Antibiotic Drug Discovery

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TOC

Understanding the problem

1.2b USD

The cost to produce a new antibiotic in the US.

Pharmaceutical companies do not have a cost-benefit incentive to produce new antibiotics.

7 years

The average length of a traditional drug discovery pipeline.

Patients infected with antibiotic resistant bacteria need urgent treatment.

50%

More resistant strains of bacteria over the past 4 years.

Organisms are evolving new mechanisms of resistance faster than we can create new treatments.

The Solution

- **Machine Learning**
  - Training models to predict successful antibiotics.
- **AI**
  - Using trained models to invent new antibiotics.

Project objective:

Develop a drug discovery pipeline.

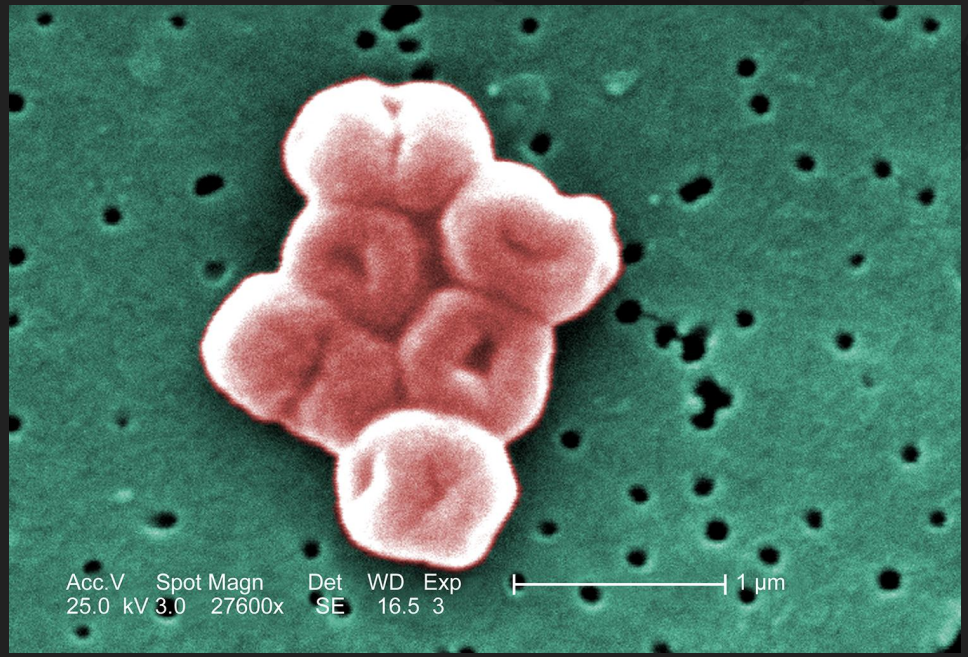
First Step:

Develop a model

Drug Discovery Pipeline

Choose an Organism

- **Acinetobacter Baumanni**
  - Blood, wound, urinary tract, and lung infections
  - Becoming resistant to most antibiotics



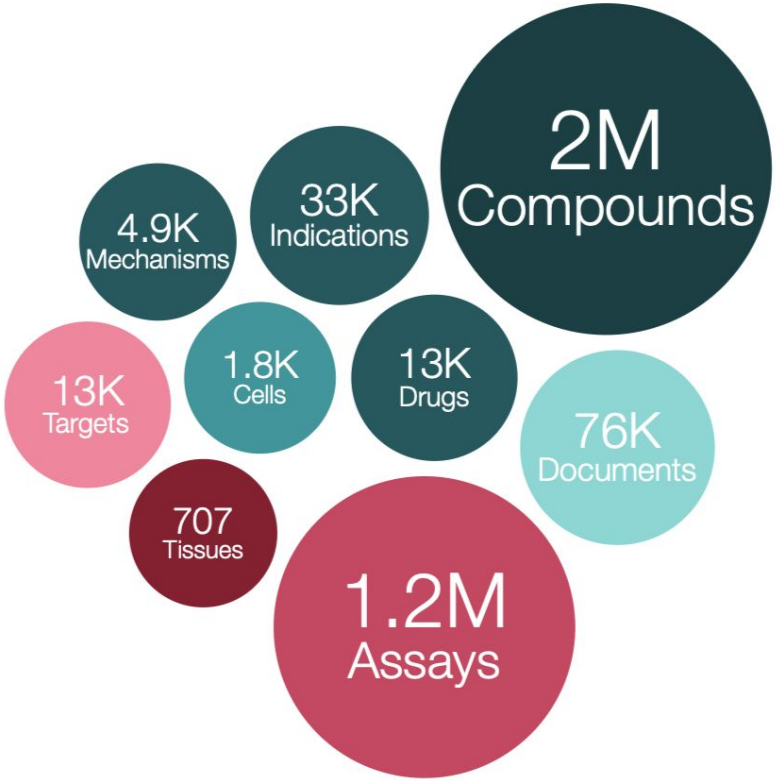
Pipeline optimized to start with any specified target, and be completely reproducible.

Drug Discovery Pipeline

Search for Classified Compounds

- ~ 5000 compounds obtained using ChEMBL web-client.
- Filtered and sorted for Minimum Inhibitory Concentration (MIC).
  - MICs ranged from <10nM (very effective) to >500,000nM (not effective).

ChEMBL

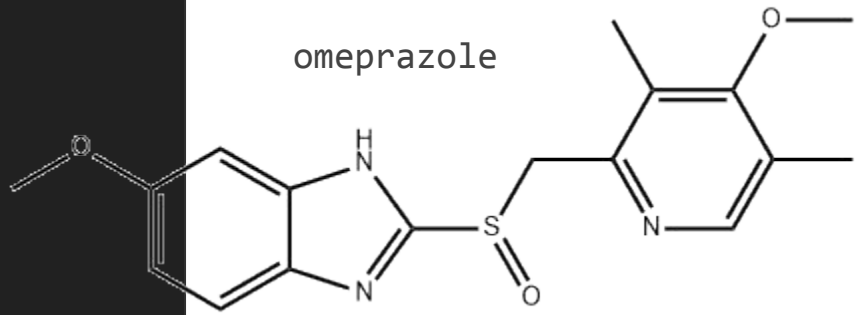


Drug Discovery Pipeline

Engineer Features

- Lipinski Descriptors
  - Molecular Weight
  - Log-p
    - Lipophilicity / Solubility
  - # Proton Donors
  - # Proton Acceptors
- Vectorization using Morgan's fingerprint algorithm.
- Standardized target with -log10
  - MIC ⇨ pMIC

omeprazole



SMILES: CC1=CN=C(C(=C1OC)C)CS(=O)C2=NC3=C(N2)C=C(C=C3)OC

Mol wt = 345.42 $g \cdot mol^{-1}$
Log-p = 2.43
H+ Donors: 1
H+ Accept: 3

Drug Discovery Pipeline

Classification Model

- HistGradient Boosting Classification
- Binary target
  - Active (<35nM MIC) vs Inactive
  - Intermediate values removed
- Standard Scaler
- Max iterations = 800

