Assessing and Predicting Protein Interactions Using Both Local and Global Network Topological Metrics

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Outline

- Background
- Related work
- Our method
  - Local network topological metric
  - Global network topological metric
- Experiments
- Summary

Background

- Protein-protein interactions play a critical role in most cellular processes and form the basis of biological mechanisms.
- High-throughput experimental techniques enable the study of protein-protein interactions at the proteome scale.
- However, high-throughput protein interaction data are often associated with high false positive and false negative rates
  - limitations of the associated experimental techniques
  - dynamic nature of protein interaction maps
  - …

Computational methods

- A weight is assigned to each interaction such that the higher the weight is, the more likely the interaction is true
- Various Information have been used
  - 3D protein structures
  - co-evolution
  - co-localization
  - gene fusion
  - literature
  - **network topology**
  - protein domains/motifs
  - …

Methods based on network topology

- Represents PPI networks as undirected graphs, where vertices are proteins, and edges represent interactions between proteins.
- IG1 [Saito et al. 2002]
  - The first one on evaluating the reliability of PPIs using solely PPI network topology
  - Mainly for PPI data generated by yeast-two-hybrid experiments
  - Given a protein pair (u,v), IG1 is calculated based on the number of proteins that interact with and only with either u or v
- IG2 [Saito et al. 2002]
  - Uses 5 local network motifs
  - Performs better than IG1
- IRAP [Chen et al. 2005]
  - the collective reliability of the strongest alternative path between two proteins
  - Expensive to compute
- CD-distance [Brun et al. 2003] and FSWeight [Chua et al. 2006]
  - Based on the number of common neighbors of two proteins
  - Easy to compute
  - They are initially proposed for function prediction
  - Outperforms the previous three methods on large PPI networks [Chen et al. 2006]

CD-distance

- Given a pair of proteins (u, v) in a PPI network $G=(V, E)$
  - N_u: the set of neighbors of u in G
  - N_v: the set of neighbors of v in G
- CD (u,v) = $\dfrac{2|N_u \cap N_v|}{|N_u|+|N_v|}$
- Consider relative intersection size of the two neighbor sets, not absolute intersection size
  - Case 1: $|N_u| = 1$, $|N_v| = 1$, $|N_u \cap N_v| = 1$, CD(u,v)=1
  - Case 2: $|N_u| = 10$, $|N_v| = 10$, $|N_u \cap N_v| = 10$, CD(u,v)=1

FSWeight

- Try to overcome the weakness of CD-distance
- FS(u,v) = $\frac{2|N_u \cap N_v|}{|N_u|+|N_u \cap N_v|+\lambda_u} \times \frac{2|N_u \cap N_v|}{|N_v|+|N_u \cap N_v|+\lambda_v}$

Where λ_u and λ_v are used to penalize those proteins with very few neighbors

$\lambda_u = \max\{0, \frac{\sum_{x \in G}|N_x|}{|V|} - |N_u|\}$, $\lambda_v = \max\{0, \frac{\sum_{x \in G}|N_x|}{|V|} - |N_v|\}$

- Suppose the average degree is 4, then
  - Case 1: $|N_u| = 1$, $|N_v| = 1$, $|N_u \cap N_v| = 1$, FS(u,v)=4/25=0.16
  - Case 2: $|N_u| = 10$, $|N_v| = 10$, $|N_u \cap N_v| = 10$, FS(u,v)=1

Our method

- CD-distance and FSWeight are local metrics
- We use both local and global network topological metric
  - Local metric
    - a variant of CD-distance
    - Computed iteratively
  - Global metric
    - Computed using interacting protein group pairs
  - These two metrics are combined to get the final score of an interaction

Local topological metric

- A variant of CD-distance which penalizes proteins with few neighbors

$$w_L(u,v) = \frac{2|N_u \cap N_v|}{|N_u|+\lambda_u+|N_v|+\lambda_v}$$

$$\lambda_u = \max\{0, \frac{\sum_{x\in G}|N_x|}{|V|} - |N_u|\}, \quad \lambda_v = \max\{0, \frac{\sum_{x\in G}|N_x|}{|V|} - |N_v|\}$$

(same as in FSWeight)

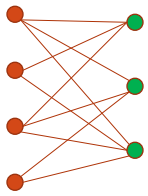
- Iterate local topological metric
  - Motivation: the weight of an interaction reflects its reliability, so can we get better results if we use this weight to re-calculate the score of other interactions?

