Deloitte Data Challenge

Estimate binding affinity

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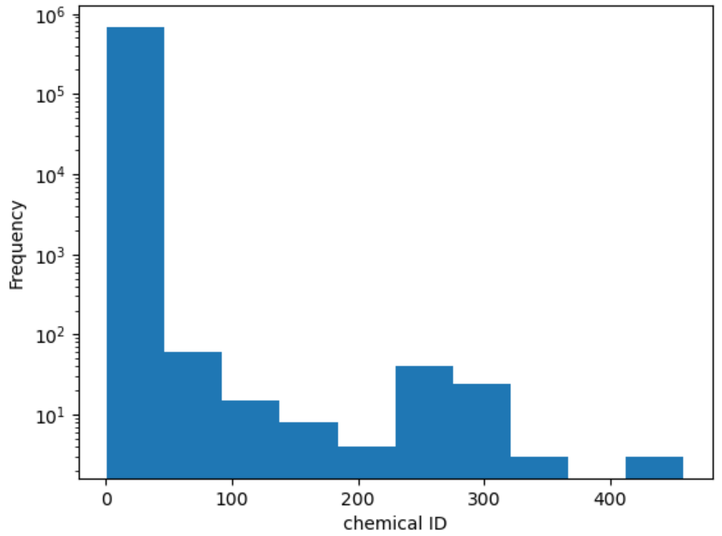
How to run my project

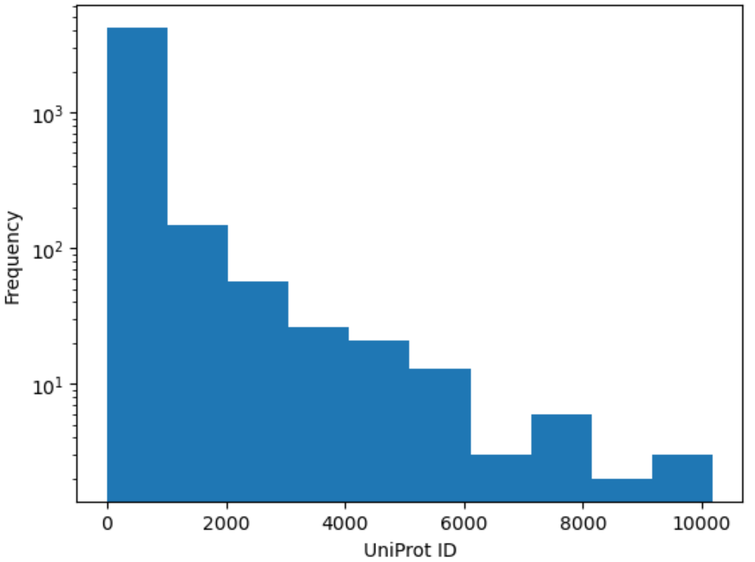
- I include Full Workflow.ipynb where I go through the data and train the model and Evaluation Workflow.ipynb , which is where a different dataset can be brought through the workflow.
- For the purpose of demonstration, I just did a small subsample of the original dataset as a test set
- I will include my conda env file. The main packages I used other than native python were Scikit-learn, pandas, XGBoost, and BioPython. Should be straightforward to install. I have python 3.12 running in my env.

Data Exploration

Basic facts

- 1,134,638 entries
- 683,413 unique pubchem IDs
- 4,480 unique UniProt IDs
- 39,611 rows with NA values - I choose to drop these. Not too many and have no idea what to do with them.
- Some repeat measurements for same UniProt ID and pubchem ID - I choose to average together these measurements to avoid train/test contamination

