# ACCELERATED DRUG DISCOVERY USING ACTIVE LEARNING

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**ABSTRACT**

This paper presents an accelerated approach for drug discovery that utilizes active learning to identify potential drug candidates more efficiently. Traditional methods for drug discovery are based on screening large chemical libraries and performing high throughput assays, which are both time consuming and expensive. In this project, we use batch active learning to sample the most informative instances and make conclusions about potential drugs in a more efficient manner. We use passive learning as a baseline, and compare it to the performance of batch uncertainty sampling and batch density based sampling to select the most promising next potential targets to test, both of which outperform traditional methods. This approach will thus help reduce the number of experiments required to identify promising drug candidates. Our results suggest that active learning has the potential to significantly accelerate the drug discovery process, while also reducing costs.

## 1 Introduction

### 1.1 Background

Today, drug discovery is a crucial yet challenging problem, where finding the best possible drug for a specific target requires extensive testing and experimentation, which comes at a high cost and takes time[1]. For rare diseases (defined as those that affect less than 200,000 persons in the US- according to FDA), it is even harder to find potential drugs since the development of orphan drugs, pharmaceutical agents that are developed to treat certain rare medical conditions, are most certainly unprofitable[2]. However, this motivates a perfect active learning problem, since the goal is to acquire a suitable drug for our target, using the least possible cost, and the fewest number of iterations which corresponds to the fewest drugs to be manufactured and tested until we find a possible candidate.

### 1.2 Specific Aims

In this project, we investigate two active learning methods' performance on drug discovery task. We plan to choose the best possible candidate for a drug by exploring and comparing the performance of different active learning approaches taught in class on this particular task. The fingerprints of each compound are calculated as our input variable and the potency of each compound (a measurement of drug activity that is defined as the amount of the dosage needed to have a specific effect) is used as our target [3].

### 1.3 Significance

If our active learning strategy could achieve a better model performance (lower loss) for predicting the interaction level within a lower time frame than if we were to use traditional passive learning methods, this will mean that we will require a fewer number of experiments to carry out (training instances) until we are able to correctly identify a potential drug target. This will save us time and cost when we are in the process of drug discovery.

## 2 Experimental Design

### 2.1 Data

For our project, we decide to focus on efficiently identifying potential drugs for a specific target, from a large pool of compounds. We use the ChEMBL Database [4] as our primary source of information for drug targets and their corresponding IC50 levels. This database contains information on bioactive molecules with properties similar to drugs. It integrates chemical, bioactive, and genomic information, and aims to expedite the process of translating genomic data into effective drugs, making it a valuable resource for drug discovery efforts. In our analysis, we mainly focus on one of the targets and test it against all the drugs, which we chose as the $\mu$-opioid receptor. After we do this, we adapt our code so it can be used on multiple targets, and also run it on other targets to ensure active learning also yields better results than passive learning.

The $\mu$-opioid receptor has the ID of 'CHEMBL233' in the ChEMBL database, and we chose it since we believe that it is a promising target for pharmacological interventions since it plays a critical role in pain modulation and is the primary receptor responsible for the effects of opioid drugs. The activation of the $\mu$-opioid receptor can provide pain relief, making it an important target for the treatment of chronic pain conditions. It is also involved in the regulation of

reward and reinforcement pathways in the brain, making it an important target for the treatment of addiction to opioids and other substances. So far, known targets of the $\mu$-opioid receptor could lead to tolerance, dependence, and addiction, and so the development of novel $\mu$ opioid receptor-targeted drugs with reduced side effects and improved safety profiles is an active area of research.

Thus, our model's input space will be the molecular structure of the all the drug compounds in the database, also known as the canonical smiles, or "fingerprints" of the compounds, and the bioactivity data against the specific target, which is the $\mu$-opioid receptor, will serve as our search space and desired output labels.

