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An empirical comparison of supervised machine learning techniques in bioinformatics

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Abstract

Research in bioinformatics is driven by the experimental data. Current biological databases are populated by vast amounts of experimental data. Machine learning has been widely applied to bioinformatics and has gained a lot of success in this research area. At present, with various learning algorithms available in the literature, researchers are facing difficulties in choosing the best method that can apply to their data. We performed an empirical study on 7 individual learning systems and 9 different combined methods on 4 different biological data sets, and provide some suggested issues to be considered when answering the following questions: (i) How does one choose which algorithm is best suitable for their data set? (ii) Are combined methods better than a single approach? (iii) How does one compare the effectiveness of a particular algorithm to the others?

Keywords: Supervised machine learning, bioinformatics, ensemble methods, performance evaluation.

1 Introduction

In the post-genome era, research in bioinformatics has been overwhelmed by the experimental data. The complexity of biological data ranges from simple strings (nucleotides and amino acids sequences) to complex graphs (biochemical networks); from 1D (sequence data) to 3D (protein and RNA structures). Considering the amount and complexity of the data, it is becoming impossible for an expert to compute and compare the entries within the current databases. Thus, machine learning and artificial intelligence techniques have been widely applied in this domain to discover and mine the knowledge in the databases. Quoting from Baldi and Brunak (Baldi and Brunak, 2001) "As a result, the need for computer / statistical / machine learning techniques is today *stronger* rather than weaker."

Shavlik et al. (Shavlik et al., 1995) described the field of molecular biology as tailor-made for machine learning approaches. This is due to the nature of machine learning approaches that performs well in domains where there is a vast amount of data but little theory – this is exactly the situation in bioinformatics. Since the introduction of machine learning to this field, various algorithms and methods have been produced and applied to study different data sets. Most of these studies compare a 'new' algorithm with the conventional ones, asserting the effectiveness and efficiencies of their methods in particular data sets. The variety of learning algorithms currently available for the researchers are enormous and the main problems faced by researchers are: (i) How does one choose which algorithm is best suitable for their data set? (ii) Are combined methods better than a single approach? (iii) How does one compare the effectiveness of a particular algorithm to the others?

The objective of this study is to provide some suggestions for the community by answering the above questions. This paper is organised as follows. Section 2 presents a brief summary of machine learning. Section 3 outlines the materials and methods used in this study. Section 4 presents the results and discussion, and the final section summarises this work.

2 Machine Learning Background

A machine learning algorithm is one that can learn from experience (observed examples) with respect to some class of tasks and a performance measure. (Mitchell, 1997). Machine learning methods are suitable for molecular biology data due to the learning algorithm's ability to construct classifiers/hypotheses that can explain complex relationships in the data. The classifiers or hypotheses can then be interpreted by a domain expert who suggests some wet-lab experiments to validate or refute the hypotheses. This feedback loop between *in silico* and *in vivo* / *in vitro* experiments accelerates the knowledge discovery process over the biological data. This feedback is an important characteristic of machine learning in bioinformatics.

Generally, there are two types of learning schemes in machine learning: supervised learning where the output has been given *a priori* labelled or the learner has some prior knowledge of the data; and unsupervised learning where no prior information is given to the learner regarding the data or the output. The overall tasks for the learner are to classify, characterise, and cluster the input data. Classification is the most common task in biological problem where given two different sets of examples, namely positive E^+ and negative E^- examples ($E^+ \cap E^- = \varnothing$), the learner needs to construct a classifier to distinguish between the positive examples and the negative set. This classifier can then be used as the basis for classifying as yet unseen data in the future. Usually, for a supervised classification problem, the training examples are in the form of a set of tuples $\{(x_1, y_{1j}),...,(x_n, y_{nj})\}$ where x_i is the class label and y_{ij} is the set of attributes for the instances. The task of the learning algorithm is to produce

a classifier (hypothesis, function) to classify the instances into the correct class. In this study, we only consider supervised machine learning applied to classification.

