Spectral methods for Global Network Alignment

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Global Network Alignment stated formally

- Finding the optimal global alignment between two or more PPI networks, aims to find a correspondence between nodes and edges of the input networks that maximizes the overall ‘‘match’’ between the networks
- Every node in one network must be mapped to another node in the other network or marked as a gap
- That is, we want to find a single best mapping covering all nodes in the graph
- Furthermore, for >2 species, this alignment must be transitive
  - If a_1 is mapped to a_2 in species 2, and a_2 is mapped to a_3 and $a_{3'}$ in species 3, a_1 must be mapped to a_3 and $a_{3'}$.

Motivation of the IsoRank algorithm

- Previous approaches have used a local and pairwise alignment approaches
- Limit the possible node mappings between species and then bring in networks to do the alignment
  - "..Lacks the flexibility of producing node-pairings that diverge from sequence-only predictions."

IsoRank overview

- An algorithm for inferring the global alignment of more than two networks
- Unlike existing algorithms which use sequence similarity first to define the mapping, IsoRank simultaneously uses both the network and the sequence similarity to define node mappings
- Key intuition: a protein in one network is a good match to a protein in another network if it is similar in sequence and its network neighborhood
- Such proteins are said to be “functionally similar” to each other across species
- The IsoRank algorithm uses eigenvalue problem to estimate the functional similarity score

Notation

- $G_k=(V_k,E_k)$ is a graph of $|V_k|$ vertices and $|E_k|$ edges for species k.
- G_k corresponds to a protein-protein interaction (PPI) network for a species k
- Edges can be weighted : $w(e)$ denotes weight of an edge e
- For a node i in V_k, $N(i)$ denotes the neighbors of i in G_k
- For two graphs G_1 and G_2, R is a $|V_1|$ by $|V_2|$ matrix where each entry R_{ij} specifies the functional similarity score of protein node j in G_1 and node j in G_2.

Two Key steps IsoRank algorithm

- Estimate the functional similarity score R that is based on network and sequence similarity for all pairs of networks
- Use R to define node mappings and to identify subgraphs that represents the conserved parts of the network

Pairwise Global Network Alignment with IsoRank

- Let us first consider the simple case of aligning two graphs, G_1 and G_2
- IsoRank has two steps
  - Estimate the functional similarity score R_{ij} that is based on network and sequence similarity of proteins i *in* V_1 and j in V_2
  - Use R to define node mappings and to identify subgraphs that represents the conserved parts of the network
    - This uses a greedy approach that starts with a seed from a bi-partite graph and grows it until no more edges can be added

Defining the functional similarity R_{ij}

- We will first consider the simple case of estimating this from the networks alone
- Assume the networks are unweighted
- R_{ij} is computed for every pair of nodes i and j where i is in V_1 and j in V_2

$$R_{ij} = \sum_{u \in N(i)} \sum_{v \in N(j)} \frac{1}{|N(u)||N(v)|} R_{uv}$$

Neighbors of i

- R_{ij} should capture a similarity based on i and j's neighborhoods in G_1 and G_2 respectively

Defining the functional similarity R_{ij} for weighted graphs

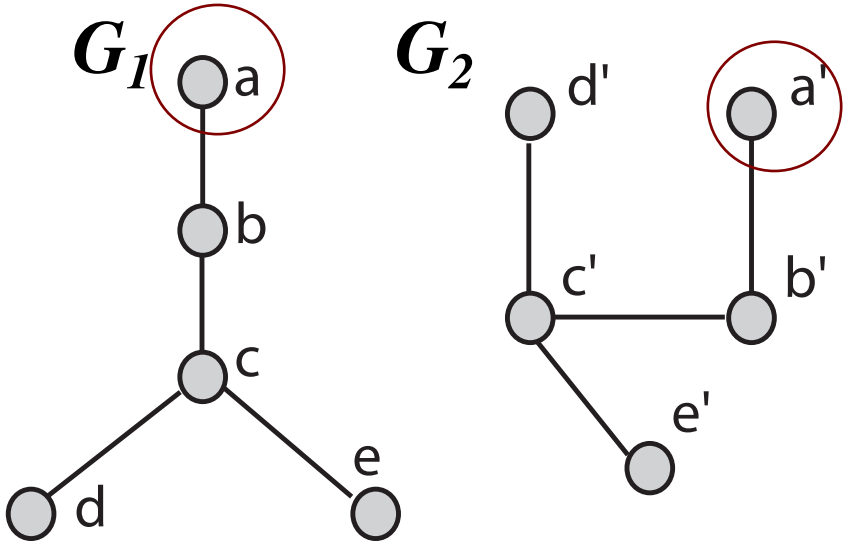
- Let $w(i,u)$ denote the weight of edge (i,u) in G_1, $0 \leq w(i,u) \leq 1$
- Let $w(j,v)$ denote the weight of edge (j,v) in G_1
- Here R_{ij} is defined as

$$R_{ij} = \sum_{u \in N(i)} \sum_{v \in N(j)} \frac{w(i,u)w(j,v)}{\sum_{p \in N(u)} w(u,p) \sum_{q \in N(v)} w(v,p)} R_{uv}$$