The structures of the compounds are represented as simplified a molecular input line-entry system, which uses a line of strings to describe the chemical structure of a compound. Each entry in this compact molecular fingerprint representation represents the existence (1) or absence (0) of a substructure or sub-graph. Thus, we represent the structure of a compound as a list of 0s and 1s, which we feed as input to our model.

Finally, the IC50, which represents the concentration at which a substance exerts half of its maximal inhibitory effect, is commonly used as a measure of antagonist drug potency in pharmacological research, is used as our output. Thus, we try to predict the IC50 levels of potential drugs based on their chemical structure, and identify potential candidates by assessing the IC50. The higher the IC50, the less active the drug/compound is to the specific target, and so we aim to look for lower IC50 values. We use the negative logarithm of IC50 in molar concentration.

### 2.2 Methods

For our base learner, we choose the XGBRegressor. We chose this model since upon research, we found that it is well-suited to large datasets with complex feature interactions and regression tasks. This fits both our large dataset of componuds, and our complex feature interactions that depict the compounds molecular structure. Since our problem is trying to model a regression to predict the IC50 levels of certain compounds in relation to the $\mu$-opioid receptor, we found that this would be a suitable model. This model fits a sequence of decision trees on the training data, and uses a gradient boosting approach to improve the accuracy of predictions by fitting decision trees to the negative gradient of

the loss function. It also uses regularization techniques and early stopping to prevent overfitting.

For all our models, we initialize them with 30 randomly sampled instances, select 12 instances based on the desired query selection method, and add these 12 instances as a batch to the model. We chose to 12 to be our batch size since using a smaller number of data points in our batch took our model a longer time to train, and larger numbers did not yield the best results of identified potential targets since more instances were chosen than what was needed, and this would reflect as performing more experiments in the real world that are costly and not that useful.

We also stop training all the models when we get to 1200 training instances, since this compromises the majority of the dataset and is well beyond the point of identified targets, and at each batch we calculate the cross validation mean squared error to assess our training performance, and then evaluate the performance of the model on the unseen test dataset (composed of the compounds that still haven't been used in training).

#### 2.2.1 Batch Passive Learning

For passive learning, we simply randomly select 12 points and add them to the model at each iteration.

#### 2.2.2 Batch Uncertainty Sampling

For uncertainty sampling, we quantify the uncertainty using variance. For all the possible candidates of compounds available, we calculate the variance of the predictions for the corresponding IC50 level of each compound made by each tree (estimator) in the model, and then select the instances with the top 12 variances, as these would reflect the most uncertain instances. We then add these points to the training data, retrain the model, and evaluate the model's performance on both observed and unobserved instances.

#### 2.2.3 Batch Diversity Sampling

For diversity sampling, we used the k-means algorithm, with k=3, to cluster the possible drug compound candidates (the test set/ unobserved data points). From each cluster, we select four instances, to have 12 instances in total to add, and add these points to the model. We then retrain the model, and evaluate the model's performance on both observed and unobserved instances.

## 3 Results

In order to compare the performance of batch passive learning, batch uncertainty sampling, and batch diversity sampling, we calculate the cross validation scores of all three methods, as shown in Figure 1. (For the validation score, we average the mean squared error over 5-fold cross validation.)

