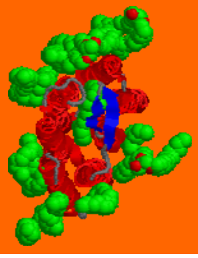
Guilt by Association:
A Tutorial on
Protein Function Inference

Limsoon Wong
(Based on work w/ Kenny Chua & Ken Sung)

Plan

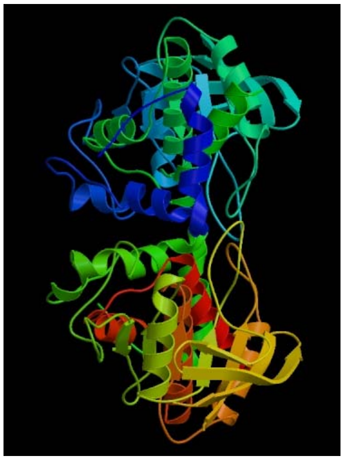
- **Protein Function Prediction**
- **Guilt by Association of Seq Similarity**
- **Twists in the Tale**
- **Guilt by Association of Other Type of Info**
- **Guilt by Association of Multiple Types of Info**

Protein Function Prediction: Motivation & Challenges



- A protein is a large complex molecule made up of one or more chains of amino acids

- Protein performs a wide variety of activities in the cell



Function Assignment to Protein Seq

```
SPSTNRKYPPLPVDKLEEEINRRMADDNKLFREEFNALPACPIQATCEAASKEENKEKNR
YVNILPYDHSRVHLTPVEGVPDSDYINASFINGYQEKNKFIAAQGPKEETVNDFWRMIWE
QNTATIVMVTNLKERKECKCAQYWPDQGCWTYGNVRVSVEDVTVLVDYTVRKFCIQQVGD
VTNRKPQRLITQFHFTSWPDFGVPFTPIGMLKFLKKVKACNPQYAGAIVVHCSAGVGRTG
TFVVIDAMLDMMHSERKVDVYGFVSRIRAQRCQMVQTDMQYVFIYQALLEHYLYGDTELE
VT
```

- **How do we attempt to assign a function to a new protein sequence?**

An Early Example of Seq Analysis

Source: Ken Sung

- **Doolittle et al. (*Science*, July 1983) searched for platelet-derived growth factor (PDGF) in his own DB. He found that PDGF is similar to v-sis oncogene**

```
PDGF-2  1        SLGSLTIAEPAMIAECKTREEVFCICRRL?DR?? 34
p28sis 61 LARGKRSLGSLSVAEPAMIAECKTRTEVFEISRRLIDRTN 100
```

⇒ "Guilt by association" of sequence similarity!

Guilt by Association of Sequence Similarity

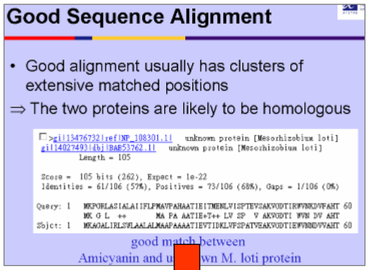
```
PDGF-2  1       SLGSLTIAEPAMIAECKTREEVFCICRRL?DR?? 34
p28sis 61 LARGKRSLGSLSVAEPAMIAECKTRTEVFEISRRLIDRTN 100
```

Guilt by Association: General Idea

- **Compare the target sequence T with sequences $S_1, \ldots, S_n$ of known function in a database**
- **Determine which ones amongst $S_1, \ldots, S_n$ are the mostly likely homologs of T**
- **Then assign to T the same function as these homologs**
- **Finally, confirm with suitable wet experiments**

Guilt by Association of Seq Similarity

Compare *T* with seqs of known function in a db



Good Sequence Alignment

- Good alignment usually has clusters of extensive matched positions

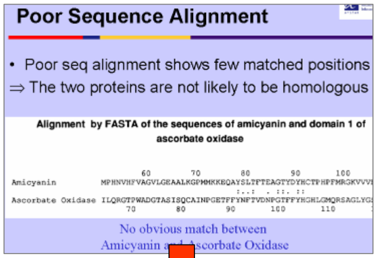
⇒ The two proteins are likely to be homologous

```
☐>gi|13476732|ref|NP_108301.1|   unknown protein [Mesorhizobium loti]
 gi|14027493|dbj|BAB53762.1|   unknown protein [Mesorhizobium loti]
          Length = 105

 Score =  105 bits (262), Expect = 1e-22
 Identities = 61/106 (57%), Positives = 73/106 (68%), Gaps = 1/106 (0%)

Query: 1   MKPGRLASIALAIIFLPMAVPAHAATIEITMENLVISPTEVSAKVGDTIRWVNKDVFAHT 60
            MK G L  ++        MA PA AATIE+T++ LV SP  V AKVGDTI WVN DV AHT
Sbjct: 1   MKAGALIRLSWLAALALMAAPAAAATIEVTIDKLVFSPATVEAKVGDTIEWVNNDVVAHT 60
```

good match between
Amicyanin and unknown M. loti protein



Poor Sequence Alignment

- Poor seq alignment shows few matched positions

⇒ The two proteins are not likely to be homologous

Alignment by FASTA of the sequences of amicyanin and domain 1 of ascorbate oxidase

```
                        60        70        80        90        100
Amicyanin         MPHNVHFVAGVLGEAALKGPMMKKEQAYSLTFTEAGTYDYHCTPHPFMRGKVVV
                                             :..:  . ::. ::
Ascorbate Oxidase ILQRGTPWADGTASISQCAINPGETFFYNFTVDNPGTFFYHGHLGMQRSAGLYG
                     70        80        90        100       110
```

No obvious match between
Amicyanin and Ascorbate Oxidase

Assign to *T* same function as homologs

Discard this function as a candidate

Confirm with suitable wet experiments

Seq Alignment

```
PDGF-2  1        SLGSLTIAEPAMIAECKTREEVFCICRRL?DR?? 34
p28sis 61  LARGKRSLGSLSVAEPAMIAECKTRTEVFEISRRLIDRTN 100
```

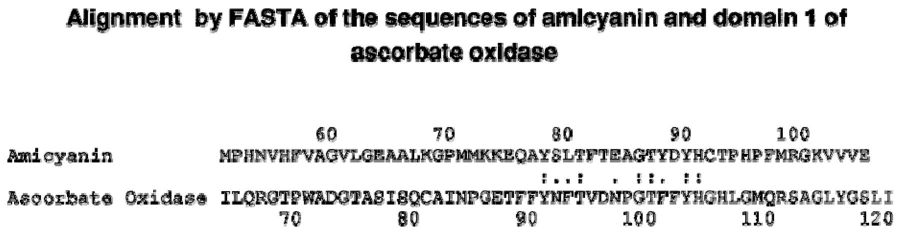
- **A seq alignment maximizes the number of positions that are in agreement in two sequences**
- **Many implementations:**
  - Global vs local alignment
  - Gapped vs ungapped
  - Filtered vs unfiltered, …

Exercise: Name a seq alignment algo

Seq Alignment: Poor Example

- **Poor seq alignment shows few matched positions**

⇒ The two proteins are not likely to be homologous



Alignment by FASTA of the sequences of amicyanin and domain 1 of ascorbate oxidase

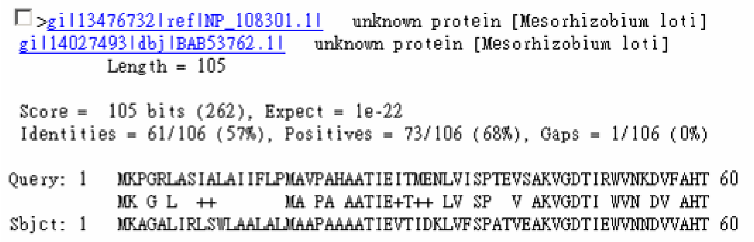
```
                          60        70        80        90       100
Amicyanin         MPHNVHFVAGVLGEAALKGPMMKKEQAYSLTFTEAGTYDYHCTPHPFMRGKVVVE
                                             :..:  . ::. ::
Ascorbate Oxidase ILQRGTPWADGTASISQCAINPGETFFYNFTVDNPGTFFYHGHLGMQRSAGLYGSLI
                       70        80        90       100       110       120
```

No obvious match between
Amicyanin and Ascorbate Oxidase

Seq Alignment: Good Example

- **Good alignment usually has clusters of extensive matched positions**

⇒ The two proteins are likely to be homologous



```
☐>gi|13476732|ref|NP_108301.1|   unknown protein [Mesorhizobium loti]
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Query: 1   MKPGRLASIALAIIFLPMAVPAHAATIEITMENLVISPTEVSAKVGDTIRWVNKDVFAHT 60
            MK G L  ++        MA PA AATIE+T++ LV SP  V AKVGDTI WVN DV AHT
Sbjct: 1   MKAGALIRLSWLAALALMAAPAAAATIEVTIDKLVFSPATVEAKVGDTIEWVNNDVVAHT 60
```
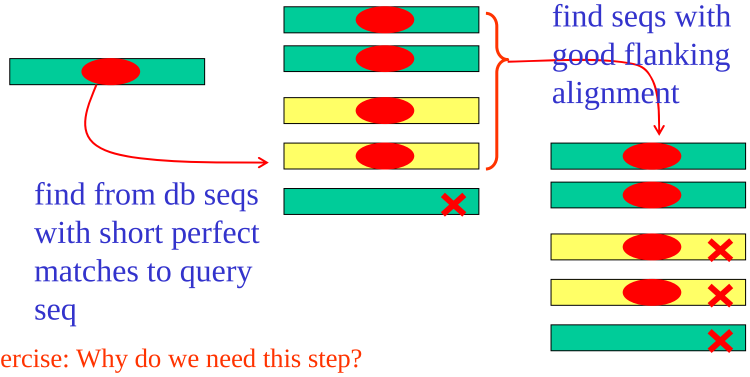

good match between
Amicyanin and unknown M. loti protein

BLAST: How It Works

Altschul et al., *JMB*, 215:403--410, 1990

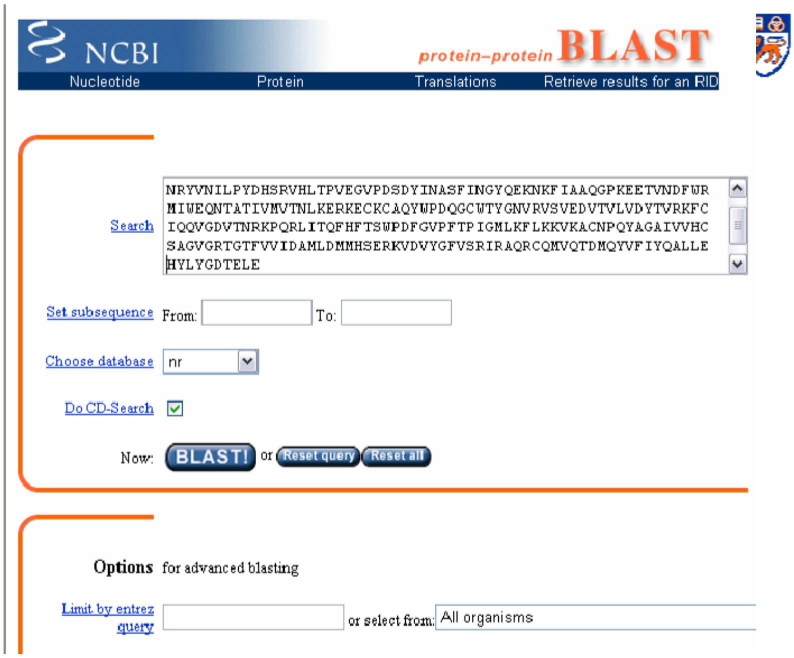
- **BLAST is the most popular tool for “guilt by association” seq homology search**



find seqs with good flanking alignment

find from db seqs with short perfect matches to query seq

Exercise: Why do we need this step?



