Comparative Network Analysis

BMI/CS 776
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Protein-protein Interaction Networks

(Jeong et al., 2001, Nature)

- Yeast protein interactions from yeast two-hybrid experiments
- Largest cluster in network contains 78% of proteins

Knock-out phenotype

🔴 lethal
🟢 non-lethal
🟠 slow growth
🟡 unknown

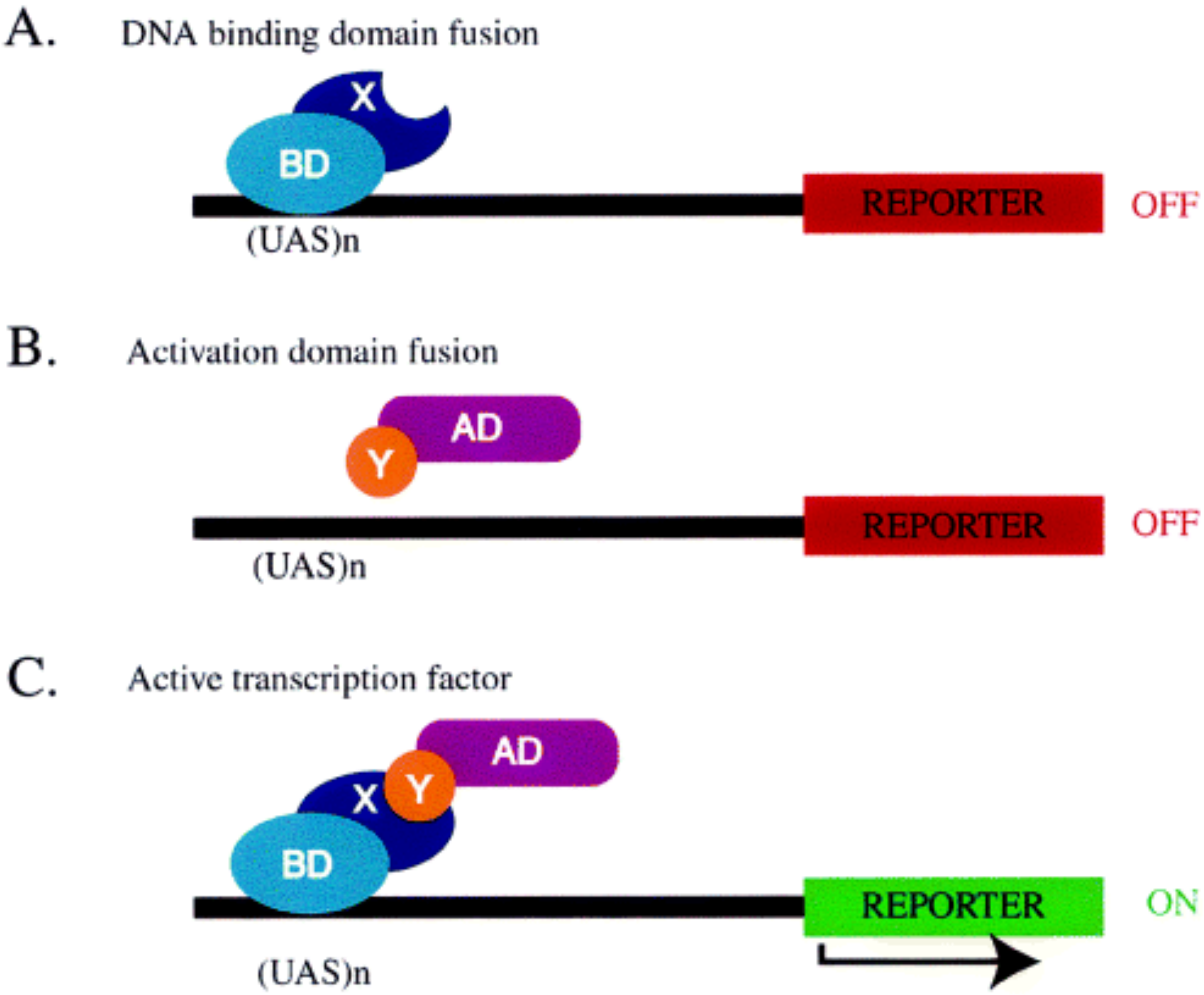
Overview

- Experimental techniques for determining networks
- Comparative network tasks

Experimental techniques

