Molecular Dynamics Simulations of p53 Inform Machine Learning of Allosteric Reactivators

Jeremy T. Zay[1], Theodore B. Sternlieb[1], and Kelly M. Thayer[1,2,3]

[1]Department of Mathematics & Computer Science Wesleyan University, Middletown, Connecticut 06459, USA
[2]Department of Chemistry Wesleyan University, Middletown, Connecticut 06459, USA
[3]Molecular Biophysics Program Wesleyan University, Middletown, Connecticut 06459, USA
jzay@wesleyan.edu

ABSTRACT

Allosteric modulators are compounds that bind to a protein at a non-active site, causing a conformational change that affects its activity. PK11000, an allosteric modulator of interest from the literature, binds to the p53 protein with a Y220C mutation. A crucial tumor suppressor, mutations in p53 are present in approximately 50% of cancers. For p53 with the Y220C mutation, the compound PK11000 was able to allosterically restore its normal function. However, PK11000 is toxic to humans, and since it binds to p53 in an unintended site, the process is poorly understood.

Understanding the Y220C mutation is a key case study for developing a pipeline for creating allosteric drugs to restore p53 native activity. In this study, we investigate the allosteric properties of p53 using molecular dynamics (MD) simulations, which provide information for machine learning (ML) approaches for the development of allosteric drugs.

INTRO & BACKGROUND

We employed an adversarial neural network based on the actor-critic framework, leveraging reinforcement learning (Figure 1) to optimize the design of potential drug candidates. Our model was critically evaluated by comparing the predicted binding affinities of molecules generated through *in silico* synthesis to known allosteric effectors with established dissociation constants (Kd) for the Y220C p53 mutant.

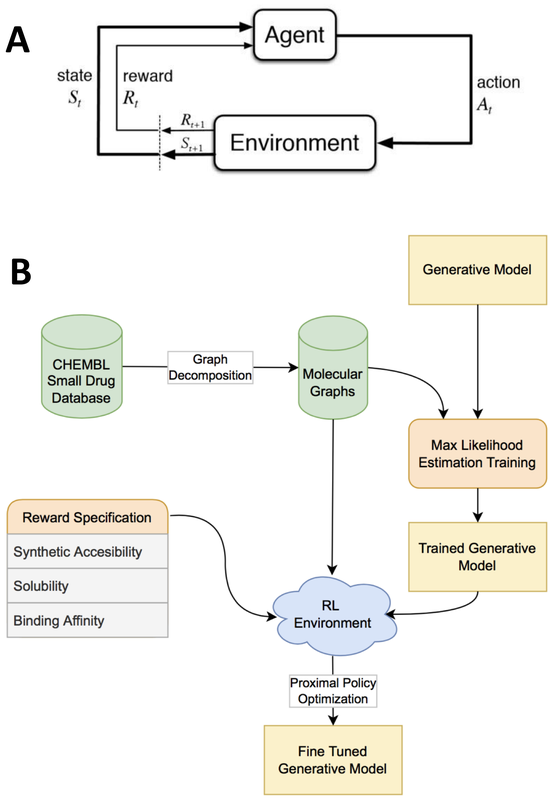

Figure 1: Reinforcement Learning Network.
A. Reinforcement learning (RL) network example.
B. Drug design strategy.

RESULTS

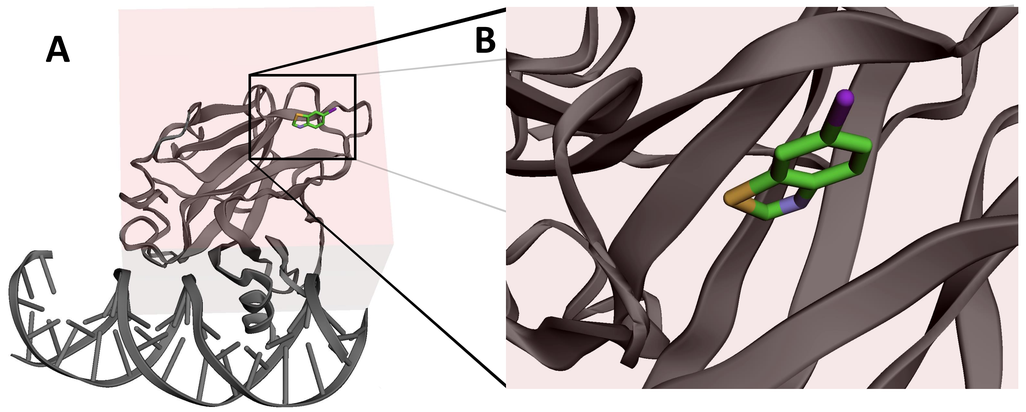

Figure 2: AutoDock Vina Visualization. A. This is a p53 bound to DNA with the binding pocket search area highlighted in red. B. Zoomed-in version of a docked drug (Effector 4).

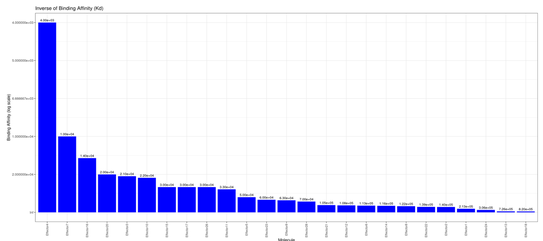

Figure 3: Binding Affinity of Effectors. Binding affinities (Kd) were sourced from BindingDB, based on published assays using the p53 Y220C mutant, curated by the University of Southampton. Sorted in order of effectiveness.

