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

Limsoon Wong

(joint work with Haiquan Li & Jinyan Li)

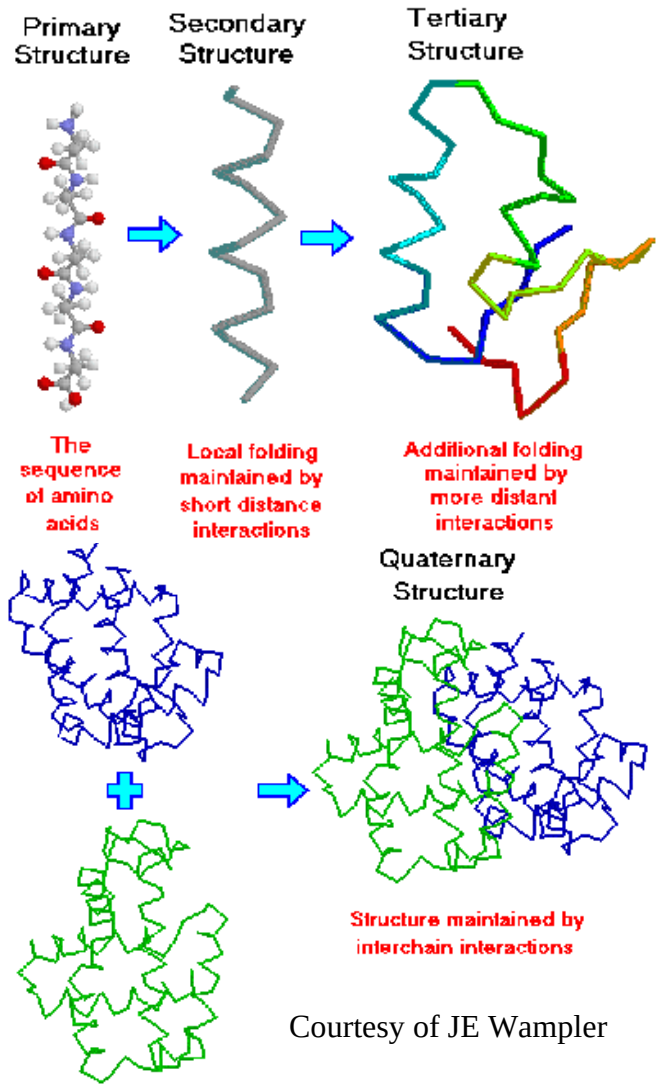
Plan

- **Problem statement:**
  - Discover binding motif pairs
- **Transform to a graph problem:**
  - Enumerate max complete bipartite subgraphs
- **Transform to a data mining problem:**
  - Mine closed patterns
- **Generate motifs from blocks**
- **Verify using known data**

Problem Statement:
Discover Binding Motif Pairs

Proteins & Their Interactions

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

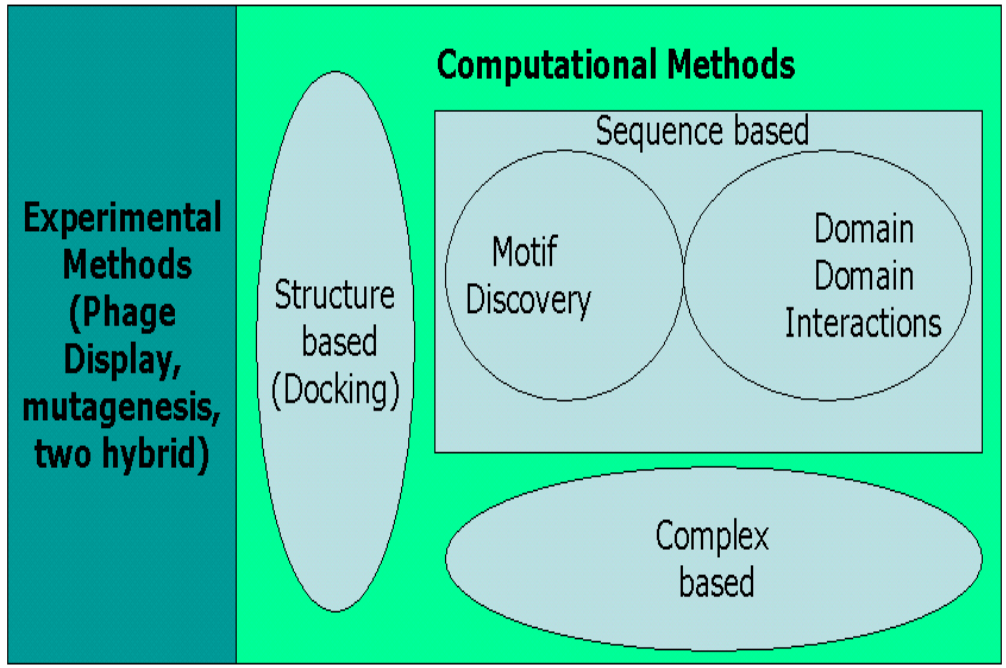


Courtesy of JE Wampler

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

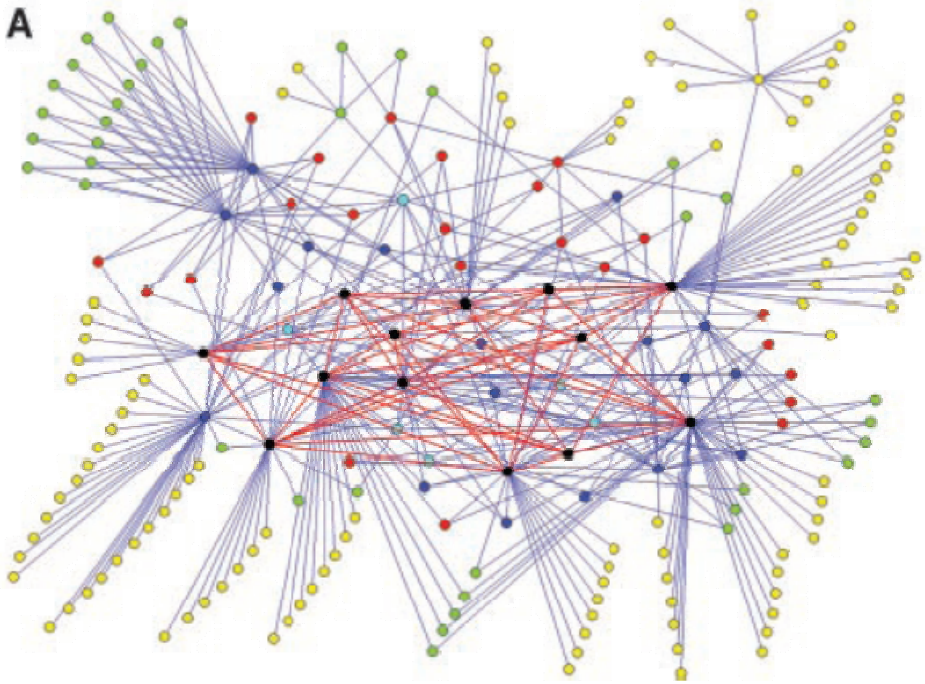
- **Typical seq-based approaches have two steps:**
  - Use pattern discovery algorithms to discover domains and/or motifs of a group of proteins
  - Use domain-domain interaction discovery methods (e.g., domain fusion) to discovery interacting domains

