Exploiting Indirect Neighbours and Topological Weight to Predict Protein Function from Protein-Protein Interactions

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Joint work with Hon Nian Chua & Wing-Kin Sung

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Protein Function Prediction Approaches

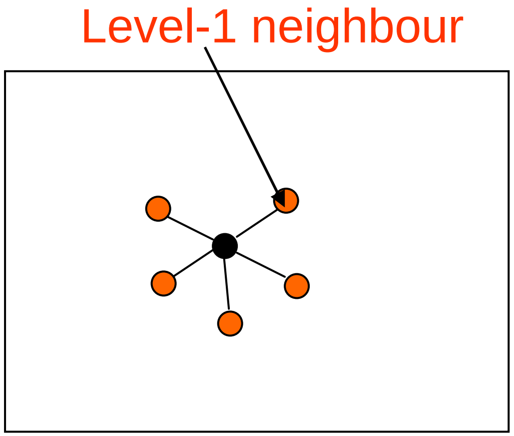
- **Sequence alignment (e.g., BLAST)**
- **Generative domain modeling (e.g., HMMPFAM)**
- **Discriminative approaches (e.g., SVM-PAIRWISE)**
- **Phylogenetic profiling**
- **Subcellular co-localization (e.g., PROTFUN)**
- **Gene expression co-relation**
- **Protein-protein interaction**
- **…**

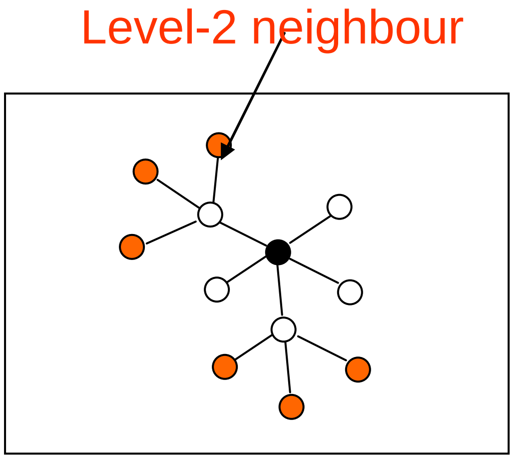
Protein Interaction Based Approaches

- **Neighbour counting** (Schwikowski et al, 2000)
  - Rank function based on freq in interaction partners
- **Chi-square** (Hishigaki et al, 2001)
  - Chi square statistics using expected freq of functions in interaction partners
- **Markov Random Fields** (Deng et al, 2003; Letovsky et al, 2003)
  - Belief propagation exploit unannotated proteins for prediction
- **Simulated Annealing** (Vazquez et al, 2003)
  - Global optimization by simulated annealing
  - Exploit unannotated proteins for prediction
- **Clustering** (Brun et al, 2003; Samanta et al, 2003)
  - Functional distance derived from shared interaction partners
  - Clusters based on functional distance represent proteins with similar functions
- **Functional Flow** (Nabieva et al, 2004)
  - Assign reliability to various expt sources
  - Function “flows” to neighbour based on reliability of interaction and “potential”

Functional Association Thru Interactions

- **Direct functional association:**
  - Interaction partners of a protein are likely to share functions w/ it
  - Proteins from the same pathways are likely to interact
- **Indirect functional association**
  - Proteins that share interaction partners with a protein may also likely to share functions w/ it
  - Proteins that have common biochemical, physical properties and/or subcellular localization are likely to bind to the same proteins

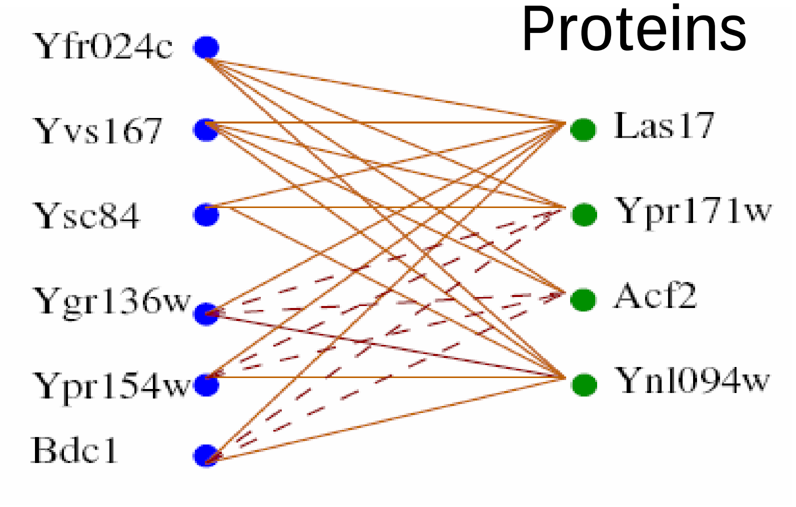




An illustrative Case of Indirect Functional Association?

SH3 Proteins

SH3-Binding Proteins



- **Is *indirect functional association* plausible?**
- **Is it found often in real interaction data?**
- **Can it be used to improve protein function prediction from protein interaction data?**

Materials

- **Protein interaction data from General Repository for Interaction Datasets (GRID)**
  - Data from published large-scale interaction datasets and curated interactions from literature
  - 13,830 unique and 21,839 total interactions
  - Includes most interactions from the Biomolecular Interaction Network (BIND) and the Munich Information Center for Protein Sequences (MIPS)

