Predicting COVID Moonshot molecule binding affinity

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Introduction

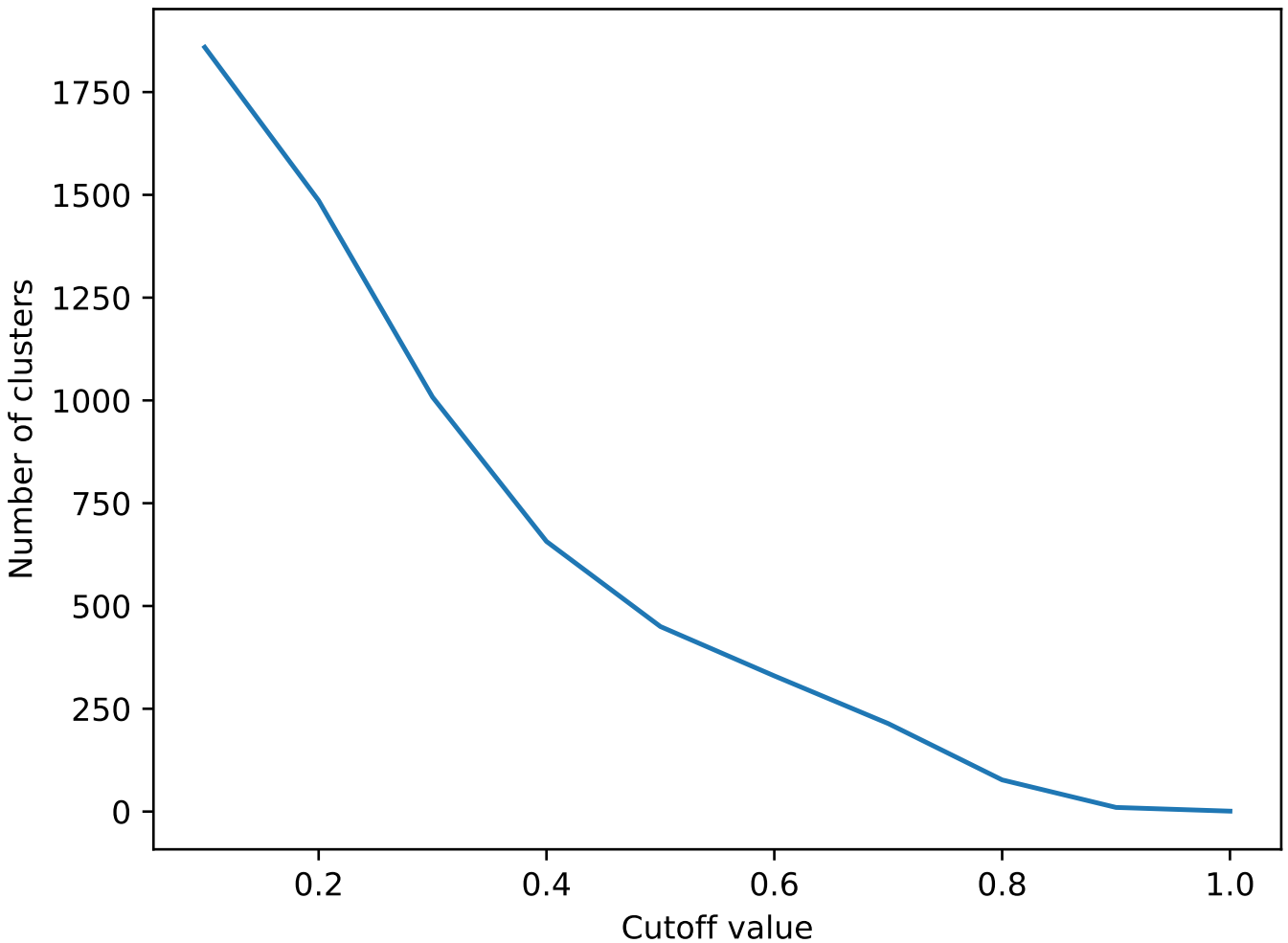
1. Determine binding affinity of putative SARS-CoV-2 protease binders
2. Strong focus on workflow automation
3. Snakemake powers the entire process

