Ensembles of Models and Metrics for Robust Ranking of Homologous Proteins

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Summary.
An ensemble of models, where each model is constructed on a diverse subset of feature variables, is proposed to rank rare class items ahead of majority class items in a highly unbalanced two class problem. The proposed ensemble relies on an algorithm to group the feature variables into subsets where the variables in a subset work better together in a model and the variables in different subsets work better in separate models. The strength of the ensemble of models depends on the algorithm’s ability to identify strong and diverse subsets of feature variables. A second phase of ensembling is achieved by aggregating several ensembles of models each optimized on a diverse evaluation metric. The resulting ensemble is called ensemble of models and metrics. Here, the diverse/complementary evaluation metrics ensure increased diversity among ensembles of models to aggregate. The ensembles are applied to the protein homology data, downloaded from the 2004 KDD cup competition website, to rank proteins in such a way that the rare homologous proteins are found ahead of the majority non-homologous proteins. The ensembles are constructed using feature variables which are various scores from sequence alignments of amino acids in a candidate protein and three dimensional descriptions of a native protein representing functional and structural similarity of proteins. While prediction performances of the ensembles of models are better than the contemporary state-of-the-art ensembles and competitive to the winning procedures of the 2004 KDD cup competition, the performances of the ensemble models and metrics are found on the top of all. In this application, we have
two diverse ensembles of models constructed on two complementary evaluation metrics \emph{average precision} and \emph{rank last}, where the former is robust against ranking \emph{close homologs} and the latter is robust against ranking \emph{distant homologs}. The advantage of using ensemble of models and metrics is that it is robust against both \emph{close} and \emph{distant} homologs.

\textbf{Keywords:} Ensemble, Algorithm, Ranking, Protein Homology.

1. \textbf{Introduction}

Ranking rare class items for highly-unbalanced two class datasets is a common problem in many applications. Some examples are as following: identifying fraudulent activities in credit card transactions (Bhusari and Patil, 2011; Bolton and Hand, 2002), intrusion detection in internet surveillance (Lippmann and Cunningham, 2000), detection of terrorist attacks or threats (Fienberg and Shmueli, 2005; Peeters, 2006), finding information on the world wide web (Gordon and Pathak, 1999), and finding drug-candidate biomolecules in a chemical library (Tomal et al., 2016).

The main application in this paper is the ranking of homologous proteins. Protein homology means biological homology between proteins. Two or more proteins are homologous in a sense that they have a common evolutionary origin. Knowing homology status helps scientists inferring evolutionary sequences of proteins (Koonin and Galperin, 2003). Detection of homologous proteins is of high importance in bioinformatics (Söding, 2005), and has widespread applications in prediction of protein’s function, 3D structure and evolution (Bork and Koonin, 1998; Kinch et al., 2003; Henn-Sax et al., 2001). Evolutionarily related homologous proteins have similar amino-acid sequences and three dimensional structures. Thus, homology modeling refers to comparing proteins based on their amino-acid sequences and three-dimensional structures to predict if the candidate proteins are homologous to the native protein.

Let $y$ be a random variable representing the \emph{class status} of a case, taking value 1 for the rare class and 0 for the uninteresting class. Let $(x_1, x_2, \cdots, x_d)$ be covariates which are measured for all the cases and that can be used for estimating the probability $\pi$ that a $y = 1$, that is, $\pi = E(y|x_1, \cdots, x_d)$. We build our model using training data for which the class status $y$ and the feature variables $(x_1, \cdots, x_d)$ are known. The trained model is then used to predict the unknown class status of test data for which only the feature variables $(x_1, \cdots, x_d)$ are known.

In the case of homology modeling, the variables $(x_1, x_2, \cdots, x_d)$ represent similarity scores between candidate proteins and the native (target) one. The feature variables exploit three-dimensional description of the native protein and sequence-related information of the candidate protein. The target sequence-related characteristics of the candidate protein are: (a) amino acid
frequency profile, (b) prediction of the secondary structure, and (c) prediction of solvent-exposed surface area. The target characteristics for the native protein are: (d) the raw sequence and profile, (e) the actual secondary structure, and (f) the actual exposed surface area. The comparisons of characteristics are converted into various scores - such as raw scores, reverse scores, E-values, Z-scores etc. - are called the feature variables. Details are in Vallat et al. (2009).

Several methods have already been applied in protein homology prediction: (i) Hidden Markov Models (Karplus et al., 1998), (ii) Support Vector Machines, Neural Network (Hochreiter et al., 2007), (iii) Markov Random Fields (Ma et al., 2014) and more. The cited methods are non-ensemble in nature, which train one model only.

Ensemble methods that combine multiple models are generally considered more powerful, in terms of prediction power, than non-ensemble methods (Dietterich, 2000). For example, the overall winner in the protein homology section of the 2004 knowledge discovery and data mining (KDD) competition was the Weka Group (Pfahringer, 2004). Weka† is an open platform software which offers a collection of machine learning algorithms for data mining tasks. The winning group tried a large number of algorithms and selected the top three classifiers: (1) a boosting ensemble (Freund and Schapire, 1997) of 10 unpruned decision trees, (2) a linear support vector machines (Cortes and Vapnik, 1995) with a logistic model fitted to the raw outputs for improved probabilities, and (3) \(10^5\) or more random rules - a variant of random forest (Breiman, 2001). The top three classifiers, where two are already ensemble methods, were aggregated to obtain the winning ensemble.

The history of injecting diversity into models to build powerful ensembles goes back to the 1990s. The most popular method for injecting diversity into models is random perturbations of the training data (Melville and Mooney, 2003; Breiman, 1996, 2001). Another popular method for injecting diversity is through random perturbations and/or clustering of the feature variables (Breiman, 2001; Wang, 2005; Gupta et al., 2014; Tomal et al., 2015). In contrast, injecting diversity into ensembles through diverse evaluation metrics is new. In this article, we injected diversity in our ensemble through both diverse models and metrics.

We propose an ensemble of models as following

\[
\hat{\pi}_M = \frac{1}{p} \sum_{i=1}^{p} f(x_{(i)}),
\]

where each model \(f\) is trained on a subset of feature variables \(x_{(i)} = \{x_{i1}, \cdots, x_{id_i}\}; 1 \leq d_i \leq d\). Here, two subsets of feature variables \(x_{(i)}\) and \(x_{(j)}\); \((i \neq j)\) are disjoint and diverse to each other.

†http://www.cs.waikato.ac.nz/ml/weka/ Accessed November 04, 2016.
The number of models \((1 \leq p \leq d)\) to be ensembled is data dependent and determined adaptively. We propose an algorithm to group the variables into subsets in a way that variables in a group appear to work better together in a model and variables in different groups appear to work better in separate models. The subsets of variables are aggregated in an ensemble by fitting a model \(f\) to each subset and averaging across the subsets. So we call *phalanx* a subset of feature variables which work well together in a particular model rather than in separate models and the ensemble of these models is then called an ensemble of phalanges (EPX). Our work here improves the method proposed by Tomal et al. (2015).

In the type of applications we have in mind the response variable \(y\) is very sparse. Therefore, it is not a good idea to evaluate a model by minimizing misclassification error. For example, in the case of homology status of candidate proteins, approximately 5 out of 1000 proteins are homologous to the native protein. A naive classifier that calls all the candidate proteins “non-homologous” would achieve a 0.5% missclassification error. Instead we evaluate a classification model by its ability to rank the test cases in such a way that the rare cases appear on the top in a list. In highly unbalanced class problems, the ranking performance of a model is better reflected by a hit curve. Consider that there are \(n\) cases in a test set, of which \(h\) are of class 1, which are ranked using their probability of being of class 1. Consider that we have a shortlist of the top \(t \in \{1, 2, \cdots, n\}\) test cases of which \(h_t \in \{0, 1, 2, \ldots, \min(h, t)\}\) are of class 1. Then the plot of \(h_t\) against \(t\) is called a hit curve. Figure (1a) shows three hit curves: \(A\), \(B\) and \(C\). In this example, we have \(n = 861\) and \(h = 50\). The hit curve \(A\) is uniformly better than the hit curve \(B\), as \(h_t^A \geq h_t^B\) at every \(t \in \{1, 2, \cdots, n\}\). So, we want hit curves towards the top left corner with most rapid early rise. On the other hand, the diagonal hit curve \(C\) shows performance similar to random ranking. A hit curve can effectively capture the ranking performance of a method. But the hit curves are difficult to optimize as they do not provide single performance value. Sometimes the hit curves may criss-cross each other making the comparison even more difficult. For example, see Figure (1b) with two hit curves \(D\) and \(E\), in an example with \(n = 949\) and \(h = 6\), crossing each other at several locations.