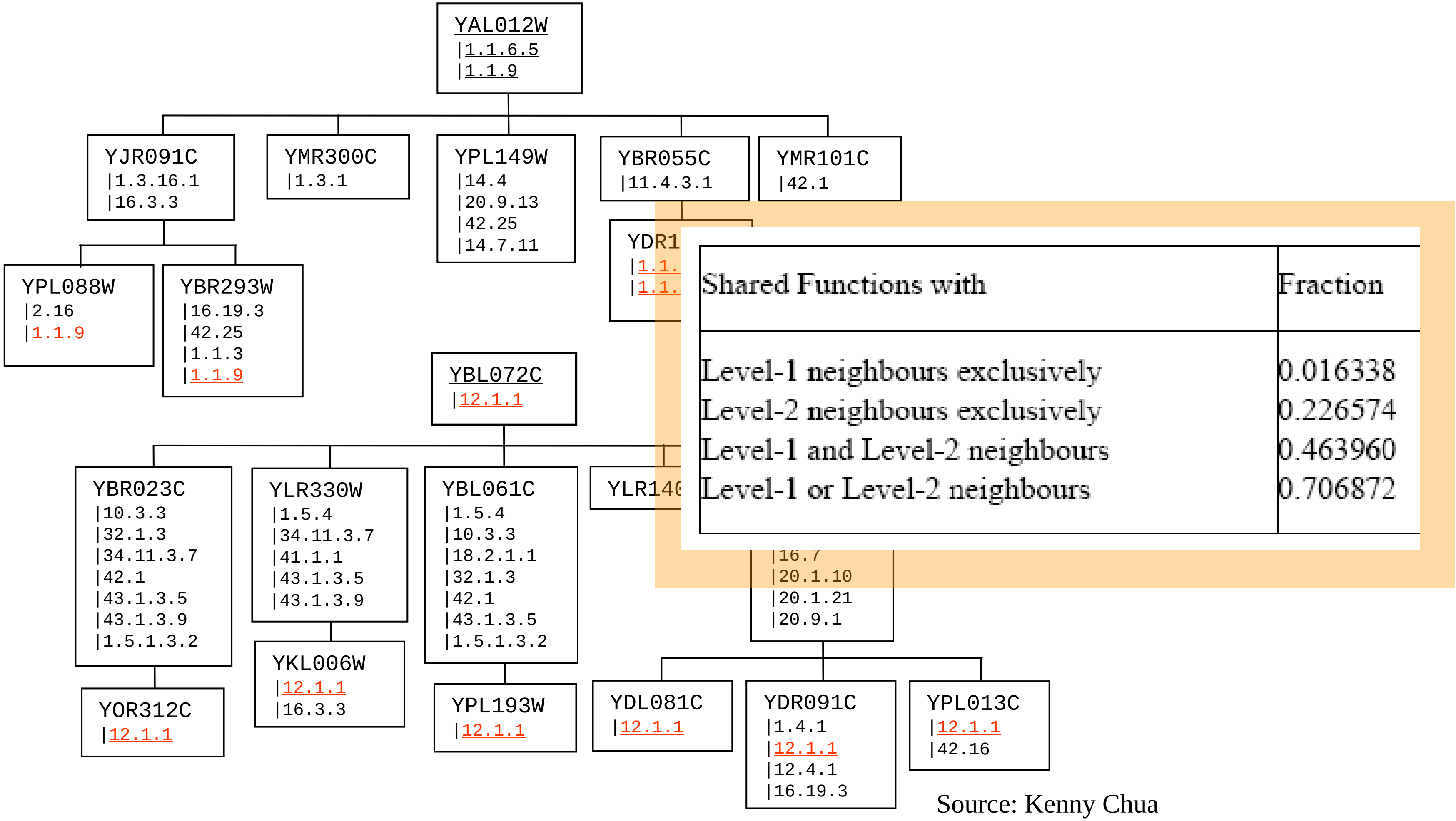
- **Functional annotation (FunCat 2.0) from Comprehensive Yeast Genome Database (CYGD) at MIPS**
  - 473 Functional Classes in hierarchical order

Validation Methods

- **Informative Functional Classes**
  - Adopted from Zhou et al, 1999
  - Select functional classes w/
    - **at least 30 members**
    - **no child functional class w/ at least 30 members**

- **Leave-One-Out Cross Validation**
  - Each protein with annotated function is predicted using all other proteins in the dataset

Freq of Indirect Functional Association



YAL012W
|1.1.6.5
|1.1.9

YJR091C
|1.3.16.1
|16.3.3

YMR300C
|1.3.1

YPL149W
|14.4
|20.9.13
|42.25
|14.7.11

YBR055C
|11.4.3.1

YMR101C
|42.1

YPL088W
|2.16
|1.1.9

YBR293W
|16.19.3
|42.25
|1.1.3
|1.1.9

YDR1
|1.1.
|1.1.

YBL072C
|12.1.1

YBR023C
|10.3.3
|32.1.3
|34.11.3.7
|42.1
|43.1.3.5
|43.1.3.9
|1.5.1.3.2

YLR330W
|1.5.4
|34.11.3.7
|41.1.1
|43.1.3.5
|43.1.3.9

YBL061C
|1.5.4
|10.3.3
|18.2.1.1
|32.1.3
|42.1
|43.1.3.5
|1.5.1.3.2

YLR14

|16.7
|20.1.10
|20.1.21
|20.9.1

YOR312C
|12.1.1

YKL006W
|12.1.1
|16.3.3

YPL193W
|12.1.1

YDL081C
|12.1.1

YDR091C
|1.4.1
|12.1.1
|12.4.1
|16.19.3

YPL013C
|12.1.1
|42.16

Shared Functions with	Fraction
Level-1 neighbours exclusively	0.016338
Level-2 neighbours exclusively	0.226574
Level-1 and Level-2 neighbours	0.463960
Level-1 or Level-2 neighbours	0.706872

