Discovering Motif Pairs at Interaction Sites from Protein Sequences on a Proteome-Wide Scale

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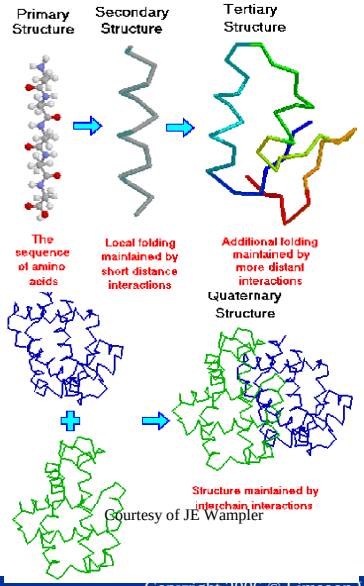
Plan

- **Motivation from biology & problem statement**
- **Recasting as a graph theory problem**
- **Recasting as a data mining problem**
- **Mining interacting protein groups**
- **Generating motif pairs**
- **Results and validation**

Motivation from Biology

Proteins

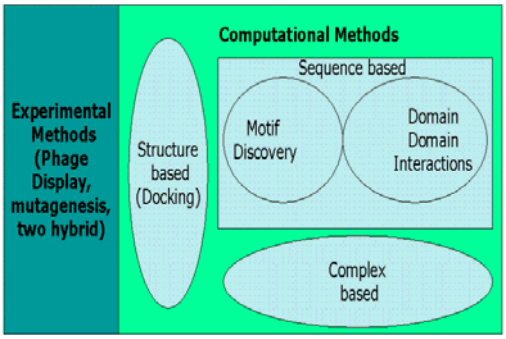
- **4 types of reps for proteins: primary, secondary, tertiary, & quaternay**
- **Protein interactions play impt role in inter cellular communication, in signal transduction, & in the regulation of gene expression**



Courtesy of JE Wampler

Binding Sites

- **Discovery of binding sites is a key part of understanding mechanisms of protein interactions**
- **Structure-based approaches**
  - E.g., docking
  - Relatively accurate
  - Struct must be known



⇒ **Sequence-based approaches**

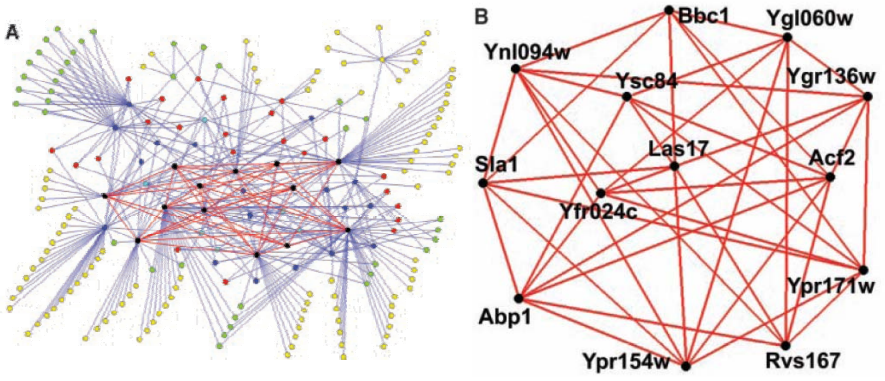
Typical Sequence-Based Approach

- **Typical seq-based approaches have two steps:**
  - Use pattern discovery algorithms to discover domains and/or motifs of a group of proteins
  - Use domain-domain interaction discovery methods (e.g., domain fusion) to discovery interacting domains
- **Shortcomings:**
  - Protein interaction information is not used by motif discovery algorithms
  - Exact positions of binding sites often not recognized

How about ...

- **How about making use of known protein-protein bindings to guide the discovery of binding motifs?**

Protein Interaction Graphs

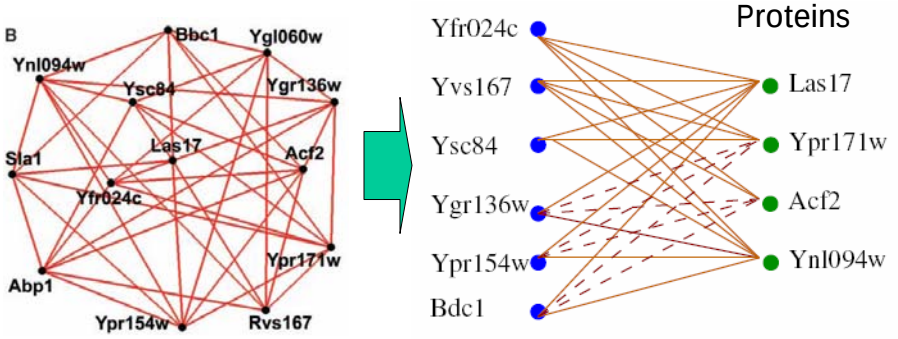


Yeast SH3 domain-domain Interaction network: 394 edges, 206 nodes

Tong et al. *Science*, v295. 2002

8 proteins containing SH3 5 binding at least 6 of them

Bipartite Subgraphs



The larger this group, the more likely their active sites will show up clearly in a multiple alignment?

