Accelerating Drug Discovery with a Fragment-Based Machine Learning

Biochemistry

Nisarg Shah, 11th grade

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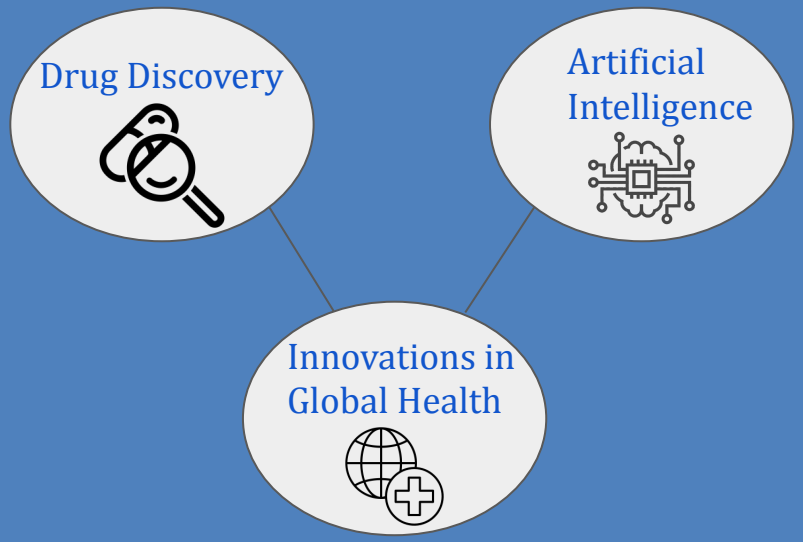


ABSTRACT

Machine-Learning is starting to emerge in modern drug discovery by enabling advanced methods to accelerate certain processes. I studied three computational strategies in order to illustrate how machine learning can address critical drug discovery challenges. First, I explored an unsupervised learning based approach on SARS-CoV-2 and lung-cancer inhibitors. From 3d structural fragmentation, I created drug sets, and ranked them using a custom Transformer VAE pipeline, and compared the ranking to docking scores. My results demonstrated that unsupervised learning can effectively cluster molecules and match predicted Molecular Docking silico data. Second, I applied a ChemBERTa-based drug classification pipeline to categorize small molecules by therapeutic class (cancer, anti-inflammatory,etc). This method uses representations of SMILES strings to achieve a good classification accuracy, in order to accurately determine the therapeutic classes of a drug. Third, I developed a specialized a fragmentation predictor for lung -cancer inhibitors, identifying “hot” fragments from multiple known drugs used to inhibit lung cancers. Fragment Drug-Discovery is a faster method of drug discovery and is more cost effective and faster compared to traditional methods, which is why it is essential to develop “hot” fragments that when used to form drugs, they can inhibit lung cancers effectively. These strategies highlight the versatility of using machine learning for drug discovery. My findings develop the concept of computational models emerging as faster and more efficient compared to existing methods and could become widespread in the future. Finally, my findings and models are available on my website so that others can test them and build off my discoveries.

INTRODUCTION

Currently, pharmaceutical research relies on high-throughput screening(HTS), in which millions of potential drug molecules are tested against a target of interest. Even though this process has been very effective at yielding many medicines, it remains very costly and resource intensive requiring certain professionals and significant capital investment. Recognizing these challenges emerged more targeted approaches, particularly Machine Learning methods in order to simplify the screening process. One such process of this is Fragment Based Drug Discovery (FBDD) in which rather than searching massive libraries of fully developed molecules, FBDD focuses on smaller "fragments" of these molecules which can be merged, or expanded into overall drugs. When combining this process with Machine Learning, it is far more cheaper, faster, and in most cases much more accurate and efficient than High Throughput Screening.

My project leverages these processes where Machine Learning can be combined with Drug Discovery in order to answer the question: "Can Machine Learning drug discovery approaches mimic existing methods and literature such as high-throughput-screening?" In particular, my project assesses 3 distinct areas of this.

