Phenotype prediction with semi-supervised learning

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Abstract. In this work, we address the task of phenotypic traits prediction using methods for semi-supervised learning. More specifically, we propose to use supervised and semi-supervised classification trees as well as supervised and semi-supervised random forests of classification trees. We consider 114 datasets for different phenotypic traits referring to 997 microbial species. These datasets present a challenge for the existing machine learning methods: they are not labelled/annotated entirely and their distribution is typically imbalanced. We investigate whether approaching the task of phenotype prediction as a semi-supervised learning task can yield improved predictive performance. The result suggest that the semi-supervised methodology considered here is helpful for phenotype prediction for which the amount of labeled data ranges from 20 to 40%. Furthermore, the semi-supervised classification trees exhibit good predictive performance for datasets where the presence of a given trait is not extremely imbalanced (i.e., less than 6%).

Keywords: semi-supervised learning, phenotype, decision trees, predictive clustering trees, random forests, binary classification

1 Introduction

The most common task in machine learning is supervised learning, where the goal is to predict the value of a target attribute of an example by using the values of descriptive attributes. Supervised methods often need a large amount of labeled data to learn a predictive model with a satisfying predictive performance. However, in many real-life problems, such as phonetic annotation of human speech, protein 3D structure prediction, and spam filtering, only a few labeled examples are available to learn from because of the expensive and/or time-consuming annotation procedures. Contrary to labeled examples, unlabeled examples are often freely available in vast amounts. For example, human speech can be recorded from radio broadcasts, while DNA sequences of proteins can

be extracted from gene databases. Semi-supervised learning (SSL) emerged as an answer to the problem of labeled data scarcity [1], with an idea to exploit freely/easily available unlabeled examples to get better predictive performance than the one achieved using labeled data alone.

In this work, we are concerned with the task of microbial phenotype prediction. Phenotypes are defined as variations in observable characteristics of an organism. Microbial organisms display a large diversity of possible phenotypic traits, such as ability to inhabit different environments, adaptation to extreme conditions and association to different hosts. The annotation of organisms with phenotypes is important for understanding the genetic basis of phenotypes. It often requires expensive experimental measurements and time-consuming manual curation, hence there is a huge amount of unlabeled organisms. On the other hand, phenotypes can be efficiently predicted from genome [2–5] and metagenome data [6].

Thanks to the emergence of DNA sequencing technology, the number of sequenced genomes is rapidly increasing, making unlabeled data easily available. This makes the problem of phenotype prediction well suited for semi-supervised learning. In this work, we explore whether better predictive performance can be achieved with semi-supervised machine learning methods than with supervised methods that have been used for this task in [7][1], namely classification trees and random forests.To the best of our knowledge, this is the first application of semi-supervised learning for microbial phenotype prediction.

In this work, we compare the predictive performance of supervised and semi-supervised classification trees and random forests thereof [8] to predict 114 phenotypes of 997 microbial organisms. These datasets pose interesting challenges for existing machine learning methods because the annotations are not complete and the available datasets are imbalanced. To this end, we investigate whether we can benefit from using semi-supervised learning under these difficult conditions. In a nutshell, the results reveal that the semi-supervised classification trees can improve the predictive performance over supervised clasification trees in cases where the amount of labeled data is in the range 20-40% and for phenotypic traits that are not extremely rare.

The rest of this paper is organized as follows. Section 2 describes the semi-supervised methods used in this study, while Section 3 describes the data used for phenotype prediction. Section 4 specifies the experimental design. The results of the empirical investigations are presented and discussed in Section 5. Finally, Section 6 concludes the paper.

2 Methods

In this work, we consider semi-supervised classification trees and semi-supervised random forests [8], which are based on the predictive clustering trees (PCTs) [9] and ensembles thereof [10]. PCTs view a decision tree as a hierarchy of clusters,

[1] Phenotype predictions from [7] are available at protraits.irb.hr.