Problem Statement

Given a PPI expt E, the problem is

(1) To find all pairs X, Y of interacting protein groups**, so that**

- **(1.1) every protein in X interacts with every protein in Y, &**
- **(1.2) X and Y are as large as possible**

&

(2) To identify "good" binding motif pairs from these pairs of interacting protein groups

Recasting as a Graph Theory Problem

PPI Expt As a Graph

- **PPI expt E as undirected graph $G^E = \langle V^E, D^E \rangle$,**
  - where V^E are the proteins and D^E the edges,
  - so that two proteins are connected in G^E iff there is a binding betw them in PPI expt E
- **Let $L^E(p)$ denote** neighborhood **of protein p in G^E**
- **Let $L^E(P) = \bigcap_{p \in P} L^E(p)$ denote the common neighborhood of all proteins in P in G^E**

Maximality

- **Proposition 2.1**

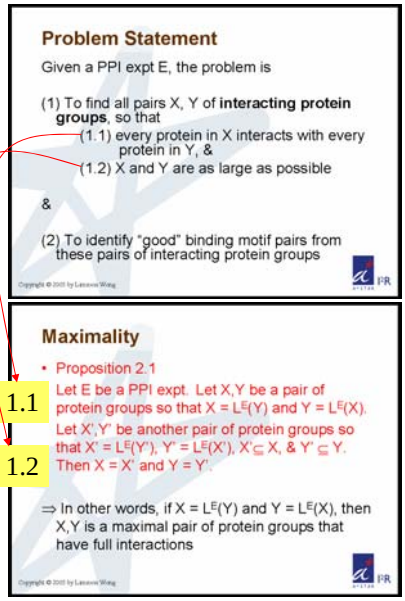
  Let E be a PPI expt.

  Let X,Y be a pair of protein groups so that X = $L^E(Y)$ and Y = $L^E(X)$.

  Let X',Y' be another pair of protein groups so that X' = $L^E(Y')$, Y' = $L^E(X')$, X'$\subseteq$ X, & Y' $\subseteq$ Y.

  Then X = X' and Y = Y'.

$\Rightarrow$ **In other words, if X = $L^E(Y)$ and Y = $L^E(X)$, then X,Y is a maximal pair of protein groups that have full interactions**

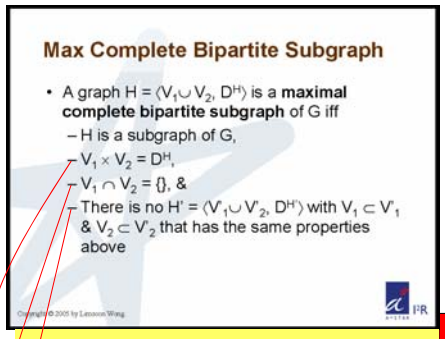


Recasting to Graph Theory

- **X, Y is a pair of interacting protein groups in PPI expt E iff X = $L^E(Y)$ and Y = $L^E(X)$**

Max Complete Bipartite Subgraph

- **A graph $H = \langle V_1 \cup V_2, D^H \rangle$ is a** maximal complete bipartite subgraph **of G iff**
  - H is a subgraph of G,
  - $V_1 \times V_2 = D^H$,
  - $V_1 \cap V_2 = \{\}$, &
  - There is no $H' = \langle V'_1 \cup V'_2, D^{H'} \rangle$ with $V_1 \subset V'_1$ & $V_2 \subset V'_2$ that has the same properties above



The Connection to Graph Theory

- **Let $H = \langle X \cup Y, D^E|_{X \cup Y} \rangle$ be subgraph of G^E with X,Y a pair of interacting protein groups**
- **$\Rightarrow$ $X = L^E(Y)$ and $Y = L^E(X)$**
- **$\Rightarrow$ Full interactions betw X & Y**
- **$\Rightarrow$ $X \times Y = D^E|_{X \cup Y}$**
- **By excluding self-binding, we have $X \cap Y = \{\}$**
- **By Prop 2.1, we have H is max**

- **X, Y is a pair of interacting protein groups in PPI expt E iff $H = \langle X \cup Y, X \times Y \rangle$ is max complete bipartite subgraph of G^E**

Therefore … But ...