Source: Kenny Chua

Over-Rep of Functions in Neighbours

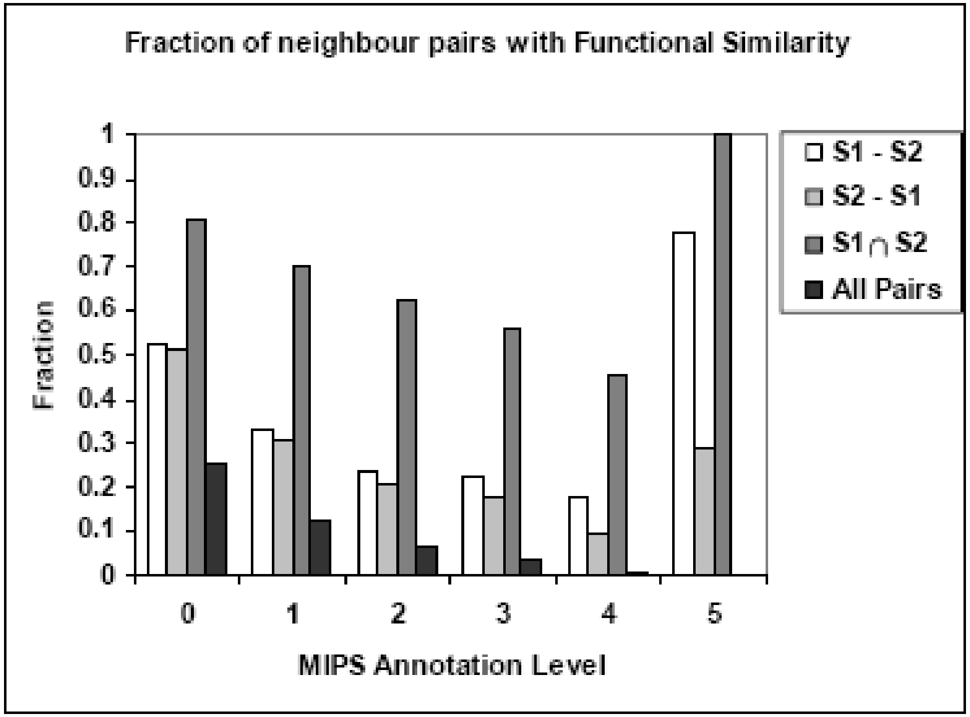
- **Functional Similarity:**

$$S(i,j) = \frac{\left|F_i \cap F_j\right|}{\left|F_i \cup F_j\right|}$$

  - **where F_k is the set of functions of protein k**

- **L1 ∩ L2 neighbours show greatest over-rep**

- **L3 neighbours show little observable over-rep**



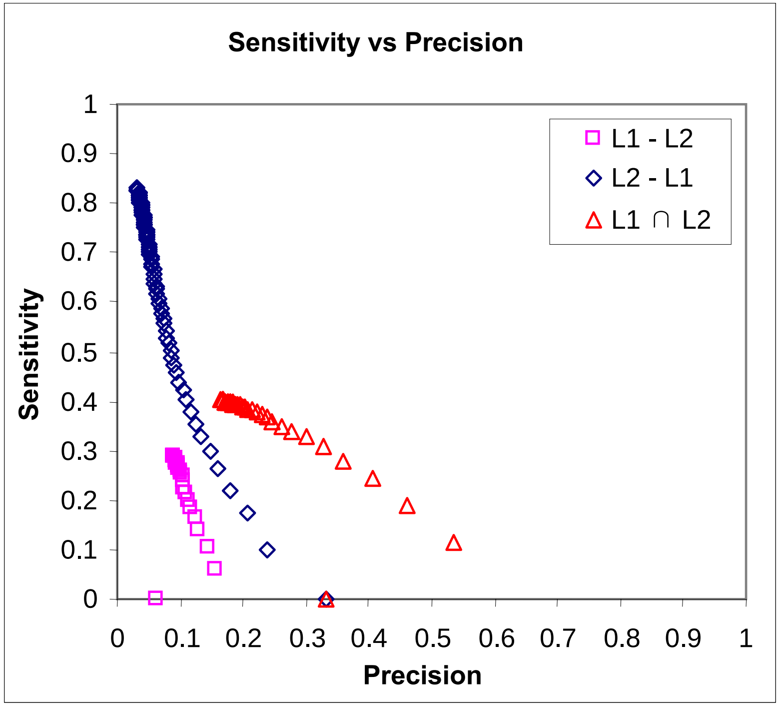
Fraction of neighbour pairs with Functional Similarity

Prediction Power By Majority Voting

- **Remove overlaps in level-1 and level-2 neighbours to study predictive power of “level-1 only” and “level-2 only” neighbours**
- **Sensitivity vs Precision analysis**

$$PR = \frac{\sum_i^K k_i}{\sum_i^K m_i} \qquad SN = \frac{\sum_i^K k_i}{\sum_i^K n_i}$$

  - **n_i is no. of fn of protein i**
  - **m_i is no. of fn predicted for protein i**
  - **k_i is no. of fn predicted correctly for protein i**



⇒ **“level-2 only” neighbours performs better**

⇒ **L1 ∩ L2 neighbours has greatest prediction power**

Functional Similarity Estimate: Czekanowski-Dice Distance

- **Functional distance between two proteins** (Brun et al, 2003)

$$D(u,v)=\frac{|N_u \Delta N_v|}{|N_u \cup N_v| + |N_u \cap N_v|}$$

  - **N_k is the set of interacting partners of k**
  - **X Δ Y is symmetric diff betw two sets X and Y**
  - **Greater weight given to similarity**

Is this a good measure if u and v have very diff number of neighbours?

$\Rightarrow$ Similarity can be defined as

$$S(u,v)=1-D(u,v)=\frac{2X}{2X+(Y+Z)}$$

Functional Similarity Estimate: FS-Weighted Measure

- **FS-weighted measure**

$$S(u,v)=\frac{2\left|N_u\cap N_v\right|}{\left|N_u-N_v\right|+2\left|N_u\cap N_v\right|}\times\frac{2\left|N_u\cap N_v\right|}{\left|N_v-N_u\right|+2\left|N_u\cap N_v\right|}$$

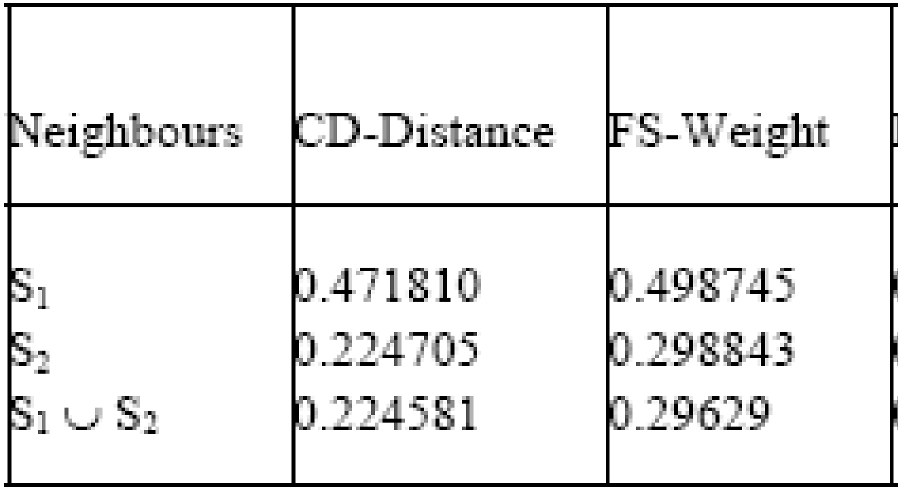
  - **N_k is the set of interacting partners of k**
  - **Greater weight given to similarity**

$\Rightarrow$ **Rewriting this as**

$$S(u,v)=\frac{2X}{2X+Y}\times\frac{2X}{2X+Z}$$

Correlation w/ Functional Similarity

- **Correlation betw functional similarity & estimates**



Neighbours	CD-Distance	FS-Weight
S_1	0.471810	0.498745
S_2	0.224705	0.298843
$S_1 \cup S_2$	0.224581	0.29629

