An Iterative Approach to Weighting PPI Networks and Its Impact on Complex Discovery

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Outline

- An iterative weighting approach to identifying false positives and false negatives from high-throughput interaction data
  - Background
  - Existing weighting methods
  - The iterative weighting approach
  - Experiments
- Complex discovery from weighted PPI networks
  - Complex discovery method: maximal cliques
  - Experiments

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
  - Based on the number of non-mutually interacting partners
- 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
  - 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 interaction size, not absolute interaction size
  - Case 1: $|N_u| = 1$, $|N_u| = 1$, $|N_u \cap N_v| = 1$, CD(u,v)=1
  - Case 2: $|N_u| = 10$, $|N_u| = 10$, $|N_u \cap N_v| = 10$, CD(u,v)=1

FSWeight

- Try to overcome the weaknesses 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: $|N_u| = 1$, $|N_u| = 1$, $|N_u \cap N_v| = 1$, FS(u,v)=4/25=0.16
  - Case 2: $|N_u| = 10$, $|N_u| = 10$, $|N_u \cap N_v| = 10$, FS(u,v)=1

Differences between CD-distance and FSWeight

- Two differences between CD-distance and FSWeight
  - FSWeight penalizes those proteins with few neighbors
  - FSWeight assigns separate weight for each protein, and then takes the product of the two weights
- We consider another weighting method, which only penalize proteins with few neighbors

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

- Suppose the average degree is 4, then
  - Case 1: $|N_u| = 1$, $|N_u| = 1$, $|N_u \cap N_v| = 1$, AdjustCD(u,v)=2/8=0.25
  - Case 2: $|N_u| = 10$, $|N_u| = 10$, $|N_u \cap N_v| = 10$, AdjustCD(u,v)=1

The iterative weighting approach

- Basic idea
  - 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 CD-distance
  - $w^k(u,v) = \dfrac{\sum_{x \in Nu \cap Nv} w^{k-1}(u,x) + \sum_{x \in Nu \cap Nv} w^{k-1}(v,x)}{\sum_{x \in Nu} w^{k-1}(u,x) + \sum_{x \in Nv} w^{k-1}(v,x)}$
  - $w^0(u,v) = 1$ if $(u,v) \in G$, otherwise $w^0(u,v)=0$
  - $w^1(u,v) = \dfrac{|N_u \cap N_v| + |N_u \cap N_v|}{|N_u| + |N_v|} = CD(u,v)$

Iterate AdjustCD

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

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

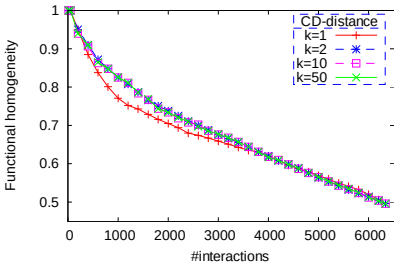
$$\frac{\#\text{protein pairs sharing same function annotation}}{\#\text{protein pairs that have function annotations}}$$

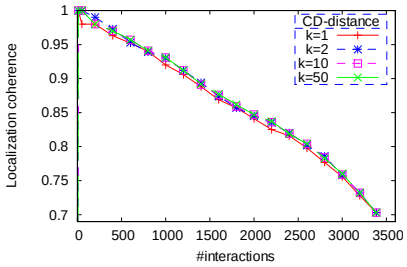
- Similarly, localization coherence is defined as

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

Experiment 1: the effect of k

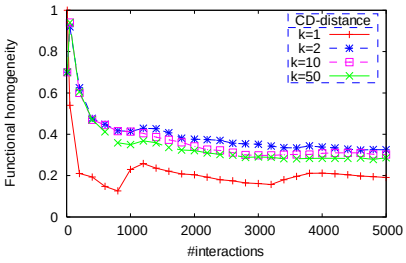
- CD-distance
- Assessing the reliability of PPIs in DIP dataset

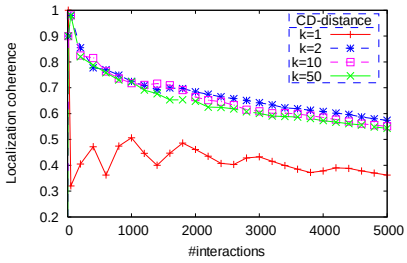




The effect of k

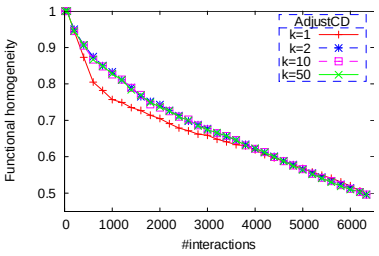
- CD-distance
- Predicting new PPIs

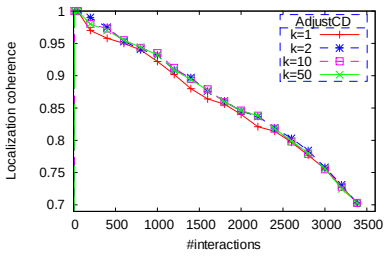




The effect of k

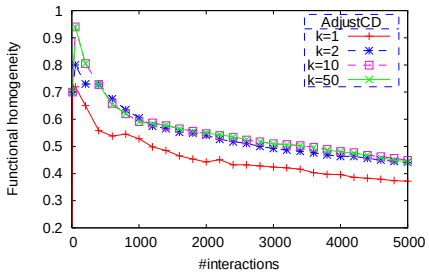
- AdjustCD
- Assessing the reliability of PPIs in DIP dataset

