Harnessing Machine Learning Insights for Precision Prediction of Chemical Blood-Brain Barrier Permeability

4/11/2024 BME 790L Final project presentation

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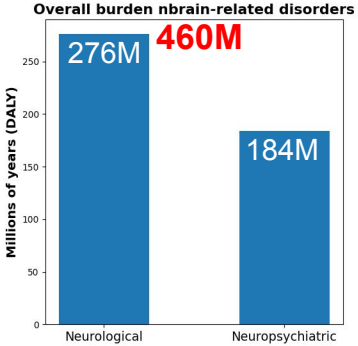
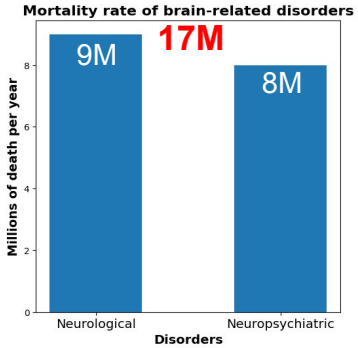
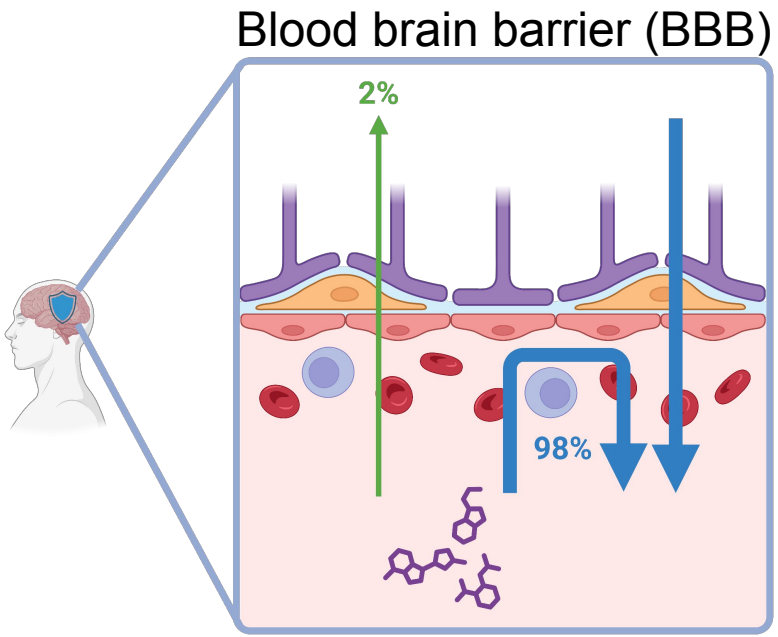
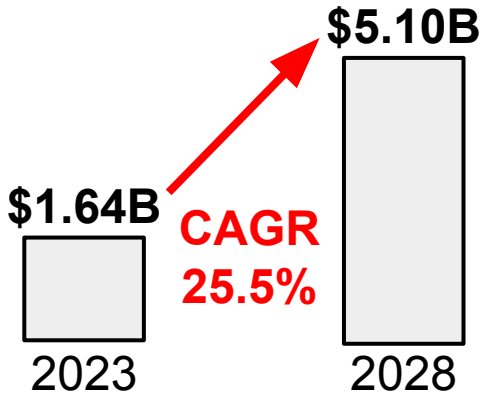
Department of Biomedical Engineering

BBB drug delivery challenge sparks huge market potential



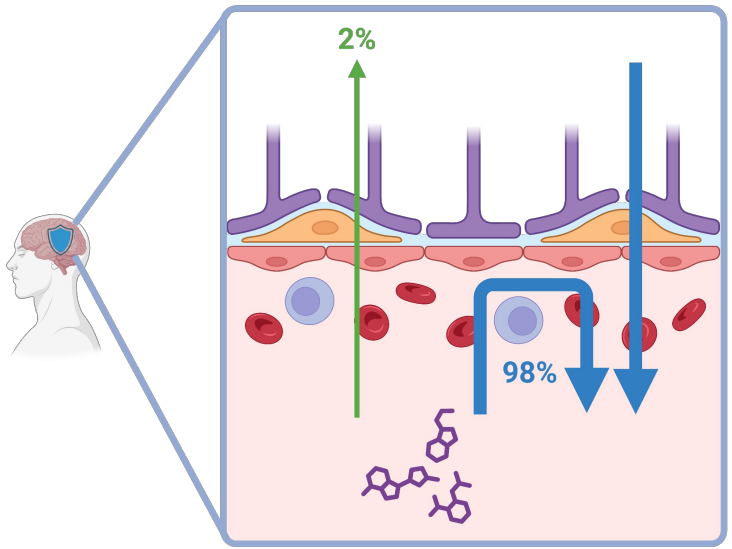


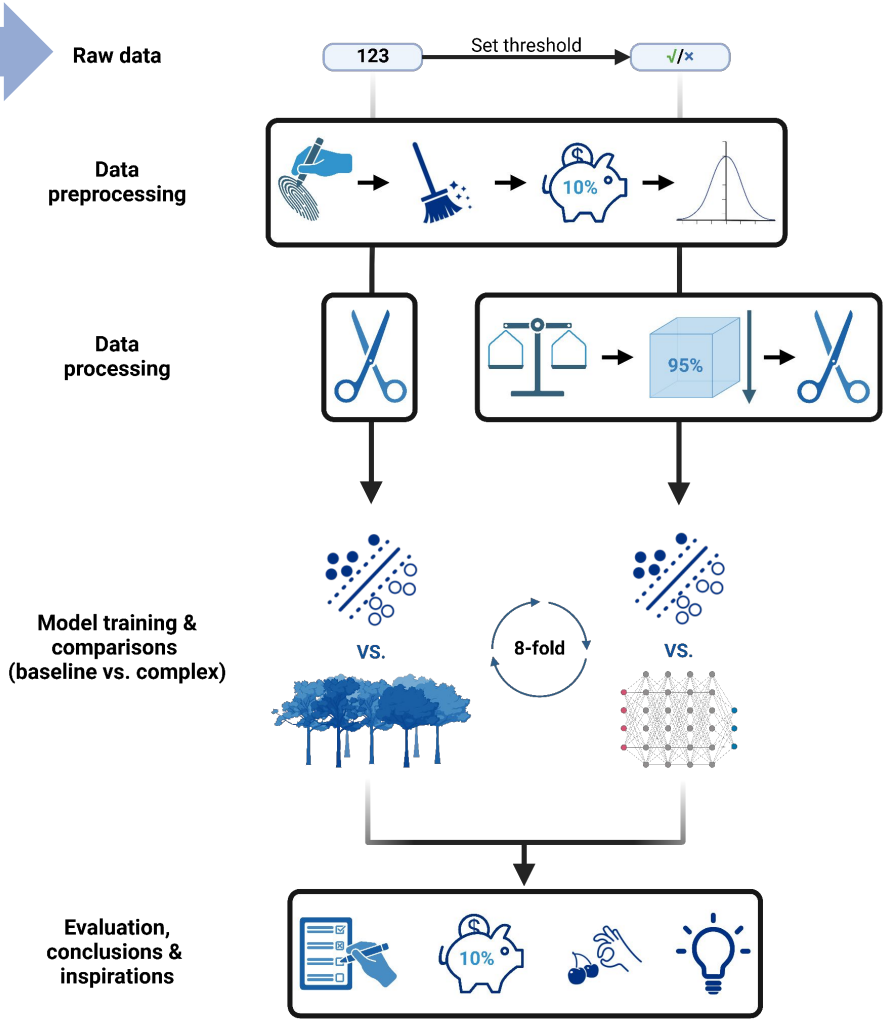




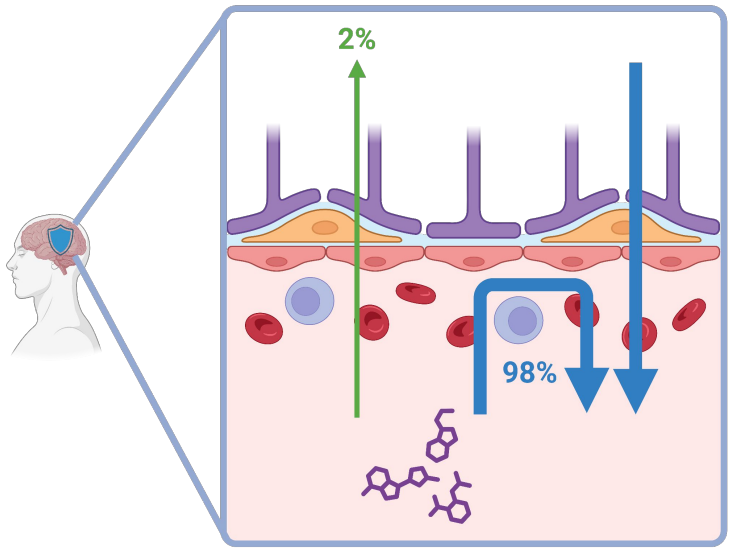
Álvaro Nuno, P., Suarez, J. & Michel Le, B. Sizing the brain. Deloitte Insights (2023).
Wu, D. et al. The blood–brain barrier: structure, regulation, and drug delivery. Signal Transduction and Targeted Therapy 8, (2023).
Fayzullin, A., Bakulina, A., Mikaelyan, K., Shekhter, A. & Guller, A. Implantable Drug Delivery Systems and Foreign Body Reaction: Traversing the Current Clinical Landscape. Bioengineering (Basel) 8 (2021). https://doi.org/10.3390/bioengineering8120205
The Insight Partners. Blood Brain Barrier Technologies Market Global Analysis by 2028. The Insight Partners https://www.theinsightpartners.com/reports/blood-brain-barrier-technologies-market (2021).