- **Equiv measure slightly better in correlation w/ similarity for L1 & L2 neighbours**

Reliability of Expt Sources

- **Diff Expt Sources have diff reliabilities**
  - Assign reliability to an interaction based on its expt sources (Nabieva et al, 2004)
- **Reliability betw u and v computed by:**

$$r_{u,v} = 1 - \prod_{i \in E_{u,v}} (1 - r_i)$$

  - **r_i is reliability of expt source i,**
  - **$E_{u,v}$ is the set of expt sources in which interaction betw u and v is observed**

Source	Reliability
Affinity Chromatography	**0.823077**
Affinity Precipitation	**0.455904**
Biochemical Assay	**0.666667**
Dosage Lethality	**0.5**
Purified Complex	**0.891473**
Reconstituted Complex	**0.5**
Synthetic Lethality	**0.37386**
Synthetic Rescue	**1**
Two Hybrid	**0.265407**

Functional Similarity Estimate: FS-Weighted Measure with Reliability

- **Take reliability into consideration when computing FS-weighted measure:**

$$S_R(u,v)=\frac{2\sum\limits_{w\in(N_u\cap N_v)} r_{u,w}r_{v,w}}{\left(\sum\limits_{w\in N_u} r_{u,w}+\sum\limits_{w\in(N_u\cap N_v)} r_{u,w}(1-r_{v,w})\right)+2\sum\limits_{w\in(N_u\cap N_v)} r_{u,w}r_{v,w}}\times\frac{2\sum\limits_{w\in(N_u\cap N_v)} r_{u,w}r_{v,w}}{\left(\sum\limits_{w\in N_v} r_{v,w}+\sum\limits_{w\in(N_u\cap N_v)} r_{v,w}(1-r_{u,w})\right)+2\sum\limits_{w\in(N_u\cap N_v)} r_{u,w}r_{v,w}}$$

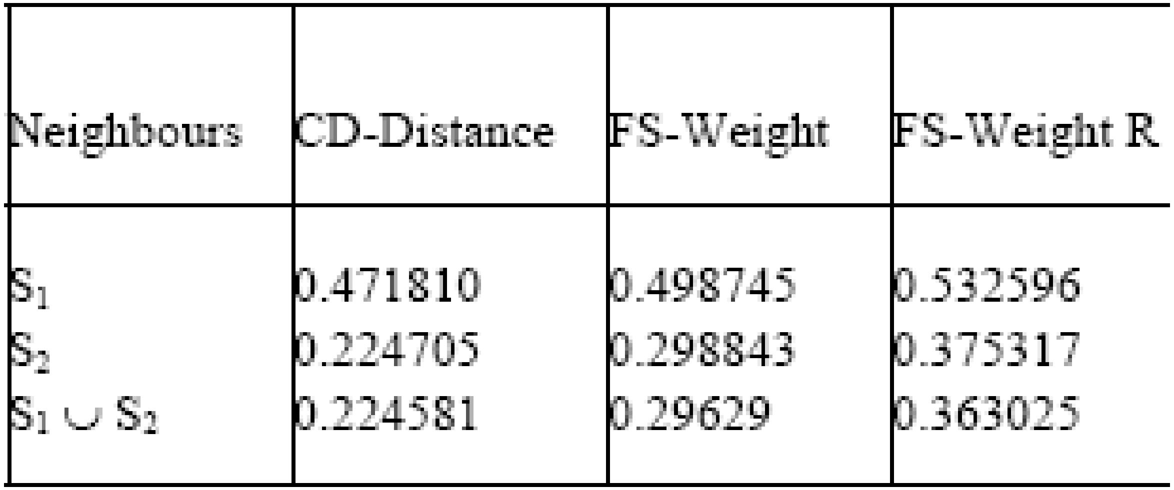
  - **N_k is the set of interacting partners of k**
  - **$r_{u,w}$ is reliability weight of interaction betw u and v**

$\Rightarrow$ **Rewriting**

$$S(u,v)=\frac{2X}{2X+Y}\times\frac{2X}{2X+Z}$$

Integrating Reliability

- **Equiv measure shows improved correlation w/ functional similarity when reliability of interactions is considered:**



Neighbours	CD-Distance	FS-Weight	FS-Weight R
S_1	0.471810	0.498745	0.532596
S_2	0.224705	0.298843	0.375317
$S_1 \cup S_2$	0.224581	0.29629	0.363025

Functional Similarity Estimate: Transitive FS Weighted Measure

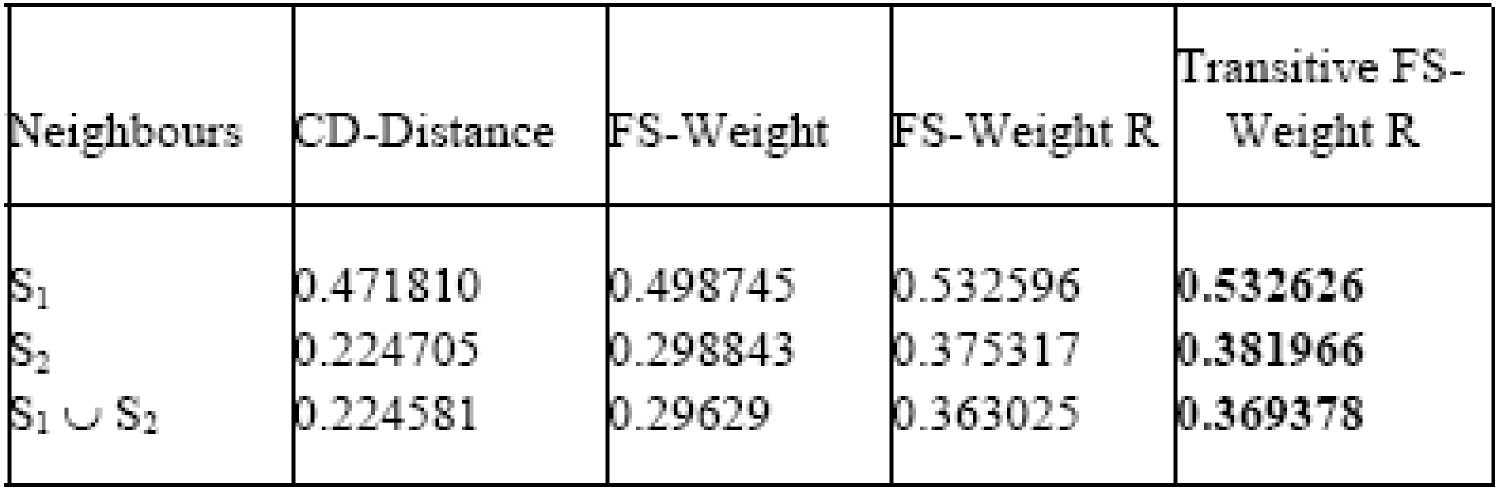
- **If protein u is similar to w, and w is similar to v, then proteins u and v may be similar also**

