Calibrated Boosting-Forest

Haozhen Wu
Department of Computer Science & Small Molecule Screening Facility
University of Wisconsin Madison
hwu84@wisc.edu

Abstract

Excellent ranking power along with well calibrated probability estimates are needed in many classification tasks. In this paper, we introduce a technique, Calibrated Boosting-Forest that captures both. This novel technique is an ensemble of gradient boosting machines that can support both continuous and binary labels. While offering superior ranking power over any individual regression or classification model, Calibrated Boosting-Forest is able to preserve well calibrated posterior probabilities. Along with these benefits, we provide an alternative to the tedious step of tuning gradient boosting machines. We demonstrate that tuning Calibrated Boosting-Forest can be reduced to a simple hyper-parameter selection. We further establish that increasing this hyper-parameter improves the ranking performance under a diminishing return. We examine the effectiveness of Calibrated Boosting-Forest on ligand-based virtual screening where both continuous and binary labels are available and compare the performance of Calibrated Boosting-Forest with logistic regression, gradient boosting machine and deep learning. Calibrated Boosting-Forest achieved an approximately 4% improvement compared to a state-of-art deep learning model and has the potential to achieve an 8% improvement after tuning the single hyper-parameter. Moreover, it achieved around 98% improvement on probability quality measurement compared to the best individual gradient boosting machine. Calibrated Boosting-Forest offers a benchmark demonstration that in the field of ligand-based virtual screening, deep learning is not the universally dominant machine learning model and good calibrated probabilities can better facilitate virtual screening process.

1 Introduction

Any increasing or decreasing score that represents the probability of each class is sufficient to produce a correct ranking of examples [9]. If the label is under a continuous distribution, typically, we either apply regression, or convert the label to a classification problem. Both techniques can be used to effectively rank. Current research in this area has been focused on improving the accuracy of an individual model. We propose an integrative technique here called Calibrated Boosting-Forest (CBF) that adopts both characteristics from regression and classification that achieves better ranking performance. In order to bridge these approaches, we exploit stacked generalization [1].

Stacked generalization is a methodology that links multiple base learners to construct a sharpened predictor. Using the original features, multiple base learners are trained and used for predictions. From the base learners predictions, a second layer model, a meta-learner, is built. Stacked generalization then produces final predictions that exhibit both low bias and low variance. Using predictions from the same training data to build the second layer model is very likely to cause over-fitting. In order to avoid this over-fitting, layer1 models are built based on a subset of training data that is disjoint from

1Code are published at https://github.com/haozhenWu/Calibrated-Boosting-Forest

Submitted to 31st Conference on Neural Information Processing Systems (NIPS 2017). Do not distribute.
training data for second layer model. An enhanced version is to use a cross-validation procedure that iteratively predicts on a valid set and then reassembles the predictions to their original order at the end. This procedure ensures the number of records in the layer2 data is the same as that of the layer1 data.

We choose gradient boosting machines, or GBMs [3] as fundamental models of CBF due to their excellent performance on ranking tasks, especially while using decision trees as base learners. GBMs are a way to consecutively fit new models to correct previous errors and provide a more accurate approximation of the response variable. During each iteration, a new weak learner is trained based on the error of the overall ensemble up to that point. GBMs primarily contain two parts, the cost function and the weak learner. In other words, one has to specify what function is going to be optimized and what kind of weak learners will be used to approximate the solution. Continuous response problems, \( y \in \mathbb{R} \), usually use either Quadratic loss, Absolute loss, Huber loss or Quantile loss, whereas binary response problems, \( y \in \{0, 1\} \), typically apply Logistic loss or Adaboost loss. In this paper, we will consider Quadratic loss for continuous response and Logistic loss for binary response. To encourage diversity, we choose both decision trees and linear models as weak learners for GBMs.

When building a GBM, most time is typically spent on the hyper-parameter selection stage. We automated the tuning step of GBM by simply building various GBMs with different hyper-parameters and combined them using the same stacked generalization framework. This approach of building various GBMs is inspired by random forests [5], which comprise multiple independent decision trees as an ensemble. Calibrated Boosting-Forest builds multiple GBMs and assigns unequal weights to each GBM within the ensemble.