Search

```
NRYVNILPYDHSRVHLTPVEGVPDSDYINASFINGYQEKNKFIAAQGPKEETVNDFWR
MIWEQNTATIVMVTNLKERKECKCAQYWPDQGCWTYGNVRVSVEDVTVLVDYTVRKFC
IQQVGDVTNRKPQRLITQFHFTSWPDFGVPFTPIGMLKFLKKVKACNPQYAGAIVVHC
SAGVGRTGTFVVIDAMLDMMHSERKVDVYGFVSRIRAQRCQMVQTDMQYVFIYQALLE
HYLYGDTELE
```

Set subsequence From: To:

Choose database nr

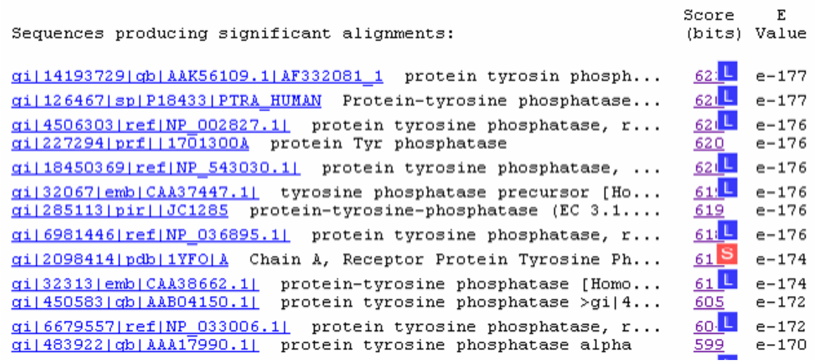
Do CD-Search ☑

Now: BLAST! or Reset query Reset all

Options for advanced blasting

Limit by entrez query or select from: All organisms

Homologs by BLAST



```
                                                                Score    E
Sequences producing significant alignments:                     (bits) Value

gi|14193729|gb|AAK56109.1|AF332081_1  protein tyrosin phosph...   62 L  e-177
gi|126467|sp|P18433|PTRA_HUMAN  Protein-tyrosine phosphatase...   62 L  e-177
gi|4506303|ref|NP_002827.1|  protein tyrosine phosphatase, r...   62 L  e-176
gi|227294|prf||1701300A  protein Tyr phosphatase                  620    e-176
gi|18450369|ref|NP_543030.1|  protein tyrosine phosphatase, ...   62 L  e-176
gi|32067|emb|CAA37447.1|  tyrosine phosphatase precursor [Ho...   61 L  e-176
gi|285113|pir||JC1285  protein-tyrosine-phosphatase (EC 3.1....   619    e-176
gi|6981446|ref|NP_036895.1|  protein tyrosine phosphatase, r...   61 L  e-176
gi|2098414|pdb|1YFO|A  Chain A, Receptor Protein Tyrosine Ph...   61 S  e-174
gi|32313|emb|CAA38662.1|  protein-tyrosine phosphatase [Homo...   61 L  e-174
gi|450583|gb|AAB04150.1|  protein tyrosine phosphatase >gi|4...   605    e-172
gi|6679557|ref|NP_033006.1|  protein tyrosine phosphatase, r...   60 L  e-172
gi|483922|gb|AAA17990.1|  protein tyrosine phosphatase alpha      599    e-170
```

- **Thus our example sequence could be a protein tyrosine phosphatase α (PTPα)**

Example Alignment with PTPα

```
 Score =  632 bits (1629), Expect = e-180
 Identities = 294/302 (97%), Positives = 294/302 (97%)

Query: 1    SPSTNRKYPPLPVDKLEEEINRRMADDNKLFREEFNALPACPIQATCEAASXXXXXXXXR 60
            SPSTNRKYPPLPVDKLEEEINRRMADDNKLFREEFNALPACPIQATCEAAS        R
Sbjct: 202  SPSTNRKYPPLPVDKLEEEINRRMADDNKLFREEFNALPACPIQATCEAASKEENKEKNR 261

Query: 61   YVNILPYDHSRVHLTPVEGVPDSDYINASFINGYQEKNKFIAAQGPKEETVNDFWRMIWE 120
            YVNILPYDHSRVHLTPVEGVPDSDYINASFINGYQEKNKFIAAQGPKEETVNDFWRMIWE
Sbjct: 262  YVNILPYDHSRVHLTPVEGVPDSDYINASFINGYQEKNKFIAAQGPKEETVNDFWRMIWE 321

Query: 121  QNTATIVMVTNLKERKECKCAQYWPDQGCWTYGNVRVSVEDVTVLVDYTVRKFCIQQVGD 180
            QNTATIVMVTNLKERKECKCAQYWPDQGCWTYGNVRVSVEDVTVLVDYTVRKFCIQQVGD
Sbjct: 322  QNTATIVMVTNLKERKECKCAQYWPDQGCWTYGNVRVSVEDVTVLVDYTVRKFCIQQVGD 381

Query: 181  VTNRKPQRLITQFHFTSWPDFGVPFTPIGMLKFLKKVKACNPQYAGAIVVHCSAGVGRTG 240
            VTNRKPQRLITQFHFTSWPDFGVPFTPIGMLKFLKKVKACNPQYAGAIVVHCSAGVGRTG
Sbjct: 382  VTNRKPQRLITQFHFTSWPDFGVPFTPIGMLKFLKKVKACNPQYAGAIVVHCSAGVGRTG 441

Query: 241  TFVVIDAMLDMMHSERKVDVYGFVSRIRAQRCQMVQTDMQYVFIYQALLEHYLYGDTELE 300
            TFVVIDAMLDMMHSERKVDVYGFVSRIRAQRCQMVQTDMQYVFIYQALLEHYLYGDTELE
Sbjct: 442  TFVVIDAMLDMMHSERKVDVYGFVSRIRAQRCQMVQTDMQYVFIYQALLEHYLYGDTELE 501
```

References

- S.F.Altshcul et al. “Basic local alignment search tool”, *JMB*, 215:403--410, 1990
- S.F.Altschul et al. “Gapped BLAST and PSI-BLAST: A new generation of protein database search programs”, *NAR*, 25(17):3389--3402, 1997
- D. Brown et al. “Homology Search Methods”, *The Practical Bioinformatician*, Chapter 10, pp 217—244, WSPC, 2004
- S.B.Needleman & C.D.Wunsch. “A general method applicable to the search for similarities in the amino acid sequence of two proteins”, *JMB*, 48:444—453, 1970
- J. Park et al. “Sequence comparisons using multiple sequences detect three times as many remote homologs as pairwise methods”, *JMB*, 284(4):1201--1210, 1998
- T.F.Smith & M.S.Waterman. “Identification of common molecular subsequences”, *JMB*, 147:195—197, 1981
- Z. Zhang et al. “Protein sequence similarity searches using patterns as seeds”, *NAR*, 26(17):3986—3990, 1996

Twists in the Tale of Guilt by Association of Seq Similarity

Image credit: Shanti Christensen, http:// static.flickr.com/46/148437681_7f2dfa977e_m.jpg

Seq Similarity: Caveats

- **Ensure that the effect of database size and other biases has been accounted for**
- Ensure that the function of the homology is not derived via invalid “transitive assignment’’
- Ensure that the target sequence has all the key features associated with the function, e.g., active site and/or domain

Law of Large Numbers

- Suppose you are in a room with 365 other people
- Q: What is the prob that a specific person in the room has the same birthday as you?
- A: 1/365 = 0.3%
- Q: What is the prob that there is a person in the room having the same birthday as you?
- A: $1 – (364/365)^{365} = 63\%$
- Q: What is the prob that there are two persons in the room having the same birthday?
- A: 100%

Interpretation of P-value

- **Seq. comparison progs, e.g. BLAST, often associate a P-value to each hit**
- **P-value is interpreted as prob that a random seq has an equally good alignment**
- **Suppose the P-value of an alignment is 10^{-6}**
- **If database has 10^7 seqs, then you expect $10^7 * 10^{-6}$ = 10 seqs in it that give an equally good alignment**

⇒ Need to correct for database size if your seq comparison prog does not do that!

Exercise: Name a commonly used method for correcting p-value for a situation like this

Lightning Does Strike Twice!

- **Roy Sullivan, a former park ranger from Virgina, was struck by lightning 7 times**
  - 1942 (lost big-toe nail)
  - 1969 (lost eyebrows)
  - 1970 (left shoulder seared)
  - 1972 (hair set on fire)
  - 1973 (hair set on fire & legs seared)
  - 1976 (ankle injured)
  - 1977 (chest & stomach burned)
- **September 1983, he committed suicide**

Cartoon: Ron Hipschman
Data: David Hand

Effect of Seq Compositional Bias

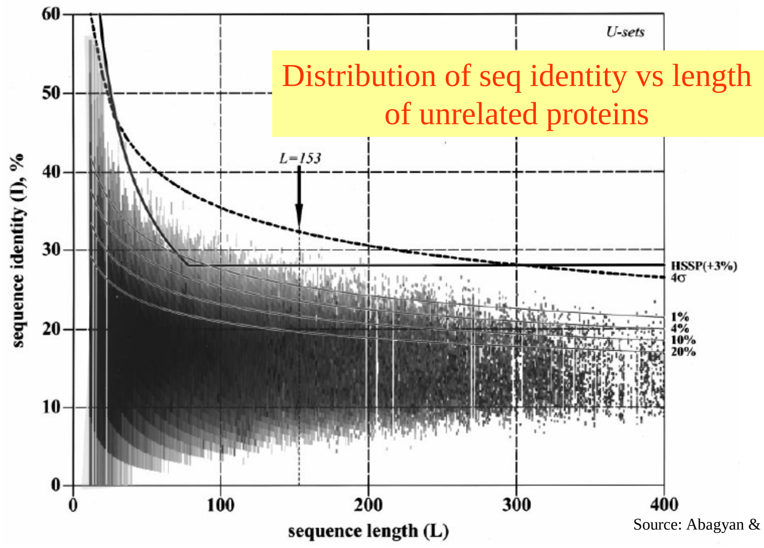
- One fourth of all residues in protein seqs occur in regions with biased amino acid composition
- Alignments of two such regions achieves high score purely due to segment composition

⇒ While it is worth noting that two proteins contain similar low complexity regions, they are best excluded when constructing alignments

- E.g., by default, BLAST employs the SEG algo to filter low complexity regions from proteins before executing a search

Source: NCBI

Effect of Seq Length



Distribution of seq identity vs length of unrelated proteins

Source: Abagyan & Batalov

Seq Similarity: Caveats

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- Ensure that the target sequence has all the key features associated with the function, e.g., active site and/or domain

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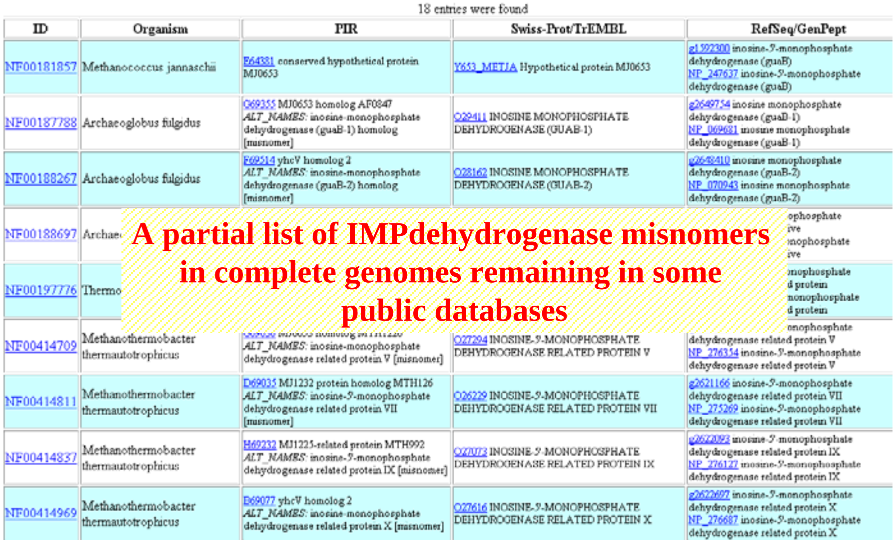
Examples of Invalid Function Assignment:

The IMP Dehydrogenases (IMPDH)