- **Transitive FS weighted measure**

$$S_{TR}(u,v) = \max\left(S_R(u,v), \max_{w \in N_u} S_R(u,w) S_R(w,v) \right)$$

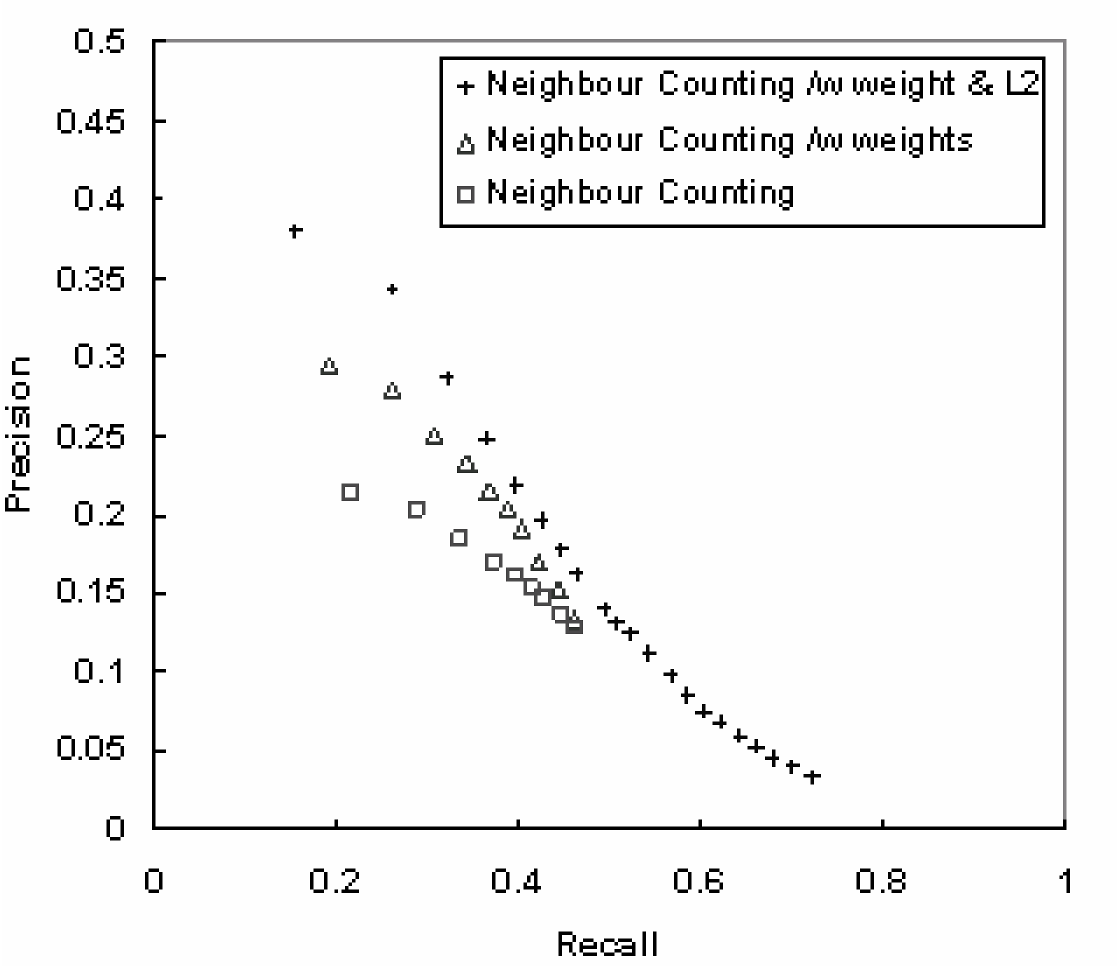
Integrating Transitivity

- **Equiv measure shows improved correlation w/ functional similarity when transitivity is considered:**



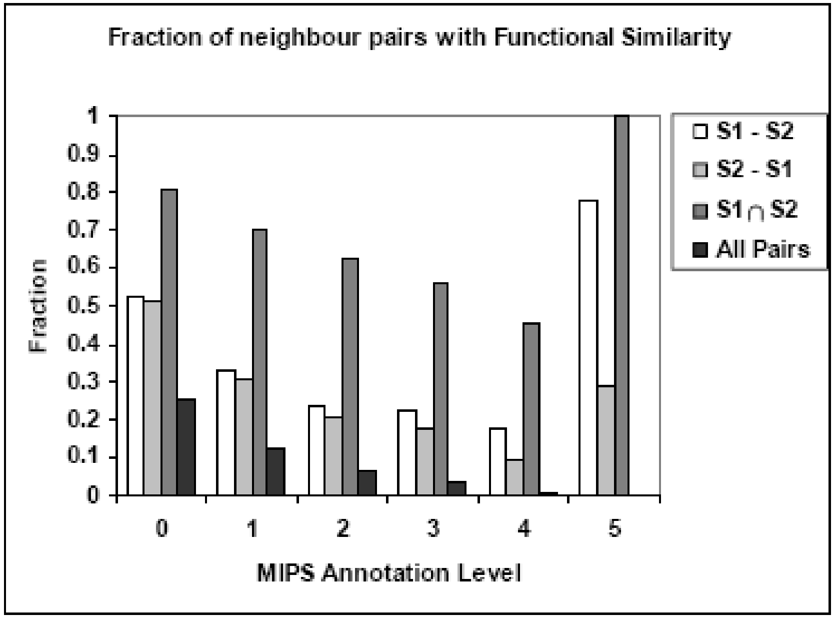
Neighbours	CD-Distance	FS-Weight	FS-Weight R	Transitive FS-Weight R
S_1	0.471810	0.498745	0.532596	**0.532626**
S_2	0.224705	0.298843	0.375317	**0.381966**
$S_1 \cup S_2$	0.224581	0.29629	0.363025	**0.369378**