Our workflow DAG

Build database

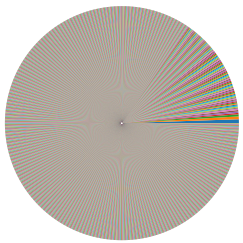
```
1  import sqlite3
2  import pandas as pd
3
4  def build_db(data_path, out_path):
5      con = sqlite3.connect(out_path)
6      cur = con.cursor()
7      df = pd.read_csv(data_path, index_col='CID')
8      assays_df = df.drop(columns=['SMILES'])
9      compounds_df = df[['SMILES']]
10     assays_table = 'assays'
11     assays_df.to_sql(assays_table, con, if_exists='
           replace', index=True)
12     compounds_table = 'compounds'
13     compounds_df.to_sql(compounds_table, con,
           if_exists='replace', index=True)
14     con.close()
```

Fingerprint clustering - sensitivity to cutoff

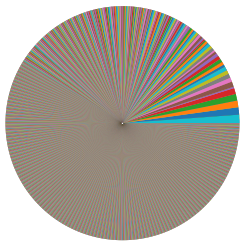


Fingerprint clustering - class composition

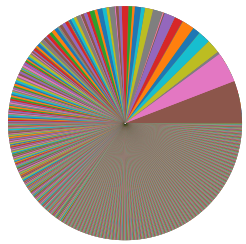
Size distribution of clusters
1859 clusters generated with a cutoff of 0.1



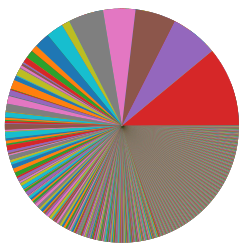
Size distribution of clusters
1486 clusters generated with a cutoff of 0.2



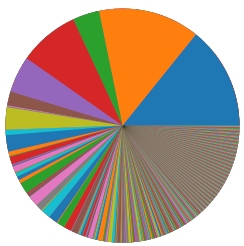
Size distribution of clusters
1008 clusters generated with a cutoff of 0.3



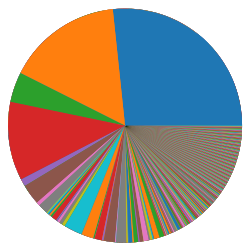
Size distribution of clusters
657 clusters generated with a cutoff of 0.4



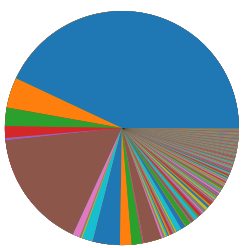
Size distribution of clusters
450 clusters generated with a cutoff of 0.5



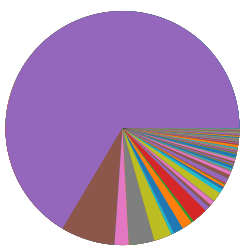
Size distribution of clusters
330 clusters generated with a cutoff of 0.6



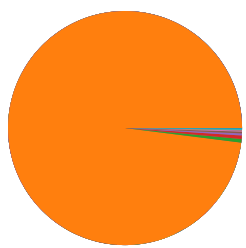
Size distribution of clusters
214 clusters generated with a cutoff of 0.7