Drug Discovery Pipeline

HistGradient Boost Metrics

- Accuracy ⇨ 98%
- Precision ⇨ 96%
- Recall ⇨ 97%
- F1 score ⇨ 0.97
- ROC AUC ⇨ 0.98

Null accuracy 60%

Drug Discovery Pipeline

Regression Model

- HistGradient Boosting Regression
- Predicting pMIC
  - -log10 of MIC
- Standard Scaler
- L2 regularization = 0.0001
- 1000 max iterations

Random Forest Regression did better with outliers. Mention residuals

Drug Discovery Pipeline

HistGradient Boost Metrics

- r^2 ⇨ 0.76
- MSE ⇨ 0.696
- RMSE ⇨ 0.834
- MAE ⇨ 0.568
- Null MSE ⇨ 3.088
- Performed 78% greater than a null model

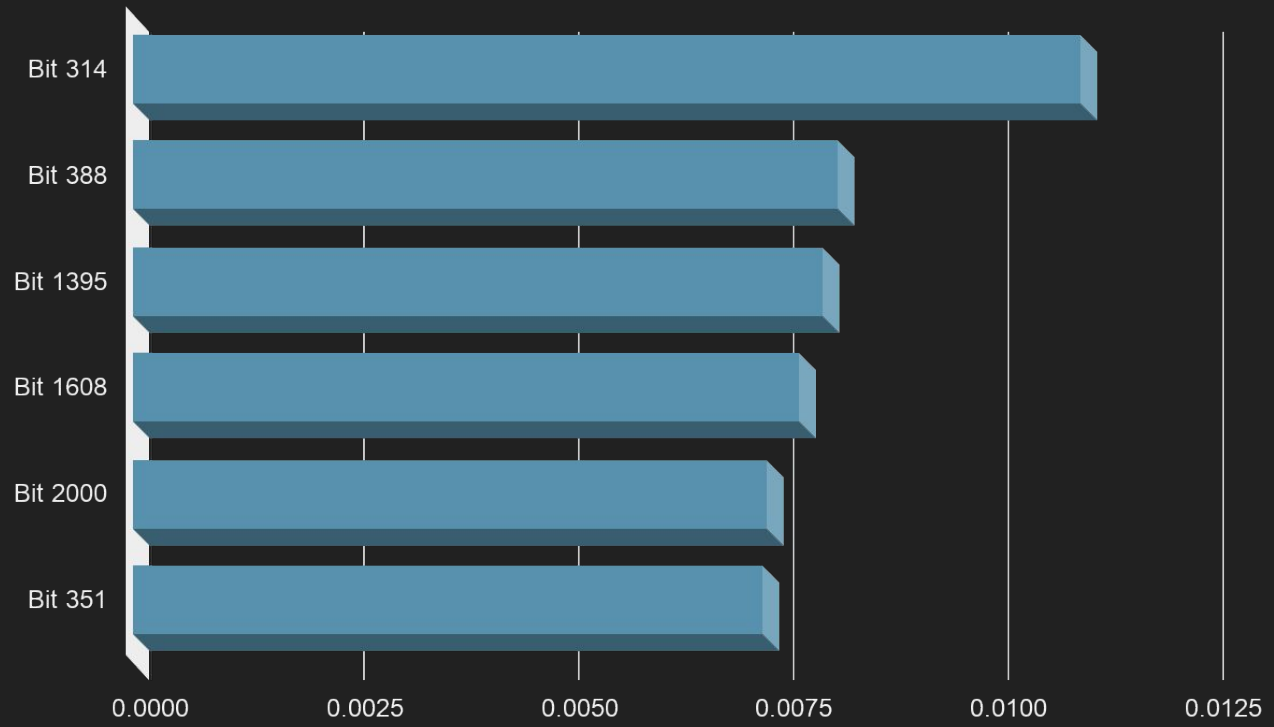
Drug Discovery Pipeline

Feature Importances

- Same molecular fragments, or “bits,” important for both classification and regression.

