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) = $\frac{2|N_u \cap N_v|}{|N_u| + |N_v|}$
- 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)

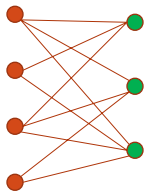
- Iterate local topological metric
  - Motivation: the weight of an interaction reflects its reliability, so can we get better results if we use this weight to re-calculate the score of other interactions?

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.

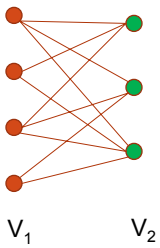
⇒We use a frequent itemset mining algorithm to find qualified protein groups

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

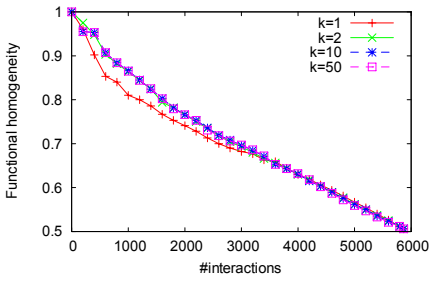
$$\frac{\#\text{protein pairs sharing same function annotation}}{\#\text{protein pairs that have function annotations}}$$

- Similarly, localization coherence is defined as

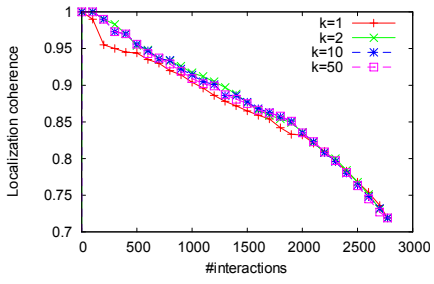
$$\frac{\#\text{protein pairs sharing same localization annotation}}{\#\text{protein pairs that have localization annotations}}$$

Experiment 1: the effect of k to local metric

- Assessing the reliability of PPIs in DIP dataset



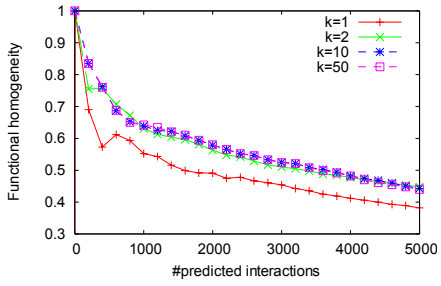
Functional homogeneity



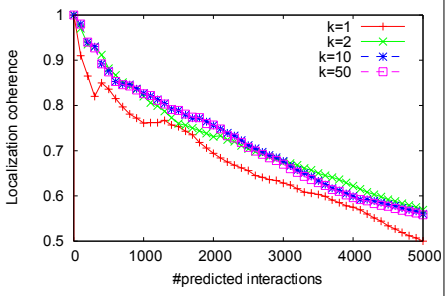
Localization coherence

The effect of k to local metric

- Predicting new PPIs



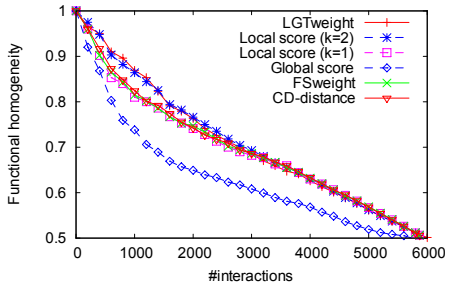
Functional homogeneity



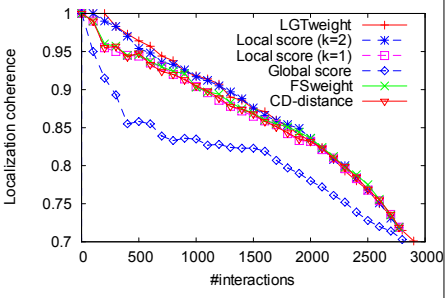
Localization coherence

Experiment 2: comparing different scoring methods

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



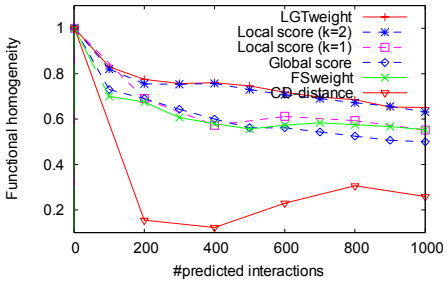
Functional homogeneity



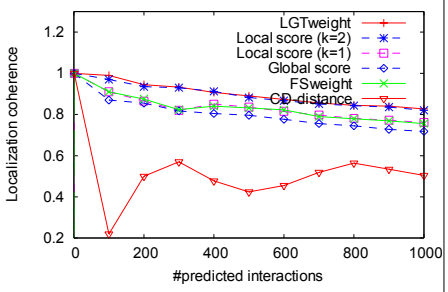
Localization coherence

Comparing different scoring methods

- Predicting new PPIs



Functional homogeneity



Localization coherence

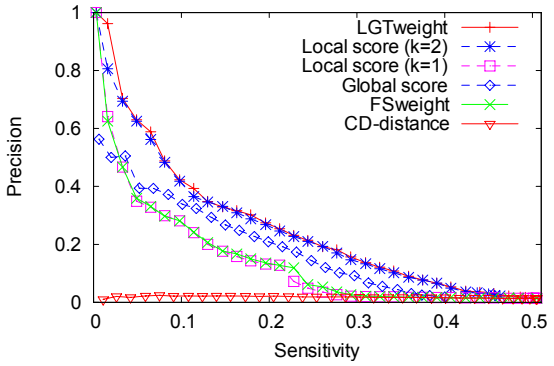
Experiment 3: 5-fold cross-validation

- 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

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

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

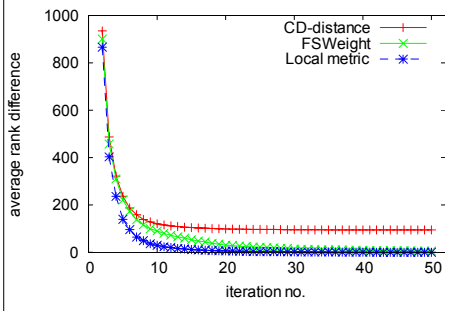
- Given a set of interactions E, the average ranking difference of all the interactions in E at k-th iteration is defined as

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

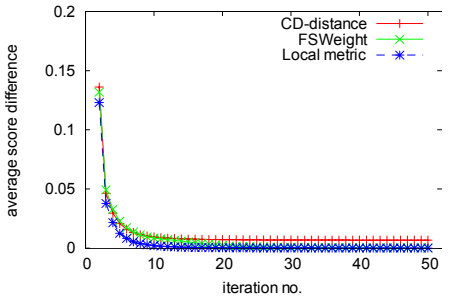
- Similarly, we can define average score difference of all the interactions in E at k-th iteration

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

Results on the DIP dataset



Rank difference



Score difference