

Conditional Random Field Approach to Prediction of Protein-protein Interactions Using Domain Information

MORISHIRO HAYASHIDA ^{†1} MAYUMI KAMADA ^{†1}
JIANGNING SONG ^{†2,†3} and TATSUYA AKUTSU ^{†1}

Analysis of functions and interactions of proteins and domains is important for understanding cellular systems and biological networks. Many methods for predicting protein-protein interactions have been developed. It is known that mutual information between residues at interacting sites can be higher than that at non-interacting sites. It is based on the thought that amino acid residues at interacting sites have coevolved with those at the corresponding residues in the partner proteins. Several studies have shown that such mutual information is useful for identifying contact residues in interacting proteins.

We propose novel methods using conditional random fields for predicting protein-protein interactions. We focus on the mutual information between residues, and combine it with conditional random fields. In the methods, protein-protein interactions are modeled using domain-domain interactions. We perform computational experiments using protein-protein interaction datasets for several organisms, and calculate AUC (Area Under ROC Curve) score. The results suggest that our proposed methods with and without mutual information outperform EM (Expectation Maximization) method proposed by Deng et al.

1. Introduction

It is one of important topics to understand protein functions and protein-protein interactions in the field of molecular biology and bioinformatics. Recently, many researchers have focused on the investigation of amino acid residues of proteins to reveal interactions and contacts between residues^{(2),(9),(18),(19)}. If residues at important sites for interactions between proteins are substituted in one pro-

tein, the corresponding residues in interacting partner proteins are expected to be also substituted by selection pressure. Otherwise, such mutated proteins may lose the interactions. Fraser et al. confirmed that interacting proteins evolve at similar evolutionary rates by comparing putatively orthologous protein sequences between *S. cerevisiae* and *C. elegans*⁽⁸⁾. It means that substitutions for contact residues occur in both interacting proteins as long as the proteins keep interacting with each other. Therefore, mutual information (MI) between residues is useful for predicting protein-protein interactions for proteins of unknown function. MI is calculated from multiple sequence alignments for homologous protein sequences. Weigt et al. identified direct residue contacts between sensor kinase and response regulator proteins by message passing, which is an improvement of MI⁽¹⁸⁾. Burger and van Nimwegen used a dependence tree where a node corresponds to a position of amino acid sequences, and predicted interactions using a Bayesian network method⁽²⁾.

On the other hand, Markov random field and conditional random field models have been well studied in fields of natural language processing^{(15),(16)}. Also in bioinformatics, protein function prediction methods from protein-protein interaction network and other biological networks were developed using Markov random fields^{(4),(6)}. On the other hand, several prediction methods have been developed based on domain-domain interactions. Deng et al. proposed a domain-based probabilistic model of protein-protein interactions, and developed EM (Expectation Maximization) method⁽⁵⁾. Based on this probabilistic model, LP (Linear Programming)-based methods were developed⁽¹⁰⁾, and Chen et al. improved the accuracy of interaction strength prediction by APM (Association Probabilistic Method)⁽³⁾. In this paper, we propose prediction methods based on domain-domain interactions using conditional random fields with and without mutual information. Furthermore, we perform computational experiments for several protein-protein interaction datasets, compare the methods with the EM method proposed by Deng et al.⁽⁵⁾, which is one of the best predictors based on domain-domain interactions, and show that our methods outperform the EM method.

2. Mutual Information between Domains

In order to investigate the relationship between two positions of proteins, MI

^{†1} Bioinformatics Center, Institute for Chemical Research, Kyoto University

^{†2} Department of Biochemistry and Molecular Biology, Monash University, Australia

^{†3} Tianjin Institute of Industrial Biotechnology, Chinese Academy of Sciences, China

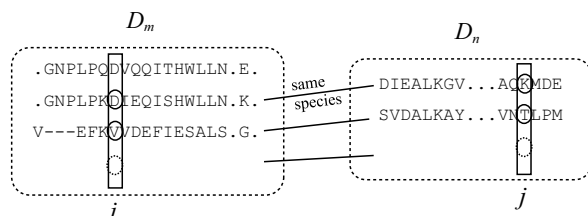


Fig. 1 Illustration on calculation of mutual information from multiple alignments of domains. Domains D_m and D_n have multiple alignments of sequences from several organisms, respectively. Mutual information is calculated for each pair of positions i and j .

for distributions of amino acids at the positions is used. Such distributions can be obtained from multiple alignments of protein sequences and domain sequences. In this section, we briefly review MI for distributions of amino acids, and explain MI between domains.