3 Materials and Methodologies

3.1 Machine learning algorithms

We performed an empirical comparison of rule-based learning systems (Decision trees, One Rule, Decision rules), statistical learning system (Naïve Bayes, Instance Based, SVM and neural networks) and ensemble methods (Stacking, Bagging and Boosting) on the data listed in Table 1 based on the accuracy, positive predicted value, specificity and sensitivity of the learning algorithms. All the learning methods used in this study were obtained from the WEKA machine learning package (http://www.cs.waikato.ac.nz/~ml/weka/).

3.2 Data set

In this study we used the following data sets obtained from UCI machine learning repository (Blake and Merz, 1998). We briefly describe the biological motivation for the data sets; interested readers should refer to the cited papers for details.

E.coli data set – The objective of this data set is to predict the cellular localisation sites of E.coli proteins (Horton and Nakai, 1996). There are 8 different cellular sites, which are cytoplasm (cp), inner membrane without signal sequence (im), periplasm (pp), inner membrane with uncleavable signal sequence (imU), outer membrane (om), outer membrane lipoprotein (omL), inner membrane lipoprotein (imL) and inner membrane with cleavable signal sequence (imS). The attributes are signal sequence recognition methods (specifically those of McGeoch and von Heijne), the presence of charge on N-terminus of predicted lipoproteins and 3 different scoring functions on the amino acid contents whether predicted as a outer membrane or inner membrane, cleavable or uncleavable sequence signal.

Yeast data set – The objective is similar to the E.coli data, which is to determine the cellular localisation of the yeast proteins (Horton and Nakai, 1996). There are 10 different sites, which include: CYT (cytosolic or cytoskeletal); NUC (nuclear); MIT (mitochondrial); ME3 (membrane protein, no N-terminal signal); ME2 (membrane protein, uncleaved signal); ME1 (membrane protein, cleaved signal); EXC (extracellular); VAC (vacuolar); POX (peroxisomal) and ERL (endoplasmic reticulum lumen). The attributes are similar to the E.coli data set with the addition of nuclear localisation information.

Promoter data set. The task of the classifier is to predict whether a DNA sequence from E.coli is either a promoter or not (Towell et al., 1990). The input data is a 57-nucleotide sequence (A, C, T or G).

HIV data set – The data set contains 362 octamer protein sequences each of which needs to be classified as an HIV protease cleavable site or uncleavable site (Cai and Chou, 1998).

Data set	**E.coli**	**Yeast**	**Promoters**	**HIV**
Continuous Attribute	2	0	57	8
Discrete Attribute	5	8	0	0
Classes	8	10	2	2
Data Size	336	1484	106	362

Table 1: Data sets used in this study.

3.3 Evaluation

We constructed a confusion matrix (contingency table) to evaluate the classifier's performance. Table 2 shows a generic contingency table for a binary class problem. True positives (TP) denote the correct classifications of positive examples. True negatives (TN) are the correct classifications of negative examples. False positives (FP) represent the incorrect classifications of negative examples into class positive and False negatives (FN) are the positive examples incorrectly classified into class negative.

		Predicted	
		Positive	**Negative**
Actual	**Positive**	TP	FN
	Negative	FP	TN

Table 2: A contingency table for a binary class problem.

Based on the contingency table, several measurements can be carried out to evaluate the performance of the induced classifier. The most popular performance evaluation measure used in prediction or classification learning is classifier accuracy which measures the proportion of correctly classified instances; $Acc = \frac{TP + TN}{TP + TN + FP + FN}$.

Positive Predictive Accuracy (PPV, or the reliability of positive predictions of the induced classifier) is computed by $PPV = \frac{TP}{TP + FP}$. Sensitivity (S_n) measures the fraction of actual positive examples that are correctly classified $S_n = \frac{TP}{TP + FN}$; while specificity (S_p) measures the fraction of actual negative examples that are correctly classified $S_p = \frac{TN}{TN + FP}$.

3.4 Cross-validation

To evaluate the robustness of the classifier, the normal methodology is to perform cross validation on the classifier. Ten fold cross validation has been proved to be statistically good enough in evaluating the performance of the classifier (Witten and Frank, 2000). In ten fold cross validation, the training set is equally divided into 10 different subsets. Nine out of ten of the training subsets are used to train the learner and the tenth subset is used as the test set. The procedure is repeated ten times, with a different subset being used as the test set.