A key feature of CBF is the calibration of its output scoring. In some applications, and particularly in the drug discovery domain for the task of virtual screening [7] where compounds are scored by the model based on likelihood of producing a drug-like effect in experimental testing, the mere ranking of examples (compounds) is not enough. Given the cost of testing each compound in high-throughput experimental screens, a measure of confidence in an estimated "hit rate" among some top ranking subset of compounds is an important factor in determining the number of compounds investigators should test experimentally in order to obtain some desired number of hits. In other words, how wide should the experimental net be cast given the anticipated abundance of "hits" based on model predictions. In this drug discovery application example as in many others, the output scores serve as inputs for subsequent procedures, such as estimating the cost/profit where the formula is \( P(buy) \times E(Pay \ amount|buy) \) or estimating total number of positive samples on test set where the formula is \( \sum_{i=1}^{N} p_i \). GBM with base learners of decision trees can achieve excellent ranking power, but predicts distorted probabilities [2]. Our Calibrated Boosting-Forest (CBF) model addresses this problem without additional cost via altering the final model to logistic regression and performing Platt scaling [12].

Calibrated Boosting-Forest has a particular value in ligand-based virtual screening and drug discovery domain. Experimental screening of molecules for desired biochemical activity typically produces continuous scores, like a dose-response curve or some normalized activity score based on percentage change in some read-out. A domain expert then assigns a cutoff to determine the so-called active and inactive molecules. Moreover, the particularly low hit/positive rate, lower than 1%, and expensive cost to conduct real experiment make the calibrated probabilities much more valuable. Beyond the merits of calibrated predicted probability scores, our Calibrated Boosting-Forest (CBF) implementation streamlines the tuning stage and provides equivalent or better ranking accuracy than the best individual GBMs.

2 Related work

Stacked generalization has been successfully applied to classification [1] and regression tasks [4] to improve performance. To our knowledge, previous work has only addressed how stacked generalization can be used to combine models that have the same objective. For instance, combining classification outputs from different models like decision trees, support vector machines (SVMs) and naïve bayes.

Random Forests [5] combine multiple tree predictors together to make predictions, where each tree is solely dependent on a sample of records and their features. Thus each tree is independent from
the others in the ensemble. The resulting final prediction is the mode of the classes for classification problems and mean prediction for regression.

Platt scaling [12] is a method that originally uses a sigmoid to map SVM outputs from \([-\infty, +\infty]\) to a posterior probability \([0, 1]\). [2] shows that they can also use Platt scaling to calibrate output from Adaboost.

MoleculeNet benchmark [6] accesses the performances of various machine learning models, in particular different neural network architectures, on a curated list of public experimental molecule screening datasets. It shows that graph convolutional model achieved a large performance boost because of the learnable featurizations.

3 Methodology

3.1 Extreme Gradient Boosting (XGBoost)

For this study we chose the XGBoost [13] implementation of GBMs. XGBoost is a scalable boosting framework that supports building GBMs with weak learners based on both decision trees and linear models. We use logistic loss as the loss function for the binary label,

$$L(y_n, f(x_n)) = -(y_n \times \log(f(x_n)) + (1 - y_n) \times \log(1 - f(x_n)))$$ (1)

where \(f(x_n) = p(y_n = 1|x_n), f(x_n) \in (0, 1)\)

And quadratic loss for the continuous label,

$$L(y_n, f(x_n)) = (f(x_n) - y_n)^2$$ (2)

where \(f(x_n) = E(y_n|x_n), f(x_n) \in \mathbb{R}\)

GBMs can be formalized in the additive form: \(f(x) = \sum_{i=0}^{T} f_i(x)\) where \(T\) is the number of iterations, \(f_0\) is the initial weak learner, and \(\{f_i\}_{i=1}^{T}\) are the additive weak learners.

