Empirical Study of Domain Adaptation with Naïve Bayes on the Task of Splice Site Prediction

Nic Herndon and Doina Caragea
Kansas State University, Computing and Information Sciences, 234 Nichols Hall, Manhattan, KS 66506, U.S.A.

Keywords: Domain Adaptation, Naïve Bayes, Splice Site Prediction, Unbalanced Data.

Abstract: For many machine learning problems, training an accurate classifier in a supervised setting requires a substantial volume of labeled data. While large volumes of labeled data are currently available for some of these problems, little or no labeled data exists for others. Manually labeling data can be costly and time consuming. An alternative is to learn classifiers in a domain adaptation setting in which existing labeled data can be leveraged from a related problem, referred to as source domain, in conjunction with a small amount of labeled data and large amount of unlabeled data for the problem of interest, or target domain. In this paper, we propose two similar domain adaptation classifiers based on a naïve Bayes algorithm. We evaluate these classifiers on the difficult task of splice site prediction, essential for gene prediction. Results show that the algorithms correctly classified instances, with highest average area under precision-recall curve (auPRC) values between 18.46% and 78.01%.

1 INTRODUCTION

In recent years, a rapid increase in the volume of digital data generated has been observed. Gantz *et al.* (2007) estimated that the total volume of digital data doubles every 18 months. Contributing to this growth, in the field of biology, large amounts of raw genomic data are generated with next generation sequencing technologies, as well as data derived from primary sequences. The availability and scale of the biological data creates great opportunities in terms of medical, agricultural, and environmental discoveries, to name just a few.

A stepping stone towards advancements in such fields is the identification of genes in a genome. Accurate identification of genes in eukaryotic genomes depends heavily on the ability to accurately determine the location of the splice sites (Bernal et al., 2007; Rätsch et al., 2007), the sections in the DNA that separate exons from introns in a gene. In addition to identifying the gene structure, the splice sites also determine the amino acid composition of the proteins encoded by the genes. Therefore, considering that the content of a protein plays a major role with respect to its function, the splice site prediction is a crucial task in identifying genes and ultimately the functions of their products.

To identify genes, we need to identify two types of splice sites: donor and acceptor. The donor splice site indicates where an exon ends and an intron begins, while the acceptor splice site indicates where an intron ends, and an exon begins. Virtually most donor sites are the GT dimer and most acceptor sites are the AG dimer, with very few exceptions. However, not every GT or AG dimer is a splice site. In fact, only about one percent of them are, which makes the task of identifying splice sites very difficult.

Nonetheless, this problem can be addressed with supervised machine learning algorithms, which have been successfully used before for many biological problems, including gene prediction. For example, hidden Markov models have been used for *ab initio* gene predictions, while support vector machines (SVMs) have been used successfully for problems such as identification of translation initiation sites (Müller et al., 2001; Zien et al., 2000), labeling gene expression profiles as malign or benign (Noble, 2006), *ab initio* gene prediction (Bernal et al., 2007), and protein function prediction (Brown et al., 2000).

However, one drawback of these algorithms is that they require large amounts of labeled data to learn accurate classifiers. And many times labeled data is not available for a problem of interest, yet it is available for a different but related problem. For example, in biology, a newly sequenced organism is generally scarce in labeled data, while a well-studied model organism is rich in labeled data. However, the use of the classifier learned for the related problem to classify unlabeled data for the problem of interest does not always produce accurate predictions. A better alternative is to learn a classifier in a domain adaptation (DA) framework. In this setting, the large corpus of labeled data from the related, well studied organism is used in conjunction with available labeled and unlabeled data from the new organism.

Towards this goal we propose two similar algorithms, described in Section 3.2. Each algorithm trains a classifier in this configuration, by using the large volume of labeled data from a well studied organism, also called source domain, some labeled data, and any available unlabeled data from the new organism, called target domain. Once learned, the classifier can be used to classify new data from the new organism. These algorithms are similar to the algorithms in (Tan et al., 2009; Herndon and Caragea, 2013a; Herndon and Caragea, 2013b), which produced good results on the tasks of sentiment analysis and protein localization, respectively.

For example, the algorithm proposed by Herndon and Caragea (2013b) uses a weighted multinomial Naïve Bayes classifier combined with the iterative approach of the Expectation-Maximization algorithm and self-training (Yarowsky, 1995; Riloff et al., 2003; Maeireizo et al., 2004). It iterates until the probabilities in the expectation step converge. In the maximization step, the posterior probabilities and the likelihood are estimated using a weighted combination between the labeled data from the source domain and the labeled and unlabeled data from the target domain. In the expectation step, the conditional class probabilities for each instance in the target unlabeled dataset are estimated with the probability values from the maximization step using Bayes theorem. After each iteration, a number of instances from the unlabeled target dataset are considered labeled and moved to the labeled dataset. The number of these instances is proportional to the prior probability, with a minimum of one instance selected from each class. For example, if the target labeled dataset had 1% positive instances and 99% negative instances, and at each iteration we select 10 instances, one instance with the top positive probability and nine instances with the top negative probabilities would be selected. In addition, the weight is shifted from the source data to the target data with each iteration.

However, this algorithm did not perform well on the task of splice site prediction and to improve its classification accuracy we made the following four changes to it:

- We normalized the counts used in computing the posterior probability and the likelihood, and assigned different weights to the target labeled and unlabeled datasets.
- We used mutual information to rank the features instead of the marginal probabilities of the features.
- We assigned different weights to the features instead of selecting which features to use from the source domain.
- We used features that took into consideration the location of nucleotides instead of counts of 8-mers generated with a sliding window.

With these changes, the two algorithms produced promising results, shown in Section 3.5, when evaluated on the splice site prediction problem with the data presented in Section 3.3. They increased the highest average auPRC from about 1% in (Herndon and Caragea, 2013b) all the way up to 78.01%.

2 RELATED WORK

Although there are good domain adaptation results for text classification, even with algorithms that make significant simplifying assumptions, such as naïve Bayes, there are only a few domain adaptation algorithms designed for biological problems. For example, for text classification, Dai *et al.* (2007) proposed an algorithm that combined naïve Bayes (NB) with expectation-maximization (EM) for classifying text documents into top categories. This algorithm performed better than SVM and naïve Bayes classifiers. Two other domain adaptation algorithms that used a combination of NB with EM are (Tan et al., 2009), which produced promising results on the task of sentiment analysis of text documents, and (Herndon and Caragea, 2013a), with good results on the task of protein localization.