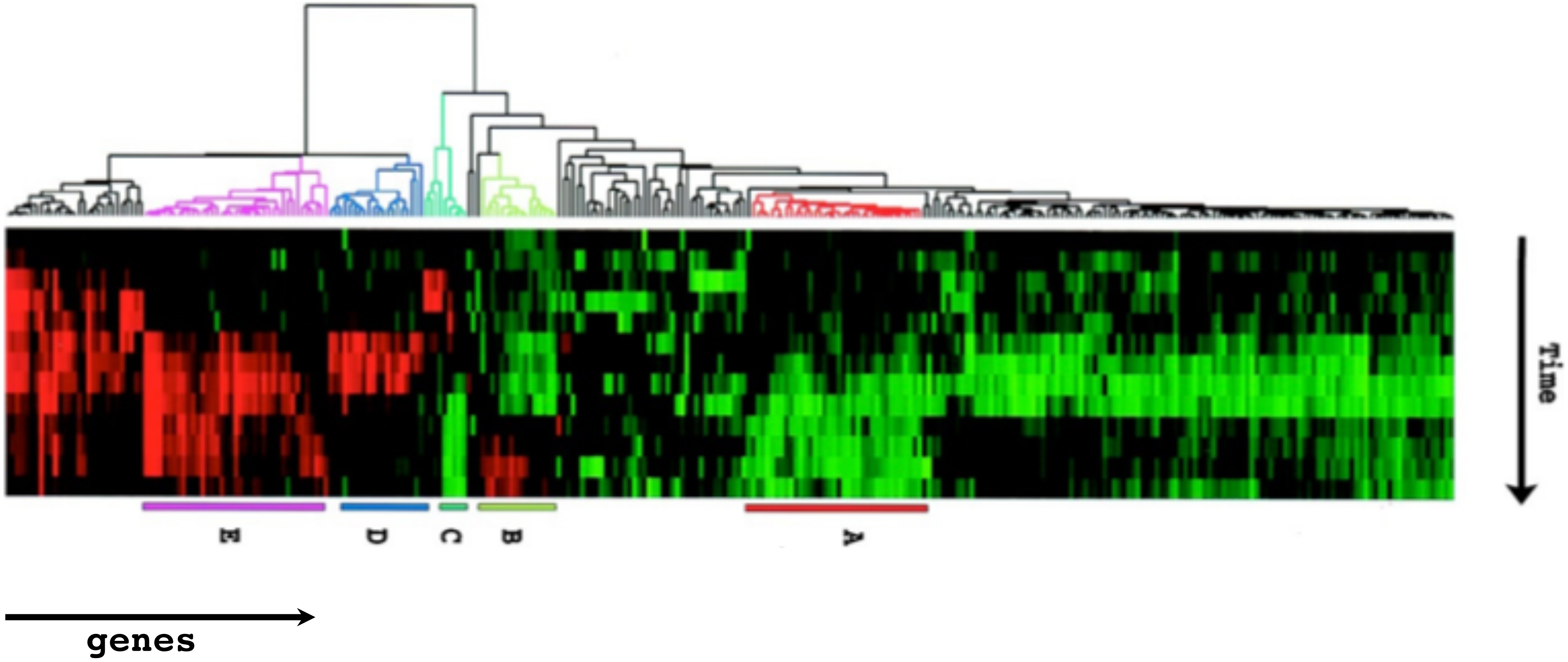
- Yeast two-hybrid system
  - Protein-protein interactions
- Microarrays/RNA-Seq
  - Expression patterns of mRNAs
  - Similar patterns imply involvement in same regulatory or signaling network
- Knock-out studies
  - Identify genes required for synthesis of certain molecules

Yeast two-hybrid system



(Stephens & Banting, 2000, Traffic)

Microarrays

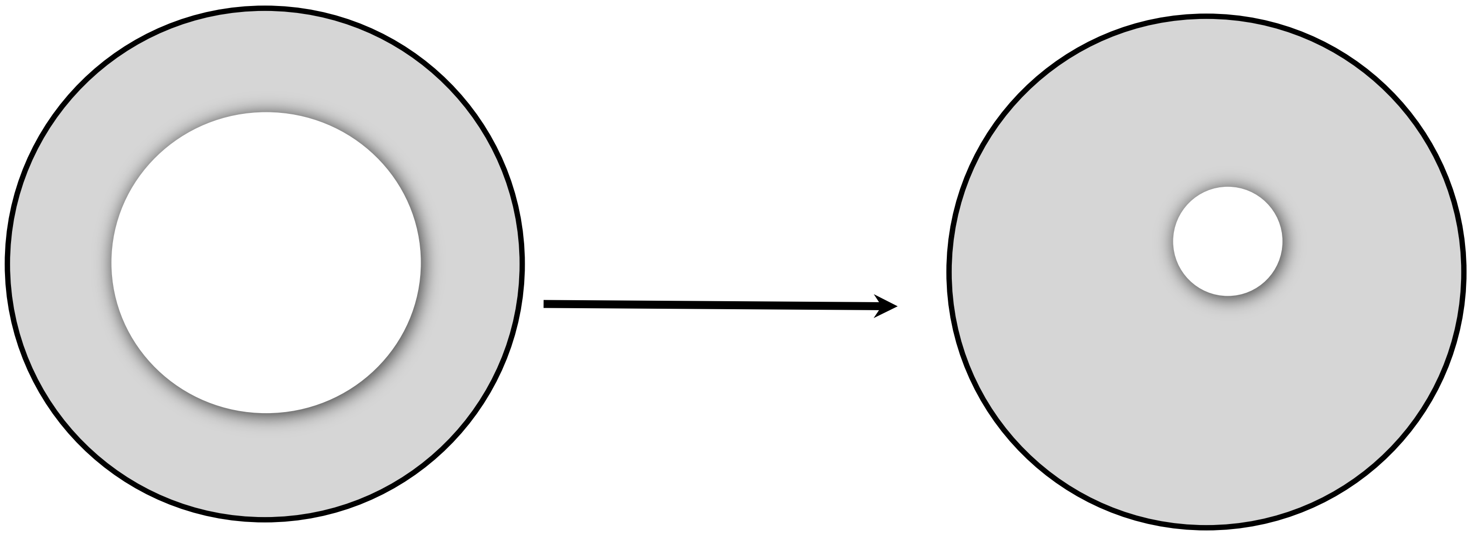


(Eisen et al., 1998, PNAS)

Knock-out studies

Yeast with one gene deleted

Growth?