Iterate local metric

- $w_L^0(u,v) = 1$ if $(u,v)\in G$, otherwise $w^0(u,v)=0$
- $w_L^1(u,v) = \frac{|N_u \cap N_v|+|N_u \cap N_v|}{|N_u|+\lambda_u+|N_v|+\lambda_v}$
- $w_L^k(u,v) = \frac{\sum_{x\in Nu\cap Nv} w_L^{k-1}(u,x) + \sum_{x\in Nu\cap Nv} w_L^{k-1}(v,x)}{\sum_{x\in Nu} w_L^{k-1}(u,x) + \lambda^k{}_u + \sum_{x\in Nv} w_L^{k-1}(v,x) + \lambda^k{}_v}$
- $\lambda^k{}_u = \max\{0, \frac{\sum_{x\in V}\sum_{y\in Nx} w_L^{k-1}(x,y)}{|V|} - \sum_{x\in Nu} w_L^{k-1}(u,x)\}$
- $\lambda^k{}_v = \max\{0, \frac{\sum_{x\in V}\sum_{y\in Nx} w_L^{k-1}(x,y)}{|V|} - \sum_{x\in Nv} w_L^{k-1}(v,x)\}$

Global topological metric

- Observation:
  - if one group of proteins interact with another group of proteins, then it is likely that the interaction between these two protein groups is mediated by an underlying complementary binding domain/motif pair.
  - In a protein pair participates in an interacting group pair, then the interaction between them is likely to be true



Calculating global topological metric

- Three steps:
  - Step1: generate protein groups that have common interacting partners
  - Step 2: calculate the interacting score of the generated protein groups
  - Step 3: calculate the global topological score of a protein pair

Step 1: generate protein groups

- A protein group is considered if it
  - Contains at least *s* proteins
  - Its members have at least *t* common interacting partners
- The adjacency matrix of an undirected graph can be regarded as a transaction database
  - Each adjacency list is a transaction
  - Each protein is an item

⇒finding protein groups can be mapped to finding frequent itemsets that contain at least *s* items and appear in at least *t* transactions.

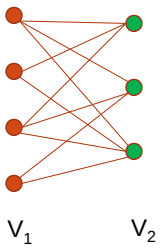
⇒We use a frequent itemset mining algorithm to find qualified protein groups

Step 2: calculate interaction score of protein groups

- Let V_1 and V_2 be two protein groups generated in Step 1, the interacting confidence score of V_1 and V_2 is defined as

$$\text{conf}(V_1, V_2) = \frac{\#\text{interactions between } V_1 \text{ and } V_2}{\#\text{possible protein pairs between } V_1 \text{ and } V_2}$$

- Example
  - #interactions: 10
  - #possible protein pairs: 12
  - $\text{conf}(V_1, V_2) = 10/12 = 0.833$



Step 3: calculating global metric score

- The global interacting score of a protein pair is computed based on the interacting confidence score of the interacting group pairs it participates in and the degree of its participation
- Given a protein pair (u,v)

$$w_G(u,v) = \max\{conf(V_1,V_2) \times \frac{2|N_u \cap V_2|}{|N_u|+|V_2|} \times \frac{2|N_v \cap V_1|}{|N_v|+|V_1|} \mid u \in V_1, v \in V_2\}$$

- $\frac{2|N_u \cap V_2|}{|N_u|+|V_2|}$ is u's participation degree in interacting protein group pair (V_1, V_2)
- $\frac{2|N_v \cap V_1|}{|N_v|+|V_1|}$ is v's participation degree in (V_1, V_2)

Combine local metric and global metric

- The final score of a protein pair (u,v) is defined as the sum of its local metric score and global metric score

$$LGTweight(u, v) = w^k_L(u, v) + w_G(u, v)$$

Experiments

- PPI dataset: DIP yeast (dated 07-Oct-2007)
  - 4932 proteins and 17491 interactions
  - Core dataset: 6459 interactions
- Evaluation methods:
  - Functional homogeneity
    - Use Gene Ontology (GO) annotations
  - Localization coherence
    - use Gene Ontology (GO) annotations
  - 5-fold cross validation
    - DIP core dataset