- **Therefore, to find pairs of interacting protein groups, we can use algorithms from graph theory for enumerating maximal complete bipartite subgraphs**
- **According to Eppstein 1994, this has complexity $O(a^3 2^{2a} n)$, where a is the aboricity of the graph and n the number of vertices**
- **This is inefficient because a is often around 10-20 in practice**

Recasting as a Data Mining Problem

From PPI Expts To Transactions

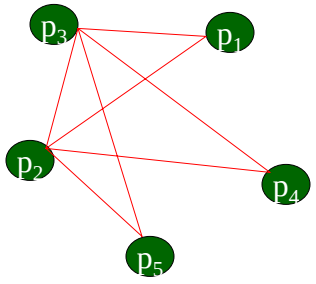
- **In PPI expt E, we obtain for each protein p, a list $L^E(p)$ of proteins that bind p**
  - assume $p \notin L^E(p)$, as such expts are not intended to detect self-binding
  - assume $q \in L^E(p)$ implies $p \in L^E(q)$, as binding is symmetric
- **$L^E(p)$ can be thought of as a transaction & $t^E(p)$ as the "id" of this transaction**

$\Rightarrow$ **E can be thought of as generating a** db of transactions **$D^E = \{t^E(p_1), \ldots, t^E(p_k)\}$, where $p_1, \ldots, p_k$ are all the proteins involved in E**

$\Rightarrow$ **a set of proteins X can be thought of as a** pattern **in D^E if there is $t^E(p) \in D^E$ st $X \subseteq L^E(p)$**

Example

- **Consider expt E with 5 proteins $p_1, \ldots, p_5$, st p_2 and p_3 bind every protein except themselves**
- **Then D^E looks like this** (as a matrix)**:**



	p_1	p_2	p_3	p_4	p_5
$t(p_1)$	0	1	1	0	0
$t(p_2)$	1	0	1	1	1
$t(p_3)$	1	1	0	1	1
$t(p_4)$	0	1	1	0	0
$t(p_5)$	0	1	1	0	0

Notations

- Let $s^E(d)$ denote the protein p st $t^E(p) = d$

$\Rightarrow$ $s^E(t^E(p)) = p$

- Let $t^E(X)$ denote the set $\{t^E(p) \mid p \in X\}$ of transaction id's, where X is a pattern in D^E
- Let $s^E(T)$ denote the pattern $\{s^E(d) \mid d \in T\}$
- Let $[|p|]^E$ denote the set $\{t^E(q) \mid p \in L^E(q)\}$ of transactions in D^E in which p occurs

$\Rightarrow$ $t^E(p) \in [|q|]^E$ implies $t^E(q) \in [|p|]^E$

- Let $[|X|]^E$ denote the set $\bigcap_{p \in X} [|p|]^E$ of transactions in which the pattern X occurs

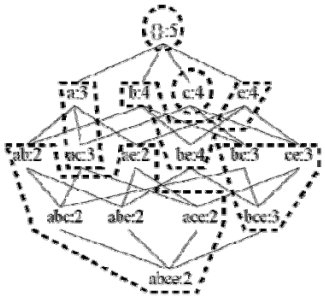
$\Rightarrow$ $t^E(Y) \subseteq [|X|]^E$ implies $t^E(X) \subseteq [|Y|]^E$

Closed Patterns

- Let $[X]^E = \{Y \mid [|Y|]^E = [|X|]^E\}$ denote the equivalence class of the pattern X in D^E
- A pattern X is said to be a closed pattern of D^E iff $X = closed^E(X)$, where $\{closed^E(X)\} = max\ [X]^E$

Table 1: A transaction database $T1$

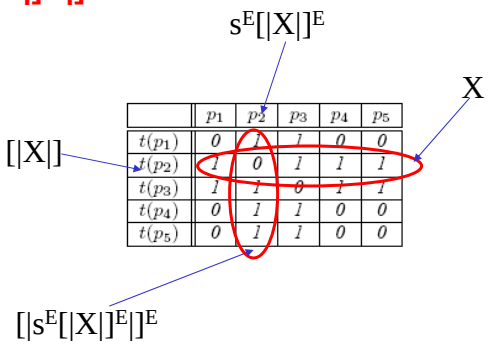
Transaction-id	Items
T_1	a, c, d
T_2	b, c, e
T_3	a, b, c, e, f
T_4	b, e
T_5	a, b, c, e



Support threshold = 2

Key Proposition

- **Proposition 3.2**
  Let X be a closed pattern in D^E.
  Then $X = s^E [|s^E [|X|]^E |]^E$



	p_1	p_2	p_3	p_4	p_5
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$t(p_2)$	1	0	1	1	1
$t(p_3)$	1	1	0	1	1
$t(p_4)$	0	1	1	0	0
$t(p_5)$	0	1	1	0	0

Proof

Lemma 3.1 $[\![X]\!]^E = [s^E([\![s^E([\![X]\!]^E)]\!]^E)]^E$.