Rich media

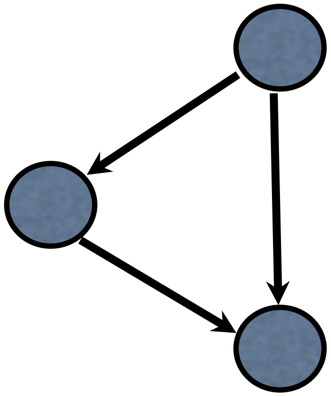
His$^-$ media

Network problems

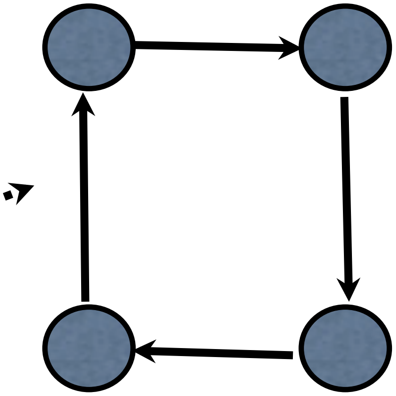
- Network inference
  - Given raw experimental data
  - Infer network structure
- Motif finding
  - Identify common subgraph topologies
- Module detection
  - Identify subgraphs of genes that perform the same function
- Network comparison/alignment
- Conserved modules
  - Identify modules that are shared in networks of multiple species

Network motifs

- Problem: Find subgraph topologies that are statistically more frequent than expected
- Brute force approach
    - Count all topologies of subgraphs of size m
    - Randomize graph (retain degree distribution) and count again
    - Output topologies that are over/under represented



Feed-forward loop: over-represented in regulatory networks



not very common

Network modules

- Modules: dense (highly-connected) subgraphs (e.g., large cliques or partially incomplete cliques)
- Problem: Identify the component modules of a network
- Difficulty: definition of module is not precise
  - Hierarchical networks have modules at multiple scales
  - At what scale to define modules?

Comparative network analysis

- Compare networks from different...
  - interaction detection methods
    - yeast 2-hybrid, mass spectrometry, etc.
  - conditions
    - heat, media, other stresses
  - time points
    - development, cell cycle
  - species