We assume that multiple sequence alignments for domains D_m and D_n are obtained, respectively (see Fig. 1). In order to calculate MI, we need joint appearance frequencies. However, we cannot see which sequence in the multiple alignment of domain D_m corresponds to a specified sequence in that of D_n . Therefore, we assume that sequences contained in the same organism can be paired. In the example of Fig. 1, the second sequence of D_m is paired with the first one of D_n , the third one of D_m is paired with the second one of D_n , and so on. The first sequence of D_m is not counted into the appearance frequencies because it is not paired with any sequence of D_n although it may be paired with sequences of other domains than D_n .

Let \mathcal{A} be a set of amino acids, $f_i(A)$ be the appearance frequency of amino acid A at position i in domains D_m and D_n , and $f_{ij}(A, B)$ be the joint appearance frequency of a pair of amino acids A at position i in D_m and B at position j in D_n , where each frequency is divided by the number of paired sequences M in the multiple alignments such that $\sum_{A \in \mathcal{A}} f_i(A) = \sum_{A, B \in \mathcal{A}} f_{ij}(A, B) = 1$.

Multiple alignments often include some gaps. Weigt et al. counted the frequencies of gaps as well as amino acids¹⁸⁾. Therefore, we also consider gaps to be a kind of amino acids, that is, the number of distinct amino acids is $|\mathcal{A}| = 21$. Then, mutual information for positions i in D_m and j in D_n is defined as the

Kullback-Leibler divergence between the multiplication of appearance frequencies, $f_i(A)f_j(B)$, and the joint appearance frequencies, $f_{ij}(A, B)$, as follows.

$$MI_{ij} = \sum_{A, B \in \mathcal{A}} f_{ij}(A, B) \log \frac{f_{ij}(A, B)}{f_i(A)f_j(B)}. \quad (1)$$

If frequency distributions of amino acids at positions i and j are independent from each other, $f_{ij}(A, B) \approx f_i(A)f_j(B)$, and MI_{ij} approaches to zero. This means that the two positions are not related with each other in the evolutionary process. If domains D_m and D_n interact at the positions, it is considered that MI_{ij} becomes high because the positions have coevolved through the evolutionary process in order to keep the interaction. It should be noted that two positions i and j do not always directly interact even if MI_{ij} is high¹⁸⁾. However, such proteins with high values of MI have a possibility to directly interact with each other at other positions in the proteins.

However, we need to reduce MI_{ij} because it can be unnecessarily high depending on distributions of $f_i(A)$ and $f_j(B)$. For that purpose, we make use of $MI_{ij}^{(random)}$, which is the mutual information MI_{ij} from the joint frequency, $f_{ij}(A, B)$, obtained by shuffling at random the combinations of sequences in multiple alignments. In this paper, we repeat the procedure 400 times according to¹⁸⁾, and take the average.

For practical uses of MI, $f_i(A)$, $f_j(B)$ and $f_{ij}(A, B)$ should be positive values. Otherwise, we cannot calculate MI_{ij} by using computers. Therefore, we use the following pseudocount as in¹⁸⁾,

$$f_i^{(pseudo)}(A) = \frac{\eta + f_i(A)M}{|\mathcal{A}|\eta + M}, \quad f_{ij}^{(pseudo)}(A, B) = \frac{\eta + f_{ij}(A, B)M}{|\mathcal{A}|\eta + M}, \quad (2)$$

where η is a constant value, in this paper we use $\eta = 1$. It should be noted that the sum over all amino acids \mathcal{A} , $\sum_{A \in \mathcal{A}} f_i^{(pseudo)}(A) = 1$ and $\sum_{A, B \in \mathcal{A}} f_{ij}^{(pseudo)}(A, B) = 1$ because $\sum_{A \in \mathcal{A}} f_i(A) = \sum_{A, B \in \mathcal{A}} f_{ij}(A, B) = 1$.