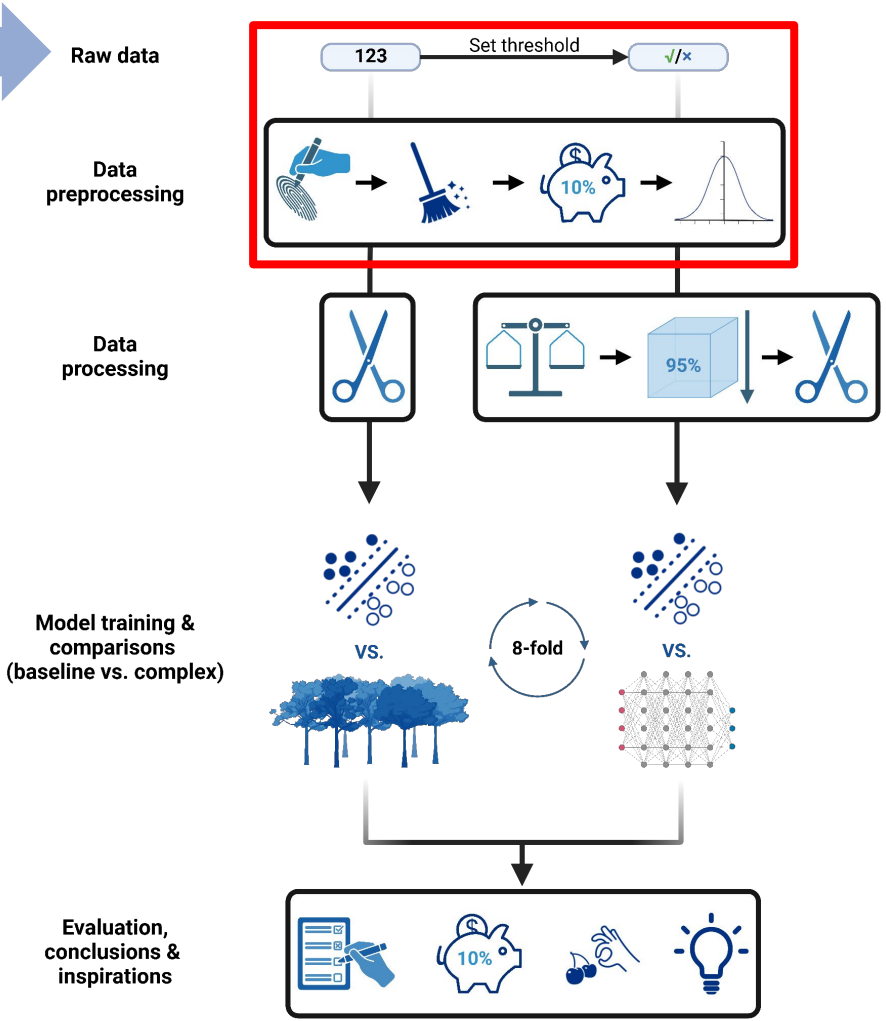
Graphical abstract





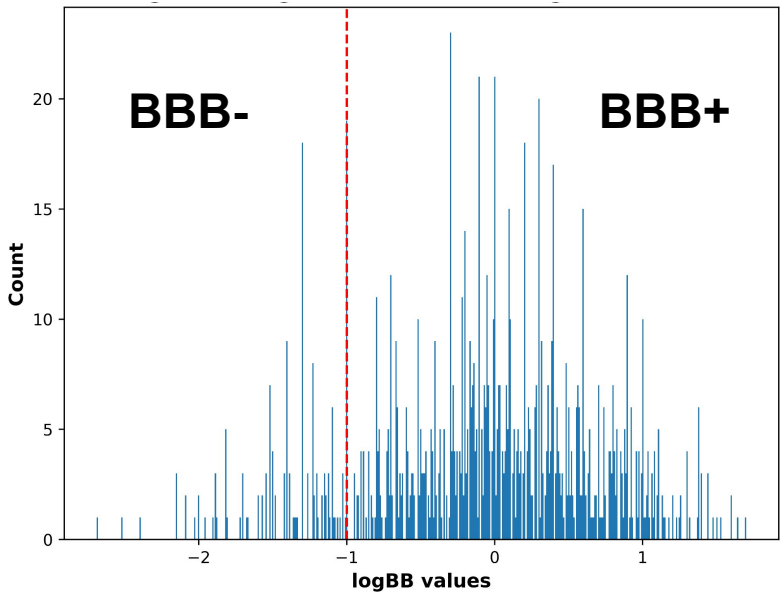
Graphical abstract



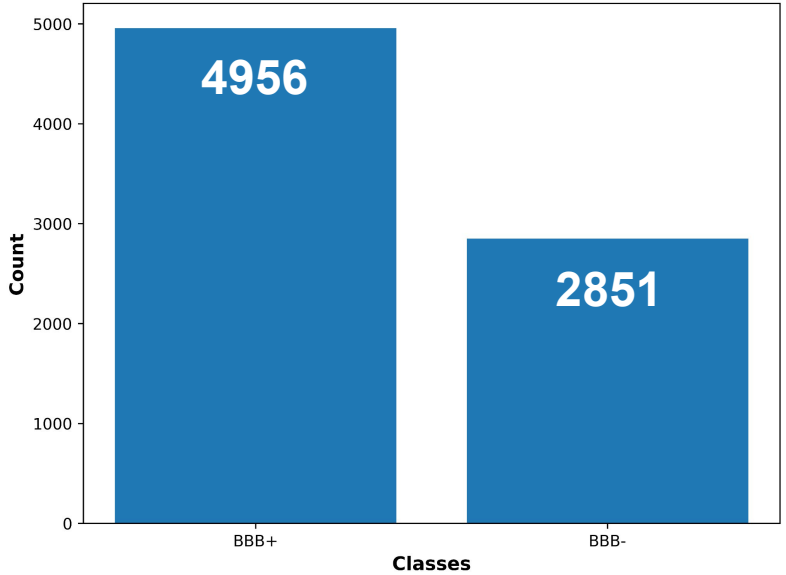


Original datasets have regression & classification data

Regression: 1058



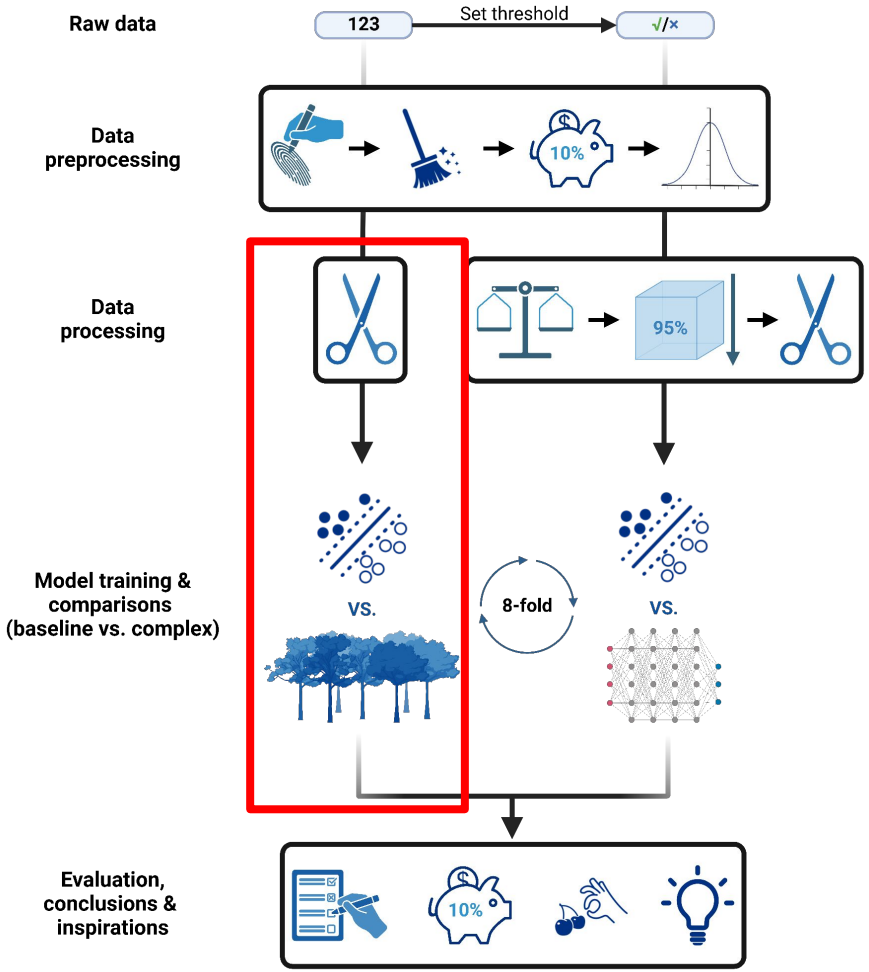
Classification: 7807



Common pre-processings on both datasets

1. Feature expansion
    a. RDKit descriptors
    b. Morgan fingerprints
    c. MACCS keys
2. Feature selection
    a. Get rid of 0 variance features
3. Hold out 10% original data
4. Center & standardization
    a. Data processing transformers specific to regression / classification problem

logBB regression prediction



Data processing & baseline & complex regressors training

- 80-20 train test split
- Transformer shared by 2 models
- Cross-validation by 8 folds
- Scoring: MAE, MSE, R2
- Refit by R2

Baseline: SVR

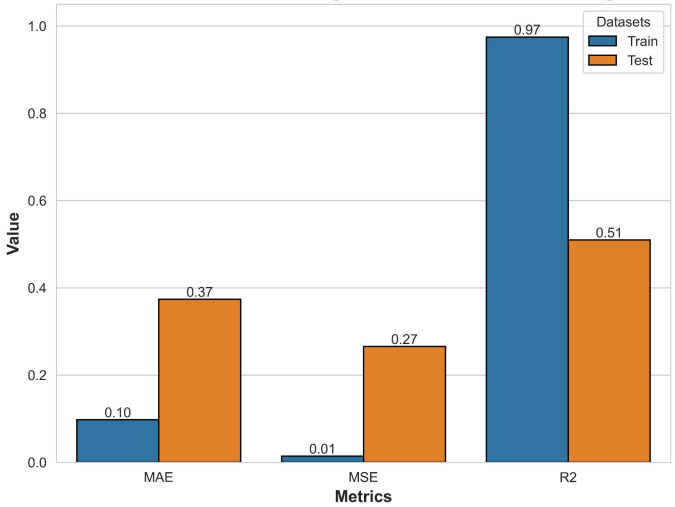
- 'kernel': ['rbf']
- 'gamma': ['auto', 3]
- 'C': [1, 5]