Table 1. The top-down induction algorithm for decision trees construction.

procedure InduceTree
Input: A dataset E
Output: A predictive clustering tree
1: $(t^*, h^*, \mathcal{P}^*) = \text{BestTest}(E)$
2: **if** $t^* \neq none$ **then**
3: **for each** $E_i \in \mathcal{P}^*$ **do**
4: $tree_i =$
5: InduceTree(E_i)
6: **return**
7: node$(t^*, \bigcup_i \{tree_i\})$
8: **else**
9: **return**
10: leaf(Prototype(E))

procedure BestTest
Input: A dataset E
Output: the best test (t^*), its heuristic score (h^*) and the partition ($\mathcal{P}^*$) it induces on the dataset (E)
1: $(t^*, h^*, \mathcal{P}^*) = (none, 0, \emptyset)$
2: **for each** possible test t **do**
3: $\mathcal{P}$ = partition induced by t on E
4: $h = Impurity(E) -$
5: $\sum_{E_i \in \mathcal{P}} \frac{|E_i|}{|E|} Impurity(E_i)$
6: **if** $(h > h^*) \wedge \text{Acceptable}(t, \mathcal{P})$ **then**
7: $(t^*, h^*, \mathcal{P}^*) = (t, h, \mathcal{P})$
8: **return** $(t^*, h^*, \mathcal{P}^*)$

where the top-node corresponds to one cluster containing all the data. This cluster is then recursively partitioned into smaller clusters while moving down the tree. Both supervised and semi-supervised PCTs are implemented in the CLUS system [11], available at http://sourceforge.net/projects/clus. In this section, we briefly describe semi-supervised trees and random forests, while for more details we refer the reader to the work of Levatić et al. [8].

Supervised classification trees evaluate the quality of splits on the basis of the class labels, by using, for example information gain or gini index as a quality measure. Consequently, the resulting clusters (i.e., groups of examples defined by splits in the tree) are homogeneous only with respect to the class label. Semi-supervised PCTs [8], on the other hand, measure the quality of splits considering both the class labels and descriptive attributes. Therefore, the resulting clusters are homogeneous with respect to both the descriptive attributes and the class labels. Note that, only the descriptive attributes are known for unlabeled examples, thus, such semi-supervised trees can exploit them during the tree construction - contrary to supervised trees. The rationale behind the described semi-supervised classification trees is the semi-supervised cluster assumption [1]: *If examples are in the same cluster, then they are likely of the same class.*

The semi-supervised PCTs are based on the standard *top-down induction of decision trees* (TDIDT) algorithm (see Table 1), which takes as input a set of examples E and outputs a tree. The heuristic score (h) that is used for selecting the tests (t) to put in the internal tree nodes is reduction of impurity caused by partitioning ($\mathcal{P}$, Table 1, line 3 of the BestTest procedure) the examples according to the tests.

In supervised PCTs, the impurity for each set of examples E is calculated as the gini index (Table 1, line 5 of the *BestTest* procedure):

$$Impurity(E) = Gini(E, Y). \tag{1}$$

As mentioned before, to identify the best splits, the impurity function of semi-supervised PCTs takes into account both the target attribute (i.e., the class labels) and the descriptive attributes. This is achieved by changing the equation for the calculation of impurity for supervised PCTs (Eq. 1). Impurity of a set of examples E (which may contain labeled and unlabeled examples) is calculated as a weighted sum of impurities over the target attribute (Y) and impurities over the descriptive attributes (X_i):

$$Impurity_{SSL}(E) = w \cdot Impurity(E_l, Y) + \frac{1-w}{D} \cdot \sum_{i=1}^{D} Impurity(E, X_i), \quad (2)$$

where $E = E_l \cup E_u$ is the dataset available at a node of the tree, D is the number of descriptive attributes, X_i is the i^{th} descriptive attribute, and $w \in [0, 1]$ is a weight parameter.

The impurity of the target attribute Y is calculated as gini index over a set of labeled examples E_l. Differently from the target attribute, which is nominal, the descriptive attributes can be either nominal or numeric, therefore, the two cases are considered separately: if the attribute is nominal as a measure of impurity gini impurity is used, whereas, if the attribute is numeric, as a measure of impurity variance is used.

The weight parameter w in (2) controls how much the target side or the descriptive side contribute to the calculation of the impurity. Consequently, this controls how much the unlabeled examples affect the learning of semi-supervised PCTs. Namely, depending on the values of the w parameter, semi-supervised PCTs can range from fully supervised trees (i.e., $w = 1$) to completely unsupervised trees (i.e., $w = 0$). This aspect is important since unlabeled examples can sometimes cause semi-supervised algorithms to perform worse than their supervised counterparts [12–14]. The w parameter acts as a safety mechanism of semi-supervised PCTs, enabling them to control the influence of unlabeled examples and adapt to a given dataset.