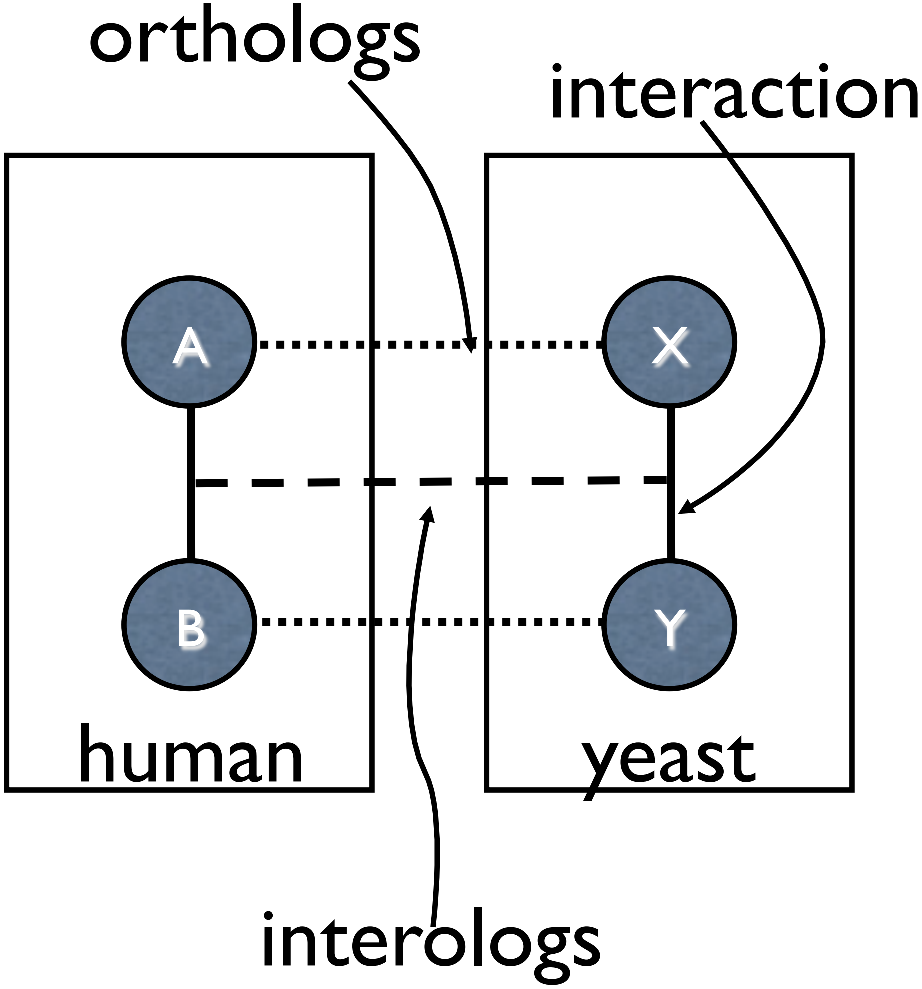
Comparative tasks

- Integration
    - Combine networks derived from different methods (e.g. experimental data types)
- Alignment
    - Identify nodes, edges, modules common to two networks (e.g., from different species)
- Database query
    - Identify subnetworks similar to query in database of networks

Conserved modules

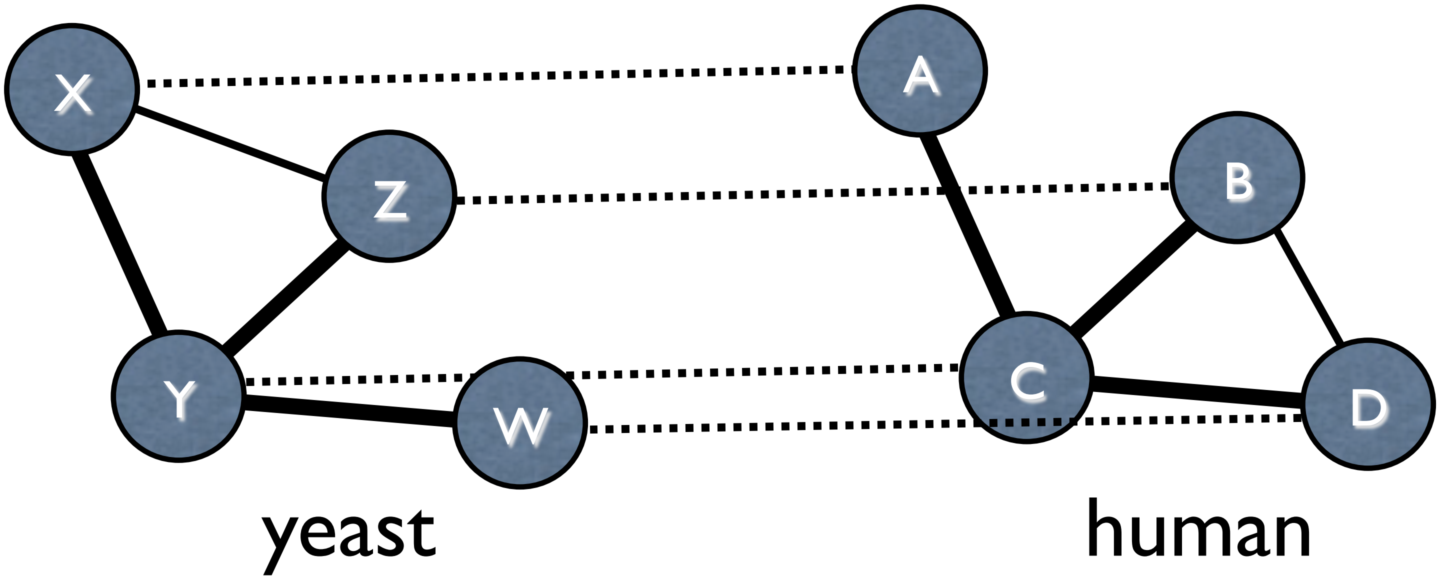
- Identify *modules* in multiple species that have “conserved” topology
- Typical approach:
  - Use sequence alignment to identify homologous proteins and establish correspondence between networks
  - Using correspondence, output subsets of nodes with similar topology