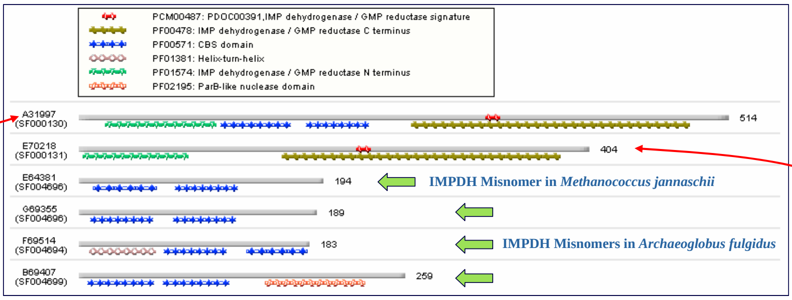


18 entries were found

ID	Organism	PIR	Swiss-Prot/TrEMBL	RefSeq/GenPept
NF00181857	Methanococcus jannaschii	E64381 conserved hypothetical protein MJ0653	Y653_METJA Hypothetical protein MJ0653	g1592300 inosine-5'-monophosphate dehydrogenase (guaB) NP_247637 inosine-5'-monophosphate dehydrogenase (guaB)
NF00187788	Archaeoglobus fulgidus	G69355 MJ0653 homolog AF0847 *ALT_NAMES:* inosine-monophosphate dehydrogenase (guaB-1) homolog [misnomer]	O29411 INOSINE MONOPHOSPHATE DEHYDROGENASE (GUAB-1)	g2649754 inosine monophosphate dehydrogenase (guaB-1) NP_069681 inosine monophosphate dehydrogenase (guaB-1)
NF00188267	Archaeoglobus fulgidus	F69514 yhcV homolog 2 *ALT_NAMES:* inosine-monophosphate dehydrogenase (guaB-2) homolog [misnomer]	O28162 INOSINE MONOPHOSPHATE DEHYDROGENASE (GUAB-2)	g2648410 inosine monophosphate dehydrogenase (guaB-2) NP_070943 inosine monophosphate dehydrogenase (guaB-2)
NF00188697	Archae			ophosphate ive nophosphate ive
NF00197776	Thermo			onophosphate d protein monophosphate d protein
NF00414709	Methanothermobacter thermautotrophicus	[illegible] *ALT_NAMES:* inosine-monophosphate dehydrogenase related protein V [misnomer]	O27294 INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE RELATED PROTEIN V	onophosphate dehydrogenase related protein V NP_276354 inosine-5'-monophosphate dehydrogenase related protein V
NF00414811	Methanothermobacter thermautotrophicus	D69035 MJ1232 protein homolog MTH126 *ALT_NAMES:* inosine-5'-monophosphate dehydrogenase related protein VII [misnomer]	O26229 INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE RELATED PROTEIN VII	g2621166 inosine-5'-monophosphate dehydrogenase related protein VII NP_275269 inosine-5'-monophosphate dehydrogenase related protein VII
NF00414837	Methanothermobacter thermautotrophicus	H69232 MJ1225-related protein MTH992 *ALT_NAMES:* inosine-5'-monophosphate dehydrogenase related protein IX [misnomer]	O27073 INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE RELATED PROTEIN IX	g2622093 inosine-5'-monophosphate dehydrogenase related protein IX NP_276127 inosine-5'-monophosphate dehydrogenase related protein IX
NF00414969	Methanothermobacter thermautotrophicus	B69077 yhcV homolog 2 *ALT_NAMES:* inosine-monophosphate dehydrogenase related protein X [misnomer]	O27616 INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE RELATED PROTEIN X	g2622697 inosine-5'-monophosphate dehydrogenase related protein X NP_276687 inosine-5'-monophosphate dehydrogenase related protein X

A partial list of IMPdehydrogenase misnomers in complete genomes remaining in some public databases

IMPDH Domain Structure



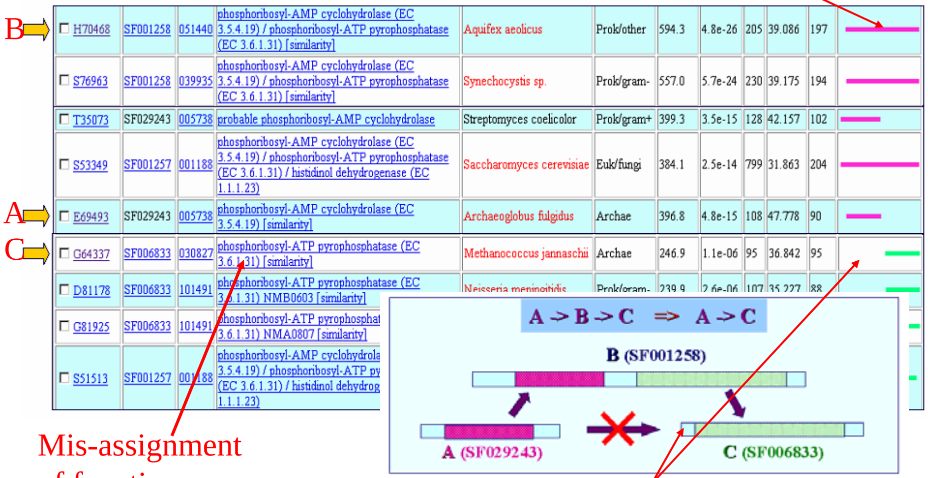
IMPDH Misnomer in *Methanococcus jannaschii*

IMPDH Misnomers in *Archaeoglobus fulgidus*

- **Typical IMPDHs have 2 IMPDH domains that form the catalytic core and 2 CBS domains.**
- **A less common but functional IMPDH (E70218) lacks the CBS domains.**
- **Misnomers show similarity to the CBS domains**

Invalid Transitive Assignment

Root of invalid transitive assignment



☐ H70468	SF001258	051440	phosphoribosyl-AMP cyclohydrolase (EC 3.5.4.19) / phosphoribosyl-ATP pyrophosphatase (EC 3.6.1.31) [similarity]	Aquifex aeolicus	Prok/other	594.3	4.8e-26	205	39.086	197
☐ S76963	SF001258	039935	phosphoribosyl-AMP cyclohydrolase (EC 3.5.4.19) / phosphoribosyl-ATP pyrophosphatase (EC 3.6.1.31) [similarity]	Synechocystis sp.	Prok/gram-	557.0	5.7e-24	230	39.175	194
☐ T35073	SF029243	005738	probable phosphoribosyl-AMP cyclohydrolase	Streptomyces coelicolor	Prok/gram+	399.3	3.5e-15	128	42.157	102
☐ S53349	SF001257	001188	phosphoribosyl-AMP cyclohydrolase (EC 3.5.4.19) / phosphoribosyl-ATP pyrophosphatase (EC 3.6.1.31) / histidinol dehydrogenase (EC 1.1.1.23)	Saccharomyces cerevisiae	Euk/fungi	384.1	2.5e-14	799	31.863	204
☐ E69493	SF029243	005738	phosphoribosyl-AMP cyclohydrolase (EC 3.5.4.19) [similarity]	Archaeoglobus fulgidus	Archae	396.8	4.8e-15	108	47.778	90
☐ G64337	SF006833	030827	phosphoribosyl-ATP pyrophosphatase (EC 3.6.1.31) [similarity]	Methanococcus jannaschii	Archae	246.9	1.1e-06	95	36.842	95
☐ D81178	SF006833	101491	phosphoribosyl-ATP pyrophosphatase (EC 3.6.1.31) NMB0603 [similarity]	Neisseria meningitidis	Prok/gram-	239.9	2.6e-06	107	35.227	88
☐ G81925	SF006833	101491	phosphoribosyl-ATP pyrophosphat 3.6.1.31) NMA0807 [similarity]							
☐ S51513	SF001257	001188	phosphoribosyl-AMP cyclohydrola 3.5.4.19) / phosphoribosyl-ATP py (EC 3.6.1.31) / histidinol dehydrog 1.1.1.23)							

Mis-assignment of function

No IMPDH domain

Seq Similarity: Caveats

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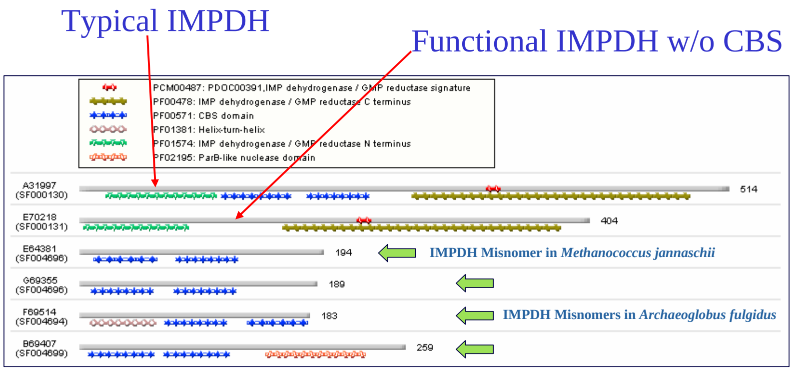
Emerging Pattern


Typical IMPDH

Functional IMPDH w/o CBS

IMPDH Misnomer in *Methanococcus jannaschii*

IMPDH Misnomers in *Archaeoglobus fulgidus*

- **Most IMPDHs have 2 IMPDH and 2 CBS domains**
- **Some IMPDH (E70218) lacks CBS domains**

⇒ Alignment must preserve IMPDH domain to infer IMPDH

Important Unsolved Challenges

- **What if there is no useful seq homolog?**
- **Guilt by other types of association!**
  - Domain modeling (e.g., HMMPFAM)
  - Similarity of dissimilarities (e.g., SVM-PAIRWISE)
  - Similarity of phylogenetic profiles
  - Similarity of subcellular co-localization & other physico-chemico properties(e.g., PROTFUN)
  - Similarity of gene expression profiles
  - Similarity of protein-protein interaction partners
  - …
  - Fusion of multiple types of info

References

- S.E.Brenner. “Errors in genome annotation”, *TIG*, 15:132--133, 1999
- D. Devos & A.Valencia. “Intrinsic errors in genome annotation”, *TIG*, 17:429--431, 2001
- T.F.Smith & X.Zhang. “The challenges of genome sequence annotation or `The devil is in the details'”, *Nature Biotech*, 15:1222--1223, 1997
- **C. Wu & W. Barker. “A Family Classification Approach to Functional Annotation of Proteins”, *The Practical Bioinformatician*, Chapter 19, pages 401—416, WSPC, 2004**

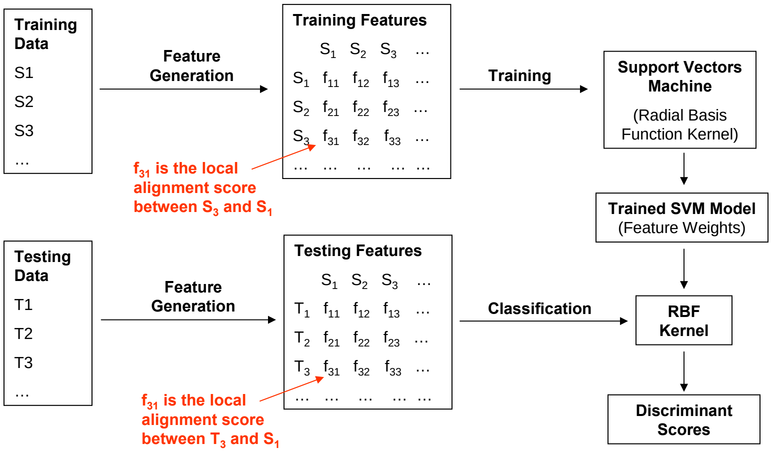
Guilt by Association of Similarity of Dissimilarities

Image credit: www.comstock.com

Similarity of Dissimilarities

	orange$_1$	**banana$_1$**	…
apple$_1$	Color = red vs orange Skin = smooth vs rough Size = small vs small Shape = round vs round	Color = red vs yellow Skin = smooth vs smooth Size = small vs small Shape = round vs oblong	…
apple$_2$	Color = red vs orange Skin = smooth vs rough Size = small vs small Shape = round vs round	Color = red vs yellow Skin = smooth vs smooth Size = small vs small Shape = round vs oblong	…
orange$_2$	Color = orange vs orange Skin = rough vs rough Size = small vs small Shape = round vs round	Color = orange vs yellow Skin = rough vs smooth Size = small vs small Shape = round vs oblong	..
…	…	…	…