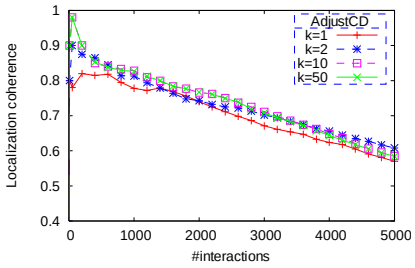




The effect of k

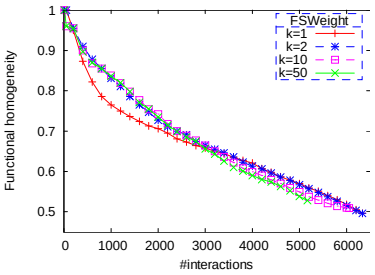
- AdjustCD
- Predicting new PPIs

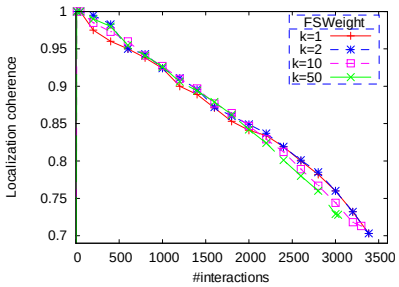




The effect of k

- FSWeight
- Assessing the reliability of PPIs in DIP dataset





The effect of k

- FSWeight
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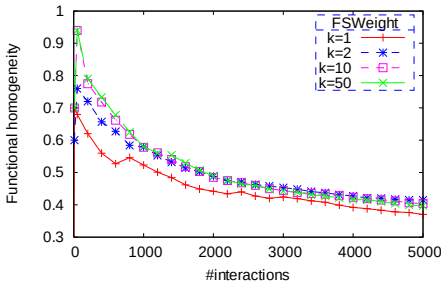
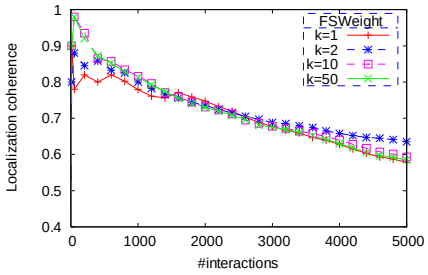
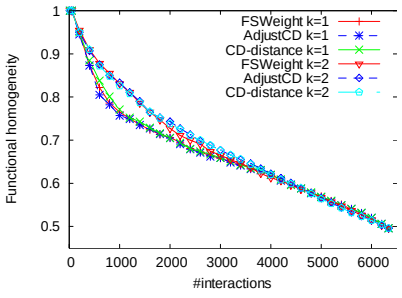
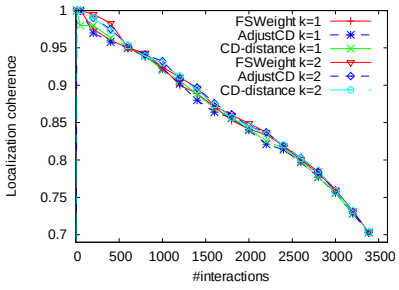




Experiment 2: comparing different scoring methods

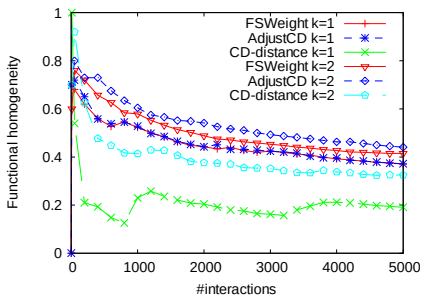
- Assessing the reliability of PPIs in DIP dataset

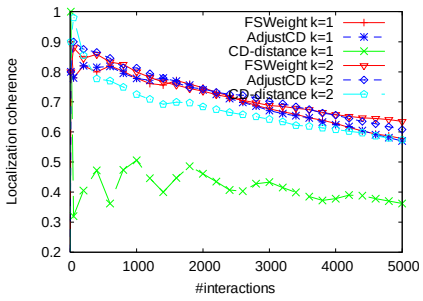




Comparing different scoring methods

- Predicting new PPIs





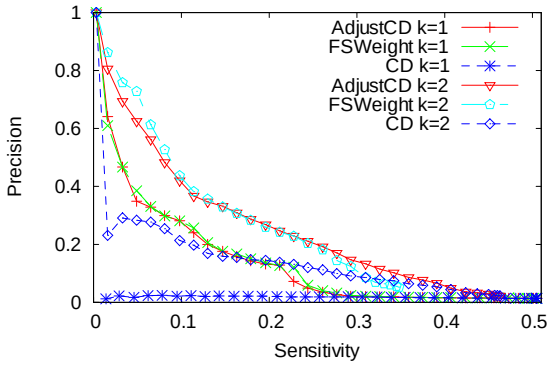
Experiment 3: 5-fold cross-validation

- 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



Roadmap

- An iterative weighting approach to identifying false positives and false negatives from high-throughput interaction data
  - Background
  - Existing weighting methods
  - The iterative weighting approach
  - Experiments
- **Complex discovery from weighted PPI networks**
  - Complex discovery method: maximal cliques
  - Experiments