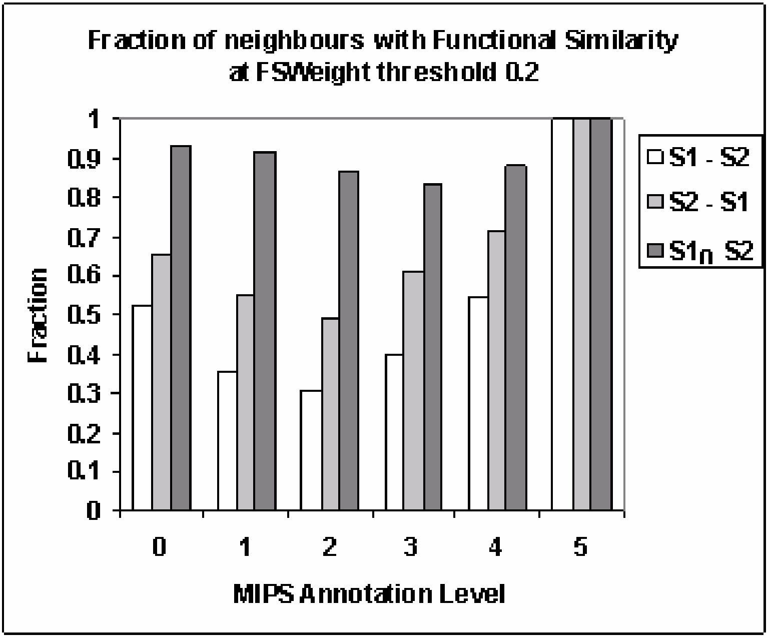
Improvement to Prediction Power by Majority Voting



Considering only neighbours w/ FS weight > 0.2

Improvement to Over-Rep of Functions in Neighbours





Use L1 & L2 Neighbours for Prediction

- **FS-weighted Average**

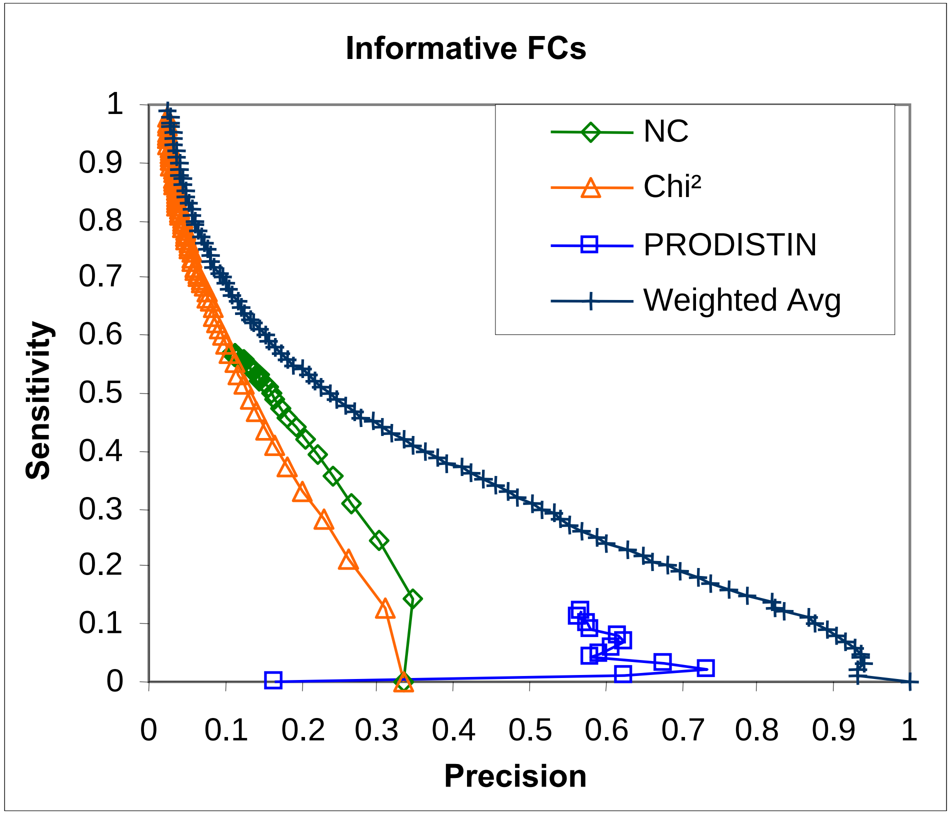
$$f_x(u) = \frac{1}{Z}\left[\lambda r_{\text{int}}\pi_x + \sum_{v \in N_u}\left(S_{TR}(u,v)\delta(v,x) + \sum_{w \in N_v} S_{TR}(u,w)\delta(w,x)\right)\right]$$

  - **r_{int} is fraction of all interaction pairs sharing function**
  - **λ is weight of contribution of background freq**
  - **$\delta(k, x) = 1$ if k has function x, 0 otherwise**
  - **N_k is the set of interacting partners of k**
  - **π_x is freq of function x in the dataset**
  - **Z is sum of all weights**

$$Z = 1 + \sum_{v \in N_u}\left(S_{TR}(u,v) + \sum_{w \in N_v} S_{TR}(u,w)\right)$$