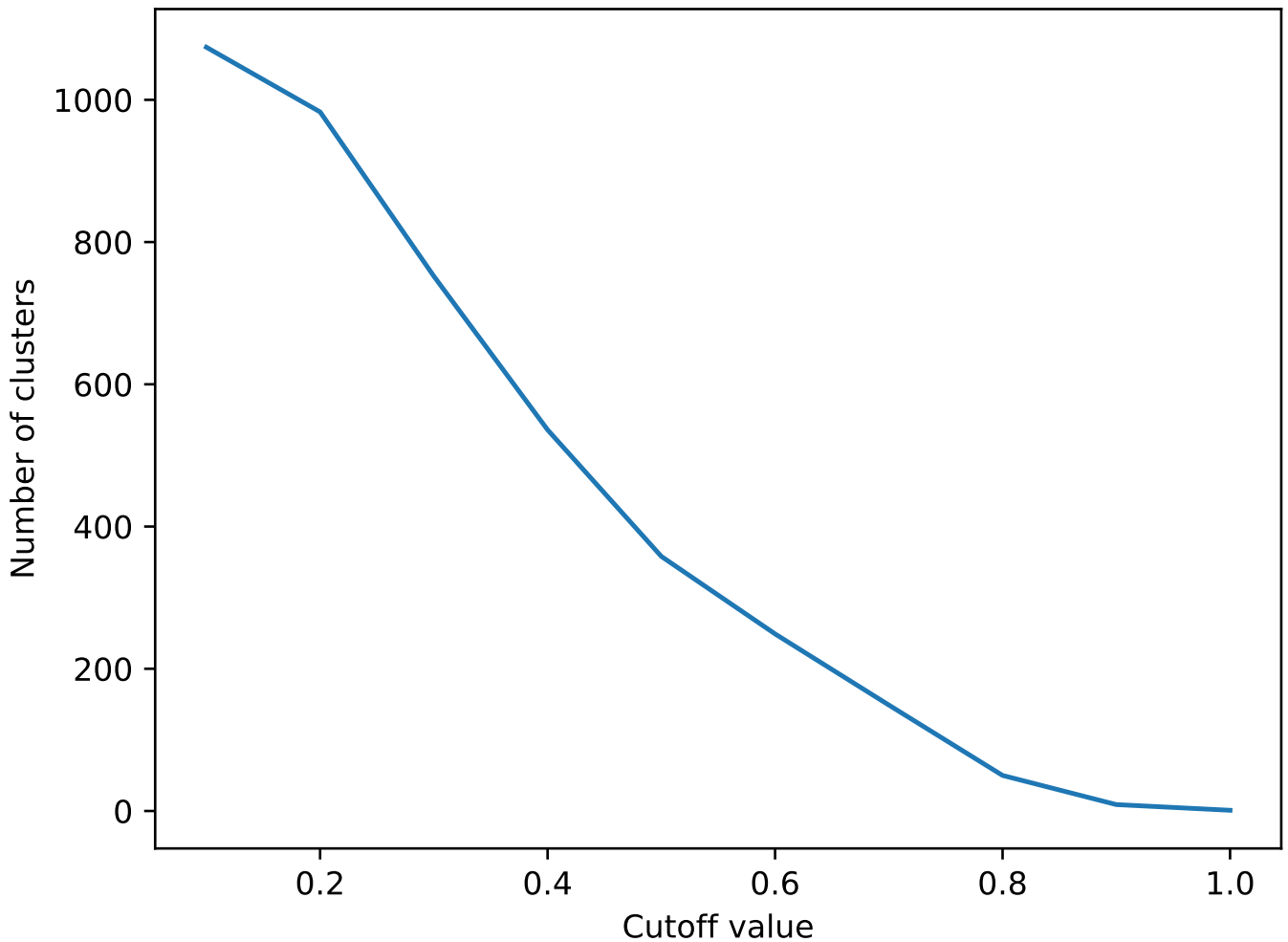
Size distribution of clusters
77 clusters generated with a cutoff of 0.8



Size distribution of clusters
10 clusters generated with a cutoff of 0.9

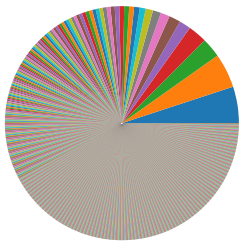


Scaffold clustering - sensitivity to cutoff

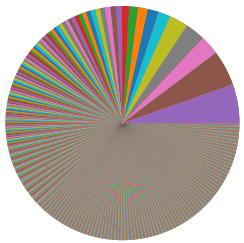


Scaffold clustering - class composition

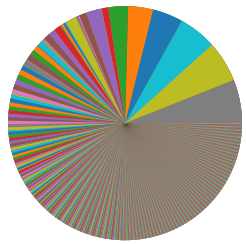
Size distribution of clusters
1074 clusters generated with a cutoff of 0.1



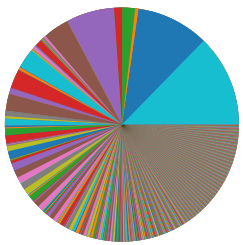
Size distribution of clusters
983 clusters generated with a cutoff of 0.2



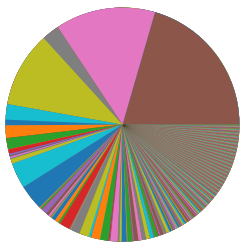
Size distribution of clusters
752 clusters generated with a cutoff of 0.3



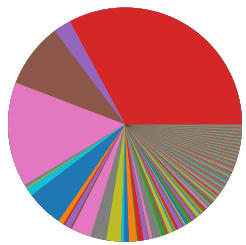
Size distribution of clusters
536 clusters generated with a cutoff of 0.4



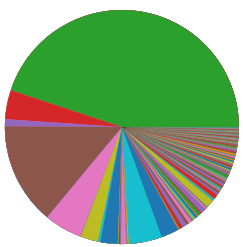
Size distribution of clusters
358 clusters generated with a cutoff of 0.5



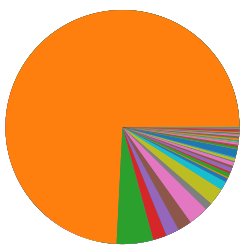
Size distribution of clusters
249 clusters generated with a cutoff of 0.6