Protein complexes

- Protein complexes are fundamental for understanding the organization of PPI networks
- With more and more PPI data available, it is possible to predict protein complexes from PPI networks.
- However, PPI networks are often noisy and incomplete, which makes it difficult to predict complexes accurately

⇒Predicting complexes from cleaned and weighted PPI networks (Chua et al. 2008, JBCB)

- Our objective:
  - Study whether the iterative weighting approach can improve the performance of complex prediction algorithms

Predicting complexes using maximal cliques

- Given a PPI network G, we first generate all the maximal cliques from G using the CLIQUES algorithm (Tomita et al. 2006)
- Calculate the score of each clique generated and rank cliques in descending order of their score
  - Score(C) = $\Sigma_{u,v \in C} w(u,v)/(|C| \cdot (|C|-1)/2)$
- Remove and merge highly overlapped cliques
  - Given two cliques C_1, C_2 and score(C_1)≥score(C2), if $|C_1 \cap C_2| / |C_2| \geq$ overlap_thres
    - Case 1: InterConnect(C_1, C_2) ≥merge_thres, then merge C_1 and C_2
    - Case 2: InterConnect(C_1, C_2) <merge_thres, then remove C_2

Inter-connectivity score

- The inter-connectivity score of C_1 and C_2 measures the connectivity between the non-overlapping part of C_1 and C_2

$$\text{InterConnec}(C_1, C_2) = \sqrt{\frac{\sum_{x \in C_1 - C_2, y \in C_2} w(x,y)}{|C_1 - C_2| \times |C_2|} \times \frac{\sum_{x \in C_2 - C_1, y \in C_1} w(x,y)}{|C_2 - C_1| \times |C_1|}}$$

where w(x,y) is the weight of the edge between x and y

Experiments

- PPI dataset: union of six datasets
  - Gavin et al. 2002
  - Gavin et al. 2006
  - Ho et al. 2002
  - Krogan et al. 2006
  - Ito et al. 2001
  - Uetz et al. 2000
- #proteins: 4673
- #interactions: 20461
- #interactions with common neighbors: 11487
- We select the top 6000 interactions

Reference complex sets

- Reference complex set (consider only size≥4)
  - MIPS (dated 18-May-2006)
  - Aloy
    - P. Aloy, B. Bottcher, H. Ceulemans, C. Leutwein, C. Mellwig, S. Fischer, A.-C. Gavin, P. Bork, G. Superti-Furga, L. Serrano, and R. B. Russell. *Structure-based assembly of protein complexes in yeast*. Science, 303(5666): 2026–2029, 2004.

	#cmplxes	#proteins	max size	avg size	median size	avg density	median density
MIPS	162	1171	95	14.93	9	0.408	0.318
Aloy	63	544	34	9.22	7	0.747	0.833

Recall & precision at complex level

- Given a true complex C and a predicted complex S
  - score(S, C)=|S∩C| / |S∪C| (Jaccard index)
  - If score(S, C)≥ match_thres, then we say S matches C
- Given a set of complexes $\{C_1, C_2, \ldots, C_n\}$ and a set predicted complexes $\{S_1, S_2, \ldots, S_m\}$, recall and precision at complex level are defined as
  - $\text{Recall}_{\text{Cmplx}} = \frac{\{C_i \mid \exists S_j, S_j \text{ matches } C_i\}}{n}$
  - $\text{Precision}_{\text{cmplx}} = \frac{\{S_j \mid \exists C_i, C_i \text{ matches } S_j\}}{m}$

Recall & precision at protein level

- Given a set of complexes $\{C_1, C_2, \ldots, C_n\}$ and a set predicted complexes $\{S_1, S_2, \ldots, S_m\}$, recall and precision at protein level are defined as
- $\text{Recall}_{\text{prtn}} = \frac{\sum_{i=1}^{n} \max\{C_i \cap S_j \mid j = 1,2,\ldots m\}}{\sum_{i=1}^{n} |C_i|}$
- $\text{Precision}_{\text{prtn}} = \frac{\sum_{j=1}^{m} \max\{S_j \cap C_i \mid i = 1,2,\ldots, n\}}{\sum_{j=1}^{m} |S_j|}$