However, for the task of splice site prediction, up until now, most of the work used supervised learning classifiers with only two exceptions in domain adaptation setting to the best of our knowledge: one that analyzed several support vector machine algorithms (Schweikert et al., 2008), and another that used naïve Bayes (Herndon and Caragea, 2013b). The latter did not obtain good results, primarily due to the features generated. It used the number of occurrences in each instance of the *k*-mers of length eight generated with a sliding window.

For supervised learning, Li et al. (2012) evaluated the discriminating power of each position in the DNA sequence around the splice site using the chi-square test. With this information, they proposed a SVM algorithm with a RBF kernel function that used a combination of scaled component features, nucleotide frequencies at conserved sites, and correlative information of two sites, to train a classifier for the human genome. Other supervised learning approaches based on SVM include (Baten et al., 2006; Sonnenburg et al., 2007; Zhang et al., 2006), while (Cai et al., 2000) proposed an algorithm for splice site prediction based on Bayesian networks, (Baten et al., 2007) proposed a hidden Markov model algorithm, and (Arita et al., 2002) proposed a method using Bahadur expansion truncated at the second order. However, supervised learning algorithms typically require a large volume of labeled data to train a classifier.

For domain adaptation setting, Schweikert *et al.* (2008) obtained good results using a SVM with weighted degree kernel (Rätsch and Sonnenburg, 2004), especially when the source and target domains were not close. However, the complexity of SVM classifiers increases with the number of training instances and the number of features, when training the classifier (Schweikert et al., 2008). Besides, the classification results are not as easy to interpret as the results of probabilistic classifiers, such as naïve Bayes, to gain insight into the problem studied. For example, Scheikert *et al.* (2008) further processed the results to analyze the relevant biological features. In addition, their algorithms did not use the large volume of target unlabeled data. Although unlabeled, this dataset could improve the classification accuracy of the algorithm.

3 METHODOLOGY

The two algorithms we propose are based on the algorithm presented in our previous work (Herndon and Caragea, 2013b). That algorithm modified the algorithm introduced by (Tan et al., 2009), by using self-training and the labeled data from the target domain, to make it suitable for biological sequences. To highlight the changes made to our previous algorithm we'll describe it here.

3.1 Naïve Bayes DA for Biological Sequences

The algorithm in (Herndon and Caragea, 2013b) was designed to use labeled data from the source domain in conjunction with labeled and unlabeled data from the target domain to build a classifier to be used on the target domain. It is an iterative algorithm that uses a combination of the Bayes' theorem with the simplifying assumption that features are independent, and the expectation-maximization algorithm (Dempster et al., 1977), to estimate the posterior probability as proportional to the product of the prior and the likelihood:

$$P(c_k \mid d_i) \propto P(c_k) \prod_{t=1}^{|V|} [P(w_t \mid c_k)]^{N_{t,i}^T} \tag{1}$$

where the prior is defined as

$$P(c_k) = \frac{(1-\lambda)\sum_{i'=1}^{|D_S|} P(c_k \mid d_{i'}) + \lambda \sum_{i''=1}^{|D_T|} P(c_k \mid d_{i''})}{(1-\lambda)|D_S| + \lambda |D_T|} \tag{2}$$

and the likelihood is defined as

$$P(w_t \mid c_k) = \frac{(1-\lambda)(\eta_t N_{t,k}^S) + \lambda N_{t,k}^T + 1}{(1-\lambda)\sum_{t=1}^{|V|} \eta_t N_{t,k}^S + \lambda \sum_{t=1}^{|V|} N_{t,k}^T + 1} \tag{3}$$

where λ is a weight factor between the two domains:

$$\lambda = \min\{\delta \cdot \tau, 1\}$$

τ is the iteration number, with a value of 0 for the first iteration, and $\delta \in (0,1)$ is a constant that indicates how fast the weight of the source domain decreases while the weight of the target domain increases; c_k stands for class k, d_i for document i, and w_t for feature t.

$|D_x|$ is the number of instances in x domain ($x \in \{S, T\}$, where S denotes the source domain and T denotes the target domain), $|V|$ is the number of features, and $N_{t,k}^x$ is the number of times feature w_t occurs in x domain in instances labeled with class c_k:

$$N_{t,k}^x = \sum_{i=1}^{|D_x|} N_{t,i}^x P(c_k \mid d_i)$$

$N_{t,i}^x$ is the number of occurrences in x domain of feature w_t in instance d_i.

$$\eta_t = \begin{cases} 1, & \text{if feature } w_t \text{ is generalizable.} \\ 0, & \text{otherwise.} \end{cases}$$

To determine which features from the source domain are generalizable to the target domain, i.e., generalizable from use on D_S to use on D_T, they are ranked with the following measure and only the top ranking features are kept:

$$f(w_t) = \log \frac{P_S(w_t) \cdot P_T(w_t)}{|P_S(w_t) - P_T(w_t)| + \alpha} \tag{4}$$

where α is a small constant used to prevent division by 0 when $P_S = P_T$, and P_x is the probability of feature w_t in x domain, i.e., the number of times feature w_t occurs in x domain divided by the sum over all features of the times each feature occurs in x domain.

This algorithm iterates until convergence. In the maximization step, the prior and likelihood are simultaneously estimated using Equations 2 and 3, respectively, while in the expectation step the posterior for the target unlabeled instances is estimated using Equation 1. In addition to expectation-maximization, this algorithm uses self-training, i.e., at each iteration it selects a number of unlabeled instances with highest class probabilities, proportional to the class distribution, and considers them to be labeled during subsequent iterations, while the remaining unlabeled instances are assigned "soft labels" for the following iteration. By soft labels we mean that the class probability distribution is used instead of the class label. For the target domain, during the first iteration, only the instances from the labeled dataset are used, and for the rest of the iterations, instances from both labeled and unlabeled datasets are used.