Complex: RF

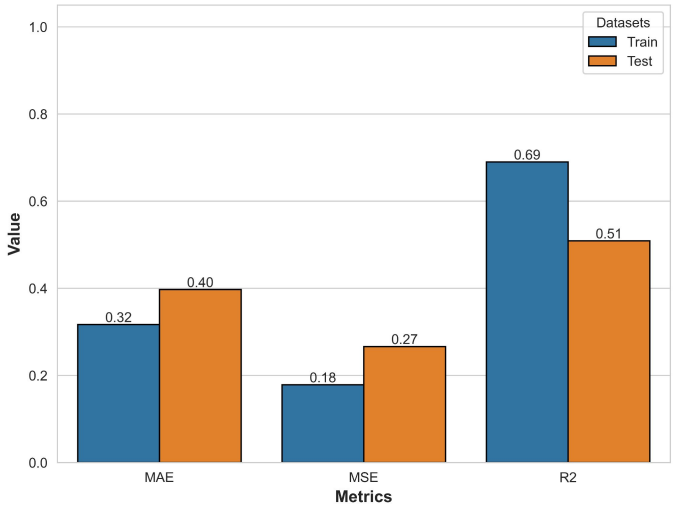
- 'n_estimators': [500, 1000]
- 'max_depth': [5, 20]
- 'min_samples_split': [2, 50]
- 'min_samples_leaf': [5, 50]
- 'criterion': ['squared_error', 'absolute_error']
- 'max_samples':[0.2, 0.85],
- 'max_features': ['sqrt']

SVR likely to be overfitting

Baseline: SVR



Complex: RF



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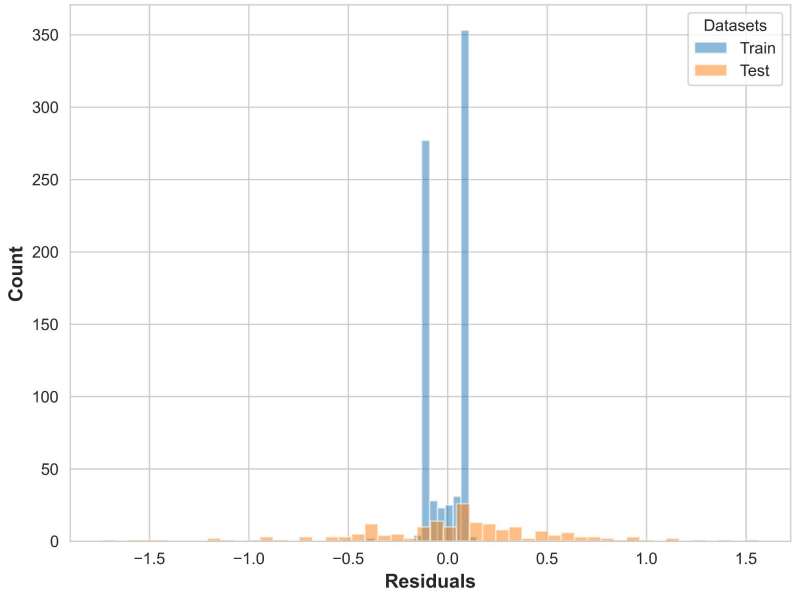
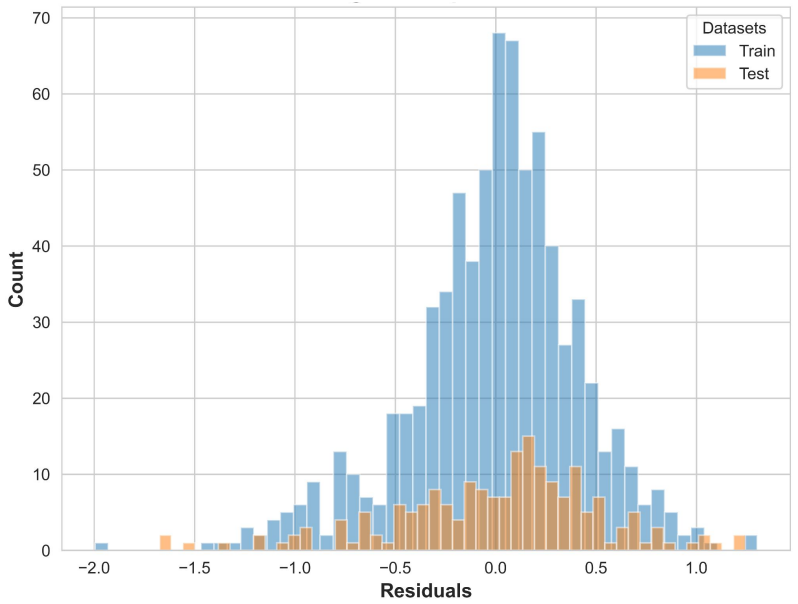


Complex: RF



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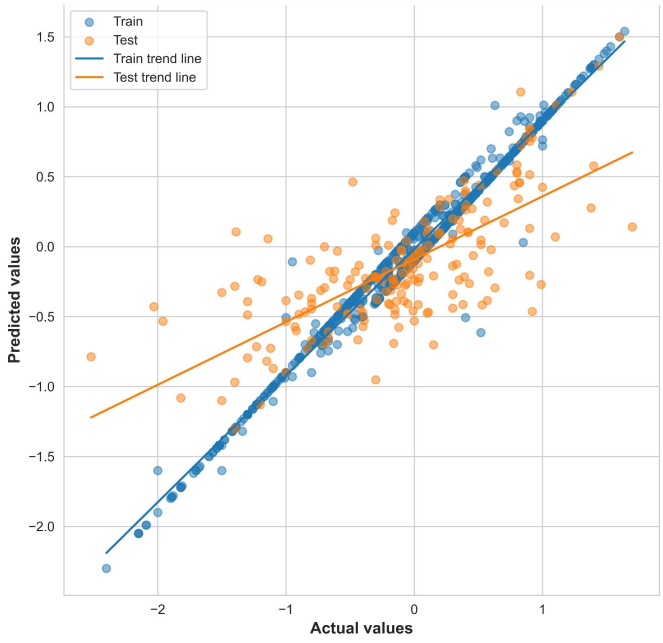
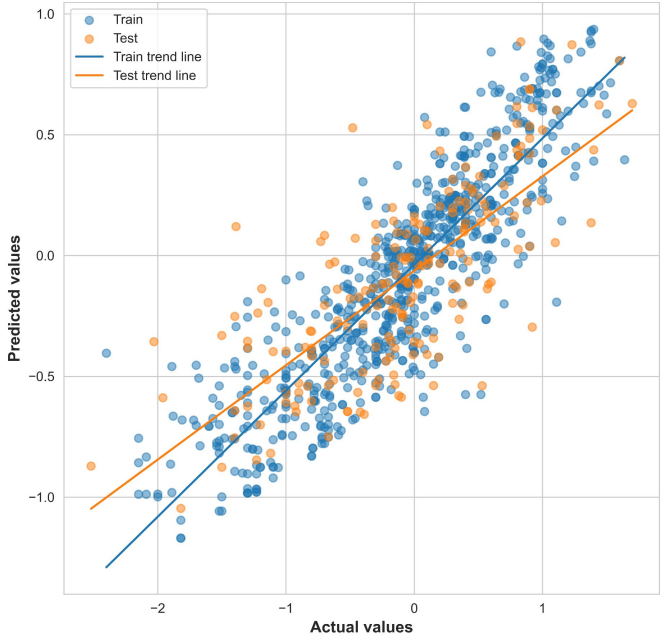