SVM-Pairwise Framework



Training Data

S1

S2

S3

…

Feature Generation

Training Features

	S_1	S_2	S_3	…
S_1	f_{11}	f_{12}	f_{13}	…
S_2	f_{21}	f_{22}	f_{23}	…
S_3	f_{31}	f_{32}	f_{33}	…
…	…	…	…	…

f_{31} is the local alignment score between S_3 and S_1

Training

Support Vectors Machine

(Radial Basis Function Kernel)

Trained SVM Model (Feature Weights)

Testing Data

T1

T2

T3

…

Feature Generation

Testing Features

	S_1	S_2	S_3	…
T_1	f_{11}	f_{12}	f_{13}	…
T_2	f_{21}	f_{22}	f_{23}	…
T_3	f_{31}	f_{32}	f_{33}	…
…	…	…	…	…

f_{31} is the local alignment score between T_3 and S_1

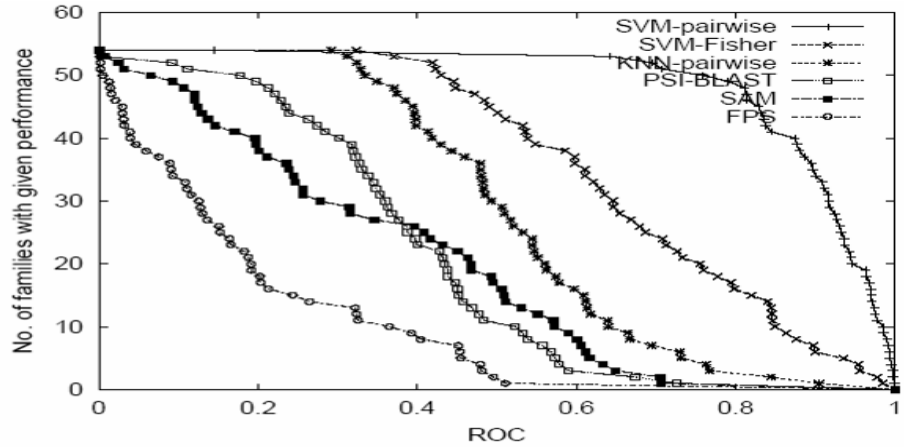
Classification

RBF Kernel

Discriminant Scores

Image credit: Kenny Chua

Performance of SVM-Pairwise



- **ROC: The area under the curve derived from plotting true positives as a function of false positives for various thresholds**

References

- Y.D. Cai & K.C. Chou. “Using functional domain composition to predict enzyme family classes”. *J. Proteome Res.,* 4(1):109-111, 2005
- **H.N. Chua & W.-K. Sung. “A better gap penalty for pairwise SVM”. Proc. *APBC05*, pages 11-20**
- T. Jaakkola, M. Diekhans, & D. Haussler. “A discriminative framework for detecting remote homologies”. *JCB*, 7(1-2):95-11, 2000
- L. Liao & W.S. Noble. “Combining pairwise sequence similarity and support vector machines for detecting remote protein evolutionary and structural relationships”. *JCB*, 10(6):857-868, 2003

Guilt by Association of Genome Phylogenetic Profiles

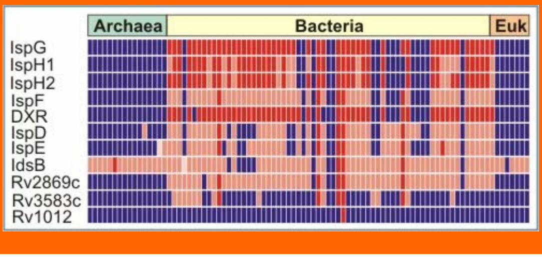


Image credit: Ed Marcotte,
http://apropos.icmb.utexas.edu/plex/tour/isoprenoid.jpg

Phylogenetic Profiling

Pellegrini et al., *PNAS*, 96:4285--4288, 1999

- Gene (and hence proteins) with identical patterns of occurrence across phyla tend to function together

⇒ Even if no homolog with known function is available, it is still possible to infer function of a protein

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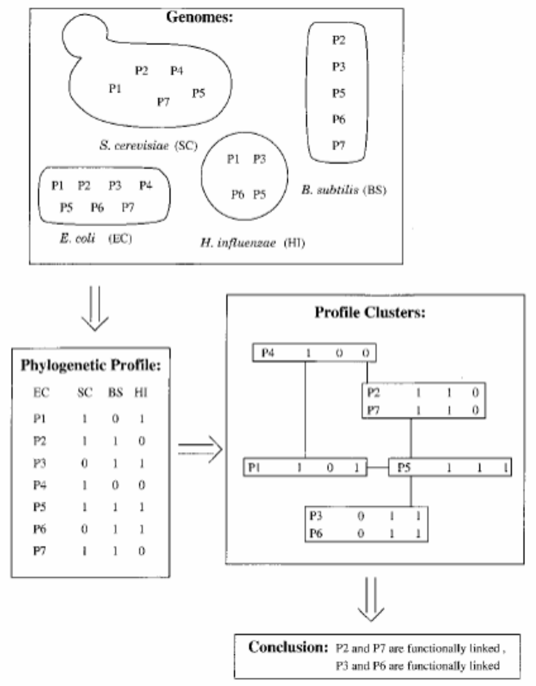

Phylogenetic Profile:

EC	SC	BS	HI
P1	1	0	1
P2	1	1	0
P3	0	1	1
P4	1	0	0
P5	1	1	1
P6	0	1	1
P7	1	1	0

Conclusion: P2 and P7 are functionally linked,
P3 and P6 are functionally linked

Phylogenetic Profiling: How It Works

Phylogenetic Profiling: P-value

The probability of observing by chance z occurrences of genes X and Y in a set of N lineages, given that X occurs in x lineages and Y in y lineages is

$$P(z|N,x,y) = \frac{w_z * \overline{w_z}}{W}$$

where

$$\begin{aligned} w_z &= \binom{N}{z} \\ \overline{w_z} &= \binom{N-z}{x-z} * \binom{N-z}{y-z} \\ W &= \binom{N}{x} * \binom{N}{y} \end{aligned}$$

No. of ways to distribute *z* co-occurrences over *N* lineage's

No. of ways to distribute the remaining *x* – *z* and *y* – *z* occurrences over the remaining *N* – *z* lineage's

No. of ways of distributing *X* and *Y* over *N* lineage's without restriction

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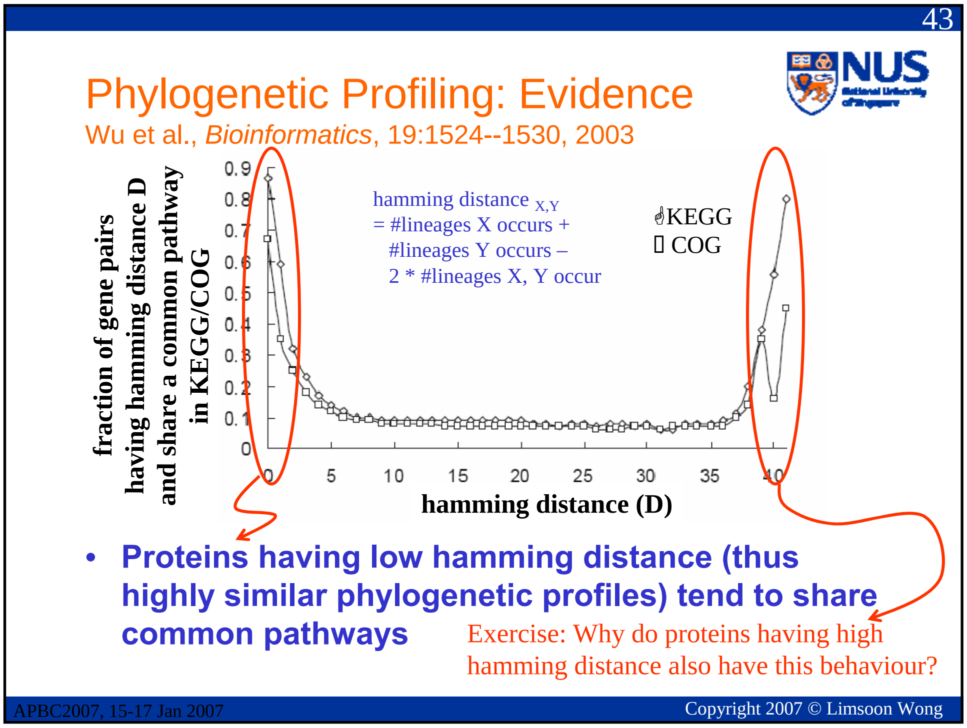
Phylogenetic Profiles: Evidence

Pellegrini et al., *PNAS*, 96:4285--4288, 1999

Keyword	No. of non-homologous proteins in group	No. neighbors in keyword group	No. neighbors in random group
Ribosome	60	197	27
Transcription	36	17	10
tRNA synthase and ligase	26	11	5
Membrane proteins*	25	89	5
Flagellar	21	89	3
Iron, ferric, and ferritin	19	31	2
Galactose metabolism	18	31	2
Molybdoterin and Molybdenum, and molybdoterin	12	6	1
Hypothetical†	1,084	108,226	8,440

- **E. coli proteins grouped based on similar keywords in SWISS-PROT have similar phylogenetic profiles**



Phylogenetic Profiling: Evidence

Wu et al., *Bioinformatics*, 19:1524--1530, 2003

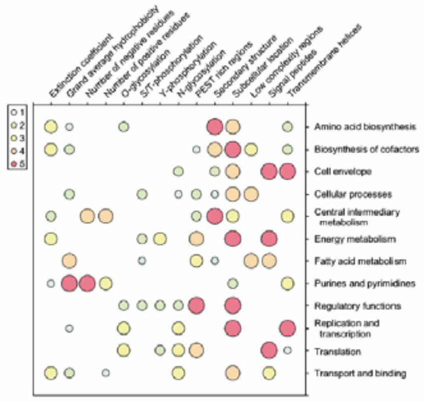
- **Proteins having low hamming distance (thus highly similar phylogenetic profiles) tend to share common pathways**

Exercise: Why do proteins having high hamming distance also have this behaviour?

References

- M. Pellegrini et al. "Assigning protein functions by comparative genome analysis: Protein phylogenetic profiles", *PNAS*, 96:4285--4288, 1999
- J. Wu et al. "Identification of functional links between genes using phylogenetic profiles", *Bioinformatics*, 19:1524--1530, 2003

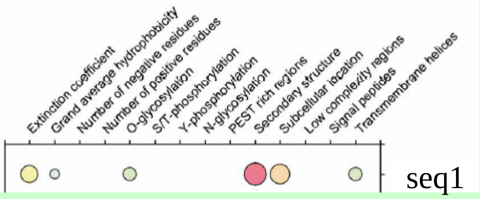
Guilt by Association of Physico-Chemico Properties



The ProtFun Approach

Jensen, *JMB*, 319:1257--1265, 2002

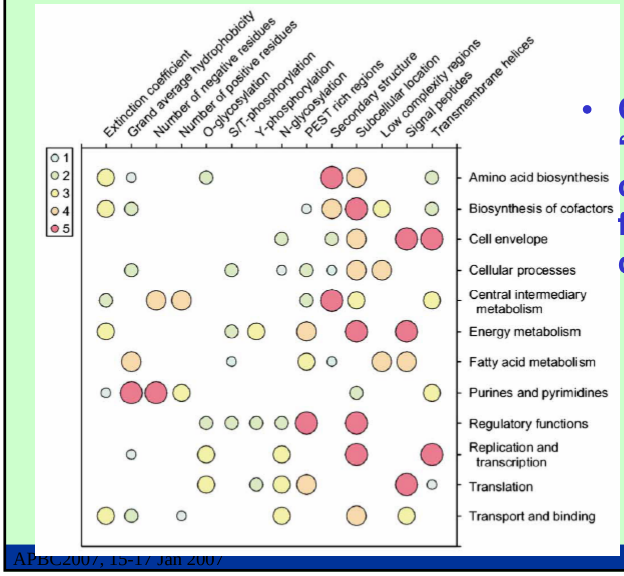
- **A protein is not alone when performing its biological function**
- **It operates using the same cellular machinery for modification and sorting as all other proteins do, such as glycosylation, phospharylation, signal peptide cleavage, …**
- **These have associated consensus motifs, patterns, etc.**



- **Proteins performing similar functions should share some such "features"**

⇒ Perhaps we can predict protein function by comparing its "feature" profile with other proteins?