GO annotations

- Select only informative GO terms.
  - A GO term is informative if no less than 30 proteins are annotated with that term, and none of its descendant terms has at least 30 proteins
- 50 molecular function terms and 110 biological process terms
  - 3251 proteins and 11229 interactions have functional annotations.
- 42 cellular component terms
  - 1615 proteins and 4246 interactions have cellular component annotations

Functional Homogeneity

- Given a set of protein pairs, its functional homogeneity is defined as

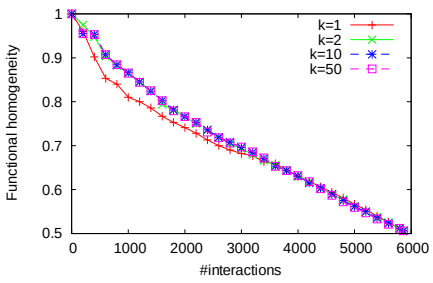
$$\frac{\#\text{protein pairs sharing same function annotation}}{\#\text{protein pairs that have function annotations}}$$

- Similarly, localization coherence is defined as

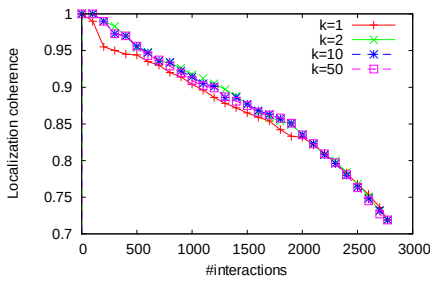
$$\frac{\#\text{protein pairs sharing same localization annotation}}{\#\text{protein pairs that have localization annotations}}$$

Experiment 1: the effect of k to local metric

- Assessing the reliability of PPIs in DIP dataset



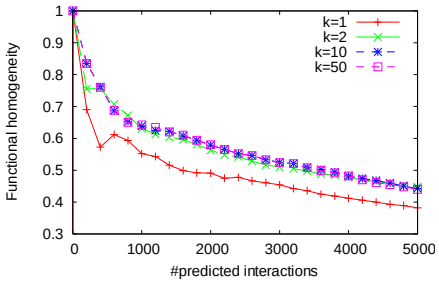
Functional homogeneity



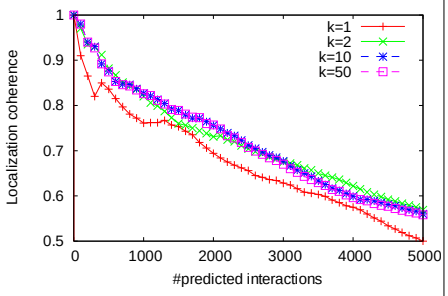
Localization coherence

The effect of k to local metric

- Predicting new PPIs



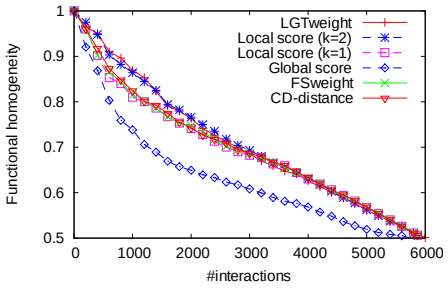
Functional homogeneity



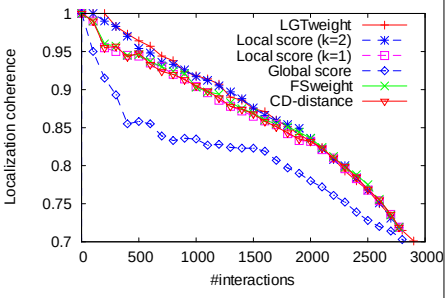
Localization coherence

Experiment 2: comparing different scoring methods

- Assessing the reliability of PPIs in DIP dataset
- For global topological metric, we set s=5, t=1