4 Results and Discussion

We summarise our experimental results in Figure 1 and 2. The full analysis of this study is available in http://www.brc.dcs.gla.ac.uk/~actan/APBC2003.

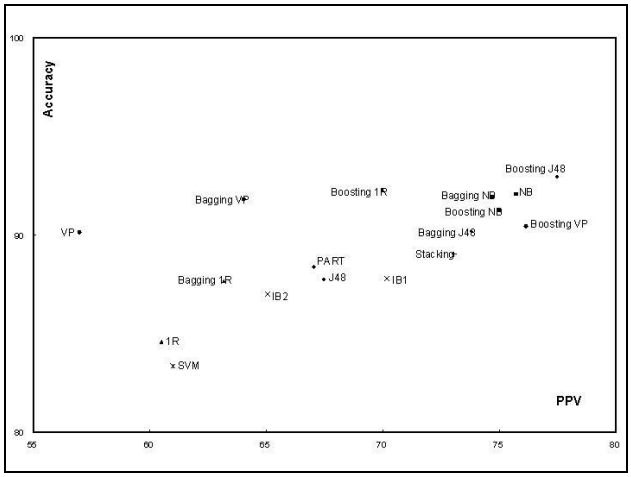

Figure 1. Accuracy vs Positive Predictive Value

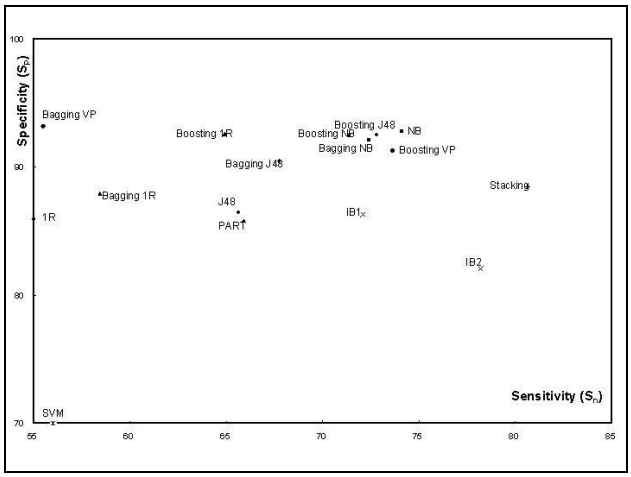

Figure 2. Specificity vs Sensitivity

From the results, we observed that most of the individual learners tend to perform well either in accuracy or specificity. Probably this is due to the induced classifier being able to characterise the negative examples (most of the training sets have large ratio of negative examples compared to positive examples). Furthermore, the results suggest that combination approaches are in general better at minimising overfitting of the training data. We also observed from this experiment that boosting performs better than bagging. This is because attributes which are highly important in discriminating between classes are randomly removed by bagging; however they are preserved in boosting and thus contribute to the final voting scheme. The only individual learning system that perform better than the combined methods is Naïve Bayes learning. This may suggest that Naïve Bayes is capable of classifying instances based on simple prior probabilistic knowledge. In this study SVM does not perform well compared to other methods, probably due to the fact that training data are not separable in the vector space.

4.1 Rules-of-thumb

In this section, we address the following questions by providing some suggested issues (rules-of-thumb) to be considered when answering them.

(i) How does one choose which algorithm is best suitable for their data set?

Ratio of the training data – From these experiments, we observed that the division of the training data plays a crucial role in determining the performance of the algorithms. If the training TPs and TNs are almost equal in size, the algorithms tend to construct much better classifiers. This observation suggested that the classifier induced from equal size of TP and TN tend to be more robust in classifying the instances. Furthermore, the classifiers generated consider all the discriminative attributes that distinguish between two different classes. If the size of the TP set is small compared to that of TN, most probably the classifier will overfit the positive examples and thus perform poorly in the cross validation stages.