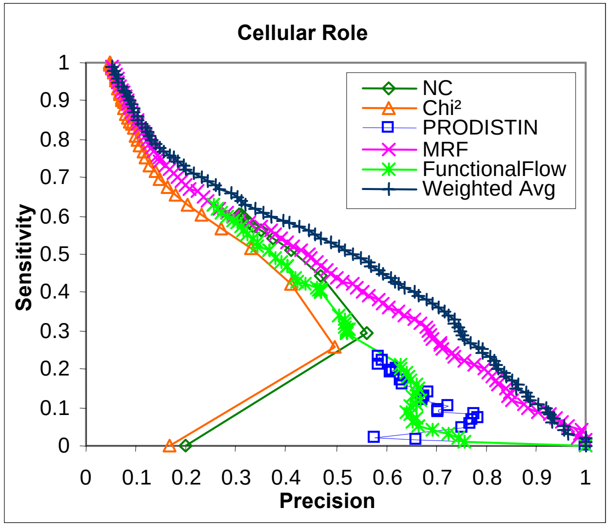
Performance of FS-Weighted Averaging

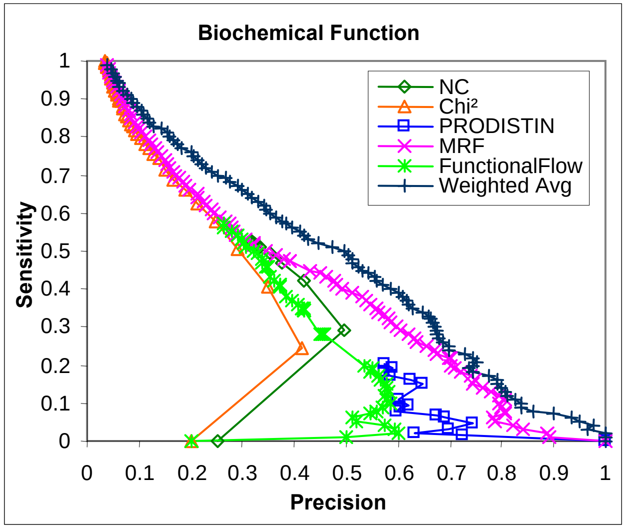
- **LOOCV comparison with Neighbour Counting, Chi-Square, PRODISTIN**

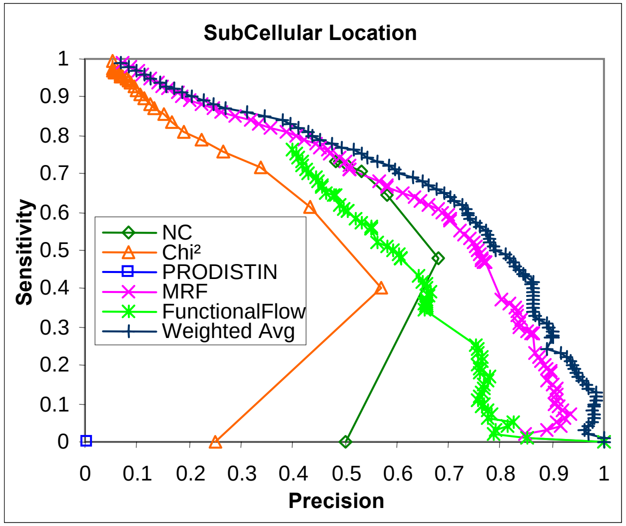


Performance of FS-Weighted Averaging

- **Dataset from Deng et al, 2003**
  - Gene Ontology (GO) Annotations
  - MIPS interaction dataset
- **Comparison w/ Neighbour Counting, Chi-Square, PRODISTIN, Markov Random Field, FunctionalFlow**

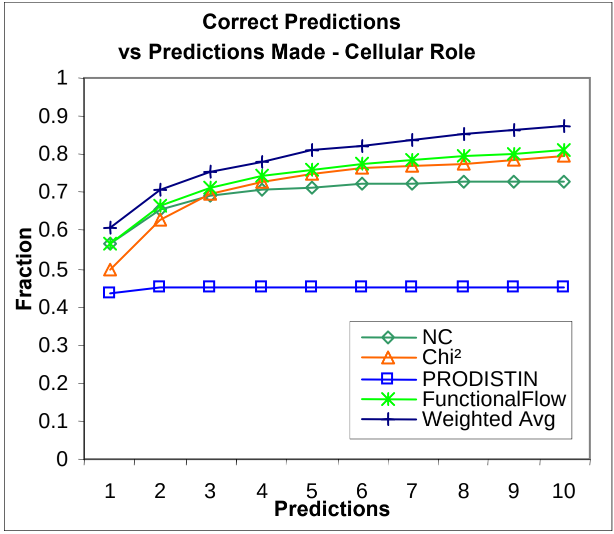




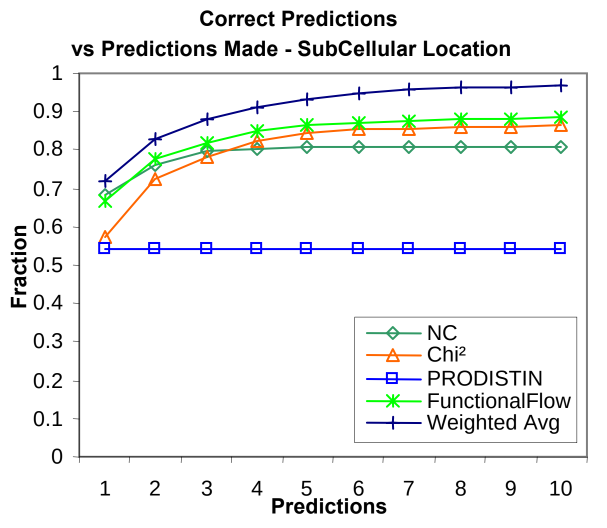


Performance of FS-Weighted Averaging

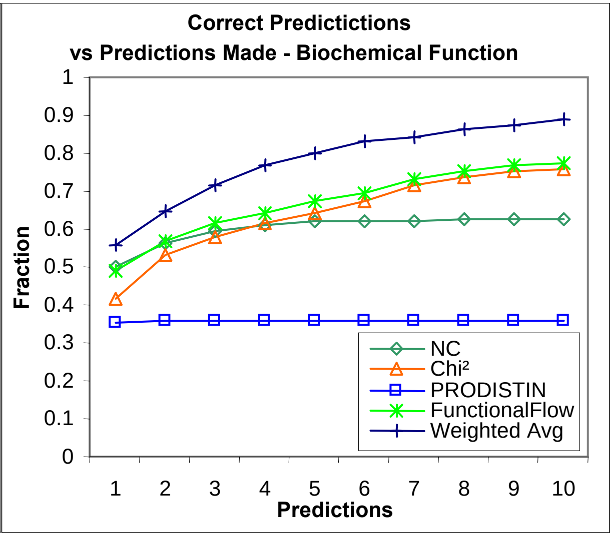
- **Correct Predictions made on at least 1 function vs Number of predictions made per protein**