Note that when the algorithm goes through just one iteration and $\lambda = 1$, the prior and likelihood Equations, 2 and 3, respectively, reduce to

$$P(c_k) = \frac{\sum_{i=1}^{|D_S|} P(c_k \mid d_i)}{|D_S|} \tag{5}$$

and

$$P(w_t \mid c_k) = \frac{\sum_{i=1}^{|D_S|} N_{t,i} P(c_k \mid d_i) + 1}{\sum_{t=1}^{|V|} \sum_{i=1}^{|D_S|} N_{t,i} P(c_k | d_i) + |V|} \tag{6}$$

respectively, which are the equations for the multinomial naïve Bayes classifier (Mccallum and Nigam, 1998) trained and tested with data from the same domain.

Although the algorithm in (Herndon and Caragea, 2013b) performed well on the task of protein localization with maximum auPRC values between 73.98% and 96.14%, on the task of splice site prediction, the algorithm performed poorly. The splice site prediction is a more difficult task because only about 1% of the AG dimer occurrences in a genome are splice sites. To simulate this proportion, unbalanced datasets were used, with each containing only about 1% positive instances. Therefore, the training sets for splice site prediction were much more unbalanced than the training sets for the protein localization, leading to worse performance for the former.

3.2 Our Approach

One major drawback of the algorithm in (Herndon and Caragea, 2013b) is that it assigns low weight to the target data (through λ in Equations 2 and 3), including the labeled data, during the first iterations. This biases the classifier towards the source domain. However, it is not effective to only assign a different weight to the target labeled data in Equations 2 and 3. This is because we'd like to use much more instances from the source domain as well as much more unlabeled instances from the target domain, i.e., $|D_S| \gg |D_{TL}|$ and $|D_{TU}| \gg |D_{TL}|$, where subscripts S, TL, and TU stand for source data, target labeled data, and target unlabeled data, respectively. This would cause the sums and counts for the target labeled data in these two equations to be much smaller than their counterparts for the source data and target unlabeled data, rendering the weight assignment useless. Instead, we need to also normalize these values, or better yet, to use their probabilities. Thus, we estimate the prior as

$$P(c_k) = \beta P_{TL}(c_k) + (1-\beta)[(1-\lambda)P_S(c_k) + \lambda P_{TU}(c_k)] \tag{7}$$

and the likelihood as

$$\begin{aligned} P(w_t \mid c_k) = {} & \beta P_{TL}(w_t \mid c_k) \\ & + (1-\beta)[(1-\lambda)P_S(w_t \mid c_k) + \lambda P_{TU}(w_t \mid c_k)] \end{aligned} \tag{8}$$

where $\beta \in (0,1)$ is a constant weight, and λ is defined the same as in our previous approach.

In addition to using different formulas for prior and likelihood, we made a second change to the algorithm in (Herndon and Caragea, 2013b). We replaced the measure for ranking the features, Equation 4, with the following measure in Equation 9. We made this change because the goal of ranking the features is to select top features in terms of their correlation with the class, or assign them different weights: higher weights to features that are more correlated with the class, and lower weights to the features that are less correlated with the class. Therefore, the mutual information (Shannon, 1948) of each feature is a more appropriate measure in determining the correlation of the feature with the class rather than the marginal probability of the feature. With this new formula, the features are ranked better based on their generalizability between the source and target domains:

$$f(w_t) = \frac{I_S(w_t; c_k) \cdot I_{TL}(w_t; c_k)}{|I_S(w_t; c_k) - I_{TL}(w_t; c_k)| + \alpha} \tag{9}$$

where

$$I_x(w_t, c_k) = \sum_{t=1}^{|V|} \sum_{k=1}^{|C|} P_x(w_t, c_k) \log \frac{P_x(w_t, c_k)}{P_x(w_t) P_x(c_k)}$$

is the mutual information between feature w_t and class c_k, and $x \in \{S, TL\}$. The numerator ranks higher the features that have higher mutual information in their domains, while the denominator ranks higher the features that have closer mutual information between the domains, as shown in Figure 1.

If instead of ranking the features and using the top ranked features, we want to assign different weights to the features and higher values for $f(w_t)$ we can compute them with the formula in Equation 10. For the splice site prediction problem using the data from Section 3.3 with the features described in Section 3.4, most of the mutual information values are close to zero since each feature contributes very little to the classification of an instance. Therefore, the nominator is about one order of magnitude smaller than the denominator in Equation 9, while in Equation 10, the numerator is close to the denominator, resulting in higher values for $f(w_t)$.

The final change we made to (Herndon and Caragea, 2013b) was the use of different features, as explained shortly in Section 3.4.

$$f(w_t) = \frac{I_S(w_t;c_k) \cdot I_{TL}(w_t;c_k)}{(I_S(w_t;c_k) - I_{TL}(w_t;c_k))^2 + \alpha} \tag{10}$$

Thus, the two algorithms we propose use the source labeled data and the target labeled and unlabeled data to train a classifier for the target domain. For the source domain, Algorithm 1 selects generalizable features to be used, while Algorithm 2 assigns different weights to the features. These differences are highlighted in italics in steps 1 and 2 of the algorithms by using italics text. The algorithms iterate until convergence. In the first iteration, they use only the source and target labeled data to calculate and assign the posterior probabilities for the unlabeled data. Proportional to the prior probability distribution, the algorithms select top instances from the target unlabeled dataset and consider them to be labeled for subsequent iterations. For the rest of the iterations, the algorithms use the source labeled data, the target labeled data, and the target unlabeled data to build a classifier for labeling the remaining unlabeled instances. For the target unlabeled data, the algorithms use the probability distributions, while for the other datasets, source and target labeled, they use the labels of each instance when computing the prior probabilities and the likelihood.