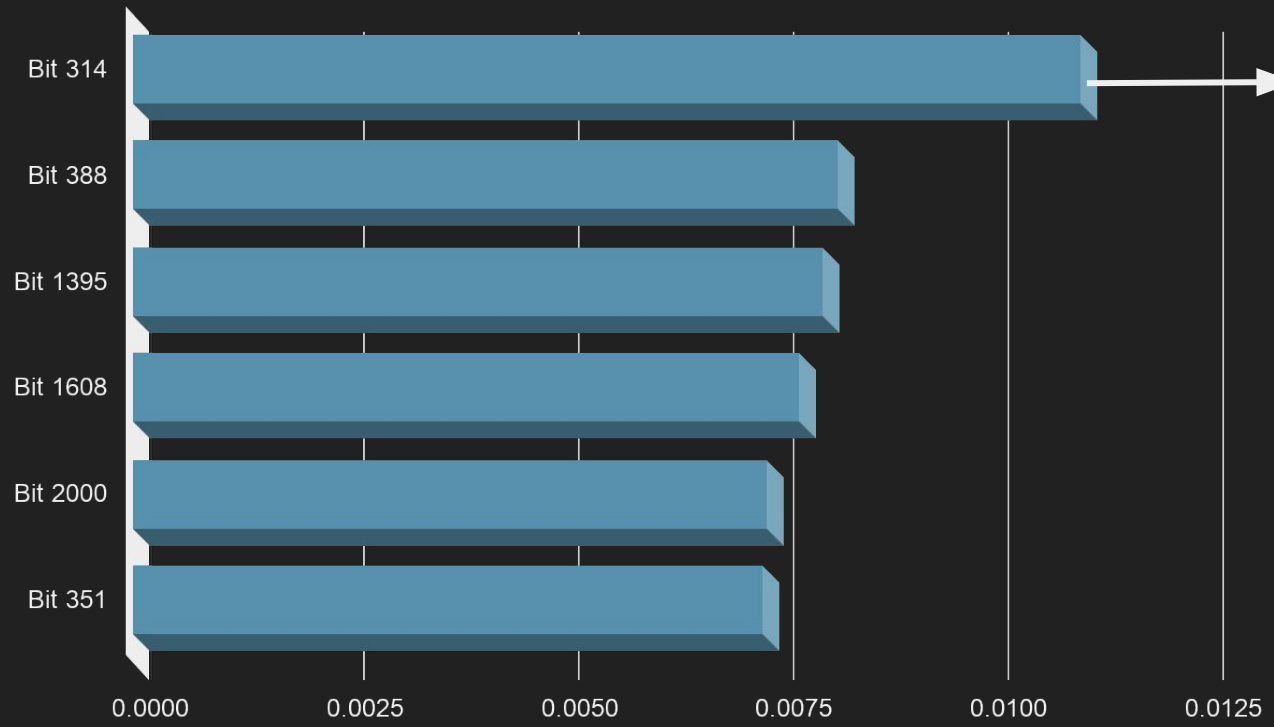
Drug Discovery Pipeline

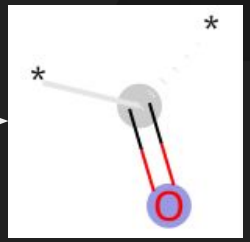
Feature Importances



Drug Discovery Pipeline

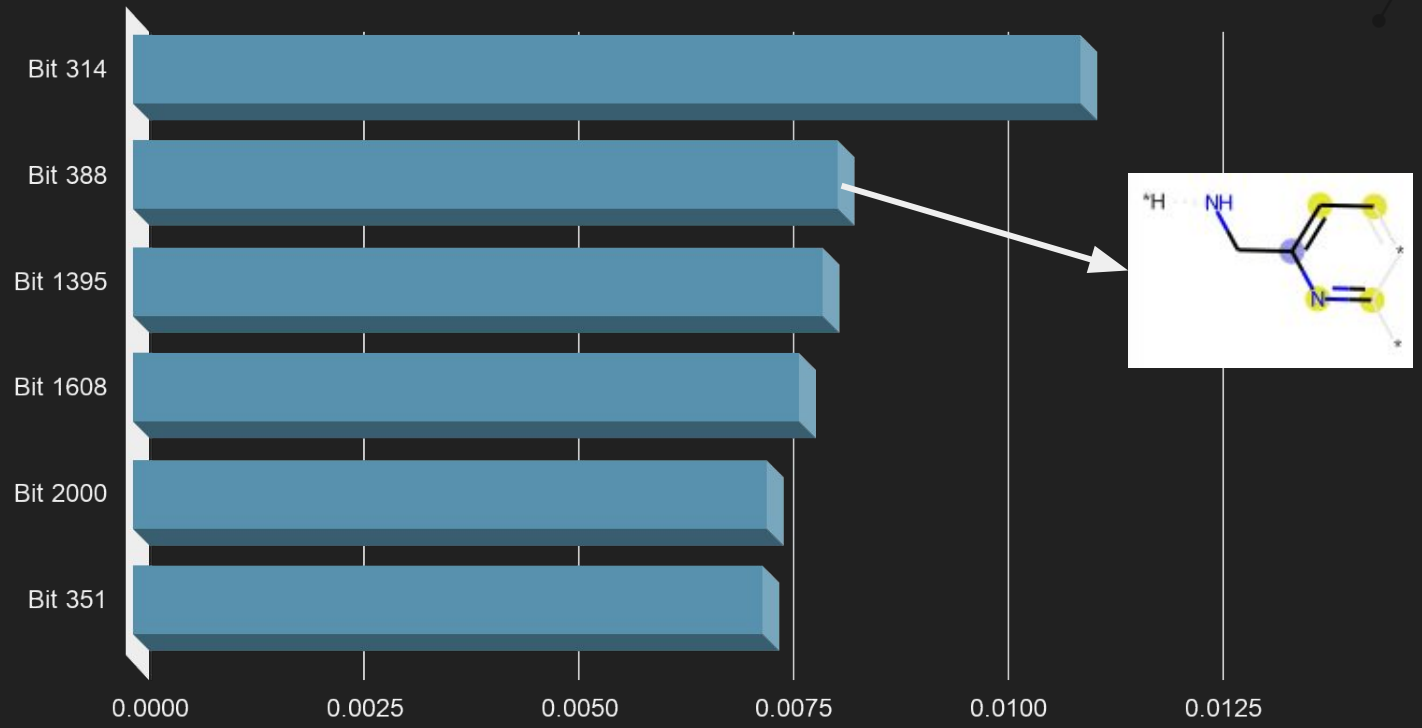
Feature Importances





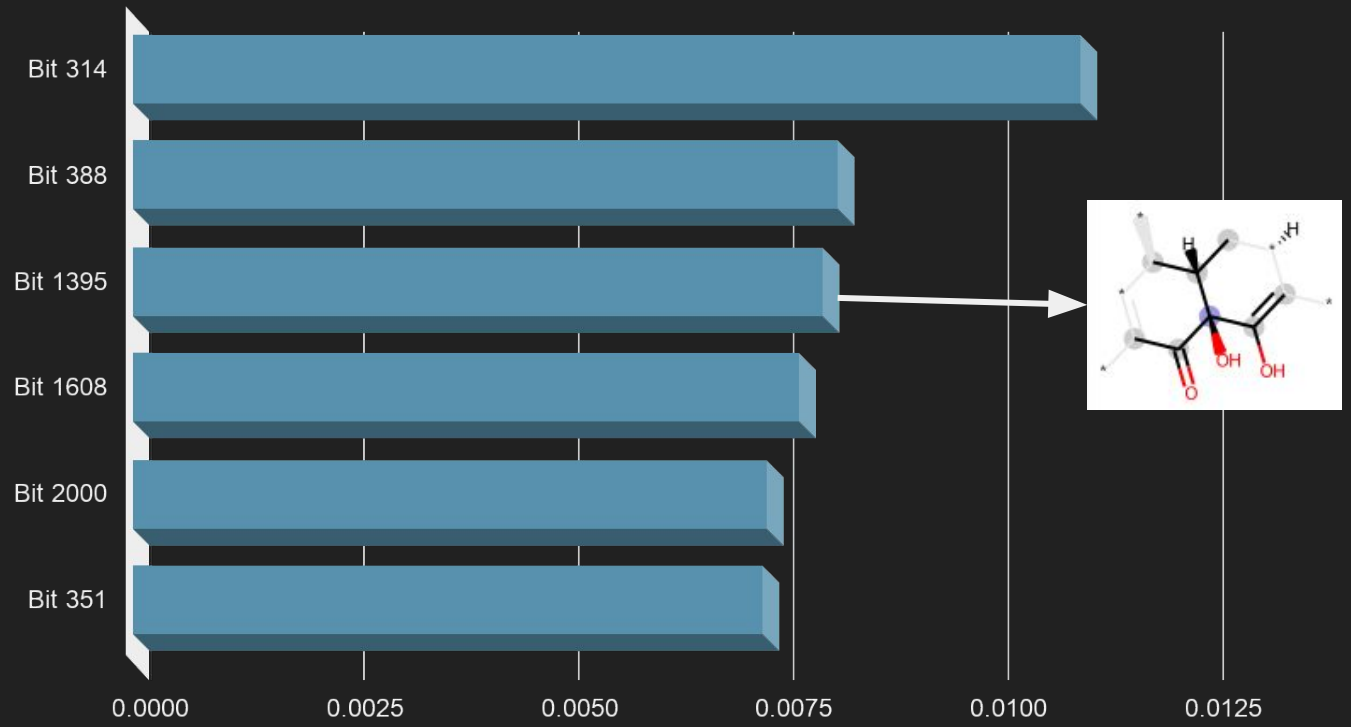