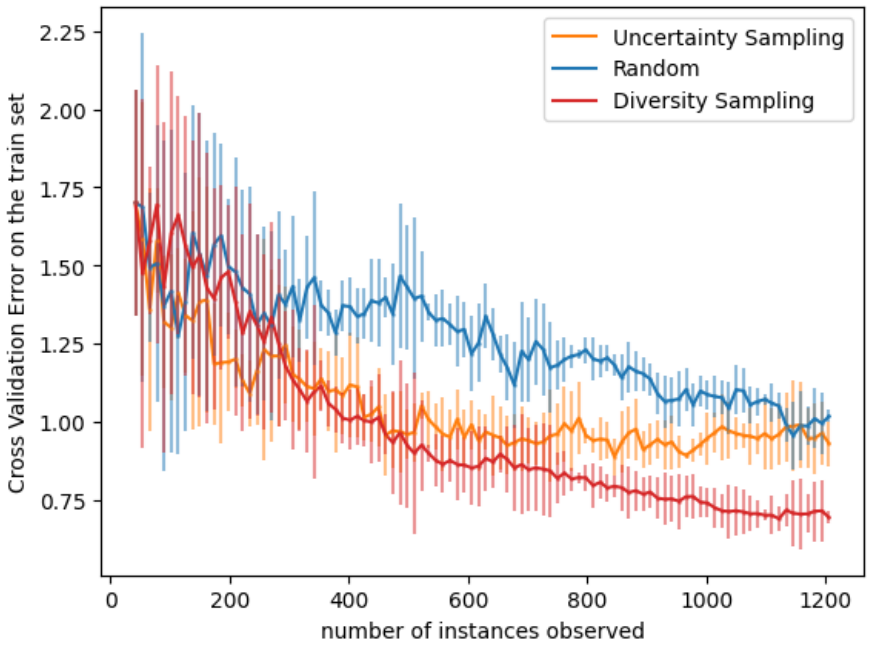


Figure 1: Mean squared error of passive learning, uncertainty sampling, and diversity sampling on training set.

As seen in the graph, with around 250 instances (12 batches), batch uncertainty sampling and batch diversity sampling performed consistently better than random sampling (Here, we took variance across 10 simulation into account). In addition, while uncertainty sampling performs better than density at first, the error rose to a higher value after 250 instances. We suspected that it's due to the nature of uncertainty sampling, where it not only sample the instances around the decision boundary but also the points that are far from the group. In our case, those points are the compounds with unusual structures.

We then assess the performance of each kind of method on the testing set to further validate our result.

In Figure 2, we showed the mean squared error of batch passive learning, batch uncertainty sampling, and batch diversity sampling across different number of instances.

Compared to validation, we find that batch uncertainty sampling doesn't always perform better than batch random sampling when predicting on unobserved sets. In fact, before 1000 instances, batch uncertainty sampling and batch random sampling performs roughly the same. We suspect that it's because the points that it's choosing are mostly outliers. Another possibility is that it's because calculating variance as uncertainty neglected some of the structural information in the fingerprint representation. On the other hand, batch diversity sampling consistently performs better than the other two methods.

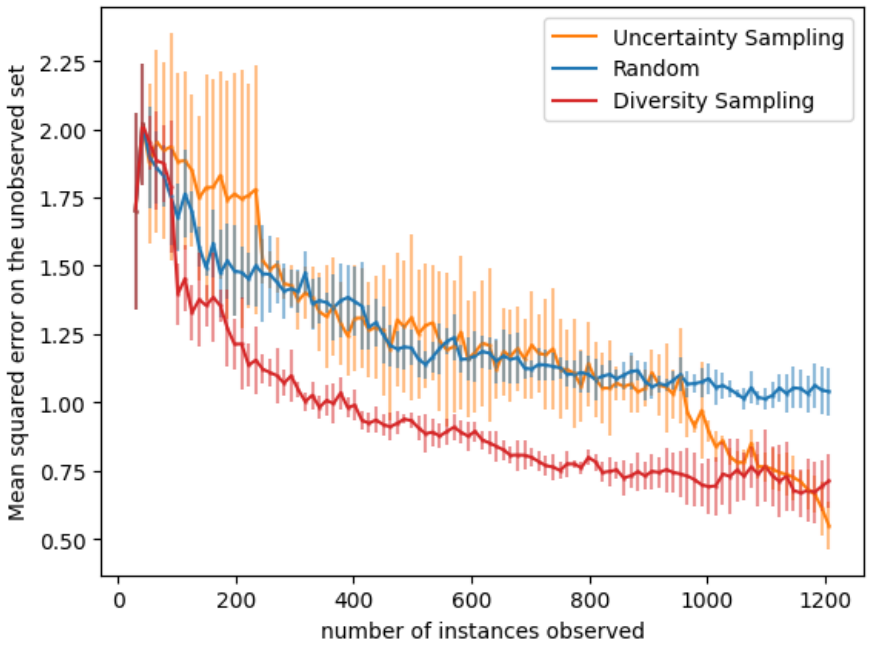


Figure 2: Mean squared error of passive learning, uncertainty sampling, and diversity sampling on unobserved set.