In order to investigate interactions between proteins, we need MI between domains included in the proteins. Thus, we define MI between domains D_m and D_n , \mathcal{M}_{mn} , to be the maximum of MI over all positions i and j as $\mathcal{M}_{mn} = \max_{i, j} (MI_{ij} - \langle MI_{ij}^{(random)} \rangle)$, where $\langle v \rangle$ means the average of v , i

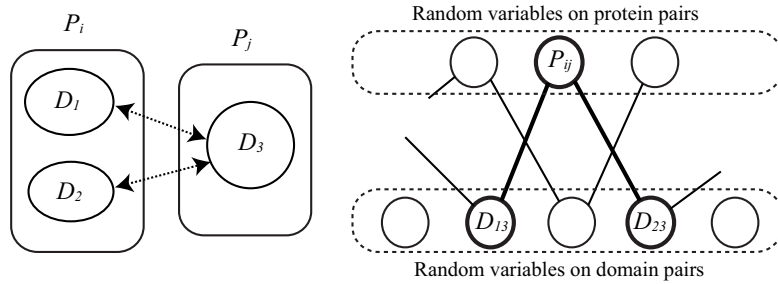


Fig. 2 Markov random field model for protein-protein interactions. Left: Example of proteins P_i and P_j . P_i consists of domains D_1 and D_2 , and P_j consists of domain D_3 , respectively. Right: Factor graph $G(U, V, E)$. There exists an edge between $P_{ij} \in U$ and $D_{mn} \in V$ if and only if $D_{mn} \in P_{ij}$.

and j are positions of D_m and D_n , respectively. Since MI_{ij} is calculated to be high for the positions i and j that include many gaps, we exclude positions that include more than 20% gaps as in¹¹⁾.

3. Conditional Random Field Model for PPI

In this section, we propose a probabilistic model for protein-protein and domain-domain interactions using conditional random fields^{15),16)} because it can be considered that two domains D_m and D_n do not always interact even if the mutual information \mathcal{M}_{mn} is large. For example, Weigt et al. improved MI and proposed direct information (DI) because residues do not always contact with each other even if the MI is large¹⁸⁾.

Most proteins contain domains as is well known. If two proteins do not interact with each other, any two domains contained in the proteins must not interact with each other. Then, Deng et al. proposed a probabilistic model for a pair of proteins as follows⁵⁾. By assuming that proteins P_i and P_j interact if and only if at least a pair of domains included in the proteins interacts, and events that domains interact are independent from each other, they defined

$$Pr(P_{ij} = 1) = 1 - \prod_{D_{mn} \in P_{ij}} (1 - Pr(D_{mn} = 1)), \quad (3)$$

where $P_{ij} = 1$ means that proteins P_i and P_j interact, $D_{mn} = 1$ means that

domains D_m and D_n interact, $D_{mn} \in P_{ij}$ means that domain D_m is included in protein P_i and D_n is included in P_j , and the product in the right hand side is calculated for all domain pairs (D_m, D_n) included in the protein pair (P_i, P_j) .

By transforming equation (3), we have

$$1 - Pr(P_{ij} = 1) = \exp \left(\sum_{D_{mn} \in P_{ij}} \lambda^{(mn)} \right), \quad (4)$$

where $\lambda^{(mn)} = \log(1 - Pr(D_{mn} = 1))$.

From this equation, we can consider the following Markov random field model for protein pair (P_i, P_j) (see Fig. 2).

$$Pr(p_{ij}, \mathbf{d}) = \frac{1}{Z_{ij}} \exp \left(\sum_{D_{mn} \in P_{ij}} \sum_{s,t \in \{0,1\}} \lambda_{s,t}^{(ij,mn)} f_{s,t}^{(ij,mn)}(p_{ij}, d_{mn}) \right), \quad (5)$$

where $p_{ij} \in \{0, 1\}$, \mathbf{d} means a set of events on domain-domain interactions, $D_{mn} = d_{mn}$ ($d_{mn} \in \{0, 1\}$), $f_{s,t}^{(ij,mn)}(p_{ij}, d_{mn})$ denotes a local feature, $\lambda_{s,t}^{(ij,mn)}$ is the corresponding weight parameter and related to the joint probability $Pr(P_{ij} = s, D_{mn} = t)$, and Z_{ij} denotes the normalization constant. For instance, equation (5) for $p_{ij} = 0$ is equivalent to equation (4) in the case that $\lambda_{s,t}^{(ij,mn)} = \lambda_{s,t}^{(mn)}$ for all protein pairs (P_i, P_j) and $f_{s,t}^{(ij,mn)}(p_{ij}, d_{mn}) = 1$ if $s = t = 0$, otherwise 0.