Drug Discovery Pipeline

Feature Importances



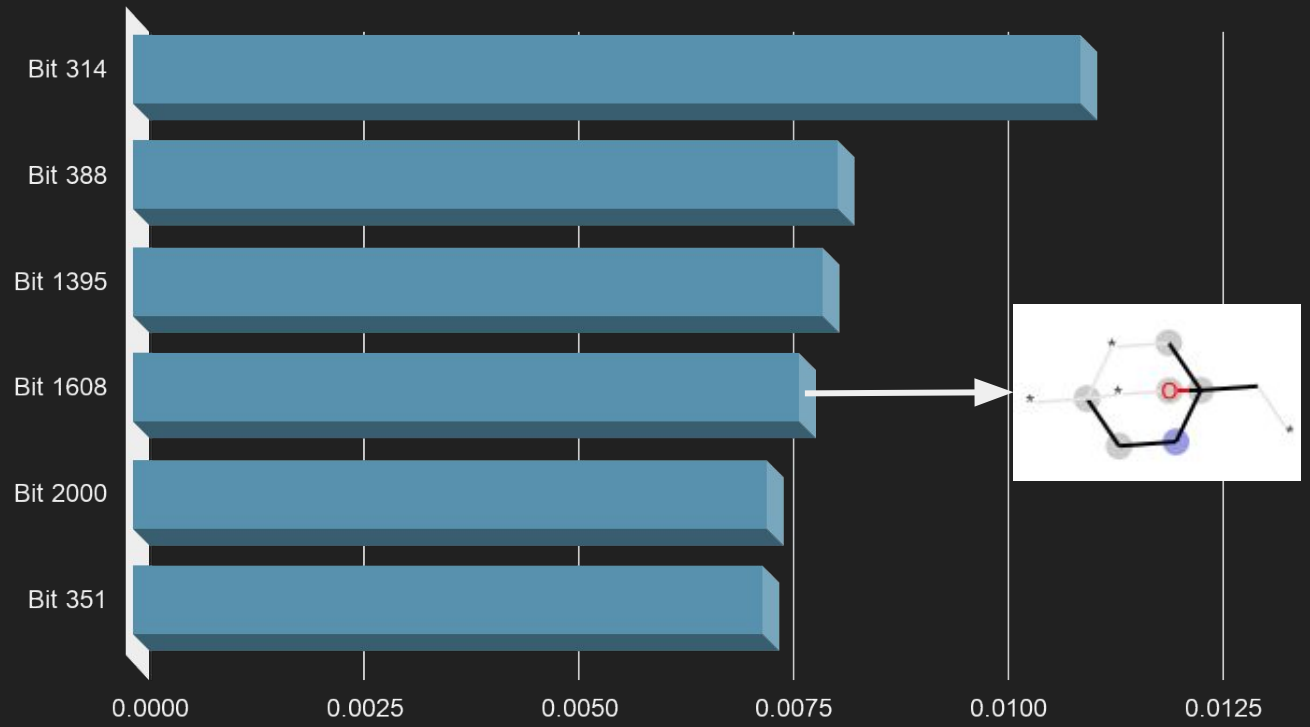
Drug Discovery Pipeline

Feature Importances



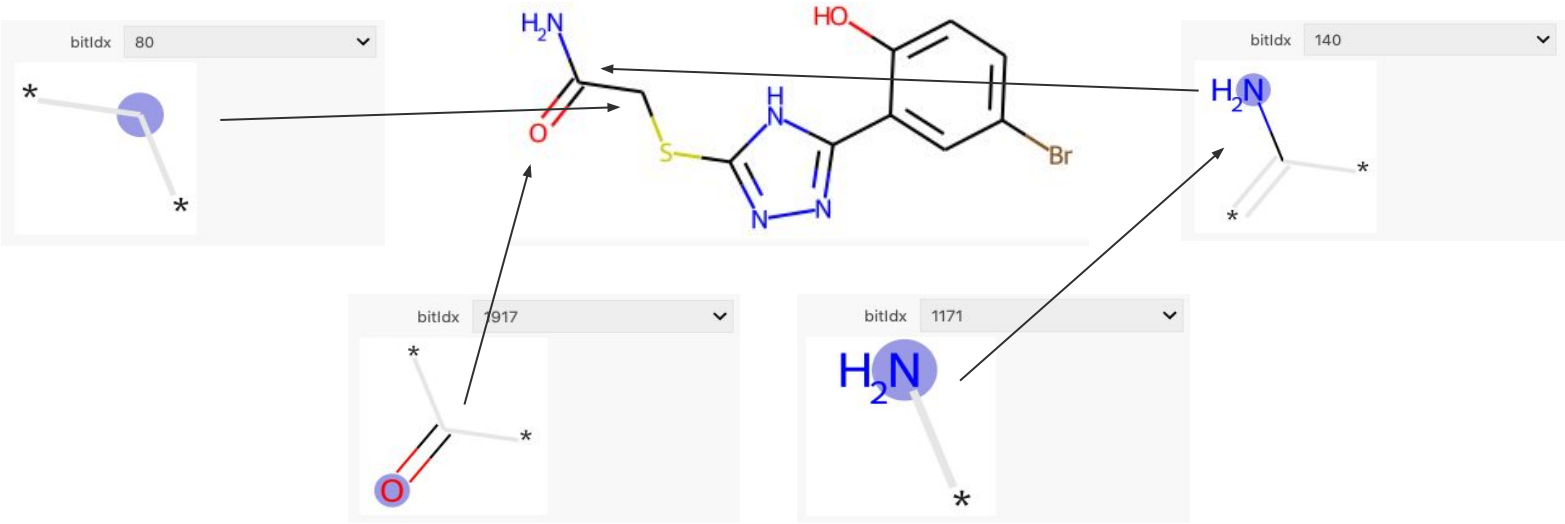
Drug Discovery Pipeline

Feature Importances



Drug Discovery Pipeline

Residuals