Algorithm 1: DA with feature selection.

```
1: Select the features to be used from the source domain
   using Equation 9.
2: Simultaneously compute the prior and likelihood,
   Equations 7 and 8, respectively. Note that for the
   source domain all labeled instances are used but only
   with the features selected in step 1, while for the
   target domain only labeled instances are used with all
   their features.
3: Assign labels to the unlabeled instances from the
   target domain using Equation 1. Note that we use
   self-training, i.e., a number of instances, proportional
   to the class distribution, with the highest class
   probability are considered to be labeled in subsequent
   iterations.
4: while labels assigned to unlabeled data change do
5:    M-step: Same as step 2, except that we also use
      the instances in the target unlabeled dataset; for
      this dataset we use the class for the self-trained
      instances, and the class distribution for the rest of
      the instances.
6:    E-step: Same as step 3.
7: end while
8: Use classifier on new target instances.
```

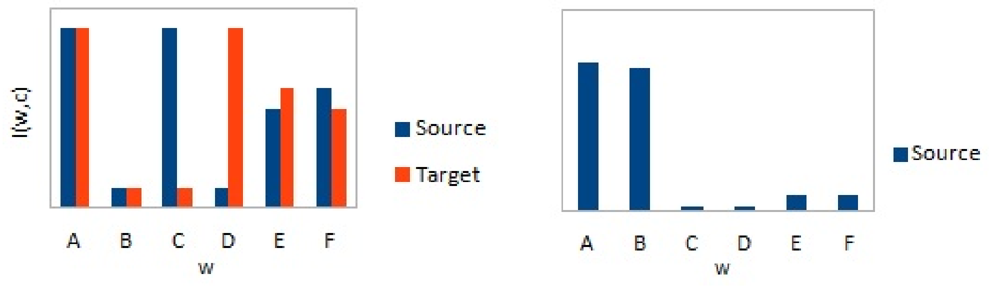
Algorithm 2: DA with weighted features.

```
1: Assign different weights to the features of the
   source dataset using either Equation 9 or Equation 10.
2: Simultaneously compute the prior and likelihood,
   Equations 7 and 8, respectively. Note that for the
   source domain all labeled instances are used but
   the features are assigned different weights in step
   1, while for the target domain only labeled
   instances are used with all their features.
3: Assign labels to the unlabeled instances from the
   target domain using Equation 1. Note that we use
   self-training, i.e., a number of instances, proportional
   to the class distribution, with the highest
   class probability are considered to be labeled in
   subsequent iterations.
4: while labels assigned to unlabeled data change
   do
5:    M-step: Same as step 2, except that we
      also use the instances in the target unlabeled
      dataset; for this dataset we use the class for the
      self-trained instances, and the class distribution
      for the rest of the instances.
6:    E-step: Same as step 3.
7: end while
8: Use classifier on new target instances.
```

3.3 Data Set

To evaluate these algorithms, we used a dataset for which (Herndon and Caragea, 2013b) did not perform well. We used the splice site dataset[1], first introduced in (Schweikert et al., 2008), which contains DNA sequences of 141 nucleotides long, with the AG dimer

[1]Downloaded from ftp://ftp.tuebingen.mpg.de/fml/cwidmer/



(a) Mutual information of features in both domains (b) Rank of features in the source domain

Figure 1: Ranking features in the source domain based on mutual information using Equation 9, showcasing the different combinations of mutual information of the features in the two domains. Feature *A* has high mutual information in both domains, as shown on the left of subfigure (a), resulting in large numerator and small denominator, and thus a high rank, as shown on the left of subfigure (b). Feature *B* has low mutual information in both domains, resulting in small denominator, and thus a high rank, but lower than the rank of *A* since the numerator for *A* is greater than the numerator for *B*. Features *C* and *D* have high mutual information in one domain and low mutual information in the other domain, resulting in large denominator, and thus a low rank. Features *E* and *F* have close mutual information between the two domains, resulting in small denominator, and thus a higher rank than Features *C* and *D*.

at sixty-first position in the sequence, and a class label that indicates whether this dimer is an acceptor splice site or not. Although this dataset contains only acceptor splice sites, classifying donor splice sites can be done similarly to classifying the acceptor splice sites.

This dataset contains sequences from one source organism, *C.elegans*, and four target organisms at increasing evolutionary distance, namely, *C.remanei*, *P.pacificus*, *D.melanogaster*, and *A.thaliana*. The source organism contains a set of 100,000 instances, while each target organism has three folds each of 1,000, 2,500, 6,500, 16,000, 25,000, 40,000, and 100,000 instances that can be used for training, as well as three corresponding folds of 20,000 instances to be used for testing. In each file, there are 1% positive instances with small variations – variance is 0.01 – and the remaining instances are negative.

3.4 Data Preparation and Experimental Setup

To limit the number of experiments, we used the following datasets, as shown in Figure 2:

- The 100,000 *C.elegans* instances as source labeled data used for training.
- Only the sets with 2,500, 6,500, 16,000, and 40,000 instances as labeled target data used for training.
- The set with 100,000 instances as unlabeled target data used for training.
- The corresponding folds of the 20,000 instances as target data used for testing.

We represent each sequence as a combination of features that indicate the nucleotide and codon present at each location, i.e., 1-mer and 3-mer, respectively. We chose these features to create a balanced combination of simple features, 1-mers, and features that capture some correlation between the nucleotides, 3-mers, while keeping the number of features small. For example, a sequence starting with AAGATTCGC... and class –1 would be represented in WEKA ARFF[2] format as:

```
@RELATION remanei_2500_0
@ATTRIBUTE NUCLEOTIDE1 {A,C,G,T}
⋮
@ATTRIBUTE NUCLEOTIDE141 {A,C,G,T}
@ATTRIBUTE CODON1 {AAA,AAC,...,TTT}
⋮
@ATTRIBUTE CODON138 {AAA,AAC,...,TTT}
@ATTRIBUTE cls {1,-1}
@DATA
A,A,G,A,T,T,C,G,C,...,AAG,AGA,GAT,...,-1
```

In our previous work we used a bag-of-words approach with *k*-mers of length eight. This led to 4^8 or 65,535 *sparse features*. Moreover, those features did not take into consideration the location of each nucleotide. We believe that the major improvement we achieved is due to the features used, fewer and more location-aware.