3.2 Calibrated Boosting-Forest Structure

3.2.1 Training

Define \(D_{\text{train}} = (y_n, x_n), n = 1, \ldots, N\) where each \(x_n\) is a feature vector and \(y_n\) is the label of the \(n_{th}\) instance and \(M_h\) as a model where

\(h = \{(i, j, r), i \in \{gbtree, gblinear\}, j = \text{hyper parameters}, r = \text{optimal round}\}\)

Gbtree and gblinear set the GBM to use decision trees or linear models, respectively, as the base learner. CBF randomly samples a unique hyper-parameters set for each GBM. The hyper-parameter space for gblinear is defined by lambda, alpha, lambda_bias and learning rate. The hyper-parameter space for gbtree is defined by gamma, maximum depth, minimum child weight, maximum delta step, subsample ratio, column sample by tree ratio, column sample by level ratio, lambda, alpha and learning rate. During the k-fold cross-validation step, stratification splits the data \(D_{\text{train}}\) into \(K\) almost equal parts \(D_1, \ldots, D_k\). Let \(D_k = D - D_k\) denote the valid data and training data, respectively, for the \(k_{th}\) fold. For each of the layer1 data, at each \(k_{th}\) fold, \(H\) models with different hyper-parameter sets \(M_1, \ldots, M_h\) are learned from the training data \(D^{(-k)}\) and these layer1 models \(M_1^{(-k)}, \ldots, M_h^{(-k)}\) are applied to the valid data \(D_k\). \(H\) is a hyper-parameter selected to set the number of layer1 and layer2 models. Prediction scores of model \(M_h^{(-k)}\) on data fold \(D_k\) are denoted by

$$Z_{h kn} = M_h^{(-k)}(x_n), \text{where} \ n \in D_k$$ (3)

The concatenated predictions of all layer1 models, together with original label \(y_n\) become the layer2 data, \(MD_k = \{(y_n, Z_{k1n}, \ldots, Z_{khn}), n \in D_k\}\).

During the cross-validation procedure, the only difference between \(M_h^{(-k)}\) with different \(k\) is the number of optimal rounds/training steps, \(r\). In other words, they all have same weak learner \(i\) and parameter set \(j\), but the optimal round \(r\) is based on early stopping evaluated on \(D_k\). After the cross-validation procedure, \(MD = \bigcup_{k=1}^{K} MD_k\) becomes the full layer2 data with instance orders the same as \(D\). Figure 1 illustrates the cross-validation procedure for one model. The layer2 model is trained using the same procedure as the layer1 models, with \(x_n\) becoming the features from \(MD\).
3.2.2 Predicting

When predicting on new data $D^{\text{new}}$, the learned layer 1 models $M_h^{(-k)}$, ..., $M_h^{(-1)}$ all predict on the whole set of records of $D^{\text{new}}$ and produce $MD^{\text{new}} = \{(Z_{1kn}, ..., Z_{hkn}), n \in D^{\text{new}}\}$. Note that we have $K$ versions of $MD^{\text{new}}$ at this time, $MD^{\text{new}} = \frac{1}{K} \sum_{k=1}^{K} MD_h^{\text{new}}$ becomes the input features for the layer 2 model. The layer 2 model then uses the same procedure to generate the final predictions. Figure 2 illustrates the prediction procedure.

3.2.3 Different labels

In many situations, the raw labels follow a continuous distribution and a mapping function $f(x)$ then converts it into a binary label. In this paper, we denote the label from a continuous distribution as the continuous label and the label from a Bernoulli distribution as the binary label. The mapping function $f(x)$ can simply be based on one threshold $t$ such that $f(x) = 1$, $x > t$ and $f(x) = 0$, $x \leq t$ or based on a more sophisticated relationship. $f(x)$ is usually defined by a domain expert. When both label types are available, Calibrated Boosting-Forest builds two layer 1 datasets, both using the same feature vectors where the first one uses a binary label and second one uses a continuous label. Each of the layer 1 dataset will generate $H$ predictions, in total $2H$ predictions. When there is more than one layer 1 dataset $D$, the final layer 2 data is simply the horizontally concatenated version of multiple $MD$. For example, when we have both labels, we would have $D_{\text{train, cont label}}^{\text{cont label}}$ and $D_{\text{train, binary label}}^{\text{binary label}}$, which will generate $MD_{\text{cont label}}^{\text{from cont label}}$ and $MD_{\text{binary label}}^{\text{from binary label}}$. The concatenated versions of these two datasets, with binary label, become the final $MD$ that will be used to build layer 2 model.