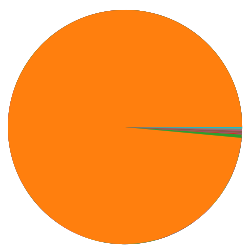
Size distribution of clusters
149 clusters generated with a cutoff of 0.7



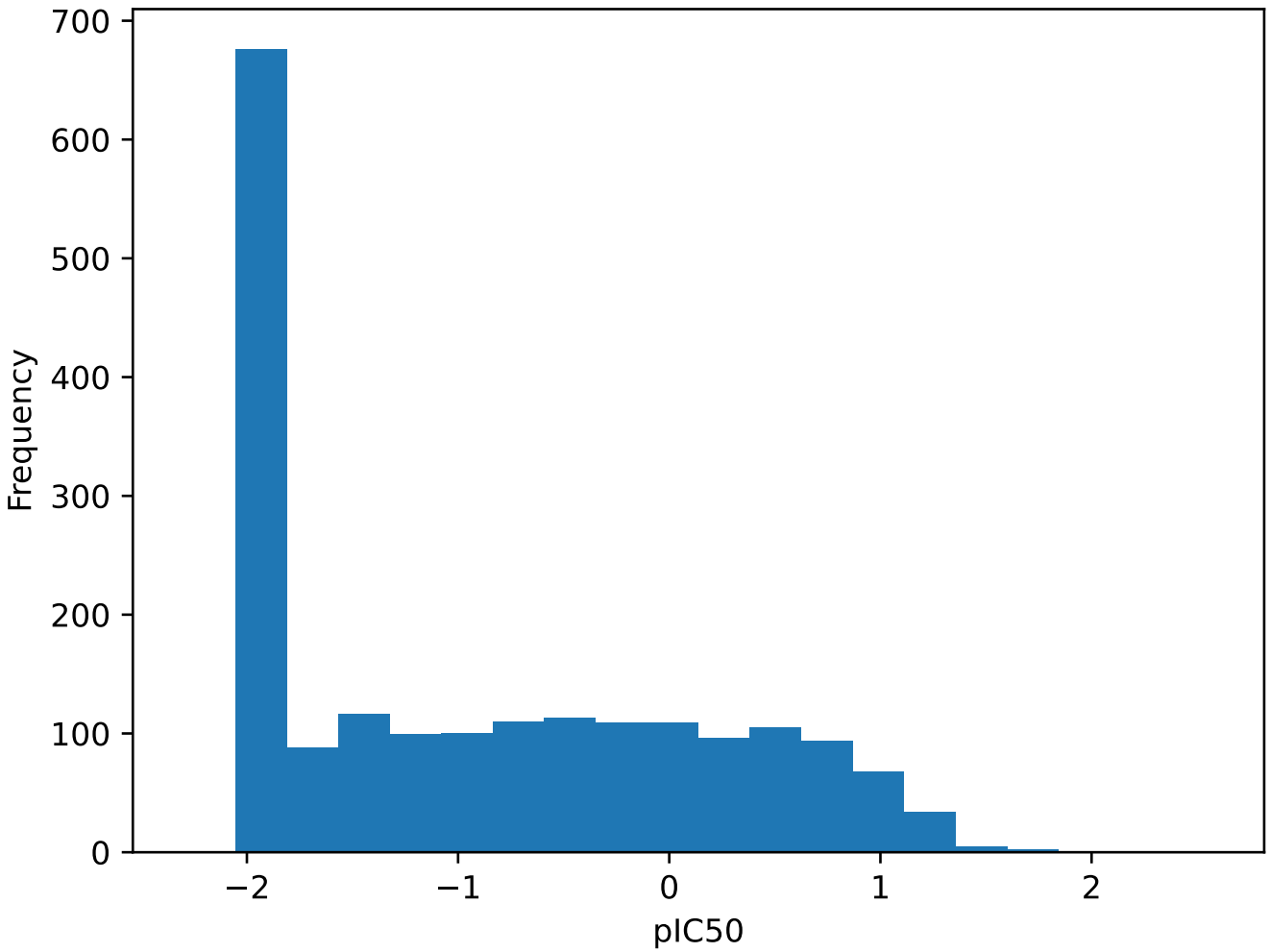
Size distribution of clusters
50 clusters generated with a cutoff of 0.8



