Evaluating the denoising techniques in protein-protein interaction prediction

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Abstract—The past decades witnessed extensive efforts to study the relationships among proteins. Particularly, sequence-based protein-protein interactions (PPIs) prediction is fundamentally important in speeding up the process of mapping interactomes of organisms. The composition vectors are usually constructed to encode proteins as real-value vectors, which is feeding to a machine learning framework. However, the composition vector value might be highly correlated to the distribution of amino acids, i.e., amino acids which are frequently observed in nature tend to have a large value of composition vector. Thus formulation to estimate the noise may be needed during representations. Here, we introduce two kinds of denoising composition vectors, which are efficient in construction of phylogenetic trees, to eliminate the noise. When validating these two denoising composition vectors on Escherichia coli (E.coli) and Saccharomyces cerevisiae (S.cerevisiae) randomly and artificial negative datasets, respectively, the predictive performance is not improved, and even worse than non-denoised prediction. These results suggest that, the denoising formulation efficient in phylogenetic trees construction can not improve the PPIs prediction, that is, what is noise is dependent on the applications.

1. INTRODUCTION

Identification of the interactions among proteins is crucial to illustrate their functions, and further, can help us to understand the underlying mechanisms of many biological phenomena, such as cell cycles, apoptosis, signal transduction and pathogenesis of diseases. It has become one of the most challenging and important tasks in the post-proteomic researches. Various experimental techniques have been developed for large-scale protein-protein interactions (PPIs) analysis, including yeast two-hybrid systems [1], [2], mass spectrometry [3], [4], protein chip [5] and so on. One computational idea is applying the machine learning methods to learn understandable rules from the available PPIs and furthermore to predict novel interactions. Comparing with costly and time-consuming biochemical experiments, computational methods for PPIs prediction have played an important role [6].

One key issue in machine learning is to extract protein attributes that are highly relevant to prediction of PPIs. Among the various attributes of proteins, the primal sequences are most popular because they are the most basic and the easiest to obtain due to the rapid development of genomic sequencing technologies. In addition, the primary sequences of proteins actually specify their structures that provide the molecular basis for PPIs. Therefore protein primary sequences hold the promise to contain virtually sufficient information to construct the most universal predicting method [6].

The first challenge to construct a universal sequence-based PPIs predictor is how to encode the given proteins as the real-value vectors. Many types of composition vectors have been proposed [6], [7], [8], [9], [10], [11]. However, the composition vector value might be highly correlated to the distribution of amino acids, i.e., amino acids which are frequently observed in nature tend to have a large value of composition vector. Thus formulation to estimate the noise seems to be needed during representations. There are some works that have discussed this problem, for example, Chang, T.H. et.al. have proposed a probability-based mechanism for transforming protein sequences into feature vectors to eliminate the noise of composition vector [12]. With an efficient classification algorithm, the newly designed PPIs predictor is essential for handling highly unbalanced Human PPIs datasets. However,
when constructing one protein denoising composition vector, more than 10 thousand times permutation are implemented, the computational consumption is very large. Chan, R.H.F. et al have proposed a low computational cost denoising mechanism, which is based on the principle of maximum entropy, to encode the proteins as real-value vectors [13]. By using the angle-based distance measures on the denoising vectors, they have constructed well-grouped phylogenetic trees.

Following the previous works, in this paper, to improve the performance of PPIs prediction, we introduce two types of low costly denoising formulas, which are successfully used in phylogenetic tree construction. By applying Signal-to-Noise Ratio as the input vector, the given protein is converted to a real-value vector, which is feeding to the machine learning approaches. To test whether the predictive results can be improved by denoising, we introduce the support vector machine (SVMs) as the PPIs predictor. SVMs, which are motivated by statistical learning theory [14], [15], [16], have been proven successful on many different classification problems in bioinformatics [17]. Identification of PPIs can be addressed as the two-classification problem: determining whether a given pair of proteins is interacting or not. Inspired by that, in this paper, two-class SVM with the composition vectors and denoising composition vectors are used to predict Escherichia coli (E.coli) and Saccharomyces cerevisiae (S.cerevisiae) PPIs, respectively. As a result, both on E.coli and S.cerevisiae randomly and artificial negative datasets, the predictive performance are not improved by introducing the denoising formulations. These results suggest that, the denoising formulation efficient in phylogenetic trees construction can not improve the PPIs prediction, that is, what is noise is dependent on the applications.

