Prediction of Protein Functions Using Protein Interaction Data

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Abstract. Information on protein-protein interactions provides valuable insight into the underlying mechanism of protein functions. However, the accuracy of protein-protein interaction data obtained by high-throughput experimental methods is low, and thus requires a rigorous assessment of their reliability. This paper proposes a computational method for predicting the unknown function of a protein interacting with a protein with known function, and presents the experimental results of applying the method to the protein-protein interactions in yeast and human. This method can also be used to assess the reliability of the protein-protein interaction data.

1 Introduction

High-throughput experimental techniques enable the study of protein-protein interactions at the proteome scale through systematic identification of physical interactions among all proteins in an organism [1]. The increasing volume of protein-protein interaction data is becoming the foundation for new biological discoveries. Protein-protein interactions play important roles in nearly all events that take place in a cell [1]. Particularly valuable will be analyses of proteins that play pivotal roles in biological phenomena in which the physiological interactions of many proteins are involved in the construction of biological pathways, such as metabolic and signal transduction pathways [2].

Here is a more elaborate example. All biochemical process is regulated through protein function. Therefore, diseases (hereditary/non-hereditary) are made manifest as a result of protein function. Also, finding protein function is necessary for the normal progression of medicinal development. Thus, with the completion of genome sequencing of several organisms, the functional annotation of the proteins is of most importance [3]. This function is considered as property of sequence or structure.

Several research groups have developed methods for functional annotation. The classical way is to find homologies between a protein and other proteins in databases using programs such as FASTA and PSI-BLAST, and then predict functions [3]. Another approach is called the *Rosetta stone method*, where two proteins are inferred to interact if they are together in another genome [3]. We propose a method for determining the reliability of the protein-protein interaction data obtained by high-

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throughput experimental methods. This method can also be used for predicting the unknown function of a protein interacting with a protein with known function.

2 Analysis of Yeast Protein Data

2.1 Data Sets

The data of yeast protein interactions were obtained from the Comprehensive Yeast Genome Database (CYGD) at MIPS [7]. After removing 1,150 redundant data, 9,490 non-redundant interactions were left. In addition to the interaction data, the information on the yeast protein catalogue such as class, enzyme code number, motif, function, complex and cell localization were extracted. Table 1 shows the number of yeast protein entries in each catalogue.

Table 1. Yeast protein catalogues

Protein catalogues	Number of protein entries
Classes	1,070
Complexes	1,321
EC number	1,152
Motifs	2,539
Phenotype	3,120
Function	11,506
Cell localization	2,407

The function catalogue in particular is important because the primary focus of this study is the prediction of protein functions. We shall now examine the function catalogue more closely.

Functions of yeast proteins were all arranged from FunCat (The Functional Catalogue) of MIPS. The FunCat is an annotation scheme for the functional description of proteins from prokaryotes, unicellular eukaryotes, plants and animals [7]. Taking into account the broad and highly diverse spectrum of known protein functions, the FunCat consists of 30 main functional categories (or branches) that cover general fields like cellular transport, metabolism and signal transduction [7]. The main branches exhibit a hierarchical, tree like structure with up to six levels of increasing specificity [7]. In total, the FunCat has 1,445 functional categories. Among of them, 215 functional categories were applied to yeast. Tables 2 and 3 show the number of yeast protein entries and yeast proteins, respectively, in each functional category of FunCat.

Table 2. The number of yeast proteins in each function category

Function category	Number of yeast proteins
Unclassified function	2,399
uncleus	764
cytoplasm	554
mitochondrion	366
transcriptional control	334
mitotic cell cycle and cell cycle control	326
C-compound and carbohydrate utilization	260
ribosome biogenesis	215
stress response	175
budding,	170
cell polarity and filament formation	167
protein modification	167
pheromone response, mating-type	160
determination, sex-specific proteins	157
endoplasmic reticulum	157
protein targeting,	146
sorting and translocation	146
plasma membrane	145
vesicular transport (Golgi network, etc.)	129
regulation of C-compound and carbohydrate utilization	120
...	...
plasma membrane	1
tRNA transcription	1

2.2 Analysis Results

The protein interaction data in each catalogue of Table 1 were analyzed. As shown in Fig. 1, the proteins in a same complex interact with the highest probability (0.33), and the proteins with a same function interact with the second highest probability (0.28). The proteins in a same complex interact *and* with a same function interact with the probability of 0.39, which is higher than 0.33 and 0.28 but not much higher. This implies that a large portion of the proteins in the two catalogues overlap.

The ratio of the number of interactions between proteins in a same complex to the total number of interactions is 0.25. The ratio of the number interactions between proteins with a same function to the number of interactions between proteins in a same complex is 0.97. This indicates that interacting proteins in a same complex also have a same function with a high probability. The inverse is not necessarily true. Consequently, we discovered an association rule: If proteins A and B are in a same complex and interact each other, proteins A and B have a same function.