Next Step:

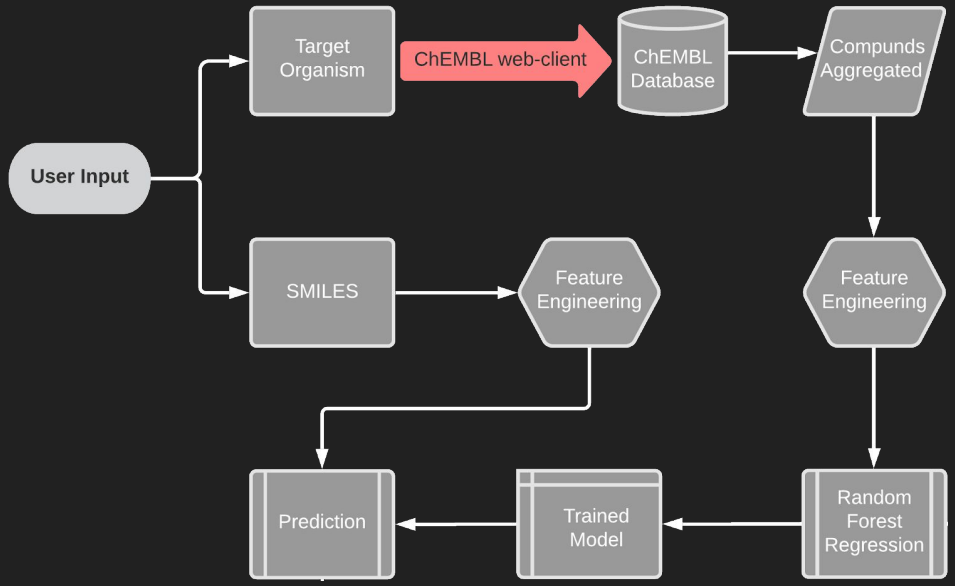
Practical Application

Drug Discovery Pipeline

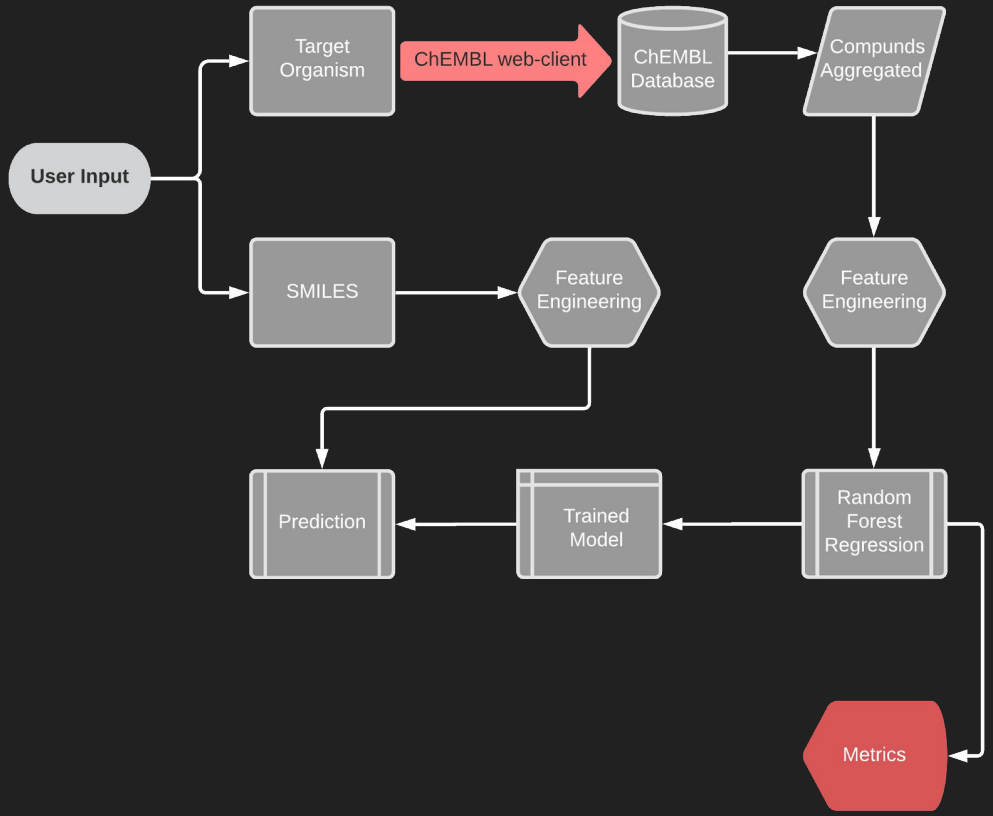
Practical Application

- User inputs a target organism and SMILES.
- App outputs model metrics and prediction.