By using semi-supervised PCTs, it is possible to build semi-supervised random forests. A random forest [15] is an ensemble of trees, where diversity among the trees is obtained by making bootstrap replicates of the training set, and additionally by randomly selecting the subset of descriptive attributes used to evaluate the splits. Random forests often substantially improve the predictive performance of single trees, however, the interpretability aspect of trees is lost. Semi-supervised random forests of PCTs are build by using semi-supervised PCTs as members of the ensemble, instead of using supervised PCTs. In semi-supervised random forests, the bootstrap sampling procedure is modified to perform stratified bootstrap sampling (considering the proportions of labeled and unlabeled examples) to avoid having bootstrap samples consisting only of unlabeled examples.

3 Data description

Prokaryotic genome sequences and gene annotations were downloaded from the NCBI Genomes database and COG/NOG gene families were downloaded from eggNOG 3 [16]. In our analysis, we considered only species having a genome quality score greater or equal to 0.9 [17]. Phenotype annotations are NCBI+Bacmap labels as in [7], collected from the NCBI microbial genome projects list ('lproks0' table) and from the BacMap database [18], in total 114 different phenotypic traits. We considered only species having at least one assigned phenotype label, resulting in 997 species. Each example corresponds to one species labeled with a set of available phenotypic traits. For each species, the labels correspond to presence or absence of traits, thus, the task of phenotype prediction corresponds to a binary classification problem.

The labelling is, however, not exhaustive: For most of the phenotypes, only 30% of species are labeled (Fig. 1a). Hence, the dataset at hand contains unlabeled data, which can be exploited with semi-supervised methods. The class distribution of most of the phenotypes is unbalanced (Fig. 1b): Many traits appear at less than 10% of species, e.g. radiation-resistance phenotype and ability to withstand extremely high (hyperthermophilic organims) or extremely low temperature (psychrophilic organims).

In all experiments, we used the gene repertoire representation [2]. The features describing the species were encoded as the presence/absence of the clusters of orthologous (COG) and non-supervised orthologous (NOG) groups of proteins, resulting in the 80576 binary valued features. In order to reduce the dimensionality of the feature set we applied principal component analysis (PCA) as a preprocessing step and retained principal components explaining 90% of the variance. This resulted in 526 features, i.e., principal components.

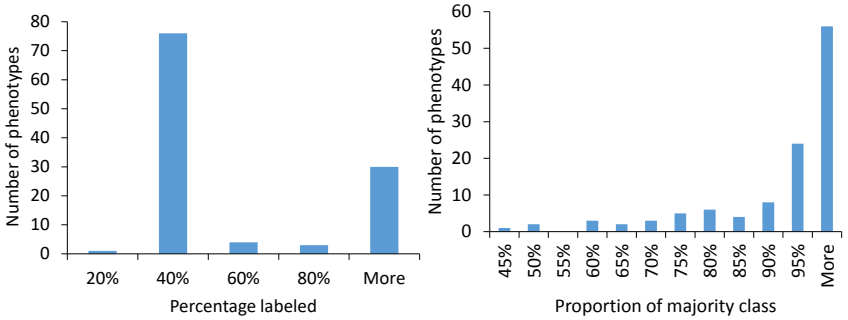


Fig. 1. a) Histogram of the amount of labeled (relative to unlabeled) examples for each phenotype. b) Histogram of the majority class distributions of phenotypes.

4 Experimental design

We learn a separate model for each phenotype, transforming the problem of phenotype prediction into 114 binary classification tasks. We then approach these tasks with two learning paradigms: supervised and semi-supervised learning. In other words, we learn predictive models in the form of supervised classification trees (PCTs) and semi-supervised classification trees (SSL-PCTs) as well as supervised random forests and semi-supervised random forests. Next, we compare the performance of semi-supervised PCTs and semi-supervised random forests to their supervised counterparts. For every phenotype, examples with unknown labels were used as unlabeled data for learning the semi-supervised PCTs and ensembles thereof.

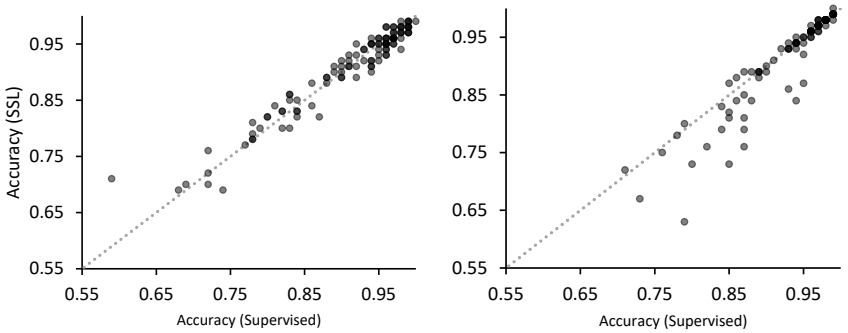
Furthermore, we investigate the influence of the amount of annotated phenotypes on the performance of the semi-supervised methods. More specifically, we analyze the performance of the predictive models across the different percentages of annotated phenotypes. Moreover, we juxtapose this influence with the influence of the imbalance of the class labels.