Localization coherence

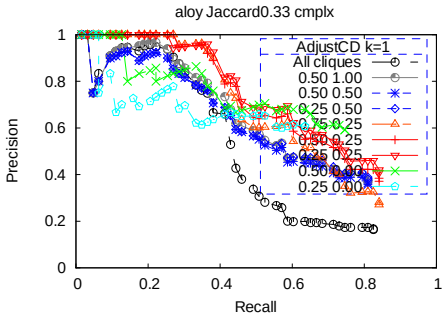
- Complexes can be formed only if its proteins have the same location in the cell
- Let $\{L_1, L_2, \cdots, L_k\}$ be a set of localization groups, where each location group contains proteins at the same location.
  - The co-localization score of a complex C is defined as the maximal fraction of proteins in C that are in the same location.
  - The co-localization score of a set of complexes $\{C_1, C_2, \ldots, C_n\}$ is defined as

$$\text{loc\_score}(\{C_1, C_2, \ldots, C_n\}) = \frac{\sum_{i=1}^{n} \max\{C_i \cap L_j \mid j = 1,2,\ldots,k\}}{\sum_{i=1}^{n} |\{p \in C_i \text{ and } p \text{ has annotations}\}|}$$

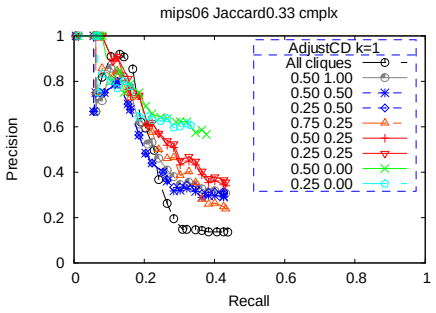
- Use informative localization GO terms

Experiment 1: the effect of overlap_thres and merge_thres

- AdjustCD k=1
- Recall & precision at complex level: match_thres=0.33



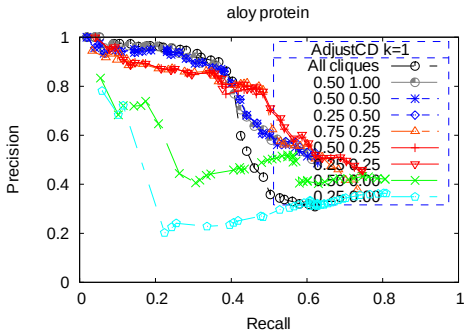
Aloy



MIPS

The effect of overlap_thres and merge_thres

- AdjustCD k=1
- Recall & precision at protein level



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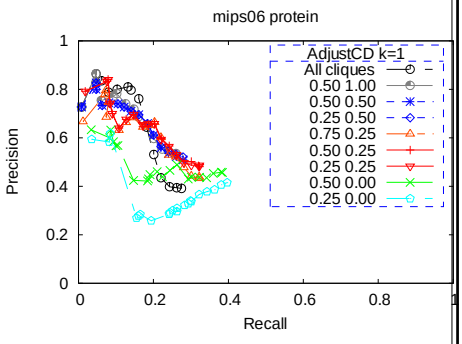
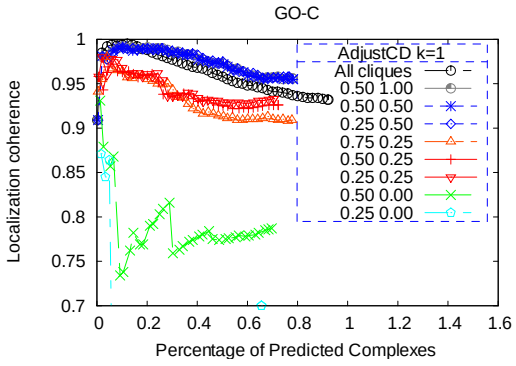


MIPS

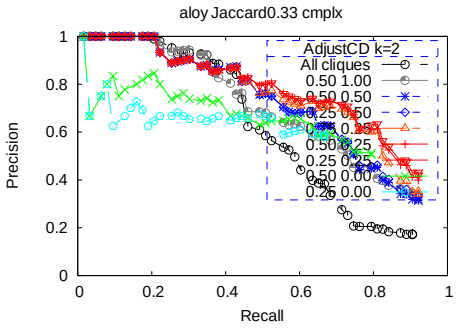
The effect of overlap_thres and merge_thres

