00  0.00     0.170 HD
ATOM     10  H3  UNL X   1      -3.183   0.278   1.125  1.00  0.00     0.173 HD
ENDROOT
BRANCH   2  11
ATOM     11  C5  UNL X   1       1.637   0.025  -0.910  1.00  0.00     0.170 C
BRANCH  11  12
ATOM     12  C6  UNL X   1       2.526  -0.888  -0.063  1.00  0.00     0.178 C
ATOM     13  O3  UNL X   1       2.096  -2.074   0.067  1.00  0.00    -0.648 OA
ATOM     14  O4  UNL X   1       3.580  -0.357   0.385  1.00  0.00    -0.648 OA
ENDBRANCH  11  12
ENDBRANCH   2  11
TORSDOF 2
```

DOCKING

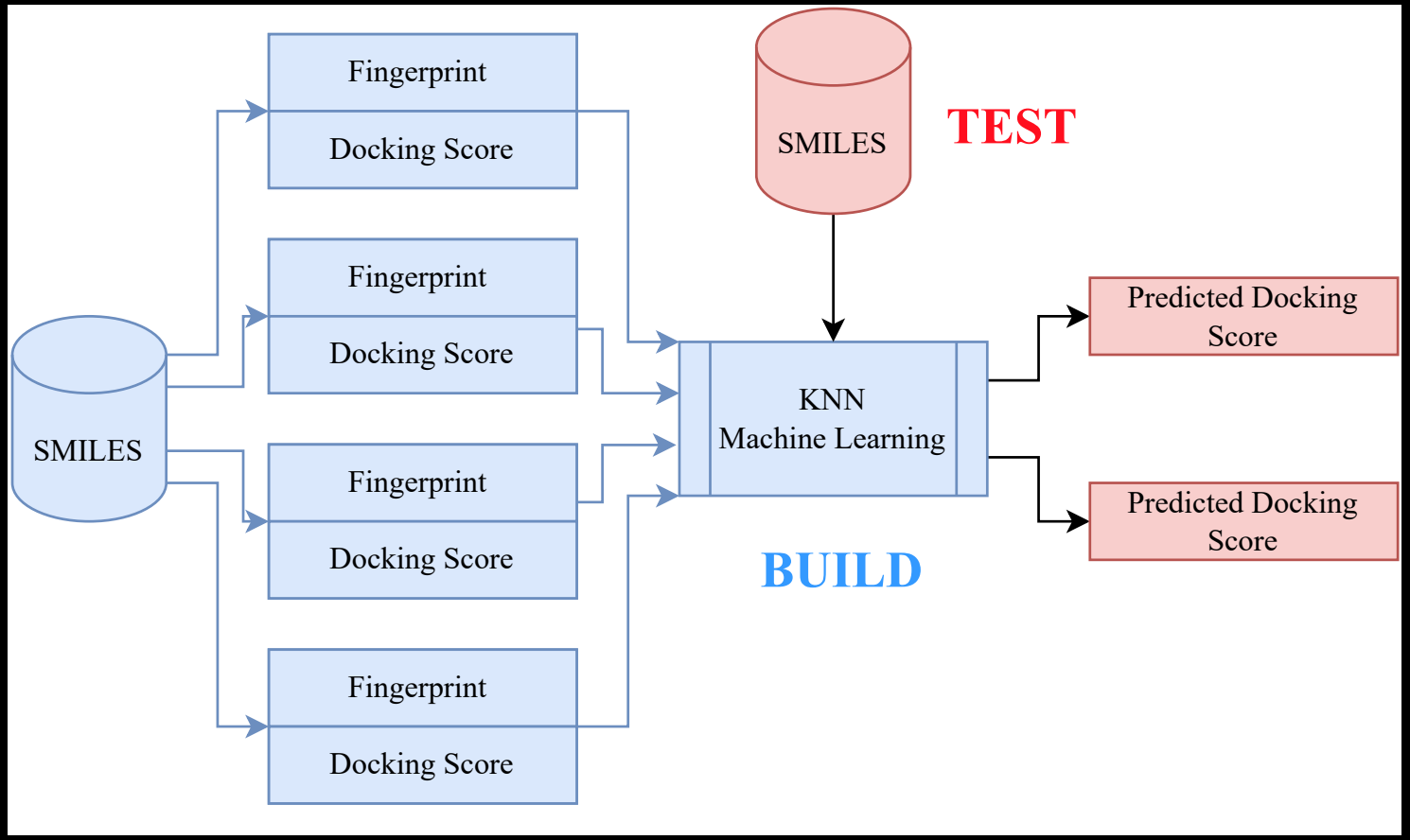
```
Scoring function : vina
Rigid receptor: 1iep_receptor.pdbqt
Ligand: DB03048-0.pdbqt
Grid center: X 15.614 Y 53.38 Z 15.455
Grid size  : X 20 Y 20 Z 20
Grid space : 0.375
Exhaustiveness: 32
CPU: 32
Verbosity: 1

Computing Vina grid ... done.