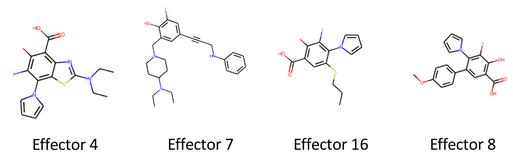

Figure 4: Effectors. These effectors were shown to have the highest docking scores (besides PK11000) out of all the molecules tested. We omitted PK11000 as it binds covalently.

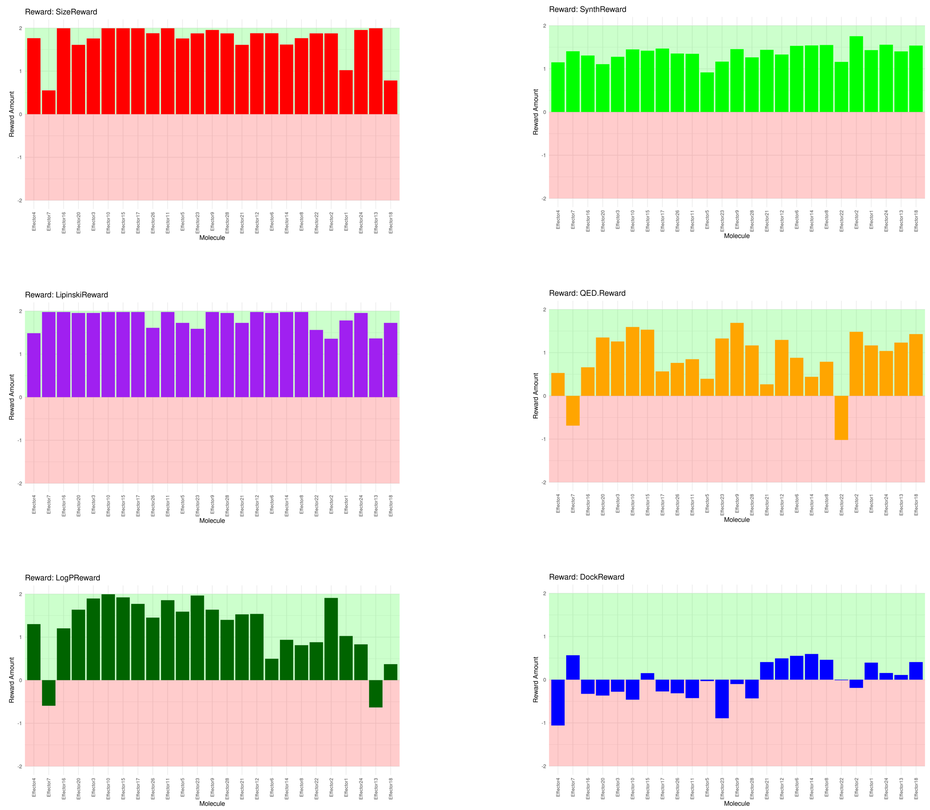

Figure 5: Tuned Rewards of RL Model. The reward functions used in training the RL model were optimized to reward drug-like molecules similar to the effectors, and each function was weighted correctly.

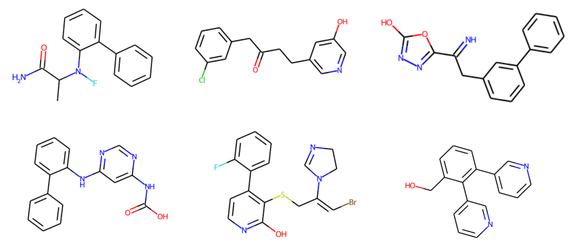

Figure 5: Generated Drug-Like Molecules. After tuning, molecules generated by the model were consistently drug-like to a much higher degree compared to prior to tuning.

CONCLUSIONS

- We successfully created a reinforcement learning algorithm to generate drug-like small molecules.
- We developed a molecule scoring dashboard, in which we can visualize rewards for known effective molecules compared to controls.

FUTURE DIRECTIONS

- Increasing the specificity of molecules generated to target p53 binding pockets would be a significant advancement towards the end goal of generating molecules that can restore mutant p53 to wild type activity. The docking reward will continue to be undergoing development to improve the specificity of p53.
- Adding position-specific docking and providing that information back to the model could be very valuable.
- Continuing to tweak the reward functions would help improve the RL model.
- Parallelizing the code would expedite the generation process.
- Integrating our model into a p53 allosteric drug design pipeline is our long-term goal.

ACKNOWLEDGEMENTS

We gratefully acknowledge Wesleyan's Molecules to Medicine Consortium, especially Prof. David L. Beveridge, Prof. Michael P Weir, and Dr. Matthew Young. Thanks to all members of the Thayer Lab for their inspiration and support. We would like to thank Mark Han for access to his trajectories. We acknowledge Conrad Fischl, whose code was instrumental in the creation of the figures on this poster. This work was supported by NIH R15 GM128102-01.

REFERENCES

Sternlieb, T. B. (2022). Target Specific Drug Design with Deep Reinforcement Learning (Master's thesis, Wesleyan University). Wesleyan University.

Han, S. M., & Thayer, K. M. (2023). Reconnaissance of allostery via the restoration of native p53 DNA-binding domain dynamics in Y220C mutant p53 tumor suppressor protein. *ACS Omega*. https://doi.org/10.1021/acsomega.3c08509

Trott, O., & Olson, A. J. (2010). AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry, 31*(2), 455-461. https://doi.org/10.1002/jcc.21334

https://www.analyticsvidhya.com/blog/2021/02/introduction-to-reinforcement-learning-for-beginners/

https://www.bindingdb.org/rwd/jsp/dbsearch/PrimarySearch_ki.jsp?tag=pol&submit=Search&target=tumor%20suppressor%20p53&polymerid=3723,9115,10190