Proof: *First we prove* $[\![X]\!]^E \subseteq [\![s^E([\![s^E([\![X]\!]^E)]\!]^E)]\!]^E$. *Suppose* $d \in [\![s^E([\![s^E([\![X]\!]^E)]\!]^E)]\!]^E$. *Suppose* $d' \in [\![s^E([\![X]\!]^E)]\!]^E$. *Suppose* $d'' \in [\![X]\!]^E$. *We have (i)* $d' \in [s^E(d'')]\!]^E$ *and (ii)* $d \in [\![s^E(d')]\!]^E$. *By the symmetry of high-throughput protein-protein interaction experiments, we also have (iii)* $d'' \in [\![s^E(d')]\!]^E$ *and (iv)* $d' \in [\![s^E(d)]\!]^E$. *Note that* d, d', *and* d'' *are arbitrary. Thus from (iii) we get* $d'' \in \bigcap_{d' \in [s^E([X]^E)]^E} [\![s^E(d')]\!]^E = \bigcap_{p \in s^E([s^E([X]^E)]^E)} [p]^E = [\![s^E([\![s^E([\![X]\!]^E)]\!]^E)]\!]^E$. *Hence* $[X]^E \subseteq [s^E([s^E([\![X]\!]^E)]\!]^E)]^E$.

Next we prove $[s^E([\![s^E([\![X]\!]^E)]\!]^E)]^E \subseteq [X]^E$. *Suppose* $p_i \in s^E([X]^E)$. *This means that* $t^E(p_i)$ *is a transaction in which* X *occurs. By our requirement of symmetry on high-throughput protein-protein interaction experiments, we have* $X \subseteq s^E([p_i]^E)$. *Note that* p_i *is arbitrary. So* $X \subseteq \bigcap_{p_i \in s^E([\![X]\!]^E)} s^E([p_i]^E)$. *So* $X \subseteq s^E([\![s^E([\![X]\!]^E)]\!]^E)$. *So* $[s^E([s^E([\![X]\!]^E)]\!]^E)]^E \subseteq [\![X]\!]^E$. *This completes the lemma.* ❑

Proposition 3.2 *Let* X *be a closed pattern in* D^E. *Then* $X = s^E([s^E([\![X]\!]^E)]\!]^E)$.

Proof: *By Lemma 3.1, we have* $[\![s^E([\![s^E([\![X]\!]^E)]\!]^E)]\!]^E = [\![X]\!]^E$. *But* X *is a closed pattern in* D^E. *So for all* X' *such that* $[\![X']\!]^E = [\![X]\!]^E$, *it is the case that* $X' \subseteq X$. *Therefore* $s^E([\![s^E([\![X]\!]^E)]\!]^E) \subseteq X^E$. *Also, from the proof of the second part of Lemma 3.1, we have* $X \subseteq s^E([\![s^E([\![X]\!]^E)]\!]^E)$. *Thus* $X = s^E([\![s^E([\![X]\!]^E)]\!]^E)$ *as desired.* ❑

Consequently...

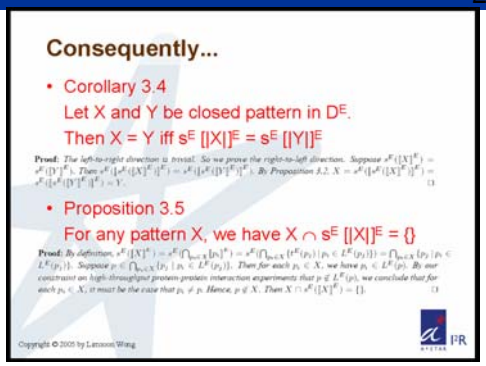
- **Corollary 3.4**
  Let X and Y be closed pattern in D^E.
  Then X = Y iff $s^E [|X|]^E = s^E [|Y|]^E$

Proof: *The left-to-right direction is trivial. So we prove the right-to-left direction. Suppose* $s^E(\lfloor X \rfloor^E) = s^E(\lfloor Y \rfloor^E)$. *Then* $s^E(\lfloor s^E(\lfloor X \rfloor^E) \rfloor^E) = s^E(\lfloor s^E(\lfloor Y \rfloor^E) \rfloor^E)$. *By Proposition 3.2,* $X = s^E(\lfloor s^E(\lfloor X \rfloor^E) \rfloor^E) = s^E(\lfloor s^E(\lfloor Y \rfloor^E) \rfloor^E) = Y$. □