Performing docking (random seed: 1849697511) ...
0%   10   20   30   40   50   60   70   80   90   100%
|----|----|----|----|----|----|----|----|----|----|
**************************************************

mode |   affinity | dist from best mode
     | (kcal/mol) | rmsd l.b.| rmsd u.b.
-----+------------+----------+----------
   1        -6.36          0          0
   2       -6.298      2.329      4.576
   3       -6.174        2.1      2.931
   4       -6.069     0.9309      1.116
   5       -5.979       1.92      4.843
   6       -5.974      1.879      4.509
   7        -5.96      1.979      4.329
   8       -5.932      2.677       4.55
   9       -5.896      2.014      3.215
  10       -5.827      1.756      2.051

3.1626994609832764: docked 1/1 1iep_receptor.pdbqt to DB03048 -6.36
dock DB03048 3.1565709114074707 -6.36
Elapsed time run:  3.1630148887634277 seconds
```

Ligand (DB03048) to Receptor (1iep)

BRUTE FORCE DOCKING



MACHINE LEARNING

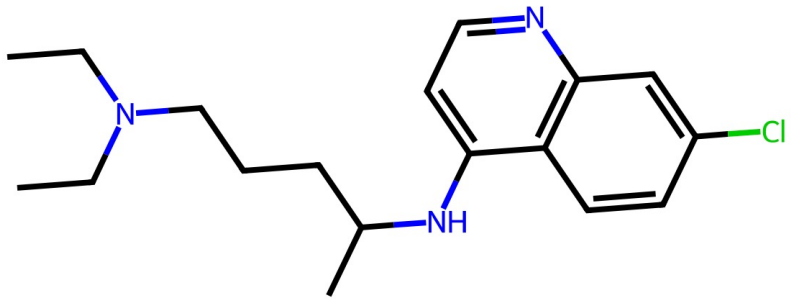


SMILES AND FINGERPRINTS

Hydroxychloroquine SMILES String

Example:
CCN(CCCC(C)NC1=C2C=CC
(=CC2=NC=C1)Cl)CCO

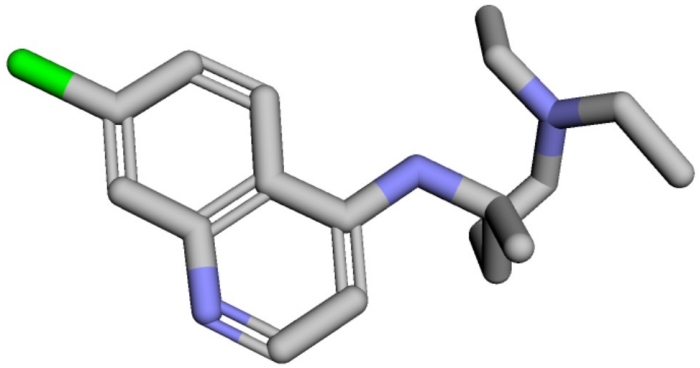
Explanation:
The simplified molecular-input line-entry system (SMILES) uses chemical notation to represent the structure of a molecule visualized in 2D below.