3.2.4 Stopping criteria

Since both base models, gbtree and gblinear are all based on gradient descent optimization, a proper stopping metric is needed in order to stop the model at the optimal number of iterations. We use one of the final evaluation metrics, Enrichment Factor, as the stopping metric. When building each model, we monitor the evaluation scores on training data $D^{(-k)}$ and valid data $D_k$. We stop training the
When we observe the evaluation score on $D_k$ does not improve for 100 rounds, the optimal number of rounds is the round that produces the best evaluation score on $D_k$.

When building the layer 1 model based on continuous labels and the stopping metric requires a binary label to compute the score, we internally convert the continuous label into a binary label based on the same mapping function $f(x)$ discussed in section 3.2.3. Thus, the layer 1 regression models are also built to optimize the same evaluation metric as the classification models.

### 3.2.5 Platt scaling

Platt scaling is a calibration method that passes the output from a single model through a sigmoid, resulting in output of posterior probabilities on $[0,1]$. This study extends the output mapping from a single model to multiple layer 1 models and use $L_1$ and $L_2$-norms for regularization. To illustrate, suppose we have two sets of layer 1 data, $D_i$, $i = 1, 2$, each producing $H$ predictions. Under Platt scaling, these $2H$ layer 1 predictions in addition to a column of 1s becomes the design matrix, $X$, in which we then train an elastic net [14] with $X$ as the input feature and the binary label as the dependent variable. Denote $\beta \in \mathbb{R}^{2H+1}$ as the learned coefficients. The elastic net model is:

$$ p(y = 1|X) = \frac{1}{1 + \exp(-X\beta) } $$

where $|\beta|_2 = \sum_{j=1}^{2H+1} \beta_j^2$ and $|\beta|_1 = \sum_{j=1}^{2H+1} |\beta_j|$. The layer 2 elastic net model performs two tasks: 1. Learning the optimal weights for the combination of layer 1 models in order to maximize ranking power 2. Performing probability/score calibration. In section 4.3 we will introduce a novel metric for evaluating the quality of probability (Reliability score). Figure 3 illustrates the overall structure of Calibrated Boosting-Forest, with two layer 1 data.

![Figure 3: Calibrated Boosting-Forest structure](image)

### 3.2.6 Layer 2 model selection

Mentioned in 3.2.1, there are $H$ models for each layer 1 $D_i$, $i = 1, 2, ..., N$ that together produce the final $MD$. While the training procedure of layer 2 model (using the elastic net model) is the same as layer 1 model, the usage of $H$ predictions from $H$ layer 2 models is different. Unlike layer 1 models, whose predictions all contribute to layer 2 data, the layer 2 model will sweep all $H$ models and select the one that has the best cross-validation scores. Notationally, we let $S$ be the evaluation metric, denote the valid score of $M_h^{(k)}$ as: $CV_{hk} = S(Z_{hkn}, y_n)$, where $n \in D_k$. And the cross-validation score of $M_h$ as: $CV_h = \frac{1}{K} \sum_{k=1}^{K} CV_{hk}$.
4 Experimental design

4.1 Datasets

Most of the existing machine learning models applied in virtual screening either directly model the binary label or the continuous label, but not both. Here we demonstrate Calibrated Boosting-Forest’s utilization of diverse label types. We use the PCBA128 dataset from MoleculeNet and add the original continuous label (logAC50) back to the dataset. PCBA128 contains 128 bioassays from PubChem BioAssay (PCBA), each bioassay represents an experimental screening of 400,000 small molecules against some protein targets for some desired activity/effect. We consider one featurization method that is typical in ligand-based virtual screening applications, Extended Connectivity Fingerprint (ECFP) [11]. ECFP produces a fixed-length bit vector describing the atom connectivity in a small molecule.