II. MATERIALS AND METHODS

Sequence-based attributes become popular in PPIs prediction not only because that the primal sequences are most basic and the easiest to obtain, but also owing to the assumption that knowledge of the amino acid sequence alone might be sufficient to estimate the evolutionary history, overall structure and function, and the interacting propensity between two proteins. Especially, Shen et.al. have proposed a much simple feature encoding method, called conjoint triad feature (CTF) to represent the protein sequences [6]. The authors have shown that SVM with the CTF outperforms other sequence-based methods in human PPIs prediction. In addition, the CTF can be implemented in an economic way and contains no predefined parameters. Inspired by these, here, we first introduce the CTF and then apply the denoising approaches to formulate the denoising CTF vectors. In results section, we test the performance of the denoising CTF vectors on E.coli and S.cerevisiae randomly and artificial negative datasets.

A. Input feature vectors

We give the description on the CTF now. Firstly, based on the dipoles and volumes of the side chains, the 20 amino acids are classified into seven classes: \{A, G, V\}, \{I, L, F, P\}, \{Y, M, T, S\}, \{H, N, Q, W\}, \{R, K\}, \{D, E\}, \{C\}. Secondly, a 343 (7 \times 7 \times 7)-dimension vector is used to represent a given protein, where each element of this vector is the frequency of the corresponding conjoint triad appearing in the protein sequence. More detailed description for the CTF can be found in [6].

1) Denoising vectors: The CTF considers the frequency of each conjoint triad type. However, the value of CTF’s element might be highly correlated to the distribution of amino acids, i.e., triads that consist of amino acid groups frequently observed in nature (e.g., group 1 and 2) tend to have a large value of frequency. To deal with this problem, we introduce two types of denoising formulas, which are efficient in phylogenetic tree construction, to remove noises.

Specially, given a conjoint triad type \(\alpha_1\alpha_2\alpha_3\), the following two formulas proposed by Hao et al. [18] and Yu et al. [19], are applied to estimate the noise of \(\alpha_1\alpha_2\alpha_3\):

Hao’s Formula:

\[
q^{Hao}(\alpha_1\alpha_2\alpha_3) = \begin{cases} 
\frac{f(\alpha_1\alpha_2)f(\alpha_2\alpha_3)}{f(\alpha_2)}, & \text{if } f(\alpha_2) \neq 0 \\
0, & \text{otherwise,}
\end{cases}
\]

where \(f(u)\) represents the frequency of any string \(u\) appearing in the sequence. The formula (1) reveals the functional and evolutionary relatedness of word sequence, and was successfully applied for the phylogenetic analysis of prokaryotes, based on whole genome sequences [18].

Yu’s Formula:

\[
q^{Yu}(\alpha_1\alpha_2\alpha_3) = f(\alpha_1)f(\alpha_2\alpha_3) + f(\alpha_1\alpha_2)f(\alpha_3),
\]

(2)

where \(f(u)\) represents the frequency of any string \(u\) appearing in the sequence. The formula (2) was commonly introduced in the area of complex and dynamic systems, and was successfully applied for the phylogenetic analysis of prokaryotes, chloroplasts and other phylogenetic problems, based on whole genome sequences [19].

Then the input vector feeding to the SVM can be formulated as the Signal-to-Noise Ratio:

\[
s(\alpha_1\alpha_2\alpha_3) = \frac{f(\alpha_1\alpha_2\alpha_3) - q(\alpha_1\alpha_2\alpha_3)}{q(\alpha_1\alpha_2\alpha_3)}. \tag{3}
\]

Comparing with the CTF, the element of the denoising vector become the Signal-to-Noise Ratio \(s\). For any string of \(\alpha_1\alpha_2\alpha_3\), when the value of \(q(\alpha_1\alpha_2\alpha_3)\) is zero, it means the corresponding noise is zero. Therefore, in this situation, we let the Signal-to-Noise Ratio \(s(\alpha_1\alpha_2\alpha_3)\) be the value of \(f(\alpha_1\alpha_2\alpha_3)\).