Hydroxychloroquine Fingerprint

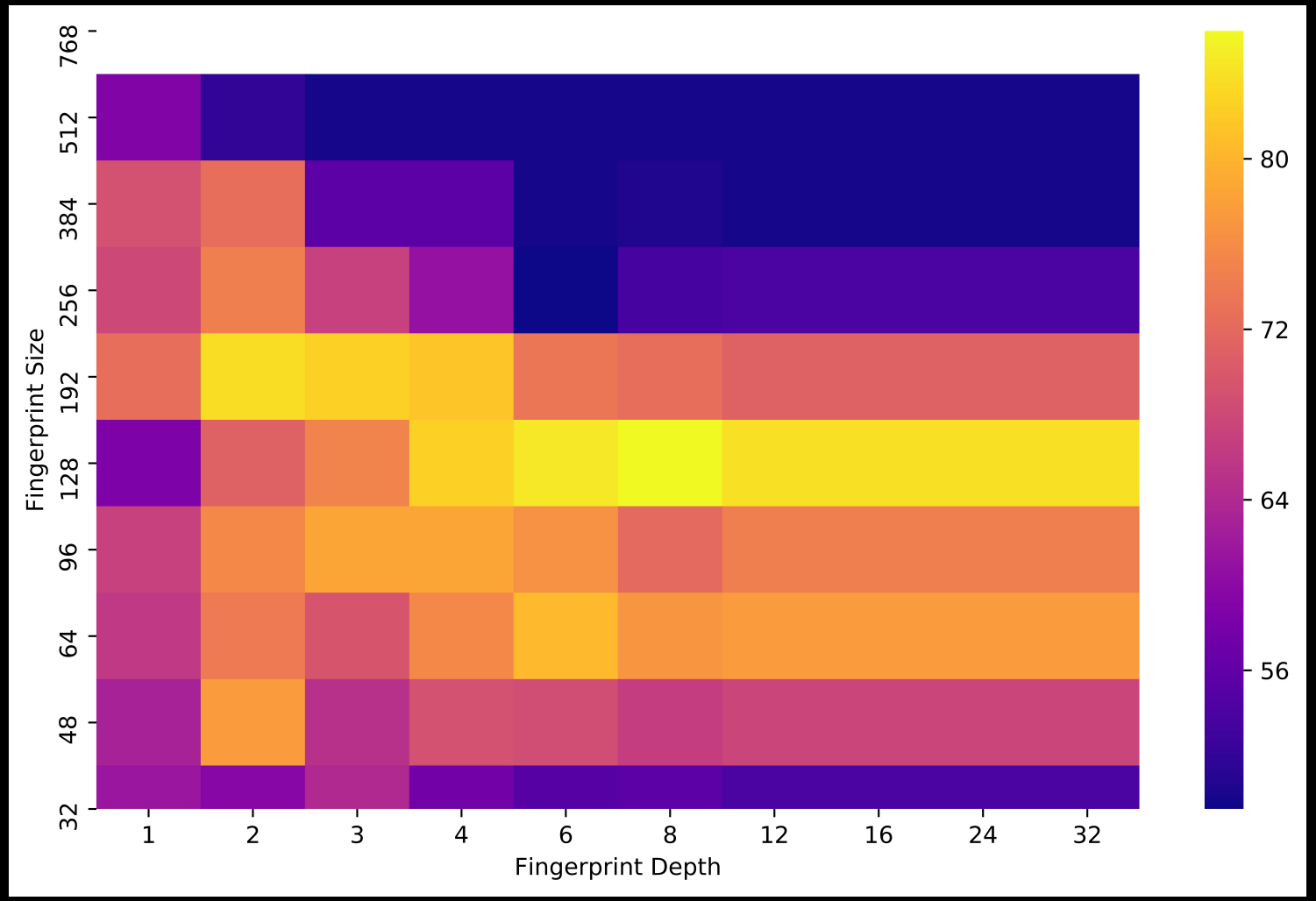
Example:
11100100111101011111001111011011
01111111100111111110000100110101

Explanation:
Molecular fingerprints are bit-vectors that help a machine learning model map a molecule description to a docking score.