1. How well can unsupervised Machine Learning group together a dataset of compounds in order to rank them from most effective of inhibition to least effective of inhibition?
2. How well can Machine Learning determine the therapeutic class of drugs?
3. How well can Machine Learning develop fragment leads from existing drugs which can be used to create potential inhibitors?

I hypothesize that when integrating machine learning to these 3 points, the models will be able to compete with existing methods.

MATERIALS

Hardware/Computer

- A personal Laptop and Desktop (Custom Built Desktop with Windows 10 and an Nvidia graphics card) in order to build, run, test, and analyze the Machine Learning models.

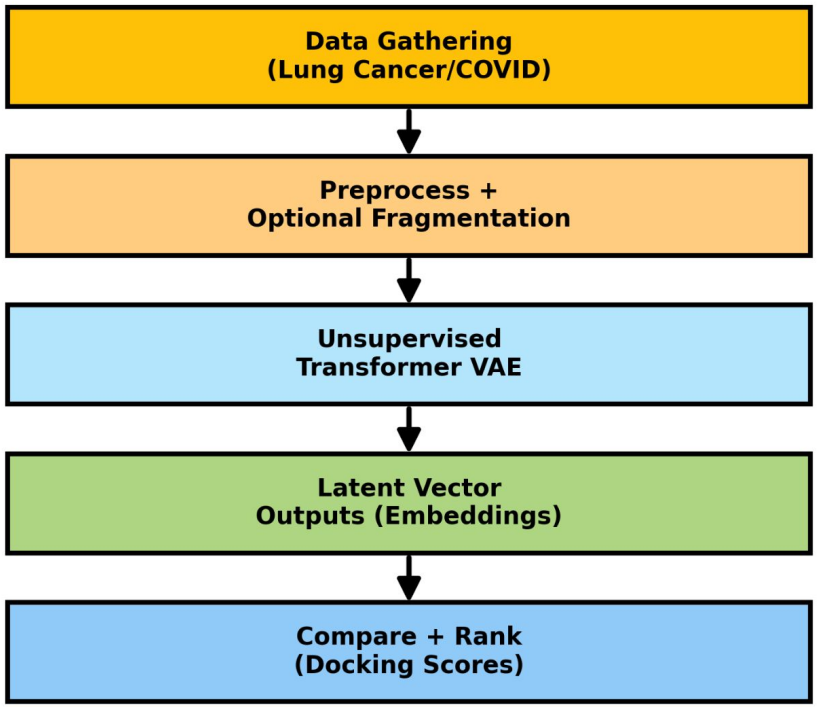
Machine Learning Software & Libraries

- Python (version 3.12)
- RDKit(SMILES parsing, canonicalization, fragmentation).
- PyTorch and Tensorflow for building the Machine Learning model
- Pandas, NumPy, matplotlib for data handling

Dataset

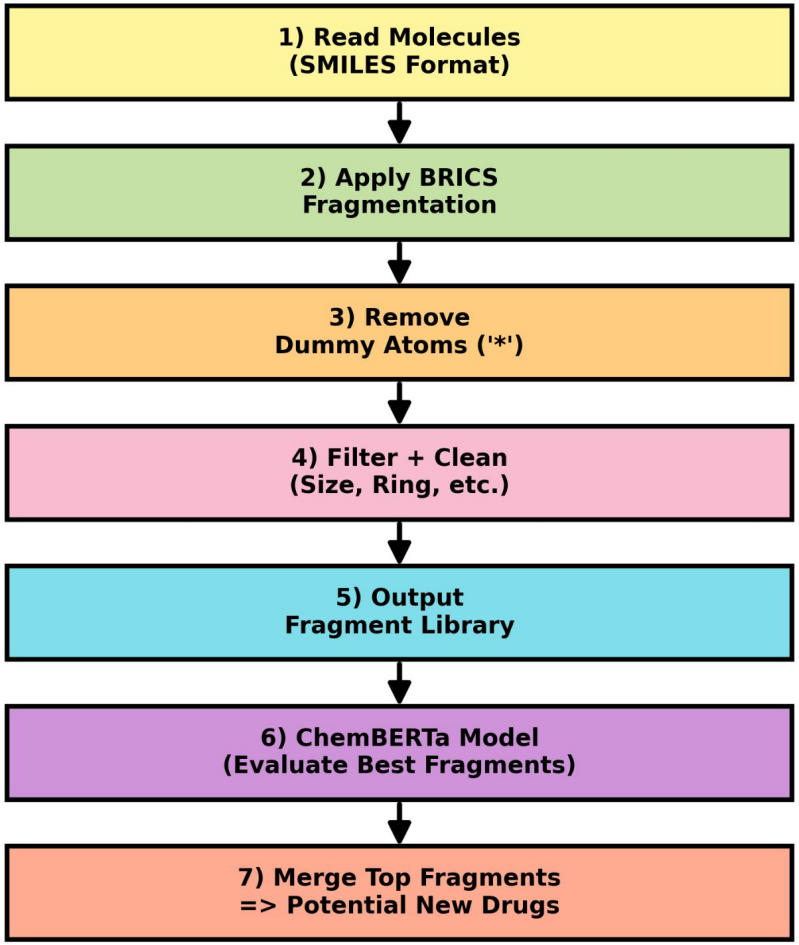
- A CSV file containing known cancer and covid inhibitors, their SMILES structures, and possibly metadata such as Indications and Targets. This will be created through Publicly available data from ChemBl and BindingDB.