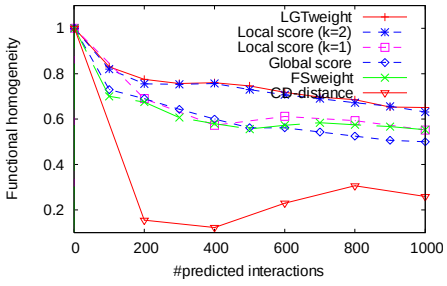
Functional homogeneity



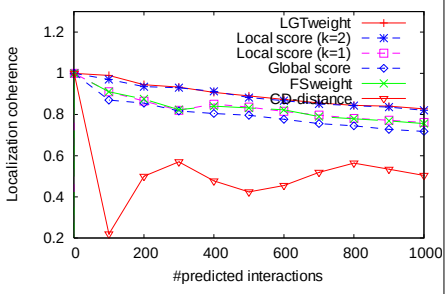
Localization coherence

Comparing different scoring methods

- Predicting new PPIs



Functional homogeneity



Localization coherence

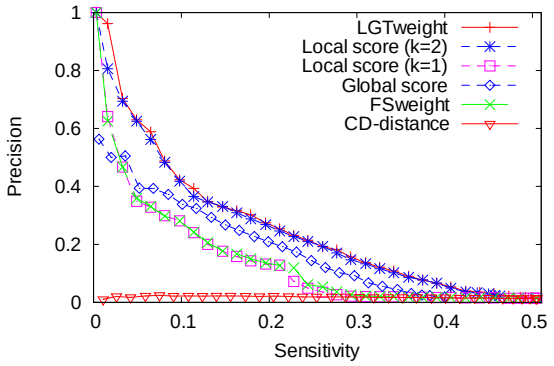
Experiment 3: 5-fold cross-validation

- Use the DIP core dataset as the golden standard
- Divide the proteins in the DIP full yeast dataset into 5 disjoint groups.
- For each group of proteins
  - Training data: remove the interactions between proteins in the group, and use the remaining interactions as training data
  - Testing data: all the protein pairs within this group
  - Correct answer PPIs: the pairs of proteins in the group that are in the core dataset

5-fold cross-validation

- Average number of proteins in 5 groups: 986
- Average number of interactions in 5 training datasets: 16723
- Average number of interactions in 5 testing datasets: 486591
- Average number of correct answer interactions: 307
- Measures:
  - sensitivity =TP/(TP + FN)
  - specificity =TN/(TN + FP)
    - #negatives >> #positives, specificity is always very high
    - >97.8% for all scoring methods
  - precision =TP/(TP + FP)

5-fold cross-validation



Summary and Conclusion

- Assessing the reliability of PPIs
  - CD-distance, FSWeight, and Local metric show similar performance
  - Iterating local metric can improve the performance slightly
- Predicting new interactions
  - CD-distance is not good at predicting new interactions
  - Iterating local metric can improve the performance significantly
- CD-distance and FSWeight can also be iterated, and they show similar improvement as local metric
- The global metric does not improve the performance much, but if an interaction has both high local metric score and high global metric score, then the interaction is more likely to be true

Q&A

- Thank you for your attention

Rank difference and score difference

- Given an interaction (u,v), the rank difference of (u,v) at k-th iteration is

$$\text{rank\_diff}^{k}(u,v) = |\text{rank}^{k}(u,v) - \text{rank}^{k-1}(u,v)|$$

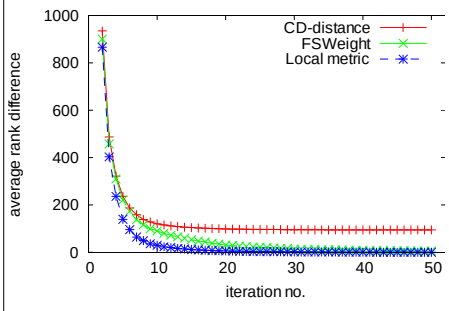
- Given a set of interactions E, the average ranking difference of all the interactions in E at k-th iteration is defined as

$$\text{avg\_rank\_diff}^{k}(E) = \frac{\sum_{(u,v)\in E} |rank^{k}(u,v) - rank^{k-1}(u,v)|}{|E|}$$

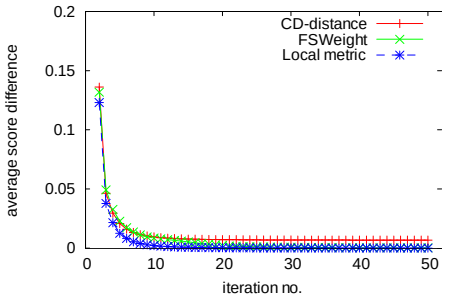
- Similarly, we can define average score difference of all the interactions in E at k-th iteration

$$\text{avg\_score\_diff}^{k}(E) = \frac{\sum_{(u,v)\in E} |score^{k}(u,v) - score^{k-1}(u,v)|}{|E|}$$

Results on the DIP dataset



Rank difference



Score difference