4.2 Data splitting

In order to have the performance results comparable, we use the same index split from MoleculeNet. However, MoleculeNet has a different design of model structure compared to Calibrated Boosting-Forest. MoleculeNet’s splitting methods all follow train/valid/test splits with default ratio 0.8/0.1/0.1. CBF has the same test split but a different train/valid splitting method that required further split the train/valid data into k folds, with each time having k-1 folds becoming the training data, 1 fold becoming valid data, and thus having k different validation scores. In order to make the results as comparable as possible, we keep the test and valid splits the same, and further split the train data into 4 folds, which gives us 5 train/valid folds. Besides reporting the overall train, valid, test performance of CBF, we also report the scores of same individual valid fold.

4.3 Evaluation

We use the same evaluation metric, AUC-ROC, as used by MoleculeNet. In addition, we add AUC-BED, AUC-PR and Enrichment factors to cover different aspects of ranking performance and add Logistic loss and Reliability score to evaluate probability quality.

Area under the receiver operating characteristic (AUC-ROC) is a widely used metric for evaluating binary classification problems. ROC measures the true positive rate (TPR) vs. false positive rate (FPR) based on different thresholds. Area under the Boltzmann-Enhanced Discrimination (AUC-BED) [10] is similar to AUC-ROC whereas it puts greater emphasize on the early retrieval. This is more suitable to drug discovery since we want to limit testing to only the top scoring molecules. Area under the precision-recall curve (AUC-PR) measures the positive predictive value and true positive rate over different thresholds. Enrichment factor (EF) at a given threshold t is another common used metric in virtual screening. The enrichment score reflects how many times better than random that a model’s top t% predictions are.

Logistic loss (Logloss) is the same one defined in section 3.1. When we don’t know the true posterior probabilities, reliability diagrams [8] are used to visualize the relationship. [2] uses reliability diagrams to visualize the effectiveness of calibration on Adaboost. A reliability diagram is constructed by splitting the predictions into ten bins, with scores fall between 0 and 0.1 assigned to first bin, between 0.1 and 0.2 assigned to second bin, etc. For each bin, the mean predicted score and the true ratio of positive records are plotted against each other. We would expect the points fall near the diagonal line if the scores are well calibrated. However, when the ratio of positive labels is extremely low, lower than 1% for example, the predictions from GBMs will have few records higher than 0.5. In this situation, the mean predicted value of higher bins becomes either highly fluctuated or N/A if no scores fall in that bin. To deal with this problem, we proposed an enhanced version that assigns 10% of the records with lowest scores into first bin, 10% of the records with lowest scores higher than previous one into second bin, etc. This procedure ensures that all the bins will have available scores and we would still expect the points fall near the diagonal line if the scores are well calibrated. Furthermore, to have a quantified and normalized score, we calculated the absolute difference between mean predicted value and true ratio of positive for each bin and divided by the true ratio of positive over the whole population and then take the arithmetic mean. We describe this value as a reliability score. The lower the reliability score is, the better the probabilities are calibrated.
5 Results

5.1 Train/valid/test result of all models on ranking performance

Models we tested include individual GBMs and Calibrated Boosting-Forest with different number of H, denoted by GBM-H and CBF-H. Scores except GBM and CBF are from MoleculeNet (MN). The train, valid and test scores report here are the average over all the targets. As we can see from table 1, individual GBM and CBF, regardless of which label used, all have scores higher than neural networks and logistic regression. Unless specific indication, the GBM and CBF reported all use both binary and continuous labels. Greater performance gains come from utilizing both labels type. CBF where H equals 1 and use both labels as input, has higher valid and test scores compared to best individual GBM, demonstrating the performance gain from utilizing diverse label types. Increasing H to 5 further boosts the performance.