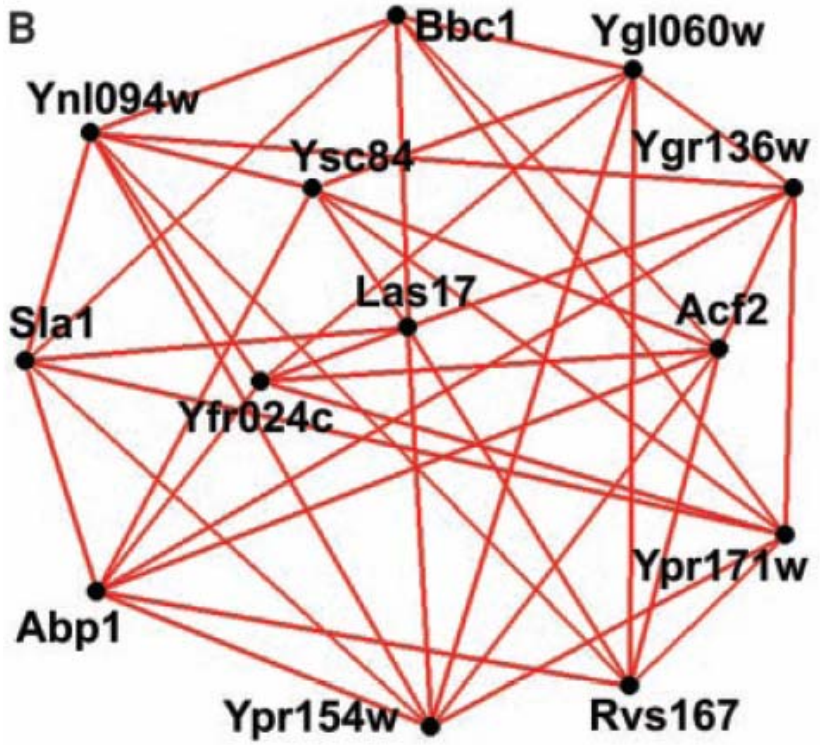
- **Shortcomings:**
  - Protein interaction information is not used by motif discovery algorithms
  - Exact positions of binding sites often not recognized

How about ...

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

Protein Interaction Graphs



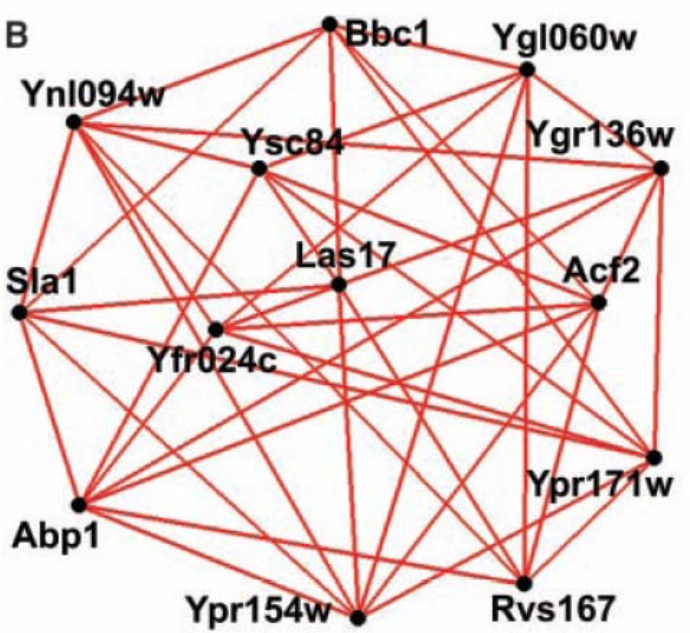


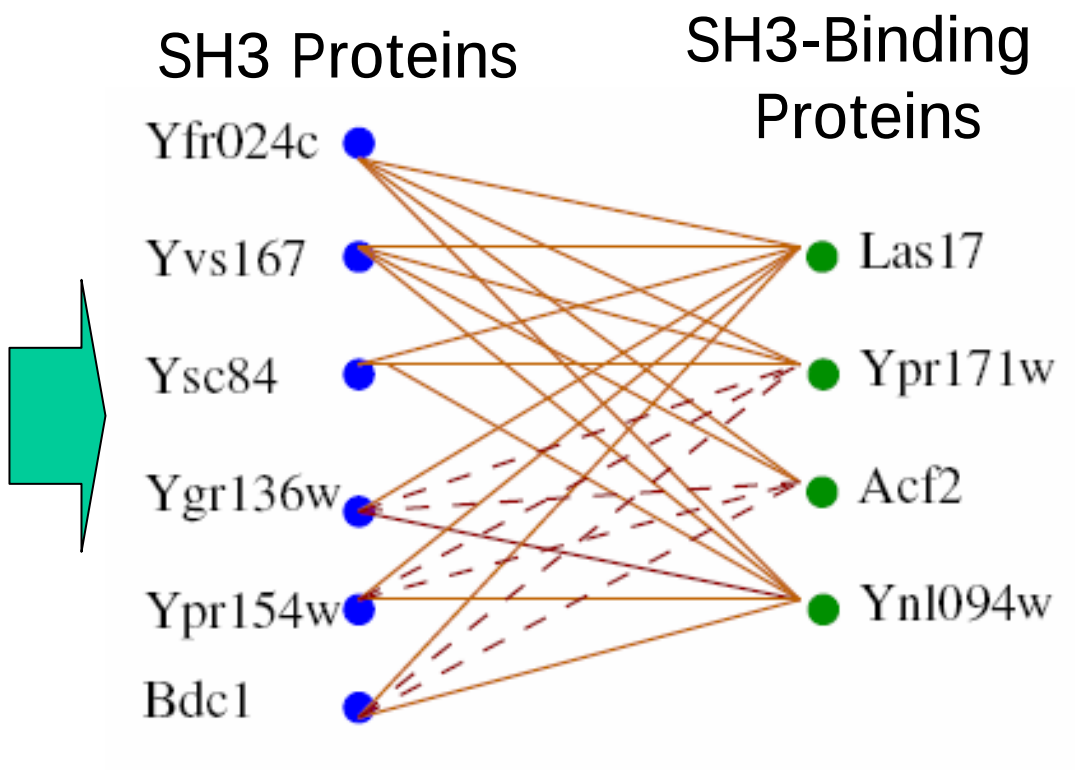
Yeast SH3 domain-domain Interaction network:
394 edges, 206 nodes