Sorting Procedure



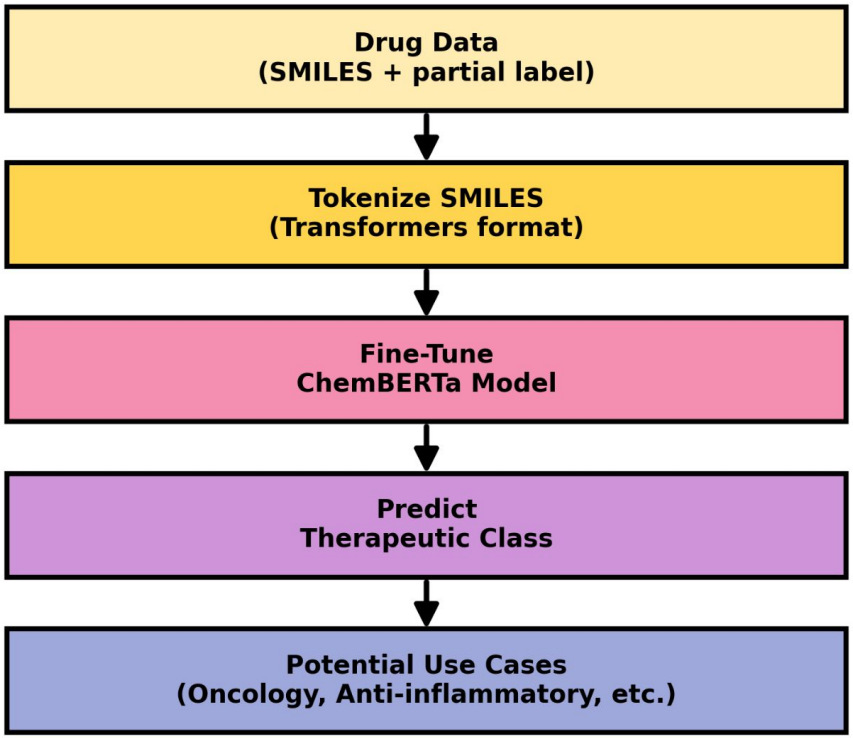
In this pipeline, molecular datasets for both Cancer and COVID are collected in SMILES format. Each molecule's SMILES string is fed into a Transformer Variational Autoencoder(unsupervised machine learning model), which learns to generate and reconstruct chemical fragments without direct supervision. By adjusting network parameters to minimize reconstruction error and a KL divergence penalty, the VAE's latent space captures different patterns of molecular structure. After training, generated fragments or full molecules can be ranked for potential binding affinity, then compared to in silico docking data to validate their predicted viability.