Table 3. Scheme of yeast function catalogue

Function category	Protein entry
modification by acetylation, deacetylation	YLR410w
	YOR023c
	YOR064c
	YPR131c
modification with sugar residues(e.g. glycosylation)	YNL048w
	YJL183w
	YDL230w
	YDR099w
unspecified signal transduction	YDR315c
	YER177w
	YOR206w
	YOR257w
	YMR131c
other control of cellular organization	YHR102w
	YDR060w
	YDR260c
	YGL029w
other detoxification	YCR083w
	YOR163w
other transposable elements, viral and plasmid proteins	YDR289c
	YGR275w
	YJL047c
	YDL235c
protein binding	YLR006c
	YIL147c
	YBR294w
homeostasis of sulfates	YPR003c
	YLR092w
vacuolar degradation	YGL227w
	YAL035w
initiation	YKL204w
mRNA processing	YNL317w
3'-end processing	YKL208w
	YBR059c
protein modification by phosphorylation, dephosphorylation	YOR090c
	YLL010c
	YIL113w
	YLR019w
	YDR499w
(Other catagofies are not shown here)

Fig. 1. The probability of interaction between proteins in each catalogue.

This rule is also confirmed in the protein-protein interaction networks of Fig. 2. Fig. 2A shows a network of interactions between proteins in a same complex, visualized by InterViewer [4, 5]. Interacting proteins with a same function are selected from this network and shown in green. Most nodes of Fig. 2A are selected as proteins involved with the interactions between proteins with a same function. Figure 2B shows a network of interactions between proteins with a same function. Interacting proteins in a same complex are selected from this network and shown in green, too. Only a small portion of the entire nodes is selected.

3 Prediction of Human Protein Function

Uetz *et al.* [8] and Ito *et al.* [9] show that the function of uncharacterized proteins can be predicted in the light of the interacting partner by using the principle of ‘guilt by association’, which maintains that two interacting proteins are likely to participate in the same cellular function [2, 6].

Since the function of many human proteins is unknown, we predicted the function of human proteins. Suppose that SP_j is a protein with unknown function, P_i is a protein interacting with SP_j , AF is the total number of functions of interacting proteins, AP is the total number of interacting proteins, and that DP_i is the degree of a particular partner protein. Then the score function for assessing the probability that protein SP_j has the same function with protein P_i can be computed by equation 1.

$$Score(j, i) = DP_i \times \frac{1}{AF} \times \frac{1}{AP} \times CP_i \quad (1)$$

where CP_i is a complex constant. Algorithms 1-3 describe how to predict the function of a protein. In the algorithms, protein_num is the number of gathered proteins, and cnt represents the number of interacting partners with a same function. All interaction data are cleaned first by Algorithm 2, and the function of interacting partners is counted in Algorithm 3.

Fig. 2. (A) Left: A network of interactions between proteins in a same complex. Interacting proteins with a same function are shown in green. The network in the right shows the same network in the left but with node labels shown. (B) Left: A network of interactions between proteins with a same function. Interacting proteins in a same complex are shown in green. The network in the right shows the same network in the left but with node labels shown.

```
Algorithm 1 CreateNode ()  
Extract structureID, structure from structure table  
FOR k=0 protein_num-1 DO  
    WRITE k, proteinID, structure IN node table  
ENDFOR
```

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Algorithm 2 ClearInteract ()  
Extract source, target from interactions  
FOR k=0 protein_num-1 DO  
    IF (source==k) THEN  
        WRITE source, target IN non-redundant_interaction  
    ELSEIF (target==k) THEN
```

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    Temp=target
    Target=source
    Source=temp
    WRITE target, source IN the non-redundant_interaction
  ENDIF
ENDFOR

```

Algorithm 3 CountPartner ()

```

Extract source, target from the non_redundant interaction table
Extract proteinID, structure from the node table
Cnt=0
FOR i=0 non_redundant interaction's row-1 DO
  IF (target==node.proteinID)
    WRITE source, target, node.structure IN temp
  ENDIF
ENDFOR
FOR j=0 temp's row-1 DO
  IF (temp.proteinID==j)
    compare_structure=temp.structure
    FOR k=0 temp's row-1 DO
      IF(compare_structure==temp.structure)
        cnt=cnt+1
      ENDIF
    ENDFOR
  ENDIF
ENDFOR

```

Table 4 summarizes the prediction results. The probability of interaction between proteins in each category is different from that in yeast proteins.

Table 4. The probability of interaction between human proteins

Items	Value
Ratio of the interactions between proteins in a same complex to the total interactions	0.26
Ration of the interactions between proteins with a same function to the total interactions	0.34
Ratio of interactions between proteins with a same function to the interactions between proteins in a same complex	0.3547
Ratio of interactions between proteins in a same complex to the interactions between proteins with a same function	0.53

4 Conclusion

Proteins have many different biological functions by interacting with other proteins, and two interacting proteins are likely to have same biological function. Therefore, if

a protein with known function is identified to interact with an uncharacterized protein, the function of the uncharacterized protein can be predicted. From the analysis of the experimental data of yeast protein interactions, we discovered a reliable association rule that “if proteins A and B exist in a same complex and interact each other, proteins A and B have a same function.” We have developed an algorithm for predicting the function of proteins based on the association rule, and applied the algorithm to the human protein interaction data. Experimental results show that the algorithm is potentially useful for predicting the function of uncharacterized proteins.

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