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) X and Y have full mutual interactions

(1.2) X and Y are as large as possible

&

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

Transform to a Graph Problem: Enumerate Max Complete Bipartite Subgraphs

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 $\beta^E(p)$ denote** neighborhood **of protein p in G^E**
- **Let $\beta^E(P) = \bigcap_{p \in P} \beta^E(p)$ 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

  $X = \beta^E(Y)$ and $Y = \beta^E(X)$.

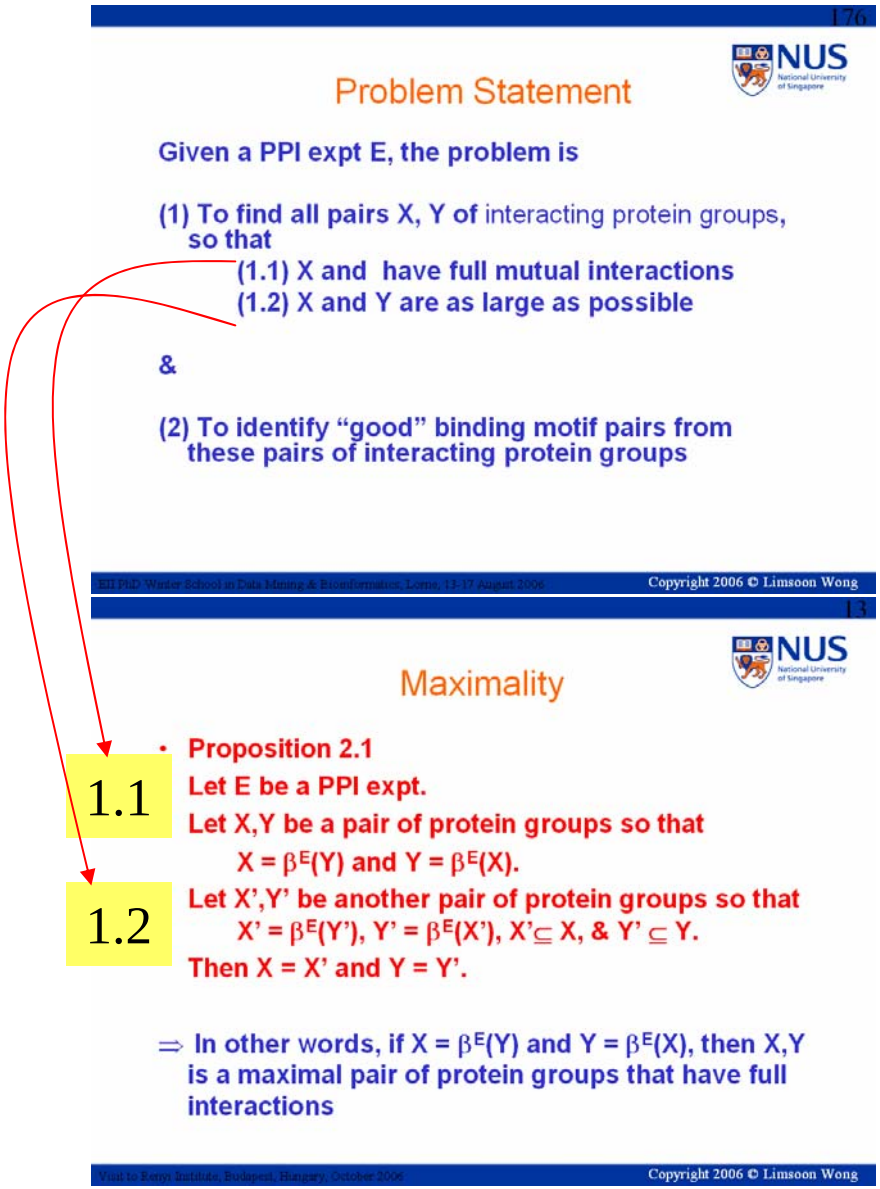
  Let X',Y' be another pair of protein groups so that

  $X' = \beta^E(Y')$, $Y' = \beta^E(X')$, $X' \subseteq X$, & $Y' \subseteq Y$.

  Then X = X' and Y = Y'.

$\Rightarrow$ **In other words, if $X = \beta^E(Y)$ and $Y = \beta^E(X)$, 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 = $\beta^E(Y)$ and Y = $\beta^E(X)$**

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

Max Complete Bipartite Subgraph

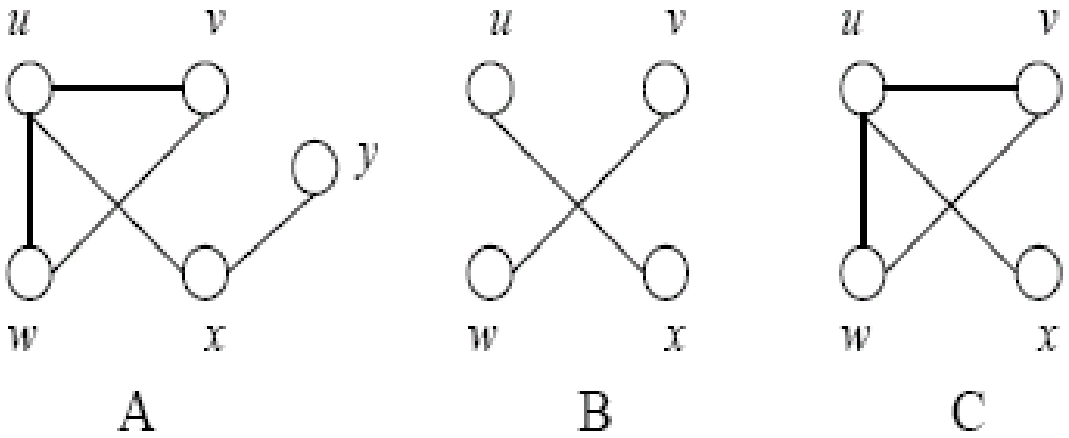
- A graph $H = \langle V_1 \cup V_2, D^H \rangle$ is a **maximal complete bipartite subgraph** of G iff
  - H is a subgraph of G,
  - $V_1 \times V_2 = D^H$,
  - $V_1 \cap V_2 = \{\}$, &
  - There is no $H' = \langle V'_1 \cup V'_2, D^{H'} \rangle$ with $V_1 \subset V'_1$ & $V_2 \subset V'_2$ that has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

- **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**

Connection to Graph Theory

- **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**

We are talking about subgraphs, not vertex-induced subgraph ….



