Cross-Cluster Weighted Forests

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Abstract

Adapting machine learning algorithms to better handle clustering or batch effects within training data sets is important across a wide variety of biological applications. This article considers the effect of ensembling Random Forest learners trained on clusters within single data sets with heterogeneity in the distribution of the features. We find that constructing ensembles of forests trained on clusters determined by algorithms such as k-means results in significant improvements in accuracy and generalizability over the traditional Random Forest algorithm. We denote our novel approach as the Cross-Cluster Weighted Forest, and examine its robustness to various data-generating scenarios and outcome models. Furthermore, we explore the influence of the data-partitioning and ensemble weighting strategies the benefits of our method over the existing paradigm. Finally, we apply our approach to cancer molecular profiling and gene expression data sets that are naturally divisible into clusters and illustrate that our approach outperforms classic Random Forest. Code and supplementary material are available at https://github.com/m-ramchandran/cross-cluster.

Keywords: Ensemble learning, Random Forest, clustering, replicability, data heterogeneity

1. Introduction

Data sets containing natural clusters or batch effects are common across most biological applications, motivating the need for prediction algorithms that can adapt to the particular challenges of handling possible cluster-like heterogeneity in the distribution of the features (Goh et al., 2017; Chauhan et al., 2010). Numerous learning algorithms have been developed in such settings where the covariate-outcome relationship varies across clusters (Luo and Schumacher, 2010; Verbeke and Lesaffre, 1996; Dietterich, 2000; Bouwmeester et al., 2013). Research has additionally suggested the possibility of improving prediction accuracy in such scenarios by partitioning data through suitable clustering algorithms before applying an ensembling framework to the pre-clustered data. (Ramchandran et al., 2020; Trivedi et al., 2015; Deodhar and Ghosh, 2007).
Learning algorithms that have been explored through the lens of data sets having natural clustering structure include Neural Networks, Random Forest, and (regularized) least squares linear regression (Patil and Parmigiani, 2018; Sharkey, 1996; Liaw and Wiener, 2002). Random Forest, itself a highly popular ensemble machine learning algorithm designed to reduce overfitting and handle high-dimensional data, has shown widespread success in many scientific realms. The method was introduced by Breiman (2001) and has since been adapted to handle a wide variety of data types and applications, including missing data imputation, survival analysis, and unsupervised clustering (Liaw and Wiener, 2002; Biau and Scornet, 2016). Ramchandran et al. (2020) previously showed that in the presence of heterogeneity in both the outcome model and distribution of the features across multiple training studies, building ensembles of forests each trained on a single study produced significantly more accurate predictions than training a single forest on all of the available data when the resulting learners contained an equivalent number of trees. Additionally, these results held when heterogeneity in the covariate-outcome relationship was removed; when trained on randomly-chosen partitions of a large single data set, forest-based ensembles considerably improved upon a single forest trained on the entire data set. Moreover, the context in which ensemble learners are built using pre-clustered data is analogous to the multi-study framework 1, as formalized by Patil and Parmigiani (2018), if one thinks of separate clusters as individual studies. In view of these results, it is therefore natural to hypothesize that for data sets containing clusters, data can be even more optimally partitioned using clustering algorithms in order to form ensembles of forests that outperform the classic Random Forest algorithm. This manuscript is motivated by exploring the aforementioned hypothesis in detail.

In this paper, we build upon the intuitions discussed above and additionally consider the situation in which the true outcome model remains relatively constant across clusters and the primary source of heterogeneity is in the distribution of the covariates; this requires prediction algorithms to now be able to disentangle the true covariate-outcome relationship from distributional variation introduced by the presence of clusters in the covariates. At first glance, this context is conceptually similar to covariate shift, in which the training and test samples are drawn from different distributions while the outcome model remains constant (Sugiyama et al., 2007). However, whereas classic covariate shift applications typically only consider dissimilarities between the training data as a whole and the test data, we investigate the addition of internal heterogeneity in the marginal distribution of the training covariates. We particularly focus on ensembles of Random Forests, in which each forest is trained on a subsection of the total available data and then combined using a weighting approach rewarding generalizability in other clusters across the training set. We propose a strategy of training ensembles of forests in which clusters of points that produce more highly generalizable predictors are given greater influence. Throughout, we will use the term 'estimated clusters' to refer to clusters obtained through clustering algorithms, and 'true clusters' to refer to the latent labels from the data-generation process.

Specifically, we introduce the **Cross-Cluster Weighted Forest**, a learning approach with the following steps: first, the data set is separated into estimated clusters using k-means

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1. Multi-study learning handles the availability of multiple training studies that measure the same outcome and many of the same covariates by building ensembles of learners each trained on a single study to form the final predictor.
or other clustering algorithms. Next, Random Forests are trained on each cluster. Finally, stacked regression weights are employed to construct the overall ensemble, in order to up-weight individual predictors that show stability across estimated clusters. We illustrate that our method greatly improves upon the existing paradigm across a variety of realistic scenarios as well as real biological data naturally divisible into clusters. Our overall aim is to improve upon the traditional Random Forest algorithm in the presence of heterogeneity in the distribution of the features, to form more replicable predictors.