We ran two different experiments with a grid search for the optimal values for $\beta \in \{0.1, 0.2, \ldots, 0.9\}$ and $\delta \in \{0.01, 0.02, \ldots, 0.08, 0.09, 0.1, 0.2\}$. In the first one, we used only the nucleotides as features, while

[2]WEKA Attribute-Relation File Format (ARFF) is described at http://www.cs.waikato.ac.nz/ml/weka/arff.html

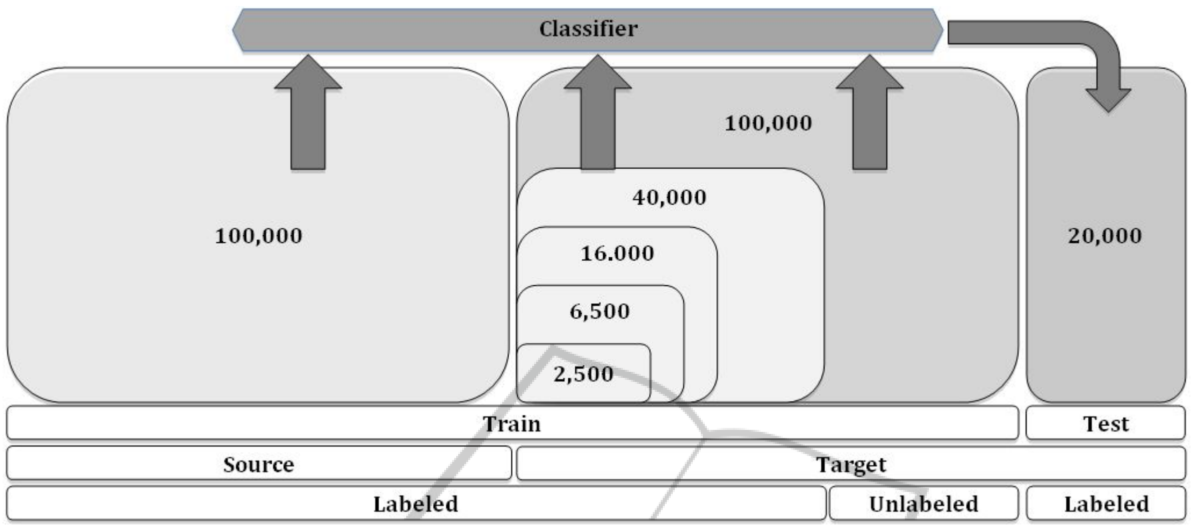


Figure 2: Experimental setup. Our algorithms are trained on the source labeled dataset (100,00 instances) from *C.elegans*, target labeled instances (2,500, 6,500, 16,000, or 40,000 instances) and target unlabeled instances (100,000 instances) from *C.remanei*, *P.pacificus*, *D.melanogaster*, or *A.thaliana*. Once trained, each algorithm is tested on 20,000 instances from the corresponding target dataset.

in the second one we used nucleotides and codons as features. In both settings, we ran Algorithm 1 to select the features in the source domain (A1), Algorithm 2 using Equation 9 to weigh the features in the source domain (A2E9), and Algorithm 2 with Equation 10 to weigh the source domain features (A2E10).

To ensure that our results are unbiased, we repeated the experiments three times with different training and test splits. We used two baselines to evaluate our classifiers. The first baseline, which we expect to represent the lower bound, is the naïve Bayes classifier trained on the target labeled data (NBT). We believe that this will be the lower bound for our classifiers because we expect that adding the labeled data from a related organism (the source domain) as well as unlabeled data from the same organism (the target domain) should produce a better classifier. The second baseline is the naïve Bayes classifier trained on the source labeled data (NBS). We expect that the more distantly related the two organisms are, the less accurate the classifier trained on the source data would be when tested on the target data.

Our goal with this experimental setup was to determine how each of the following influence the performance of the classifier:

1. Features used, i.e., nucleotides, or nucleotides and codons.
2. Algorithm used, i.e., Algorithm 1 which keeps only the generalizable features in the source domain, or Algorithm 2 which assigns different weights to the features in the source domain.
3. Number of target labeled instances used in training the classifier, i.e., 2,500, 6,500, 16,000, or 40,000.
4. The evolutionary distance between the source and target domains.
5. Using source labeled data and target unlabeled data when training the classifier.

3.5 Results

Since the class distribution is highly skewed, with each set containing about 1% positive instances and the rest, about 99%, negative instances, we used the area under the precision-recall curve as a metric for evaluating the accuracy of our classifiers, and we present the highest auPRCs averaged over the three folds.

In Table 1, we list the auPRC for our classifiers, the best overall algorithm in (Schweikert et al., 2008), $SVM_{S,T}$, and for the classifiers in (Herndon and Caragea, 2013b). An additional view, that presents the trends of our classifiers, is shown in the Appendix. Although our results are not as good as the ones in (Schweikert et al., 2008), they are greatly improved compared to results in (Herndon and Caragea, 2013b), yet not as much as we expected. Even though they are not as good as the $SVM_{S,T}$ in (Schweikert et al., 2008), they could be superior in some contexts. In addition, as we mentioned in Section 2, the complexity of SVM classifiers increases with the number of training instances and the number of features, when training the classifier (Schweikert et al.,

Table 1: auPRC values for four target organisms based on the number of labeled target instances used for training: 2,500, 6,500, 16,000, and 40,000. The tables on the left (a, c, g, and e) show the values for the algorithms trained with nucleotide features, while the tables on the right (b, d, f, and h) show the values for the algorithms trained with nucleotide and codons features. NBT and NBS are baseline naïve Bayes classifiers trained on target labeled and source data, respectively, for the two algorithms we proposed, Algorithm 1 (A1) and Algorithm 2 (A2E9 and A2E10 when using Equation 9 and 10, respectively). We show for comparison with our algorithms the values for the best overall algorithm in (Schweikert et al., 2008), $\mathrm{SVM}_{\mathrm{S,T}}$, and the values in (Herndon and Caragea, 2013b), ANB. Note that these values are shown in each table even though the $\mathrm{SVM}_{\mathrm{S,T}}$ and ANB algorithms used different features.