There are several derived metrics which evaluate the ranking performances of methods by summarizing hit curve into a single numeric value. The use of those metrics make the comparisons of ranking performances among several methods easier. However, some of the metrics focus on towards the beginning of the hit curve and the others focus on towards the tail of the hit curve. In other words, there is considerable diversity among evaluation metrics as well. In this article, we exploit the diversity in metrics to construct ensemble of models and metrics as following:

\[
\pi_{MM} = \frac{\sum_{l=1}^{L} \pi_M(\text{met}[l])}{L},
\]
where $\pi_M(\text{met}_l)$ is the ensemble of models optimized using $l$th metric. Here, the value of $L$, the number of diverse evaluation metrics to ensemble, is application dependent. In this article, the ensemble of models and metrics is obtained by aggregating two diverse ensembles of models: one obtained on optimizing an evaluation metric called \textit{average precision} (see Section 3.1) and the other obtained on optimizing another evaluation metric called \textit{rank last} (see Section 3.2).

The significance of using \textit{average precision} and \textit{rank last} lies in the fact of their applications in protein homology. In this protein homology data, there are candidate proteins where some are close and some are distant homologs to the native proteins. The ensemble of models optimized using average precision (APR) ranks close homologs well and pays less attention to distant or remote homologs. But it is often interesting to detect remote homologs as it can facilitate the assignment of putative function to uncharacterized proteins improving genomic function annotations (Söding, 2005; Eddy, 1998, 2011; Kaushik et al., 2016). Optimization of rank last (RKL) to build an ensemble of models helps us achieving this latter goal. Aggregating two ensemble of models, one based on APR and the other based on RKL, helps us achieving both of the goals. The performances of the aggregated ensemble of models and metrics are robust in detecting both the \textit{close} and \textit{distant} homologous proteins.
Another metric TOP1 (Section 3.3) could also be used to evaluate ranking performance of the ensembles. This metric, however, is not used to optimize the ensemble of models. The reasons are following. First, TOP1 achieves its largest possible value 1 when one of the homologous proteins is ranked in the top position, and is completely ignorant to distant homologs. This metric does not pay any attention to the homologous proteins other than the one ranked in the top position. Thus, a method might not need many predictor variables to do well in this evaluation metric. For example, in a particular run of the ensemble of models optimized using TOP1, only one subset with 10 variables (out of 74) was selected. This phenomenon is intuitively opposite to the ensemble of models which requires many complementary subsets of predictor variables to aggregate. Second, the behavior of the metric TOP1 is not complementary to the metric average precision. It will be further shown in the results section that one can achieve a decent value of TOP1 by maximizing average precision.

The intend of this paragraph is to make our argument of complementary metrics clearer. Table 1 shows behavior of APR, RKL, and TOP1 using a toy example. In this example, we have considered 1000 candidate proteins out of which one is homologous to the native protein. Homologous and non-homologous proteins are denoted by 1 and 0, respectively. Rows 1 to 5 show five possible orderings of the proteins, where the homologous protein is found in the 1st, 3rd, 10th, 100th and 800th positions, respectively. The value of three evaluation metrics APR, RKL, and TOP1 are shown in the last 3 columns. According to orderings numbers 1 to 3, the homologous protein is easy to rank high in the list: The worst ordering ranks the homologous protein in the 10th position with normalized rank 0.1. The ranks are normalized to 0 and 1 in a way that low ranks stand for ranking in the top positions and large ranks stands for ranking in the bottom-down positions. In this cohort of orderings, APR better reflect ranking performances than RKL. For example, in orderings 1 & 3, the change in APR is $\frac{(1.0 - 0.1)/1.0}{100} = 90.00\%$ whereas the change in RKL is $\frac{(3 - 1)/1000}{100} = 0.90\%$. Note that, the maximum possible APR and RKL are 1.0 and 1000, respectively. Using TOP1, to which the maximum value is 1, the change in ranking performances in orderings 1 & 2 and 1 & 3 is straight $\frac{(1 - 0)/1}{100} = 100\%$. Here, TOP1 does not reflect the difference between orderings 2 & 3.

In cases 4 & 5, the homologous protein is tough to rank high in the list: the best possible orderings ranks the homologous protein in the 100th position with normalized rank 0.1. Here, RKL reflects better the difference in ranking performances than APR. The changes in APR and RKL are 0.88% and 87.5%, respectively. In contrast, TOP1 could not detect the change in ranking performances. This example shows that APR and RKL are good choices to reflect complementary
Table 1. A toy example showing complementary behavior of APR and RKL.

| Proteins\Orderings | Ranks | Metrics |
|---------------------|-------|---------|
|                     | 1     | 3 10 100 800 1000 | APR RKL TOP1 |
| 1                   | 1 0 0 0 0 0 | 1.00000 1 1 |
| 2                   | 0 1 0 0 0 0 | 0.33333 3 0 |
| 3                   | 0 0 1 0 0 0 | 0.10000 10 0 |
| 4                   | 0 0 0 1 0 0 | 0.01000 100 0 |
| 5                   | 0 0 0 0 1 0 | 0.00125 800 0 |

behavior of ranking performances.

Unlike the approach of the winning procedures of the 2004 KDD cup competition - where the sole purpose was to achieve top predictive performance on each single metric separately - we have developed methodologies for building robust predictive ensembles by carefully inducing diversity through complementary \(a\) subsets of feature variables/phalanxes and \(b\) evaluation-metrics. While most participants in the the 2004 KDD cup (including the winners) used separate sets of probabilities for each metric we have used here a single set of probabilities because we are seeking a robust model that nearly maximizes the entire hit curve.

The rest of the article is organized as follows. Sections 2 describes the protein homology data and the feature variables. Section 3 defines three evaluation metrics specific to ranking. Section 4 describes the base learner logistic regression model which is the main ingredient of our ensemble. The details of the algorithm of subset/phalanx formation and its optimization through complementary evaluation metrics are presented in Section 5. Section 6 showcases the results of the ensemble of models and metrics and compares to the winners of the 2004 KDD cup competition and other state-of-the-art ensembles. Finally, Section 7 summarizes the results and draws conclusion.

## 2. Data: Protein Homology

The protein homology data are downloaded from the 2004 knowledge discovery and data mining (KDD) cup competition website\footnote{http://osmot.cs.cornell.edu/kddcup/datasets.html}. Registration is required to download the data, submit predictions, and getting results.

In the data file, the columns represent variables and the rows represent proteins. The first column is BLOCK ID where each block relates to one native protein, and each row within a block relates to a candidate protein which is tested for homology against that native protein. Hundreds
of candidate proteins are tested for homology against each native protein. The variable BLOCK ID is apparently less important in a sense that is not used for model building. However, it is required to compute the evaluation metrics (Section 3).

Two important types of variables in this data are the response variable and feature variables. The response variable representing homology status scores 1 if a candidate protein is homologous to the native protein, and 0 otherwise. The feature variables represent structural similarity or match between a candidate protein with known amino acid sequence and a native protein with known structural template. The feature variables are: global sequence alignment, local sequence alignment, global threading, local threading, PSI-BLAST, global secondary structure alignment, sequence to profile matching - global, local exposed surface area alignment, and so forth. For details of the feature variables, please see the appendix of Vallat et al. (2008). There are 74 feature variables in total.