Trend line for train: y=0.91x-0.02
Trend line for test: y=0.45x-0.09

Complex: RF

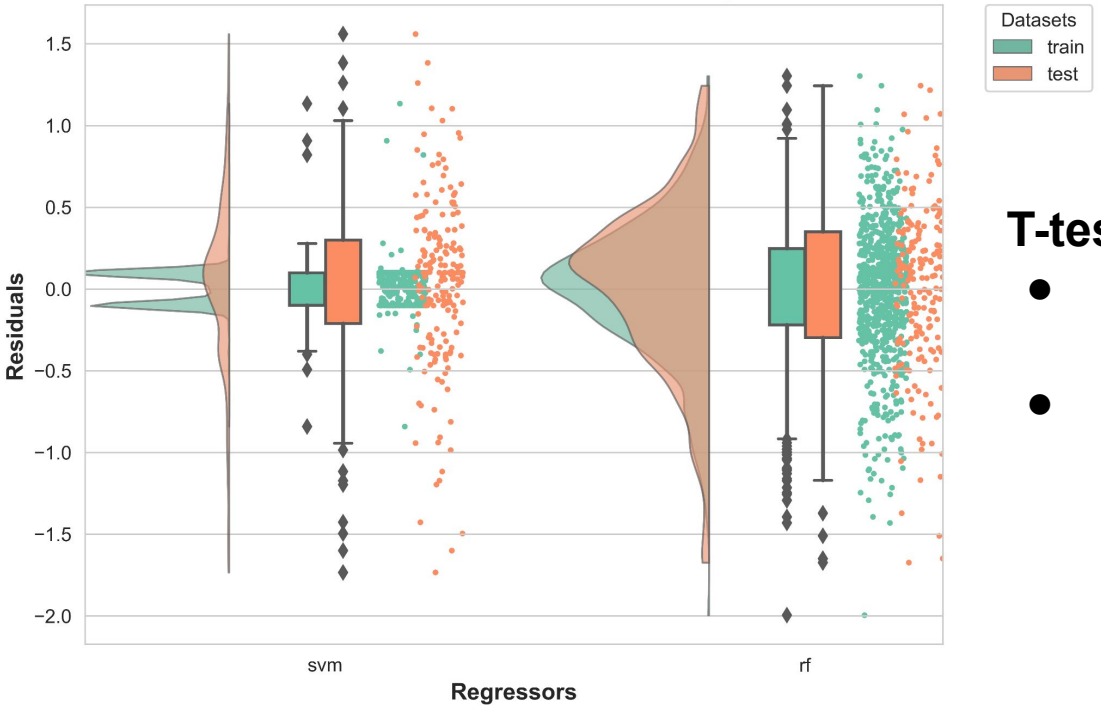


Trend line for train: y=0.52x-0.04
Trend line for test: y=0.39x-0.06

SVR likely to be overfitting

Baseline: SVR

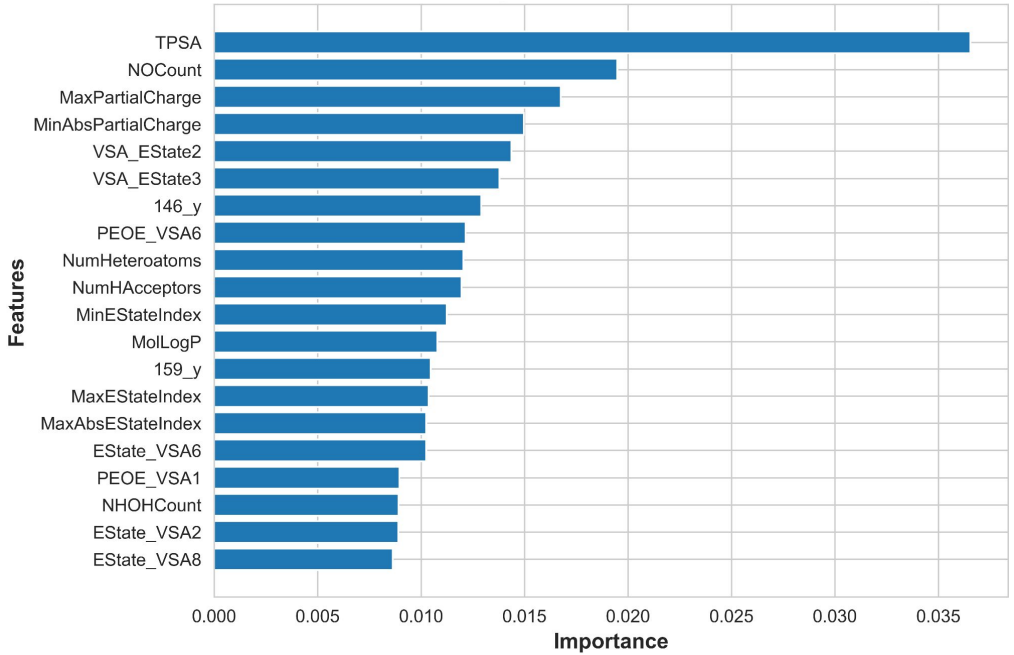
Complex: RF



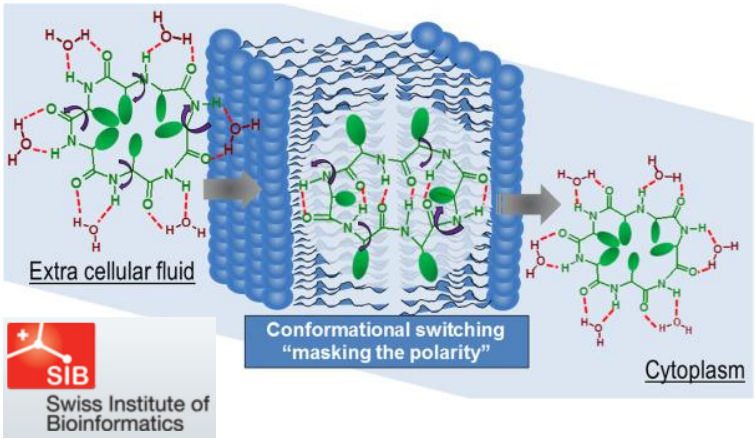
T-test showed

- **Between 2 train sets: p-value = 0.32**
- **Between 2 test sets: p-value = 0.06**

RF shows important features related to polarity & charges

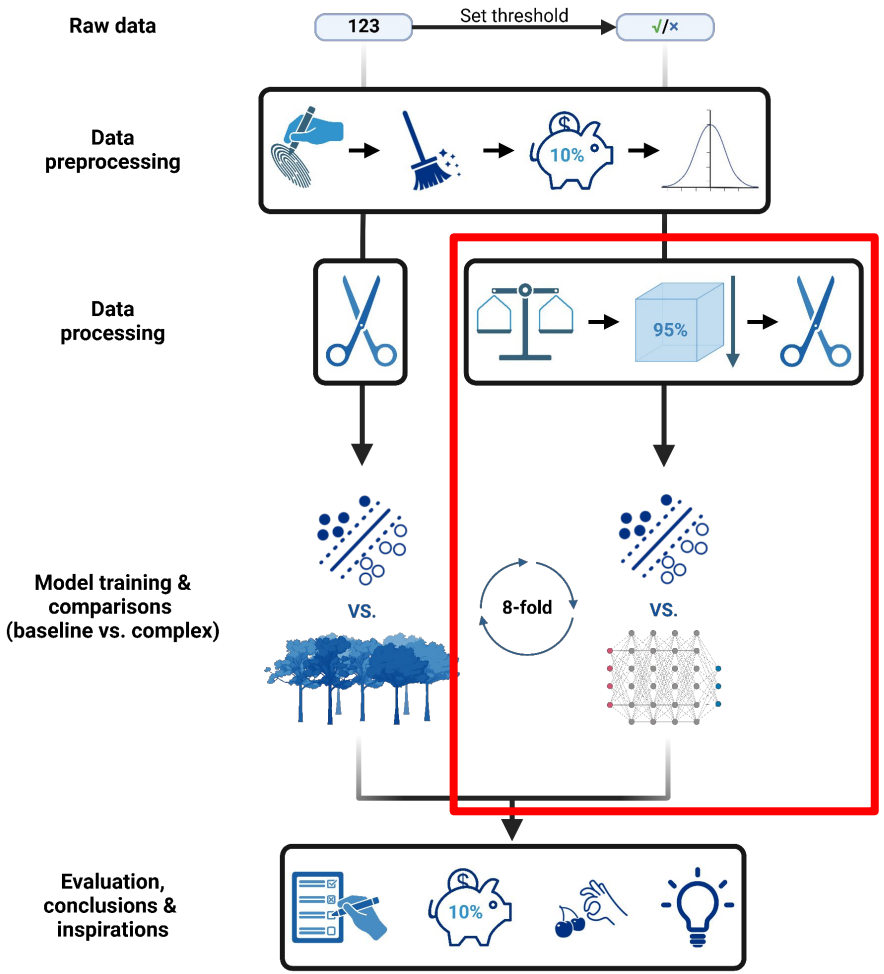


Topological polar surface area (TPSA): measure of molecule's polar surface area

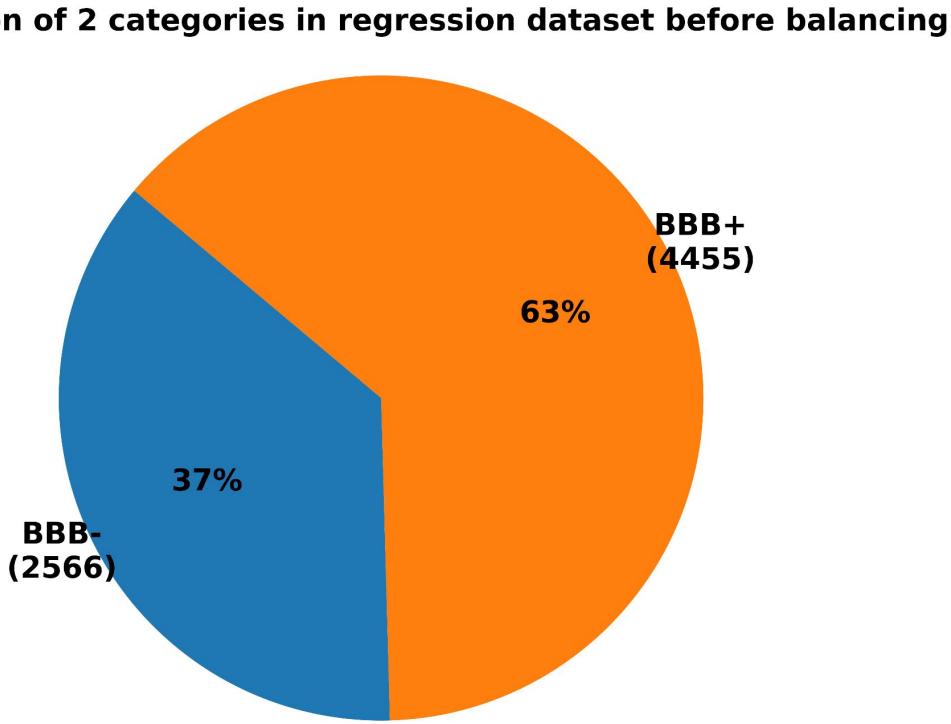


Gillet, V. J. & Leach, A. R. Chemoinformatics. Elsevier eBooks 235–264 (2007) doi:https://doi.org/10.1016/b0-08-045044-x/00085-7.