	2,500	6,500	16,000	40,000
ANB	1.13	1.13	1.13	1.10
NBT	23.42	45.44	54.57	59.68
A1	**59.18**	63.10	63.95	63.80
A2E9	35.03	46.08	54.89	59.73
A2E10	48.92	60.83	63.06	63.59
NBS	63.77			
SVM	77.06	77.80	77.89	79.02

(a) *C.remanei* (nucleotides)

	2,500	6,500	16,000	40,000
ANB	1.13	1.13	1.13	1.10
NBT	22.94	58.39	68.40	75.75
A1	45.29	**72.00**	74.83	77.07
A2E9	24.96	61.45	69.11	75.91
A2E10	49.22	70.23	**75.43**	**78.01**
NBS	77.67			
SVM	77.06	77.80	77.89	79.02

(b)*C.remanei* (nucleotides+codons)

	2,500	6,500	16,000	40,000
ANB	1.00	0.97	1.07	1.10
NBT	19.22	37.33	45.33	52.84
A1	**45.32**	49.82	52.09	54.62
A2E9	19.85	37.51	45.64	52.91
A2E10	37.20	48.71	52.31	55.62
NBS	49.12			
SVM	64.72	66.39	68.44	71.00

(c) *P.pacificus* (nucleotides)

	2,500	6,500	16,000	40,000
ANB	1.00	0.97	1.07	1.10
NBT	26.39	48.54	59.29	68.78
A1	20.21	53.29	62.33	69.88
A2E9	20.16	43.95	57.44	65.80
A2E10	20.19	**57.21**	**65.99**	**70.94**
NBS	67.10			
SVM	64.72	66.39	68.44	71.00

(d) *P.pacificus* (nucleotides+codons)

	2,500	6,500	16,000	40,000
ANB	1.07	1.13	1.07	1.03
NBT	14.90	26.05	35.21	39.42
A1	**33.31**	**36.43**	**40.32**	42.37
A2E9	16.27	26.21	35.12	39.16
A2E10	22.86	32.92	36.95	37.55
NBS	31.23			
SVM	40.80	37.87	52.33	58.17

(e) *D.melanogaster* (nucleotides)

	2,500	6,500	16,000	40,000
ANB	1.07	1.13	1.07	1.03
NBT	13.87	25.00	35.28	45.85
A1	25.83	32.58	39.10	**47.49**
A2E9	15.03	26.45	34.73	42.90
A2E10	22.53	29.47	36.18	42.92
NBS	34.09			
SVM	40.80	37.87	52.33	58.17

(f) *D.melanogaster* (nucleotides+codons)

	2,500	6,500	16,000	40,000
ANB	1.20	1.17	1.20	1.17
NBT	7.20	17.90	28.10	34.82
A1	**18.46**	**25.04**	31.47	36.95
A2E9	8.42	18.39	28.22	34.79
A2E10	13.61	22.28	29.05	34.66
NBS	11.97			
SVM	24.21	27.30	38.49	49.75

g) *A.thaliana* (nucleotides)

	2,500	6,500	16,000	40,000
ANB	1.20	1.17	1.20	1.17
NBT	3.10	8.76	28.11	40.92
A1	3.99	13.96	**33.62**	**43.20**
A2E9	2.65	8.72	29.39	40.35
A2E10	3.64	10.00	30.85	40.40
NBS	13.98			
SVM	24.21	27.30	38.49	49.75

h) *A.thaliana* (nucleotides+codons)

2008). While their algorithms "required an equivalent of about 1,500 days of computing time on state-of-the-art CPU cores" to tune their parameters (Schweikert et al., 2008), and additional computing to analyze the biological features, our algorithms required the equivalent of only 300 days of computing, and the results can be easily interpreted. Furthermore, we believe that our algorithms are interesting from a theoretical perspective and it is useful to know how well they perform.

Based on these results, we make the following observations:

1. Using a classifier with both the nucleotides and the codons as features performs better as the size of the target labeled data increases, while a classifier using only the nucleotides as features performs better with smaller target labeled datasets. We believe that this is caused by the fact that the codon features are sparser than the nucleotide features, and when there is little target labeled data the classifier does not have enough data to separate the positive from the negative instances.

2. The A1 classifier, based on Algorithm 1, and the A2E10 classifier, based on Algorithm 2, performed better than the other classifier, A2E9, each producing the best results in 11 and 5 cases, respectively. As mentioned above, the sparsity of the data affects the performance of the classifiers based on the features used. The A1 classifier, which uses only the nucleotides as features, performs better when the target labeled dataset is small, and also when the two organisms are more distantly related, while the A2E10 classifier, which uses the nucleotides and codons as features, performs better when the target labeled dataset is larger and the two organisms are more closely related.
3. The general trend in all classifiers is that they perform better as more target labeled instances are used for training. This conforms with our intuition that using a small dataset for training does not produce a good classifier.
4. As the evolutionary distance increases between the source and target organisms, the performance of our classifiers decreases. When the source and target organisms are closely related, as is the case with *C.elegans* and *C.remanei*, the large volume of labeled source data significantly contributes to generating a better classifier, compared to training a classifier on the target data alone. However, as the source and target organisms diverge, the source data contributes less to the classifier.
5. Using the source data and the target unlabeled data in addition to the target labeled data improves the performance of the classifier (e.g., A1 v. NBT for *A.thaliana* with 2,500 instances) compared to training a classifier on just the target labeled data. The improvement occurs even with larger datasets, although less substantial than with smaller datasets.

4 CONCLUSIONS AND FUTURE WORK

In this paper, we presented two similar domain adaptation algorithms based on the naïve Bayes classifier. They are based on the algorithms in (Herndon and Caragea, 2013a; Herndon and Caragea, 2013b), to which we made four changes. The first change was to use probabilities for computing the prior and likelihood, Equations 7 and 8, instead of the counts in Equations 2 and 3. The second change was to use mutual information in Equations 9 and 10 instead of marginal probabilities to rank the features in Equation 4. The third change was to assign different weights to the features from the source domain instead of selecting the features to use during training. The final change was to use fewer but more informative features. We used nucleotides and codons features that are aware of their location in the DNA sequence instead of 8-mers generated with a sliding window approach.

With these changes, we significantly improved the classification performance as compared to (Herndon and Caragea, 2013b). In addition, empirical results on the splice site prediction task support our hypothesis that augmenting a small labeled dataset with a large labeled dataset from a close domain and unlabeled data from the same domain improves the performance of the classifier. This is especially the case when we have small amounts of labeled data but the same trend occurs for larger labeled datasets as well.

In future work, we would like to more thoroughly evaluate the predictive power of the features we used, and to investigate whether other algorithms might produce better results when used with these features. To evaluate the features, we plan to use data from other organisms, and also shuffle the existing data and the labels, and see how this affects the performance of the classifiers. To identify algorithms that might potentially be better for the task addressed in this work, we will investigate other transfer learning algorithms and compare their results with the results of our proposed algorithms.