Many native proteins are considered in this protein homology data. A total of 303 native proteins provide BLOCK ID numbers from 1 to 303. The blocks are randomly assigned into two sets of data: training and test. The training set contains 153 native proteins (i.e., 153 blocks) and the test set contains 150 native proteins (i.e., 150 blocks). The homology status is known for the training set, and unknown for the test set. The training and test sets contain 145,751 and 139,658 candidate proteins, respectively.

The minimum, first quartile, median, third quartile and maximum block sizes of the training set are 612, 859, 962, 1048 and 1244, respectively; and for the test set are 251, 847, 954, 1034 and 1232, respectively. The distributions of the training and test block sizes are similar except that the test set contains 3 smaller blocks of sizes 251, 256 and 372. The prediction for the 3 smaller test blocks is not a major issue here as the training blocks are larger than these 3 test blocks. We consider that the training blocks contain sufficient information to build a model which might predict test proteins with reasonable accuracies.

The blocks in the training set contain a few homologous proteins comparing to the non-homologous proteins. The minimum, first quartile, median, third quartile and maximum of within-block-proportions of homologous proteins are 0.00080, 0.00143, 0.00470, 0.01206 and 0.05807, respectively. More than 75% of the training blocks contain at most 2 homologous proteins per 100 candidate proteins. It’s a highly unbalanced classification problem, and appropriate evaluation metrics will be considered in section 3 to tackle this issue.

Some of the feature variables in this protein homology data are useful and some are not. Figure 2 shows two examples. Panel 2a shows the density plots of the feature variable 63 for the homologous
Fig. 2. Density plots of the feature variables 63 (panel a) and 47 (panel b) for the homologous (solid line) and non-homologous proteins (dashed line) in the training data.

proteins (the solid line) and for the non-homologous proteins (the dashed line) in the training data. This variable seems to differentiate the homologous and non-homologous proteins fairly well. There is also evidence of less-informative feature variables. Panel (2b) shows the density plots of the feature variable 47 for the homologous proteins (the solid line) and for the non-homologous proteins (the dashed line) in the training data. This variable does not differentiate the homologous and non-homologous proteins well. The presence of such less-informative feature variables motivates us to perform variable selection in this article.

3. Evaluation Metrics

We evaluate a model by its ability to rank the homologous proteins ahead of the non-homologous proteins. By ranking we mean sequencing candidate proteins using their probabilities of homogeneity to the native protein. The candidate protein with the largest probability of homogeneity is ranked first, followed by the protein with the second largest probability and so on.

Three metrics, specific to ranking rare homologous proteins, are used to evaluate prediction performances of a model. Since the protein homology data come in blocks, each of the three metrics is computed in each block independently. For a metric, the average performance across the blocks is used as the final value of the metric. Thus, in order to perform well a model has to
rank the rare homologous proteins well across many blocks. The definitions of the three evaluation metrics are given below.

3.1. Average Precision

Average precision (APR) is a variant of the metric average hit rate (AHR) (Zhu, 2004), and the application of APR is common in information retrieval. Suppose \( n \) candidate proteins are ranked in a block using their probabilities of homogeneity. Consider that we have a shortlist of top \( t \) (\( \leq n \)) candidate proteins of which \( h \) are homologous to the native protein. Then \( a(t) = \frac{h_t}{t} \in [0, 1] \) is called precision (or hit rate) computed at \( t \), the number of top ranked candidate proteins. Naturally, \( a(t) \) is expected to be as large as possible at every \( t \in [1, n] \). Let \( 1 \leq t_1 < t_2 < \cdots < t_h \leq n \) be the ranking positions of the \( h \) homologous proteins in that block. Then APR is defined as

\[
\text{APR} = \frac{1}{h} [a(t_1) + a(t_2) + \cdots + a(t_h)].
\]  

APR averages “precisions” at the ranking positions of the homologous proteins, and larger APR implies better predictive ranking of the homologous proteins. APR reaches its maximum 1, if all of the homologous proteins are ranked before the non-homologous proteins. If a model ranks more homologous proteins ahead of the non-homologous proteins, APR rewards the model by assigning a bigger number. The lowest value of average precision depends on the number of candidate proteins and proportion of homologous proteins in a block. Our goal is to maximize APR.

APR gives large weight to the homologous proteins rank at the start of a hit curve. The weight becomes smaller at a very fast rate for the homologous proteins rank towards the back of the hit curve. Hence, APR focuses at the start of a hit curve.

3.2. Rank Last

The metric rank last (RKL) gives the rank of the last homologous protein. RKL measures how far the last true homologous protein falls among the sorted candidate proteins. Ties are treated conservatively: if there is a tie, the last protein in the tied group determines rank last. So ties are not helpful. An RKL of 1 means that the last true homologous protein is sorted in the top position. This is excellent but can happen in a block containing one homologous protein only. The maximum possible value of RKL is the size of the block, i.e., the number of candidate proteins in that block. Our goal is to minimize RKL. In summary, RKL is the rank of the homologous protein found at the very back of a hit curve.
3.3. **TOP1**

After sorting the candidate proteins if the top ranked candidate is found homologous to the native protein, TOP1 scores 1, otherwise 0. TOP1 is calculated conservatively when there are ties: If multiple proteins are tied for rank 1, all of them must be homologous to score a 1. If any of the tied proteins is non-homologous, TOP1 scores 0. It is never beneficial to have ties. Our goal is to maximize TOP1. However, it would be difficult to maximize TOP1 if a block contains a few homologous proteins, and *vice versa*. In summary, TOP1 evaluates a hit curve only through the top ranked protein.

The codes for computing the 3 metrics can be downloaded from the KDD Cup Website.¶

4. **Logistic Regression Model**

Let \( y \) be the response variable *homology status* and \((x_1, x_2, \cdots, x_d)\) be the vector of *feature variables*. Consider \( \pi \) denotes the probability of homogeneity of a candidate protein as following

\[
\pi = Pr(y = 1|x_1, x_2, \cdots, x_d). \tag{2}
\]

The logistic regression model, which describes the relationship between the response and the feature variables, is defined as

\[
\pi = E(y|x_1, x_2, \cdots, x_d) = \frac{\exp(\beta_0 + \sum_{i=1}^{d} \beta_i x_i)}{1 + \exp(\beta_0 + \sum_{i=1}^{d} \beta_i x_i)}, \tag{3}
\]

where \( E \) stands for expectation on the response variable \( y \) conditioned on the vector of feature variables \((x_1, x_2, \cdots, x_d)\). The model parameters \( \beta_0 \) and \( \beta_i \ (i = 1, \cdots, d) \) are called regression coefficients.

Considering Bernoulli as the distribution of \( y \) with mean \( \pi \), the model parameters are estimated using *maximum likelihood method* applied to the training data. The \( R \) statement `glm` of the package MASS is used to fit the model. The feature variables corresponding to the test data are then sent down the fitted model to obtain probability of homogeneity. The test probability of homogeneity is then uploaded to the 2004 KDD Cup website to get the numbers for APR, RKL and TOP1.

The reasons for using logistic regression model in this application are the following. First, the group used logistic regression model in predicting protein homology. The group comprised of Ruben Zamar, William Welch, Guohua Yan, Hui Shen, Ying Lin, Weiliang Qiu, Fei Yuan of the University of British Columbia did relatively well in the 2004 KDD cup competition in predicting protein homology. The group used logistic regression model

¶[http://osmot.cs.cornell.edu/kddcup/metrics.html](http://osmot.cs.cornell.edu/kddcup/metrics.html) Accessed November 04, 2016.
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for the prediction, and so did we in this article. Second, the fitting of logistic regression model is computationally much cheaper than other models such as random forests.