We begin this article by describing the Cross-Cluster Weighted Forest approach and the additional ensembling methods we will be comparing throughout our analysis. We then present the results of our experimental explorations of its performance on single data sets containing clusters, organizing our discussion by isolating the beneficial effects of each step in our algorithm on the behavior of the overall ensemble. We additionally determine the robustness of our method to realistic variety in data generation, demonstrating that our proposed approach has greater generalizability across scenarios than all other methods considered. Next, we explore the multi-study setting, and illustrate that our proposed addition of the clustering step improves upon the existing paradigm of simply ensembling forests trained on each study. Finally, we consider real gene expression and clinical data plausibly containing heterogeneity in the distribution of the features, and demonstrate our method’s superior performance over classic Random Forest.

The general strategy of utilizing clustering algorithms to partition data and build ensembles of learners trained on each discovered cluster has been previously explored in Deodhar and Ghosh (2007). They present a regime in which co-clustering and model fitting are performed simultaneously, and primarily consider prediction algorithms fitting into the generalized linear model class as base learners. Their work highlights the efficacy of allowing ensemble members to learn different aspects of the input space, and particularly applies to the setting in which the independent variables contain two or more known groups that are associated with their corresponding modes. In our work, we remove such requirements and instead simply allow clustering algorithms to find any natural substructure in the data prior to ensembling. Additionally, by focusing on Random Forest as a base learner, we allow for more complex interactions between covariates in the modeling process. Through our particular choice of ensembling weights, we additionally explore the relationship between the partitioning step and the generalizability of the resulting models. In particular, the clustering step efficaciously removes within-cluster feature distribution heterogeneity while maximizing cross-cluster heterogeneity, and thus the strategy of ensembling learners trained on these diverse partitions reflects the common ensemble learning standard of combining dissimilar learners in order to improve prediction generalizability (Schapire, 2003; Dietterich, 2000). In fact, this is the very paradigm that motivates the classic Random Forest algorithm, in which the randomness of the bootstrapping step and the subset of total variables available at each split serve to create diversity in the trees that comprise the ensemble and thus lower its variance (Breiman, 1996a; Liaw and Wiener, 2002).

2. Methods

The Cross-Cluster Weighted Forest (CCWF) approach is outlined in Algorithm 1. We denote by \( \hat{Y}_j(x_\star) \) the prediction of the forest trained on cluster \( j \) on new point \( x_\star \), for \( j = \)
Algorithm 1 Cross-Cluster Weighed Forest (CCWF)

Set the number of clusters $k \geq 2$; then,

1. Run a clustering algorithm on the entire set of covariates

2. For $j = 1, ..., k$
   - Train a Random Forest on the $j^{th}$ estimated cluster
   - Compute $\hat{Y}_j(x_\star)$

3. Compute stacked regression weights $w_1, ..., w_k$ using the full data set and all cluster-level forests as predictors.

4. Construct the ensemble-level prediction: $\hat{Y}_E(x_\star) = \sum_{j=1}^{k} w_j \hat{Y}_j(x_\star)$

The majority of previous work connecting Random Forest with clustering utilizes Random Forest itself as a clustering method (Yan et al., 2013; Shi and Horvath, 2006; Bicego, 2019). To our knowledge, the only manuscript which displays conceptual similarity in broadly using the estimated clusters produced by clustering algorithms to train ensemble learners including Random Forest is Trivedi et al. (2015). They present a slightly different paradigm, in which the prediction for a given test point involves first running k-means for several different values of $k$, approximating the cluster from each iteration that most closely fits the test point, and then ensembling learners trained solely on these successive clusters in order to form the final prediction. This requires assigning the test point to a cluster for each value of $k$ and then removing all other data points from consideration. Their results showed statistically significant improvements in certain scenarios of their ensembling approach using Random Forest over the use of a single forest, highlighting the potential efficacy of using clustering algorithms to build ensembles of forests.

To construct the ensembling weights in step (3) of our algorithm, we adapted the multi-study version of the stacked regression method, an approach which by construction rewards empirical cross-cluster generalizability of cluster-specific learners (Patil and Parmigiani, 2018; Ramchandran et al., 2020). Stacked regression forms linear combinations of multiple predictors that have been shown to improve upon the performance of any single component.
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(Breiman, 1996b). The weights given to each predictor are determined by cross-validation and least squares regression with $L_2$-norm regularization. Our extension of stacking to the multi-cluster context proceeds as follows: once the training set is split up into $k$ clusters and forests are trained on each, all forest-level predictions are then 'stacked' into matrix $\mathbf{T} = [\hat{\mathbf{Y}}'_1, ..., \hat{\mathbf{Y}}'_k]'$, where $\hat{\mathbf{Y}}'_j = [\hat{\mathbf{Y}}'_{1j}, ..., \hat{\mathbf{Y}}'_{kj}]'$ for $j = 1, \ldots, k$; $\hat{\mathbf{Y}}'_{ij}$ is the column vector of predictions of forest $j$ on cluster $i$, and $\hat{\mathbf{Y}}'_j$ is the stacked vector of all predictions made by forest $j$ on every cluster within the training set. $\mathbf{T}$ is $n \times k$, with $n$ equaling the total number of observations in the training set. The observed outcomes are similarly aggregated across the entire training data set into the $n \times 1$ vector $\mathbf{Y}$. $\mathbf{Y}$ is then regressed against $\mathbf{T}$ with a ridge penalization and non-negativity constraint. The learner-specific weights $\mathbf{w}$ are determined by solving $\min_\mathbf{w} ||(\mathbf{Y} - (\mathbf{T} \times \mathbf{w}))||^2$ such that $\mathbf{w} > 0$ and $||\mathbf{w}||^2 \leq \lambda$, where $\lambda$ is optimized using the cross-validation procedure in the glmnet package in R (Friedman et al., 2010).