Conserved interactions



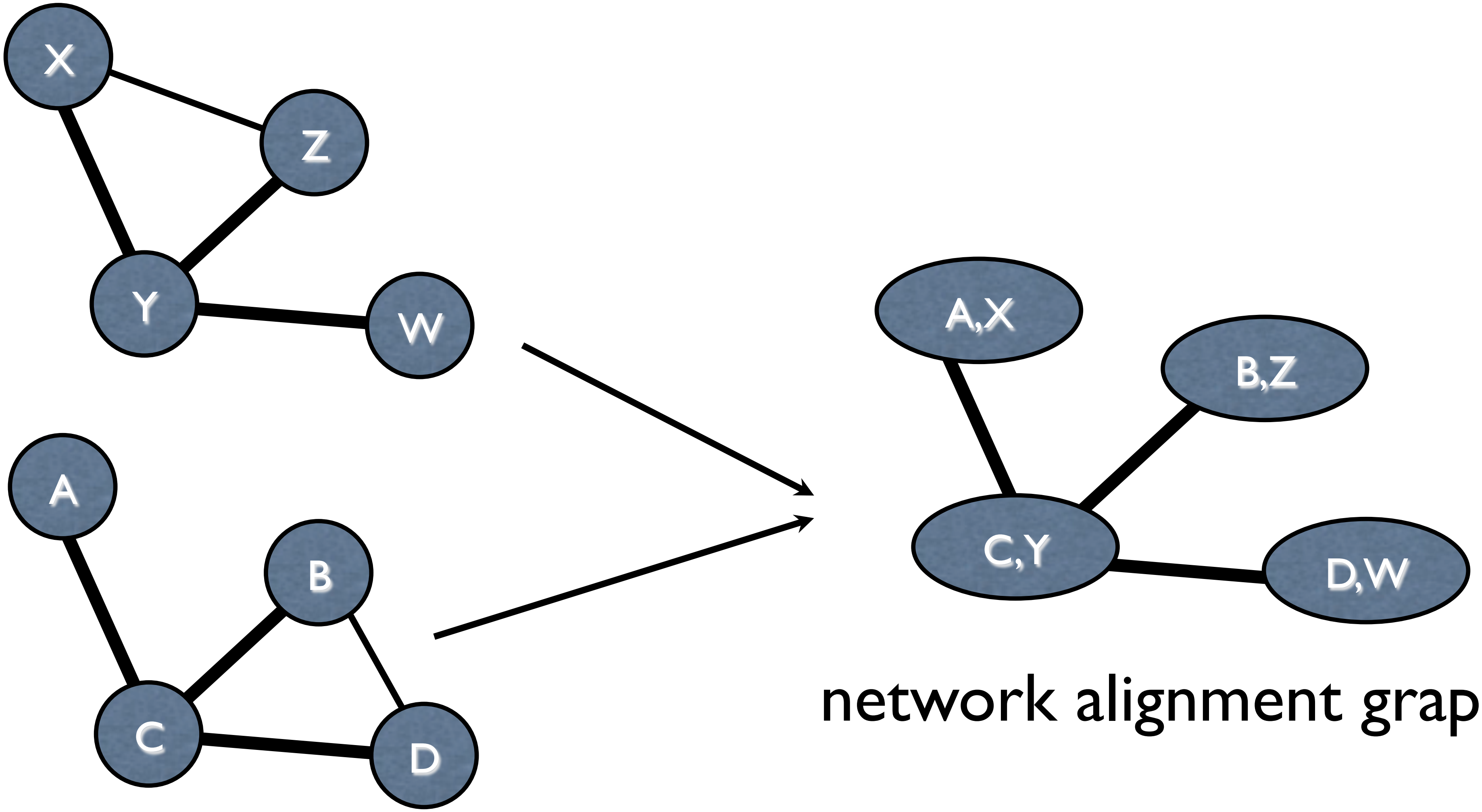
- Network comparison between species also requires sequence comparison
- Protein sets compared to identify orthologs
- Common technique: highest scoring BLAST hits used for establishing correspondences

Conserved modules



- Conserved module: orthologous subnetwork with significantly similar edge presence/absence

