Cornell Future Of Care

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Grab Today's Code

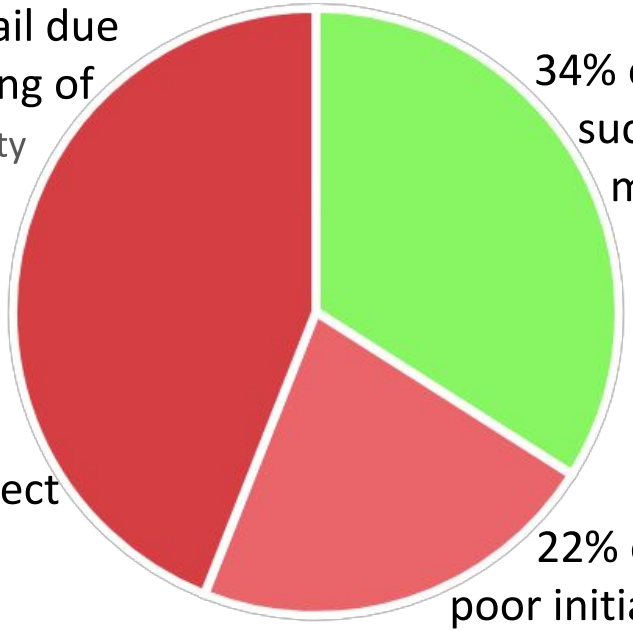
https://github.com/lilleswing/future_of_care

Drug Discovery An Overview

- “It’s damned tough to discover a drug.” –Eugene Cordes

Why is Drug Discovery So Difficult?

44% of preclinical projects fail due to optimized ligands not being of sufficient quality: ligand toxicity problems; efficacy not observed at achievable dose; poor PK/PD



34% of preclinical projects succeed in sending a molecule into the clinic

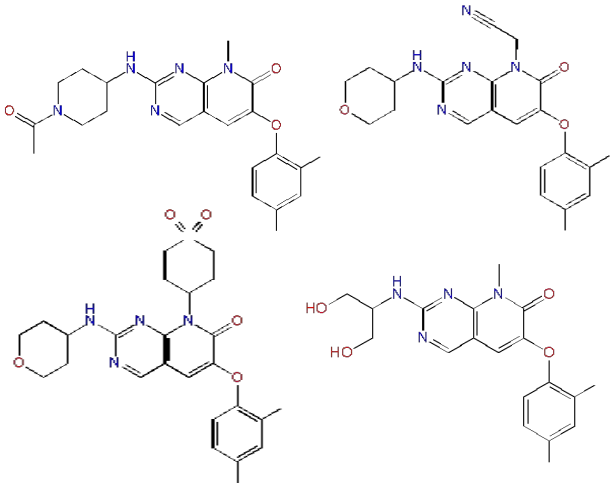
When a preclinical project fails, there are 2:1 odds the ligands delivered by the project team weren't good enough

22% of preclinical projects fail due to poor initial target selection: target engagement not efficacious for treating the disease; on-target toxicity problems; corporate project portfolio rebalancing

Data extracted from: **Nature Review Drug Discovery, 2016,** *14*, 475; **Nature Review Drug Discovery, 2014,** *13*, 419; **Nature Review Drug Discovery 2010**, *9*, 203

SCHRÖDINGER.

The Challenge of Preclinical Drug Discovery



2,000 Design Ideas Synthesized

- Only a 34% chance at least 1 of these 2,000 design ideas might be good enough to send into the clinic
- On-target potency, off-target toxicity, ligand phys. chem. properties, and PK/PD must be within very tight tolerances

Data extracted from: **Nature Review Drug Discovery, 2016,** *14*, 475; **Nature Review Drug Discovery, 2014,** *13*, 419; **Nature Review Drug Discovery 2010**, *9*, 203

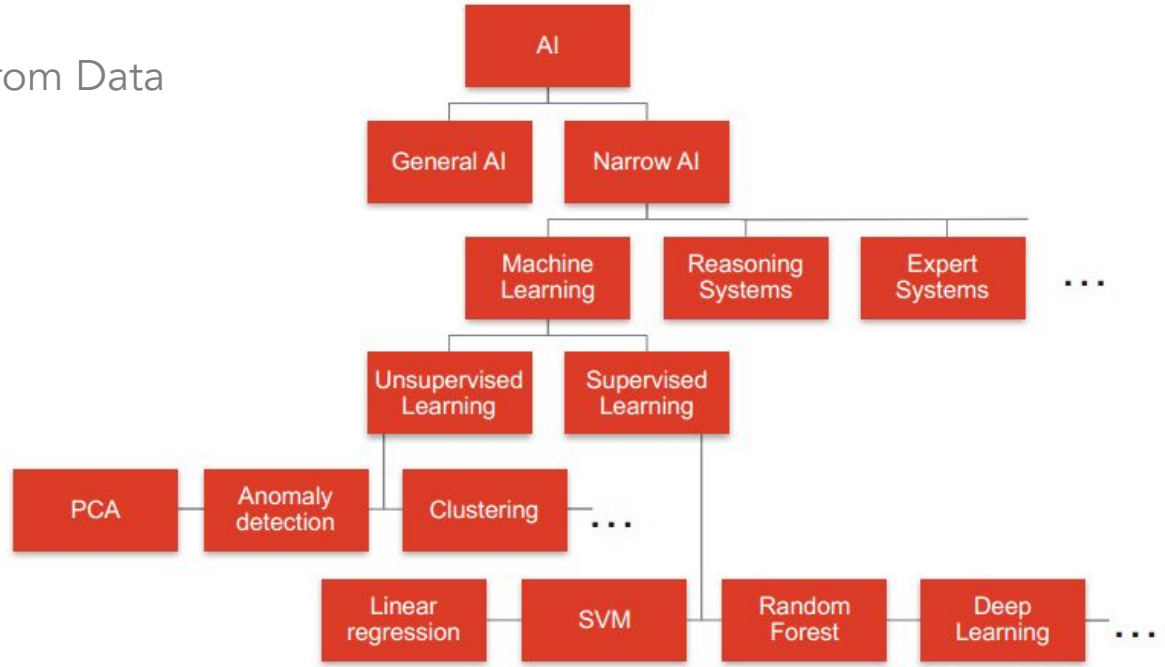
Costs of Drug Discovery

Phase of Drug Discovery	Total Costs (USD millions)
Target-to-hit	$94
Hit-to-lead	$166
Lead-optimization	**$414**
Preclinical	$150
Phase I	$273
Phase II	$319
Phase III	$314
Submission to launch	$48
Total	**$1,778**

Paul SM et al. *Nat. Rev. Drug Disc.* 9:203-214. 2010.