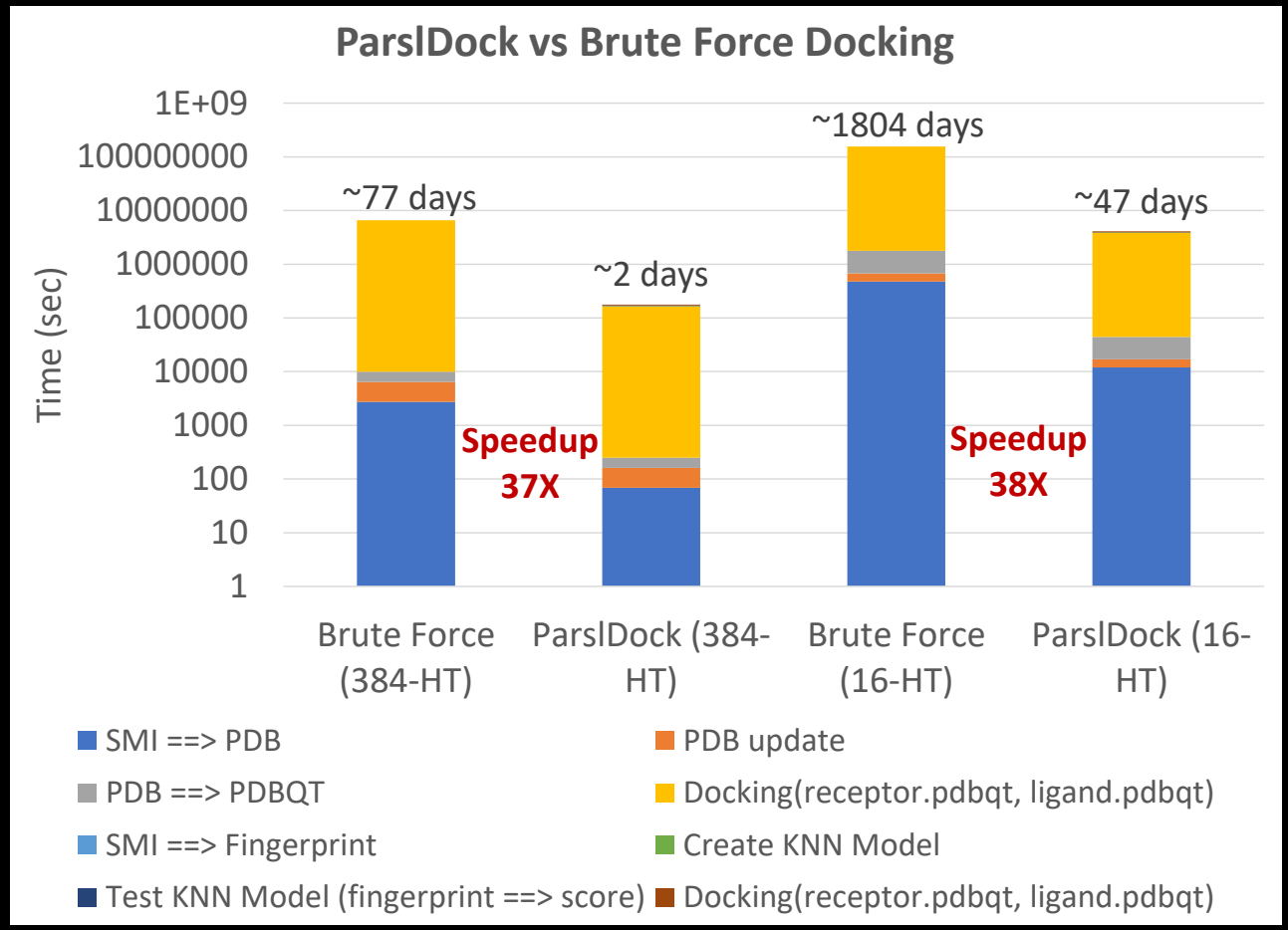
OPTIMIZING MACHINE LEARNING PARAMETERS

- KNN performance is sensitive to Morgan Fingerprint parameters (size and depth)
- Significantly better performance is achieved at a bit vector size of 128 and depth of 8



PARSLDOCK PERFORMANCE

- Up to 38X speedup on ParslDock vs. Brute Force Docking
- Linear scalability from 8-core laptop to 192-core server
- Docking (yellow) consumes the most compute time at 97%



CONCLUSION

- ParslDock: A Python-powered automated pipeline that uses Parsl and machine learning to accelerate the docking process, efficiently utilize compute resources, and reduce the time to discovery
- ParslDock achieves 38X speedup in performance that makes it possible to execute the virtual drug screening pipeline on a personal computer
- Submitted a poster to IEEE/ACM SuperComputing/SC 2023

Navigating the Molecular Maze: A Python-Powered Approach to Virtual Drug Screening

John Raicu [‡] Valerie Hayot-Sasson (Advisor) [‡] Kyle Chard (Advisor) [‡ ‡] Ian Foster (Advisor) [‡ ‡]

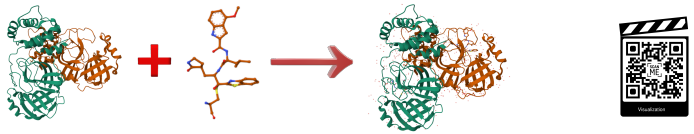
[‡]University of Chicago [‡]Argonne National Laboratory

Abstract

The COVID-19 pandemic has highlighted the power of using computational methods for virtual drug screening. However, the molecular search space is enormous and the common protein docking methods are still computationally intractable without access to the world's largest supercomputers. AI methods provide a powerful new tool to help guide docking campaigns. In such approaches, a lightweight surrogate model is trained and then used to identify promising candidates for screening. We present ParslDock, a Python-based pipeline using the Parsl parallel programming library and the K-Nearest Neighbors machine learning model to screen a huge molecular space of molecules against arbitrary receptors. We achieved a 38X speedup with ParslDock compared to a brute-force docking approach.