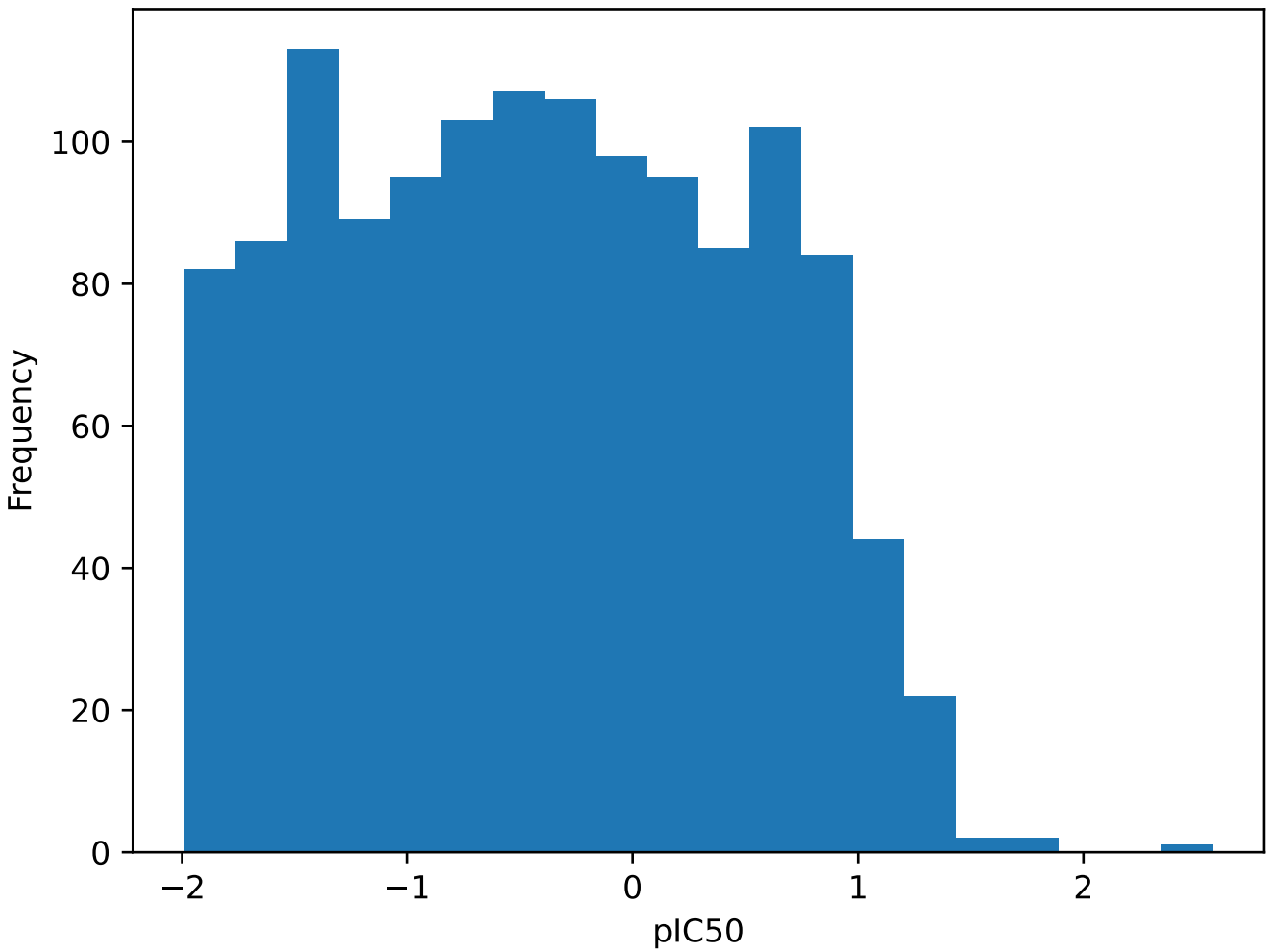
Size distribution of clusters
9 clusters generated with a cutoff of 0.9



pIC50 distribution



pIC50 distribution (only binders)



Strategy

1. Classification for binders vs. non-binders
2. Regression for binding strength (pIC50)
3. Can use similar model for both since learning very similar properties

Compute Descriptors

```
1  def compute_descriptors(molecule):
2      descriptors ={}
3      for d in Descriptors.descList:
4          try:
5              value = d[1](molecule)
6              descriptors[d[0]] = value
7
8          except:
9              value = np.nan
10             descriptors[d[0]] = np.nan
11     descriptors = pd.Series(descriptors)
12     return descriptors
```