In Markov random fields, random variables have Markov properties represented as an undirected graph¹²⁾. The factor graph for our model is represented to be a bipartite graph $G(U, V, E)$ with a set of vertices U corresponding to protein-protein interactions P_{ij} , a set of vertices V corresponding to domain-domain interactions D_{mn} , and a set of edges E between U and V as the right figure of Fig. 2. There exists an edge between $P_{ij} \in U$ and $D_{mn} \in V$ if and only if $D_{mn} \in P_{ij}$. Since $Pr(P_{ij} = 0 | D_{mn} = t) = 1 - Pr(P_{ij} = 1 | D_{mn} = t)$, it is redundant to consider both $s = 0, 1$, and it is sufficient to consider only $s = 1$. Therefore, in order to simplify the model, we substitute $\lambda_{s,t}^{(ij,mn)} = \lambda_t^{(mn)}$, $f_{1,t}^{(ij,mn)} = f_t^{(mn)}$, and $f_{0,t}^{(ij,mn)} = 0$ for all protein pairs (P_i, P_j) . Then, we have

$$Pr(\mathbf{p}, \mathbf{d}) = \frac{1}{Z} \exp \left(\sum_{P_{ij}} \sum_{D_{mn} \in P_{ij}} \sum_{t \in \{0,1\}} \lambda_t^{(mn)} f_t^{(mn)}(p_{ij}, d_{mn}) \right), \quad (6)$$

where \mathbf{p} means a set of events on protein-protein interactions, $P_{ij} = p_{ij}$.

We here introduce mutual information between domains $\mathcal{M} = \{\mathcal{M}_{mn}\}$ as given conditional data in order to combine it with the probabilistic model. Then, equation (6) can be written as

$$Pr(p_{ij}, d_{mn} | \mathcal{M}) = \frac{1}{Z_{ij\mathcal{M}}} \exp \left(\sum_{D_{mn} \in P_{ij}} \sum_{t \in \{0,1\}} \lambda_t^{(mn)} f_t^{(mn)}(p_{ij}, \mathcal{M}_{mn}) \right), \quad (7)$$

where

$$f_t^{(mn)}(p_{ij}, \mathcal{M}_{mn}) = \begin{cases} \sigma(\mathcal{M}_{mn} - c) & (\text{if } p_{ij} = 1 \text{ and } t = 1) \\ \sigma(c - \mathcal{M}_{mn}) & (\text{if } p_{ij} = 0 \text{ and } t = 0) \\ 0 & (\text{if } p_{ij} = 1 \text{ and } t = 0) \\ -1 & (\text{if } p_{ij} = 0 \text{ and } t = 1) \end{cases}, \quad (8)$$

$\sigma(x) = 1/(1+e^{-x})$ is an increasing function, and c is a positive constant. It should be noted that a negative value, -1 , is given to $f_t^{(mn)}$ because it is undesired that a pair of domains interact although proteins having the pair do not interact. In this way, the local feature $f_t^{(mn)}$ correlates protein-protein interactions P_{ij} with domain-domain interactions D_{mn} (see Fig. 2).

For a conditional random field model without MI, we use the following local feature instead of $f_t^{(mn)}(p_{ij}, \mathcal{M}_{mn})$. $f_t^{(mn)}(p_{ij}, d_{mn}) = 1$ if $p_{ij} = t$, 0 if $p_{ij} = 1$ and $t = 0$, and -1 if $p_{ij} = 0$ and $t = 1$.