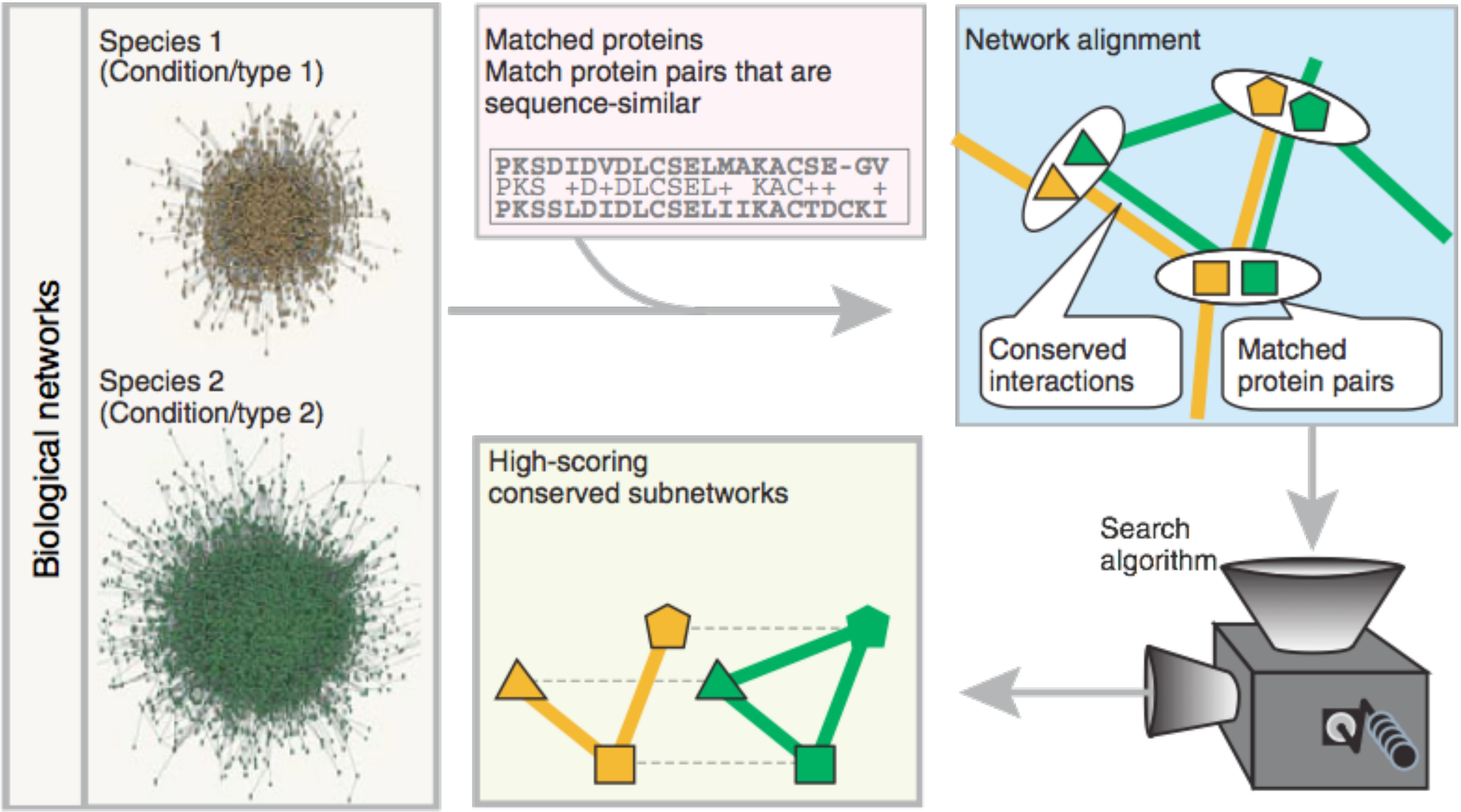
Network alignment graph



network alignment graph

- Analogous to pairwise sequence alignment

Conserved module detection



Biological networks

Species 1
(Condition/type 1)

Species 2
(Condition/type 2)

Matched proteins
Match protein pairs that are
sequence-similar

```
PKSDIDVDLCSELMAKACSE-GV
PKS +D+DLCSEL+ KAC++   +
PKSSLDIDLCSELIIKACTDCKI
```

Network alignment

Conserved
interactions

Matched
protein pairs

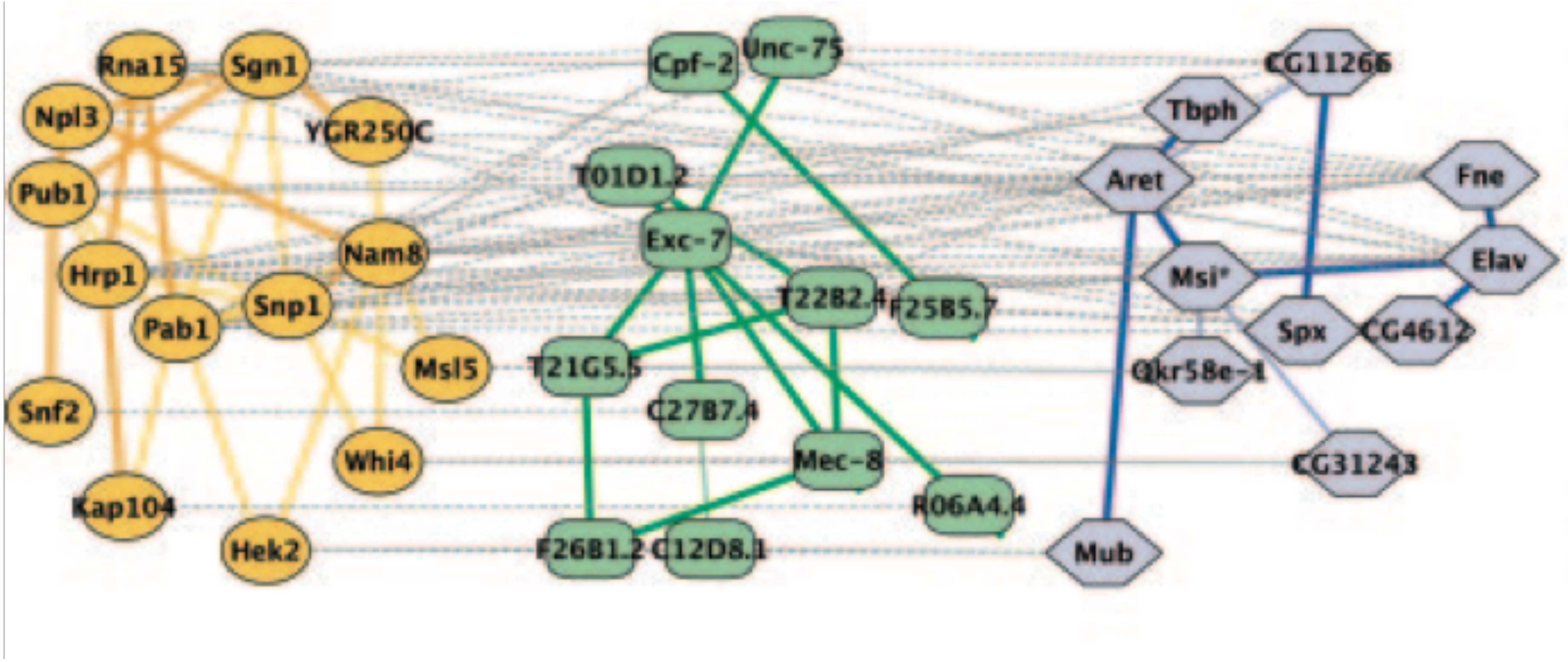
Search
algorithm

High-scoring
conserved subnetworks

(Sharan & Ideker, 2006)