- AdjustCD k=1
- Localization coherence

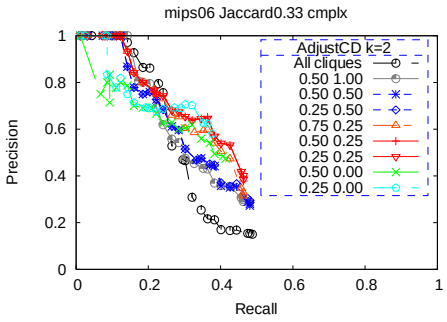


The effect of overlap_thres and merge_thres

- AdjustCD k=2
- Recall & precision at complex level: match_thres=0.33



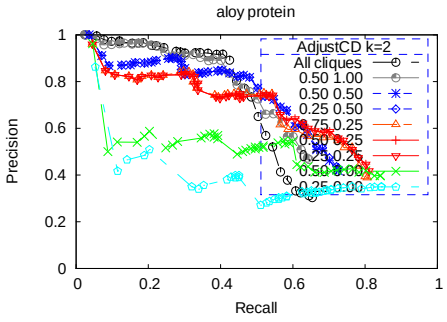
Aloy



MIPS

The effect of overlap_thres and merge_thres

- AdjustCD k=2
- Recall & precision at protein level



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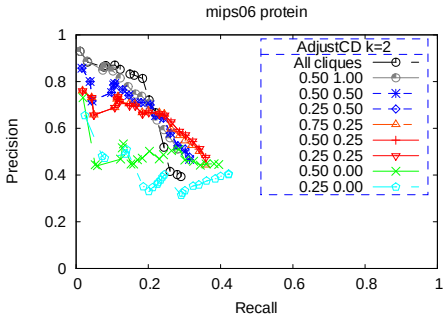
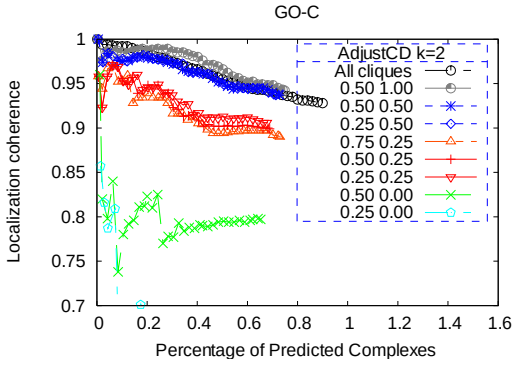


MIPS

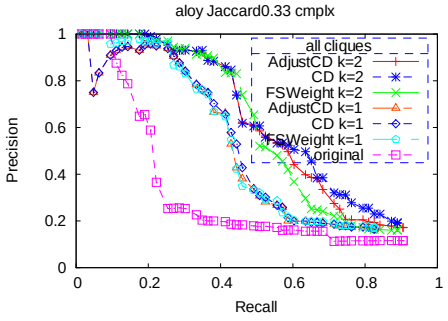
The effect of overlap_thres and merge_thres

- AdjustCD k=2
- Localization coherence

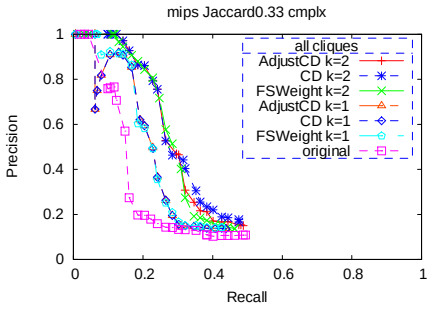


Experiment 2: comparing different PPI weighting methods

- All maximal cliques (without removing and merging overlapped cliques)
- Recall & precision at complex level: match_thres=0.33



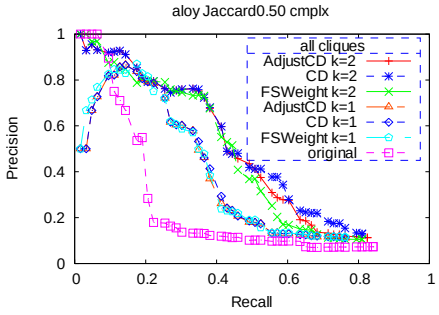
Aloy



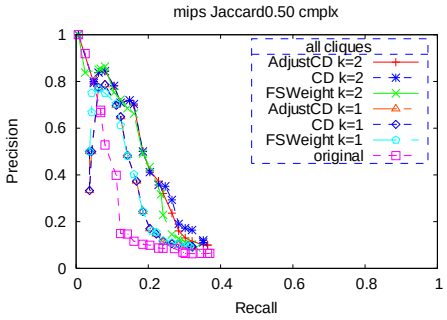
MIPS

Comparing different PPI weighting methods

- All maximal cliques (no removing and merging overlapped cliques)
- Recall & precision at complex level: match_thres=0.50



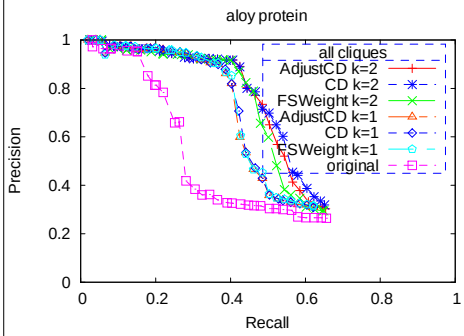
Aloy



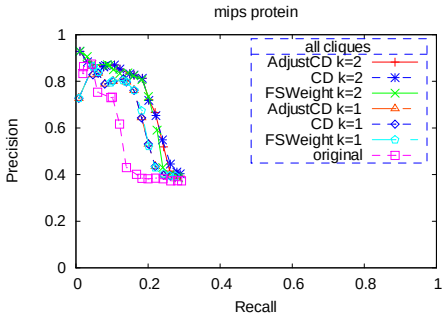
MIPS

Comparing different PPI weighting methods

- All maximal cliques (no removing and merging overlapped cliques)
- Recall & precision at protein level