If the value of noise \(q\) is zero for a string \(\alpha_1\alpha_2\alpha_3\), we let \(s(\alpha_1\alpha_2\alpha_3)\) be the value of \(f(\alpha_1\alpha_2\alpha_3)\).

2) Protein pairs vectors: PPIs prediction treats each protein pair as the input, the vectors representing the protein pairs should be proposed. The concatenation operator are common used in protein pairs representation. However, the asymmetry problem will arise due to the fact that the prediction result will be different on protein pair A-B and B-A. To solve this
problem, we concatenate the arithmetical and the geometric average of protein vectors to represent the protein pairs, i.e.: 

$$F_{AB} = \frac{F_A + F_B}{2} \oplus F_A \ast F_B,$$

(4)

where $F_A, F_B$ represent the feature vector of protein A and B, the operator $\oplus$ means the multiplication of the corresponding elements, and $\oplus$ represents the concatenation operator. The above representation method for protein pairs can not only maintain symmetry (A-B identical to B-A), but also make the feature vectors representing proteins constructed uniquely from the protein pair representing vector.

B. Training negative datasets

With the above feature vector construction scheme, the PPI prediction task is ready to be formalized as a classification problem with the publicly available PPIs as the positive samples, and the others as the negative samples. The training data imbalance problem will arise, because there are only a relatively small number of known PPIs. This situation will make the SVM ineffective in determining the class boundary [20]. To maintain a balance between training positive and negative datasets in SVM training procedure, we introduce two types of negative datasets. The first one is the randomly negative dataset. The randomly negative samples are sampled randomly from the complementary graph of the known PPI network. Comparing with the method for generating the training negative dataset with the help of the functional annotation of proteins, this randomly generating scheme for training negative data can lead to unbiased estimates of prediction accuracy [21]. The second one is the artificial negative dataset. The artificial negative samples are constructed by uShuffle based on the positive datasets, which is successfully used in S.cerevisiae PPIs prediction [23].

C. Benchmark datasets and SVM implementation

Here, PPIs on two different organisms: E.coli and S.cerevisiae are used to validate the performance of the proposed predictive models. The detailed information of these benchmark datasets can be found in Table 1 in [10]. The protein sequences are downloaded from the RefSeq database of NCBI. In addition, the interactions which contain missing proteins in the corresponding proteome sequence datasets are excluded. Thus the number of interactions is 6954 and 6635 for E.coli and S.cerevisiae, respectively.

We train the two-class SVM with denoising CTF and CTF by using LibSVM [24]. In the implementation of two-class SVM, the RBF kernel function is used. The penalty parameter $C$ and the RBF kernel parameter $\gamma$ are optimized by grid search approach with 3-fold cross-validation. To evaluate the performance of our methods, we use the 10-fold cross-validation. The performances of our proposed methods are evaluated by the following evaluation criterions: AUC (area under the receiver operating curve (ROC) curve [25], Accuracy (Acc) = $\frac{TP}{TP + TN + FP + FN}$, Sensitivity (Sn) = $\frac{TP}{TP + FN}$, Specificity (Sp) = $\frac{TN}{TN + FP}$, Precision (Pre) = $\frac{TP}{TP + FP}$, and F-measure = $\frac{2 \times Sn \times Sp}{Sn + Sp}$.

III. RESULTS

A. The performance on the randomly negative datasets

We first test the effect of two kinds of denoising CTF (Denoising$^{\text{Yao}}$ CTF and Denoising$^{\text{Yu}}$ CTF) on E.coli and S.cerevisiae randomly negative datasets, respectively. The evaluation criterions obtained by denoising CTF and CTF on E.coli and S.cerevisiae randomly negative datasets when the corresponding F-measure is the largest are shown in Table 1. From Table 1, we can see that, on both E.coli and S.cerevisiae randomly negative datasets, Denoising$^{\text{Yu}}$ CTF outperforms Denoising$^{\text{Yao}}$ CTF with high AUC and all other criterions. However, both Denoising$^{\text{Yu}}$ CTF and Denoising$^{\text{Yao}}$ CTF perform worse than the CTF. For example, on E.coli randomly negative dataset, comparing with the CTF, the AUC and Sn obtained by Denoising$^{\text{Yao}}$ CTF decrease by one percent, and the other criterions decrease by more or less to a certain extent. On S.cerevisiae randomly negative datasets, comparing with the CTF, the AUC and Sn obtained by Denoising$^{\text{Yu}}$ CTF are not as good as that of CTF, and even worse than it. That is, the denoising procedure can not improve the performance of PPIs prediction.