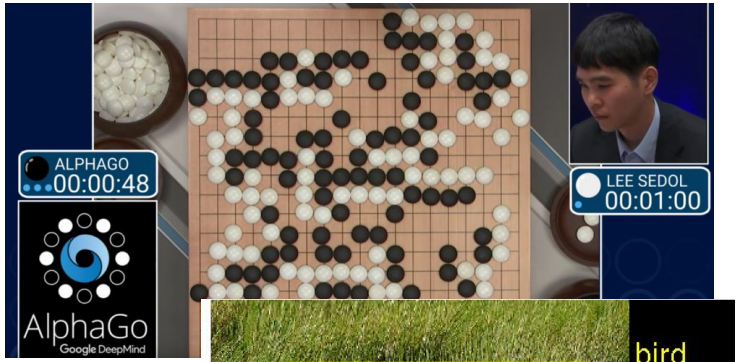
What Is Machine Learning

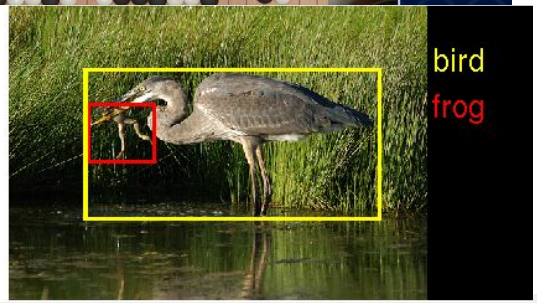
- Supervised Learning
  - Generate Functions From Data



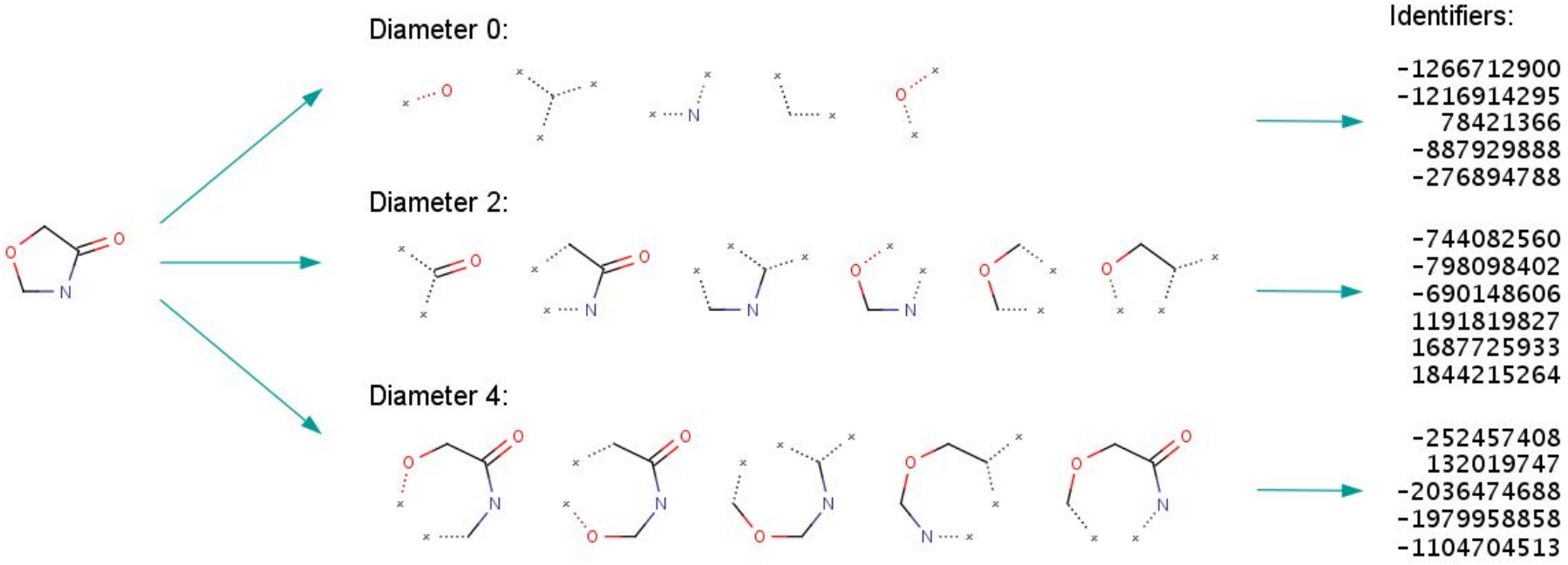
Deep Learning

- Deep learning methods are becoming very popular in image recognition, game playing, and question and answer systems.





ECFP4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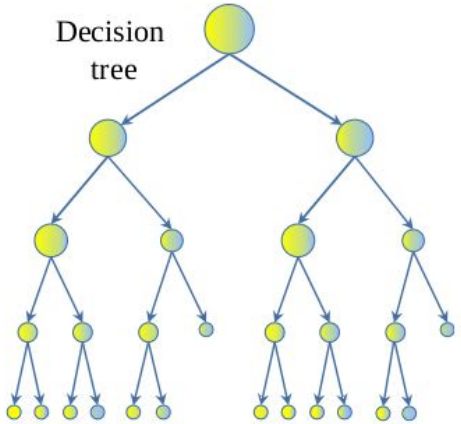
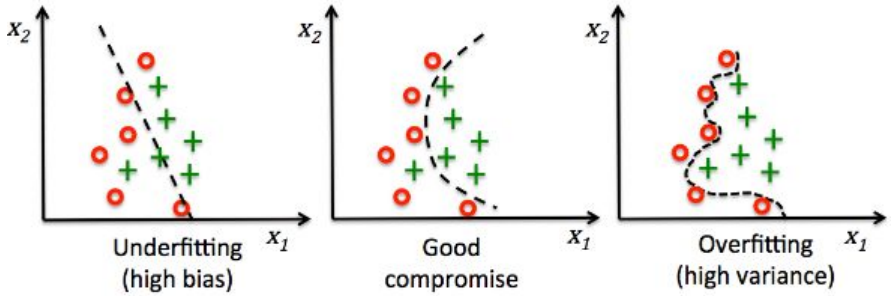
Decision Trees

- Based on the data “split” on a cut off of a single feature
- Can use the most informative feature of all the samples
- Leaf nodes hold predicted values



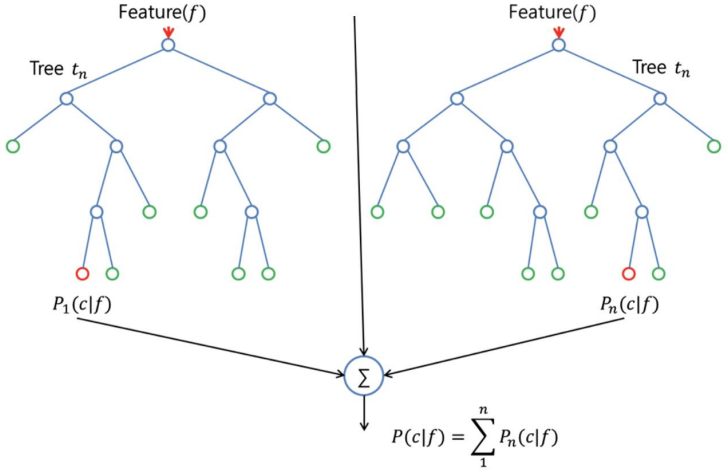
High Variance Low Bias

- Standard decision trees are prone to overfitting
- When there is “noise” in the response with respect to the input we need a more general model