ProtFun: Evidence



- Combinations of "features" seem to characterize some functional categories

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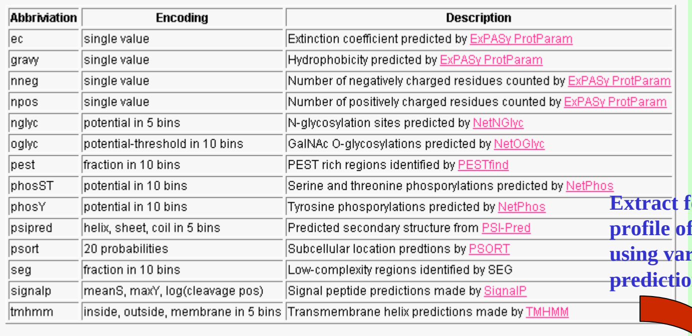
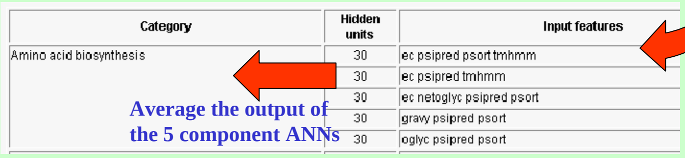
ProtFun: How it Works



Abbriviation	Encoding	Description
ec	single value	Extinction coefficient predicted by ExPASy ProtParam
gravy	single value	Hydrophobicity predicted by ExPASy ProtParam
nneg	single value	Number of negatively charged residues counted by ExPASy ProtParam
npos	single value	Number of positively charged residues counted by ExPASy ProtParam
nglyc	potential in 5 bins	N-glycosylation sites predicted by NetNGlyc
oglyc	potential-threshold in 10 bins	GalNAc O-glycosylations predicted by NetOGlyc
pest	fraction in 10 bins	PEST rich regions identified by PESTfind
phosST	potential in 10 bins	Serine and threonine phosporylations predicted by NetPhos
phosY	potential in 10 bins	Tyrosine phosporylations predicted by NetPhos
psipred	helix, sheet, coil in 5 bins	Predicted secondary structure from PSI-Pred
psort	20 probabilities	Subcellular location predtions by PSORT
seg	fraction in 10 bins	Low-complexity regions identified by SEG
signalp	meanS, maxY, log(cleavage pos)	Signal peptide predictions made by SignalP
tmhmm	inside, outside, membrane in 5 bins	Transmembrane helix predictions made by TMHMM

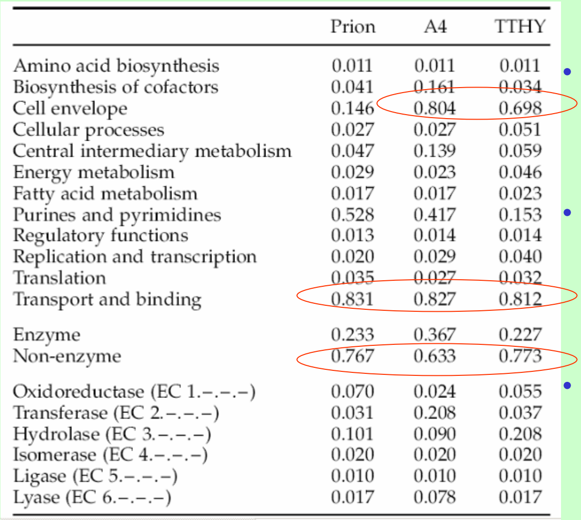
Extract feature profile of protein using various prediction methods



Category	Hidden units	Input features
Amino acid biosynthesis	30	ec psipred psort tmhmm
	30	ec psipred tmhmm
	30	ec netoglyc psipred psort
	30	gravy psipred psort
	30	oglyc psipred psort

Average the output of the 5 component ANNs

ProtFun: Example Output



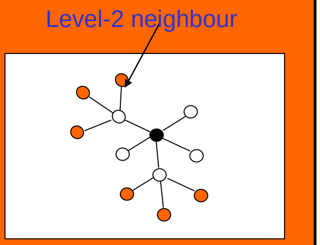
	Prion	A4	TTHY
Amino acid biosynthesis	0.011	0.011	0.011
Biosynthesis of cofactors	0.041	0.161	0.034
Cell envelope	0.146	0.804	0.698
Cellular processes	0.027	0.027	0.051
Central intermediary metabolism	0.047	0.139	0.059
Energy metabolism	0.029	0.023	0.046
Fatty acid metabolism	0.017	0.017	0.023
Purines and pyrimidines	0.528	0.417	0.153
Regulatory functions	0.013	0.014	0.014
Replication and transcription	0.020	0.029	0.040
Translation	0.035	0.027	0.032
Transport and binding	0.831	0.827	0.812
Enzyme	0.233	0.367	0.227
Non-enzyme	0.767	0.633	0.773
Oxidoreductase (EC 1.–.–.–)	0.070	0.024	0.055
Transferase (EC 2.–.–.–)	0.031	0.208	0.037
Hydrolase (EC 3.–.–.–)	0.101	0.090	0.208
Isomerase (EC 4.–.–.–)	0.020	0.020	0.020
Ligase (EC 5.–.–.–)	0.010	0.010	0.010
Lyase (EC 6.–.–.–)	0.017	0.078	0.017

- **At the seq level, Prion, A4, & TTHY are dissimilar**
- **ProtFun predicts them to be cell envelope-related, tranport & binding**
- **This is in agreement w/ known functionality of these proteins**

References

- L. Han et al. “Recent progresses in the application of machine learning approach for predicting protein functional class independent of sequence similarity”, *Proteomics*, 6(14):4023-4037, 2006
- L.J.Jensen et al. “Prediction of human protein function from post-translational modifications and localization features”, *JMB*, 319:1257--1265, 2002

Guilt by Association of Common Interaction Partners: Protein Function Prediction from Protein Interactions

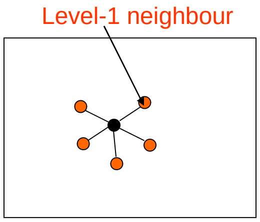


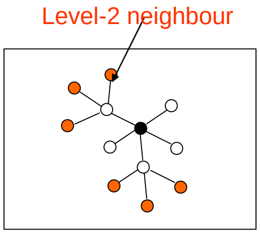
Protein Interaction Based Approaches

- **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"
- **Indirect Functional Assoc** (Chua et al, 2006)
  - Identification of reliable common interaction partners

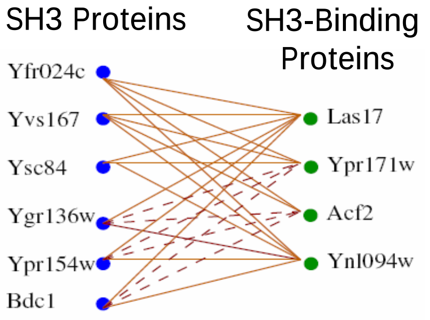
Functional Association Thru Interactions

- **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?



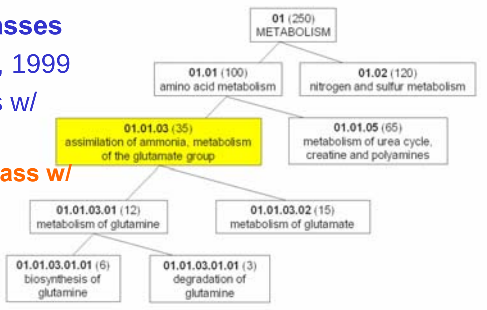
- **Is indirect functional association plausible?**
- **Is it found often in real interaction data?**
- **Can it be used to improve protein function prediction from protein interaction data?**

Materials

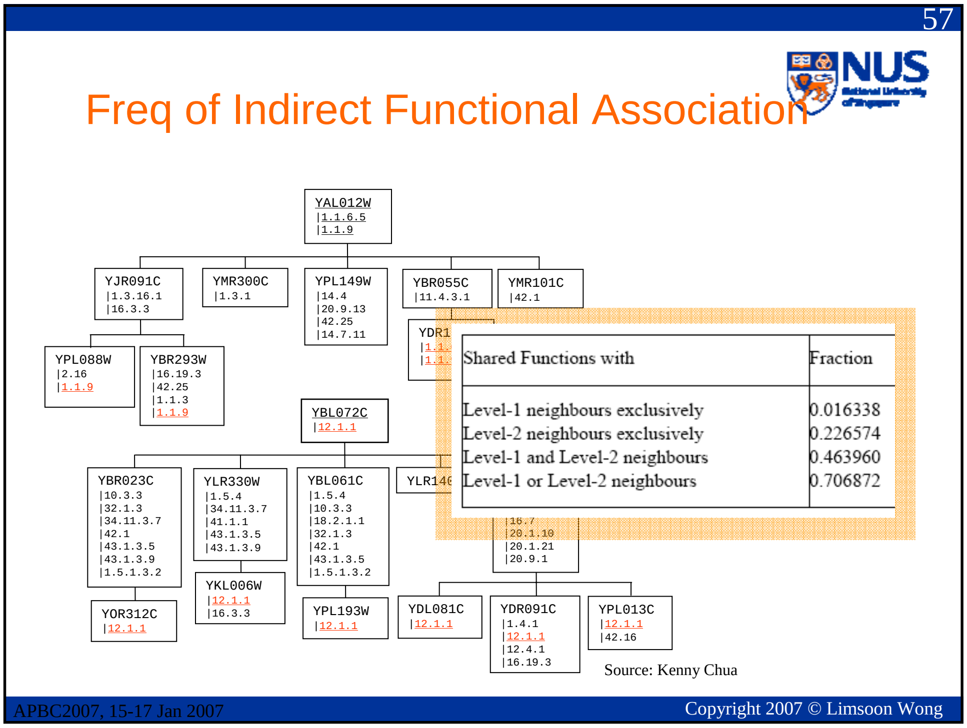
- **Protein interaction data from General Repository for Interaction Datasets (GRID)**
  - Data from published large-scale interaction datasets and curated interactions from literature
  - 13,830 unique and 21,839 total interactions
  - Includes most interactions from the Biomolecular Interaction Network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



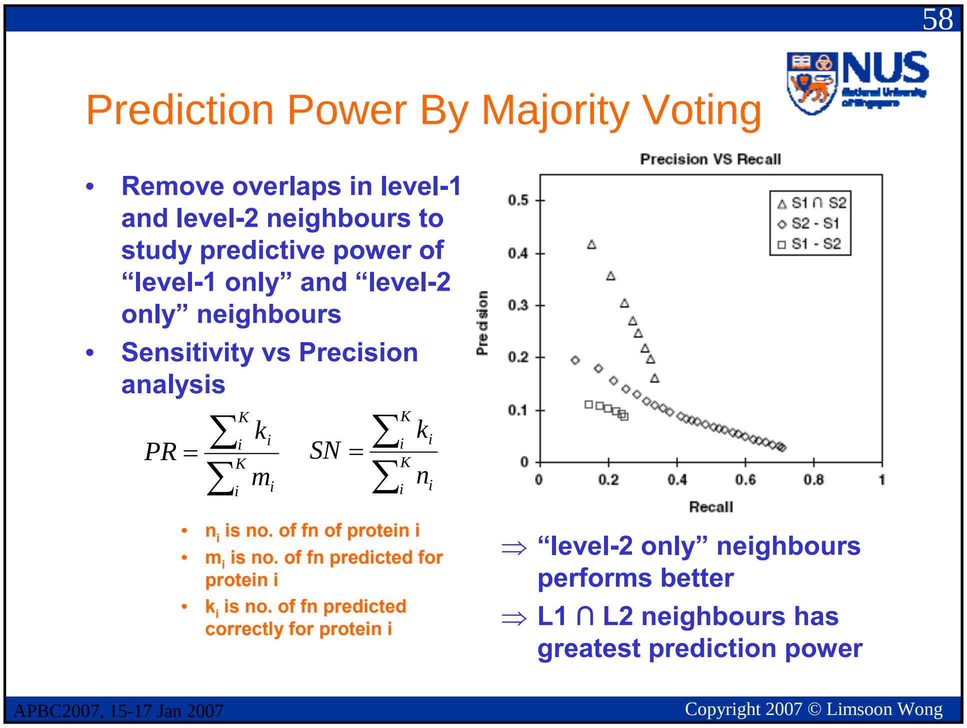
- **Leave-One-Out Cross Validation**
  - Each protein with annotated function is predicted using all other proteins in the dataset