In the following section, we assess the utility of the CCWF algorithm across various scenarios of naturally clustered data which will be described in more detail in Section 3. Throughout, the abbreviation Cluster will refer to training an ensemble through the CCWF approach. We additionally compare the performance of CCWF with other forest-based ensembles representing variations from Algorithm 1, in order to isolate the effect of each step on conferring advantages to the method. The moniker Random will indicate the ensemble formed by using $k$ equally sized random partitions of the data set instead of clusters. Multi will refer to training a forest on each of the true clusters (which are known from the simulation) and combining again using stacking weights to form the final ensemble. The name derives from its similarity to the multi-study paradigm, in which learners are trained on known studies prior to ensembling. Finally, the term Merged will refer to a single forest with $k \times 100$ trees trained on the entire data set. We kept the number of trees in the overall ensemble consistent across methods, so that the comparison consists solely in how the training data is differently used to train the trees in each ensemble. We set the number of trees per forest at 100 (other than the Merged, as previously described) based on the observation that higher number of trees did not significantly improve the prediction results nor alter the relationship between approaches.

3. Simulation Experiments: Strategies and Results

In this section, we use simulations to evaluate the overall behavior of the ensembling approaches described above on a variety of data generating mechanisms and outcome-covariate models that we would expect to find in real genomic data sets. We begin by delineating our choice of data generation and simulation strategy. We then discuss the importance of partitioning the data prior to the training of each component forest, where we particularly focus on the benefits of using clustering algorithms as opposed to other methods. We then examine the robustness of CCWF to realistic data situations, in which we vary parameters such as the signal to noise ratio, the number of true clusters within the data set, and the total sample size. Finally, we examine the effect of ensemble weighting strategy on overall performance, specifically highlighting the advantages of stacked regression weights over simple averaging as well as how the differences in the distribution of weights across the ensembling methods correlate with prediction accuracy. Throughout this section
we report averages over 250 simulations per scenario, with 95% confidence bands computed as mean ±1.96× standard error.

### 3.1 Generating multivariate clustered data

We utilized two primary approaches to generate the necessary clustered data sets for simulations. The first was to draw clusters from multivariate gaussian mixture models, in order to easily simulate many data sets with analytically tractable characteristics. We used the implementation within the R package clusterGeneration, with specific parameters outlined in the following section (Qiu and Joe, 2020). However, a major disadvantage is that simulated clusters using this setup may lack important features of the real biologic clusters for which we would want the methods to work well in practice.

Thus, we additionally considered simulating clustered data sets that more closely mimic what we find in relevant applications. Specifically, we utilized the method proposed by Waller et. al. and implemented in R via the 'monte' function within the fungible package (Waller, 2020). Their algorithm produces artificial plasmodes with clusters that resemble authentic clusters with respect to important features such as cluster size, shape, and orientation. Throughout, we evaluated our ensembling approaches on clusters generated using both methods for a variety of different scenarios, as described below.

### 3.2 Simulation setup

For N = 250 iterations at each set of generative parameters, we simulated a training data set with \( n_{\text{train}} \) number of clusters and \( n_{\text{test}} \) test data sets with two clusters using either the mixture model or the plasmode framework, all with \( n_{\text{coef}} \) number of covariates. At baseline, \( n_{\text{train}} = n_{\text{test}} = 5 \) and \( n_{\text{coef}} = 20 \). Per iteration, we then randomly sampled 10 of these covariates to create a linear data-generating model with gaussian noise, with coefficients drawn uniformly from \([-5, -0.5] \cup [0.5, 5]\) so that each has a non-trivial contribution to the outcome. We additionally considered non-linear relationships of the covariates to the outcome, adding quadratic terms, between-covariate interaction terms, and binarization of the covariates before application of the linear model in order to form a step function. Since the focus of our investigation is to evaluate the effect of feature distribution heterogeneity on ensemble performance, we kept the covariate-outcome relationship relatively similar across clusters, by drawing the amount of coefficient perturbation between clusters uniformly from the interval \([0, .25]\). The size of each cluster was set at baseline to be 500, resulting in training data sets with 2500 total samples. Using either the clusterGeneration or fungible packages, the level of between-cluster separation was set at median values, resulting in clusters with some overlap that would still ostensibly be distinguishable using clustering strategies. All modifications to this baseline strategy are outlined in the relevant results sections.

### 3.3 The importance of data partitioning on prediction accuracy

We commence with an exploration of how the choice of data partitioning method affects the accuracy of the resulting ensemble. The Cluster and Random methods train the component forests on the same number of partitions - however, the composition of each partition is
what constitutes primary difference between the two. The Multi uses a fixed number of partitions corresponding to the true clusters, while the Merged simply uses the bootstrap sampling inherent to the Random Forest algorithm to build each tree. We denote by $k$ the number of partitions used to construct the Cluster and Random, and investigate throughout this section the effect of increasing $k$ on the results from both approaches. We additionally examine whether changes in the distribution of the training clusters influences the accuracy and relationship between all four methods considered.

![Graphs showing percent change in average RMSE from Merged compared to various ensembling approaches for different data-generating scenarios as a function of $k$.](image)

Figure 1: Percent change in average RMSE of ensembling approaches (color labeled) compared to the Merged across different data-generating scenarios, as a function of $k$. The first row depicts results using the non-gaussian cluster simulation approach, while the second row uses a gaussian data generating model. (A.1-A.2) A linear model was used to generate the outcome from the covariates. (B.1-B.2) The binary outcome was created by using a cutoff from the linear model to create a binary step function. (C.1 - C.2) Quadratic terms for two of the variables were added to the linear outcome-generating model.