- **B is a subgraph of A, but it is not a vertex-induced subgraph**
- **C is a subgraph of A, and it is a vertex-induced subgraph**

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**

Transform to a Data Mining Problem: Mine Closed Patterns

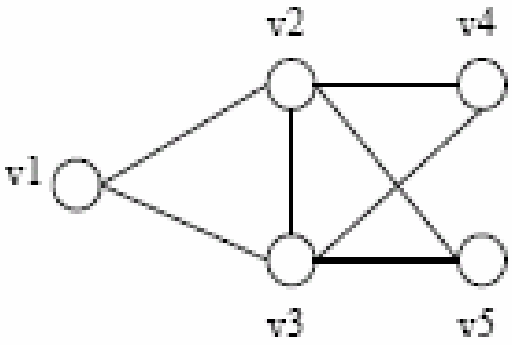
From PPI Expts To Transactions

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

$\Rightarrow$ **E can be thought of as generating a** db of transactions **$D^E = \{\beta^E(p_1), \ldots, \beta^E(p_k)\}$, 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 $p \in D^E$ st $X \subseteq \beta^E(p)$**

Example



A graph G

	v_1	v_2	v_3	v_4	v_5
v_1	0	1	1	0	0
v_2	1	0	1	1	1
v_3	1	1	0	1	1
v_4	0	1	1	0	0
v_5	0	1	1	0	0

its adjacency matrix

We use the protein v to be id(β(v))

$id(T)$	T	items				
		v_1	v_2	v_3	v_4	v_5
v_1	$\beta(v_1)$	0	1	1	0	0
v_2	$\beta(v_2)$	1	0	1	1	1
v_3	$\beta(v_3)$	1	1	0	1	1
v_4	$\beta(v_4)$	0	1	1	0	0
v_5	$\beta(v_5)$	0	1	1	0	0

transformation to DB_G

Occurrence Set

- **The occurrence set of a pattern P in database D is defined as**

$$occ^D(P) = \{ id(T) \mid T \in D, P \subseteq T\}$$
$$= \{ id(T) \mid T \in f^D(P)\}$$

- **Proposition**

$$occ^{D^E}(P) = \beta^E(P)$$

Closed Patterns

- **Let**
  - I be a set of items and D a transaction db on I
  - $f^D(P) = \{T \in D \mid P \subseteq T\}$,
  - $g(D') = \bigcap_{T \in D'} T = \bigcap D'$, for $D' \subseteq D$

  Then $CL^D(P) = g(f^D(P))$ is the closure of P, and P is called a closed pattern iff $P = CL^D(P)$

- **Proposition**

  CL^D is a closure operation. That is, CL^D is monotonic, idempotent, and inflationary

- **Proposition**

$$CL^{D^E}(P) = \beta^E(\beta^E(P))$$

Proof of CL(P) = β(β(P))

- **β(β(P))**
  - **= β(occ(P)), since β(P) = occ(P)**
  - **= $\bigcap_{id(T) \in occ(P)}$ β(id(T)), defn of β(.)**
  - **= $\bigcap_{id(T) \in occ(P)}$ T, defn of id(.) and β(.)**
  - **= $\bigcap_{T \in f(P)}$ T, since occ(P) = {id(T) | T ∈ f^D(P)}**
  - **= g(f(P)), defn of g(.)**
  - **= CL(P), defn of CL(.)**

- **Proposition**

  Let C_1, C_2 be closed patterns in D^E

  Then $C_1 = C_2$ iff $occ(C_1) = occ(C_2)$

- **Proposition**

  If C is closed pattern in D^E, then $C \cap occ(C) = \{\}$

- **Proposition**

  Let C be a closed pattern in D^E.

  Then occ(C) is a closed pattern in D^E

- **Corollary**

  The number of closed patterns in D^E is even

NUS National University of Singapore

Proofs

Proposition 7 *Let G be a graph. Let C_1 and C_2 be two closed patterns of DB_G. Then $C_1 = C_2$ iff $occ^{DB_G}(C_1) = occ^{DB_G}(C_2)$.*

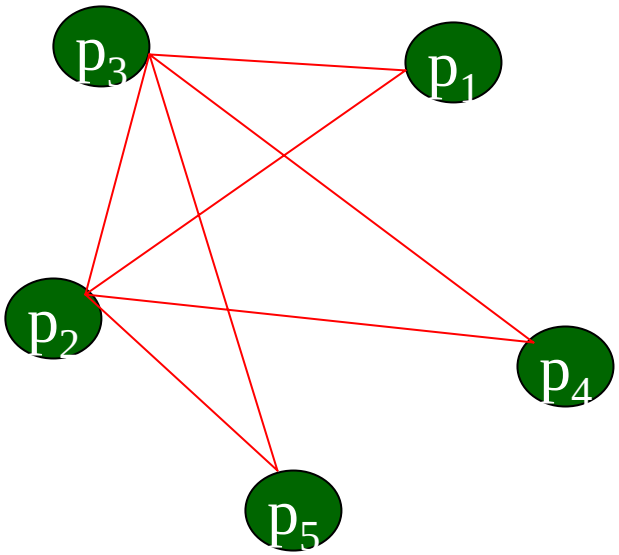
Proof: *The left-to-right direction is trivial. To prove the right-to-left direction, let us suppose that $occ(C_1) = occ(C_2)$. It is straightforward to see that $id(T) \in occ(P)$ iff $T \in f(P)$. Then we get $f(C_1) = f(C_2)$ from $occ(C_1) = occ(C_2)$. Since C_1 and C_2 are closed patterns of DB_G, it follows that $C_1 = g(f(C_1)) = g(f(C_2)) = C_2$, and finishes the proof.* □

Lemma 1 *Let G be a graph. Let C be a closed pattern of DB_G. Then $f^{DB_G}(occ^{DB_G}(C)) = \{\beta^G(c) \mid c \in C\}$.*

Proposition 9 *Let G be a graph and C a closed pattern of DB_G. Then $occ^{DB_G}(C)$ is also a closed pattern of DB_G.*