Freq of Indirect Functional Association

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



Prediction Power By Majority Voting

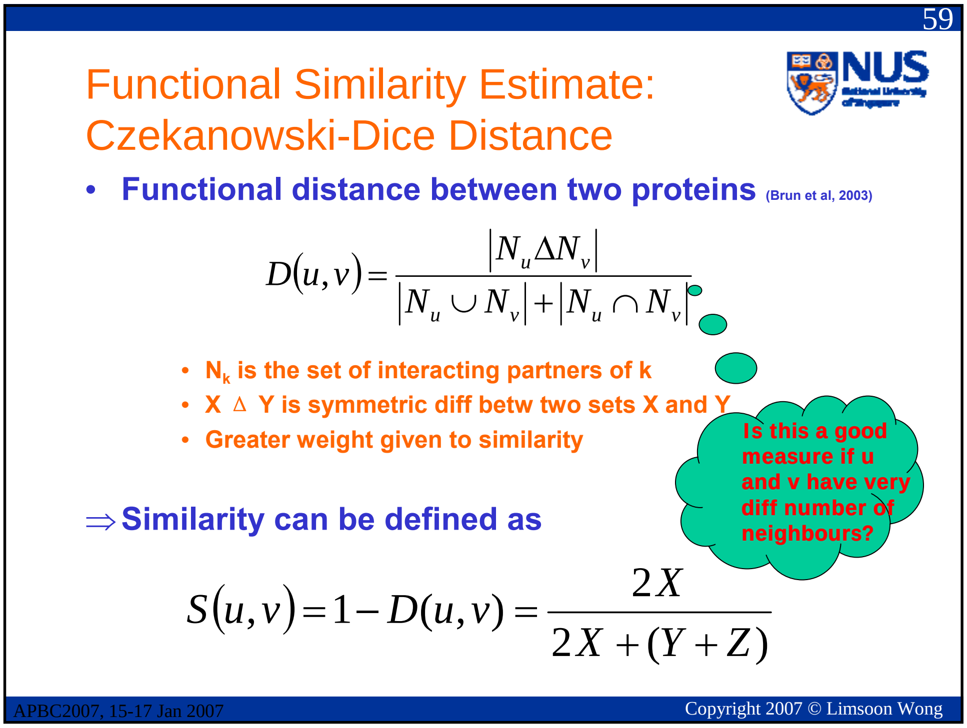
- Remove overlaps in level-1 and level-2 neighbours to study predictive power of “level-1 only” and “level-2 only” neighbours
- Sensitivity vs Precision analysis

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

- 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)

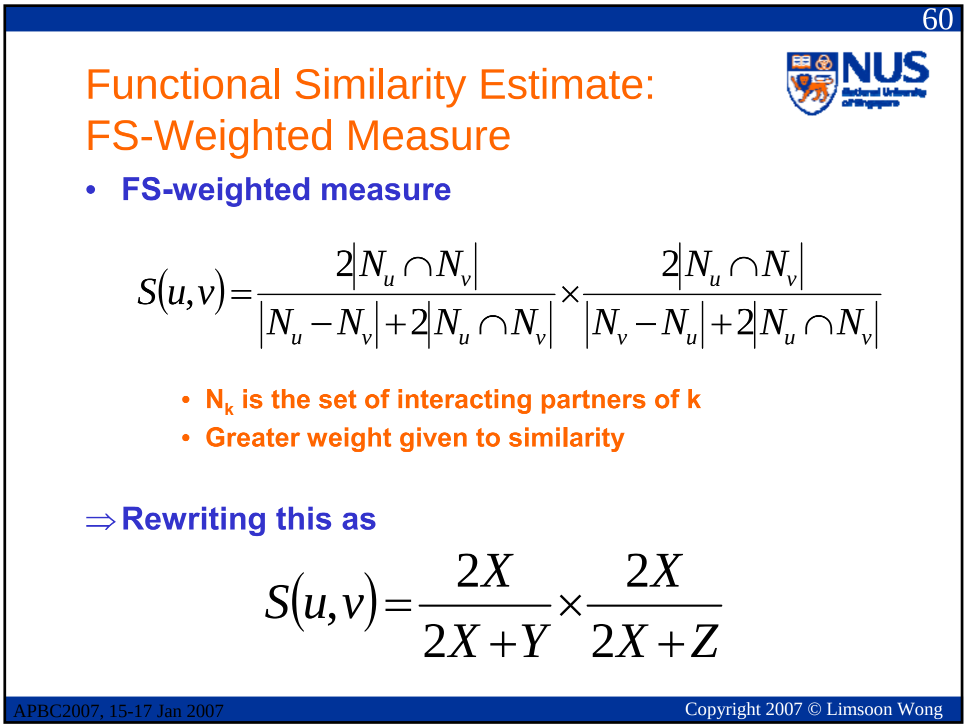
$$D(u,v) = \frac{|N_u \Delta N_v|}{|N_u \cup N_v| + |N_u \cap N_v|}$$

  - 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?

⇒ **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**

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

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

⇒ **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 S_2 $S_1 \cup S_2$	0.471810 0.224705 0.224581	0.498745 0.298843 0.29629

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

Source: Kenny Chua

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:**

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

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

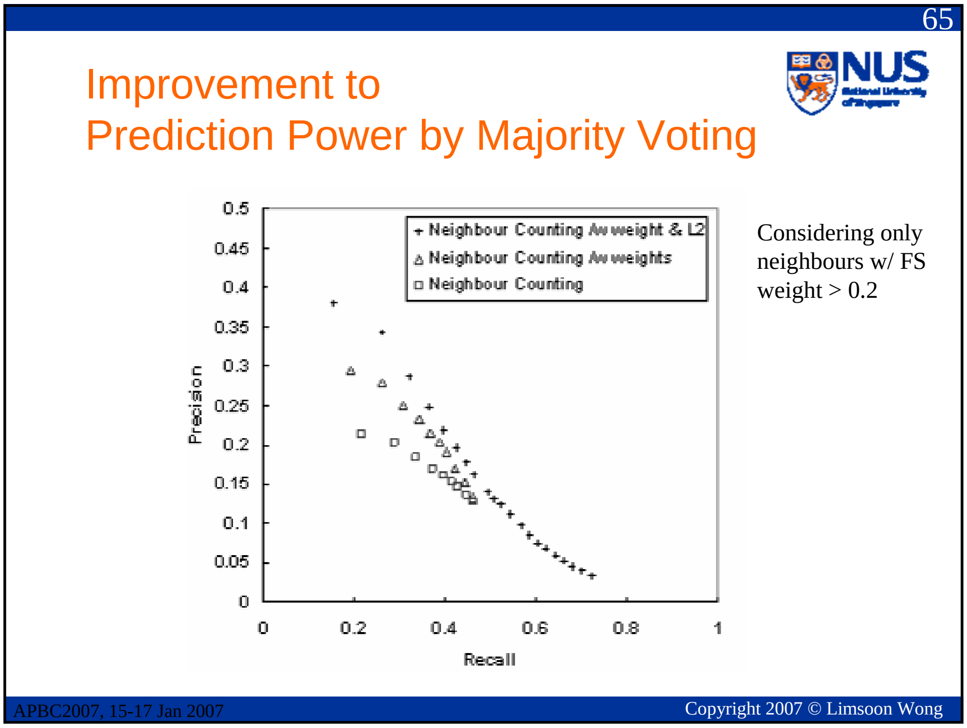
⇒ **Rewriting**

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

Integrating Reliability

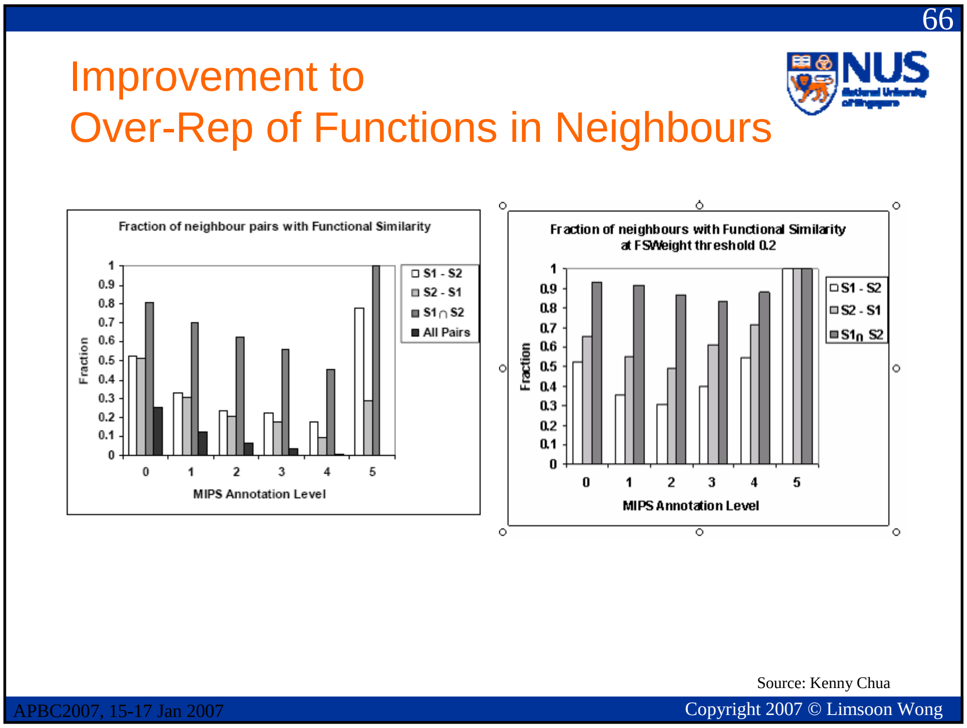
- **Equiv measure shows improved correlation w/ functional similarity when reliability of interactions is considered:**

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



Improvement to Prediction Power by Majority Voting

Considering only neighbours w/ FS weight > 0.2



Improvement to Over-Rep of Functions in Neighbours

Source: Kenny Chua

Use L1 & L2 Neighbours for Prediction

- **FS-weighted Average**

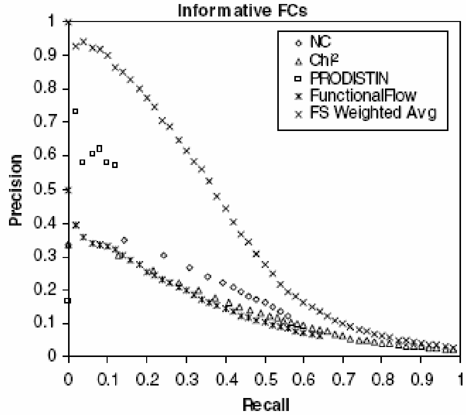
$$f_x(u) = \frac{1}{Z}\left[\lambda r_{\text{int}}\pi_x + \sum_{v\in N_u}\left(S_{TR}(u,v)\delta(v,x) + \sum_{w\in N_v} S_{TR}(u,w)\delta(w,x)\right)\right]$$