Real module example

Module for RNA metabolism (Sharan et al., 2005)



🟨 yeast 🟩 worm 🟪 fly

- Note: a protein may have more than one ortholog in another network

Basic alignment strategy

- Define scoring function on subnetworks
  - high score ⇒ conserved module
- Use BLAST to infer orthologous proteins
- Identify “seeds” around each protein: small conserved subnetworks centered around the protein
- Grow seeds by adding proteins that increase alignment score

Scoring functions via Subnetwork modeling

- We wish to calculate the likelihood of a certain subnetwork U under different models
  - Subnetwork model (M_s)
    - Connectivity of U given by target graph H, each edge in H appearing in U with probability β (large)
  - Null model (M_n)
    - Each edge appears with probability according to random graph distribution (but with degree distribution fixed)

(Sharan et al., 2005)

Noisy observations

- Typically weight edges in graph according to confidence in interaction (expressed as a probability)
- Let
  - T_{uv}: event that proteins u, v interact
  - F_{uv}: event that proteins u, v do not interact
  - O_{uv}: observations of possible interactions between proteins u and v

Subnetwork model probability

- Assume (for explanatory purposes) that subnetwork model is a clique:

$$\begin{aligned}
Pr(O_U|M_s) &= \prod_{(u,v)\in U\times U} Pr(O_{uv}|M_s) \\
&= \prod_{(u,v)\in U\times U} [Pr(O_{uv}|T_{uv},M_s)Pr(T_{uv}|M_s) + Pr(O_{uv}|F_{uv},M_s)Pr(F_{uv}|M_s)] \\
&= \prod_{(u,v)\in U\times U} [\beta Pr(O_{uv}|T_{uv}) + (1-\beta)Pr(O_{uv}|F_{uv})]
\end{aligned}$$

Null model probability

- Given values for p_{uv}: probability of edge (u,v) in random graph with same degrees

$$Pr(O_U|M_n) = \prod_{(u,v)\in U\times U} [p_{uv}Pr(O_{uv}|T_{uv}) + (1-p_{uv})Pr(O_{uv}|F_{uv})]$$

- How to get random graph if we don't know true degree distribution? Estimate them:

$$d_i = \sum_j Pr(T_{ij}|O_{ij})$$

$$Pr(T_{uv}|O_{uv}) = \frac{Pr(O_{uv}|T_{uv})Pr(T_{uv})}{Pr(O_{uv}|T_{uv})Pr(T_{uv}) + Pr(O_{uv}|F_{uv})(1-Pr(T_{uv}))}$$

Likelihood ratio

- Score subnetwork with (log) ratio of likelihoods under the two models

$$\begin{aligned} L(U) &= \log \frac{Pr(O_U|M_s)}{Pr(O_U|M_n)} \\ &= \sum_{(u,v)\in U\times U} \log \frac{\beta Pr(O_{uv}|T_{uv}) + (1-\beta) Pr(O_{uv}|F_{uv})}{p_{uv} Pr(O_{uv}|T_{uv}) + (1-p_{uv}) Pr(O_{uv}|F_{uv})} \end{aligned}$$

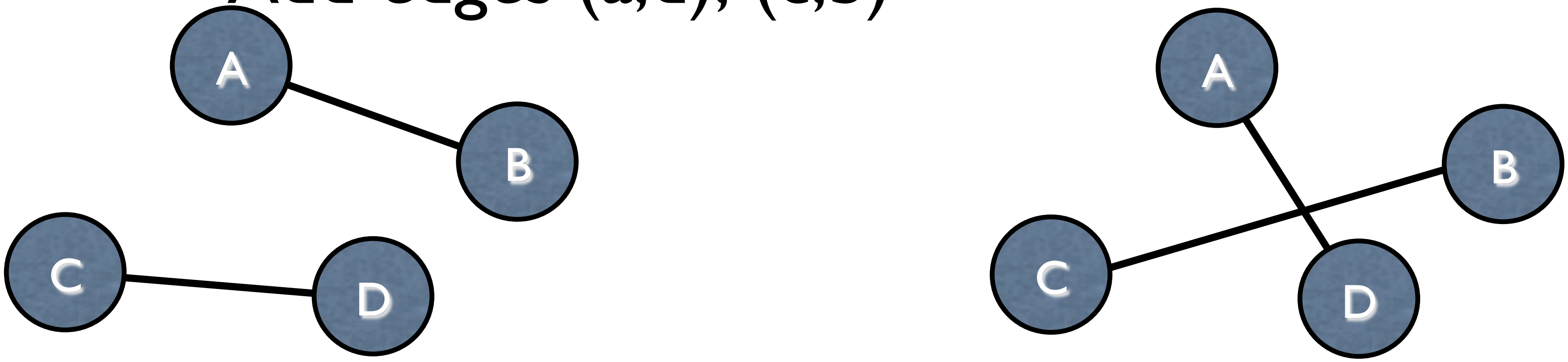
- Note the decomposition into sum of scores for each edge