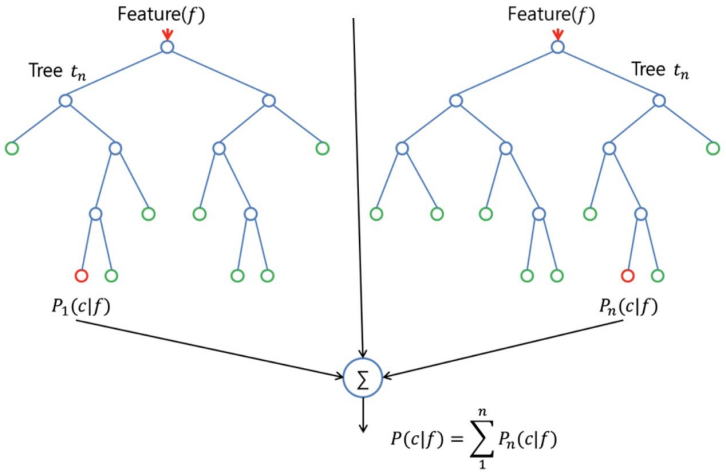
Bootstrap Aggregating (Bagging)

- Make many decision trees!
  - Each one on a subset of the training data, selected uniformly random WITH replacement
- Average results from all decision trees
- More robust to outliers

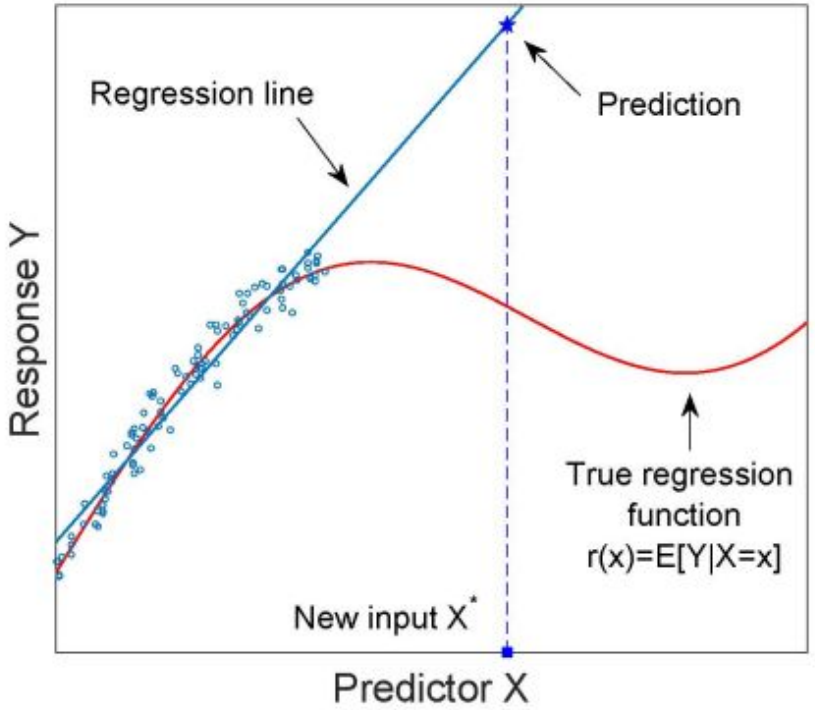


Feature Bagging (Random Forests)

- Many of the trees can be very similar
- E.X if one feature is very predictive all trees use this feature
  - No longer have good ensembling to lower variance
- Solution: At each split only select from a random subset of features



Interpolation

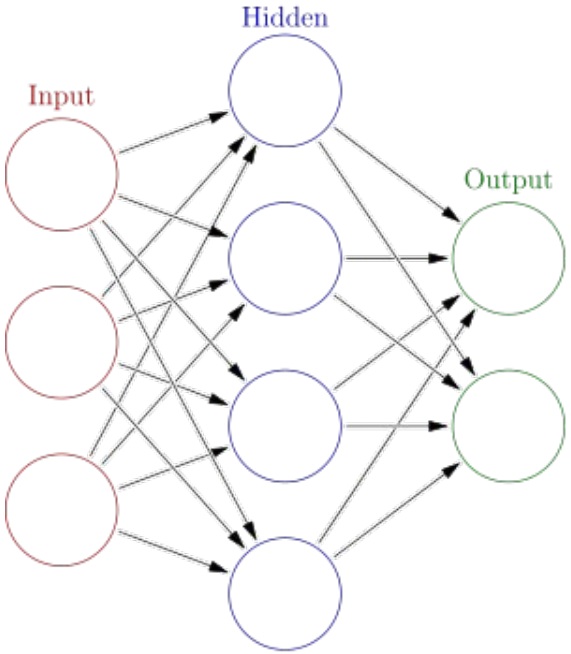


Deep Learning

- Lots of excitement to try to use these methods in other contexts
- Should deep learning be used in materials?
- Where does it provide the greatest benefit?

Artificial Neural Network Overview

- Collection of units called neurons (Circles Here)
- Each neuron computes a function over its inputs (real numbers)
- Each neuron and can be connected to multiple outputs
- Trained using back propagation

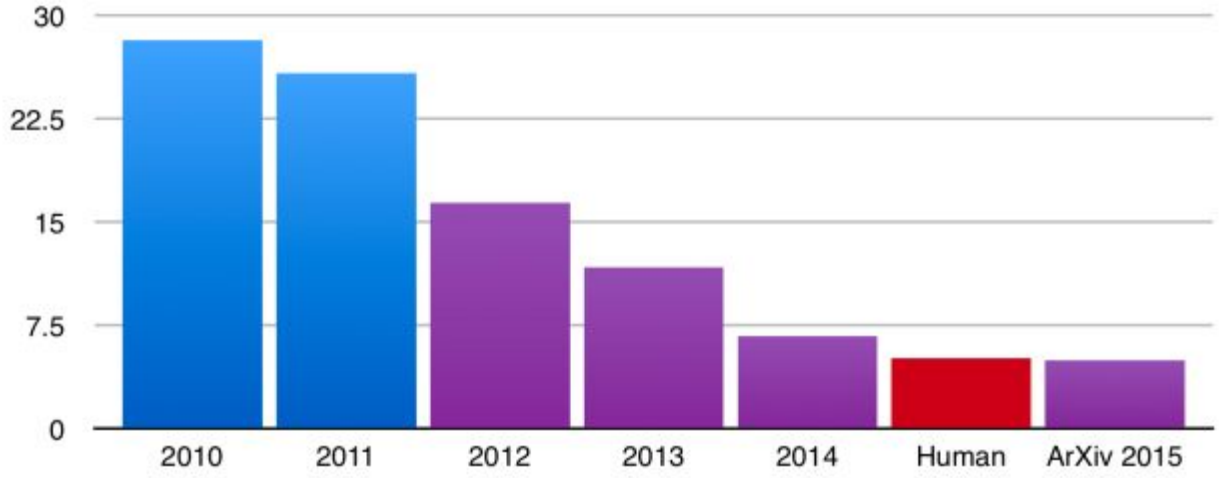


Universal Function Approximation Theorem

- Artificial Neural Networks can represent ANY function
- This does not pan out in practice
  - Limited data and compute power
- Requires us to create data and compute efficient models.