BBB+/BBB- classification prediction

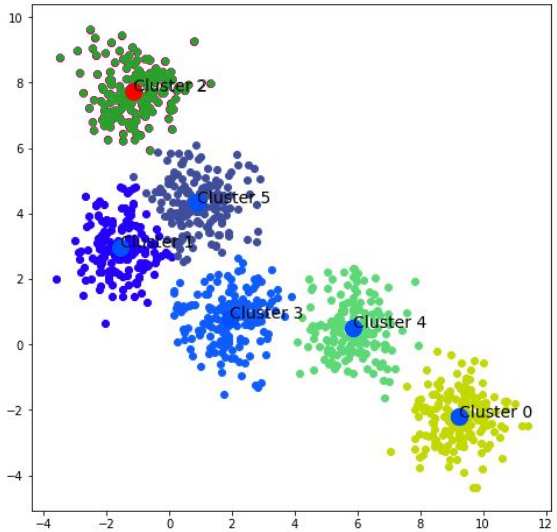


Continue dataset preprocessing for classification problem

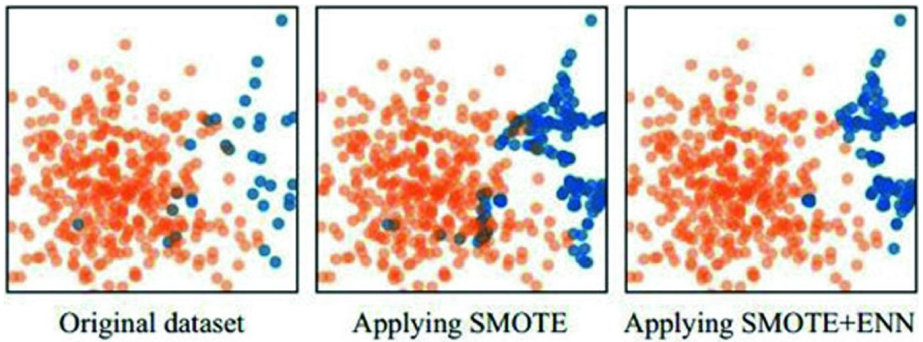


Balancing classification dataset by 2 methods

- **ClusterCentroids**
  - ↓ bigger category



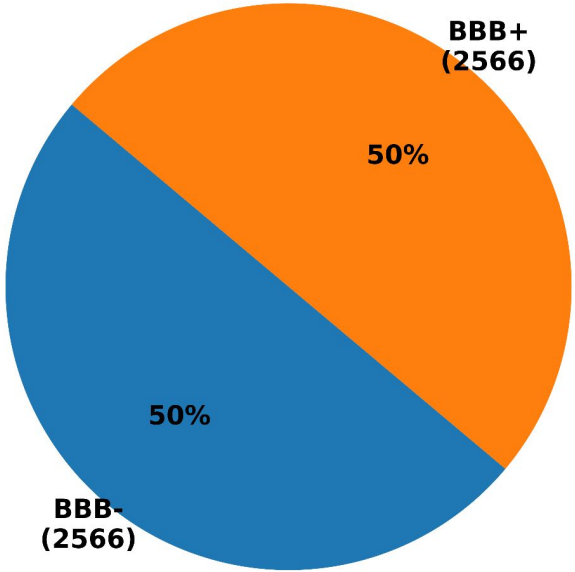
- **SMOTEENN (SMOTE+ENN)**
  - ↑ smaller category
  - Cleaning



tranleanh/centroid-neural-networks: Centroid Neural Networks for Clustering. GitHub https://github.com/tranleanh/centroid-neural-networks (2024).
Cho E, Chang T-W, Hwang G. Data Preprocessing Combination to Improve the Performance of Quality Classification in the Manufacturing Process. Electronics. 2022; 11(3):477. https://doi.org/10.3390/electronics11030477
Mouna Lamari et al. SMOTE–ENN-Based Data Sampling and Improved Dynamic Ensemble Selection for Imbalanced Medical Data Classification. Advances in intelligent systems and computing 37–49 (2020) doi:https://doi.org/10.1007/978-981-15-6048-4_4.

Balancing classification dataset by 2 methods

- **ClusterCentroids**



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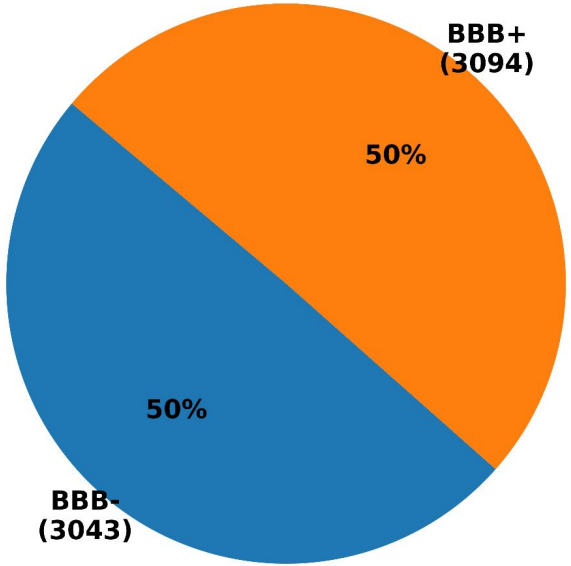
- **SMOTEENN (SMOTE+ENN)**



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Data processing & baseline regressors training

- PCA to cover 95% variance
- 80-20 stratified train test split
- Transformer shared by 2 models
- Repeated stratified cross validation by 8 folds & 2 repeats
- Scoring: recall, precision, F1, accuracy, balanced accuracy, AUROC
- Refit by AUROC

Baseline: SVC on ClusterCentroids

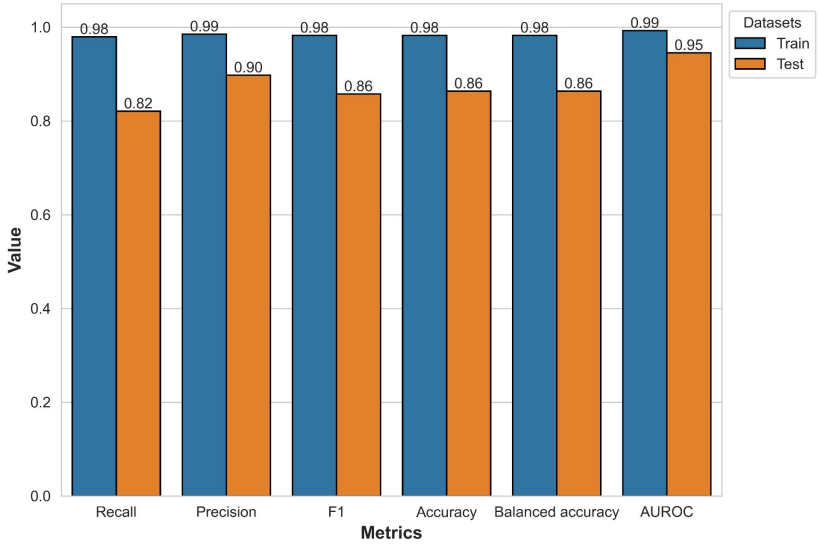
- 'kernel': ['rbf']
- 'gamma': ['auto', 3]
- 'C': [1, 5]

Baseline: SVC on SMOTEENN

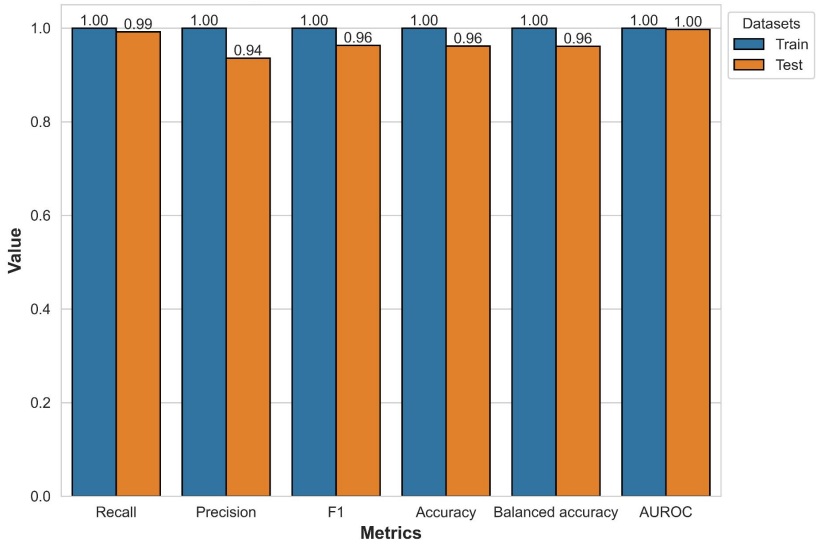
- 'kernel': ['rbf']
- 'gamma': ['auto', 3]
- 'C': [1, 5]