- **Proposition 3.5**
  For any pattern X, we have $X \cap s^E [|X|]^E = \{\}$

Proof: *By definition,* $s^E(\lfloor X \rfloor^E) = s^E(\bigcap_{p_i \in X} \lfloor p_i \rfloor^E) = s^E(\bigcap_{p_i \in X} \{t^E(p_j) \mid p_i \in L^E(p_j)\}) = \bigcap_{p_i \in X} \{p_j \mid p_i \in L^E(p_j)\}$. *Suppose* $p \in \bigcap_{p_i \in X} \{p_j \mid p_i \in L^E(p_j)\}$. *Then for each* $p_i \in X$, *we have* $p_i \in L^E(p)$. *By our constraint on high-throughput protein-protein interaction experiments that* $p \notin L^E(p)$, *we conclude that for each* $p_i \in X$, *it must be the case that* $p_i \neq p$. *Hence,* $p \notin X$. *Then* $X \cap s^E(\lfloor X \rfloor^E) = \{\}$. □

Implication



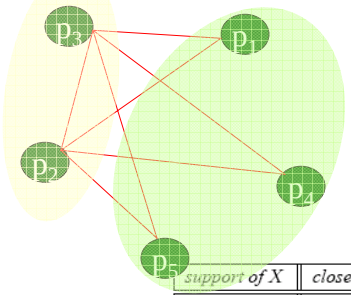
- **Corollary 3.6**
  Let E be a PPI expt.
  Let C be the set of closed patterns of D^E.
  Then |C| is even

Proof: *By Corollary 3.4,* $s^E \circ \lfloor \cdot \rfloor^E$ *is a bijective function from C to C. Thus, if* $|C|$ *is odd, there must be some* $X \in C$ *such that* $X = s^E(\lfloor X \rfloor^E)$. *But this contradicts Proposition 3.5. So* $|C|$ *must be even.* □

More Important Implication

- **Theorem 3.7**

  The bijective function $s^E o[|\cdot|]^E$ partitions the set of closed patterns of D^E into bipartite graphs



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$t(p_3)$	1	1	0	1	1
$t(p_4)$	0	1	1	0	0
$t(p_5)$	0	1	1	0	0

support of X	*close pattern X*	$Y = s^E([\![X]\!]^E)$	*support of Y*
3	$\{p_2, p_3\}$	$\{p_1, p_4, p_5\}$	2
4	$\{p_2\}$	$\{p_1, p_3, p_4, p_5\}$	1
4	$\{p_3\}$	$\{p_1, p_2, p_4, p_5\}$	1

Even More Interesting...

- **For each pair X and Y,**
  - X is the largest group of proteins that bind all the proteins in Y; and
  - Y is the largest group of proteins that bind all the proteins in X

⇒ **X,Y is a pair of interacting protein groups**

	p_1	p_2	p_3	p_4	p_5
$t(p_1)$	0	1	1	0	0
$t(p_2)$	1	0	1	1	1
$t(p_3)$	1	1	0	1	1
$t(p_4)$	0	1	1	0	0
$t(p_5)$	0	1	1	0	0

support of X	*close pattern X*	$Y = s^E([\![X]\!]^E)$	*support of Y*
3	$\{p_2, p_3\}$	$\{p_1, p_4, p_5\}$	2
4	$\{p_2\}$	$\{p_1, p_3, p_4, p_5\}$	1
4	$\{p_3\}$	$\{p_1, p_2, p_4, p_5\}$	1

A Couple More Propositions

- **Proposition 3.3**
  For any pattern X,
  $s^E[|X|]^E$ is closed pattern in D^E

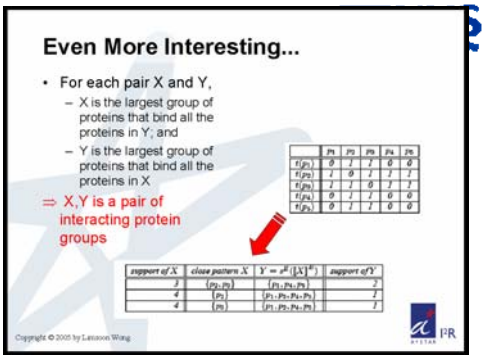
Proof: *Let $Y = closed(s^E(\lfloor X \rfloor^E))$. Then $\lfloor Y \rfloor^E = \lfloor s^E(\lfloor X \rfloor^E) \rfloor^E$. Then $s^E(\lfloor Y \rfloor^E) = s^E(\lfloor s^E(\lfloor X \rfloor^E) \rfloor^E)$. Then $s^E(\lfloor s^E(\lfloor Y \rfloor^E) \rfloor^E) = s^E(\lfloor s^E(\lfloor s^E(\lfloor X \rfloor^E) \rfloor^E) \rfloor^E)$. Since Y is a closed pattern in D^E, by Proposition 3.2 and Lemma 3.1, $Y = s^E(\lfloor s^E(\lfloor Y \rfloor^E) \rfloor^E) = s^E(\lfloor s^E(\lfloor s^E(\lfloor X \rfloor^E) \rfloor^E) \rfloor^E) = s^E(\lfloor X \rfloor^E)$. Hence $s^E(\lfloor X \rfloor^E)$ is also a closed pattern in D^E.* ❑

- **Corollary 3.7**
  X is a closed pattern in D^E iff $X = s^E[|s^E[|X|]^E|]^E$

Proof: *This follows directly from Proposition 3.2 and Proposition 3.3.* ❑

"each side of a protein interaction group is a closed pattern" ← "X is one side of a protein interaction group" ← "the common neighbours of the common neighbours of X are X themselves."