Deep Neural Network Image Classification

ImageNet Large Scale Visual Recognition Challenge Model Accuracy



As of 2015, a 27 layer DNN was more accurate than a human (Stanford student) at sorting 100,000 images into 1,000 different pre-specified categories

Deep Neural Network Image Classification

- The ImageNet classification challenge is *very* difficult:


Ruler


King crab

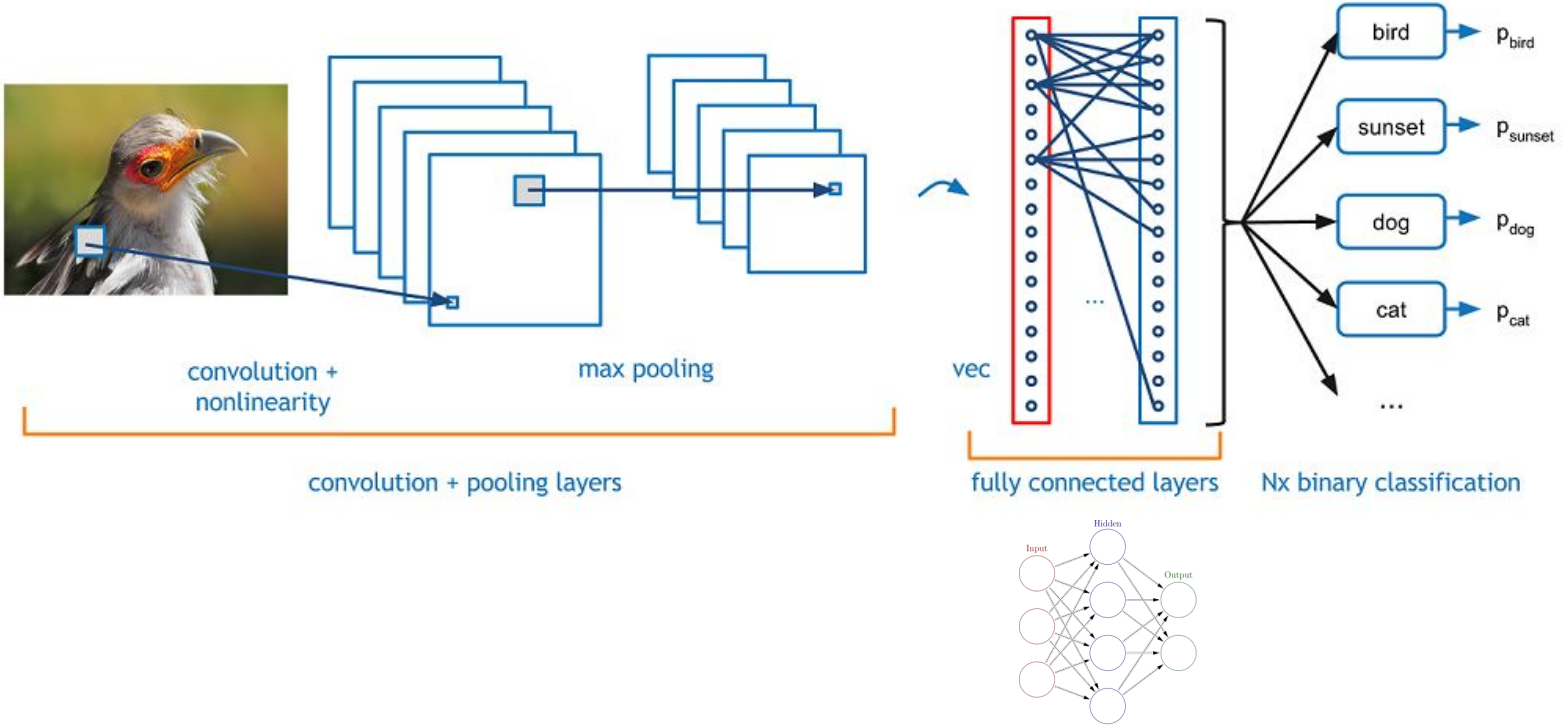

Sidewinder

Salt shaker


Reel


Hatchet

Convolutional Neural Networks



Convolution Layer

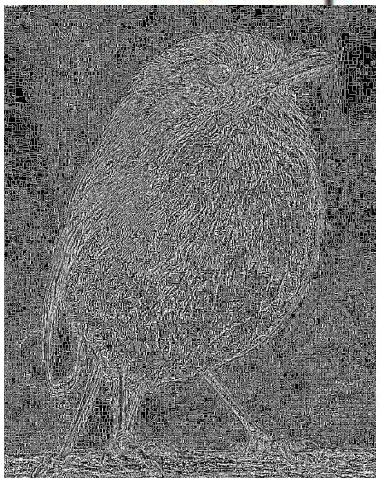
- Slide a learnable mask across the image.

Input image

Convolution Kernel

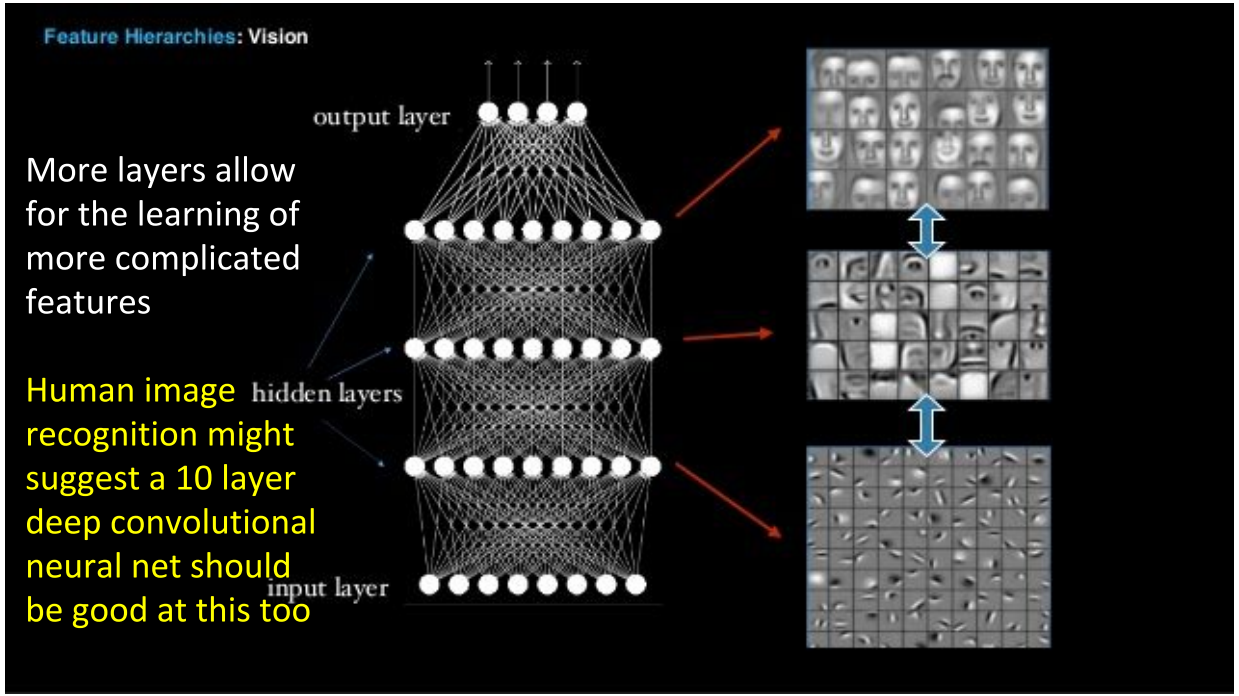
$$\begin{bmatrix} -1 & -1 & -1 \\ -1 & 8 & -1 \\ -1 & -1 & -1 \end{bmatrix}$$

Feature map



Deep Neural Network Image Classification

- A unique aspect of Deep Learning is the ability learn new features as the network is trained:



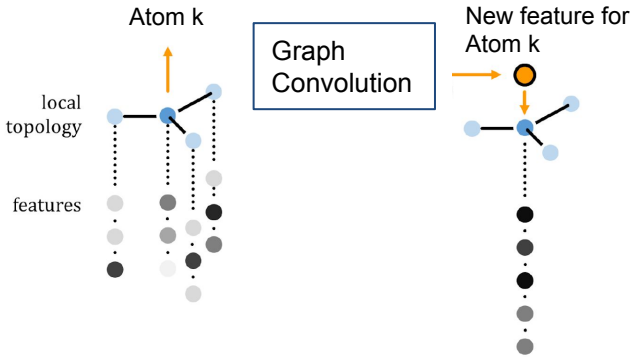
AutoQSAR w/ DeepChem Feature Generation

2D Graphic description of molecules

- Each node represents an atom
- Each edge represents a bond
- Atom features include atoms-type, valences, formal charges, and hybridization

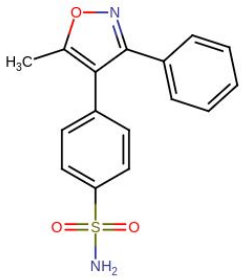
Graph Convolution

- **Automatically learn new local features that suit the endpoint**
- These new features are then converted to molecular feature which is feed to dense neural network for model building

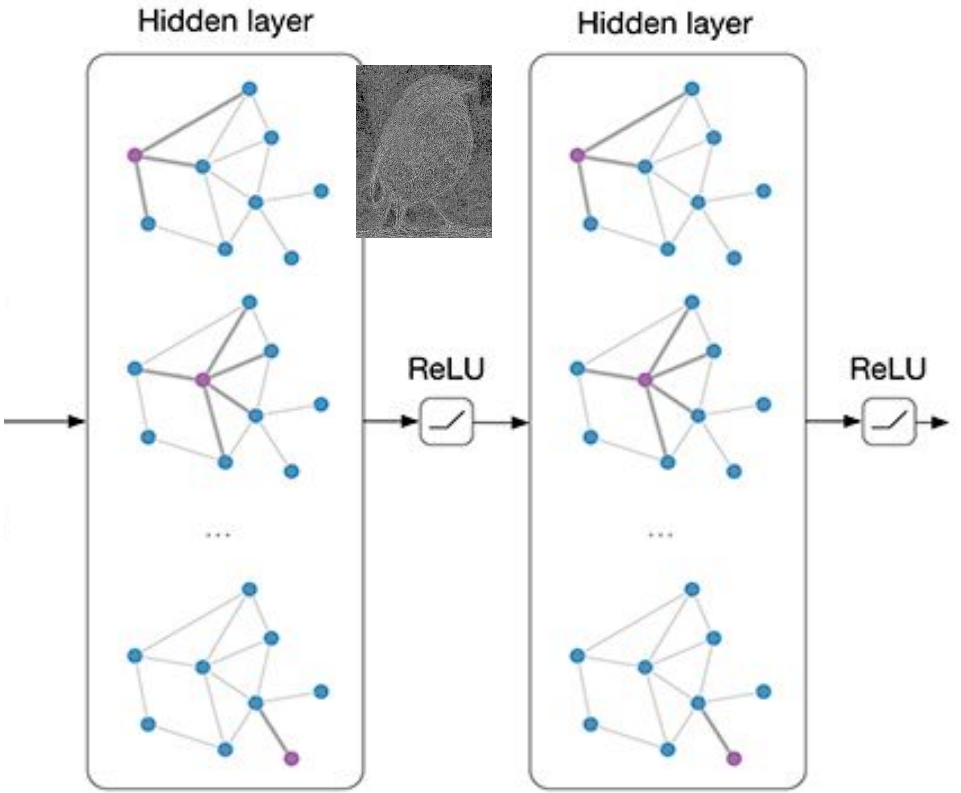


Graph Convolutions

Input



Valdecoxib (pain relief)

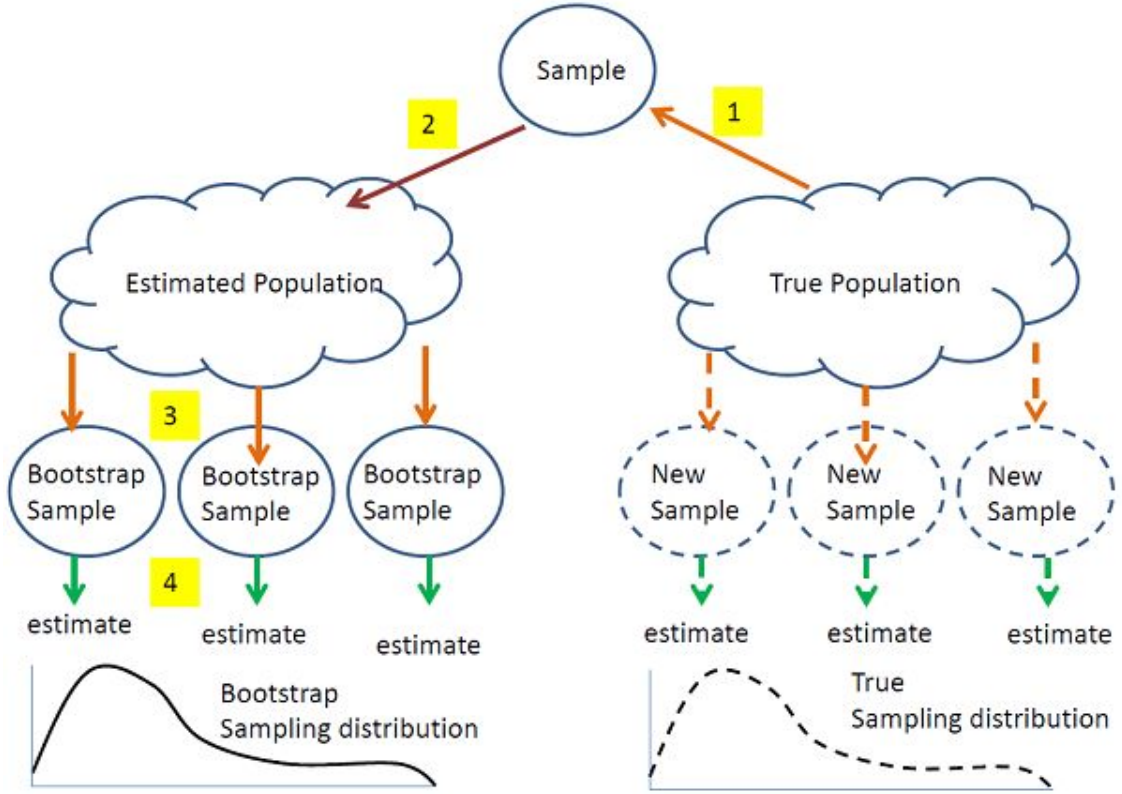


Can We Detect Bad/Interesting Labels In Chemical Data?