ClusterCentroids gave more reliable SVC

Baseline: SVC on ClusterCentroids



Baseline: SVC on SMOTEENN



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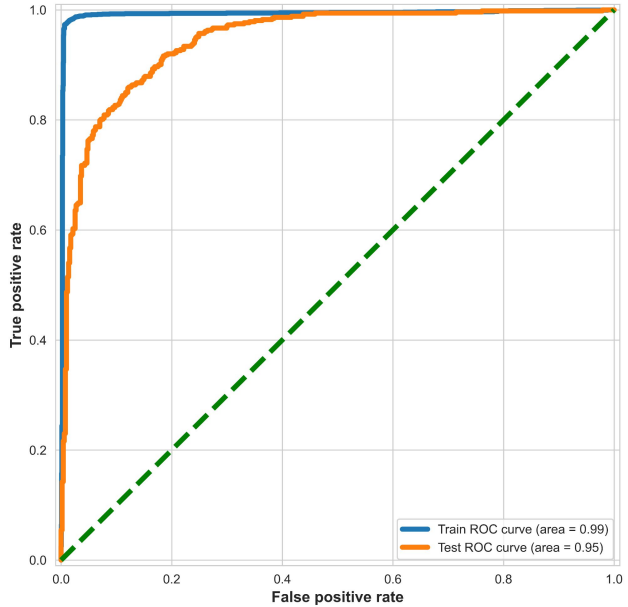
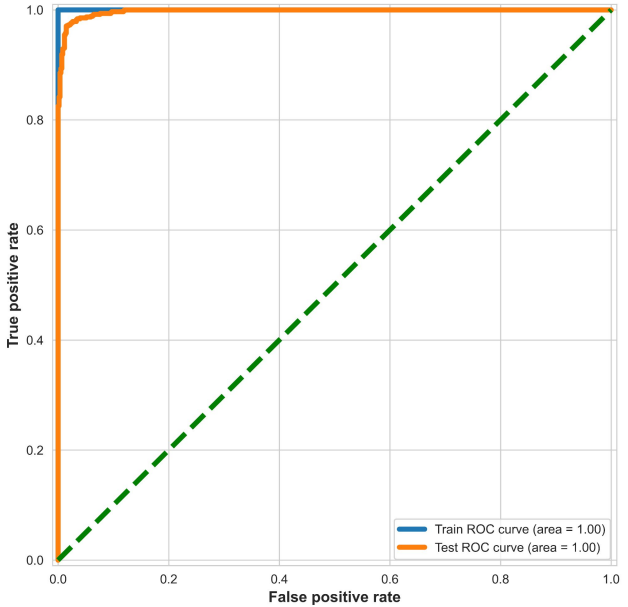
Baseline: SVC on ClusterCentroids

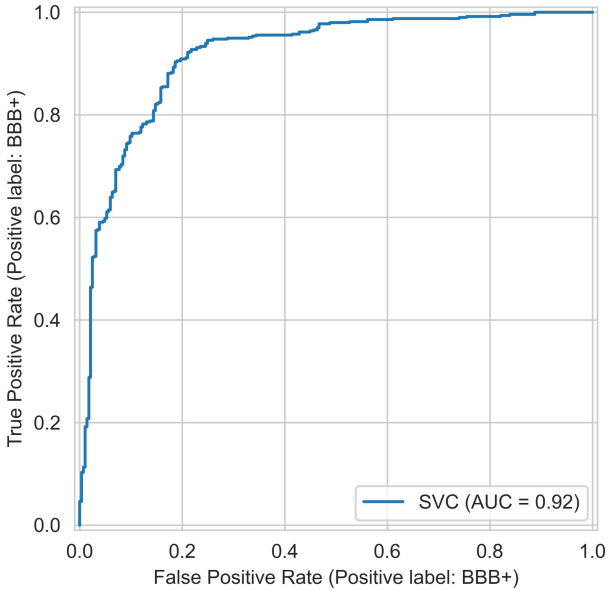


Baseline: SVC on SMOTEENN

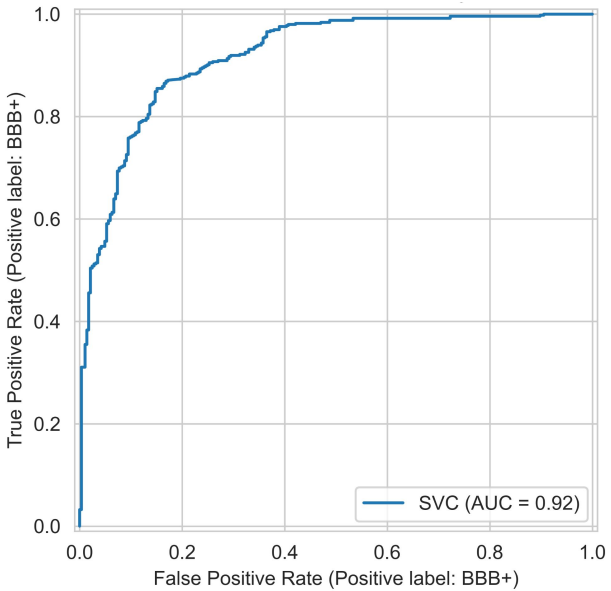


ClusterCentroids gave more reliable SVC performance on holdout

Baseline: SVC on ClusterCentroids



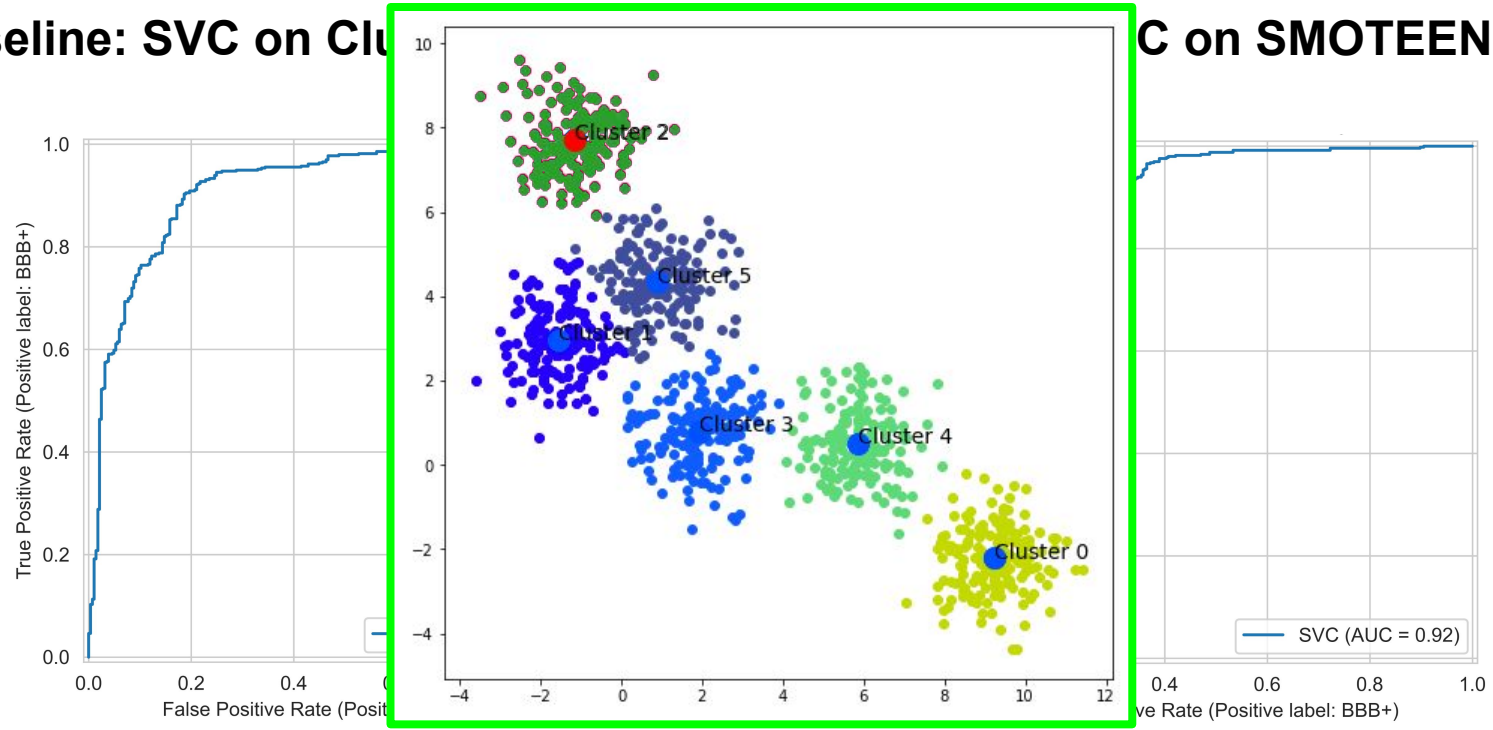
Baseline: SVC on SMOTEENN



DeLong's test gives p-value = 0.944

ClusterCentroids gave more reliable SVC performance

Baseline: SVC on Clu **C on SMOTEENN**



DeLong's test gives p-value = 0.944

Data processing & regressors training

- ClusterCentroids to undersample
- PCA to cover 95% variance
- 80-20 stratified train test split
- Transformer shared by 2 models
- Repeated stratified cross validation by 8 folds & 2 repeats
- Scoring: accuracy, balanced accuracy, AUROC
- Refit by AUROC