Figure 1 displays the result of varying both $k$ and the data-generating mechanism for a total of 6 different scenarios. Overall, we observe that the Cluster and Random improve upon ensembling using the true clusters or the entire data set for values of $k$ higher than the true number of clusters. The level of improvement that the $k$-dependent approaches show over the Merged (and Multi) is substantial, typically over 20-30% at optimal values of $k$. On the other hand, the Multi is inconsistent in its relationship to the Merged over the scenarios considered, showing that the perhaps more intuitive approach of splitting the
data into its true clusters does not necessarily produce the best results. The Cluster and Random are robust to changes in the outcome model and the distribution of the data, as evidenced by the similar performance patterns seen over three separate covariate-outcome relationships and two covariate-generating mechanisms. Finally, in the majority of cases, the Cluster exhibits superior accuracy over the Random, indicating that using k-means is generally preferable over randomly partitioning the data. As $k$ increases, the accuracy of both the Cluster and Random improves until finally plateauing, typically at the point in which each forest is being trained on 35-40 observations out of 2500 total. The average depth of the trees within each forest decreases correspondingly with the sample size per partition. Tree depth is a measure of model complexity, indicating that for high values of $k$, we are essentially ensembling locally weak learners in an approach akin to local smoothing.

The differences between the Cluster and Random ensembles reveal the particular advantages of using clustering as the partitioning strategy. The data partitioning step reduces the range of the covariate space used to train each tree, and we see throughout Figure 1 that in general, increasing the number of partitions improves the performance of the ensemble. This additionally supports the observation that for $k$ smaller than the number of true clusters, the Multi approach typically outperforms the Random and Cluster. The manner and efficacy to which this partitioning step is performed correlates with the prediction performance. In fact, when examining the association of prediction accuracy to the range reduction of the covariate space induced by $k$, we find a clear relationship; at the optimal value of $k$, randomly partitioning results in a slightly higher average covariate range than k-means (4.22 CI:(4.13, 4.31) and 3.17 CI:(3.08, 3.26) respectively), while the true clusters have a significantly larger average range (7.33 CI:(7.21, 7.45)). Furthermore, using k-means (or other clustering methods) results in not only greater range reduction but also greater between-cluster separation than by random partitions of the data, which additionally contributes to the better performance of the Cluster over the Random. We conjecture that clustering may allow the learners to be uncorrelated and dissimilar, a property that has been previously shown to be effective in other boosting and sequential ensembling approaches (Friedman, 2002; Schapire, 2003).

It is additionally important to note that projecting the distinct partitions produced by clustering onto the 1-dimensional space corresponding to a single variable results in ranges that are highly overlapping between clusters. This mitigates perhaps the greatest downside to the clustering strategy of minimizing the euclidean distance, as Random Forest lacks the ability to extrapolate beyond the data it is trained on. However, the marginal degree of range restriction for a single variable is highly variable across clusters, allowing in aggregate over all cluster-level forests for total coverage of not only the complete range but also fluctuating relationships between covariates in different regions of the joint distribution. While this may present a slight trade-off by sacrificing accuracy in the areas of highest density for better precision in the tails, the loss is not significant enough to counteract the benefits.

We next examine the implications of these improvements on our understanding of the classic Random Forest algorithm. Each tree within a Random Forest is trained by formulating successive partitions of the bootstrapped covariate space that maximize the amount of information gained by each split. A prediction for a new point is then obtained by averaging the outcomes of the training data in the same leaf node as the test point across all trees. In this way, the Random Forest algorithm can itself be seen as an combination of learners
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across different partitions of the data - however, since the available training data for each learner is simply obtained by bootstrapping, the partitions influencing final predictions are not achieved by optimization of any criterion, simply randomness.

While this is often a very powerful paradigm, the improvement of the Cluster over the Merged indicates that in the presence of heterogeneity in the training data, more useful data partitions for the training of each component tree in the overall ensemble can be obtained. Clustering the data prior to training restricts each forest to a smaller subset of the covariate space. We imagine that, as a result, these forests can more effectively form splits to learn nuances in this restricted space that would not be possible were the same number of total trees trained on the entire data set. Insight into this phenomenon may be gleaned by considering how the bootstrap samples of the data used to train each tree are differentially obtained between the two approaches. A forest trained on a partition mostly comprising of observations from one of the tails of the joint distribution of the covariates will consist of trees trained on bootstrap samples of solely these observations, resulting in a far greater representation of these observations within trees in the overall ensemble than in trees trained on bootstrap samples of the merged data set. Supplementary Figure S1 displays the differences in how the Cluster and Merged learn the underlying covariate-outcome function when there is only one covariate. The Cluster more effectively learns the function at the tails of the covariate distribution whereas the Merged primarily learns the highest density regions.

Interestingly, the estimated clusters produced by k-means do not correspond with the true clusters for either simulation strategy, or when tested on real genomic clustered data. This holds even when the value of $k$ is equal to the number of true clusters. Furthermore, across all values of $k$ considered, each estimated cluster typically (> 90% of time) contains observations from all of the true clusters - as $k$ increases, the total number of observations from each true cluster simply decreases, but there is still full representation. This further supports that the true clusters are not necessarily the best partitions of the data for building ensembles of forests, and that in fact the k-means algorithmic strategy of producing estimated clusters with minimal variance within and maximal variance across is more effective at capturing feature distribution heterogeneity regardless of underlying data structure.