Fragmentation Procedure



Starting from a curated set of drug molecules (lung cancer inhibitors), a BRICS algorithm in RDKit splits them into chemically meaningful fragments. These fragments are then filtered to remove dummy atoms, enforce size constraints, and remove unstable substructures. Once a clean “fragment library” is obtained, a ChemBERTa model is used to evaluate which fragments appear most effective for a given therapeutic aim. Finally, top-ranking fragments can be recombined to propose new drug candidates that inherit potency from each of the drug fragments.

Drug Classification Procedure



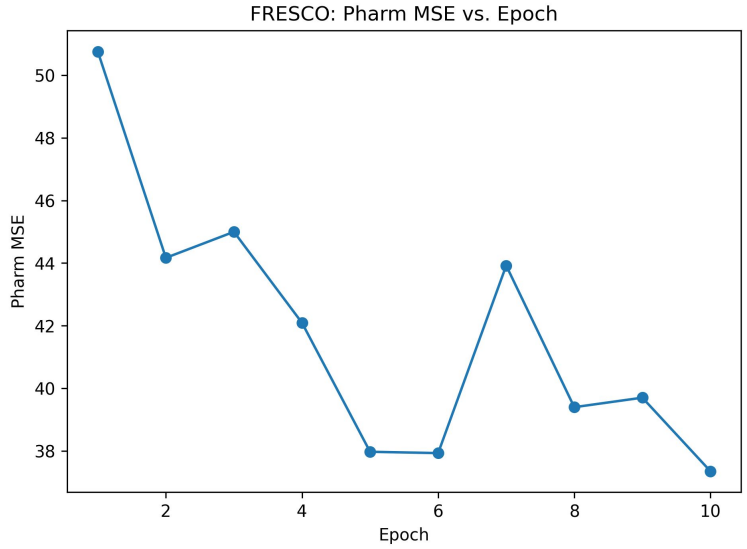
For the drug classification feature, known drugs across multiple therapeutic domains (anticancer, cardioprotective, anti-inflammatory) are represented in SMILES form. A ChemBERTa-based model is fine-tuned on these labeled examples to learn associations and structural patterns between molecular features and therapeutic class. In this process, a newly proposed molecule is tokenized and fed into the model, yielding probabilities across the learned classes. Because of this, Researchers can assign a likely usage domain (e.g., oncology vs. cardiovascular), guiding early experimental design and hypothesis testing before extensive in vitro validation.

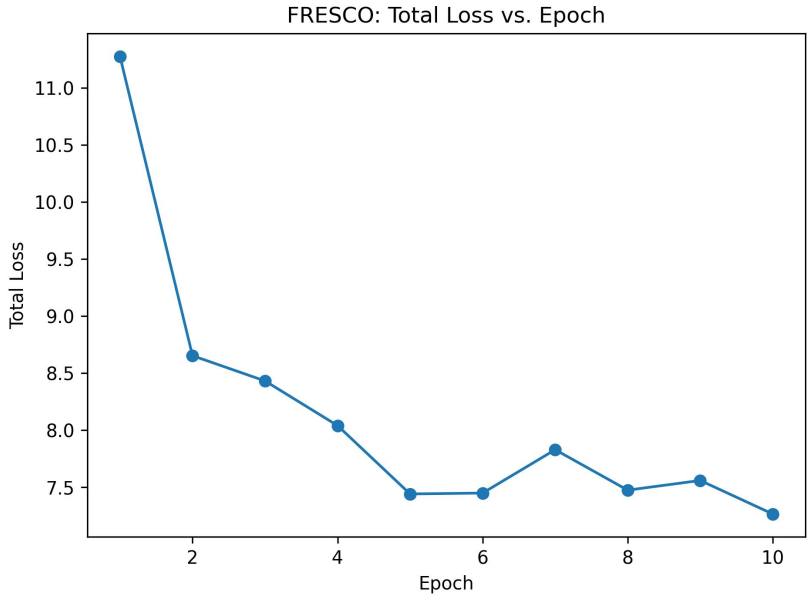
Results

Visit my website: https://nisargrhino.github.io/SmileBERTa-portal/

My website showcases all of the Machine Learning models discussed in this project, and users can test and visualize these models.