### 3.1 Further Testing Other Targets

We also modified our code so that it is compatible for testing with other targets. We tested the code with these targets to ensure that active learning does yield lower model loss indicating better model performance, and we do obtain the desired results. Although not all experiments showed improved performance of both active learning strategies, most of them do have at least one active learning strategy that performs better than passive learning. Shown in Figure 3 is another

demonstration of improved performance achieved by our active learning model (with Angiotensin-converting enzyme as the target), where uncertainty sampling outperforms diversity sampling and passive learning after approximately 300 training instances, achieving a lower MSE, and random and diversity sampling have similar overall performance.

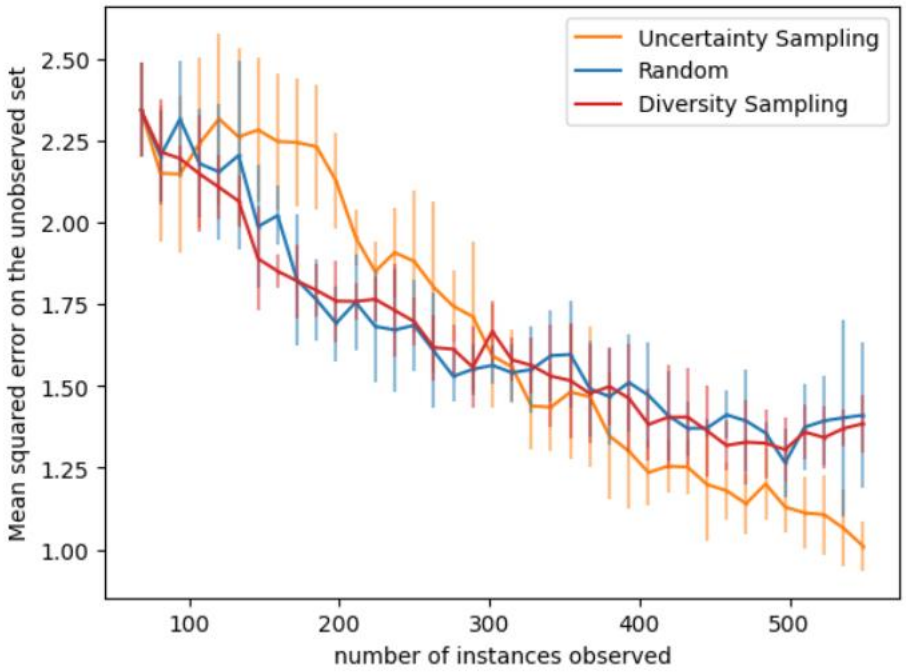


Figure 3: Mean squared error of passive learning, uncertainty sampling, and diversity sampling on unobserved set, with Angiotensin-converting enzyme as the target

## 4 Conclusions

From the graphs above, we can conclude that choosing the right active learning method has significant value in drug discovery. In our example, diversity sampling achieves lower mean squared error with the same number of instances than batch random sampling and batch uncertainty sampling on unobserved data. With structural data, we are able to make better predictions using a lower number of instances with active learning approach, which would correspond to less need for running unnecessary experiments, which would save both time and cost, and which would potentially lower the overall cost and timeline for drug discovery.

### 4.1 Future Work

In the future work for this project, a potential next step would be to assess the instances that were selected by our active learning model, to confirm that our active learning approach has the potential to find effective compounds. We could compare the chosen compounds to previously identified targets of the $\mu$-opioid receptor, and if we have the budget the actually trying out the chosen compounds would be ideal. Finally, we could also compare the chosen molecules' structural components and see if the commonly chosen drugs have a specific structure or component within them similar between all possible choices.

## References


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