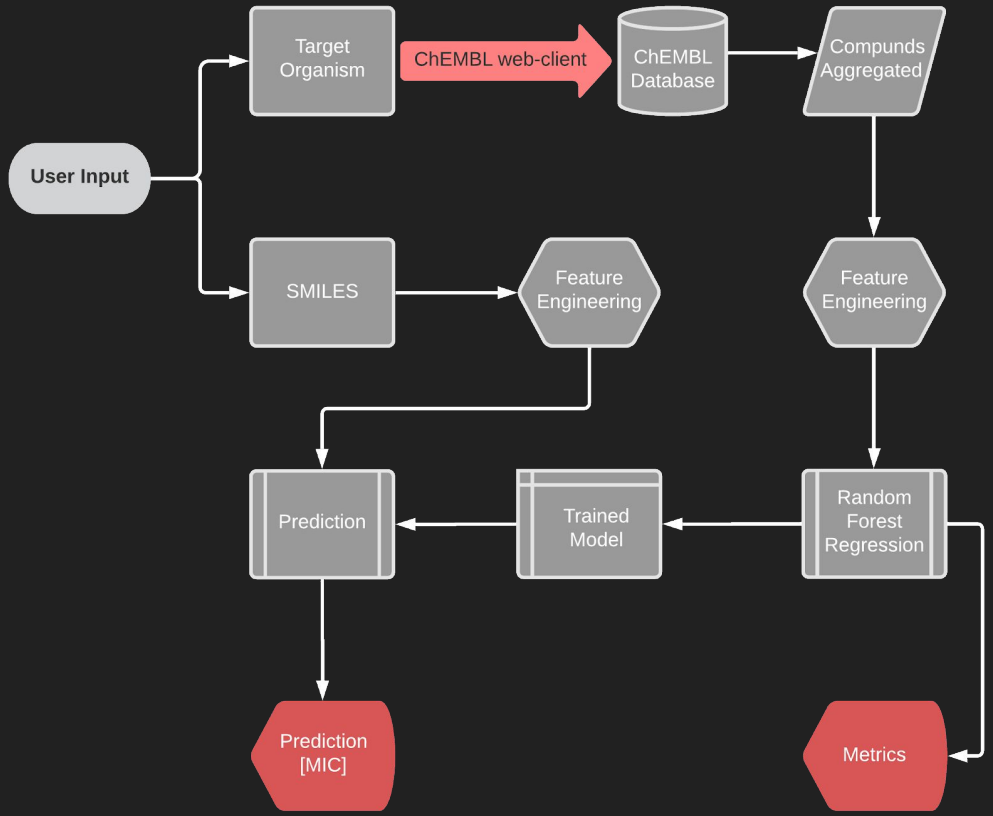
Drug Discovery App



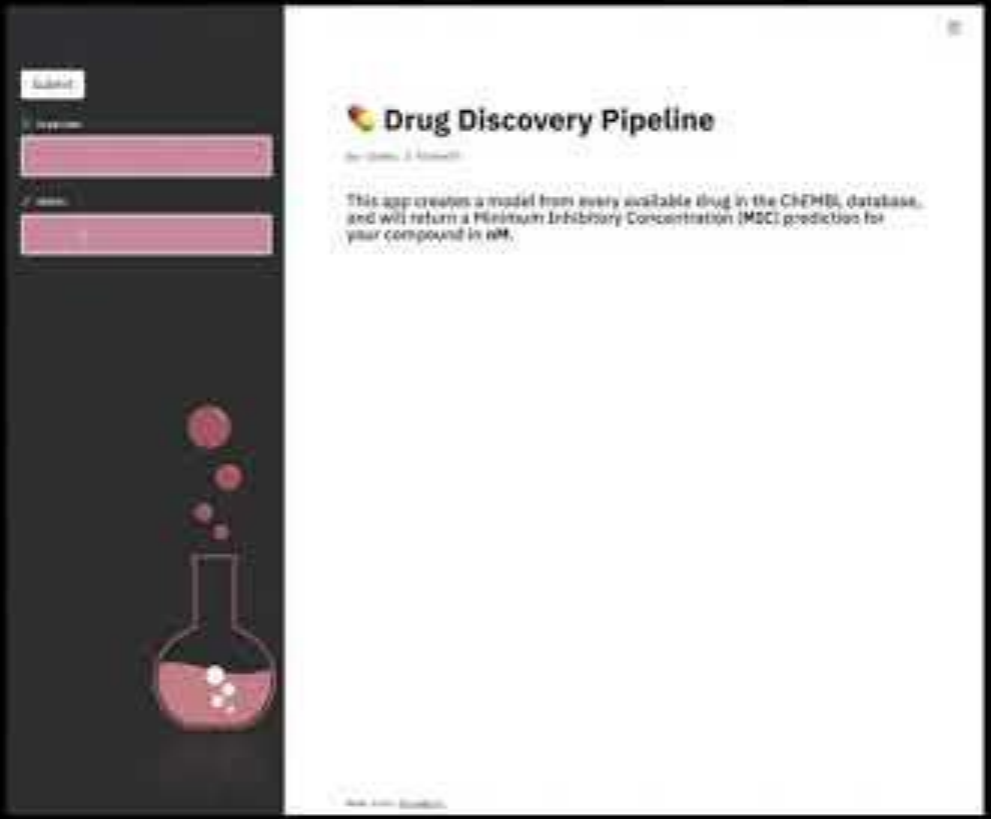
Drug Discovery App



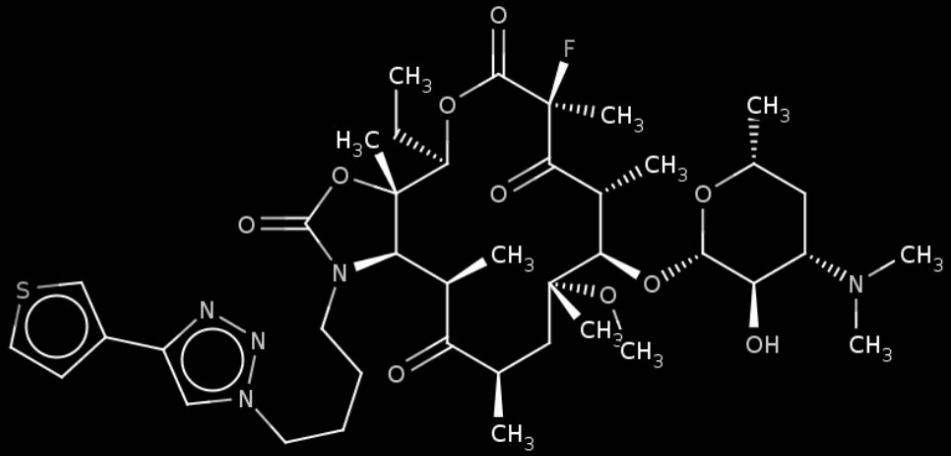
Drug Discovery App

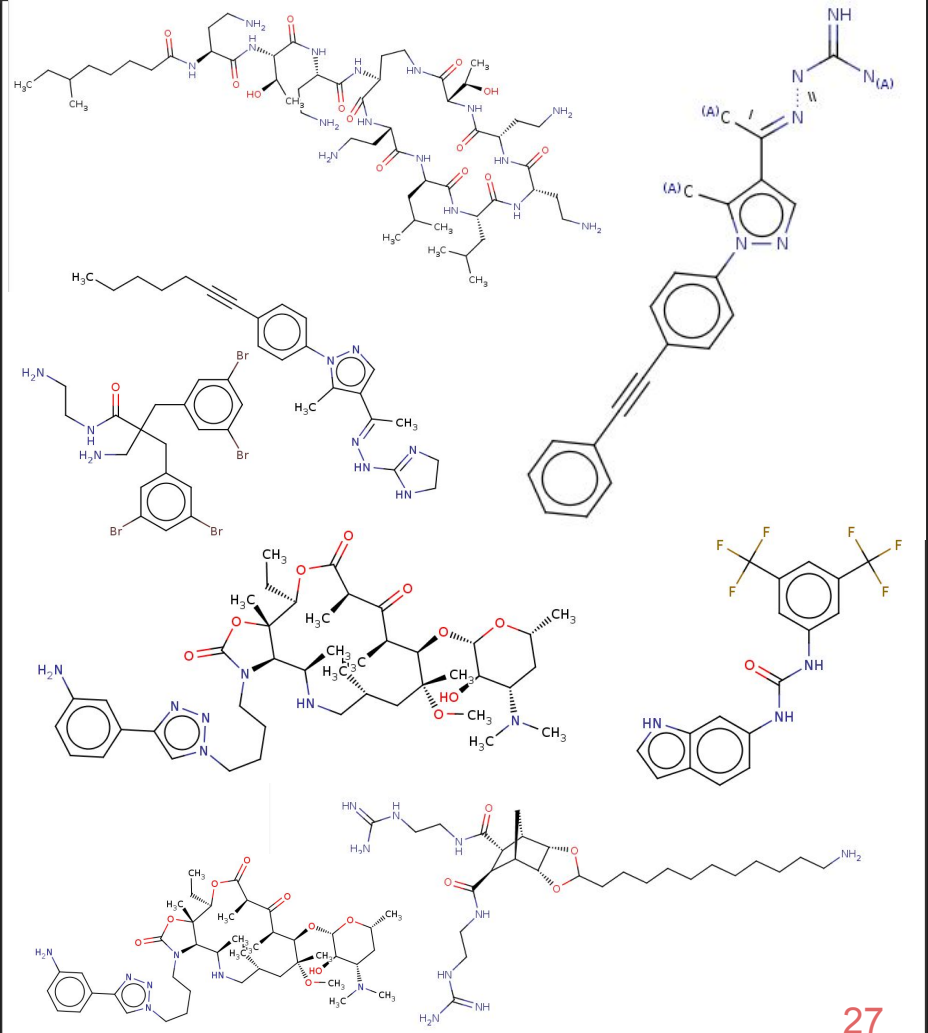


App Demo


Drug Discovery Pipeline
This app creates a model from every available drug in the ChEMBL database, and will return a Minimum Inhibitory Concentration (MIC) prediction for your compound in nM.

What’s next?





Drug Discovery Pipeline

What's next?

- New molecules generated by recurrent neural networks.