Table 1: Performance between MoleculeNet and CBF on AUC-ROC

| PCBA-128       | Train | Valid (MN’s fold) | Valid (5 folds) | Test  |
|----------------|-------|-------------------|-----------------|-------|
| Logistic Regression | 0.809 | 0.776             | -               | 0.781 |
| Multitask Network | 0.821 | 0.776             | -               | 0.781 |
| Bypass Network   | 0.814 | 0.785             | -               | 0.782 |
| Graph Convolution| 0.877 | 0.848             | -               | 0.845 |
| CBF-1 (Binary)  | 0.976 | 0.852             | 0.845           | 0.849 |
| Best GBM-1 (Binary)| 0.991 | 0.855             | 0.844           | 0.858 |
| Best GBM-1      | 0.990 | 0.862             | 0.852           | 0.864 |
| CBF-1           | 0.990 | 0.863             | 0.861           | 0.873 |
| CBF-5           | 0.994 | **0.868**         | **0.869**       | **0.879** |

All the models reported here have large gaps between train and valid scores, indicating over-fitting is a general issue and proper regularization and stopping criteria are important. GBMs and CBFs all have higher training scores than neural networks and logistic regression. One possible explanation is that logistic regression and neural networks provided by MoleculeNet are multitasked, which serves as a strong regularization.

5.2 Best individual GBMs and Calibrated Boosting-Forest on probability quality performance

As we can see from table 2 and table 3, CBFs that incorporate Platt scaling achieve huge improvement in probability quality measurements. CBF with continuous label achieved 0.77 on test reliability score, which means the average difference between estimated percentage of active samples and true percentage of active samples is around 77% of actual percentage of active samples over all the bins. Having this property, we are able to quickly screen a large set of potential molecules and give a close estimate of the real active molecules over top K performing molecules. This can help users better estimate the cost and profit before doing real experiments. Although Logloss is hard to be directly translated in practical value, it is well known and we use it to demonstrate that the novel metric, RS, is working. CBF achieved improvement over both Logloss and RS.

Table 2: Performance between best GBM and CBF on Logloss

| PCBA-128       | Train | Valid | Test  |
|----------------|-------|-------|-------|
| Best GBM-1 (Binary) | 44576 | 9919  | 5266  |
| CBF-1 (Binary)   | 9639  | 2583  | 1387  |
| CBF-1           | 8780  | **2346** | **1284** |
Table 3: Performance between best GBM and CBF on Reliability score

|              | PCBA-128 | Train | Valid | Test |
|--------------|----------|-------|-------|------|
| Best GBM-1 (Binary) | 69.2     | 75.1  | 62.7  |      |
| CBF-1 (Binary)      | 3.9      | 3.3   | 3.4   |      |
| CBF-1              | 1.19     | 0.74  | 0.77  |      |

5.3 Scaling up CBF

Table 4 demonstrates the effect of scaling up layer1 model with continuous label included, evaluated on various metrics. Since the computation will be long when applying to all 128 targets, we stratified sample 12 targets based on AUC-ROC performance of CBF-1 on PCBA128 test set. Thus these samples represent easy and challenging tasks from PCBA128.

CBFs gain continuous improvement over AUC-BED, EF@0.01 and EF@0.02, especially when increasing H from 5 to 10. Logloss and RS become similar for CBFs when H is greater than 5. Except for AUC-PR, best scores of rest evaluation metrics all come from CBFs with H equals 10 or 15. In practice, we would suggest choosing the highest H possible given the constraints of time and computation resource.

Table 4: Effect of scaling up layer1 model (Test set)

|              | PCBA-12 | AUC-ROC | AUC-PR | AUC-BED | EF@0.01 | EF@0.02 | Logloss | RS  |
|--------------|---------|---------|--------|---------|---------|---------|---------|-----|
| Best GBM-1   | 0.814   | 0.136   | 0.516  | 28.3    | 18.7    | 5316.58 | 96.33  |
| Best GBM-5   | 0.821   | 0.144   | 0.530  | 32.3    | 19.59   | 3011.59 | 104.41 |
| Best GBM-10  | 0.826   | 0.151   | 0.530  | 33.99   | 20.52   | 2386.81 | 133.77 |
| Best GBM-15  | 0.822   | 0.151   | 0.537  | 33.86   | 20.41   | 3810.68 | 124.42 |
| CBF-1        | 0.798   | 0.141   | 0.509  | 28.4    | 18.1    | 864.40  | 10.05  |
| CBF-5        | 0.809   | 0.150   | 0.537  | 34.03   | 20.14   | 534.65  | 0.82   |
| CBF-10       | 0.833   | 0.149   | 0.579  | 37.33   | 21.98   | 526.73  | 0.75   |
| CBF-15       | 0.828   | 0.150   | 0.578  | 37.55   | 22.12   | 526.97  | 0.76   |