Silhouette analysis is often utilized to choose the optimal value of $k$ for k-means; the $k$ that maximizes the silhouette score is the one for which the ratio of between-cluster variance to within-cluster variance is maximized. We found that the Cluster strategy was more effective than the Merged only if silhouette analysis indicated that the optimal $k$ was greater than 1, regardless of whether the data set was actually constructed to contain true clusters or not. Furthermore, even when varying the separation of the simulated true clusters from mostly overlapping to completely separated, we found no exceptions to this observation. Of course, we do remark that in the case of having completely separated true clusters, it is unlikely that silhouette analysis will indicate the optimal number of partitions to be equal to 1, but regardless, the algorithmic clusterability of the data set is the criterion that matters in determining the efficacy of the Cluster approach, not necessarily the presence of true clusters. We found similar results when applying other clustering methods instead of k-means; in general, the unsupervised clustering step seems to provide a good metric of whether the supervised ensembling step will perform well.
3.4 Robustness of method to realistic data set variety

Our next simulations evaluate the robustness of these methods to a range of data set characteristics likely to be encountered in real data, while holding the value of $k$ constant at the optimal value chosen by Silhouette analysis. We determine how prediction performance is affected by the number of true clusters in training, the sample size of the training set, and the strength of the relationship between the covariates and the outcome. For this set of simulations, we are showing results using a quadratic outcome model and the non-gaussian cluster generating setup, to present a fairly complex and realistic data paradigm.

Figure 2: Percent change in average RMSE of ensembling approaches (color labeled) compared to the Merged across different data-generating scenarios. All simulations used a quadratic outcome and the non-gaussian cluster generating algorithm.  

(a) Varying the magnitude of the coefficients in the outcome-generating model to determine the effect of signal strength on prediction accuracy gains.  

(b) Varying the number of true clusters within the training set, while keeping the total sample size constant at 2500.  

(c) Varying the sample size per cluster, while keeping the total number of clusters per data set constant at 5.

In the simulation used to generate Figure 2a, the norm of the coefficients relating the covariates to the outcome in the quadratic model was varied in order to determine how well the approaches picked up signals of different strength from the covariates. We see that as the signal from the covariates increases, the magnitude of the change in performance from all ensembling methods over the Merged expands significantly, eventually plateauing at rates of improvement ranging from 20-60%. The Cluster is by far the most effective learner, especially at higher coefficient norms, while the Random displays a similar trajectory of
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| Value of k | 2   | 5   | 10  | 20  | 30  | 50  | 70  | 80  |
|------------|-----|-----|-----|-----|-----|-----|-----|-----|
| **Simple Averaging** | 11.93 | 29.97 | 43.60 | 59.63 | 68.17 | 79.09 | 86.65 | 89.48 |
| **Stacked Regression** | -9.88 | -13.35 | -19.73 | -25.21 | -27.73 | -29.99 | -31.96 | -32.27 |

Table 1: Simple averaging vs. stacked regression weights. Percent change in average RMSE compared to Merged for differently-weighted ensembles built on estimated clusters determined by k-means, using the non-gaussian data set simulation framework. The first row shows results for weighting each forest equally and the second row depicts results from using stacked regression weights.

Improvement, albeit significantly lower than that of the Cluster. Furthermore, the much smaller improvement of the Multi over the Merged indicates that increasing the signal does not necessarily signify that the true clusters will more effectively pick it up. This supports the conjecture that reducing the amount of within-cluster variation (as most effectively accomplished by clustering for optimally high values of $k$) allows for more accurate discernment of the covariate-outcome relationship, since it is no longer being obscured by heterogeneity in the distribution of the covariates.

Next, we evaluated the effect of varying the number of true clusters within each training data set while keeping the total sample size constant at 2500. Figure 2b demonstrates that as the number of true clusters increases, the Cluster method remains significantly better than all other approaches, while the performance of the Multi catches up to that of the Random at higher numbers of true clusters. This latter phenomenon makes sense in light of what we have seen before, as the number of true clusters determines the number of forests in the Multi. As illustrated in Figure 1, increasing the amount of ensemble members through $k$ augments prediction accuracy, whereas the Multi was set in those simulations to always include only 5 component forests. However, when the number of true clusters is high, the difference between the Cluster and the other two ensembles remains constant, highlighting that the benefits of clustering persist no matter the true composition of the data.

In the simulation used to generate Figure 2c, we set the number of clusters per training set constant at 5 while increasing the sample size of each data set incrementally from 500-5000. We observe that as the sample size of each cluster grows, the difference in prediction accuracy between the Cluster and the other approaches similarly increases. On the other hand, the Multi becomes less distinguishable from the Merged, primarily because the accuracy of the Merged increases proportionally to the sample size. However, the Cluster and Random methods continue to improve upon the Merged regardless of the sample size, since the optimal number of partitions $k$ increases proportionally with the sample size.

### 3.5 Importance of ensemble weighting strategy on performance

Our next simulations explore the importance of the ensemble weighting strategy on prediction performance. We specifically highlight the importance of using stacked regression weights over equally weighting component learners or other weighting approaches. The weighting step is critical in determining the success of the ensemble; for instance, if we weight the cluster-trained forests either equally or by the inverse of their sample sizes, the resulting
ensembles often perform similarly to the *Merged*, or worse. Table 1 displays the percent change in average RMSE from the *Merged* achieved by ensembles of forests trained on clusters determined by k-means and then combined using either simple averaging or stacked regression weights. We observe that as $k$ increases to its optimally performing value of around 80, the stacking approach continuously advances while equal weighting progressively declines. In fact, the best number of partitions for equal weighting is 2, at which point it is still significantly worse than merging.