5. Algorithm of Subset/Phalanx Formation

This section describes the algorithm of phalanx formation (APF) using logistic regression model (LRM). The APF has three basic steps: (1) Filtering predictor variables: The $d$ predictor variables are filtered down to $s \leq d$ predictors, (2) Merging predictors into phalanxes: The $s$ post-filtered predictors are clustered hierarchically into $c \leq s$ candidate phalanxes, and (3) Filtering candidate phalanxes: The $c$ candidate phalanxes are filtered down to $p \leq c$ phalanxes.

The APF is an updated version of the algorithm proposed by Tomal et al. (2015). The old algorithm requires repeated fits of random forests. But random forests itself is fairly computationally demanding and the repeated fits of RF increases the computational time substantially. In this new APF, a popular and widely used logistic regression model is incorporated to form the subsets and to build the ensemble. The goals are three-folds: (i) improving the performance of the ensemble of models in terms of predictive ranking, (ii) reducing computational burden of the algorithm, and (iii) showing that the ensemble of models is adaptable to a base learner other than random forests.

Besides, the new algorithm optimizes two complementary evaluation metrics - average precision and rank last - independently to form the phalanxes. This shows that the algorithm can be adapted to optimize diverse evaluation metrics. Let $a$ and $r$ represent average precision and rank last, respectively. The optimization of APF by maximizing $a$ will be explained in details, and by minimizing $r$ will be introduced briefly.

1. Filtering predictor variables. The vector of predictor variables is denoted by $(x_1, x_2, \cdots, x_d)$, where $d = 74$. A predictor variable $(x_i, i = 1, \cdots, d)$ is filtered out if it is: (i) weak by itself, (ii) weak when putting together with other variables, and (iii) weak when ensembling with other variables.

To detect whether the performance of a predictor variable is weak, the reference distribution of $a$ is determined using random permutation. In step one, the orders of the candidate proteins are recorded within each block. In step two, the response variable $y$ is randomly permuted. In step three, the metric $a$ is computed and averaged over the blocks. The reference distribution of $a$ is then obtained by repeating that second and third steps many (2000, here) times. Finally, $\alpha$th quantile ($\alpha \in [0, 1]$) and median - $a_{\alpha}$ and $a_{0.50}$ - of the reference distribution of $a$ are recorded.

We record the indexes of a random $v$-fold cross-validation (CV) defined at the block level. In [http://stat.ubc.ca/~will/ddd/kdd_result.html](http://stat.ubc.ca/~will/ddd/kdd_result.html) Accessed November 04, 2016.
this work, we have considered $v = 10$. This cross-validation is used to evaluate every models during phalanx formation. Note that the old algorithm uses sub-optimal out-of-bag (OOB) samples in random forests to evaluate models during phalanx formation. The reason for using OOB samples is to avoid computational expenses of multiple fits of random forests in cross-validation.

For each predictor variable $x_i, i = 1, 2, \ldots, d$, fit an LRM and obtain cross-validated probability of homogeneity vector $\hat{\pi}(x_i)$. The strength of the $i$th predictor variable $x_i$ is reflected through the metric $a_i = a(\hat{\pi}(x_i))$. The higher the values of $a_i$, the stronger the strength of the $i$th predictor is. Note that the old algorithm uses random forests as the base learner. As LRM is computationally fast, the near-optimal cross-validated estimate of the evaluation metric $a$ is now feasible.

To determine if the performance of a predictor variable $x_i$ is strong while putting together in a model with another variable $x_j, j \neq i$, fit an LRM using $x_i \cup x_j$ and obtain CV probability of homogeneity vector $\hat{\pi}(x_i \cup x_j)$. The joint strength of $x_i$ and $x_j$ is reflected through the evaluation metric $a_{ij} = a(\hat{\pi}(x_i \cup x_j))$. The larger the values of $a_{0.50} + a_{ij} - a_j$, the stronger the marginal strength of $x_i$ is while putting together in a model with another predictor variable $x_j, j \neq i$.

The predictor variable $x_i$ is ensembled with another predictor variable $x_j, j \neq i$ by averaging individual probability of homogeneity vectors and computing evaluation metric as $a_{ij} = a((\hat{\pi}(x_i) + \hat{\pi}(x_j))/2)$. The larger the values of $a_{0.50} + a_{ij} - a_j$, the stronger the marginal strength of $x_i$ is while ensembling with $x_j, j \neq i$.

Combining all 3 aspects, the $i$th predictor variable $x_i$ is considered weak/noise and filtered out if

$$\max[a_i, a_{0.50} + a_{ij} - a_j, a_{0.50} + a_{0.50} - a_j] < a_{\alpha} ; \forall j(\neq i) = 1, 2, \ldots, d,$$

where $\alpha = 0.95$ and $a_{\alpha}$ is the 95th quantile of the reference distribution of $a$.

While optimizing APF by minimizing $r$, the $i$th predictor variable $x_i$ is considered weak/noise and filtered out if

$$\min[r_i, r_{0.50} + r_{ij} - r_j, r_{0.50} + r_{0.50} - r_j] > r_{\alpha} ; \forall j(\neq i) = 1, 2, \ldots, d,$$

where $\alpha = 0.05$ and $r_{\alpha}$ is the 5th quantile of the reference distribution of $r$.

After filtering, a vector of gleaming predictor variables $(x_1, x_2, \ldots, x_s), s \leq d$ is passed to the next step merging predictors into subsets/phalanxes. The presented step offers non-aggressive filtering of the predictor variables. In other words, it ensures that every useful predictor variable gets its due chance to be used in the final ensemble of models or phalanxes.

2. Merging predictors into subsets/phalanxes. Assign $x_i$ to $g_i$, where $g_i$ is a set of predictor variables. At start, each set contains one predictor variable only.
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The APF uses LRM as the base learner, and the performance of an LRM might degrade from its optimal in the presence of unimportant predictors. In order to cluster only the important predictors in the phalanxes and thus to avoid mixing up unimportant predictors, the following criterion is minimized

\[ m_{ij} = \frac{\max(a_{ij}, a_i, a_j)}{a_{ij}} \]

over all possible pairs \((i, j); j > i = 1, 2, \cdots, s\). If \(a_{ij} > \max(a_{ij}, a_i, a_j)\), the joint performance of the groups of predictors \(g_i\) and \(g_j\) is better than their ensemble performance

\[ a_{ij} > a_{ij} \quad (4) \]

and individual performances

\[ a_{ij} > a_i \quad \text{and} \quad a_{ij} > a_j. \quad (5) \]

When both (4) and (5) hold, \(m_{ij}\) is less than 1 and the groups \(g_i\) and \(g_j\) are merged together. After each merge, the number of groups \(s\) is reduced down by 1, and one of the new groups is the union of the two old groups. The algorithm continues until \(m_{ij} \geq 1\) for all \(i, j\), suggesting that merging either degrades individual performances or their ensembling performance. Note that the old algorithm in Tomal et al. (2015) might appear suboptimal as it minimizes \(m_{ij} = a_{ij}/a_{ij}\), and by which justifies only (4) and ignores (5).

While optimizing APF by minimizing \(r\), the following criterion is maximized

\[ m_{ij} = \frac{\min(r_{ij}, r_i, r_j)}{r_{ij}} \]

over all possible pairs \((i, j); j > i = 1, 2, \cdots, s\). Here, the two groups of variables \(g_i\) and \(g_j\) are merged if \(m_{ij} > 1\).

Assign \(s \rightarrow c\) and \(g_i \rightarrow x_i\) and pass the vector of candidate phalanxes \((x_1, \cdots, x_c)\) to the filtering candidate phalanxes step.