Seed construction

- Finding “heavy induced subgraphs” is NP-hard (Sharan et al., 2004)
- Heuristic:
  - Find high-scoring subgraph “seeds”
  - Grow seeds greedily
- Seed techniques: for each node v:
  - Find heavy subgraph of size 4 including v
  - Find highest-scoring length 4 path with v

Randomizing graphs

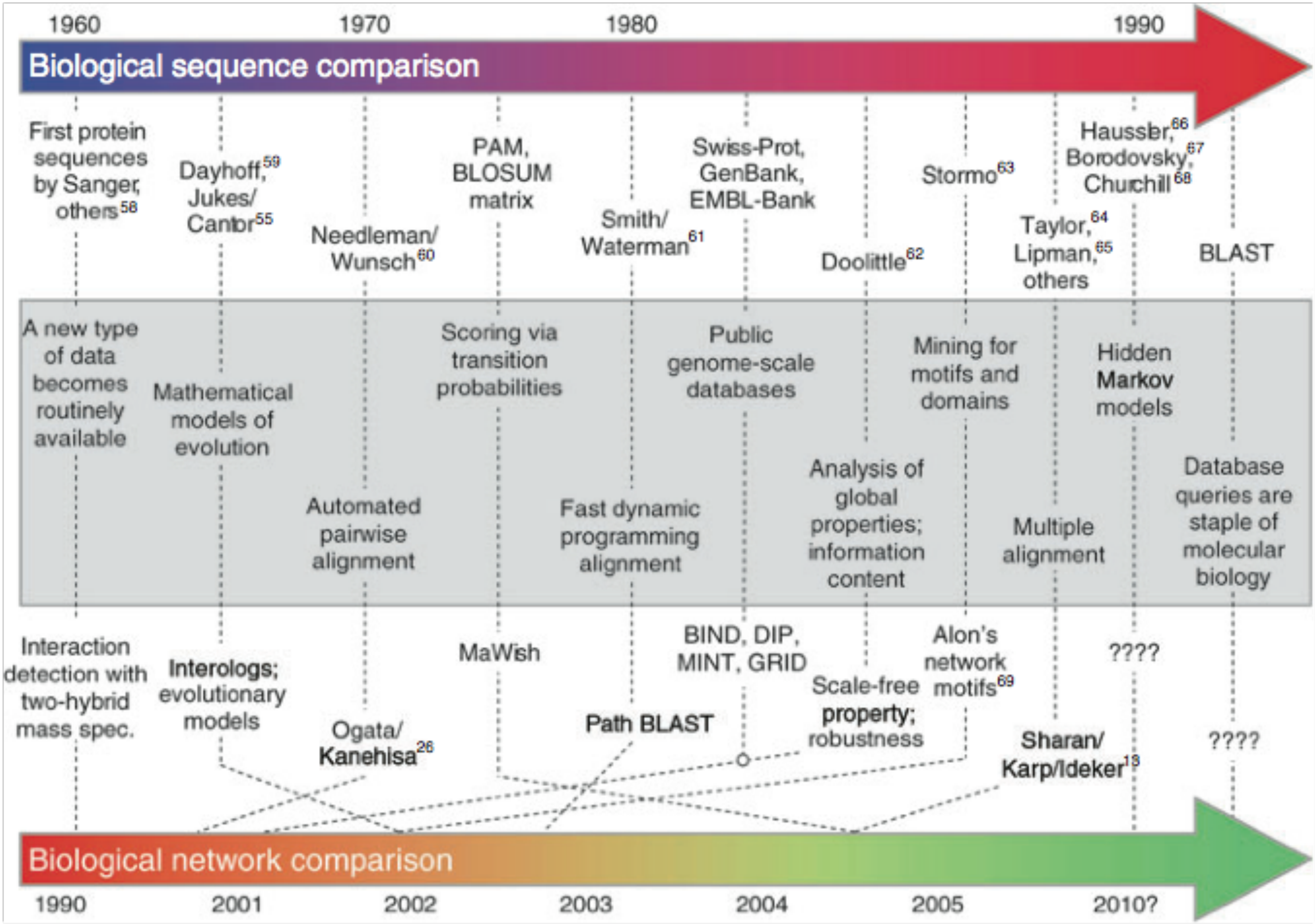
- For statistical tests, need to keep degree distribution the same
- Shuffle step:
  - Choose two edges (a,b), (c,d) in the current graph
  - Remove those edges
  - Add edges (a,d), (c,b)



Predictions from alignments

- Conserved modules of proteins enriched for certain functions often indicate shared function of other proteins
  - Use to predict function of unannotated proteins
  - Sharan et al., 2005: annotated 4,645 proteins with estimated accuracy of 58-63%
- Predict missing interactions
  - Sharan et al., 2005: 2,609 predicted interactions in fly, 40 –52% accurate

Parallels to sequence analysis



(Sharan & Ideker, 2006)