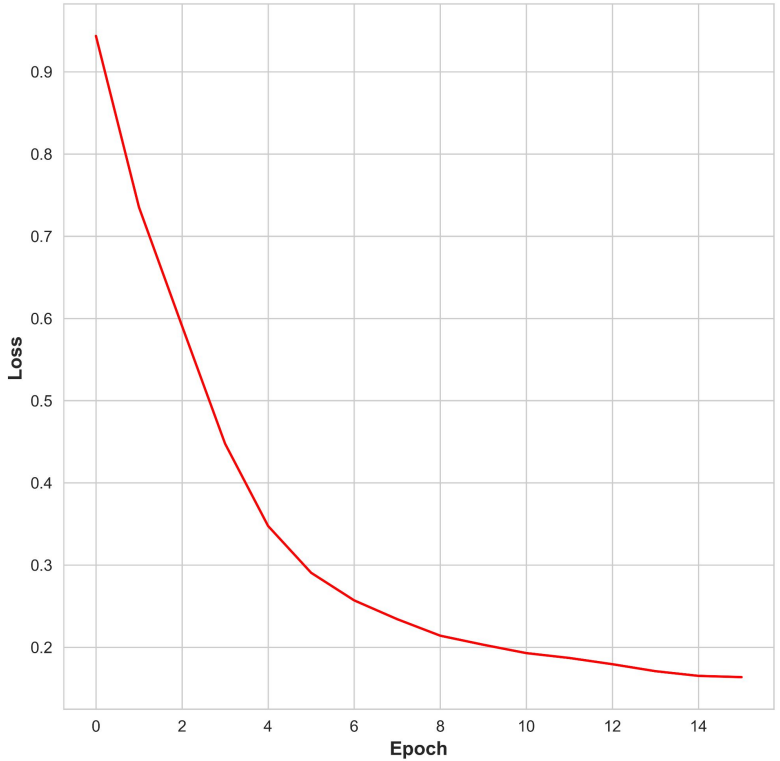
Baseline: SVC on ClusterCentroids

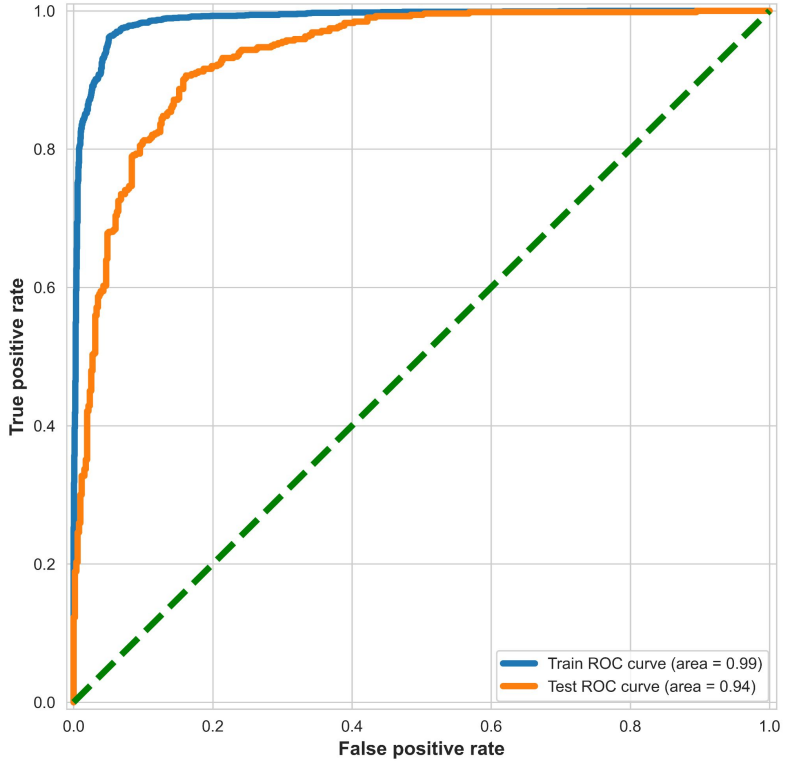
- 'kernel': ['rbf']
- 'gamma': ['auto', 3]
- 'C': [1, 5]

Complex: MLP on ClusterCentroids

- 'hidden_layer_sizes': [(5,), (10,), (10,10)],
- 'alpha': [1e-3, 1],
- 'activation': ['relu', 'tanh'],
- 'batch_size': [16, 64],
- 'learning_rate': ['constant', 'adaptive']

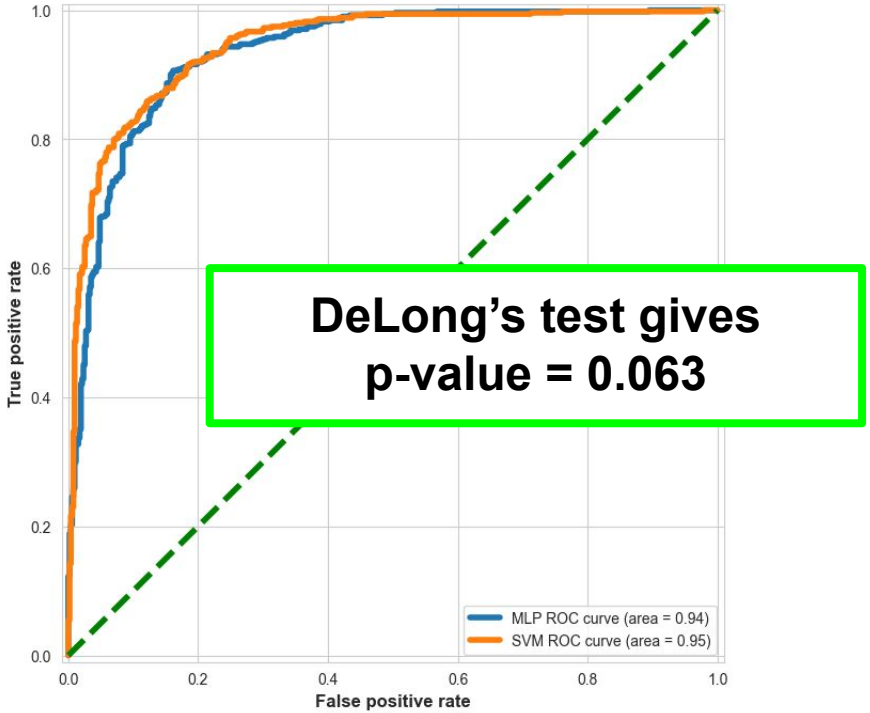
Best MLP classifier showed reasonable learning procss





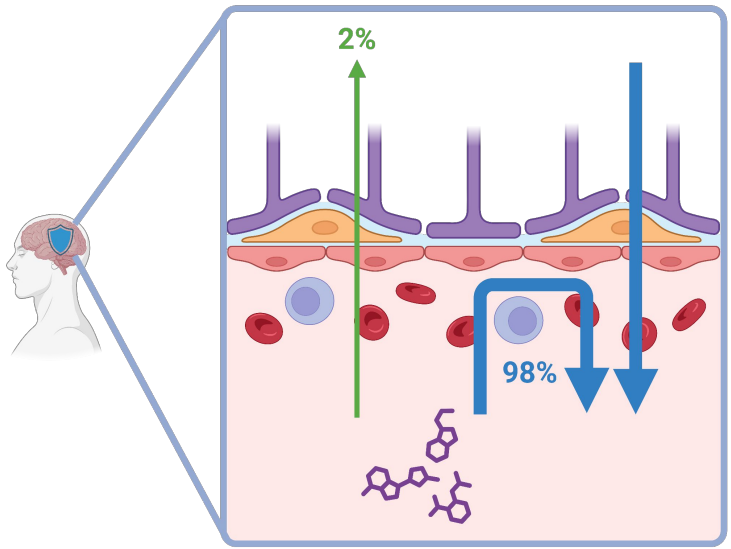
ClusterCentroids gave more reliable SVC

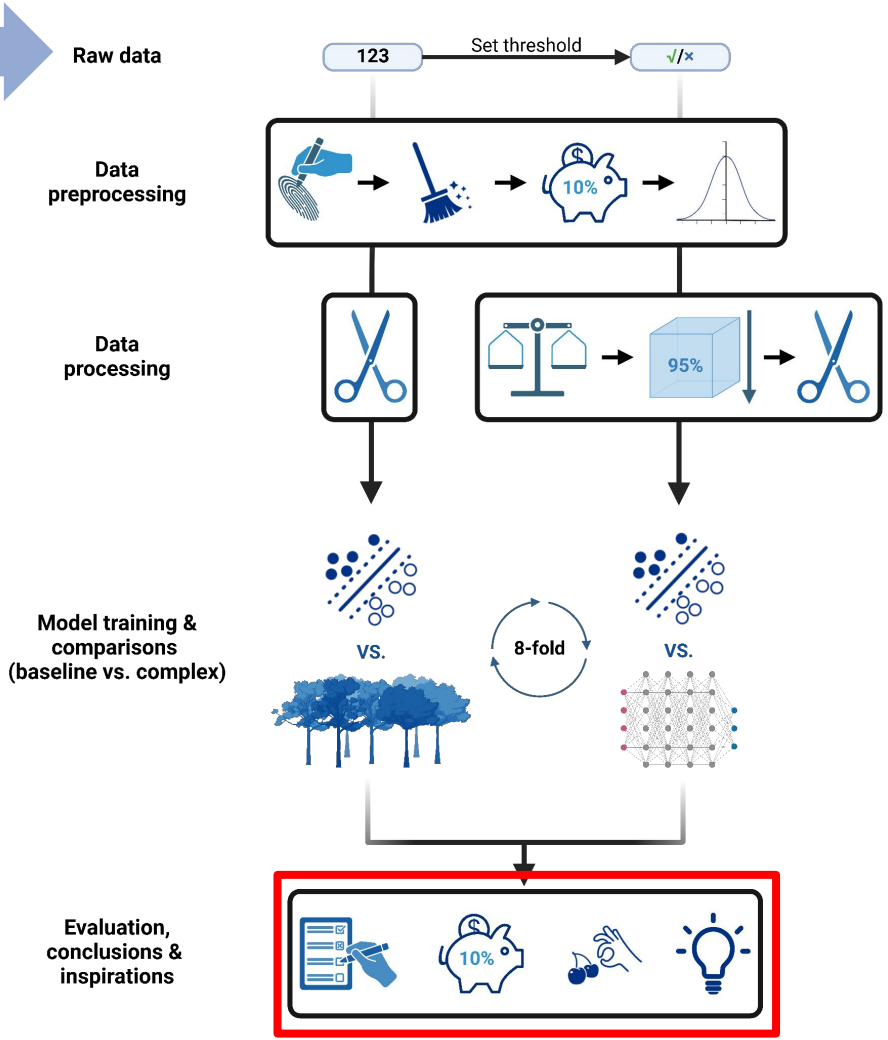
Baseline: SVC on ClusterCentroids **Complex: MLP on ClusterCentroids**