3. Filtering candidate phalanxes. The APF identifies candidate phalanxes that help all other phalanxes in the final ensemble. The candidate phalanxes that do not help other phalanxes in the final ensemble are filtered out. To detect weak phalanxes to filter, the following criterion is minimized

\[ f_{ij} = \frac{a_{ij}^c}{\max(a_i, a_j)} \]

over all possible pairs of candidate phalanxes \((i, j); j > i = 1, 2, \cdots, c\). If \(a_{ij}^c < \max(a_i, a_j)\), the ensembling performance of the \(i\)th and \(j\)th candidate phalanxes \(x_i\) and \(x_j\) is weaker than that of the top performing individual phalanx. Equality of \(a_{ij}^c\) and \(\max(a_i, a_j)\) shows that the ensemble of the two does not improve individual performances. In these cases, the criterion \(f_{ij}\) is less than
or equal to 1 ($f_{ij} \leq 1$) and the weak phalanx is filtered out: If $a_i \leq a_j$, the $i$th phalanx is filtered out; otherwise, the $j$th phalanx is filtered out. After filtering a phalanx, the number of candidate phalanxes $c$ is reduced down by 1. The filtering of phalanxes then proceed hierarchically until $f_{ij} > 1$ or $c = 1$. Such filtering always keeps the strongest candidate phalanx, and all phalanxes in the set $(x_1, x_2, \cdots, x_p)$ help all others.

The old algorithm keeps a candidate phalanx in the final ensemble if the phalanx is strong by itself

$$a_i \geq a_\alpha,$$

or strong in an ensemble with any other phalanx

$$a_{0.50} + a_{ij} - a_j \geq a_\alpha \quad \text{for at least one } j(\neq i) = 1, 2, \cdots, c.$$

The old algorithm is vulnerable to including a phalanx that is strong individually but harmful to other phalanxes in the ensemble. At the same time, a retained phalanx can be helpful to some and harmful to the other phalanxes. Such weaknesses of the old algorithm are taken care of in this new APF.

While optimizing the algorithm by minimizing $r$, the following criterion is maximized

$$f_{ij} = \frac{r_{ij}}{\min(r_i, r_j)}$$

over all pairs $(i, j); j > i = 1, 2, \cdots, c$. Here, a candidate phalanx is filtered if $f_{ij} \geq 1$. Finally, APF outputs a set of final phalanxes $(x_1, x_2, \cdots, x_p)$.

### 5.1. Ensemble of Models/Phalanxes

Let $\hat{\pi}(x_i)$ be the probability of homogeneity vector obtained from an LRM applied to the subset $x_i$. The probability of homogeneity vector for the ensemble of models (EM) is obtained by averaging individual probability vectors as following:

$$\hat{\pi}_M = \frac{\hat{\pi}(x_1) + \hat{\pi}(x_2) + \cdots + \hat{\pi}(x_p)}{p}. \quad (6)$$

This probability vector $\hat{\pi}_M$ is used to compute evaluation metrics for EM.

### 6. Results

To construct phalanxes, the algorithm is run on the protein homology training data. Table 2 shows the total number of variables, post-filtered variables, candidate phalanxes and post-filtered phalanxes. The algorithm is independently optimized twice, first by maximizing APR and second by minimizing RKL.
Table 2. Total number of variables, post-filtered variables, candidate phalanxes, and post-filtered phalanxes obtained after running the algorithm of phalanx formation to the protein homology training data. The algorithm is independently optimized using average precision (APR) and rank last (RKL).

| Metrics | Number of Variables | Number of Phalanxes |
|---------|---------------------|---------------------|
|         | Total | Post-filtered | Candidate | Post-filtered |
| APR     | 74    | 74           | 5         | 3            |
| RKL     | 74    | 74           | 7         | 2            |

While optimizing the algorithm with respect to APR, none of the 74 variables were filtered out. The 74 post-filtered variables are then clustered into 5 candidate phalanxes of which 3 passed the filtering. A total of 64 variables survived eventually, and phalanxes 1, 2 and 3 bagged 36, 23 and 5 variables, respectively.

When optimized using RKL, the algorithm filtered none of the 74 variables. The 74 post-filtered variables are then clustered into 7 candidate phalanxes of which 2 survived filtering. A total of 56 variables survived eventually, and phalanxes 1 and 2 bagged 29, 27 variables, respectively.

Given the phalanxes, the ensemble of models (EM) is obtained as presented in equation 6. The results of EM relating to APR will be presented first followed by the results relating to RKL.

6.1. Ensemble of Models - Optimized on APR

The second column of Table 3 shows cross-validated (10-fold) training average precisions for the three phalanxes and for the ensemble of models/phalanxes (EM-APR). The 10-fold cross-validation is defined at the block level of the training data. The average precisions for the first, second and third phalanxes are 0.7939, 0.7847 and 0.7808, respectively. As larger values of average precision imply better predictive ranking, the ensemble of models (EM-APR) with average precision 0.8091 shows an improvement over the three individual models/phalanxes.

Figure 3 shows the scatter plots of phalanx 2 versus phalanx 3 based on a 10-fold cross-validated training probabilities of homogeneity. The reason for choosing phalanx 2 and phalanx 3 is the clearer reflection of diversity in their scatter plots. Panels (3a) and (3b) are for the homologous and non-homologous proteins, respectively, against the target native proteins. Note that proteins with larger probabilities of homogeneity are ranked higher in the sequence.

Both phalanxes 2 and 3 are able to rank a good proportion of the homologous proteins: The first...
Fig. 3. Scatter plots of phalanx 2 versus phalanx 3 obtained after maximizing average precision (APR). The plots are obtained from a 10-fold cross-validated training probabilities of homogeneity. The panels (a) and (b) are for homologous and non-homologous proteins, respectively, against the target native proteins.

top-right and second top-right corners of panel 3a contain 55.09% and 58.80% homologous proteins of all of the homologous proteins in the training data, respectively. The ranking accuracies of the two phalanxes are very high: The first top-right and second top-right corners of panel 3a contain 99.31% and 98.83% homologous proteins of all of the proteins within each corner, respectively. It is also observed that some of the homologous proteins are hard to rank high (remote homologs): The bottom-left corner of panel 3a contains 24.38% homologous proteins of all the homologous proteins in the training data. Within this cell there are 0.22% and 99.78% homologous (panel 3a) and non-homologous (panel 3b) proteins, respectively. The two phalanxes are diverse which is reflected through the location of homologous proteins in the top-left and bottom-right corners. Similar results are obtained in the other scatter plots (phalanx 1 versus phalanx 2 and phalanx 1 versus phalanx 3). Such diversity among phalanxes helps to improve overall performance of the ensemble: If one phalanx fails to rank one homologous protein well, the other phalanx ranks that protein high up and so does their ensemble.

The logistic regression model corresponding to the 3 phalanxes are applied to the test proteins and 3 probability of homogeneity vectors are recorded. The 3 probability of homogeneity vectors are averaged over 3 phalanxes to obtain a probability of homogeneity vector for the ensemble of
Three phalanxes of variables are obtained by maximizing average precision (APR). The numbers in columns 2 and 3 are the training (10-fold cross-validation) and test APRs for the three phalanxes and for the ensemble of phalanxes (EM-APR). The top performance is highlighted in dark gray.

| Phalanxes | Average Precisions |
|-----------|--------------------|
| Train (CV) | Test               |
| 1         | 0.7939             | 0.8001             |
| 2         | 0.7847             | 0.7832             |
| 3         | 0.7808             | 0.7958             |
| EM-APR    | 0.8091             | 0.8398             |

models/phalanxes (EM-APR). The vectors of probabilities are submitted to the 2004 KDD Cup website to obtain numbers for APR. The column 3 of Table 3 shows average precisions of 0.8001, 0.7832, 0.7958 and 0.8398 for phalanxes 1, 2, 3 and EM-APR, respectively. It is evident that the ensemble secured a very good average precision of 0.8398 and outperformed individual phalanxes.

It is diversity and strengths of individual phalanxes which helped to obtain such a good ensemble EM-APR. The metrics APR and RKL measure two completely opposite characteristics of ranking performance. The next subsection is intended to show that the algorithm of subset formation is generalizable to other metric such as RKL as well, where the algorithm is optimized by minimizing the metric.