At Last!



- **These are ALL the interacting protein groups**

⇒ **To mine these protein groups, it suffices to mine closed patterns in D^E**

An Extension

- **Not all interacting protein groups X, Y are equally interesting**
  - X and Y are both singleton, vs
  - X is a large group, Y is small group, vs
  - X is a large group, Y is a large group

⇒ **Set "interestingness" threshold on X, Y st a pair of interacting protein groups X, Y is interesting only if $|X| \geq m$ and $|Y| \geq n$**

An Optimization

- **Let X, Y be a pair of interacting protein groups**
  - By Theorem 3.7, $X = s^E [|Y|]^E$ and $Y = s^E [|X|]^E$
  - By Definition of $[|\bullet|]^E$, $|X|$ = times Y occurs in D^E
  - By Definition of $[|\bullet|]^E$, $|Y|$ = times X occurs in D^E

⇒ **To mine interesting pairs X, Y of interacting protein groups in an expt E such that $|X| \geq m$ and $|Y| \geq n$, it suffices to mine closed patterns X that appears $\geq n$ times in D^E and $|X| \geq m$**

Mining Closed Patterns Efficiently

Closed Pattern Mining Algorithms

- **CLOSET, Pei et al. 2000**
- **CARPENTER, Pan et al. 2003**
- **FPclose*, Grahne & Zhu 2003**
- **GC-growth, Li et al. 2005**
- **...**

⇒ **We have efficient algorithms for mining interesting interacting protein groups**

Example Breitkreutz et al, Genome Biology, 4, R23, 2003

X and $s^E[|X|]^E$ both occur with freq at least that of support threshold

support threshold	# of frequent close patterns	# of qualified close patterns	time in sec.
1	121314	121314	3.859
2	117895	114554	2.734
3	105854	95920	2.187
4	94781	80306	1.763
5	81708	60038	1.312
6	66429	36478	0.937
7	50506	15800	0.625
8	36223	3716	0.398
9	25147	406	0.281
10	17426	34	0.171
11	12402	2	0.109
12	9138	0	0.078

As there are many physical protein interaction networks corresponding to different species, here we take the simplest and most comprehensive yeast physical and genetic interaction network (Breitkreutz et al., 2003) as an example. This graph consists of 4904 vertices and 17440 edges (after removing 185 self loops and 1413 redundant edges from the original 19038 interactions). Therefore, the adjacency matrix is a transactional database with 4904 items and 4904 transactions. On average, the number of items in a transaction is 3.56. That is, the average size of the neighborhood of a protein is 3.56.

Generating Motif Pairs

Many Motif Discovery Methods

- **MEME, Bailey & Elkan 1995**
- **CONSENSUS, Hertz & Stormo 1995**
- **PROTOMAT, Henikoff & Henikoff 1991**
- **CLUSTAL, Higgins & Sharp 1988**
- **…**

- **For illustration, we use PROTOMAT here**

PROTOMAT

- **Core of Block Maker, a WWW server that return blocks (ungapped multiple alignments) for any submitted set of protein sequences**
- **Comprises 2 steps:**
  - MOTIF, Smith et al. 1990
    - **Look for spaced triplets in given set of proteins**
  - MOTOMAT, Henikoff & Henikoff 1991
    - **Merge overlapping blocks produced by MOTIF**
    - **Extend blocks in both directions until similarity falls**
    - **Determine best set of blocks that are in the same order and do not overlap**

we treat every block, instead of whole set of blocks generated by PROTOMAT, as a binding motif

Example, Breitkreutz et al, Genome Biology, 4, R23, 2003

- Comprises 19038 genetic and physical interactions in yeast among 4907 proteins
- Look for interesting pairs with m = n = 5
- About 1s to generate 60k closed patterns

⇒ Too many for PROTOMAT. So consider only maximal closed patterns, giving 7847 pairs

- PROTOMAT produces 17256 left blocks and 19350 right blocks after 6 hours
- Most groups yield 1 to 3 blocks
- Ave length of blocks = 11.696, std dev = 5.45