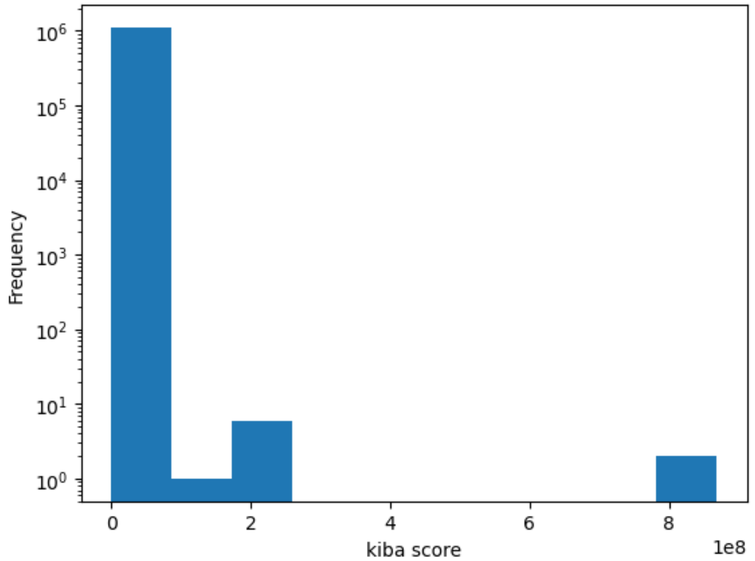


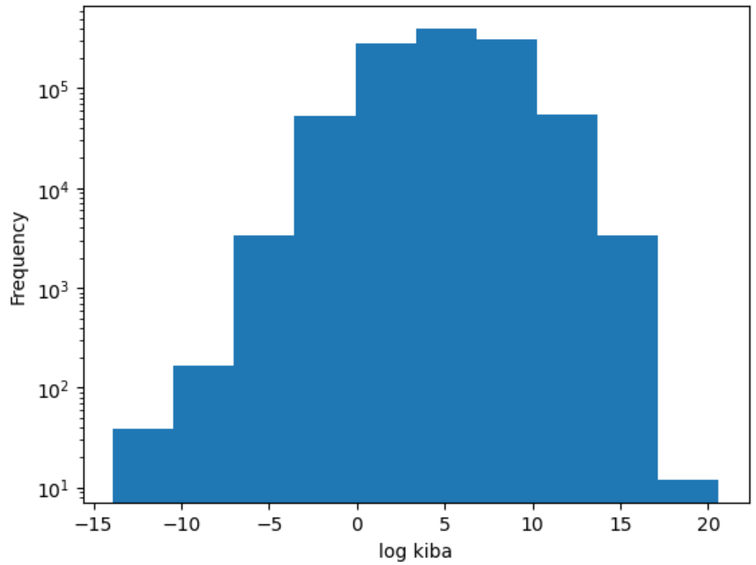


Data Exploration 2

Kiba score

- KIBA score itself seems to be fairly unevenly distributed.
- Therefore, I am choosing to take (natural) log of KIBA score for this exercise - a much more beautiful distribution





External Data Acquisition

From PubChem

- I devised a query system to retrieve all quantitative “properties” for batches of 400 pubchem IDs at a time. The properties were taken from the API documentation and included things like molecular weight, number of heavy atoms, etc.
    - Also includes how many patents and papers the molecule was in - this will be important later :)
    - Total of 35 features per chemical id
- Querying in batches was necessary because it crashed if I tried to query all 600,000+ chem IDs at once. I apologize if this portion of the code takes a while to run. Could not come up with a faster way to query in my limited time.
- I queried for the Canonical SMILE as well - but ultimately I just ran out of time to find a good way to use this. I tried the RDKit package, but it was too slow on my 2019 MacBook Pro.

External Data Acquisition

From UniProt

- Similarly had to query in batches of 100, but at least there were only 4400 or so unique protein IDs.
- Again apologize if this takes a while - since proteins are more widely represented, even in my test set, there are plenty of them.
- I query for the sequence, annotation count, and a list of “extra attributes” with counts. I wind up with about 40 features that come from these “extra attributes”

Additional Features from Protein Seq

Using Biopython

- I use the ProteinAnalysis module from BioPython to calculate additional properties about the protein from the sequence
- This feels fairly old-fashioned in a world where sequences and structures can be fed directly into neural networks, but I have limited time and an old laptop.
- Also calculate fraction of each type of amino acid.
- 28 features derived this way