In the experiments, both supervised and semi-supervised trees are pruned with the procedure used in C4.5 classification trees [19]. The weight parameter w of semi-supervised algorithms was chosen from the set $\{0, 0.1, \ldots, 0.9, 1\}$ by using internal 3-fold cross validation on the labeled part of the training set. We construct random forests consisting of 100 trees. The trees in random forest are not pruned and the number of random features at each internal node is set to the square root of the number of features, which in our case amounted to 23.

We used 10-fold cross validation procedure to estimate the performances of the methods. The predictive performance reported in the results is the average of the performance values obtained from the 10 folds.

5 Results and discussion

The accuracies of predicting 114 microbial phenotypic traits with supervised and semi-supervised trees and random forests in terms of wins, ties and losses are presented in Figure 2. We can observe that for many of the traits, semi-supervised algorithms outperform their supervised counterparts, suggesting that semi-supervised methods can successfully exploit unlabeled data and more accurately predict microbial phenotypes. The advantage of semi-supervised methods is, however, not observed for all phenotypes: The number of wins, ties and losses of semi-supervised PCT versus supervised PCT is 40, 21 and 53, while the corresponding numbers for semi-supervised random forests are 14, 70 and 30. This is expected, since several researchers found that the success of semi-supervised methods is, in general, dataset dependent [20]. In other words, it cannot be expected that semi-supervised methods will win against supervised ones for all cases. Furthermore, several researchers have found that semi-supervised learning may sometimes perform worse than supervised learning [12–14].

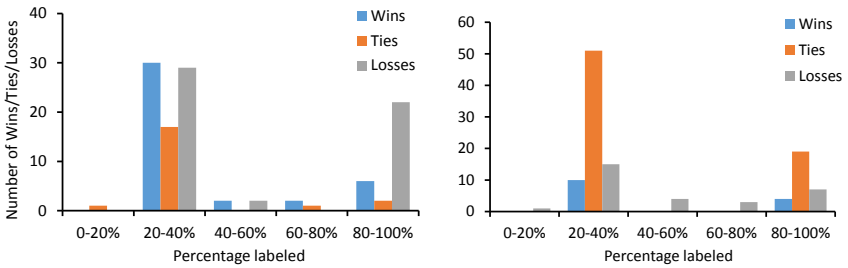


a) Single trees b) Random forests

Fig. 2. Each dot represents an accuracy of prediction of one phenotype of supervised and semi-supervised PCTs (a) and random forests (b). Values above/below the diagonal (dashed line) denote that the semi-supervised/supervised algorithm is better.

Our results also suggest that improving (with unlabeled data) a supervised random forest is a harder task than improving over a supervised tree: The number of wins of semi-supervised random forests is lower than the number of wins of semi-supervised PCTs. This observation complies with previous findings [8]. We consider that this is due to the fact that ensembles are very powerful predictive models, which are able to exploit all the information in a given (labeled) dataset and approach the learnability borders of a given domain closer than a single predictive model. Thus, arguably, random forests do not benefit so much from additional information that unlabeled data bring, as compared to single trees.

We further analyze the results with the goal to identify phenotypes that are suitable for prediction with semi-supervised methods. The amount of available labeled data (relative to unlabeled) is an important factor for the performance of semi-supervised methods [8], we, therefore, analyze the results from that aspect



a) Single trees b) Random forests

Fig. 3. The number of wins, ties and losses of semi-supervised PCTs (a) and semi-supervised random forests (b) versus their supervised counterparts, achieved for phenotypes with different amounts of labeled data.