Proof: *By Lemma 1, $f(occ(C)) = \{\beta(c) \mid c \in C\}$. So $CL(occ(C)) = g(f(occ(C))) = \bigcap f(occ(C)) = \bigcap_{c \in C} \beta(c) = \beta(C)$. By Proposition 5, $\beta(C) = occ(C)$. Thus $occ(C)$ is a closed pattern.* □

Example



	v_1	v_2	v_3	v_4	v_5
$\beta(v_1)$	0	1	1	0	0
$\beta(v_2)$	1	0	1	1	1
$\beta(v_3)$	1	1	0	1	1
$\beta(v_4)$	0	1	1	0	0
$\beta(v_5)$	0	1	1	0	0

$sup(X)$	$closed\ pattern\ X$	$Y = occ(X)$	$sup(Y)$
3	$\{v_2, v_3\}$	$\{v_1, v_4, v_5\}$	2
4	$\{v_2\}$	$\{v_1, v_3, v_4, v_5\}$	1
4	$\{v_3\}$	$\{v_1, v_2, v_4, v_5\}$	1

Isomorphism

- **Theorem**

  Let G^E be PPI graph, and C closed pattern of D^E.

  Then $H = \langle C \cup occ(C), C \times occ(C) \rangle$ is a max complete bipartite subgraph of G^E

- **Theorem**

  Let $H = \langle V_1 \cup V_2, E' \rangle$ be max complete bipartite subgraph of G^E. Then V_1, V_2 are closed pattern of D^E, $occ(V_1) = V_2$, and $occ(V_2) = V_1$

$\Rightarrow$ An isomorphism exists betw max complete bipartite subgraphs of G^E & closed patterns of D^E

Proofs

Theorem 1 *Let G be an undirected graph without self-loop. Let C be a closed pattern of DB_G. Then the graph*

$$H = \langle C \cup occ^{DB_G}(C), C \times occ^{DB_G}(C) \rangle$$

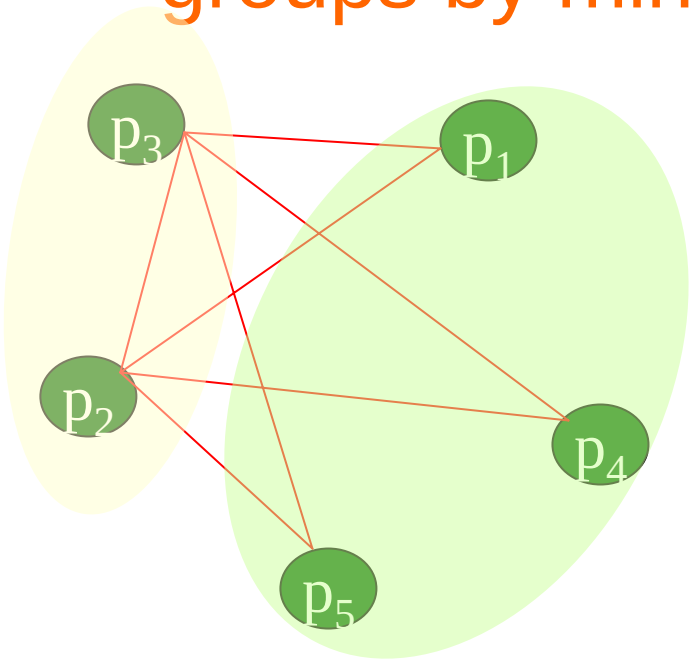
is a maximal complete bipartite subgraph of G.

Proof: *By assumption, C is non-empty and C has a non-zero support in DB_G. Therefore, $occ(C)$ is non-empty. By Proposition 8, $C \cap occ^{DB_G}(C) = \{\}$. Furthermore, for every $v \in occ(C)$, v is adjacent in G to every vertex of C. So, $C \times occ(C) \subseteq E^G$, and every edge of H connects a vertex of C and a vertex of $occ(C)$. Thus, H is a complete bipartite subgraph of G. By Proposition 5, we have $occ^{DB_G}(C) = \beta^G(C)$. By Proposition 6, $C = \beta^G(\beta^G(C))$. By Proposition 5, we derive $C = \beta^G(occ^{DB_G}(C))$. So H is maximal. This finishes the proof.* □

Theorem 2 *Let G be an undirected graph without self-loop. Let graph $H = \langle V_1 \cup V_2, E \rangle$ be a maximal complete bipartite subgraph of G. Then, V_1 and V_2 are both a closed pattern of DB_G, $occ^{DB_G}(V_1) = V_2$ and $occ^{DB_G}(V_2) = V_1$.*

Proof: *Since H is a maximal complete bipartite subgraph of G, then $\beta(V_1) = V_2$ and $\beta(V_2) = V_1$. By Proposition 6, $CL(V_1) = \beta(\beta(V_1)) = \beta(V_2) = V_1$. So, V_1 is a closed pattern. Similarly, we can get V_2 is a closed pattern. By Proposition 5, $occ(V_1) = \beta(V_1) = V_2$ and $occ(V_2) = \beta(V_2) = V_1$, as required.* □

Thus, can mine protein interaction groups by mining close patterns



	v_1	v_2	v_3	v_4	v_5
$\beta(v_1)$	0	1	1	0	0
$\beta(v_2)$	1	0	1	1	1
$\beta(v_3)$	1	1	0	1	1
$\beta(v_4)$	0	1	1	0	0
$\beta(v_5)$	0	1	1	0	0

$sup(X)$	$closed\ pattern\ X$	$Y = occ(X)$	$sup(Y)$
3	$\{v_2, v_3\}$	$\{v_1, v_4, v_5\}$	2
4	$\{v_2\}$	$\{v_1, v_3, v_4, v_5\}$	1
4	$\{v_3\}$	$\{v_1, v_2, v_4, v_5\}$	1

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 $|X| \geq p$ and $|Y| \geq q$**

An Optimization

- **A max complete bipartite subgraph $H = \langle V_1 \cup V_2, E' \rangle$ is (p,q)-large if $|V_1|$ or $|V_2|$ is at least p, and the other is at least q**

- **Theorem**

  Let G^E be PPI graph, and C closed pattern of D^E.