08/28/2018

Bootstrapping Interesting Datapoint Identification

- Repeatedly train a model on a random 80% of the data
- Predict on remaining 20%
- Find samples whose predictions are farthest from labels



Models

- Classification Model **Descriptors.MolLogP(m) > 0**

- **We will randomly incorrectly label x% [0,10,20,50] of compounds and see if we can find the molecules we incorrectly labeled**

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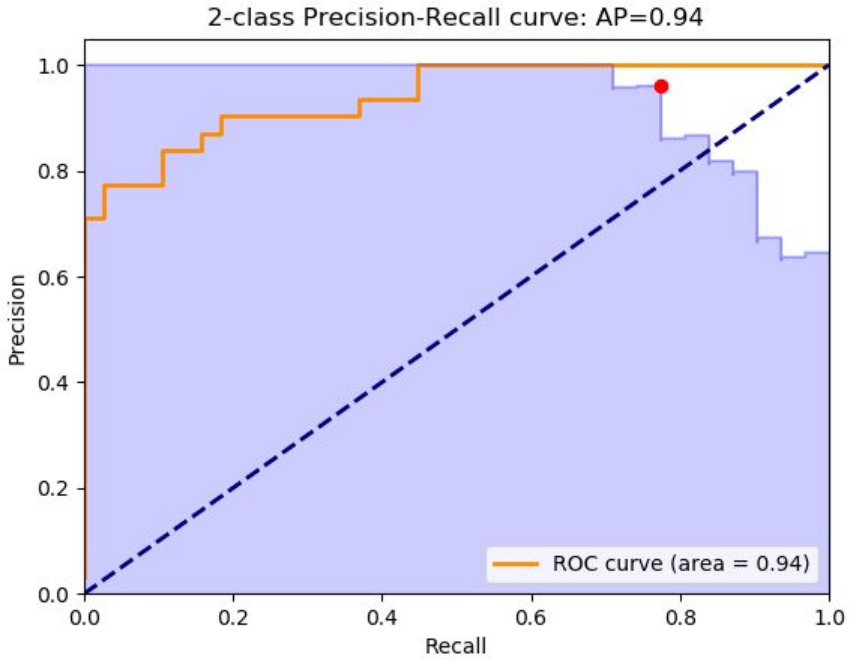

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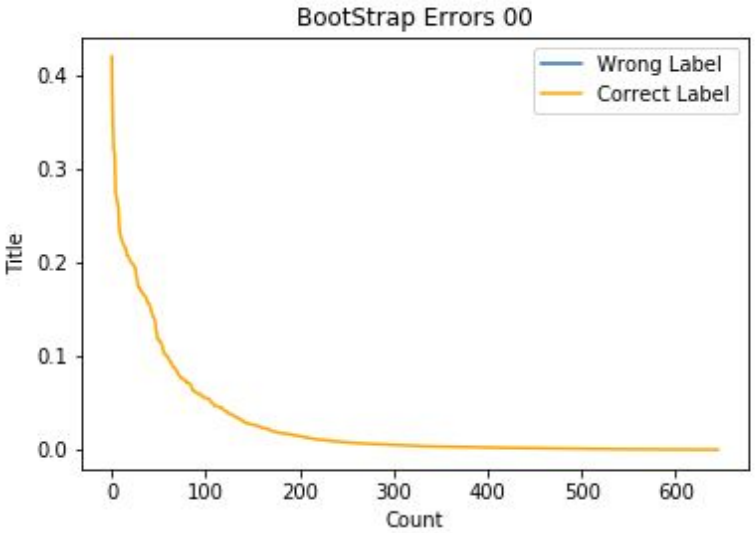

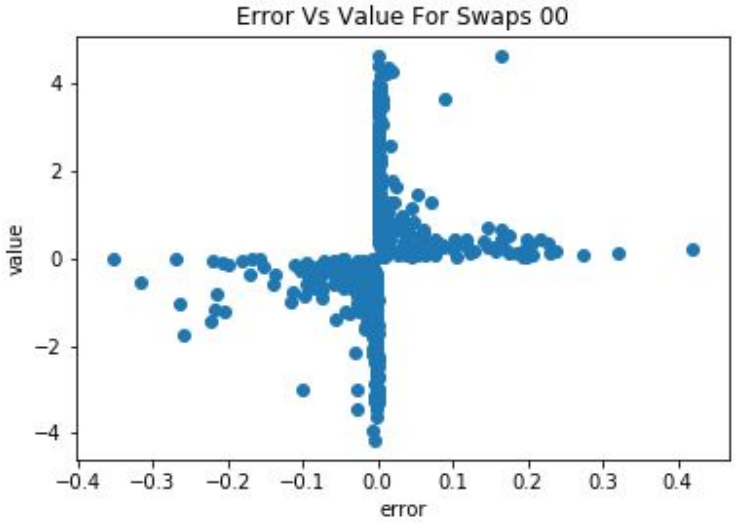

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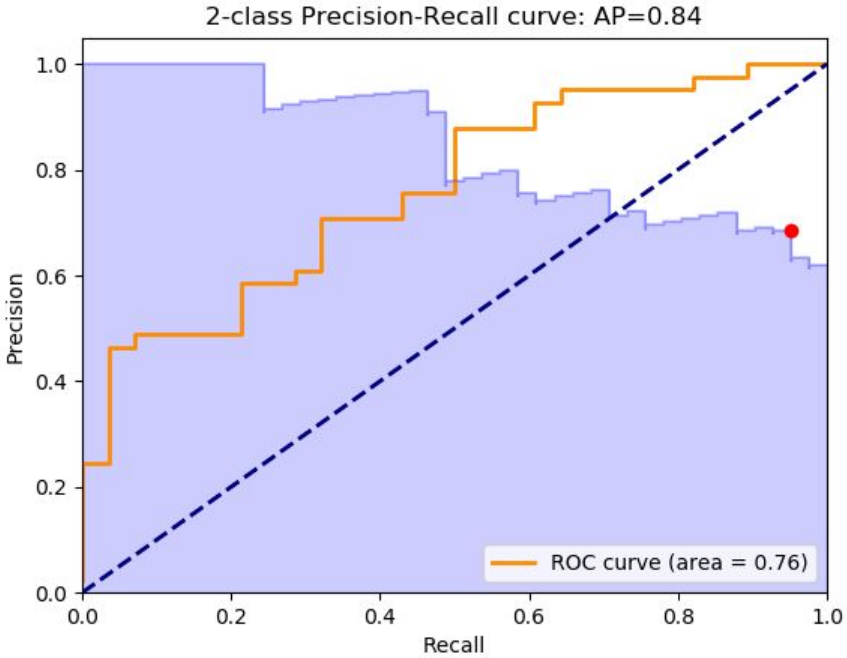