Drug Ranking





A batch of 300 lung cancer compounds and 3000 COVID compounds were giving to a VAE unsupervised machine learning model. The model tracked patterns, correlations, and ranked these compounds from most effective to least effective determined by how well the drugs would inhibit cancer proteins and the SARS protein. **The Mean Squared error of this model was 37 and the loss after 10 epochs was 7.5.** Since

Drug Ranking

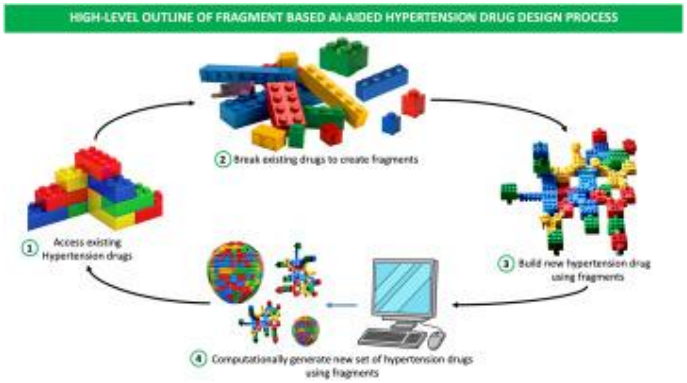
Name	Predicted Rank	Actual Rank	Model Score
Lorlatinib	1	1	30.2
Repotrectinib	2	2	25.33
Thioguanine	3	4	18.41
Mercaptopurine	4	7	17.13
Fluorouracil	5	12	16.38

Top 5 Cancer Drugs ranked by the model vs. Actual rank of inhibition.

The model appears to be “somewhat” accurate as the 1st and 2nd compound matched the actual rank when docking the inhibitors to lung cancer proteins. However, the 3rd-5th compounds do not match the actual rank from the Model score. However, this approach shows potential as with more training, the model exponentially increases in accuracy.

Model score was created by the unsupervised model to predict how well each compound would be able to inhibit the lung cancer/ covid proteins. It uses structural properties and creates nodes and patterns in order to generate this score.

Fragmentation

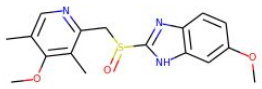


Source: ScienceDirect

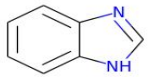
Fragments can be compared to legos! Just like building up legos into creations, fragments can combined to create potent drugs!

A batch of 15,000 lung cancer compounds were broken into fragments are were trained on a ChemBERTa model. The model looks at the SMILES strings of the drugs, best performing fragment, and other 3d/pharmacokinetic properties in order to correlate specific fragments with better inhibition. This makes it easier to identify certain “hot” fragments associated with a drug. After running the Machine Learning Model for **10 epochs**, the Training loss was **0.52** and the accuracy of the model for predicting the best fragment was **60%.** The accuracy was determined through Tanimoto Similarity, in which the predicted drug fragments were compared to the original drug fragments through molecular structure. This proves an accurate model was created which identified a drugs “best” fragment for inhibition of lung cancer proteins.