In addition, we would like to further improve our classifier and are considering three approaches. In one approach, besides the features derived from biological background, nucleotides (1-mers) and codons (3-mers), we would like to use additional features, such as 2-mers, for example, or biological features, such as pyrimidine-rich motifs around the acceptor splice site. In another approach, we would like to address the splice site prediction problem as an anomaly detection problem, since the preponderance of positive instances is so small. And in the final approach, we would like to balance the ratio of positive and negative instances going as far as using only the positive labeled data for training.

ACKNOWLEDGMENTS

The computing for this project was performed on the Beocat Research Cluster at Kansas State University, which is funded in part by NSF grants CNS-1006860, EPS-1006860, EPS-0919443, and MRI-1126709.

REFERENCES

Arita, M., Tsuda, K., and Asai, K. (2002). Modeling splicing sites with pairwise correlations.

Baten, A., Chang, B., Halgamuge, S., and Li, J. (2006). Splice site identification using probabilistic parameters and SVM classification.

Baten, A. K., Halgamuge, S. K., Chang, B., and Wickramarachchi, N. (2007). Biological Sequence Data Preprocessing for Classification: A Case Study in Splice Site Identification. In *Proceedings of the 4th international symposium on Neural Networks: Part II–Advances in Neural Networks*, ISNN '07, pages 1221–1230, Berlin, Heidelberg. Springer-Verlag.

Bernal, A., Crammer, K., Hatzigeorgiou, A., and Pereira, F. (2007). Global Discriminative Learning for Higher-Accuracy Computational Gene Prediction. *PLoS Comput Biol*, 3(3):e54.

Brown, M. P. S., Grundy, W. N., Lin, D., Cristianini, N., Sugnet, C., Furey, T. S., M.Ares, J., and Haussler, D. (2000). Knowledge-based Analysis of Microarray Gene Expression Data Using Support Vector Machines. *PNAS*, 97(1):262–267.

Cai, D., Delcher, A., Kao, B., and Kasif, S. (2000). Modeling splice sites with Bayes networks. *Bioinformatics*, 16(2):152–158.

Dai, W., Xue, G., Yang, Q., and Yu, Y. (2007). Transferring Naïve Bayes Classifiers for Text Classification. In *Proceedings of the 22nd AAAI Conference on Artificial Intelligence*.

Dempster, A. P., Laird, N. M., and Rubin, D. B. (1977). Maximum Likelihood from Incomplete Data via the EM Algorithm. *Journal of the Royal Statistical Society. Series B (Methodological)*, 39(1):1–38.

Gantz, J. H., Reinsel, D., Chute, C., Schlinchting, W., McArthur, J., Minton, S., Xheneti, I., Toncheva, A., and Manfrediz, A. (2007). The Expanding Digital Universe.

Herndon, N. and Caragea, D. (2013a). Naïve Bayes Domain Adaptation for Biological Sequences. In *Proceedings of the 4th International Conference on Bioinformatics Models, Methods and Algorithms*, BIOINFORMATICS 2013, pages 62–70.

Herndon, N. and Caragea, D. (2013b). *Predicting protein localization using a domain adaptation approach*. Communications in Computer and Information Science (CCIS 2013). Springer-Verlag.

Li, J., Wang, L., Wang, H., Bai, L., and Yuan, Z. (2012). High-accuracy splice site prediction based on sequence component and position features. *Genet Mol Res*, 11(3):3432–51.

Maeireizo, B., Litman, D., and Hwa, R. (2004). Co-training for predicting emotions with spoken dialogue data. In *Proceedings of the ACL 2004 on Interactive poster and demonstration sessions*, ACLdemo '04, Stroudsburg, PA, USA. Association for Computational Linguistics.

Mccallum, A. and Nigam, K. (1998). A Comparison of Event Models for Naïve Bayes Text Classification. In *AAAI-98 Workshop on 'Learning for Text Categorization'*.

Müller, K.-R., Mika, S., Rätsch, G., Tsuda, S., and Schölkopf, B. (2001). An Introduction to Kernel-Based learning Algorithms. *IEEE Transactions on Neural Networks*, 12(2):181–202.

Noble, W. S. (2006). What is a support vector machine? *Nat Biotech*, 24(12):1565–1567.

Rätsch, G. and Sonnenburg, S. (2004). Accurate Splice Site Prediction for Caenorhabditis Elegans. In *Kernel Methods in Computational Biology*, MIT Press series on Computational Molecular Biology, pages 277–298. MIT Press.

Rätsch, G., Sonnenburg, S., Srinivasan, J., Witte, H., Müller, K.-R., Sommer, R., and Schölkopf, B. (2007). Improving the C. elegans genome annotation using machine learning. *PLoS Computational Biology*, 3:e20.

Riloff, E., Wiebe, J., and Wilson, T. (2003). Learning subjective nouns using extraction pattern bootstrapping. In *Proceedings of the seventh conference on Natural language learning at HLT-NAACL 2003 - Volume 4*, CONLL '03, pages 25–32, Stroudsburg, PA, USA. Association for Computational Linguistics.

Schweikert, G., Widmer, C., Schölkopf, B., and Rätsch, G. (2008). An Empirical Analysis of Domain Adaptation Algorithms for Genomic Sequence Analysis. In *NIPS'08*, pages 1433–1440.

Shannon, C. E. (1948). A mathematical theory of communication. *The Bell System Technical Journal*, 27:379–423, 623–656.

Sonnenburg, S., Schweikert, G., Philips, P., Behr, J., and Rätsch, G. (2007). Accurate Splice site Prediction Using Support Vector Machines. *BMC Bioinformatics*, 8(Supplement 10):1–16.

Tan, S., Cheng, X., Wang, Y., and Xu, H. (2009). Adapting Naïve Bayes to Domain Adaptation for Sentiment Analysis. In *Proceedings of the 31th European Conference on IR Research on Advances in Information Retrieval*, ECIR '09, pages 337–349, Berlin, Heidelberg. Springer-Verlag.