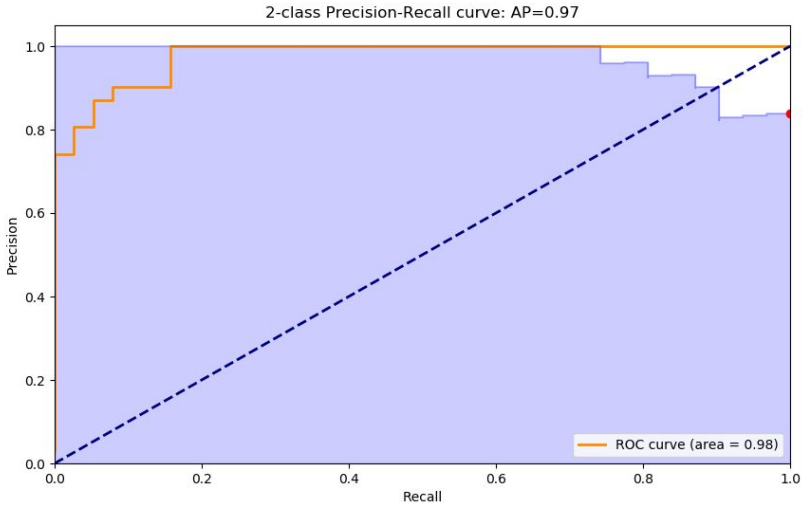

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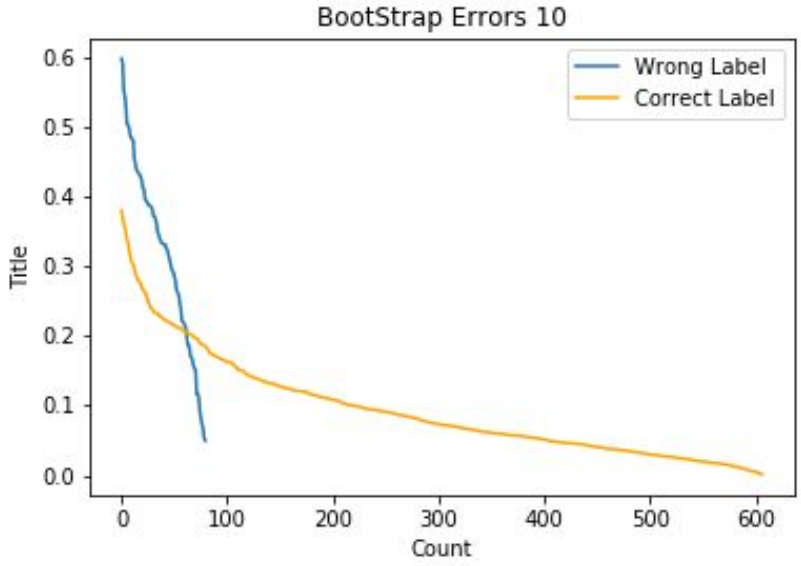

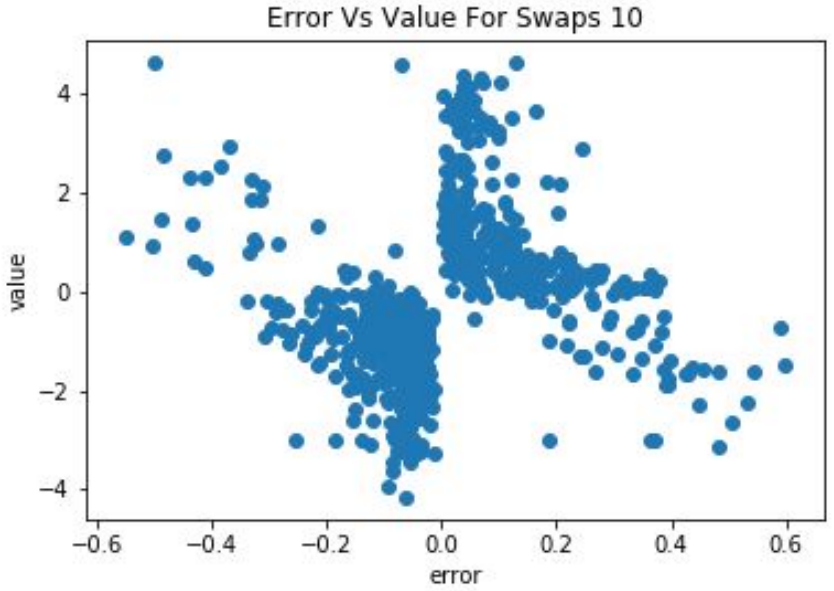

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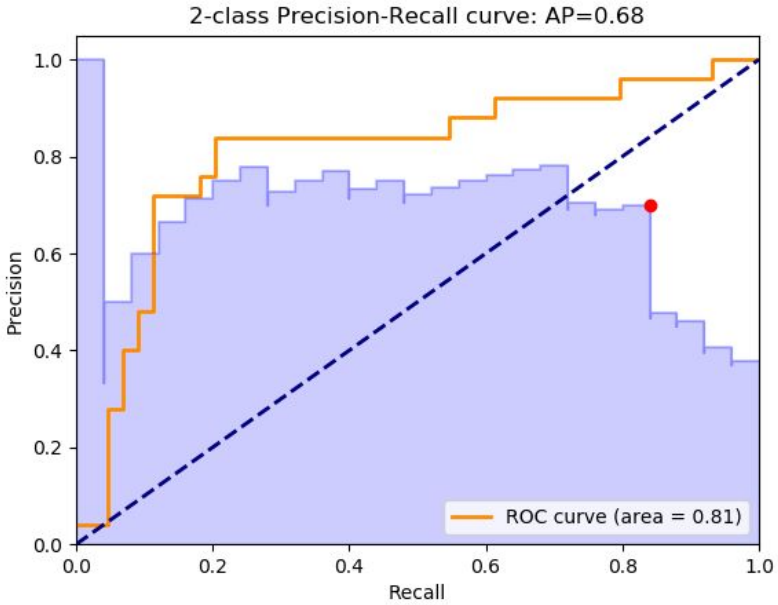

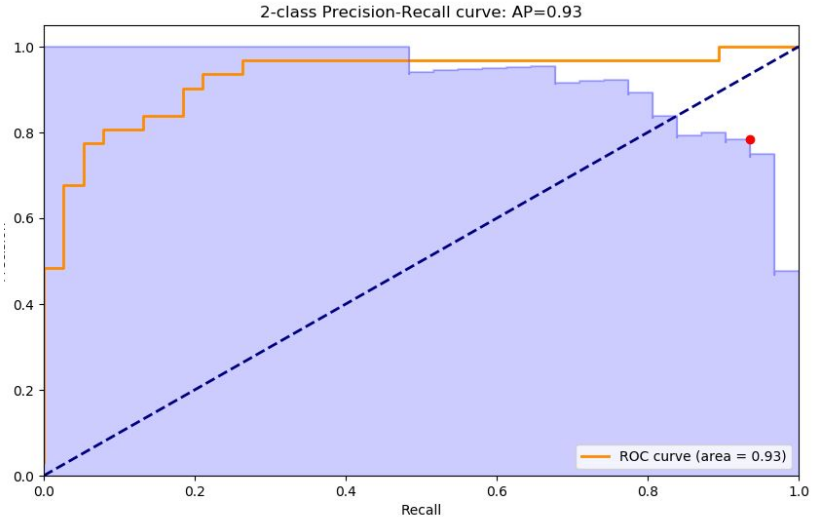

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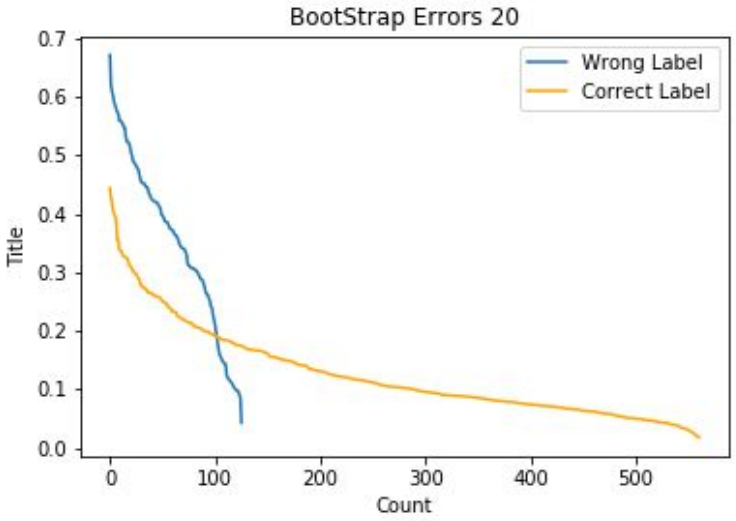