DeLong's test gives p-value = 0.063

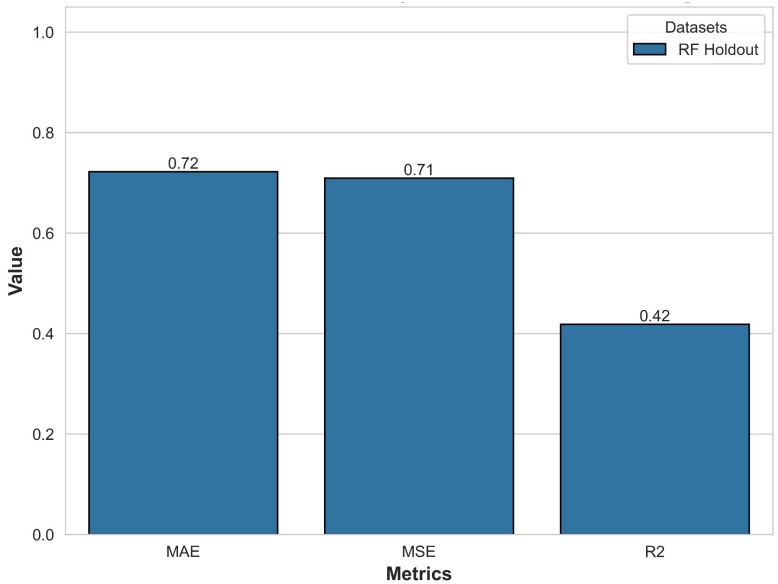
Graphical abstract



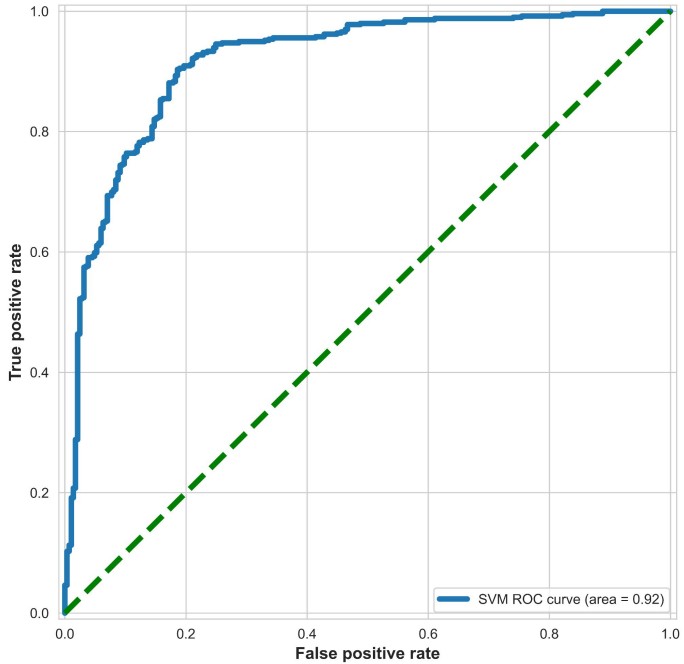


Sanity check: Holdout dataset

RF regressor

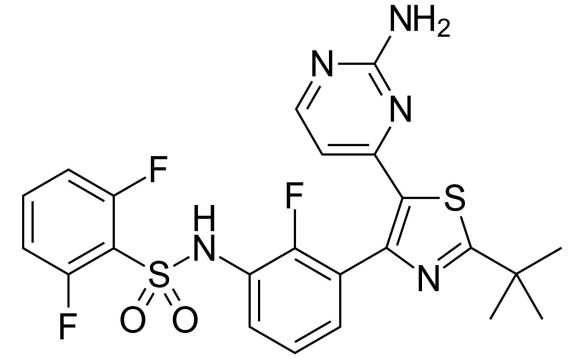


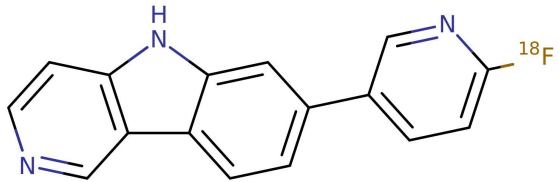
SVC

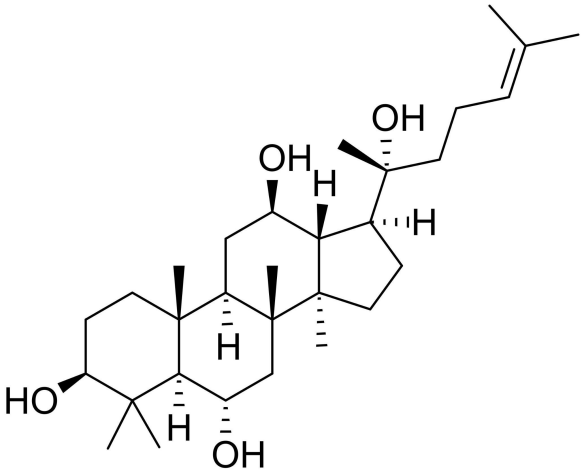


Sanity check: cherry picking for SVC

- BBB-
  - Dabrafenib: predicted to be BBB-
  - Protopanaxatriol: predicted to be BBB-
- BBB+
  - Flortaucipir F-18: predicted to be BBB-







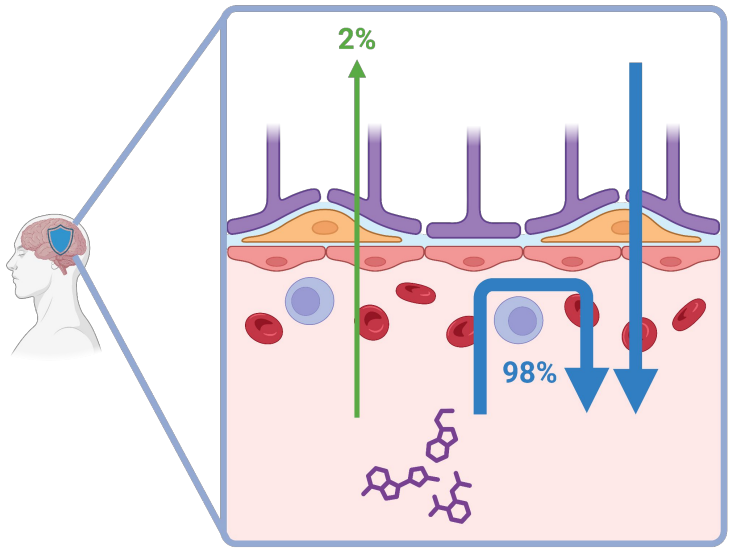
Conclusions

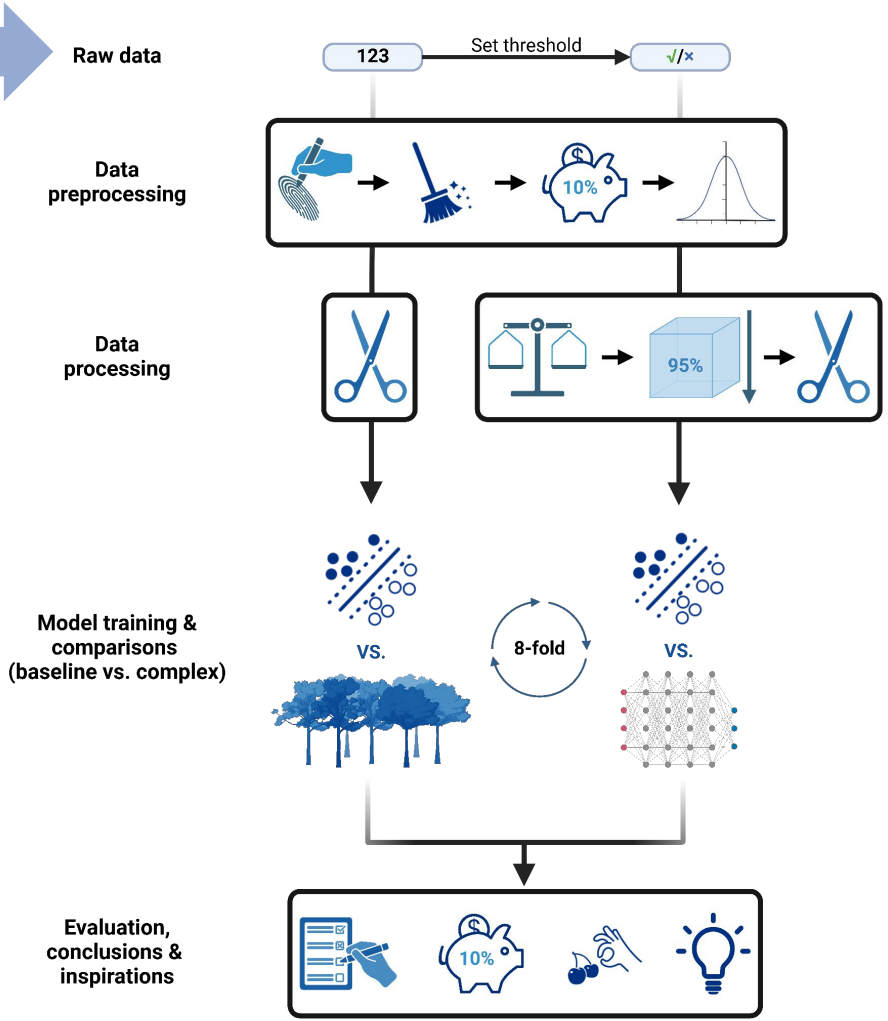
- Categorical dataset successfully balanced using multiple methods
- RF regressor & SVC performed & generalized better than other models
- Successful sanity check with orthogonal domain knowledge, holdout dataset verification, cherry picking (mostly)

- Complex models tend to overfit & require heavier regulations
- Polarity & charges play critical roles in determining ability to penetrate BBB
  - Agreed with commercial tool SwissADME

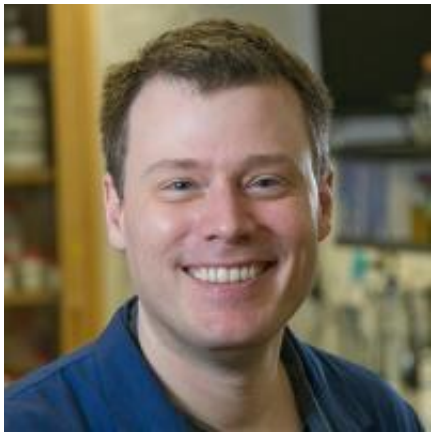
- Improvements & future directions
  - Correlation doesn’t guarantee causation
  - Validations in vitro & in vivo

Graphical abstract





Thank you!



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Thank you!