  - **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**

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

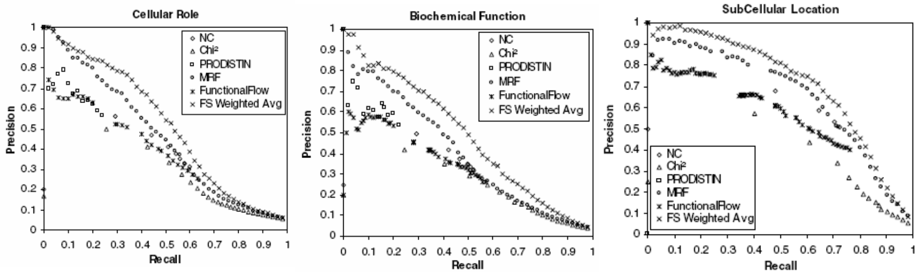
Performance of FS-Weighted Averaging

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



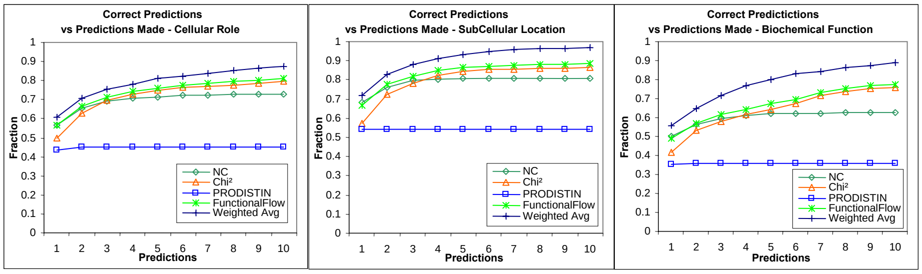
Performance of FS-Weighted Averaging

- **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

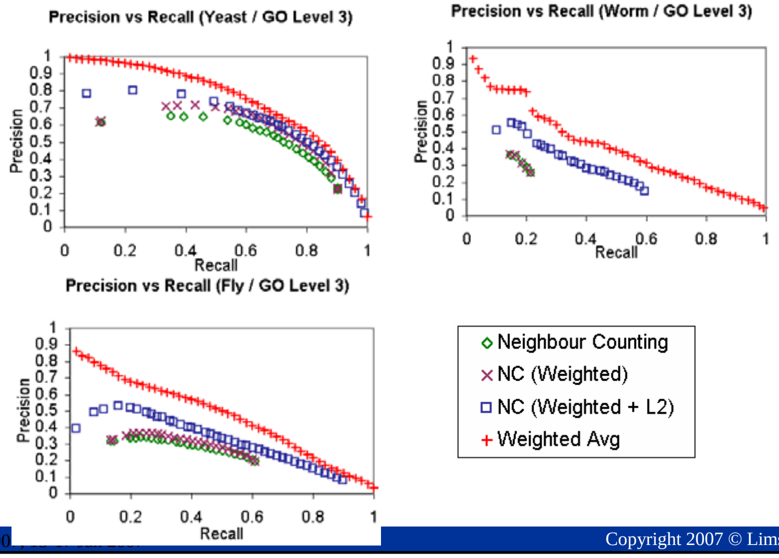
- **Correct Predictions made on at least 1 function vs Number of predictions made per protein**



Freq of Indirect Functional Association in Other Genomes

Genome	Annotation	S_1-S_2	S_2-S_1	$S_1 \cap S_2$	$S_1 \cup S_2$
S. cerevisiae	MIPS	0.007193	0.226574	0.463960	0.706872
D. melanogaster	GO	0.008801	0.168622	0.138138	0.315561
C. elegans	GO	0.007193	0.051237	0.061080	0.119510

Effectiveness of FS Weighted Averaging in Other Genomes



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**

References

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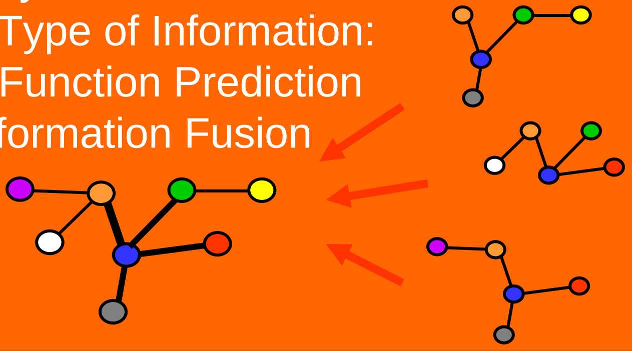
Guilt by Association of Multiple Type of Information: Protein Function Prediction by Information Fusion



Information Fusion

- **Markov Random Fields (Deng et al., *JCB*, 2004)**
  - Maximum Likelihood
  - Model data sources as binary relation betw proteins
- **Kernel Fusion (Lanckriet et al., *PSB*, 2004)**
  - Discriminative approach
  - Models each data source w/ diff feature vectors
  - Weighted linear combination of kernels via semi-definite programming

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Difficulties w/ Information Fusion

- **Differences in nature**
  - E.g., sequence homology vs PPI are very different relationships
- **Differences in reliability**
  - E.g., noisy datasets such as Y2H PPI and gene expression
- **Differences in scoring metrices**
  - E.g., E-Score from BLAST vs Pearson correlation between expression profiles

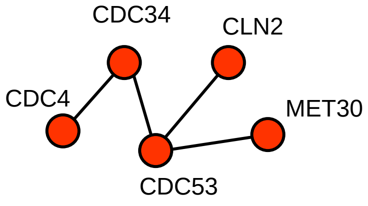
Motivation

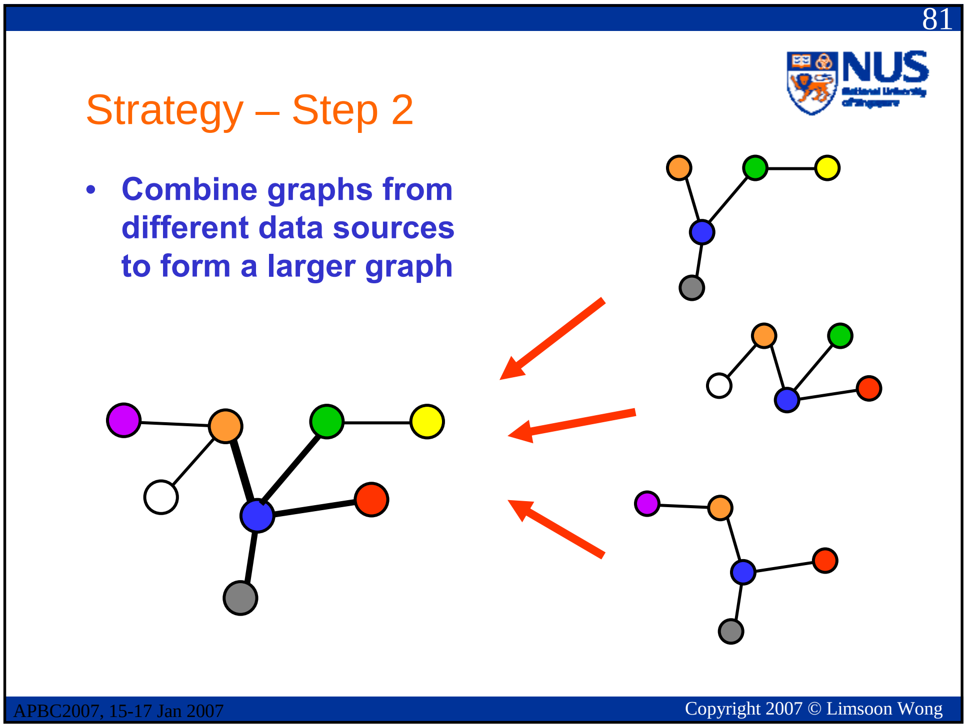
- **Problems:**
  - Complex models such as MRF and Kernel Fusion are computationally expensive
  - Difficult or not possible to identify contributing sources in a prediction
- **Unified scoring of multiple sources has potential (Lee et al., *Science*, 2004)**
  - Simple scoring using Log Likelihood
  - Identified many functional clusters

⇒ A simple, flexible, and effective way to integrate data sources that reports contributing sources in predictions to allow users to exercise judgment

Strategy – Step 1

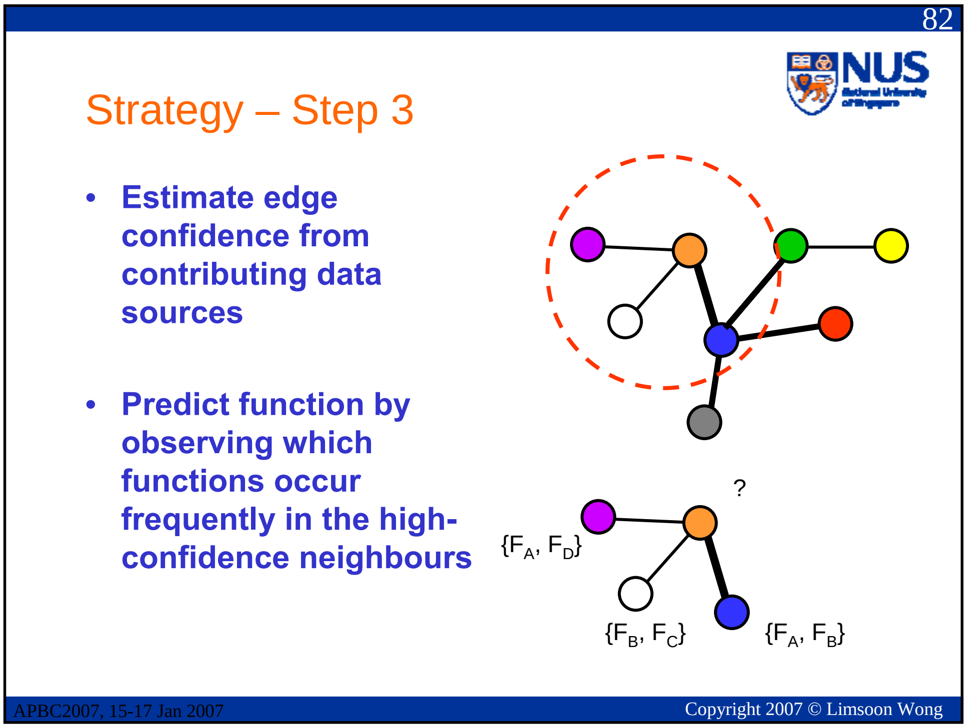
- **Model a data source as undirected graph G = ⟨V,E⟩**
  - V is a set of vertices; each vertex reps a protein
  - E is a set of edges; each edge (u , v) reps a relationship (e.g. seq similarity, interaction) betw proteins u and v





Strategy – Step 2

- **Combine graphs from different data sources to form a larger graph**



Strategy – Step 3

- **Estimate edge confidence from contributing data sources**
- **Predict function by observing which functions occur frequently in the high-confidence neighbours**

Unified Confidence Evaluation

- **Subdivide each data source into subtypes to improve precision (e.g., expt sources, sub-ranges of existing scores like E-scores)**

- **Estimate confidence of subtype k for sharing function f by:**

$$p(k,f)=\frac{\sum_{(u,v)\in E_{k,f}} S_f(u,v)}{\left|E_{k,f}\right|+1}$$

  - $E_{k,f}$ is subset of edges of subtype k where each edge has either one or both of its vertices annotated with function f
  - $S_f(u,v)$ = 1 if u and v shares function f, 0 otherwise

Discretization of Existing Scores

- **Scores may come in many forms**
  - E.g., Blast e-values, Pearson’s correlation

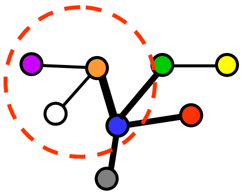
- **A simple approach to discretization**
  - Split ranges into n equal intervals
  - Each interval becomes a new subtype
  - Assume linearity in range
  - Other strategies possible

Combination of Confidence

- **Combine confidence of data sources contributing to each edge:**

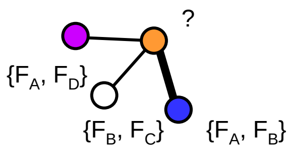
$$r_{u,v,f} = 1 - \prod_{k \in D_{u,v}} \left(1 - p(k, f)\right)$$

