**Project Proposal for BME 590L - Machine Learning in Pharmacology - Fall 2022**

**William Ladd, Pooja Parameswaran, Rutwik Palaskar**

#### **a) Problem Description**

In drug discovery, molecules can be found that accomplish some biological goal using chemical mechanisms. Despite discovering an optimal drug for activating a chemical mechanism, it is necessary to ensure that the drug is not toxic. If the drug is toxic, it will have side effects that can make it unusable regardless of how well it performs for said chemical mechanisms. Therefore, it is necessary to predict if a drug is toxic so that it may be eliminated from the testing pool so that money is wasted on testing a drug that is not useful.

#### **b) Dataset**

Toxicology in the 21st Century (Tox21) is a U.S. federal government program which has produced a dataset specifically for crowdsourcing methods of predicting the toxicity of chemicals based on which human chemical processes they disturb [1]. There are thousands (~7,831) of chemicals in the dataset, and each chemical is classified by its performance in twelve (12) different assays [‘AhR’, ‘AR’, ‘AR-LBD’, ‘ARE’, ‘aromatase’, ‘ATAD5’, ‘ER’, ‘ER-LBD’, ‘HSE’, ‘MMP’, ‘p53’, ‘PPAR-gamma’]. The following seven (7) are nuclear signaling pathways [‘AhR’, ‘AR’, ‘AR-LBD’, ‘aromatase’, ‘ER’, ‘ER-LBD’, ‘PPAR-gamma’], and five (5) of which are stress response pathways [‘ARE’, ‘ATAD5’, ‘HSE’, ‘MMP’, ‘p53’]. This is the dataset we will be using (Tox21 dataset from TDC).

#### **c) Modeling Approach**

Many machine learning models have been previously developed for de novo drug design where they attempt to predict which drug candidates have desired physical, chemical and bioactivity properties [2]. Our modeling approach will be to construct a reinforcement learning system similar to [3] but with a different dataset, prediction model, and generative model. We will first train a machine learning prediction model using the Tox21 dataset to predict if a molecule is toxic or not based on whether it disrupts the chemical signaling pathways. We plan on using a state-of-the-art machine learning approach for generating non-toxic molecules by combining a Message Passing Neural Network (MPNN), such as documented here [4] and implemented here [5], for the prediction model and a Generative Adversarial Network (GAN) or Transformer for the generative model. The generative model will be trained with a reinforcement learning approach with a reward function for generating new molecules that the prediction model predicts as non-toxic.

The predictive model neural network will be trained on all of the 12 assays. We will extract features from the SMILES strings with the following three methods: (i) ECFP/Morgan fingerprints or MACCS fingerprints, (ii) Molecular descriptors in the python package ‘rdkit’ to extract the Molecular Descriptors and, (iii) AtomFeaturizer and BondFeaturizer (from this code [5]) to consider structural features. For method (iii), we will consider the following atom features: ‘atomic element’, ‘number of valence electrons’, ‘number of Hydrogen bonds’, and ‘orbital hybridization’; and covalent bonding and conjugation for BondFeaturizer. The performance on each of these featurization methods will be compared to determine which features are optimal to train our predictive model.

We will optimize our Reinforcement system towards creating non-toxic molecules. Our reward system will allow us to assign to reward the GAN model for molecules predicted to be non-toxic by the MPNN, optimizing the GAN model’s performance. Our goal is to get novel molecules that are non-toxic, class label of ‘0’. Consequently, we will reward for molecules that are predicted to have a class label of 0 with some value *r,* and we will punish predictions that have a class label of 1, with a reward value of *‘r = 0’*. The reward function will be implemented with the GAN by adding the reward to the inherent loss function. We will plot the distribution of non-toxic and toxic molecules from a pure GAN against the Reinforcement GAN.

The GAN will be our generative model and we will utilize ‘MolGanFeaturizer’ from DeepChem to featurize our SMILES dataset. Using a BasicGanModel, we will train a model with an ‘Exponential Decay’ learning rate, with an appropriate initial learning rate and decay rate to accurately train or GAN to output optimal novel molecules. The GAN will use the adjacency matrix and node features from a SMILES string to extract details from the input data, and create novel random molecules. We will form a minimum of 1000 new molecules, and these de novo molecules will be predicted using the MPNN, and a reward will be assigned, as described previously.