Problem Statement

- **What is Protein Docking?** Predicting the optimal binding conformation of a protein receptor and ligand using a binding affinity scoring function



- **What are the challenges?** Machine learning model accuracy, sampling efficiency, and computational cost and complexity of docking workflow
- **What is the problem?** Identify the "best" ligands from a large dataset of potential molecules by efficiently combining simulation and machine learning algorithms on high performance computing resources

Background

Hydroxychloroquine SMILES String

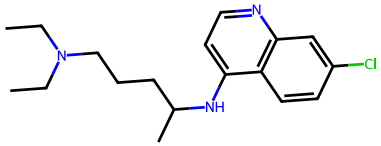
Example:
CCN(CCCC(C)NC1=C2C=CC(=CC2=NC=C1)Cl)CCO

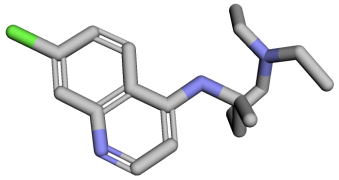
Explanation:
The simplified molecular-input line-entry system (SMILES) uses chemical notation to represent the structure of a molecule visualized in 2D below.

Hydroxychloroquine Fingerprint

Example:
11100100111101011111001111011101111111110011111111100000100110101

Explanation:
Molecular fingerprints are bit-vectors that help a machine learning model map a molecule description to a docking score.





Experimental Setup

Programming Tools

- Python 3.8.3 implements the computational pipeline
- Parsl 1.3.0.dev0 parallelizes various stages of the computational pipeline
- Jupyter Notebook 6.5.4 runs the Python code of the pipeline

Libraries

- AutoDock Vina 1.2.3 utilizes a scoring function and gradient-based optimization algorithm
- Visual Molecular Dynamics 1.9.3 visualizes and analyzes molecular simulations; Py3Dmol 2.0.3 enables interactive 3D molecular visualization directly in web browser; Matplotlib was used for general visualization
- Scikit-learn 1.3.0 was used for the machine learning KNN implementation
- NumPy 1.24.3 and Pandas 1.5.3 was used for general data processing and analysis

Hardware

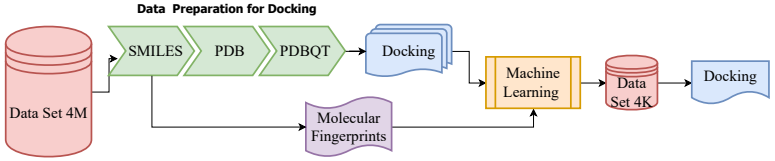
- 8c-laptop: 8-core Intel Core i9 CPU, 2.4GHz, 64GB DDR4, 8TB NVMe, MacOS 12.6.3
- 192c-server: 8x 24-core x86 Intel Xeon CPU, 2.1GHz, 786GB DDR4, 16TB SSD, Ubuntu Linux 22.04

Dataset

- 0.9 GB file containing four million ligands stored as SMILES strings

Proposed Solution

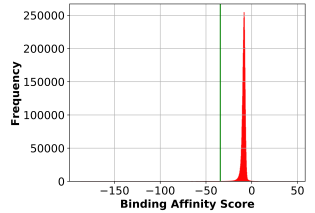
A python-powered automated pipeline that uses Parsl and machine learning to accelerate the docking process and improve resource utilization.