Make Dataframe

```
1  def pack_df(df_with_SMILES):
2      descriptorsdf = pd.DataFrame()
3      for index, row in df_with_SMILES.iterrows():
4      # Get the SMILES string of the compound
5          smiles = row['SMILES']
6      # Create a rdkit molecule object from SMILES
7          mol = Chem.MolFromSmiles(smiles)
8          des = compute_descriptors(mol)
9          for i in range(len(des)):
10                 descriptorsdf.at[index,'{}'.format(
                       des.index[i])] = des.values[i]
11     return descriptorsdf
```

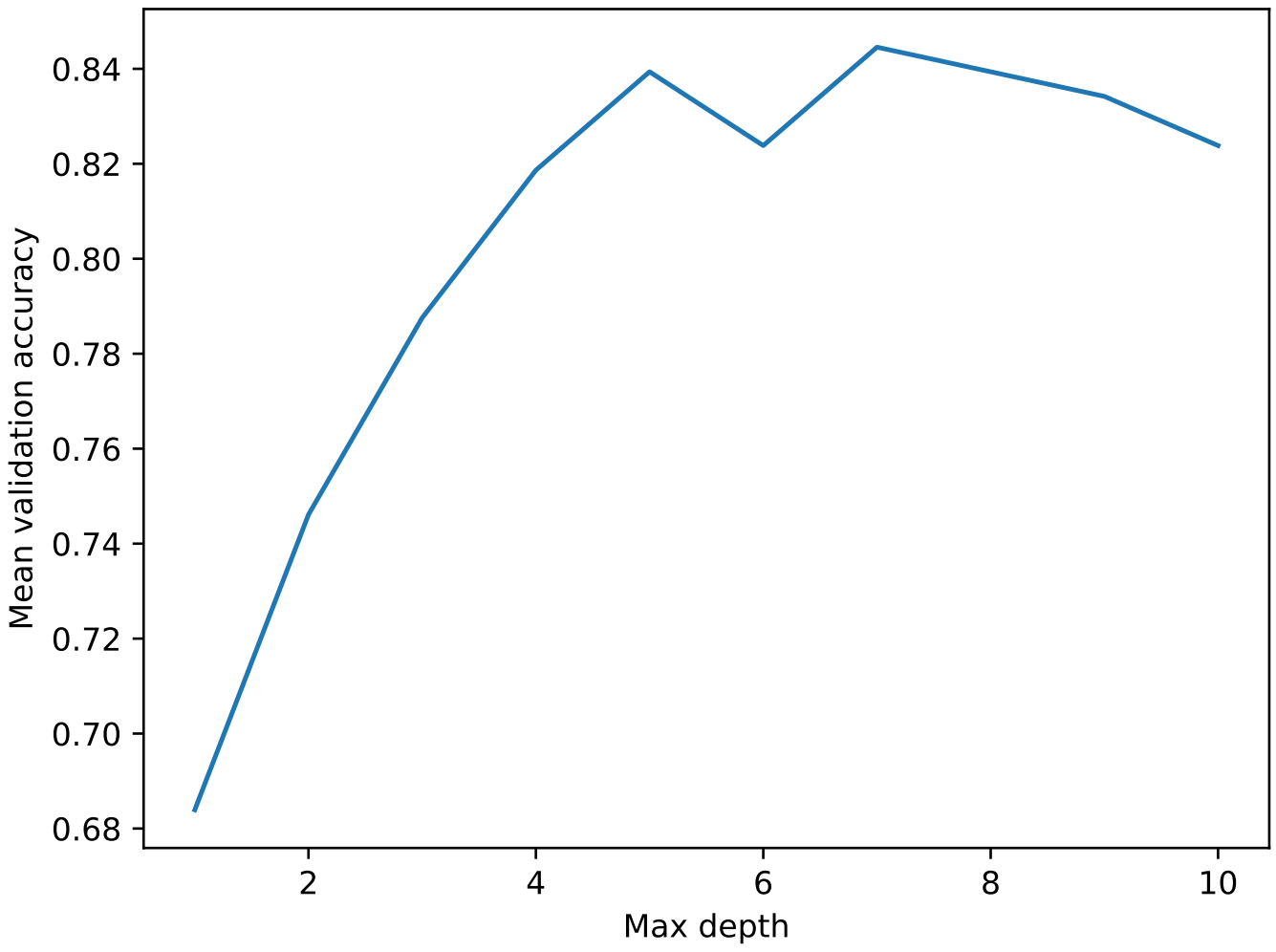
Feature Selection

```
1  def feature_selection(Descriptors_df, y_df, k_feature
       = 10, task = 'regress', way = 'simple', rfe_step
       = 0.2):
2      if task == 'regress':
3          estimator = SVR(kernel="linear")
4      if task == 'classification':
5          estimator = LogisticRegression()
6      if way == 'simple':
7          selector = SelectKBest(f_classif, k=k_feature
               )
8      if wat == 'rfe':
9          selector = RFE(estimator,
               n_features_to_select=k_feature, step=
               rfe_step)
10     selector.fit(Descriptors_df, y_df)
11     top_k_idx = selector.get_support(indices=True)
12     return Descriptors_df.columns[top_k_idx]
```