  - P(k.f) is confidence of edges of subtype k sharing function f
  - $D_{u,v}$ is the set of subtypes of data sources which contains the edge (u,v)



Function Prediction

- **Weighted Average**

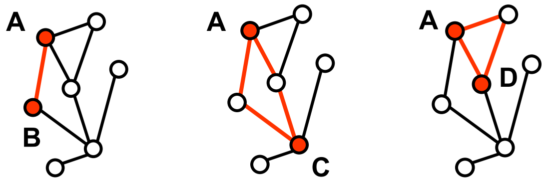


$$S_f(u) = \frac{\sum_{v \in N_u} \left(e_f(v) \times r_{u,v,f}\right)}{1 + \sum_{v \in N_u} r_{u,v,f}}$$

  - $S_f(u)$ is score of function f for protein u
  - $e_f(v)$ is 1 if protein v has function f, 0 otherwise
  - N_u is set of neighbours of u
  - $r_{u,v,f}$ is confidence of edge (u, v)

Level-2 Neighbours

- **Increase coverage of Protein-Protein interactions**
  - Indirect function association (Chua et al. 2006)
  - Topological weight applied to PPI
  - Divide into 3 subtypes:



Level-1 Neighbours **Level-2 Neighbours** **Level-1&2 Neighbours**

  - A theshold of 0.01 is applied on L2 neighbours to limit false positives

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Topological Weight Applied to PPI: 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**

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

Comparison w/ Existing Approaches

- **Dataset from Deng et al, 2004**
- **4 data sources (Saccharomyces cerevisiae)**
  - Protein-Protein Interactions
    - **2,448 edges**
  - Protein Complexes
    - **30,731 edges**
  - Pfam Domains
    - **28,616 edges**
  - Expression Correlation
    - **1,366 edges**

Comparison w/ Existing Approaches

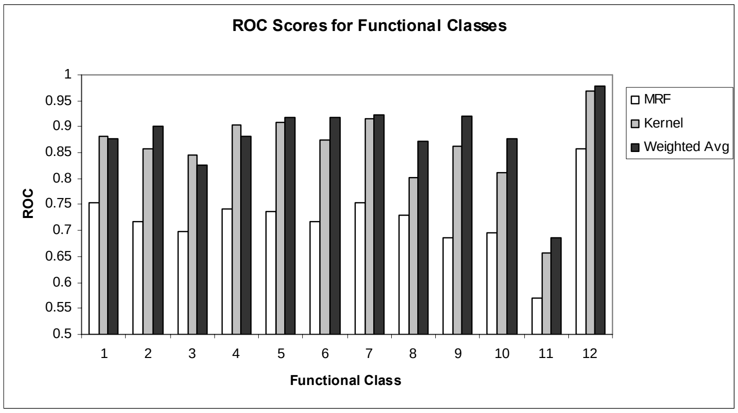
- **12 functional classes**

	Category	**Size**
1	Metabolism	1048
2	Energy	242
3	Cell cycle & DNA processing	600
4	Transcription	753
5	Protein synthesis	335
6	Protein fate	578
7	Cellular transport & transport mechanism	479
8	Cell rescue, defense & virulence	264
9	Interaction with the cellular environment	193
10	Cell fate	411
11	Control of cellular organization	192
12	Transport facilitation	306

Comparison w/ Existing Approaches

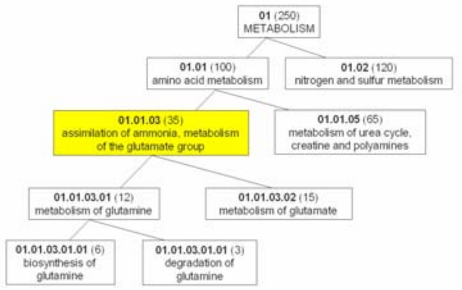
- **Validation Method (Lanckriet et al, 2004)**
  - Receiver Operating Characteristics (ROC)
  - True Positives vs False Positives
  - Area under ROC curve for each function
  - Averaged over 3 repetitions of 5-fold cross validation

Comparison w/ Existing Approaches



GO Terms Prediction for Yeast Proteins

- **Proteins from Saccharomyces Cerevesiae**
  - 5448 proteins from GO Annotation (SGD)
- **Functional Annotation**
  - Gene Ontology
  - Hierarchical
  - 3 Namespaces (molecular function, biological process, cellular component)



- **Informative GO Terms (for evaluation)**
  - Zhou et al. (2002)
  - FC associated with at least 30 proteins and no subclass associated with at least 30 proteins

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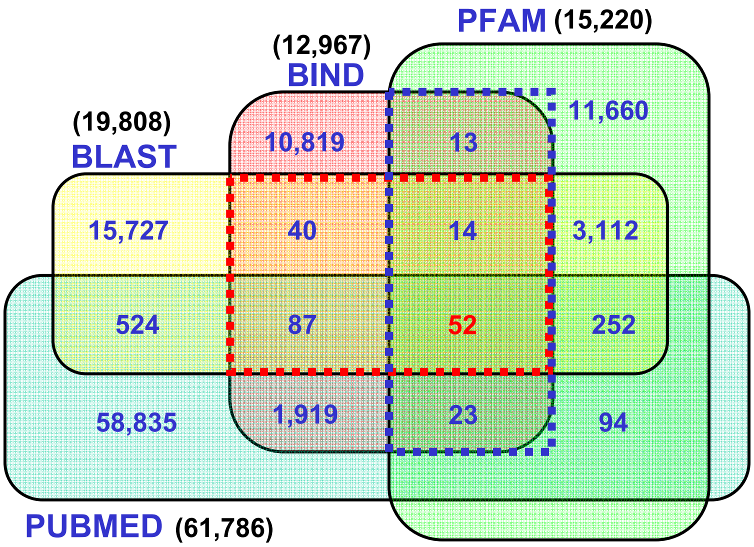
Data Sources

- **PPI**
  - BIND
  - 12,967 unique interactions betw yeast proteins
  - FS weight used as score
- **Protein Sequences**
  - Seqs from GO database (archive.godatabase.org)
  - Each yeast seq is aligned w/ rest using BLAST (cutoff E-Score = 1)
  - -log(e-score) used as score
  - Top 5 results w/ known annotations
  - 19,808 unique pairs involving yeast proteins

Data Sources

- **Pfam Domains**
  - SwissPfam database (http://www.sanger.ac.uk/Software/Pfam/ftp.shtml)
  - Precomputed Pfam domains for SwissProt and TrEMBL proteins w/ E-value threshold 0.01
  - Number of common domains used as score
  - 15,220 unique pairs involving yeast proteins
- **Pubmed Abstracts**
  - Pubmed abstracts obtained by searching protein's name and aliases on Pubmed
  - Limit to first 1000 abstracts returned
  - Fraction of abstracts w/ co-occurrence used as score
  - 61,786 unique pairs involving yeast proteins

Multiple Data Sources



PFAM (15,220)

(12,967) **BIND**

(19,808) **BLAST**

10,819

13

11,660

15,727

40

14

3,112

524

87

52

252

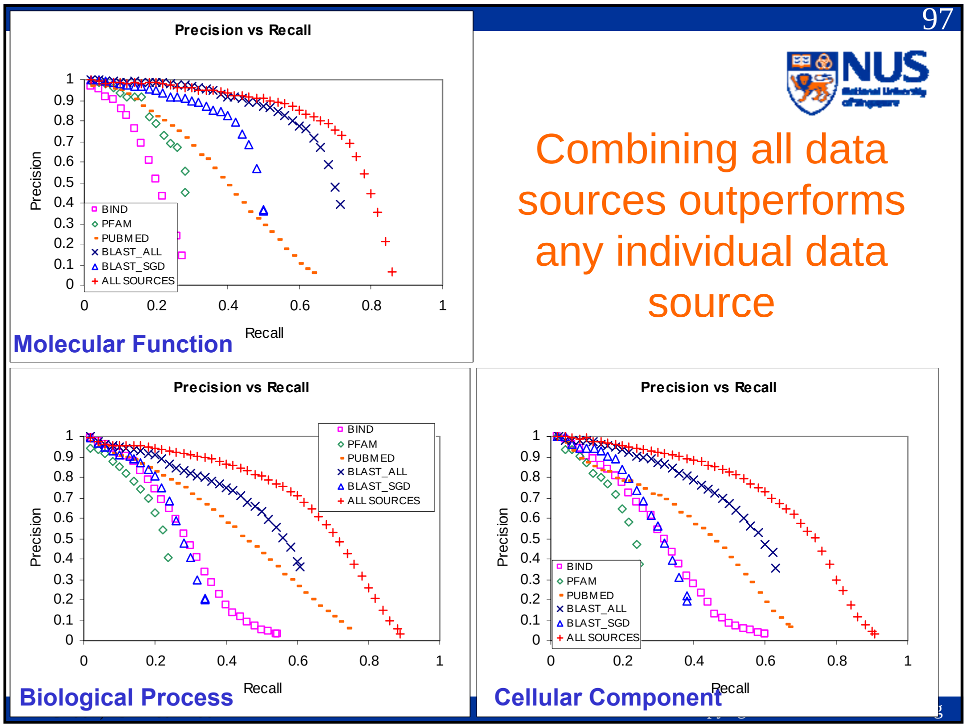
58,835

1,919

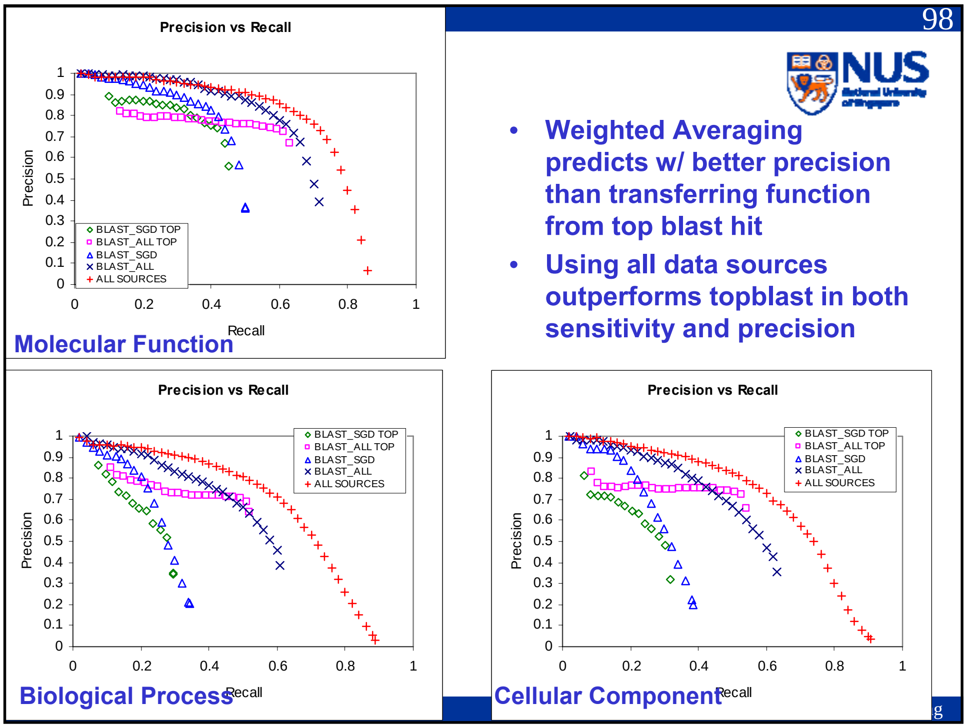
23

94

PUBMED (61,786)



Combining all data sources outperforms any individual data source



- **Weighted Averaging predicts w/ better precision than transferring function from top blast hit**
- **Using all data sources outperforms topblast in both sensitivity and precision**

Conclusions

- **We developed a simple graph-based method that combines multiple sources of data sources for function prediction**

- **Our method is simple, flexible and can report datasources contributing to each prediction**

- **We have shown that our method performs comparable, if not better, than existing approaches**

References

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Any Question?

APBC2007, 15-17 Jan 2007