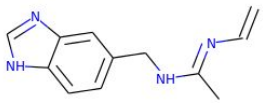
Fragmentation



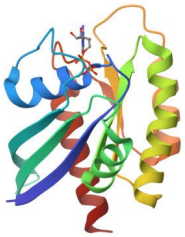
Omeprazole
Docking Score -7.3



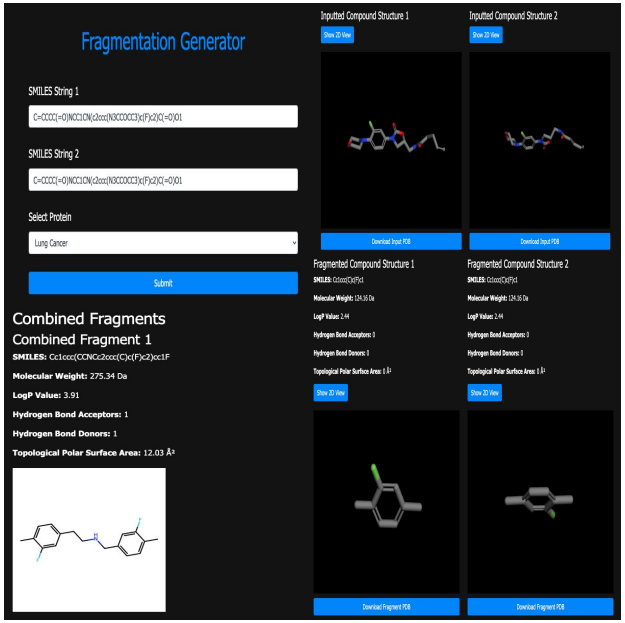
Benzimidazole
Docking Score -6.3



Combined Fragment
Docking Score -7.4



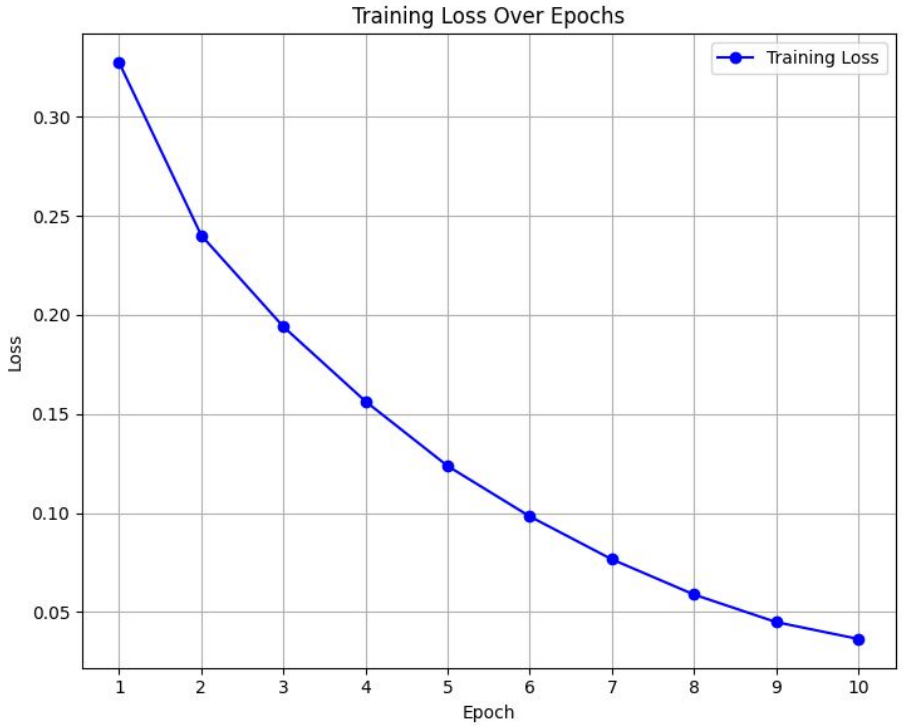
Lung Cancer
Protein(KRAS)



My Website:
Users can test out the model and visualize the model predict the best “hot” fragments for the existing drug.