6.2. Ensemble of Models - Optimized on RKL

Optimization of the algorithm of subset formation by minimizing rank last (RKL) resulted in two phalanxes. Ten-fold cross-validated training RKLs for the two phalanxes and for their ensemble (EM-RKL) are shown in column 2 of Table 4. The RKLs for phalanxes 1, 2 and EM-RKL are 59.203, 54.320 and 50.726, respectively. As smaller values of RKL imply better predictive ranking, we claim that the ensemble improves over the individual phalanxes.

Figure 4 shows the scatter plots of cross-validated probabilities of homogeneity for phalanx 1 and phalanx 2. Panels (4a) and (4b) are for the homologous and non-homologous proteins, respectively, against the target native proteins. The first top-right, second top-right, and bottom-left corners
Ensembles of Models and Metrics

Fig. 4. Scatter plots of probabilities of homogeneity for two phalanxes obtained by minimizing rank last (RKL). The plots are obtained from a 10-fold cross-validated training probabilities of homogeneity. Panels (a) and (b) are for the homologous and non-homologous proteins, respectively, against the target native proteins.

Panels of panel 4a contain 59.95%, 65.36%, and 20.22% homologous proteins, respectively, of all of the homologous proteins in the training data. They contain 98.98%, 98.03%, and 0.18% homologous proteins, respectively, of all the proteins within each cell. The numbers for the first and second top-right corners show that the combined strength of phalanx 1 and phalanx 2 are good as they contain more homologous proteins than their counterparts in Figure 3. Note that the bottom-left corner contains less proportion of homologous proteins than its counterpart in Figure 3. This shows that the EM-RKL is good in terms of bottom ranked (i.e., remote) homologous proteins. However, EM-RKL also pulls non-homologous proteins high-up in the list (panel 4b).

Phalanxes 1 and 2 reflect moderate level of diversity as the bottom-right and top-left corners of panel 4a contain a handful of homologous proteins. We speculate that the strengths of the phalanxes 1 and 2 may overturn moderate diversity to build a strong ensemble.

The 3rd column of Table 4 shows test results for phalanxes 1, 2 and their ensemble EM-RKL. Phalanxes 1, 2 and ensemble EM-RKL produced RKLs of 67.553, 56.927 and 54.567, respectively. The results show that the ensemble EM-RKL outperforms individual models/phalanxes in terms of RKL.
Table 4. Two phalanxes are obtained by minimizing rank last (RKL). The numbers in columns 2 and 3 are the training (ten-fold cross-validation) and test RKLs for the two phalanxes and for the ensemble of phalanxes (EM-RKL). The top performance is highlighted in dark gray.

| Phalanxes | Rank Lasts |
|-----------|------------|
|           | Training (CV) | Test     |
| 1         | 59.203      | 67.553   |
| 2         | 54.320      | 56.927   |
| EM-RKL    | 50.726      | 54.567   |

6.3. Ensemble of Models and Metrics

We first show that the ensembles of models EM-APR and EM-RKL are diverse to each other, and then construct ensemble of models and metrics EMM-APR&RKL as following

\[ \hat{\pi}^{\text{MM}} = \frac{\hat{\pi}_M^{(\text{APR})} + \hat{\pi}_M^{(\text{RKL})}}{2} \]

This probability vector \( \hat{\pi}^{\text{MM}} \) is used to compute evaluation metrics for EMM-APR&RKL.

The ensembles of models optimizing APR and RKL both provide good ranking performances for the test proteins. The reason for such good performances is that the ensembles aggregate over strong and diverse phalanxes. Here, we will show that the two ensembles EM-APR and EM-RKL are diverse too, and ensembling across them improves ranking performances for the test proteins as well.

The columns 2 to 4 of Table 7 show the 10-fold cross-validated training performances of EM-APR, EM-RKL and their ensemble EMM-APR&RKL. The second column shows APRs of 0.8091, 0.7975 and 0.8159 for EM-APR, EM-RKL and EMM-APR&RKL, respectively. As the larger values of average precision imply better predictive ranking, the aggregated ensemble EMM-APR&RKL improves over individual ensembles. The second column shows TOP1s of 0.8431, 0.8235 and 0.8497 of EM-APR, EM-RKL and EMM-APR&RKL, respectively. As like average precision, the aggregated ensemble EMM-APR&RKL improves over individual ensembles in terms of TOP1 as well. The smaller values of rank last imply better predictive ranking. The corresponding RKLs of EM-APR, EM-RKL and EMM-APR&RKL are: 62.268, 50.726 and 50.059, respectively. The aggregated ensemble EMM-APR&RKL shows improvement over EM-APR and EM-RKL.

Figure 5 shows scatter plots of probabilities of homogeneity for EM-APR and EM-RKL based
Fig. 5. Scatter plots of EM-APR versus EM-RKL from 10-fold cross-validated training probabilities of homogeneity. Panels (a) and (b) are for the homologous and non-homologous proteins, respectively, against the target native proteins.

on a 10-fold cross-validation of the training blocks. Panels (a) and (b) are for the homologous and non-homologous proteins, respectively, against the target native proteins. The disagreement between EM-APR and EM-RKL is visible in this plot: EM-RKL assigns larger probability of homogeneity to the proteins than EM-APR. This disagreement may be considered as diversity in probabilities between EM-APR and EM-RKL. The following table makes the argument more clear.

Table 5 shows the number of winnings of EM-APR and EM-RKL over the other in various ranking scenarios. The ranking scenarios are constructed from the ranks of the aggregated ensemble EMM-APR&RKL. Note that EMM-APR&RKL is the average of the two ensembles of models EM-APR and EM-RKL. The ranks are normalized to 0 and 1 in a way that low ranks stand for ranking in the top positions and large ranks stands for ranking in the bottom-down positions. The first column shows 4 ranges of ranks based on three quartiles: 0.00000, 0.00264 and 0.02051. The winning numbers in the four scenarios are highlighted in dark gray. In the first scenario [0.00000, 0.00264), where the homologous proteins are very easy to rank high, EM-APR wins over EM-RKL by a big margin. In the second scenario [0.00264, 0.00868), where the homologous proteins are relatively easy to rank high, EM-APR wins over EM-RKL. In the third scenario [0.00868, 0.02051), where the homologous proteins are relatively hard to rank high, EM-RKL wins over EM-APR. In the fourth
Table 5. Number of winnings of EM-APR and EM-RKL over the other in various ranking scenarios poses by the aggregated ensemble EMM-APR&RKL. The first column shows 4 ranges of ranks based on three quartiles: 0.00264, 0.00868 and 0.02051. The ranks are normalized to 0 and 1 in a way that low ranks stand for ranking in the top positions and high ranks stands for ranking in the bottom-down positions. The winning numbers in the four scenarios are highlighted by dark gray.

| Range of Ranks       | Easy/Tough | H. Proteins | RKL-Best | Equal | APR-Best |
|----------------------|------------|-------------|----------|-------|----------|
| [0.00000, 0.00264)   | Very Easy Cases | 323         | 41       | 223   | 59       |
| [0.00264, 0.00868)   | Easy Cases  | 325         | 105      | 103   | 117      |
| [0.00868, 0.02051)   | Tough Cases | 323         | 142      | 63    | 118      |
| [0.02051, 0.50000)   | Very Tough Cases | 325         | 188      | 34    | 103      |
| [0.50000, 0.00000)   | All Cases   | 1296        | 476      | 423   | 397      |

scenario [0.02051, 0.50000), where the homologous proteins are very hard to rank high, EM-RKL wins over EM-APR by a big margin. In a nutshell, EM-APR rank easy to rank homologous proteins better than EM-RKL, and vice versa. Hence, the two ensembles of models EM-APR and EM-RKL are diverse to each other.