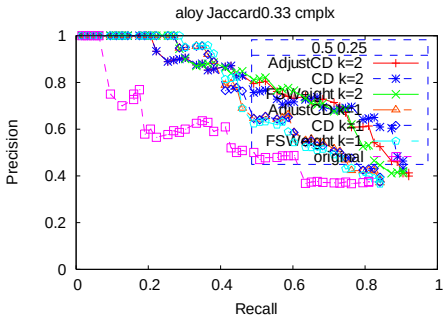
Aloy

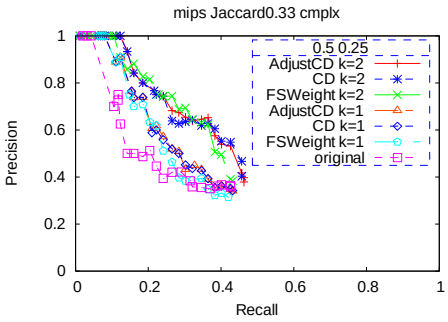


MIPS

Comparing different PPI weighting methods

- overlap_thres=0.50, merge_thres=0.25
- Recall & precision at complex level: match_thres=0.33



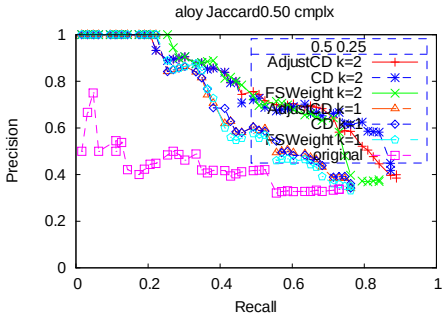


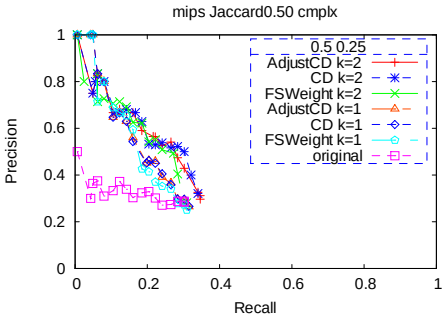
Aloy

MIPS

Comparing different PPI weighting methods

- overlap_thres=0.50, merge_thres=0.25
- Recall & precision at complex level: match_thres=0.50



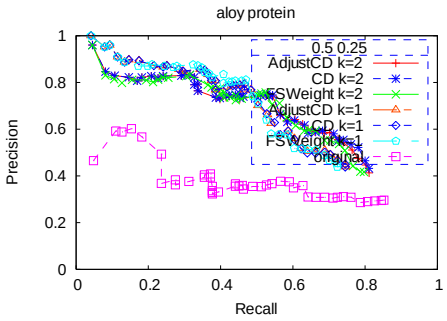


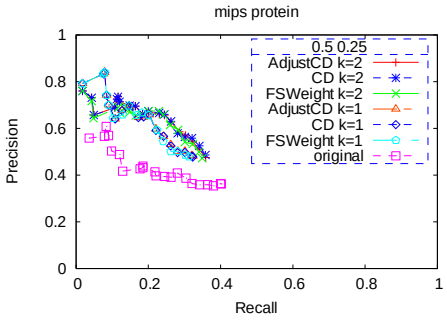
Aloy

MIPS

Comparing different PPI weighting methods

- overlap_thres=0.50, merge_thres=0.25
- Recall & precision at protein level



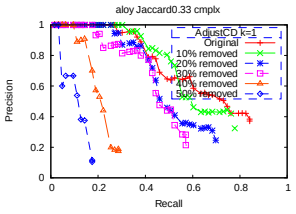


Aloy

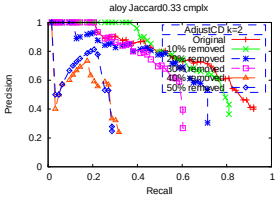
MIPS

Experiment 3: Robustness

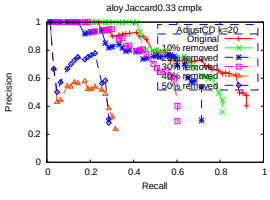
- AdjustCD
- overlap_thres=0.50, merge_thres=0.25
- Random removal of interactions
- Reference complex set: Aloy
- Recall & precision at complex level: match_thres=0.33



k=1



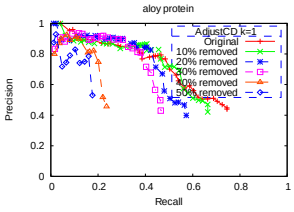
k=2



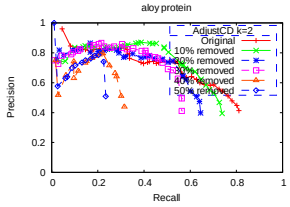
k=20

Robustness: random removal

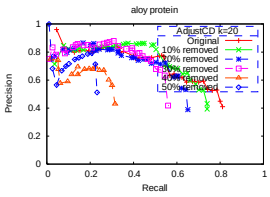
- AdjustCD
- overlap_thres=0.50, merge_thres=0.25
- Reference complex set: Aloy
- Recall & precision at protein level



k=1



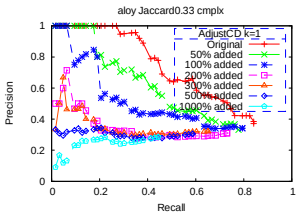
k=2



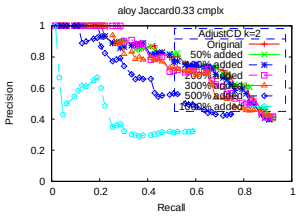
k=20

Robustness: random addition

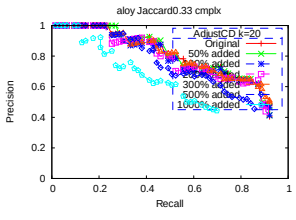
- AdjustCD
- overlap_thres=0.50, merge_thres=0.25
- Reference complex set: Aloy
- Recall & precision at complex level: match_thres=0.33