Final Dataset

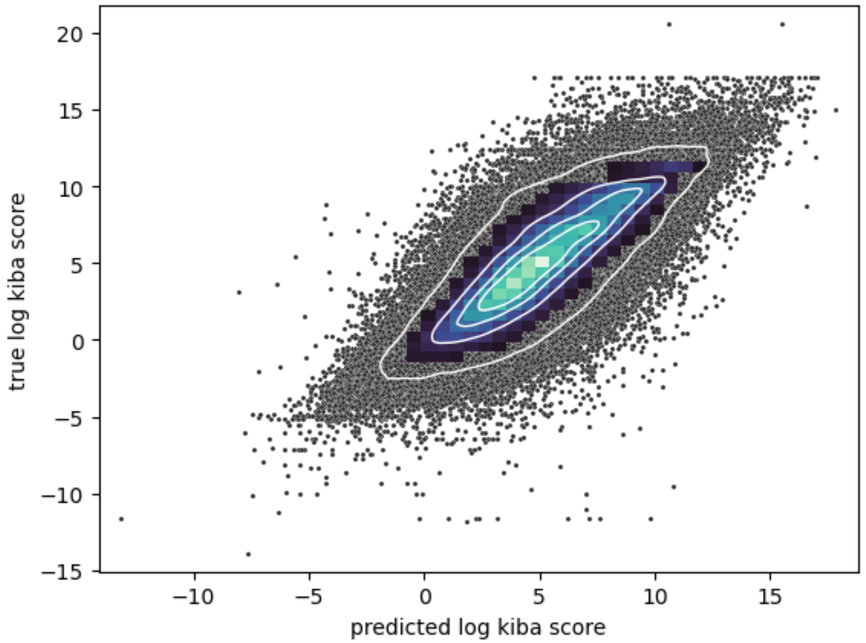
- 103 features
- 1071302 samples
- In the interest of time, I will not be doing k-fold cross validation and instead just use a simple 67/33 train/test split.
- Maybe before submitting the assignment I should re-train with all of the training data, but I trust that it should be robust enough :)

Model Selection

- I tried:
  - Linear Regression (with and without feature normalization).
    - Maxed out at R2 = 0.1 or so
  - NLP regression (dense neural nets)
    - Maxed out at R2 = 0.3 for both training and test
  - Random Forest Regression
    - With unlimited depth can get to R2 = 0.9 for train set, R2=0.7 for test set
    - But with reasonable depth limits, maxes out closer to R2=0.5
  - **XGBoost Regression**
    - **With Depth=15 can get similar results to Random Forest Regressor, but is much faster to train and more reliable.**

Best fit model

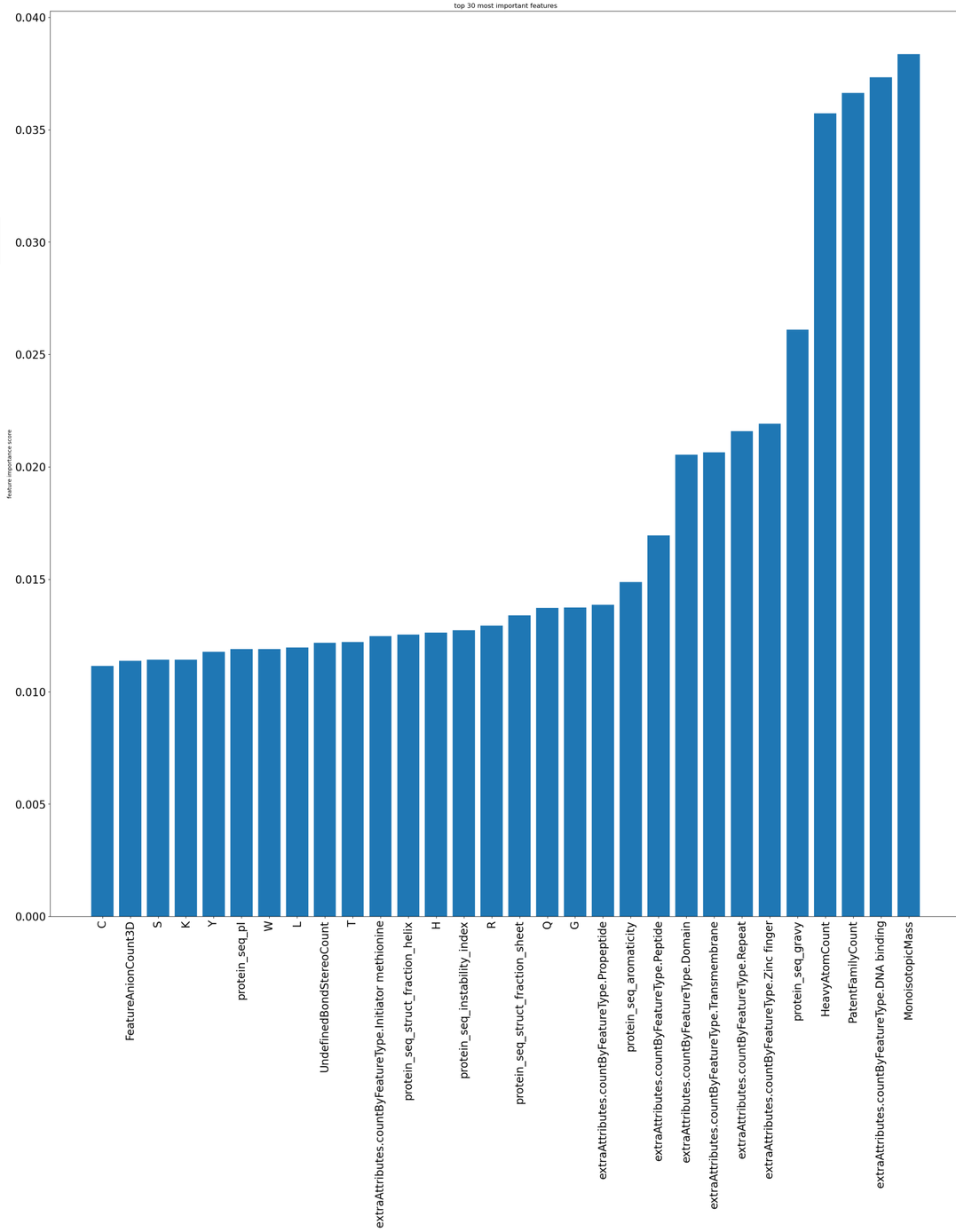
- XGBoost Regression model with max_depth = 15
- R2 = 0.678 (on validation set)
- MSE = 3.54
- It’s a bit messy, but it looks pretty smooth, and especially looks so much better than other types of models I tried to train!