We now focus on checking robust ranking performances by the aggregated ensemble EMM-APR&RKL. The robustification would depend on the complementary behavior of EM-APR and EM-RKL in ranking homologous proteins. First we claim that (i) when the homologous proteins are easy to rank at the start of the list, optimization through APR is preferable, (ii) when some of the homologous proteins are hard to rank at the start of the list, optimization through RKL is preferable. Four examples are provided below.

Table 6 shows cross-validated APR, TOP1 and RKL for EM-APR, EM-RKL and EMM-APR&RKL for the 4 training blocks 95, 216, 96 and 238. In each block, the top performance among EM-APR and EM-RKL is marked by dark gray.

The homologous proteins in the two blocks 95 and 216 are relatively easy to rank high as the largest normalized rank by any method is 0.0098. In another word, the proteins in those two blocks are close homologs to their respective native proteins. In those blocks EM-APR performs better than EM-RKL. The other two blocks 96 and 238 show difficulties in ranking homologous proteins: the smallest normalized rank by any method is 0.289. In another word, some of the proteins are distant homologs to their respective native proteins. In the latter two blocks EM-RKL outperforms EM-APR.

1. Ranking close homolog in Block 95. A small change in ranks of the homologous proteins in
the top positions causes large change in APR, and an ensemble that optimizes APR provides better predictive ranking. The block 95 contains 1120 candidate proteins out of which 1 is homologous to the native protein. The ensembles EM-APR and EM-RKL rank this homologous protein in the first and eleventh positions, respectively. As a result, the APR of EM-APR and EM-RKL are 1.0000 and 0.0909, respectively. The change in the two APR is \((1.0000 - 0.0909)\times 100 = 90.91\%\). On the other hand, the two RKLs are 1 and 11, respectively, and the change in the two RKL is only \(((11 - 1)/1120)\times 100 = 0.89\%\).

2. **Ranking close homologs in Block 216.** The block 216 contains 1068 candidate proteins out of which 3 are homologous to the native protein. The ensemble EM-APR ranks the three homologous protein in the first, second and fourth positions; whereas the other ensemble EM-RKL ranks them in the first, second and sixth positions. As a result of such ranking, the APR for EM-APR and EM-RKL are 0.9167 and 0.83333, respectively. The change in the two APR is 8.34%. On the other hand, the RKL for EM-APR and EM-RKL are 4 and 6, respectively, and the change in the two RKL is only 0.19%. The change in ranks of the homologous proteins is better reflected by APR than RKL. And an ensemble which optimizes APR is recommended.

3. **Ranking distant homolog in Block 96.** The block 96 contains 974 candidate proteins out of which 2 are homologous to the native protein. The ensemble EM-APR ranks the two homologous proteins in the 4th and 492th positions; whereas EM-RKL ranks them in the 4th and 394th positions. Here, the homologous proteins that are ranked high and bottom in the sequence are close and distant homologs, respectively. The ranking performances of EM-APR and EM-RKL in terms of APR are 0.1270 and 0.1275, respectively. The change in the ranking performances through APR is only 0.05%. The RKL of EM-APR and EM-RKL are 492 and 394, respectively, and the change in the ranking performances is 10.06%. One of the homologous proteins was hard to rank, and EM-RKL did better ranking than EM-APR as the change in ranking performances was better reflected by RKL.

4. **Ranking distant homologs in Block 238.** This block contains 861 candidate proteins out of which 50 are homologous to the native protein. A handful of proteins of this block are ranked high by both of the methods. However, some of the homologous proteins are not easy to rank high. That is, there are some close homologs and some distant homologs. For example, EM-APR and EM-RKL rank the last homologous protein in the 584th and 249th positions, respectively. The changes in ranking performances of EM-APR and EM-RKL are better reflected by RKL (38.91%) than APR (21.6%), and hence the ensemble of phalanxes which optimizes RKL provides better predictive ranking.
Table 6. Cross-validated APR, TOP1 and RKL for EM-APR, EM-RKL and EMM-APR&RKL for the 4 training blocks 95, 216, 96 and 238. In each block, the top performance among EM-APR and EM-RKL is marked by dark gray.

| Blocks | # Proteins | # H. Proteins | Methods          | Metrics        |
|--------|------------|---------------|------------------|----------------|
|        |            |               | APR   | TOP1 | RKL   | APR   | TOP1 | RKL   | APR   | TOP1 | RKL   |
| 95     | 1120       | 1             | EM-APR | 1.0000 | 1   | 1     | 0.0909 | 0   | 11    | 1.0000 | 1   | 1     |
|        |            |               | EM-RKL | 0.9167 | 1   | 4     | 0.8333 | 1   | 6     | 0.9167 | 1   | 4     |
| 216    | 1068       | 3             | EM-APR | 0.1270 | 0   | 492   | 0.1275 | 0   | 394   | 0.1274 | 0   | 415   |
|        |            |               | EM-RKL | 0.5651 | 1   | 584   | 0.7811 | 1   | 249   | 0.7125 | 1   | 346   |

The two metrics APR and RKL are complementary to each other: the former focuses at the start of the list and the latter focuses at the bottom of the list. If a block contains homologous proteins that are ranked at the start of the sequence, the APF is recommended to be optimized by maximizing APR. On the other hand, if a block contains some homologous proteins that are ranked far down the sequence, the APF is recommended to be optimized by minimizing RKL. In the first and second situations EM-APR and EM-RKL would do better ranking, respectively, than the other. However, we don’t know the difficulty level of ranking homologous proteins in the test blocks in advance. How would then one robustify performances of EM-APR and EM-RKL? Our proposal is aggregating over EM-APR and EM-RKL.

Table 6 shows cross-validated APR, TOP1 and RKL for EMM-APR&RKL as well. For the easy-to-rank blocks 95 and 216, the performance of EMM-APR&RKL is exactly the same as the top performer EM-APR. For the hard-to-rank blocks 96 and 238, the performance of EMM-APR&RKL is closer to the top performer EM-RKL. As we have both hard-to-rank and easy-to-rank blocks in this protein homology data, aggregation of EM-APR and EM-RKL is recommended.

The results of EM-APR, EM-RKL and EMM-APR&RKL corresponding to the test proteins are produced in columns 5 to 7 of Table 7. The fifth column shows APRs of 0.8398, 0.8349 and 0.8437 for EM-APR, EM-RKL and EMM-APR&RKL, respectively. The ensemble EMM-APR&RKL im-
Table 7. Ten-fold cross-validated training performances and test performances - in terms of APR, TOP1 and RKL - of the ensemble of phalanxes optimizing APR (EM-APR), ensemble of phalanxes optimizing RKL (EM-RKL), and their ensemble (EMM-APR&RKL). For each metric, the top performance is highlighted in dark gray.

| Ensembles   | Training (CV) | Test          |
|-------------|---------------|---------------|
|             | APR | TOP1 | RKL | APR | TOP1 | RKL |
| EM-APR      | 0.8091 | 0.8431 | 62.268 | 0.8398 | 0.9200 | 59.027 |
| EM-RKL      | 0.7975 | 0.8235 | 50.726 | 0.8349 | 0.9000 | 54.567 |
| EMM-APR&RKL | 0.8159 | 0.8497 | 50.059 | 0.8437 | 0.9200 | 54.080 |

The sixth column shows their TOP1s of 0.9200, 0.9000 and 0.9200, respectively: EMM-APR&RKL retains the results of the best performing individual ensemble. The seventh column shows the results in terms of RKLs of 59.027, 54.567 and 54.080: EMM-APR&RKL outperforms the top performing individual ensemble. The result of the 10-fold cross-validated training data resembled the corresponding test data: averaging ensembles across APR and RKL improves performances over individual ensembles.

The test performances of EM-APR, EM-RKL and EMM-APR&RKL are compared to the winners of the 2004 knowledge discovery and data mining (KDD) cup competition in Table 8. Four different research groups (Weka, ICT.AC.CN, MEDai/Al Insight and PG445 UniDo) won the competition of its protein homology section. The overall winner among the four groups was Weka. Table 8 includes results for all of the four winners of the competition. The first part of Table 8 shows results corresponding to EM-APR, EM-RKL and EMM-APR&RKL, the central part shows results for the winners of the competition.