3.1 Parameter Estimation

In this section, we discuss how to estimate the parameters $\boldsymbol{\lambda} = \{\lambda_t^{(mn)}\}$. We assume that protein-protein interaction data $\mathbf{p} = \{p_{ij}\}$ are given. Then, the log-likelihood function is represented by

$$l(\boldsymbol{\lambda}) = \sum_{p_{ij} \in \mathbf{p}} \left(\sum_{D_{mn} \in P_{ij}} \sum_{t \in \{0,1\}} \lambda_t^{(mn)} f_t^{(mn)}(p_{ij}, \mathcal{M}_{mn}) - \log Z_{ij\mathcal{M}} \right). \quad (9)$$

We estimate the parameters by maximizing the log-likelihood function, $l(\boldsymbol{\lambda})$. For that purpose, we use the Broyden-Fletcher-Goldfarb-Shanno (BFGS)¹⁾ method, which is one of quasi-Newton methods that approximates the Hessian matrix by some efficient method.

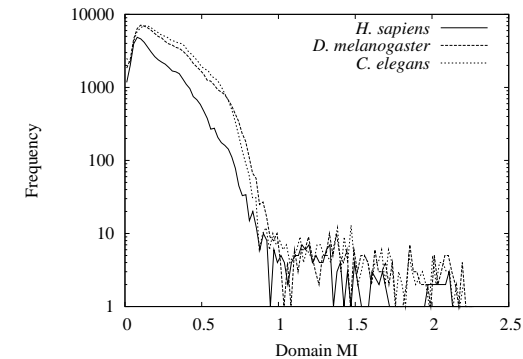


Fig. 3 Distributions of domain MIs for *H. sapiens*, *D. melanogaster*, and *C. elegans*.

4. Computational Experiments

4.1 Data and Implementation

We used protein-protein interaction data of *H. sapiens*, *D. melanogaster*, and *C. elegans* from the DIP database¹⁴⁾, the file name is 'dip20091230.txt'. We used the UniProt Knowledgebase database (version 15.4)¹⁷⁾ as protein domain inclusion data. We deleted proteins that did not have any domain, and obtained 294 interacting protein pairs as positive data that included 300 distinct proteins and 320 domains for *H. sapiens*, 449 interacting pairs that included 562 proteins and 449 domains for *D. melanogaster*, and 250 interacting pairs that included 602 proteins and 476 domains for *C. elegans*.

We used the Pfam database (version 24.0)⁷⁾ to obtain multiple sequence alignments for domains, and calculated MI, \mathcal{M}_{mn} , for each pair of domains. Fig. 3 shows the distributions of domain MI \mathcal{M}_{mn} for *H. sapiens*, *D. melanogaster*, and *C. elegans*. We can see from the figure that most domain MIs are distributed in the part of less than about 0.8 for all organisms. It is considered that domains D_m and D_n with \mathcal{M}_{mn} less than 0.8 may not interact, and domains with \mathcal{M}_{mn} more than 0.8 have more possibilities to interact with each other. Therefore, we set the constant c in equation (8) to be 0.8. Although we tried several values from 0.6 to 1.0 for c , the results were similar to the case of $c = 0.8$.

Table 1 The AUC results for training and test datasets of *H. sapiens* by the CRF method with MI, that without MI, and the EM method.

iteration	CRF with MI		CRF without MI		EM	
	training	test	training	test	training	test
1st	0.999366	0.989247	0.999366	0.881720	0.999819	0.709677
2nd	0.998787	0.919355	0.999312	0.923387	0.999909	0.875000
3rd	1.000000	0.847222	1.000000	0.833333	1.000000	0.861111
4th	0.999351	0.989583	0.999369	1.000000	0.999856	0.989583
5th	0.999333	0.842365	0.999369	0.827586	0.999982	0.798030
average	0.999367	0.917554	0.999483	0.893205	0.999913	0.846680

We selected non-interacting protein pairs as negative data uniformly at random such that negative data did not overlap with the positive data. The number of negative data was the same as that of positive data for each organism.

We used libLBFGS (version 1.9) with default parameters to estimate the parameters $\lambda_t^{(mn)}$, which is a C implementation of the limited memory BFGS method¹³⁾, and is available on the web page, <http://www.chokkan.org/software/liblbfgs/>.