k=1



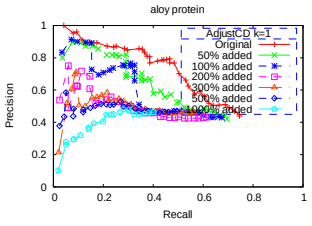
k=2



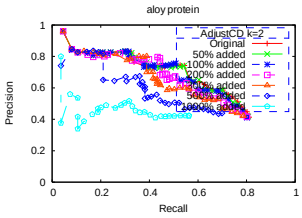
k=20

Robustness: random addition

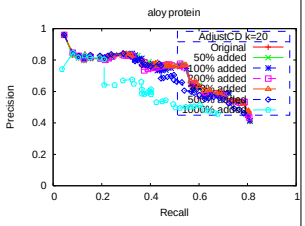
- AdjustCD
- overlap_thres=0.50, merge_thres=0.25
- Reference complex set: Aloy
- Recall & precision at protein level



k=1



k=2



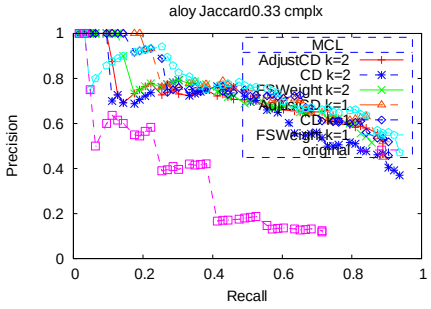
k=20

Experiment 4: Impact of PPI weighting methods on MCL

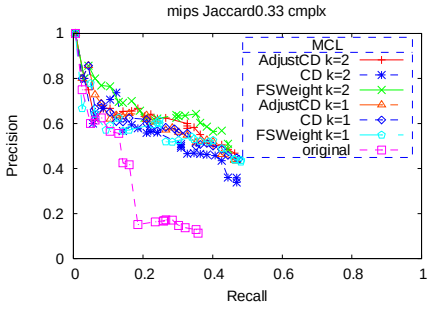
- MCL (Stijn van Dongen, 2000)
  - Flow simulation
  - Do not allow overlap among clusters
  - Parameter setting:
    - Inflation: 1.8
    - Other parameters: default

Impact of PPI weighting methods to MCL

- Top 6000 interactions
- Recall & precision at complex level: match_thres=0.33



Aloy



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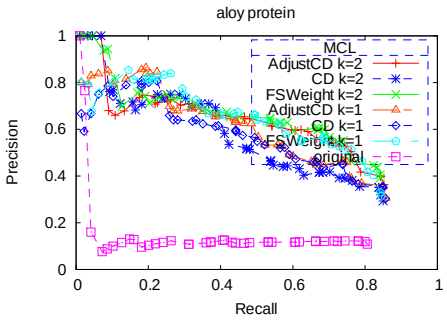
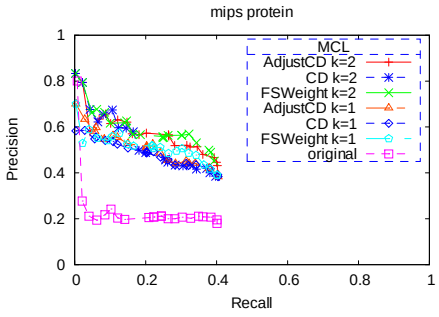
Impact of PPI weighting methods to MCL

- Recall & precision at protein level



Aloy



MIPS

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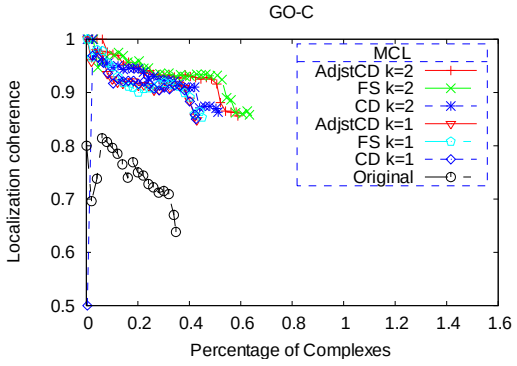
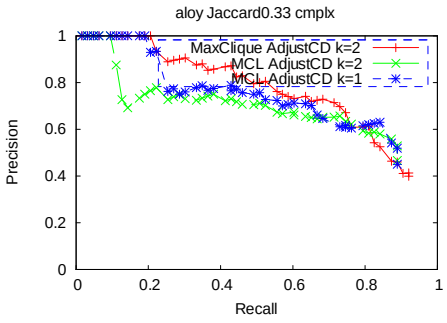
Impact of PPI weighting methods to MCL