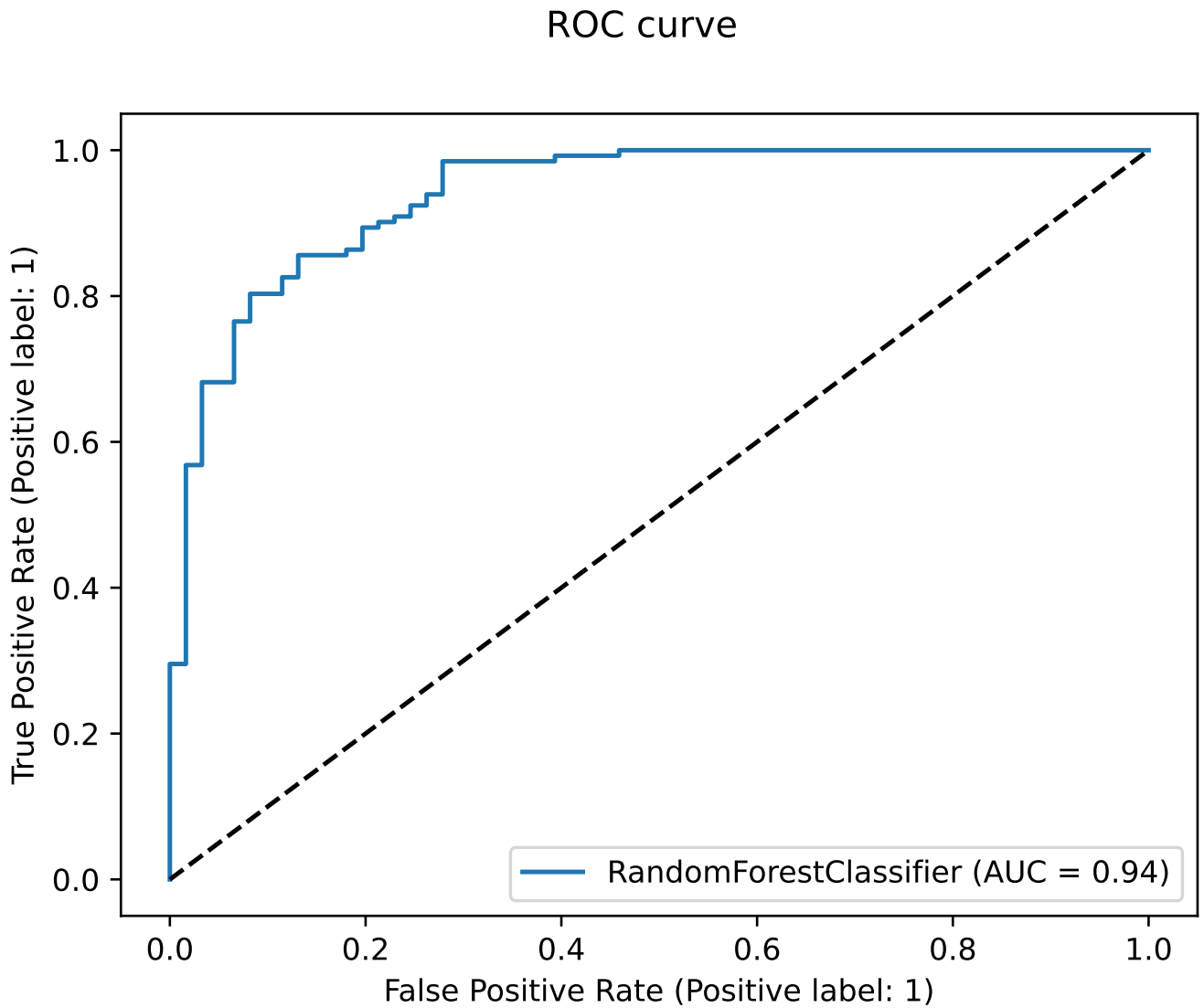
Best 10 parameters

Feature Descriptor	**Meaning**
PEOE_VSA8	Polarizability based on Eigenvalues of the Overlap matrix (PEOE) with 8 VSA
fr_N_O	Nitro group
fr_diazo	Diazo group
fr_dihydropyridine	Dihydropyridine group
fr_hdrzine	Hydrazine group
fr_ketone_Topliss	Ketone group using Topliss method
fr_lactam	Lactam group
fr_oxazole	Oxazole group
fr_sulfonamd	Sulfonamide group
fr_sulfone	Sulfone group