The results are also ranked. For example, the performances of the methods specific to APR are ranked, and the numbers are produced in the third column. The top performing method (EMM-APR&RKL) is ranked first followed by the second top performing method (ICT.AC.CN) and so on. The ranks of the methods corresponding to TOP1 and RKL are produced independently in columns 5 and 7, respectively. For TOP1, the best three methods (EMM-APR&RKL, EM-APR and MEDai/Al Insight) are tied and received an average rank of 2 (average of 1, 2 and 3). The 8th column shows average ranks (average ranks across the columns 3, 5 and 7) corresponding to each method.

As the metrics change, the performances of the methods vary. Among the four winners of
Table 8. Comparisons of test performances of EM-APR, EM-RKL and EMM-APR&RKL (top part) to the winners of the 2004 knowledge discovery and data mining (KDD) cup competition (center part), and to RF and EPX-RF (bottom part). The top performance in each metric is highlighted in dark gray.

| Methods          | APR  | Rank | TOP1  | Rank | RKL  | Rank | Average Rank |
|------------------|------|------|-------|------|------|------|--------------|
| EM-APR           | 0.8398 | 4    | 0.9200 | 2    | 59.027 | 7    | 4.333        |
| EM-RKL           | 0.8349 | 6    | 0.9000 | 6    | 54.567 | 6    | 6.000        |
| EMM-APR&RKL      | 0.8437 | 1    | 0.9200 | 2    | 54.080 | 4    | 2.333        |
| Weka             | 0.8409 | 3    | 0.9067 | 5    | 52.447 | 2    | 3.333        |
| ICT.AC.CN        | 0.8412 | 2    | 0.9133 | 4    | 54.087 | 5    | 3.667        |
| MEDai/Al Insight | 0.8380 | 5    | 0.9200 | 2    | 53.960 | 3    | 3.333        |
| PG445 UniDo      | 0.8300 | 7    | 0.8667 | 9    | 45.620 | 1    | 5.667        |
| RF               | 0.8089 | 9    | 0.8733 | 7.5  | 143.733 | 9    | 8.500        |
| EPX-RF           | 0.8140 | 8    | 0.8733 | 7.5  | 82.307 | 8    | 7.833        |

The KDD Cup competition, the top performing methods in terms of APR, TOP1 and RKL were ICT.AC.CN, MEDai/Al Insight and PG445 UniDo, respectively. Surprisingly, the top performing method in terms of RKL (PG445 UniDo) was found at the bottom in terms of APR and TOP1.

The smaller the overall rank in column 8, the better the method is. The lowest average rank 2.333 corresponds to the method EMM-APR&RKL followed by methods Weka and MEDai/Al Insight both with rank 3.333. The method EMM-APR&RKL achieves the largest APR (0.8437) and tied with the largest TOP1 (0.9200). This method ranks 4 in terms of RKL among all of the seven methods. While the performances of the methods EM-APR and EM-RKL are marginally behind the winners of the KDD Cup competition, the ensemble of the two methods outperforms the four winners.

The bottom part of Table 8 shows results from a random forests (RF by Breiman (2001)) and ensemble of phalanxes based on random forests (EPX-RF by Tomal et al. (2015)). The ensembles of models and metrics based on logistic regression model provide better results than both RF and EPX-RF.

Note that, people can submit new predictions to the 2004 KDD Cup and get results back. Hence, it is important to report that no new results - dated November 04, 2016 - are better or even equal to our results in terms of APR (0.8437) and TOP1 (0.92).
6.4. Computational Gain of EM-LRM over EPX-RF

The computational time for the ensemble of models based on logistic regression model (EM-LRM) is much smaller than the ensemble of phalanxes using random forests (EPX-RF). A total of 32 processors of the bugaboo machine∥ in the Western Canada Research Grid (westgrid) computing network were parallelized. For each of those 32 processors 8 gigabyte of memory was allocated. The computation times to train and test EPX-RF and EM-LRM on the protein homology data were 1569 and 80 minutes, respectively. Here, EM-LRM ran much faster than EPX-RF.

Through parallel computation, the computing time of EM-LRM was brought down similar to a random forests. For an RF, the task of training and testing was completed using 1 processor with 8 gigabyte memory. The total running time was 67 minutes. Note that, one can easily assign more processors to further reduce down the computation time of EM-LRM.

7. Summary and Conclusion

An ensemble is an aggregated collection of models. To build a powerful ensemble, the constituent models need to be strong and diverse. In this article, the term strong stands for predictive ranking ability of a model. The proposed algorithm of subset/phalanx formation clusters a number of predictor variables into a subset. The variables in a subset, make the model strong in terms of predictive ranking. On the other hand, two or more models are diverse in a sense that they predict different sets of homologous proteins. The algorithm keeps putting predictor variables into subsets until a set of predictors help each other in a model, and ends up with more than one subsets (generally) of predictor variables. The subsets are diverse between each other and can predict different sets of homologous proteins well. In a nutshell, the ensemble of models is equipped with methods to search for and putting good variables together into a subset to increase its strength, and clustering variables into different subsets to induce diversity between the models.

One nice properties of the ensemble of models is filtering weak variables. A variable is considered weak if it shows poor predictive performance, (a) individually in a model, (b) jointly when paired with another variable in a model, and (c) jointly when ensembled with another variable in different models. The algorithm also filters unhelpful subsets/phalanxes of variables. The term unhelpful stands for weaker predictive ranking through ensembling than the maximum predictive ranking of two individual subsets/phalanxes. A subset of variables is filtered out if it appears unhelpful with any other subsets used in the final ensemble. The merging/clustering step of the algorithm of phalanx formation is sandwiched by filtering weak variables and subsets of variables.

∥http://www.westgrid.ca/support/quickstart/bugaboo Accessed November 06, 2016.
An apparently less highlighted properties of our ensemble is model selection. Regular model selection methods - such as forward stepwise, backward elimination and regularization (Hastie et al., 2009) - select a subset of variables and build one model. In contrast, our ensemble selects a collection of models and aggregates them in an ensemble. Each of those models can be considered as an alternative to the models conveniently selected by the regular model selection methods. Furthermore, the constituent models in our ensemble predict diverse collection of homologous proteins, which is similar to examining a problem from different vantage points to have a clear perspective of a situation.

The old ensemble of phalanxes uses random forests as base learner. The old ensemble is also applied to the protein homology data, and its results are found better than the base learner random forests. Our ensemble which uses logistic regression model outperforms the old ensemble. Furthermore, the results of our ensemble are comparable to the winners of the 2004 KDD cup competition. Those findings are encouraging and are in favor of using any suitable base learners such as classification tree, recursive partitioning (Breiman et al., 1984), neural networks (McCulloch and Pitts, 1943; Widrow and Hoff, 1960; Rosenblatt, 1962) etc. whichever is reasonable to an application.

Our ensemble of models is independently optimized by maximizing average precision and minimizing rank last. This exemplifies the fact that the algorithm of subset formation is flexible to any evaluation metric. The choice of evaluation metrics will depend on specific applications, and the merits of the chosen metric to quantify overall performance of the ensemble. These facts drive us towards a new goal of extending the ensemble of phalanxes in linear regression and multi-class classification optimizing evaluation metrics such as mean-squared loss, misclassification error etc.

To induce diversity between two ensembles of models, the algorithm was optimized using two complementary evaluation metrics, APR and RKL. The metric APR was useful to rank close homologs and the other metric RKL was useful to rank distant homologs. The aggregated ensemble provided robust ranking performances than its constituents EM-APR and EM-RKL. Now, it would be interesting to examine if such improvement can be achieved by aggregating ensembles of models based on independent base learners as well. At this point it is not clear how the diversity would be induced through different base learners, but might appear to be an interesting research question to be examined.
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