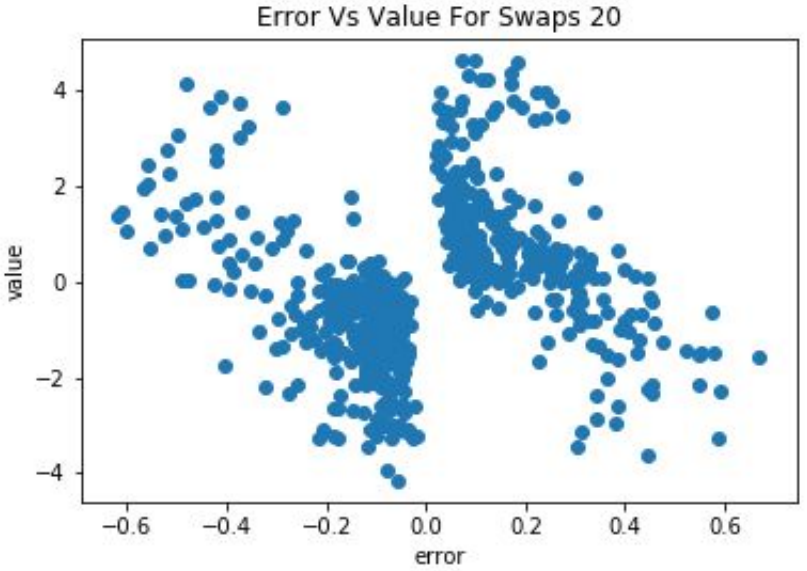

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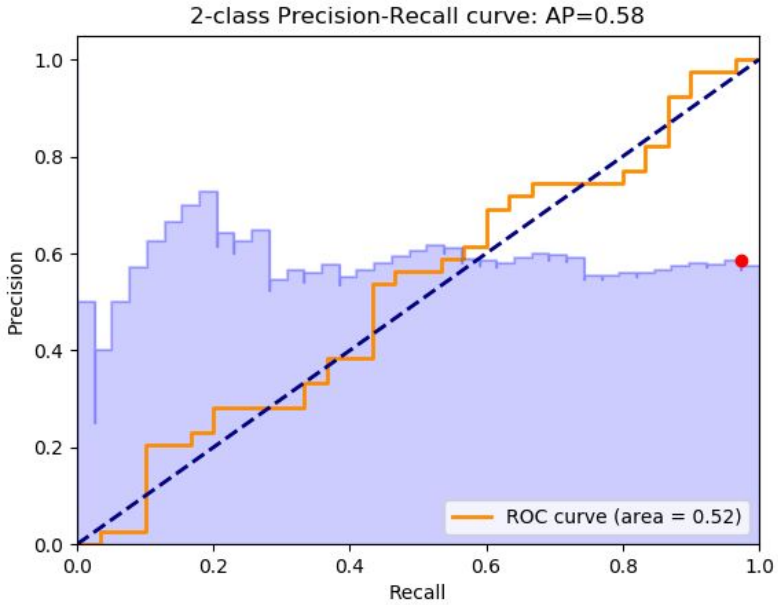

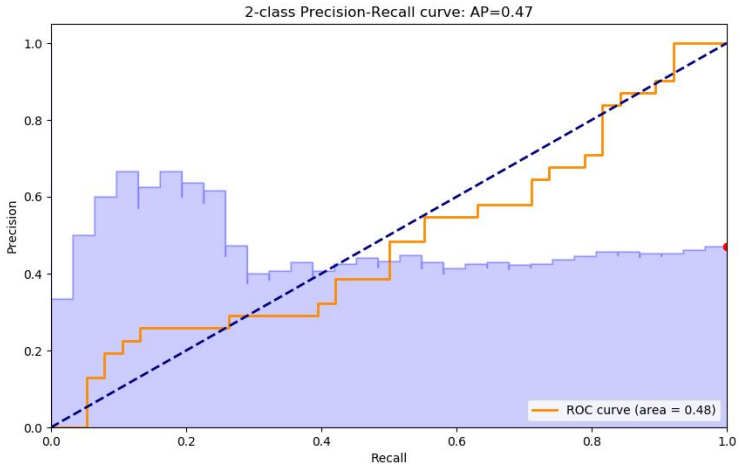

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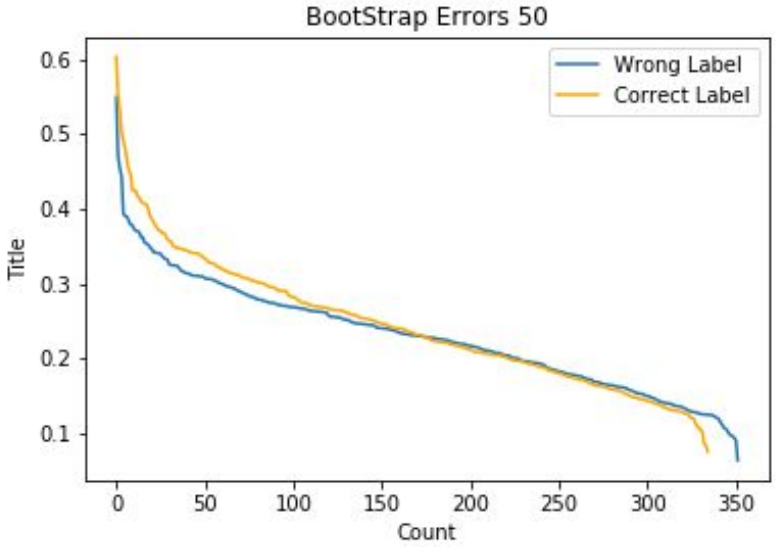

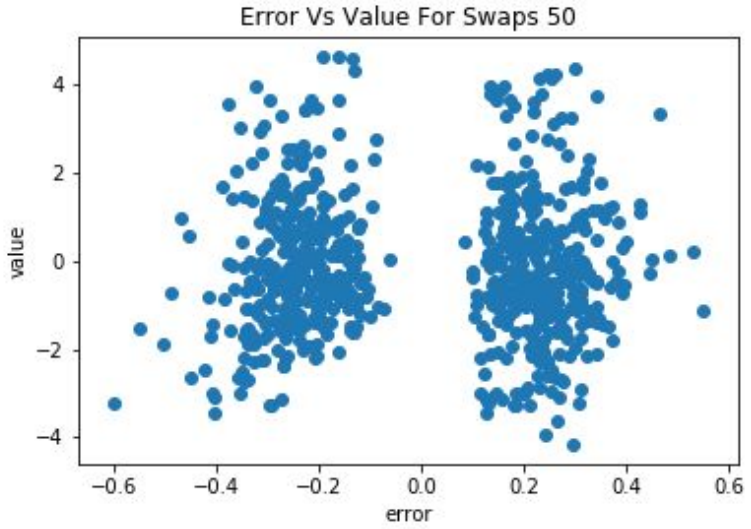

Interested in Learning More?

- Book is in pre-release looking for feedback!
- https://www.facebook.com/groups/1362916627160962/
  - Facebook Group
- https://gitter.im/deepchem/Lobby