This phenomenon indicates that not all estimated clusters from k-means produce accurate predictors, but certain subsets in combination produce better predictions than the *Merged*. Stacking, in the multi-study implementation we use wherein studies are replaced by estimated clusters, up-weights the cluster-specific learners that show the best cross-cluster prediction ability, which likely translates into accuracy and robustness to test data. If a cluster-level forest is performing well on other clusters, this indicates that it has more effectively learned the true covariate-outcome rule and is generalizable to training data dissimilar from its own, as clusters are designed to have as much distributional separation as possible.

Figure 3 displays the distribution of stacking weights across ensembling methods using the gaussian cluster-generating framework and a linear outcome model, although results for the non-gaussian simulations were virtually indistinguishable. For each simulated data set, we isolated the highest weight, and show the distribution in green. The *Cluster* method most strongly up-weights beneficial predictors out of all approaches considered, demonstrating the presence of certain estimated clusters that produce highly generalizable forests. Furthermore, we see significantly more upweighting in the *Cluster* approach as compared to the *Random*, whose stacking weights all occupy a more restricted, and lower, range. Forests within the *Random* approach perform more similarly to each other, which stands to reason given that all the partitions used to train each forest are randomly selected. The benefit of clustering thus lies in producing more optimal partitions for training, although we note through both the results from equally weighting all predictors as well as the distributional range of stacking weights that only some of these clusters produce predictors that are decidedly effective. To the latter point, the *Cluster* produces a larger difference between the most up-weighted forests and the weights given to the rest of the ensemble members than the *Random*. The *Multi* displays the smallest difference of the three, which also corresponds with its worse performance.

Stacking can be considered as an indirect form of reweighting the influence of each training data point on the overall predictor. The clustering step helps the stacking algorithm to identify the most effective points to up-weight by grouping together data that are likely to exert a similar influence. Points belonging to estimated clusters that are not weighted as highly are still necessary for the overall ensemble function, and should not be removed entirely - when we regularized the stacked regression weights using Lasso instead of Ridge, the effect was to zero out the contributions of several clusters per ensemble. The resulting predictors were far more variable in their accuracy across data-generating scenarios, likely because they adapted too strongly to random noise in the training data. Thus, stacking with a Ridge constraint gives more importance to data points in heavily up-weighted estimated clusters while still recognizing the necessity of the remaining clusters to prevent overfitting and promote generalizability.
Figure 3: Distribution of the ensemble weights determined by stacked regression for (a) the Cluster, (b) the Random, and (c) the Multi for \( k = 20 \) and \( k = 80 \) for the first two methods, and 5 true clusters for the latter. We used the gaussian cluster-generation framework. The distribution of the largest weight per ensemble is depicted in green, while the rest of the weights are visualized in purple. Results are shown over 100 iterations at each value of \( k \).

3.6 Extension to Multiple Studies

We next examine whether we can more optimally partition the total amount of data when multiple studies are available for training that measure the same covariates and outcome variable. The traditional multi-study ensembling paradigm is to train a single learner on each study and combine using some weighting strategy, such as stacking (Patil and Parmigiani, 2018). This is analogous to the Multi method when we are able to separate data into its true clusters. We now explore whether training k-means on the the merged data (comprising covariate data from all of the training studies) produces improvements comparatively to the single data set setting. We furthermore evaluate the performance of these approaches on real gene expression data from the CuratedOvarianData repository from Bioconductor in R (Ganzfried et al., 2013). Finally, we explore whether the general strategy of ensembling learners built on clusters also works for Neural Nets, and compare the results to those when using Random Forest.

The general framework for the simulation setup used to create Figure 4 was drawn from Ramchandran et al. (2020) and Patil and Parmigiani (2018). CuratedOvarianData provides data for gene expression meta-analysis of patients with ovarian cancer. In this study, we used all 15 studies in CuratedOvarianData that include survival information without any missing data in the features. For \( N = 250 \) iterations per value of \( k \), we randomly separated the 15 data sets from CuratedOvarianData into 10 training and 5 validation sets. We then generated the outcome using the non-linear model defined in the caption in order to test the ability of the candidate learning methods to detect more difficult covariate-outcome...
Multistudy setting: Comparing performance of various learners

Figure 4: Average RMSE’s of ensembling approaches (color labeled) as a function of $k$ in the multi-study analysis. 20 total covariates, 10 associated with the outcome; nonlinear outcome model of the form $y = \beta^T X + 4.4x_1 - 1.8x_2 + 10\sin(10\pi x_1)$.

relationships. We simulated baseline levels of coefficient perturbation per study as described in the Methods section. Using either Random Forest or Neural Nets as the base learner, we then constructed ensembles using the four main approaches compared throughout this paper: the Merged, Cluster, Random, and Multi. The Multi in this case trained a learner on each study to form the final ensemble. All ensembles were built using stacked regression weights with a ridge constraint.

We commence by discussing the performance of the Random Forest-based ensembles. In the multi-study setting, ensembling based on k-means clustering is significantly more accurate than ensembling based on study membership for values of $k$ higher than the number of training studies. The relationship between approaches follows exactly the pattern we observe in the single clustered data set setting, with the Cluster performing the most effectively, the Random performing on a similar trajectory but less accurately, the Multi at a yet worse accuracy, and the Merged by far the worst of the four. The true cluster or study-membership does not represent the most effective data partitioning for Random Forest; again, it is more effective to partition the data based on minimizing within-cluster heterogeneity and maximizing across. Overall, these results suggest that for either single or multiple training data sets, the Cluster approach should be used for Random Forest learners.