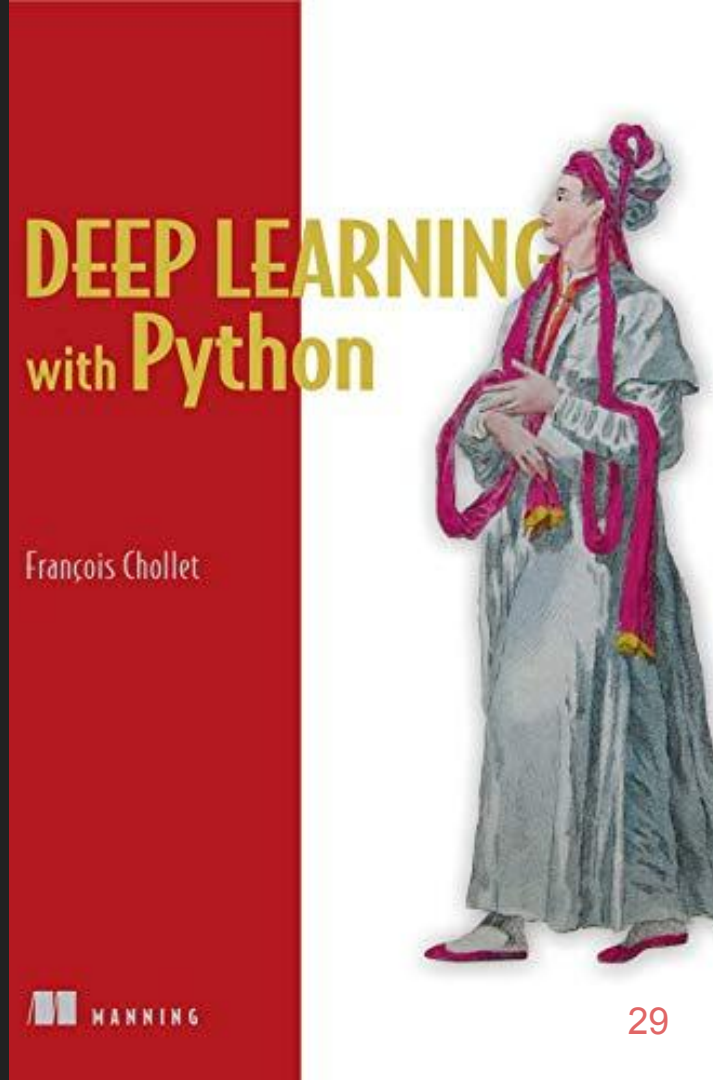
Drug Discovery Pipeline

Molecule Generator

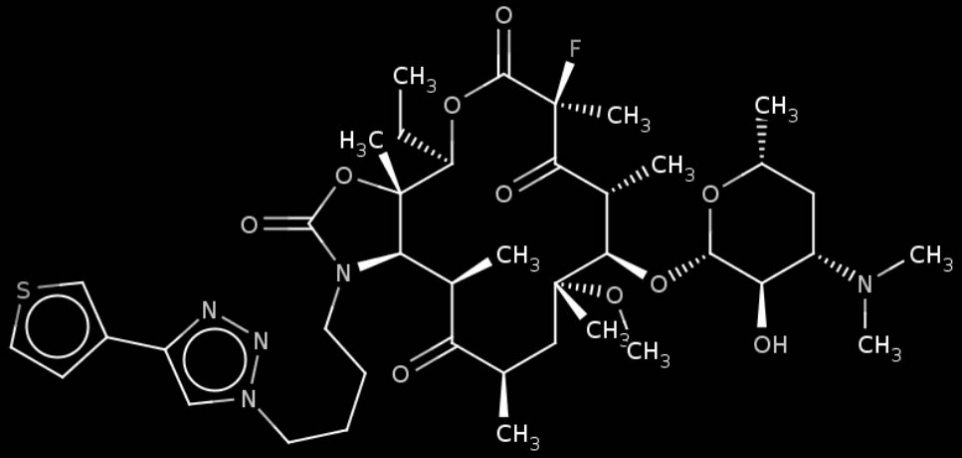
- Tensorflow NN
- LSTM layers
- Trained on every available compound.
- X variable is an individual character from a molecule.
- Y variable is the following character.

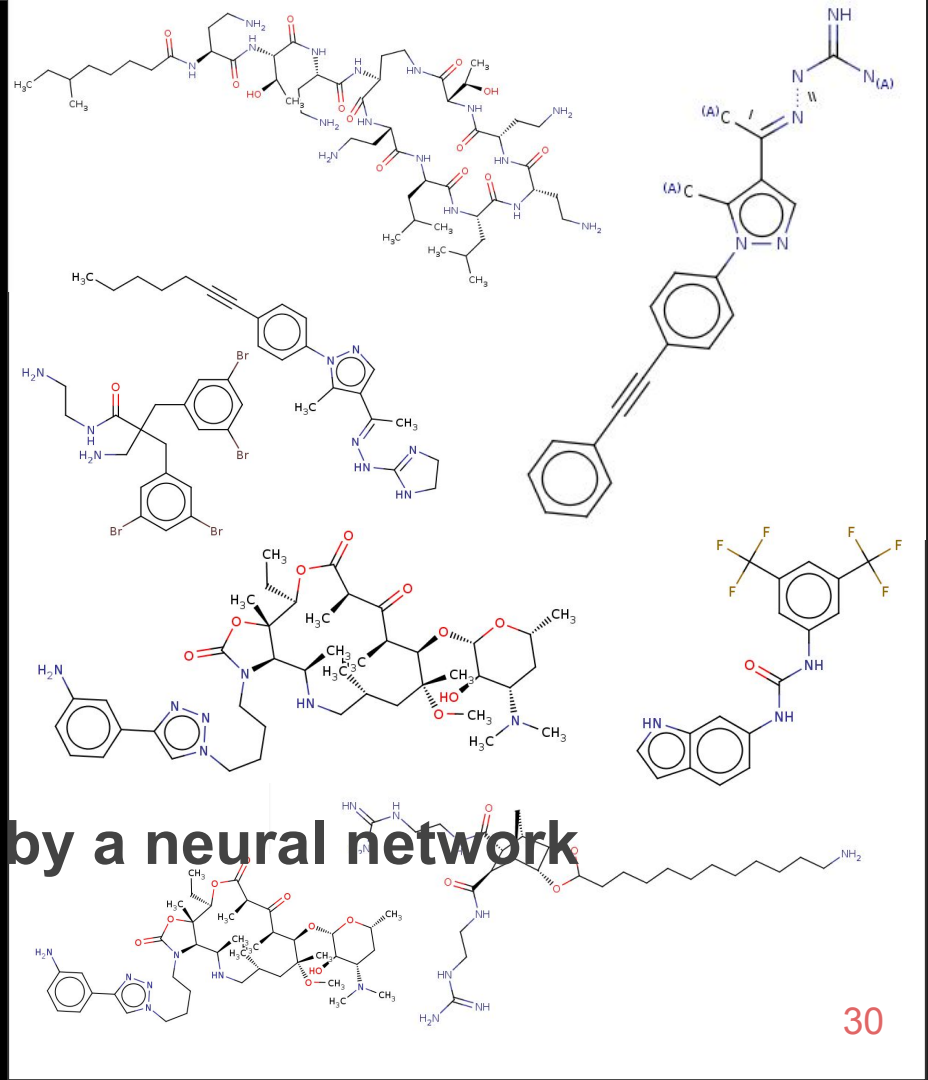
Adapted from Deep Learning with Python

Work in-progress



What’s next?





These molecules were generated by a neural network

Generator Demo

Conclusion

A robust, simple drug discovery pipeline was created.

Drug Discovery Pipeline

Classify

Classify successful antibiotics with 98% accuracy.

Identify

Identify molecular fragments most important to model.

Predict

App can give an estimate of efficacy for a new drug in under a minute.

Generate

Ability to create new drugs with an RNN is evolving.

Any Questions?

Thanks!

Corey J Sinnott

Data Scientist

Sources

1. A Deep Learning Approach to Antibiotic Discovery: https://www.cell.com/cell/fulltext/S0092-8674(20)30102-1?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420301021%3Fshowall%3Dtrue
2. Antibiotic resistance: bioinformatics-based understanding as a functional strategy for drug design: https://pubs.rsc.org/en/Content/ArticleLanding/2020/RA/D0RA01484B#!divAbstract
3. MIC database: A collection of antimicrobial compounds from literature: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2823385/
4. Machine learning-powered antibiotics phenotypic drug discovery: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6428806/
5. Helping Chemists Discover New Antibiotics: https://pubs.acs.org/doi/10.1021/acsinfecdis.5b00044
6. New Statistical Technique for Analyzing MIC-Based Susceptibility Data: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3294928/
7. Applying machine learning techniques to predict the properties of energetic materials: https://www.nature.com/articles/s41598-018-27344-x
8. QBMG: quasi-biogenic molecule generator with deep recurrent neural network: https://jcheminf.biomedcentral.com/articles/10.1186/s13321-019-0328-9
9. Are the physicochemical properties of antibacterial compounds really different from other drugs?: https://jcheminf.biomedcentral.com/articles/10.1186/s13321-016-0143-5
10. Deep Learning with Python by Francois Chollet