Feature importance

Top 30 most important features plotted

- Top 5 most important features:
  - MonoisotopicMass
  - extraAttributes.countByFeatu reType.DNA binding
  - PatentFamilyCount
  - HeavyAtomCount
  - protein_seq_gravy



Thoughts about Feature Importance

And other ponderances.

- Different iterations of (tree-based) models I've fit generally have differences in the feature importance rankings. This suggests some covariance in the data, maybe some instability, or maybe I am not unlocking the full potential of the data by using more estimators.
- Max_depth = 15 is quite large — the model is definitely overfitting. However, performance on the validation set is still improving with max_depth levels. If I had more time I'd explore other ways to prevent overfitting while perhaps still leveraging as many things as I could
- There is an interesting mix of features that derive from chemical properties of the small molecule, annotated attributes of the protein, and some sequence-derived properties of the protein.
- One cheeky thing - the PatentFamilyCount feature importance is a bit of a cheat - it seems that by knowing how many patents the small molecule has been involved in allows you to predict whether it will bind or not :). Other times, I've seen the Literature Count be the #1 most predictive feature. Obviously does not seem conducive to de-novo discovery of novel interactions, but it does make sense in a data science way

Conclusion

- I think my model did a decent job, at least in log space, of predicting binding affinity values.
- A variety of features turned out to be fairly predictive, at least when they were leveraged by the tree model. This includes chemical properties of the small molecules, annotated attributes of the protein, and some chemical properties derived from the protein sequence. The sign of a healthy model!
- I was a bit surprised at how much better tree models were in this regime, as compared to the dense neural net that I tried, but I guess it is possible that there are many non-linear effects that are difficult to model without some specialization.
- I did not use much deep learning for this project (aside from the dense MLP regressor), but recognize that there are lots of places where I could have - supplementary ideas follow!

Things I did not get to try: Protein Seq

I had better ideas for protein sequence data,
But I just didn't quite have the resources to execute on it

- Kmer embedding feature for protein sequence
  - For k=3, I get feature vectors of length 8000. Just too much for my laptop to handle
- CNN approach with one-hot embedding for protein sequence
- ProtBERT embeddings from protein data
  - I was getting size 1024 per protein sequence. This seemed promising, but it was just taking too long to calculate them all on my laptop.

Things I did not get to try: Chemicals

Similarly, just kinda ran out of time to work on this

- Using RDkit, I can extract Molecular Descriptors or Morgan Fingerprint data
- I got all this set up and was getting ready to try it out, but again it was just taking too long to run on my old laptop.

Other Ideas: Recommender system!

- There was a way to solve the problem without even querying any data - if I just made a matrix of all possible chem IDs vs protein IDs and their KIBA score, and used a matrix factorization approach to fill in missing values
- This could have been fun, but then I would have to find a custom workflow to add in “new users” and that’s a little straightforward