Attributes – Another factor that must be taken into consideration when choosing a learning method is the nature of the attributes. Generally, statistical methods (e.g. SVM, neural networks) tend to perform much better over multi-dimensions and continuous attributes. This is because the learning strategy embedded in these algorithms enables the learners to find a maximal margin that can distinguish different classes in the vector space. By contrast, rule-based systems (e.g. Decision trees, PART) tend to perform better in discrete / categorical attributes. The algorithms of these methods operate in a top-down manner where the first step is to find the most discriminative attribute that classifies different classes. The process is iterated until most of the instances are classified into their class.

Credibility vs. Comprehensibility – When choosing a machine learning technique, users need to ask themselves what they really want to "discover" from the data. If they are interested in generating understandable hypotheses, then a rule-base learning algorithm should be used instead of statistical ones. Most machine learning algorithms follow Occam's principle when constructing the final hypothesis. According to this principle, the algorithm tends to find the simplest hypotheses by avoiding overfitting the training data. But does this principle still hold in bioinformatics? In bioinformatics we often wish to explore data and explain results, and hence we are interested in applying intelligent systems to provide an insight to understand the relations between complex data. The question then arises as to whether we prefer a simple classifier or a highly comprehensible model. In general, there is a trade off between the credibility and comprehensibility of a model. Domingos (1999) suggested applying domain constraints as an alternative for avoiding overfitting the data. We agree with Muggleton et al. (1998) that when comparing the performance of learning systems in a bioinformatics context, the hypothesis with better explanatory power is preferable when there exist more than one hypotheses with statistical equivalent predictive accuracy.

(ii) Are combined methods better than a single approach?

From the experiments most of the combined methods perform better than the individual learner. This is because none of the individual methods can claim that they are superior to the others due to statistical, computational and representational reasons (Dietterich, 2000). Every learning algorithm uses a different search strategy. If the training data is too small, the individual learner can induce different hypotheses with similar performances from the search space. Thus, by averaging the different hypotheses, the combined classifier may produce a good approximation to the true hypotheses. The computational reason is to avoid local optima of individual search strategy. By performing different initial searches and combining the outputs, the final classifier may provide a better approximation to the true hypotheses. Lastly, due to the limited amount of training data, the individual classifier may not represent the true hypotheses. Thus, through considering different classifiers, it may be possible to expand the final classifier to an approximate representation of the true hypotheses. Ensemble learning has been an active research topic in machine learning but not in the bioinformatics community. Since most of the hypotheses induced are from incomplete biological data, it is essential to generate a good approximation by combining individual learners.

(iii) How does one compare the effectiveness of a particular algorithm to the others?

Predictive accuracy – Most of the time, we can find in the literature reports that a learning scheme performs better than another in term of one model's accuracy when applied to a particular data set. From this study, we found that accuracy is not the ultimate measurement when comparing the learner's credibility. Accuracy is just the measurement of the total correctly classified instances. This measurement is the overall error rate, but there can be other measures of the accuracy of a classifier rule. If the training data set has 95 TNs and 5 TPs, by classifying all the instances into a negative class, the classifier still can achieve a 95% accuracy. But the sensitivity and the positive predicted value is 0% (both measurements evaluate the performance in classifying TPs). This means that although the accuracy of the classifier is 95% it still cannot discriminate between the positive examples and the negatives. Thus, when comparing the performance of different classifiers, accuracy as a measure is not enough. Different measures should be evaluated depending on what type of question that the user seeks to answer. See Salzberg (Salzberg, 1999) for a tutorial on comparing classifiers.

5 Conclusions

Machine learning has increasingly gained attention in bioinformatics research. With the availability of different types of learning methods, it has become common for the researchers to apply the off-shelf systems to classify and mine their databases. In the research reported in this paper, we have performed a comparison of different supervised machine learning techniques in classifying biological data. We have shown that none of the single methods could consistently perform well over all the data sets. The performance of the learning techniques is highly dependant on the nature of the training data. This study also shows that combined methods perform better than the individual ones in terms of their specificity, sensitivity, positive predicted value and accuracy. We have suggested some rules-of-thumb for the reader on choosing the best suitable learning method for their dataset.

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