  Then $H = \langle C \cup occ(C), C \times occ(C) \rangle$ is (p,q)-large iff C occurs at least p times in DE and $|C| \geq q$

$\Rightarrow$ To mine interesting pairs X, Y of interacting protein group in expt E st $|X| \geq p$ and $|Y| \geq q$, it suffices to mine closed patterns X that appears $\geq$ q times in D^E and $|X| \geq p$

Proofs

Corollary 3 *Let G be a graph. Then $H = \langle C \cup occ^{DB_G}(C), C \times occ^{DB_G}(C)\rangle$ is a (p,q)-large maximal complete bipartite subgraph of G iff C is a closed pattern such that C occurs at least p times in DB_G and $occ^{DB_G}(C)$ occur at least q times in DB_G.*

Theorem 5 *Let G be a graph. Then $H = \langle C \cup occ^{DB_G}(C), C \times occ^{DB_G}(C)\rangle$ is a (p,q)-large maximal complete bipartite subgraph of G iff C is a closed pattern such that C occurs at least p times in DB_G and $|C| \geq q$.*

Proof: *Suppose $H = \langle C \cup occ^{DB_G}(C), C \times occ^{DB_G}(C)\rangle$ is a (p,q)-large maximal complete bipartite subgraph of G. By Theorem 2, $C = occ(occ(C))$. By definition of $occ(\cdot)$, $sup(occ(C)) = |occ(occ(C))| = |C|$. Substitute this into Corollary 3, we get H is a (p,q)-large maximal complete bipartite subgraph of G iff C is a closed pattern such that C occurs at least p times in DB_G and $|C| \geq q$ as desired.* □

NUS National University of Singapore

Closed Patterns

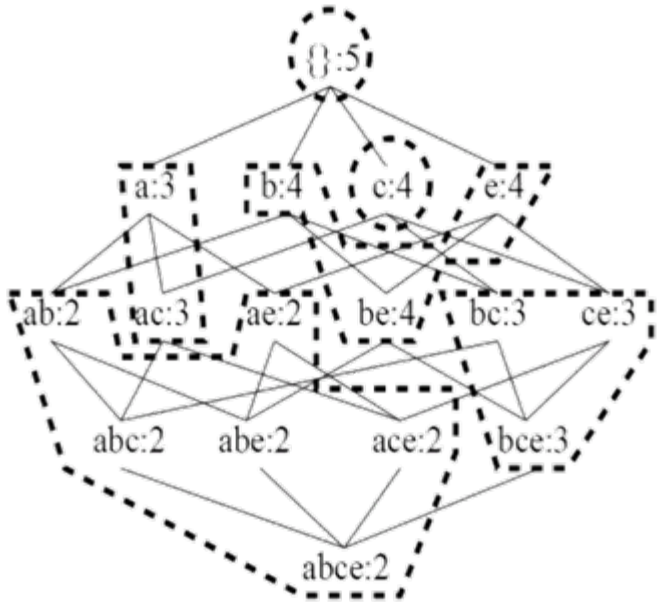
- Let $[X]^D = \{Y \mid f^D(Y) = f^D(X)\}$ denote the equivalence class of the pattern X in D
- Then max $[X]^D = \{CL^D(X)\}$

⇒ A closed pattern is the most specific pattern in its equivalence class

⇒ To mine patterns, it is sufficient & more efficient to mine just the closed patterns

Table 1: A transaction database Tl

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

Closed Pattern Mining Algorithms

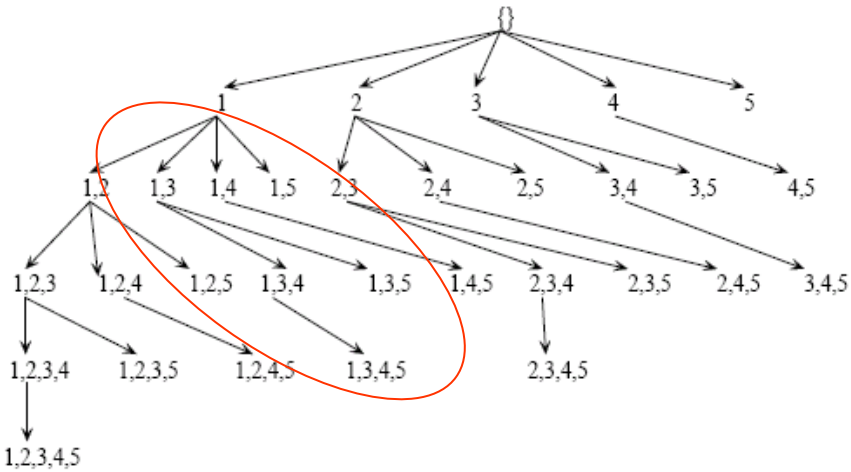
- **CLOSET, Pei et al. 2000**
- **CARPENTER, Pan et al. 2003**
- **FPclose*, Grahne & Zhu 2003**
- **LCM, Uno et al., 2004**
- **GC-growth, Li et al. 2005**
- **...**

⇒ **We have efficient algo for mining closed patterns**

- **But these algo have size constraint only on one side---occ(C), and do not pair up closed patterns**

Pruning Small Max Complete Bipartite Subgraphs

- **Search space of typical closed pattern mining algo**



  - **An order is assumed on items**
  - **Only items after last item in X can appear in sub search space of X**
  - **E.g.,**
    - 4 is in tail{1, 3}
    - 2 is not in tail{1,3}

- **To find closed pattern Y st $|Y| \geq q$ & $sup(Y) \geq p$**

- **Itemset Y in sub search space of X is subset of $X \cup tail(X)$**

⇒ **Skip if $|X \cup tail(X)| < q$**

- **Itemset Y in sub search space of X st $|Y| \geq q$ & $sup(Y) \geq p$ is subset of $X \cup \{x \in tail(X) \mid sup(X \cup \{x\}) \geq p\}$**

⇒ **Skip if there is less than $p - |X|$ items $x \in tail(X)$ st $sup(X \cup \{x\}) \geq p$**

Pruning Duplicate Max Complete Bipartite Subgraphs

- Max complete bipartite subgraphs are generated twice if we output all closed patterns

- Set sup threshold to max(p, q)

⇒ Maximize pruning power

- Do not extend if size of closed pattern exceeds its support

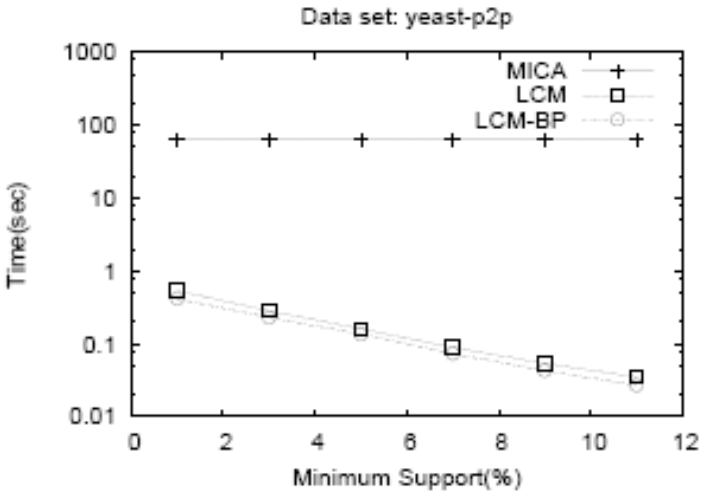
⇒ Max complete bipartite subgraphs w/ vertex sets of diff sizes enumerated only once