To indicate reinforcement learning, we will train our predictive model with the optimal chosen fingerprint, generate new molecules with the GAN and then feed these new molecules through the prediction model which will generate results that will be input into a reward function for re-training GAN to optimize non-toxic molecules. It is our goal to have the proportion of non-toxic molecules generated with this reinforcement learning model be higher than that of pure GAN without the reinforcement system. The de novo molecules (generated as SELFIES by the GAN model) will be evaluated for validity by checking the SELFIES string for a valid molecule and for toxicity using the predictive model.

#### **d) Evaluation Approach**

There will be 3 parts to evaluating our model. The performance model and dataset will be evaluated for having meaningful predictions using k-folds cross validation by calculating Matthews Correlation Coefficients (MCC) without and with y-randomization. For the performance model itself, we will calculate AUC and BEDROC to determine how much better than random it performs and the model’s ability to make high-certainty predictions respectively. AUC and BEDROC values can then be used for comparing our model to published models. For the generative model, we can measure what proportion of molecules it prints out are valid molecules, how well those molecules perform in the predictive model, and what proportion of those molecules are favored by the prediction model

We can distinguish novel structures of the de novo- generated molecules by comparing the content of Murcko scaffolds between our ‘Tox21’ training set and the new virtual molecules created by our RL system. Murcko scaffolds display a hierarchical molecular organization scheme by dividing small molecules into scaffolds, linkers, and R groups.

#### **e) Anticipated Challenges and Workaround Alternatives**

If the complexity of MPNN models is too much or if we have performance issues with MPNN models (or even if we have extra time) we could attempt other predictive models such as random forest to see if the predictive model performance goes up and the generated molecule quality goes up. In the event of poor-quality GAN reinforcement iterations (or if we have extra time), we can use predictive probability from the prediction model with a continuous rewarding function (such as a sigmoid) for the reinforcement mechanism for the GAN model. Google Colab may limit the size of the model (RAM) or the runtime of the model in which case we would resize the model (smaller fingerprint arrays, less epochs, less neurons) to fit within these limits.

#### **f) Anticipated Outcomes and Measurement of Success**

We anticipate that the predictive model will perform at or better than the models from literature that used Tox21 in publication [6]. Given that there are so many instances of predictive models in the literature for Tox21 [6], it will likely not perform as well as the best but will be close as it is a state-of-the-art neural network. Measurement of success for the predictive part of the model comes from how well it does compared to other literature, one source we are comparing with is a graph convolutional neural network [7] and the other is TrimNet [8], a special triplet message neural network designed specifically to do better than MPNNs. A metric for performance could be AUC score, which is provided for a few publications here [6]. For the generative model, high rates of valid molecules and desired molecules generated out of the overall generated molecule pool (with desirability of molecules being determined by the prediction model), and performance similar or better to another GAN model from literature such as [9] are all measurements of success.

#### **g) References**

[1] National Institutes of Health, Tox21 Data Challenge 2014, <https://tripod.nih.gov/tox21/challenge/about.jsp>

[2] Wu et. al., MoleculeNet: a benchmark for molecular machine learning (2018), *Chemical Science*, <https://pubs.rsc.org/en/content/articlelanding/2018/sc/c7sc02664a>

[3] Popova et. al., Deep reinforcement learning for de novo drug design (2018), *Science Advances* <https://www.science.org/doi/10.1126/sciadv.aap7885>

[4] Gilmer et. al., Neural Message Passing for Quantum Chemistry (2017), *Proceedings of the 34th International Conference on Machine Learning*, <https://arxiv.org/pdf/1704.01212.pdf>

[5] Keras Team, Keras io, *Github*, <https://github.com/keras-team/keras-io/blob/master/examples/graph/ipynb/mpnn-molecular-graphs.ipynb>

[6] Paperswithcode.com, Drug Discovery on Tox21, <https://paperswithcode.com/sota/drug-discovery-on-tox21>

[7] Duvenaud et. al., Convolutional Networks on Graphs for Learning Molecular Fingerprints (2015), *NeurlPS Proceedings*, <https://arxiv.org/pdf/1509.09292v2.pdf>

[8] Li et. al., TrimNet: learning molecular representation from triplet messages for biomedicine (2020), *Briefings in Bioinformatics*, <https://doi.org/10.1093/bib/bbaa266> (Available through Duke Library)

[9] Polykovskiy et. al., Molecular Sets (MOSES): A Benchmarking Platform for Molecular Generation Models (2020), *Frontiers in Pharmacology*, <https://www.frontiersin.org/articles/10.3389/fphar.2020.565644/full>