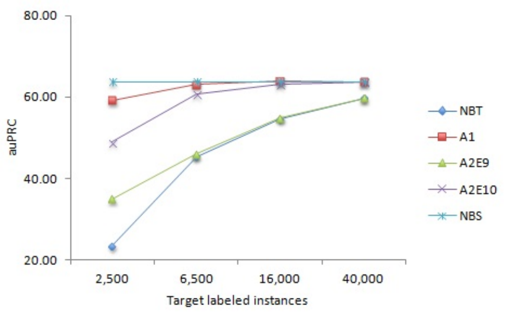
Yarowsky, D. (1995). Unsupervised word sense disambiguation rivaling supervised methods. In *Proceedings of the 33rd annual meeting on Association for Computational Linguistics*, ACL '95, pages 189–196, Stroudsburg, PA, USA. Association for Computational Linguistics.

Zhang, Y., Chu, C.-H., Chen, Y., Zha, H., and Ji, X. (2006). Splice site prediction using support vector machines with a Bayes kernel. *Expert Syst. Appl.*, 30(1):73–81.

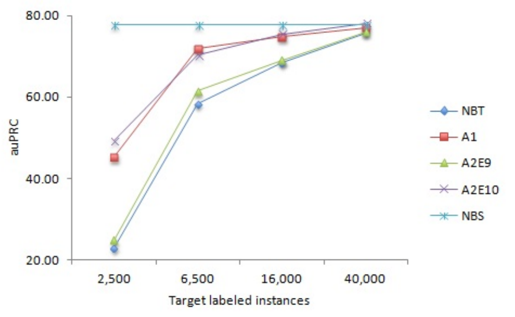
Zien, A., Rätsch, G., Mika, S., Schölkopf, B., Lengauer, T., and Müller, K.-R. (2000). Engineering support vector machine kernels that recognize translation initiation sites. *Bioinformatics*, 16(9):799–807.

APPENDIX

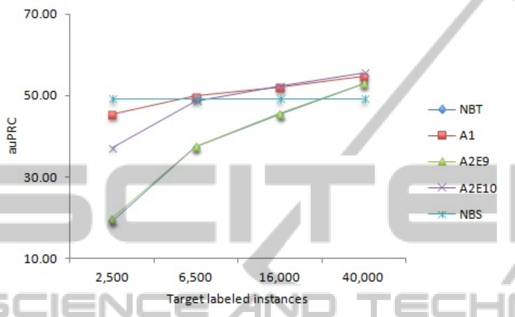
In this appendix we show the trends in our classifier based on the size of the target labeled dataset and the features used.



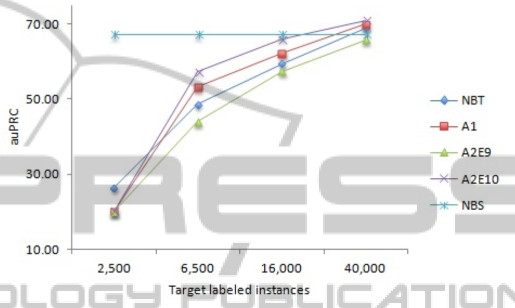
(a) *C.remanei* (nucleotides)



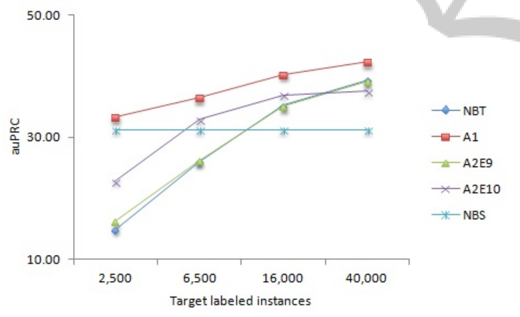
(b) *C.remanei* (nucleotides+codons)



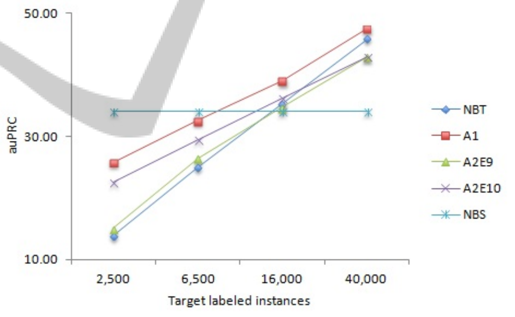
(c) *P.pacificus* (nucleotides)



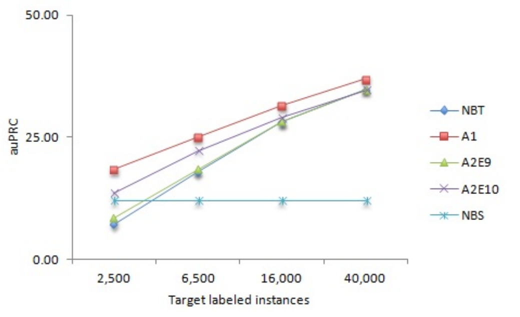
(d) *P.pacificus* (nucleotides+codons)



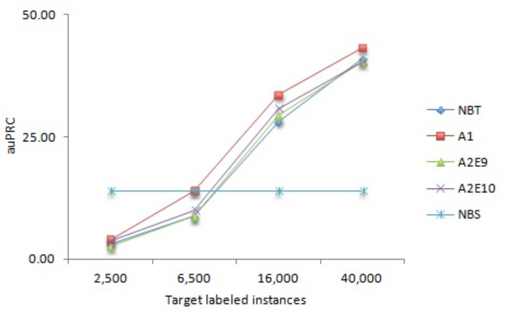
(e) *D.melanogaster* (nucleotides)



(f) *D.melanogaster* (nucleotides+codons)



(g) *A.thaliana* (nucleotides)



(h) *A.thaliana* (nucleotides+codons)

Figure 3: auPRC for four target organisms when using nucleotide features (a, c, g, and e), and nucleotide and codons features (b, d, f, and h). The names of the algorithms are the same as in Table 1. Note that the NBS baseline is always horizontal because we used the same dataset, the 100,000 instances from *C.elegans*. The following patterns can be observed from these graphs: (i) The performance increases with the size of the target labeled dataset used for training. (ii) The influence of the source dataset decreases as the distance between the source and target domains increases, as seen by decreasing performance of the naïve Bayes algorithm trained on the source dataset. (iii) Using labeled data from a related domain, some labeled data and as much unlabeled data leads to increased performance compared to an algorithm trained on only the labeled data from the target domain.