- Do not output closed pattern if smaller than its occurrence set

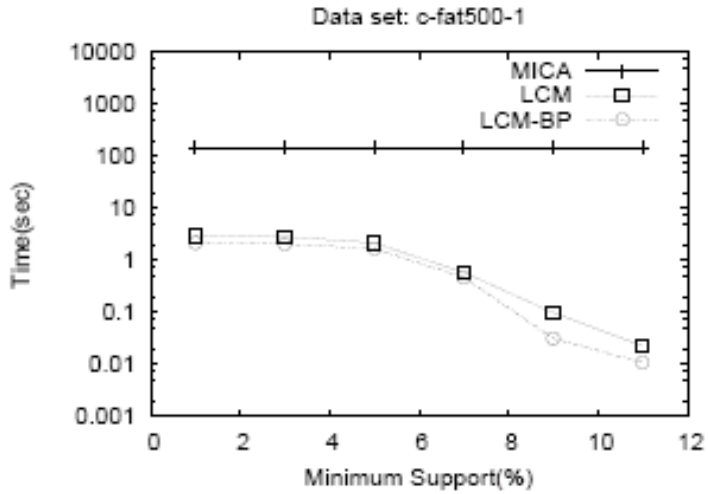
⇒ Max complete bipartite subgraphs w/ vertex sets of same size enumerated only once

MICA: a previous consensus-based max complete bipartite mining algo
LCM: state-of-art closed pattern mining algo
LCM-BP: our modified LCM

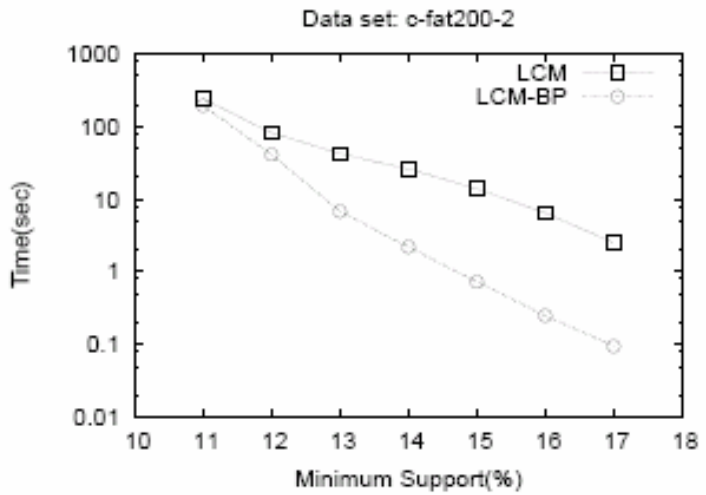
Effectiveness



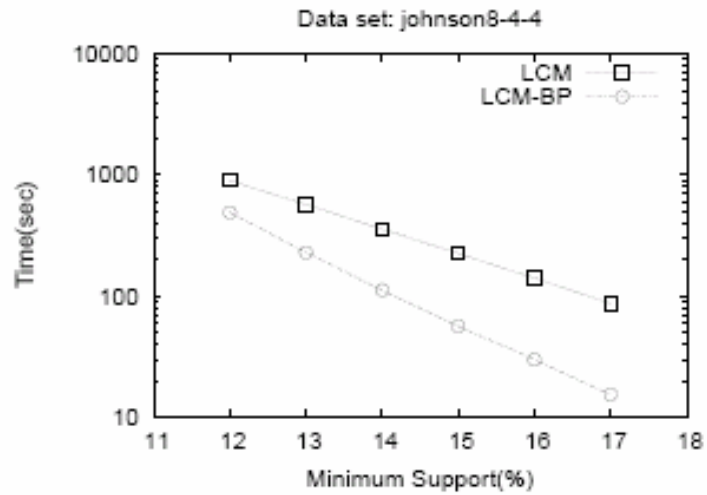
(a) yeast-p2p



(b) c-fat500-1



(e) c-fat200-2



(f) johnson8-4-4

Experiment

- **So let's use LCM-BP to mine interesting protein interaction groups …**

- **Consider the yeast PPI graph from Breitkreutz et al, *Genome Biology*, 4, R23, 2003**
  - 4904 vertices
  - 17440 edges (after removing 185 self-loops, 1413 redundant edges)
  - Ave number of interactions per protein = 3.56

Resulting Max Complete Bipartite Subgraphs

support threshold (ms)	# of frequent closed patterns	# of qualified closed patterns	time in sec.
1	121314	121314	0.59
2	117895	114554	0.50
3	105854	95920	0.44
4	94781	80306	0.40
5	81708	60038	0.36
6	66429	36478	0.32
7	50506	15800	0.25
8	36223	3716	0.21
9	25147	406	0.11
10	17426	34	0.07
11	12402	2	0.06
12	9138	0	0.05

Generate Motifs From Blocks , Verify Binding 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 17440 genetic and physical interactions in yeast among 4904 proteins**
- **Look for interesting pairs with p = q = 5**
- **<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**

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 db**
  - 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**