- Localization coherence



Experiment 5: comparing different clustering methods

- Recall & precision at complex level: match_thres=0.33



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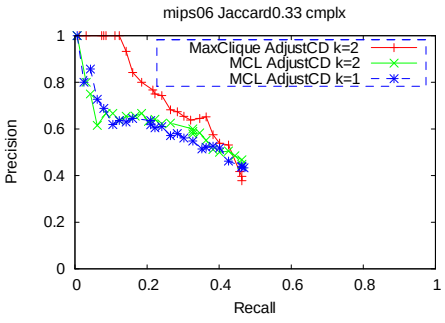
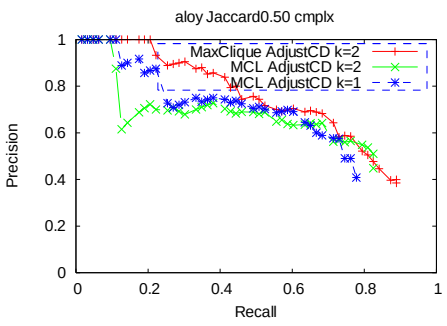


MIPS

Comparing different clustering methods

- Recall & precision at complex level: match_thres=0.50



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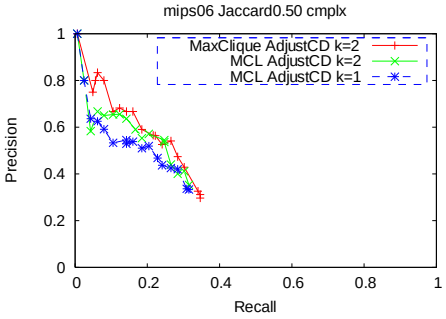
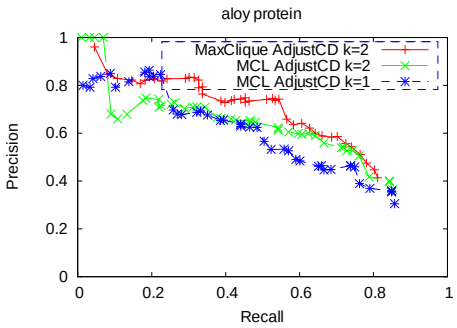


MIPS

Comparing different clustering methods

- Recall & precision at protein level



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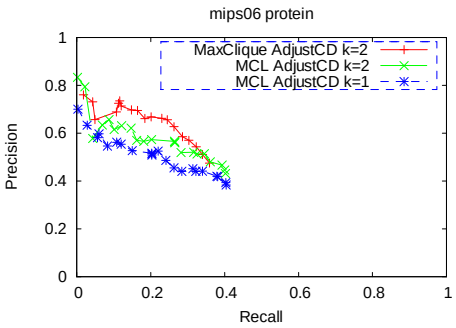
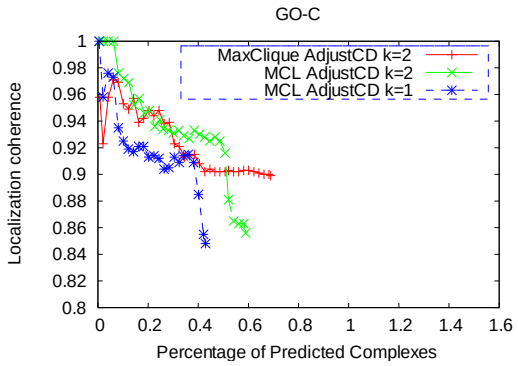


MIPS

Comparing different clustering methods

- Localization coherence



Summary and Conclusion

- Assessing the reliability of PPIs
  - CD-distance, FSWeight, and AdjustCD show similar performance
  - The iterative approach can improve the performance slightly
- Predicting new interactions
  - FSWeight and AdjustCD perform much better than CD-distance
  - The iterative approach can improve the performance significantly

Summary and Conclusion

- Complex discovery
  - Dense complexes are easier to detect than sparse complexes
  - For the maximal clique based algorithm, the iterative approach improves the performance considerably
  - For the MCL algorithm, the iterative approach has no obvious improvement
  - The iterative approach is more robust to random noise

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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

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

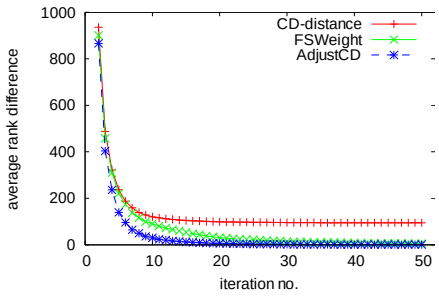
- Given a set of interactions E, the average ranking difference of all the interactions in E at k-th iteration is defined as

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

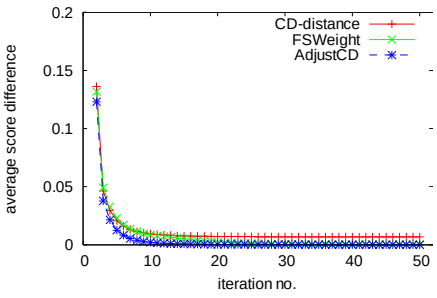
- Similarly, we can define average score difference of all the interactions in E at k-th iteration

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

Results on the DIP dataset



Rank difference



Score difference