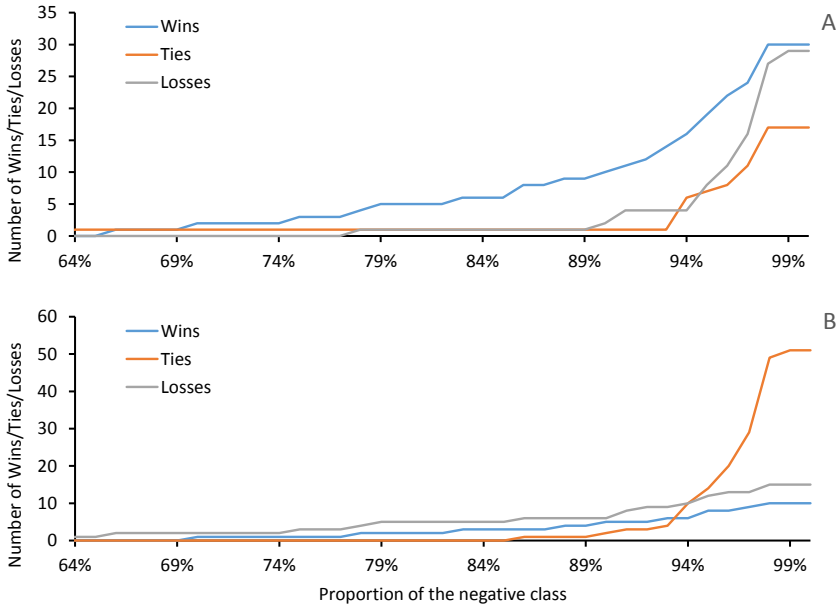


Fig. 4. The cumulative number of wins, ties and losses of semi-supervised PCTs (a) and semi-supervised random forests (b) versus their supervised counterparts, achieved for phenotypes with 20-40% of labeled examples. The y values denote the total number of wins, ties and losses for all phenotypes where $\leq x\%$ of examples have negative class.

(Fig. 3. We can observe that for smaller amounts of labeled data, i.e., from 20-40%, semi-supervised methods win more frequently (especially for single trees) than for larger amounts of labeled data. In such situations, i.e., when few labeled examples are available, the need for semi-supervised learning is pronounced the most – low amount of labeled data can present a limiting factor for supervised methods.

We show that semi-supervised methods win mostly for phenotypes which have 20 to 40% of labeled data, but still, the number of losses there is similar to the number of wins, i.e., the probably of improving the accuracy with SSL is similar to the probably of degrading the performance. Recall that, many of the phenotypes have very unbalanced classes (Fig. 1b). We next analyze whether the imbalance of the classes affects the performance of semi-supervised methods (Fig. 4). Interestingly, semi-supervised PCTs are superior in performance to supervised PCTs for phenotypes that are not very rare (Fig. 4a). More specifically, for phenotypes where the proportion of the negative class is smaller than 94% (i.e., more than 6% species have the trait), semi-supervised PCTs win, with very few exceptions, over supervised ones. As the proportion of the negative class increases beyond 94%, the number of losses starts to increase rapidly, suggesting that semi-supervised PCTs are not suitable for predicting very rare phenotypes. For semi-supervised random forests (Fig. 4b), the advantage over supervised

random forests is not entirely clear: Semi-supervised random forests might help, but there is a smaller chance to do so, the most probable result is that they will perform the same as supervised random forests, as the number of ties is by far the highest.

6 Conclusions

In this work, we approach the task of phenotypic traits prediction using methods for semi-supervised learning. This task is important to understand the genetic basis for appearance of specific phenotypes. More specifically, we consider 114 datasets with different phenotypic traits referring to 997 microbial species. The datasets are not completely labelled and different amount of annotation is available for the different traits.

We investigate whether approaching the task of phenotype prediction as a semi-supervised learning task can yield improved predictive performance. More specifically, we learn supervised and semi-supervised classification trees as well as supervised and semi-supervised random forests of classification trees. We then compare the performance of predictive models learned using supervised and semi-supervised methods.

The result suggest that the semi-supervised methodology considered here is helpful for phenotype prediction for which the amount of labeled data ranges from 20 to 40%. Furthermore, the semi-supervised classification trees exhibit good predictive performance for datasets where the presence of a given trait is not extremely imbalanced (i.e., less than 6%). Next, in applications where interpretable models are needed, semi-supervised classification trees should be favored over the supervised classification trees.

We plan to further extend this work along several dimensions. To begin with, we plan to use phenotypes from other sources, specifically phenotypes from GOLD database [21] and especially biochemical phenotypes from [7] where the labeled examples are extremely scarce. Furthermore, we plan to consider other feature spaces, namely the proteome composition, gene neighborhoods and translation efficiency representations [7]. Next, we will compare the approaches presented here with other methods used for phenotype prediction including, but not limited to, SVMs and semi-supervised SVMs. Finally, we can treat the problem as a multi-label classification problem and obtain a partially labelled dataset that can be then approached from this perspective.

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