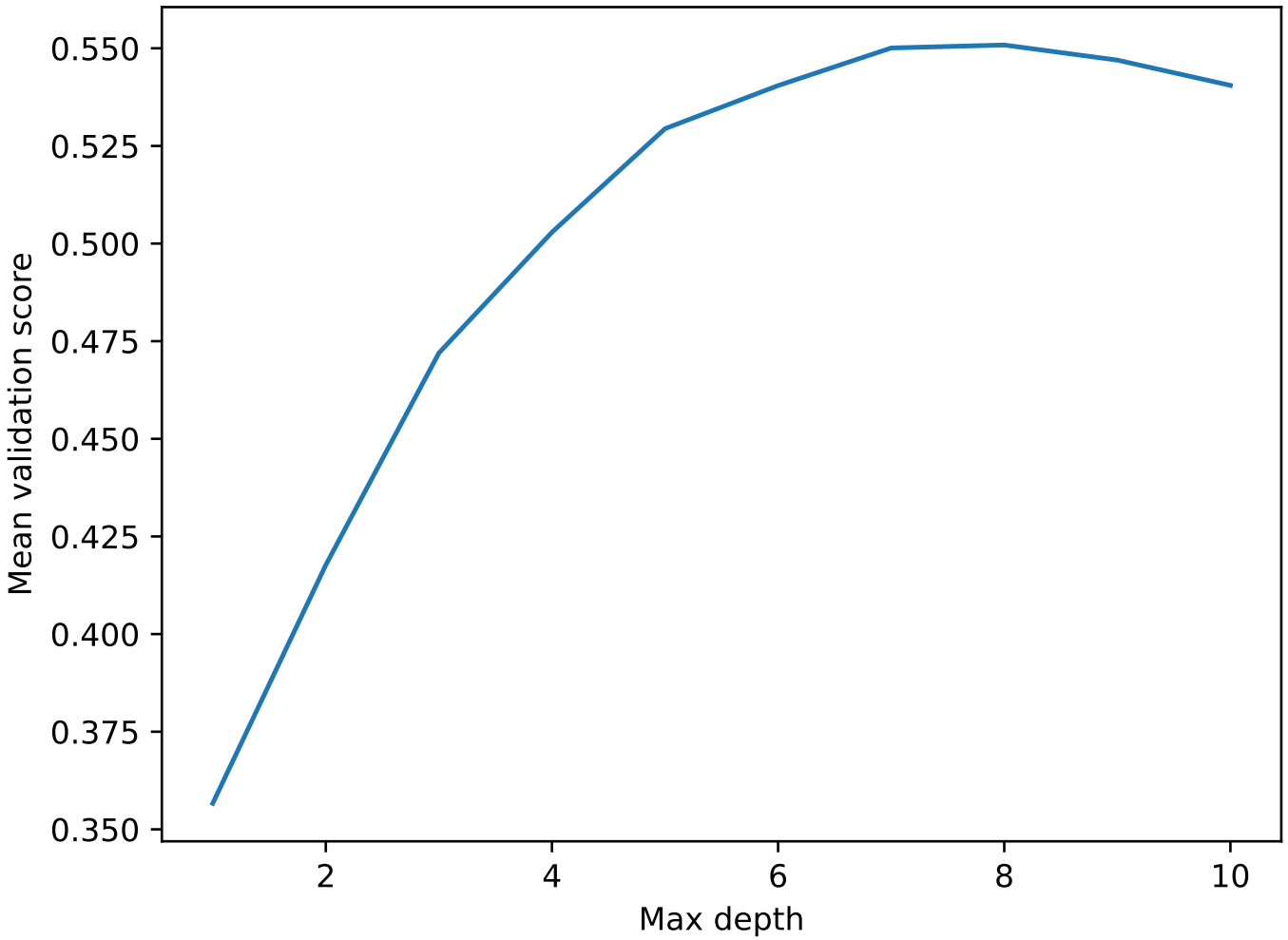
Classifier parameter tuning



Classifier testing ROC



Regressor paramter tuning



Regressor testing residuals