Correct Predictions vs Predictions Made - Cellular Role



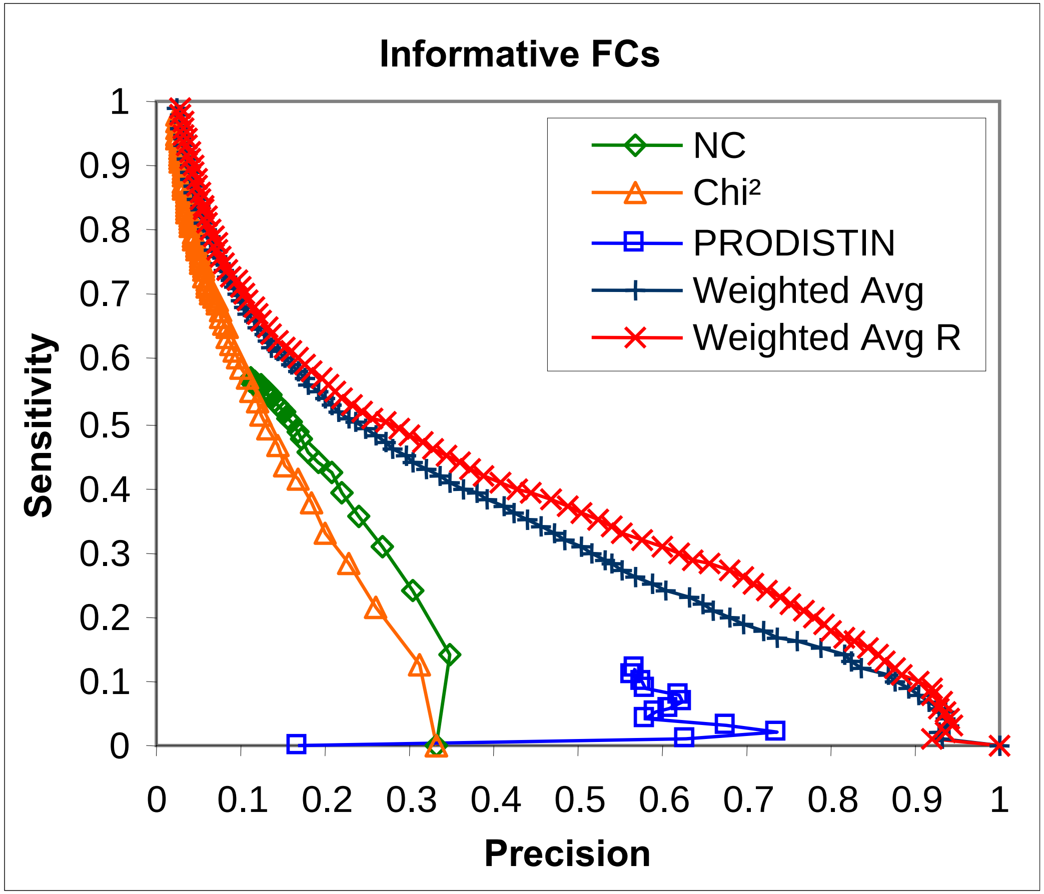
Correct Predictions vs Predictions Made - SubCellular Location



Correct Predictictions vs Predictions Made - Biochemical Function

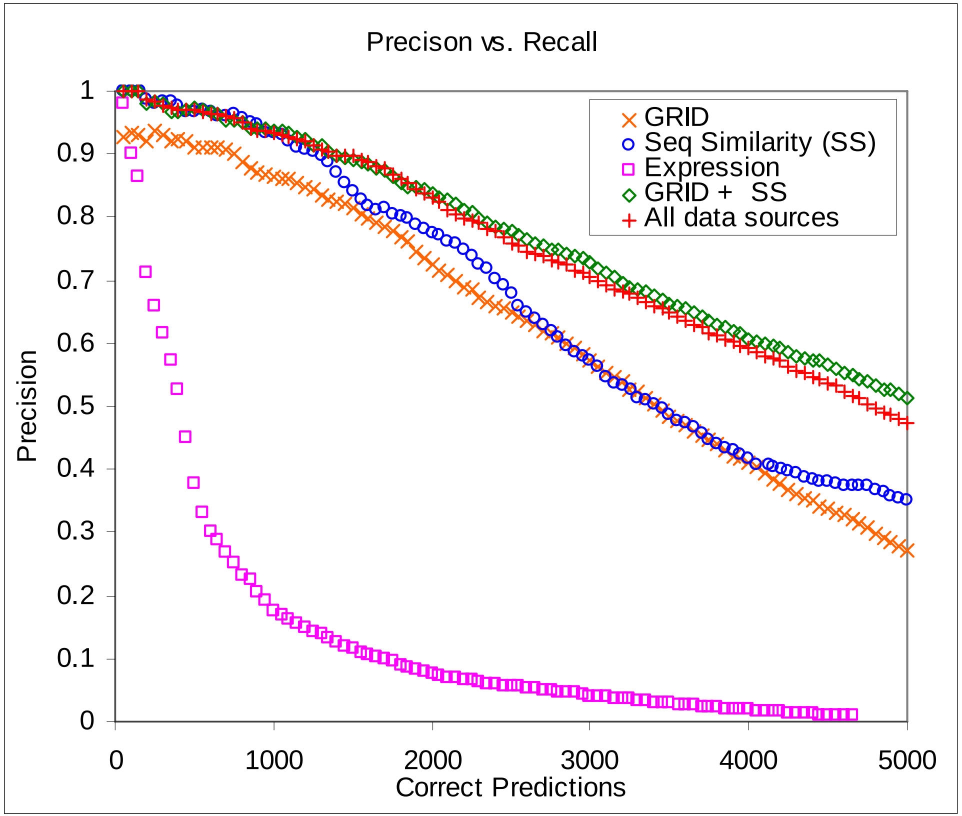
Performance of FS-Weighted Averaging

- **Prediction performance further improves after incorporation of interaction reliability**



Incorporating Other Info Sources

- **PPI Interaction Data**
  - General Rep of Interaction Data
  - 17815 Unique Pairs, 4914 Proteins
  - Reliability: 0.366 (Based on fraction with known functional similarity)
- **Sequence Similarity**
  - Smithwaterman betw seq of all proteins
  - For each seq, among all SW scores w/ all other seq, extract seq w/ SW score >= 3 standard deviations from mean
  - 32028 Unique Pairs, 6766 Proteins
  - Reliability: 0.659
- **Gene Expression**
  - Spellman w/ 77 timepoints
  - Extract all pairs w/ Pearson's > 0.7
  - 11586 Unique Pairs, 2082 Proteins
  - Reliability: 0.354



Conclusions

- Indirect functional association is plausible
- It is found often in real interaction data
- It can be used to improve protein function prediction from protein interaction data
- It should be possible to incorporate interaction networks extracted by literature in the inference process within our framework for good benefit

Acknowledgements

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