1. **Dataset 4M**: four million ligands represented by SMILES strings
2. **SMILES→PDB→PDBQT**: To prepare the data for docking, the SMILES strings are converted into PDB files and then into PDBQT files
3. **Docking**: Docking runs Monte Carlo simulations on the 1iep protein receptor PDBQT file with a ligand PDBQT file and outputs a binding-affinity score
4. **Molecular Fingerprints**: Morgan fingerprints are generated as a 128-bit vector with a depth of 8 from a SMILES string
5. **Machine Learning**: Morgan Fingerprints and docking scores are paired as the input to the machine learning model K-Nearest Neighbor (KNN)
6. **Dataset 4K**: four thousand ligands with the best docking scores (lowest binding-affinity scores)
7. **Docking**: Runs docking simulations on a smaller optimal subset of data containing four thousand ligands instead of four million

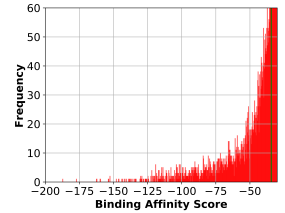
Results

Total Distribution of Docking Scores



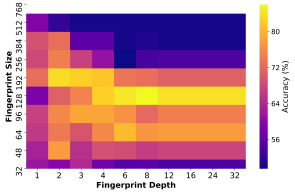
- Binding affinity scores have a normal distribution

Top 0.1% of Docking Scores



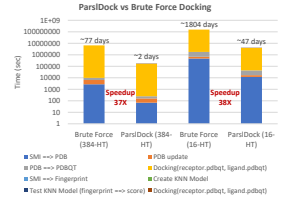
- Top-4k samples based on binding affinity score

Machine Learning Parameter Optimization



- KNN performance is sensitive to Morgan Fingerprint parameters (size and depth)
- Significantly better performance is achieved at a bit vector size of 128 and depth of 8.

ParslDock Performance Evaluation



- Up to 38X speedup on ParslDock vs. Brute Force Docking
- Linear scalability from 8-core laptop to 192-core server

Conclusions

- ParslDock: A Python-powered automated pipeline that uses Parsl and machine learning to accelerate the docking process, efficiently utilize compute resources, and reduce the time to discovery
- ParslDock achieves 38X speedup in performance that makes it possible to execute the virtual drug screening pipeline on a personal computer

References

[1] Yadu Babuji, Anna Woodard, Zhuozhao Li, Daniel S. Katz, Ben Clifford, Rohan Kumar, Łukasz Lacinski, Ryan Chard, Justin M. Wozniak, Ian Foster, Michael Wilde, and Kyle Chard. Parsl: Pervasive parallel programming in python. In *Proceedings of the 28th International Symposium on High-Performance Parallel and Distributed Computing*, HPDC '19, page 25–36, New York, NY, USA, 2019. Association for Computing Machinery. ISBN 9781450366700. doi:10.1145/3307681.3325400. URL `https://doi.org/10.1145/3307681.3325400`.

[2] Austin Clyde, Thomas Brettin, Alexander Partin, Hyunseung Yoo, Yadu Babuji, Ben Blaiszik, Andre Merzky, Matteo Turilli, Shantenu Jha, Arvind Ramanathan, et al. Protein-ligand docking surrogate models: A sars-cov-2 benchmark for deep learning accelerated virtual screening. *arXiv preprint arXiv:2106.07036*, 2021.

[3] T. Cover and P. Hart. Nearest neighbor pattern classification. *IEEE Transactions on Information Theory*, 13(1):21–27, 1967. doi:10.1109/TIT.1967.1053964.

[4] Jerome Eberhardt, Diogo Santos-Martins, Andreas F Tillack, and Stefano Forli. Autodock vina 1.2. 0: New docking methods, expanded force field, and python bindings. *Journal of chemical information and modeling*, 61(8):3891–3898, 2021.

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ONGOING WORK

- Containerize ParslDock for accessibility and ease of use
- ParslDock to showcase Parsl support for fine grained parallelism – joint work with Jamison Kerney (IIT) aiming for the WORKS Workshop at SC23

FUTURE WORK

- Screen ligands against the 7JKV protein receptor (brainstorming ideas with Aarvind Ramanathan, ANL)
- KNN relies on accurate distance metrics between samples
  - Explore various types of distance measures: Jaccard Coefficient, Tanimoto, Hamming Distance
- Explore additional ML models: deep neural networks (brainstorming with Ian Wang, MSOE)

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PARSLDOCK PERFORMANCE DETAILS

Stage	# of Tasks	Time/task (sec)	Parallelism	Total Time (sec)
SMI ==> PDB	100000	0.264	384	69
PDB update	100000	0.352	384	92
PDB ==> PDBQT	100000	0.340	384	88
Docking(receptor, ligand)	100000	634.459	384	165224
SMI ==> Fingerprint	4000000	0.001	1	1425
Create KNN Model	200	0.019	1	4
Test KNN Model (fingerprint ==> score)	4000000	0.368	384	3836
Docking(receptor, ligand)	4000	634.459	384	6609