We next investigate the use of Neural Nets in this setting and compare the results with Random forest. Figure 4 displays that the Cluster method with Neural Net component learners improves upon training each learner on the true studies or training a single Neural Net on the merged data. The level of improvement of the Cluster over the Merged is less than that for Random Forest, as the Neural Net Merged learner is significantly more
Figure 5: Squared bias, variance, and MSE of the Merged and Multi learners (color coded) for data sets ranging from 500-5000 total samples (100-1000 samples per cluster). data sets were generated using the gaussian cluster framework. Each panel shows the breakdown for a given sample size.

accurate than its Random Forest counterpart. Interestingly, the Cluster method produces almost identically accurate predictors using either algorithm as its base learner. While the traditional multi-study paradigm, or simply training a single learner on the merged data, favors Neural Nets, Random Forest catches up when trained on estimated clusters. This displays the magnitude of improvement capable by the cluster-based ensemble framework when applied to Random Forest, and further highlights that even when the traditional Random Forest algorithm falls short of the performance of a Neural Network, the Cluster approach can elevate the two to the same level. In our view, the Cluster strategy can itself be compared to a convolutional neural network, in which the estimated clusters represent the convolutional neighborhoods and the stacking weights delineate the relationship between the tree-learning and the stacking layers. While this analogy does not numerically explain the similar performance of the two algorithms, it provides intuitive insight into why we may be seeing these results.

3.7 Examining the bias and variance

Our final set of simulations decomposes the MSE of the Merged and the Multi into its bias and variance terms in order to individually characterize each. As the sample size of the training data set increases, the MSE of both ensembling approaches decreases as expected. However, there is a far more minimal decrease from \( n = 2500 \) to 5000 than from 500 to 2500, indicating that there is an asymptotic limit to how well the ensembles can perform. Most strikingly, across all sample sizes considered, the squared bias term comprises almost the entirety of the MSE while the variance contribution is minimal. All improvements in performance from the Multi over the Merged arise through decreasing the bias of the ensemble - in fact, the variance slightly increases between the two but is proportionally so
small as to have almost no effect. We limit our comparison to the Multi, since this ensemble construction method can be analytically characterized much more easily than the Cluster or Random. These results indicate that the squared bias defines the overall performance of the Multi ensemble, and that any theoretical analysis of this general approach can be largely restricted to the bias term.

4. Data Application

To explore the performance of these classifiers on real biological data with natural feature-outcome relationships, we considered data sets measuring gene expression and clinical data which plausibly contain clusters.

4.1 Low Grade Gliomas (LGG) data set

We applied our methods to the Low Grade Gliomas (LGG) data set within TCGA Network (2015). We considered one binary and one continuous outcome in order to assess the performance of the ensembles on both regression and classification tasks. The binary variable measures the tumor grade, in which the value 0 indicates the presence of a low-grade tumor (WHO grades II and III) and the value 1 indicates high-grade glioblastoma (WHO grade IV). The continuous outcome measures the number of mutations present in each sample. These two outcomes were chosen for their importance in diagnosing and informing the treatment of glioblastoma. We additionally experimented with two different sets of covariate data. The first represents molecular profiling data (for example, measures such as percent aneuploidy and TERT expression), in which there are 513 total patients and 50 covariates. Twelve of the covariates are continuous while the remainder are categorical; missing covariate data was imputed using Random Forest through the mice package in R prior to training. We additionally considered gene expression data for the same set of patients; the original authors previously demonstrated that the patient gene expression data is separable into clusters using unsupervised approaches, so we included this information in our analysis to determine the efficacy of the clusters they discovered within our ensembling paradigm Network (2015).

We used a variable selection and clustering strategy based on mclust (as implemented in the vscc package in R) for the molecular profiling covariate data (Andrews and McNicholas, 2013; Scrucca et al., 2016). We chose this method over k-means due to its simultaneous ability to perform variable selection and cluster the data without prior specification of the number of estimated clusters \(k\), and to additionally display that the general cluster-weighted ensemble framework is robust to the choice of clustering method. mclust performs model-based clustering using Gaussian mixture models, in which the variable selection step chooses the candidate variables that result in estimated clusters with the highest likelihood. The algorithm can handle only uniform data types, so we chose to solely restrict the clustering and variable selection steps to the 12 continuous covariates. No further clustering was necessary for the gene expression data beyond the analysis previously conducted by the original authors. Per iteration, we randomly chose 100 sample points for the test set and used the rest of the samples for training, ultimately repeating this procedure 500 times to obtain the distributional and median measures of prediction accuracy.

For this analysis, we consider modified definitions for the ensembling strategies we have investigated thus far. The Merged will have the same definition as before, representing
Figure 6: Percent change in average RMSE of ensembling approaches (color labeled) compared to the Merged across two sets of covariate data and two different outcomes from the LGG study. The top row shows 500 iterations of splitting the available data into training and test sets, while the second row displays the median over all iterations with associated confidence intervals. (a) Molecular profiling covariate data, mutation count outcome. (b.1) Gene expression covariate data, mutation count outcome. (b.2) Gene expression covariate data, tumor grade outcome.