Results & Validation

Databases Used for Validation

- **BLOCKS,** Pietrokovski et al. 1996
- **PRINTS,** Attwood & Beck 1994
- **Pfam,** Sonnhammer et al. 1997
- **InterDom,** Ng et al. 2003

	BLOCKS	PRINTS	Pfam	InterDom
Version	14.0	37.0	16.0	1.1
Num. of groups / families	4944	1850	7677	3535
Num. of entries	24294	11170	7677	30037

Validation for Single Motifs

- **Compare all single motifs in our discovered motif pairs with all domains of specific domain databases**
  - LAMA, Pietrokovski 1996
  - transform blocks into position-specific scoring matrices (PSSM)
  - run Smith-Waterman to align pairs of PSSM using Pearson correlation coefficient to measure similarity betw 2 columns
  - a block is mapped to another block if 95% of positions in a block occuring in the optimal alignment is common to another block and Z-score is > 5.6, where Z-score is the number std dev away from the mean generated by millions of shuffles of the BLOCKS database
- **Determine number of motifs that can be mapped to these domains and the overall correlation in the portions that are mapped**

Results for Single Motifs

	Mapped / total num. in BLOCKS	Mapped / total num. in PRINTS	Mapped / total num. in BOTH
Unique blocks	8401 / 24294	2872/ 11170	11273/ 35464
Unique groups	3568 / 4944	1325/ 1850	4893 / 6794

- **Our blocks map to 32% of blocks in BLOCKS and PRINTS, yet motifs from our blocks cover 72% of domains in BLOCKS and PRINTS**

⇒ **Maybe most domains in BLOCKS and PRINTS have less than half a block as binding motifs, or may not be related to binding behaviour**

Validation for Motif Pairs

- **Map our motif pairs into domain-domain interacting pairs**
- **Determine the number of overlaps between our motif pairs and those in the domain-domain interaction database**
- **Use InterDom as the domain-domain interaction database**

	BLOCKS	PRINTS	Pfam	InterDom
Version	14.0	37.0	16.0	1.1
Num. of groups / families	4944	1850	7677	3535
Num. of entries	24294	11170	7677	30037

30037 interactions among 3535 domains

Linking Our Motif Pairs to InterDom

- **InterDom represents domains by Pfam entries**

⇒ **To x-link, we have to**

- Map our motifs to blocks in BLOCKS and PRINTS
- Link from BLOCKS and PRINTS to InterPro
- Link from InterPro to Pfam
- Match Pfam to InterDom

Results for Motif Pairs

Domain-domain interactions inferred from protein complexes or from interactions between single domain proteins

	BLOCKS overlaps	PRINTS overlaps	Combined overlaps	Confident overlaps	Complex confirmed
Domain pairs	862	26	1163	396	241

Both sides mapped to BLOCKS

Both sides mapped to PRINTS

One side mapped to PRINTS, one side mapped to BLOCKS

Example Confirmed Binding Motif

- **1 of the 241 binding motifs we found that can be confirmed using protein complexes is #1781...**

```
ID none; BLOCK
AC 1781xxxxx; distance from previous block=(26,378)
DE none BL GNL motif=[5,0,17] motomat=[1,80,-10] width=14 seqs=6
      YBL026W    ( 27 ) G T L Q S V D Q F  L N L K L
      YCR077C    ( 379) G N S S  Q D N K Q  A N T V L
      YER112W    ( 27 ) G I  L T N V D N W  M N L T L
      YER146W    ( 32 ) G T L V G F D D F  V N V I  L
      YNL147W    ( 42 ) G V L K G Y D Q L  M N L V L
      YOL149W    ( 129) G K T L  S G K D I  Y N Y G L

      gdb1mgq_A  ( 38 ) G V L K S F D 1  h M N L V L
```

```
ID none; BLOCK
AC 1781xxigh; distance from previous block=(2,316)
DE none BL LDN motif=[4,0,17] motomat=[1,80,-10] width=9 seqs=4
      YDR378C    ( 75 ) L E S I D G F M N
      YGL173C    ( 317) L L H T D G Y I  N
      YJL124C    ( 68 ) L R T F D Q Y A N
      YJR022W    ( 46 ) L N G F D K N T  N

      pdb1mgq_B  ( 40 ) L k S F D 1  h M N
```

As shown in the next slide, this pair corresponds to interaction sites between LSM domains. E.g., all 7 pairs of adjacent LSM domains of pdb1mgq exhibits it.