6 Conclusion

This work introduces Calibrated Boosting-Forest, an integrative technique that leverages both continuous and binary labels and output calibrated posterior probabilities. We demonstrate that CBFs can achieve superior ranking performance over state-of-art deep learning models while preserving well calibrated probabilities. Together with a novel metric Reliability Score, we also show how good probability scores are critically important in virtual screening domain. We recommend when building standard datasets for ligand-based virtual screening, include all the related labels. As a general technique, CBF can be applied to other application in the future.

Acknowledgments

The author thanks Anthony Gitter, Spencer Ericksen, and Liam Johnston who helped reviewing the paper and provided useful feedback. This work was funded by NIH/NCI P30 CA014520 to the UW Carbone Cancer Center and by the UW-Madison Office of the Vice Chancellor for Research and Graduate Education with funding from the Wisconsin Alumni Research Foundation.

References

[1] Wolpert, David H. “Stacked generalization.” Neural networks 5, no. 2 (1992): 241-259.
[2] Niculescu-Mizil, Alexandru, and Rich Caruana. "Obtaining Calibrated Probabilities from Boosting." In UAI, p. 413. 2005.

[3] Friedman, Jerome H. "Greedy function approximation: a gradient boosting machine." Annals of statistics (2001): 1189-1232.

[4] Breiman, Leo. "Stacked regressions." Machine learning 24, no. 1 (1996): 49-64.

[5] Breiman, Leo. "Random forests." Machine learning 45, no. 1 (2001): 5-32.

[6] Wu, Zhenqin, Bharath Ramsundar, Evan N. Feinberg, Joseph Gomes, Caleb Geniesse, Aneesh S. Pappu, Karl Leswing, and Vijay Pande. "MoleculeNet: A Benchmark for Molecular Machine Learning." arXiv preprint arXiv:1703.00564 (2017).

[7] Geppert, Hanna, Martin Vogt, and Jurgen Bajorath. "Current trends in ligand-based virtual screening: molecular representations, data mining methods, new application areas, and performance evaluation." Journal of chemical information and modeling 50, no. 2 (2010): 205-216.

[8] DeGroot, Morris H., and Stephen E. Fienberg. "The comparison and evaluation of forecasters." The statistician (1983): 12-22.

[9] Zadrozny, Bianca, and Charles Elkan. "Obtaining calibrated probability estimates from decision trees and naive Bayesian classifiers." In ICML, vol. 1, pp. 609-616. 2001.

[10] Swamidass, S. Joshua, Chloe-Agathe Azencott, Kenny Daily, and Pierre Baldi. "A CROC stronger than ROC: measuring, visualizing and optimizing early retrieval." Bioinformatics 26, no. 10 (2010): 1348-1356.

[11] Rogers, David, and Mathew Hahn. "Extended-connectivity fingerprints." Journal of chemical information and modeling 50, no. 5 (2010): 742-754.

[12] Platt, John. "Probabilistic outputs for support vector machines and comparisons to regularized likelihood methods." Advances in large margin classifiers 10, no. 3 (1999): 61-74.

[13] Chen, Tianqi, and Carlos Guestrin. "Xgboost: A scalable tree boosting system." In Proceedings of the 22nd acm sigkdd international conference on knowledge discovery and data mining, pp. 785-794. ACM, 2016.

[14] Zou, Hui, and Trevor Hastie. "Regularization and variable selection via the elastic net." Journal of the Royal Statistical Society: Series B (Statistical Methodology) 67, no. 2 (2005): 301-320.