B. The performance on the artificial negative datasets

We then test the effect of two kinds of denoising CTF on E.coli and S.cerevisiae artificial negative datasets, respectively. The evaluation criterions obtained by denoising CTF and CTF on E.coli and S.cerevisiae artificial negative datasets when the corresponding F-measure is the largest are shown in Table 2. Table 2 show that, on both E.coli and S.cerevisiae artificial negative datasets, Denoising$^{\text{Yao}}$ CTF decreases by more or less to a certain extent. On E.coli, Acc, Sp, Pre and F-measure obtained by Denoising$^{\text{Yao}}$ CTF decrease by two or three percent, and the Sn drops by seven percent. These results suggest that, on randomly negative dataset, the performance of Denoising$^{\text{Yao}}$ CTF and Denoising$^{\text{Yu}}$ CTF are not as good as that of CTF, and even worse than it. That is, the denoising procedure can not improve the performance of PPIs prediction.
TABLE I

THE PERFORMANCE COMPARISON OF DENOISING CTF WITH CTF ON RANDOMLY GENERATED NEGATIVE SET.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Encoding methods</th>
<th>AUC</th>
<th>Acc</th>
<th>Sn</th>
<th>Sp</th>
<th>Pre</th>
<th>F-measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>CTF</td>
<td>0.886</td>
<td>0.797</td>
<td>0.794</td>
<td>0.799</td>
<td>0.798</td>
<td>0.797</td>
</tr>
<tr>
<td></td>
<td>Denoising&lt;sup&gt;Hao&lt;/sup&gt; CTF</td>
<td>0.849</td>
<td>0.763</td>
<td>0.726</td>
<td>0.799</td>
<td>0.784</td>
<td>0.761</td>
</tr>
<tr>
<td></td>
<td>Denoising&lt;sup&gt;Yu&lt;/sup&gt; CTF</td>
<td>0.877</td>
<td>0.791</td>
<td>0.782</td>
<td>0.799</td>
<td>0.796</td>
<td>0.791</td>
</tr>
<tr>
<td>S.cerevisiae</td>
<td>CTF</td>
<td>0.948</td>
<td>0.808</td>
<td>0.879</td>
<td>0.927</td>
<td>0.909</td>
<td>0.882</td>
</tr>
<tr>
<td></td>
<td>Denoising&lt;sup&gt;Hao&lt;/sup&gt; CTF</td>
<td>0.924</td>
<td>0.853</td>
<td>0.806</td>
<td>0.899</td>
<td>0.889</td>
<td>0.851</td>
</tr>
<tr>
<td></td>
<td>Denoising&lt;sup&gt;Yu&lt;/sup&gt; CTF</td>
<td>0.929</td>
<td>0.862</td>
<td>0.824</td>
<td>0.899</td>
<td>0.891</td>
<td>0.861</td>
</tr>
</tbody>
</table>

On S.cerevisiae 1-let datasets, comparing with the CTF, although Acc, Sn, Pre and F-measure obtained by Denoising<sup>Yu</sup> CTF increase by one percent, the AUC increases only 0.1 percent. On 2-let dataset, comparing with the CTF, although Acc, Sn and F-measure obtained by Denoising<sup>Yu</sup> CTF increase by two to four percent, the AUC only has 0.1 percent improvement. These results suggest that, on S.cerevisiae artificial negative dataset, the Denoising<sup>Yu</sup> CTF outperforms the CTF with 0.1 percent AUC improvement. However, this little improvement is insufficient to support the fact that the prediction performance can be improved by introducing the denoising procedure.