Example: LSM Domains of pdb1mgq

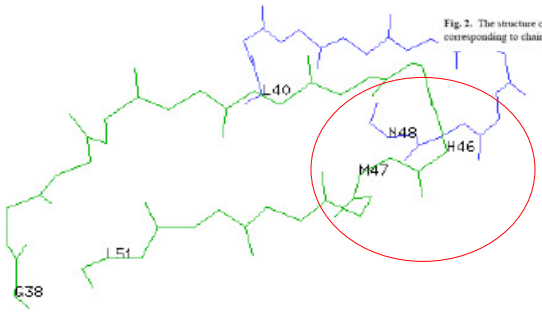
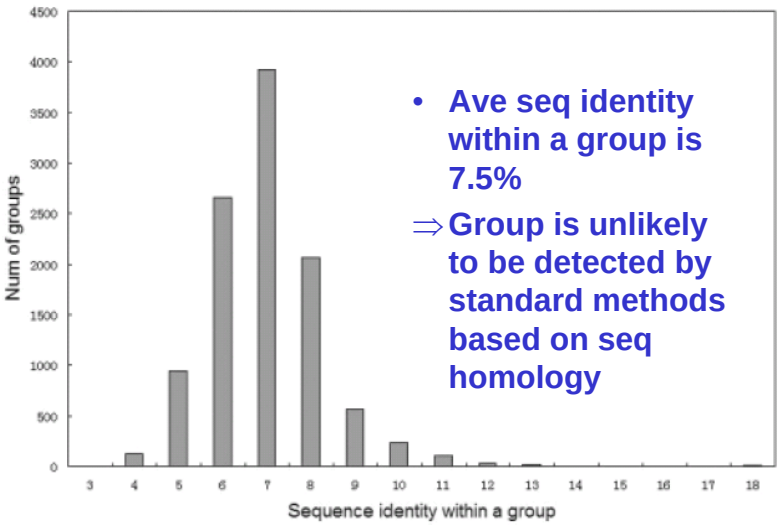


Fig. 2. The structure of the complex pdb1mgq consisting of 7 LSM domains corresponding to chain A, Chain B, ..., to chain G.

Fig. 3. Interactions between segment [38G, 51L] of LSM A and segment [40L,48N] of LSM B in the complex pdb1mgq (showing only the backbone).

Sequence Identity Within a Group



- **Ave seq identity within a group is 7.5%**

⇒ **Group is unlikely to be detected by standard methods based on seq homology**

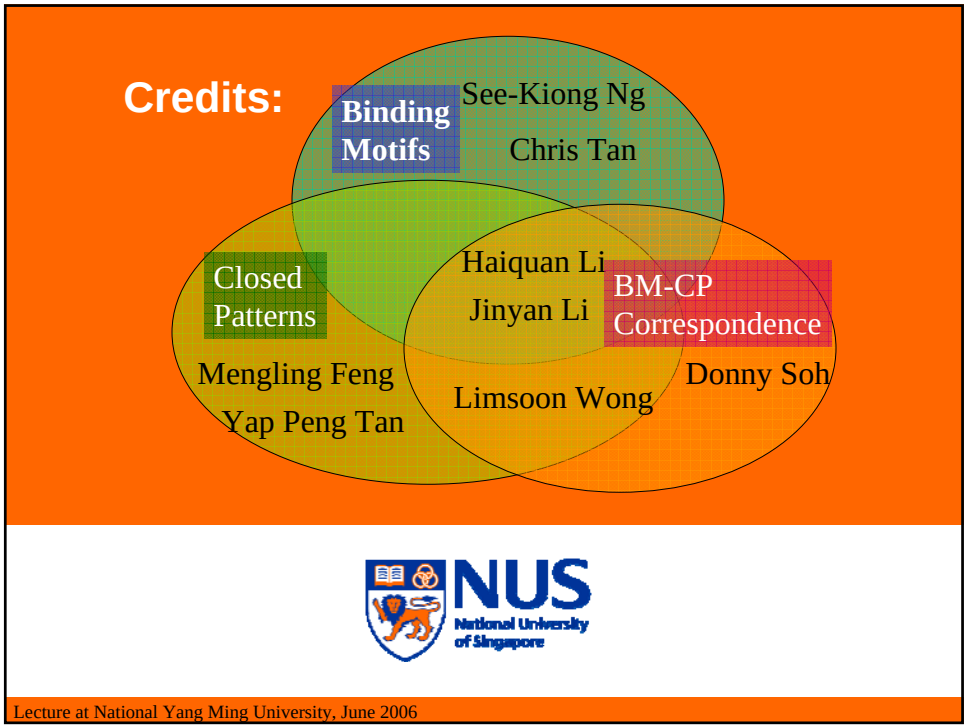
Conclusions

- **Connection between maximal complete bipartite subgraphs and closed patterns**

⇒ **Closed pattern mining algorithms can be used to enumerate maximal complete bipartite subgraphs efficiently**

- **Connection between pairs of interacting protein groups and closed patterns**

⇒ **Discovery of binding motifs is accelerated because we need not execute expensive motif discovery algorithms on insignificant groups**



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