...a single forest with 500 trees trained on the entire data set with all 50 covariates. We denote by Subset Merged a single forest with 500 trees trained only on the 12 continuous candidate variables used to cluster the molecular profiling data. Sample Weighted indicates first clustering the training data using the vscc package, training a forest with 100 trees on each estimated cluster, and ensembling using weights proportional to the sample size of each cluster. While clusters are determined by only considering the continuous covariates, all 50 covariates are utilized during training. Finally, Stack Ridge represents the clustering and ensembling method described above, instead employing stacked regression weights with a ridge constraint to form the final predictor.

4.2 Results

Overall, Figure 6 illustrates that across combinations of both types of covariate data and outcomes, the clustering methods demonstrate remarkable improvement over the merging approaches. Figure 6A shows the results from the molecular profiling data, in which we observe a median improvement of 20-30% of the ensembles over the merged-based learners.
when predicting the number of mutations. This suggests that the variable selection and model-based clustering strategy in vsc is highly effective for construction of ensembles. Figure 6b highlights the impressive improvement of the Sample Weighted and Stack Ridge over the Merged when considering gene expression data and the continuous mutation count outcome, with median percent changes around or above 75%. As described in the original paper, the clusters previously determined through nonparametric methods were found to align with biologically relevant characteristics. Interestingly, we observe across all scenarios that while the Stack Ridge does improve upon the Sample Weighted, the difference between the two is fairly marginal. This indicates that there are settings in which the choice of weighting scheme does not drastically influence the prediction ability of the ensemble; however, even in this case, the Stack Ridge proves optimal, albeit by a lower margin than in many of our other demonstrative examples. In 6c, we see a greater improvement from the Stack Ridge compared to the Sample Weighted, with decreased but still significant improvements over the Merged. Overall, these results display the remarkable robustness of the CCWF method to different types of outcomes, covariate data, and cluster construction, all in a real-life biological setting.

Finally, we explore the influence of variable importance measures on ensemble performance. We posit that the CCWF approach is most effective when the variables that determine the estimated clusters are not also the variables most associated with the outcome. Otherwise, the true outcome model is obscured within each cluster and the cluster-specific learners are unlikely to generalize. We additionally experimented with simply training ensembles on the variables chosen to cluster over within the molecular profiling data, and obtained significantly worse overall performance. To check whether our conjecture holds within this data set, we examined the variable importance rankings from the Subset Merged of the variables chosen for clustering. The Random Forest algorithm computes the importance of each variable in accurately predicting the outcome in training; these metrics can be used to categorize which variables are most essential and those that have less influence (Archer and Kimes, 2008). We found that there was a median of 20% overlap between the two sets (IQR 0 - 33%); this fairly low level supports our hypothesis that the variables determining the clustering are not important in predicting the outcome within this particular data set. These findings provide insight into when ensembling over estimated clusters is a better strategy over merging.

5. Conclusions

We have demonstrated how to build CCFWs—ensembles of forests trained on estimated clusters, that result in more generalizable and accurate predictors. We improve upon the traditional Random Forest algorithm with equivalent total numbers of trees when the data is naturally divisible by clustering methods. Biological data sets (among several other applications) often contain heterogeneity in the distribution of the features, so we posit that the CCWF method may be potentially useful across a variety of settings. Based on the experiments and data considered here, CCWF are robust to changes in the covariate-outcome model as well as the structure and distribution of the covariate data. We additionally illustrate the utility of this general framework when dealing with multiple data sets, in which we improve upon the existing multi-study ensemble paradigm.
The results of our simulations and data application provide insight into the importance of data partitioning for the Random Forest algorithm. We have demonstrated that it is not necessarily optimal to divide the data based on true clusters (or studies, for the multi-study setting) even if those were known. Interestingly, reducing within-cluster covariate heterogeneity appears to encourage the forest to learn the covariate-outcome rule more efficiently even though the sample size may be greatly reduced from that of the total data set. Finally, we have established that a CCWF has the ability to equal the performance of a complex Neural Net even when the traditional Random Forest algorithm does not.

The utility of weighting each individual tree in the ensembles through stacking weights instead of simply weighting the forests should be explored further. Ramchandran et al. (2020) have previously demonstrated this paradigm to be highly effective within the multi-study setting, and Supplementary Figure S2 shows that similarly, weighting trees within ensembles built on clusters produces improvements compared to the strategy of weighting forests. We chose to limit the scope of the analysis within this paper to weighting forests in order to characterize the general strategy more clearly and present an analytically tractable and generalizable framework. However, future work could more closely examine the effect of individually weighting the trees within ensembles and determine whether the conclusions of this paper still hold in that case.

In subsequent work, Ramchandran and Mukherjee (2021) have begun to investigate the theoretical underpinnings of the success of this approach by analyzing linear least squares and random forest regressions under a linear model. Their primary findings demonstrate that the benefit of ensembling over merging is to reduce the squared bias of the resulting predictor, confirming the empirical result from Figure 5. Furthermore, for Random Forest regression under fixed dimensional linear models, they provide upper bounds on the mean square error that imply a strict improvement of ensembling over merging. Overall, the theoretical insights from their work support the conclusions of this paper.

Random forests are among the most widely used methods in machine learning, with thousands of published applications across a broad spectrum of data types. We identified a simple method to provide substantial improvements. We hope that in the immediate term, this will contribute to concrete advances in predictive ability in many areas. We also believe that the architecture we outlined, as a general concept, may provide further important insight into combining simple and successful machine learning tools via multi-layer approaches.

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