NUS National University of Singapore

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

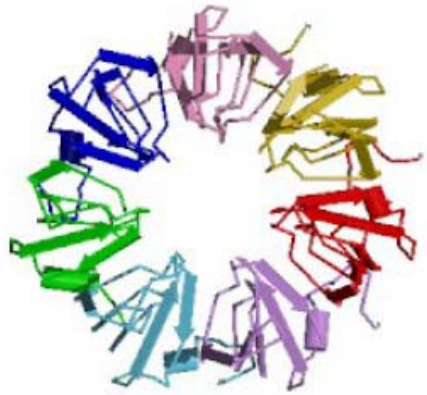
- **1 of the 241 binding motifs we found that can be confirmed using protein complexes is #1781...**

```
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 1781xrigh; 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



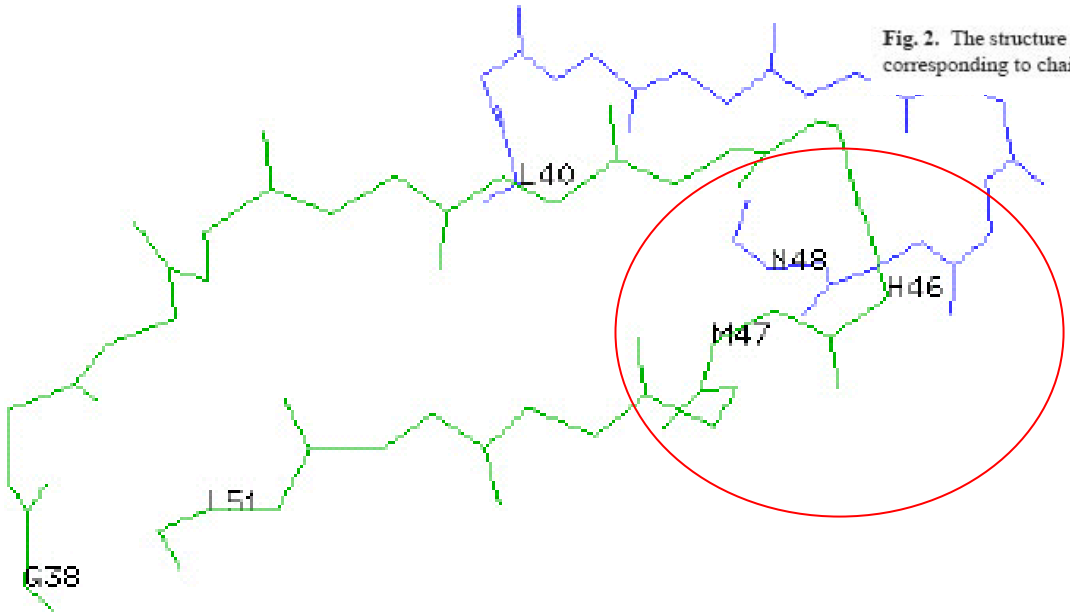
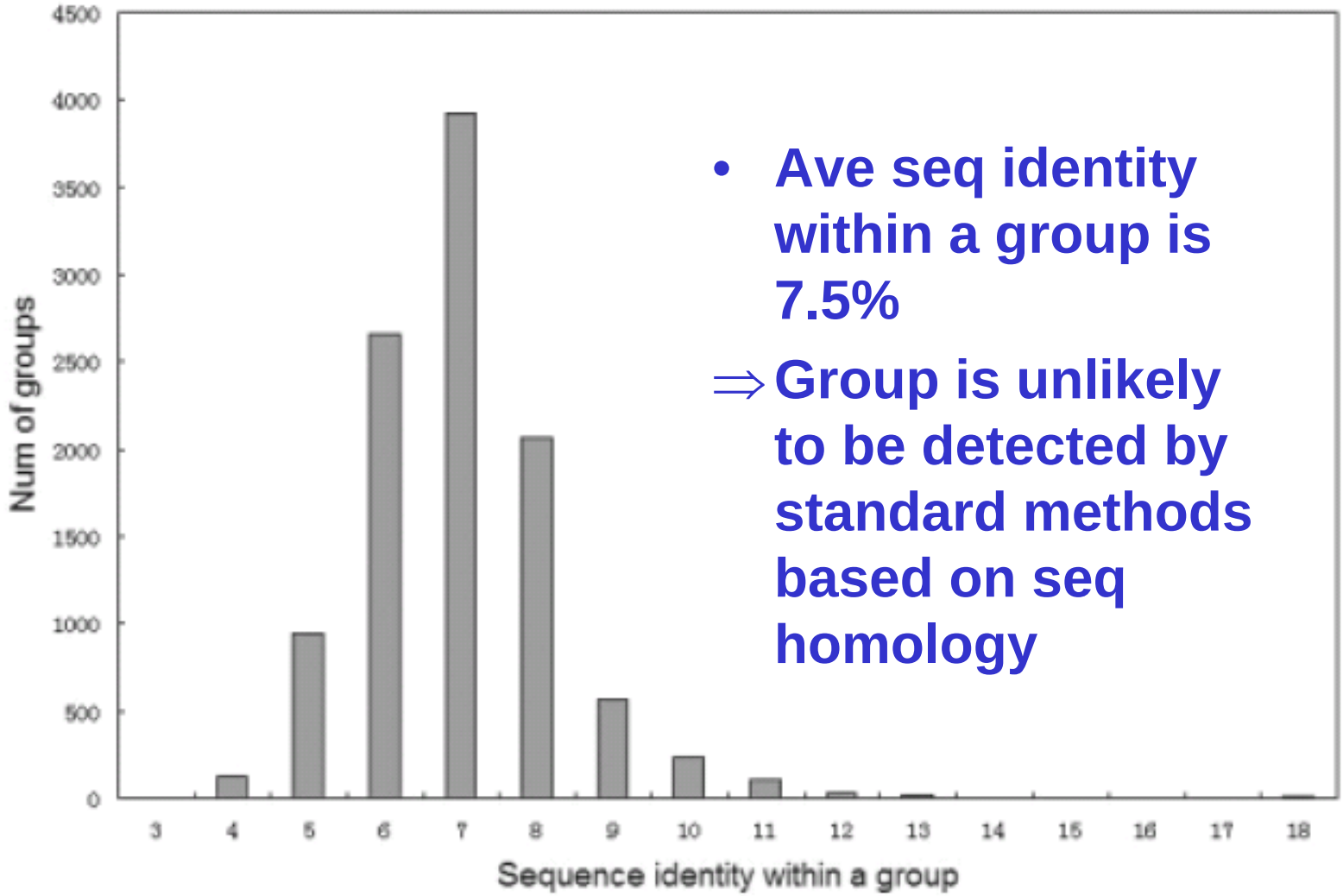


Fig. 2. The structure of the complex pdb1mgq consisting of 7 LSM domains corresponding to chain A, Chain B, …, to chain G.

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**

References

- Haiquan Li, Jinyan Li, Limsoon Wong. Discovering Motif Pairs at Interaction Sites from Protein Sequences on a Proteom-Wide Scale. *Bioinformatics*, 22(8):989--996, 2006

- Jinyan Li, Haiquan Li, Donny Soh, Limsoon Wong. A Correspondence Between Maximal Complete Bipartite Subgraphs and Closed Patterns. *Proceedings of 9th European Conference on Principles and Practice of Knowledge Discovery in Databases*, pages 146--156, Porto, Portugal, October 2005

- Smith et al., Finding Sequence Motifs in Groups of Functionally Related Proteins. *PNAS*, 87:826-830, 1990

- Henikoff & Henikoff. Automated assembly of protein blocks for database searching. *NAR*, 19:6565-6572, 1991