4.2 Result

In order to evaluate our method, we compared the proposed CRF method with MI and that without MI with the EM method by Deng et al.⁵⁾ In the EM method, probabilities λ_{mn} that domains D_m and D_n interact are estimated by the recursive formula, $\lambda_{mn}^{(t)} = \frac{\lambda_{mn}^{(t-1)}}{N_{mn}} \sum_{\{P_{ij}|D_{mn} \in P_{ij}\}} \frac{(1-fn)^{o_{ij}} fn^{(1-o_{ij})}}{Pr(o_{ij}|\lambda_{mn}^{(t-1)})}$, where $o_{ij} = 1$ denotes that it was observed that proteins P_i and P_j interact with each other, and $fn = 0.8$.

We performed five-fold cross-validation, that is, split the data into 5 datasets (4 for training and 1 for test), estimated $\lambda_t^{(mn)}$ from the training datasets, and calculated $Pr(P_{ij} = 1|\mathcal{M})$ of equation (7) for each protein pair in the test dataset and AUC (Area Under ROC Curve) score, where among the test dataset only protein pairs that included at least a parameter estimated from the corresponding training dataset were always used. We repeated 5 times, and took the average.

Tables 1, 2, and 3 show the results on AUC for training and test datasets by the CRF method with MI, that without MI, and the EM method for *H. sapiens*, *D. melanogaster*, and *C. elegans*, respectively. An AUC score is the area under

Table 2 The AUC results for training and test datasets of *D. melanogaster* by the CRF method with MI, that without MI, and the EM method.

iteration	CRF with MI		CRF without MI		EM	
	training	test	training	test	training	test
1st	0.999255	0.707692	0.999977	0.738462	0.999961	0.769231
2nd	0.997928	0.818182	0.997905	0.848485	0.999938	0.727273
3rd	0.997920	0.708333	0.997920	0.562500	0.999922	0.645833
4th	0.998660	0.863636	0.999318	0.886364	0.999814	0.840909
5th	0.999234	0.819444	0.999954	0.833333	0.999861	0.527778
average	0.998599	0.783458	0.999015	0.773829	0.999899	0.702205

Table 3 The AUC results for training and test datasets of *C. elegans* by the CRF method with MI, that without MI, and the EM method.

iteration	CRF with MI		CRF without MI		EM	
	training	test	training	test	training	test
1st	0.999975	0.657143	0.999975	0.514286	1.000000	0.542857
2nd	0.997899	0.923077	0.996873	0.948718	0.999875	0.743590
3rd	0.998775	0.900000	0.998825	0.933333	0.999875	0.866667
4th	0.998950	0.966667	0.999850	0.966667	0.999850	0.633333
5th	0.998900	1.000000	0.998875	1.000000	0.999675	1.000000
average	0.998900	0.889377	0.998879	0.872601	0.999855	0.757289

an ROC (Receiver Operating Characteristic) curve, and takes a value between 0 and 1. The ROC curve of a random classifier lies on the diagonal line, and the AUC score is 0.5. The ROC curve of a perfect classifier goes through the point (0 (false positive rate), 1 (true positive rate)), and the AUC score is 1. A classifier with the AUC score closer to 1 has better performance. We can see from these tables that the results by the CRF method with MI are better than those by the CRF method without MI, and that the results by the CRF method without MI are better than those by the EM method. For training datasets, the results by all of the methods were almost perfect. For test datasets, the CRF method with MI outperformed that without MI, and the EM method.

5. Conclusions

We proposed novel methods which combine conditional random fields with the domain-based model of protein-protein interactions. In order to give better performance, we introduced mutual information to the probabilistic model. In

the improved model, mutual information between domains is given as conditions, where MI between domains is defined as the maximum of MIs between residues in the domains. This method was developed based on the fact that amino acid residues at important sites for interactions have coevolved with each other, and MI has been used for identifying contact residues in interactions.

We performed five-fold cross-validation experiments, and calculated AUC for probabilities that two proteins interact. The results suggested that our proposed methods, especially the CRF method with mutual information, are useful. However, the results of AUC for training datasets implied that estimated parameters were overfitting to training datasets. For avoiding that problem, we can improve the methods, for instance, by adding regularization terms, l_1 -norm of parameters to the log-likelihood function. Since CRF has an advantage to be able to incorporate large number of features, it remains as a future work to improve the model itself to obtain better accuracy by, for instance, modifying the local feature and adding new features.

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