C. The performance of denoising formula on the gene level

Hao’s and Yu’s formulas were primal proposed on the gene level in [13]. By introducing these denoising formulas, the well-grouped phylogenetic trees have been constructed. Therefore, we test the effect of these two denoising formulas on the gene level on E.coli and S.cerevisiae randomly negative datasets, respectively. That is, we encode protein sequences by codon composition, and introduce the denoising formulas (1) and (2) as the noise of the codon composition, respectively, then apply the Signal-to-Noise Ratio as the input vectors for representing the proteins. The equation (4) is also applied as the representation vector for protein pairs, and it is denoted as denoising codon. The evaluation criterions obtained by denoising codon and codon composition on E.coli and S.cerevisiae randomly negative datasets, respectively. The lower accuracy of denoising methods here may be caused by that the CTF first classifies twenty amino acids into seven classes based on the dipoles and volumes of the side chains, and then apply conjoint triad composition to represent the given protein. That is, the denoising is already done by fusing amino acids, and further denoising will make information shrink. In the future, we will test the denoising effect based on protein composition vector without fusion amino acids, and further test the conclusions obtained in this article.

Although the dimension reduction is already done by fusing twenty amino acids into seven classes, the most elements of CTF might be redundant and irrelevant, and might not contribute significantly to the PPIs prediction. Therefore, the performance of PPIs prediction might be improved by selecting only relevant elements. Future work will try to do some related works by introducing some wonderful feature selection approaches.

IV. DISCUSSION AND CONCLUSION

In this paper, to improve the performance of PPIs prediction, we introduce the denoising idea which is proved to be useful in construction of phylogenetic trees into the prediction algorithm. Specially, we first encode the given protein sequence by the composition vector, and then introduce two denoising formulas proved to be useful in phylogenetic tree construction as the noise vector, finally apply the Signal-to-Noise Ratio as the input vector for representing the given protein. The concatenation of arithmetical and geometric average of protein vectors is used as the protein pair representation vector, which can not only maintain symmetry, but also make the protein representing vectors constructed uniquely from the protein pair representing vector. We test the effect of the denoising vectors on E.coli and S.cerevisiae randomly and artificial negative datasets, and compare it with the primal composition vectors. The evaluation criterions obtained by both two denoising vectors are not improved. These results suggest that, although the denoising methods can improve the performance of phylogenetic trees construction, it can not improve the performance of PPIs prediction. That is, what is noise is dependent on the applications.

ACKNOWLEDGMENT

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<table>
<thead>
<tr>
<th>Organism</th>
<th>Encoding methods</th>
<th>AUC</th>
<th>Acc</th>
<th>Sn</th>
<th>Sp</th>
<th>Pre</th>
<th>F-measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>1let-CTF</td>
<td>0.957</td>
<td>0.891</td>
<td>0.882</td>
<td>0.899</td>
<td>0.898</td>
<td>0.891</td>
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<td>0.910</td>
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<td>0.809</td>
<td>0.823</td>
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<td>0.890</td>
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<td>0.882</td>
<td>0.879</td>
<td>0.887</td>
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<td>0.868</td>
<td>0.899</td>
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<td>1let-Denoising\textsuperscript{\textregistered} CTF</td>
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<td>0.845</td>
<td>0.899</td>
<td>0.894</td>
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</tbody>
</table>

**TABLE III**

The performance comparison of denoising codon composition with codon composition on randomly generated negative set.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Encoding methods</th>
<th>AUC</th>
<th>Acc</th>
<th>Sn</th>
<th>Sp</th>
<th>Pre</th>
<th>F-measure</th>
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<td>E.coli</td>
<td>codon</td>
<td>0.897</td>
<td>0.812</td>
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<td>0.868</td>
<td>0.775</td>
<td>0.751</td>
<td>0.799</td>
<td>0.789</td>
<td>0.774</td>
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<tr>
<td>S.cerevisiae</td>
<td>codon</td>
<td>0.942</td>
<td>0.881</td>
<td>0.863</td>
<td>0.899</td>
<td>0.896</td>
<td>0.881</td>
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**REFERENCES**