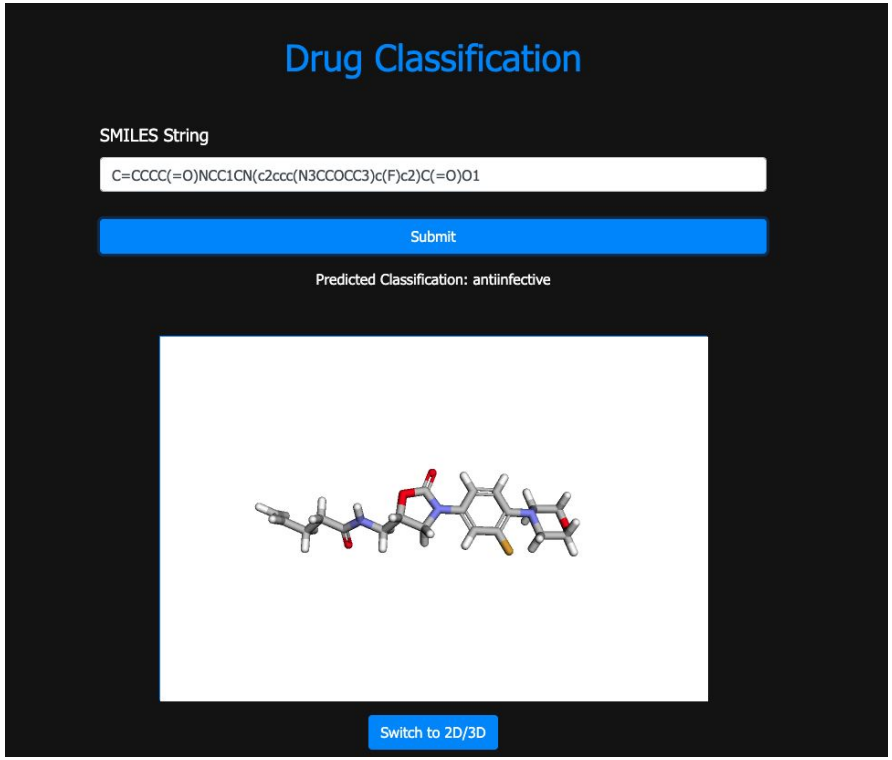
In order to hypothesize that the model could generate fragments that when combined, would perform up to the performance of current FDA approved drugs for lung cancer, we compared the Molecular Docking scores for Omeprazole and Benzimidazole(2 current Lung cancer inhibitors) to a drug that was generated through our model. These 3 drugs were docked to KRAS(Kirsten Rat Sarcoma Virus), a known protein in most Lung Cancers which causes cell growth and proliferation of lung cancer tumor cells. As shown to the figure to the left, the combined fragment achieved a docking score of -7.4(docking scores represent the amount of energy released during the docking of the 2 compounds, a higher negative number correlates to better inhibition), meaning that it had a better inhibition rate to KRAS compared to the other 2, highlighting the benefits of using Machine Learning when determining “leads” for drug discovery.

Drug Classification



A batch of 100,000 drugs with the SMILES string of the drug, its use case(anti infective, antibacterial, cardiovascular, cancer, etc.), as well as 3d/pharmacokinetic properties were trained on a ChemBERTa model. The model was able to associate a certain drug and correlated it with a use case effectively. The loss of the model was **0.031** and the accuracy of determining the use case of the drug was **90%**. The accuracy was calculated by comparing the use case prediction to the actual use case of the original drug. This proves an accurate model that was created in order to effectively predict the use case for any drug.

Drug Classification



My Website: Users can test out the model and see which drugs correlate to certain use cases in the medical field.

The drug classification component fulfills a key role in evaluating novel compounds by predicting their most likely therapeutic categories. Although it was initially trained on existing molecules annotated with known clinical indications, its predictive capability extends to newly designed drugs. By inputting the molecular structure or drug into the classification model, users can see whether the compound aligns with oncology, anti-inflammatory, cardiovascular, or other therapeutic domains. This also streamlines early hypothesis testing in which people can generate new leads before in vitro testing.

DISCUSSION/CONCLUSION

Overall, this project successfully demonstrates how Machine Learning can be integrated into drug discovery, by offering a faster and more effective alternative to traditional approaches. Three computational approaches were explore: unsupervised clustering for drug ranking, drug classification, and a fragment based predictor for lung cancer inhibitors.

The results indicate that machine learning can effectively analyze and rank drug molecules based on inhibition potential, with a Transformer VAE model correctly predicting the top-ranked lung cancer inhibitors with moderate accuracy.

The ChemBERTa-based drug classification model achieved 90% accuracy in categorizing drugs by therapeutic use, demonstrating its reliability for rapid screening of novel compounds.

Finally, the fragmentation model successfully identified "hot" fragments, with combined fragments outperforming individual inhibitors in docking simulations against KRAS, highlighting its potential for lead optimization.

While the models showed promising results, improvements like more advanced datasets, tweaking the training parameters, and integration with experimental validation could enhance accuracy. These findings reinforce the role of AI in accelerating drug discovery, and also pave the way for further advancements in computational pharmacology. Future work will focus on refining these models and expanding their applicability to a wider range of diseases.

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