Instead of the size of the neighborhood, we use a weighted sum over all nodes in the neighborhood of u

Computing R_{ij} with two 5 node networks

$N(a)=\{b\}$
$N(a')=\{b'\}$

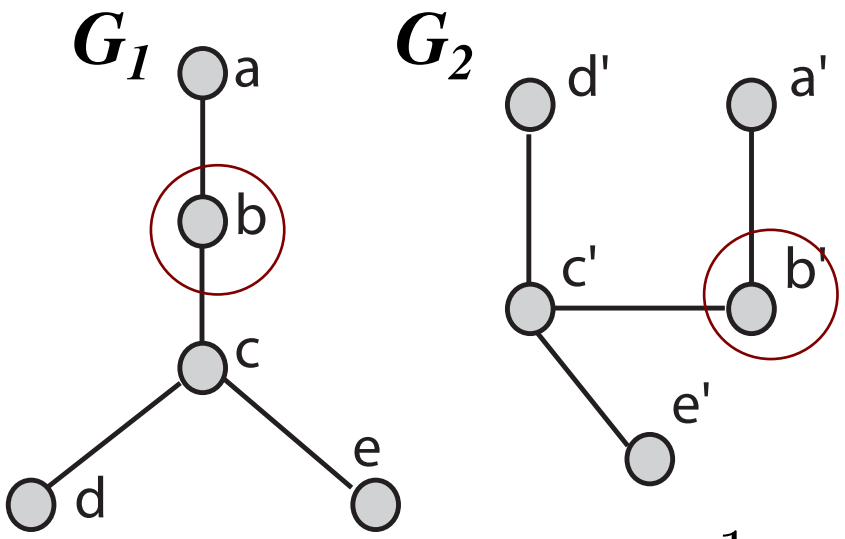


$$R_{aa'} = \frac{1}{|N(b)||N(b')|} R_{bb'}$$

$$R_{aa'} = \frac{1}{4} R_{bb'}$$

Computing R_{ij} with two 5 node networks

$N(b)=\{a,c\}$
$N(b')=\{a',c'\}$

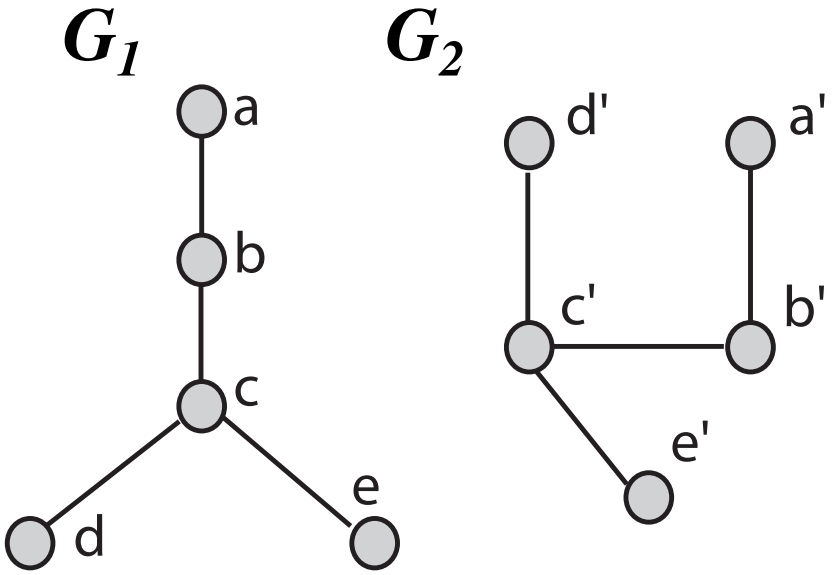


$$R_{bb'} = \sum_{u \in N(b)} \sum_{v \in N(b')} \frac{1}{|N(u)||N(v)|} R_{uv}$$

$$R_{bb'} = \frac{1}{|N(a)||N(a')|} R_{aa'} + \frac{1}{|N(a)||N(c')|} R_{ac'} + \frac{1}{|N(c)||N(a')|} R_{ca'} + \frac{1}{|N(c)||N(c')|} R_{cc'}$$

$$R_{bb'} = \frac{1}{1} R_{aa'} + \frac{1}{3} R_{ac'} + \frac{1}{3} R_{ca'} + \frac{1}{9} R_{cc'}$$

Similarly for the other node pairs



Only a partial set of scores are shown

R

	a'	b'	c'	d'	e'
a	0.0312		0.0937		
b		0.1250		0.0625	0.062
c	0.0937		0.2812		
d		0.0625		0.0312	0.031
e		0.0625		0.0312	0.031

$$R_{aa'} = \frac{1}{4} R_{bb'}$$

$$R_{bb'} = \frac{1}{3} R_{ac'} + \frac{1}{3} R_{a'c} + R_{aa'} + \frac{1}{9} R_{cc'}$$

$$R_{dd'} = \frac{1}{9} R_{cc'}$$

$$R_{cc'} = \frac{1}{4} R_{bb'} + \frac{1}{2} R_{be'} + \frac{1}{2} R_{bd'} + \frac{1}{2} R_{eb'} + \frac{1}{2} R_{db'} + R_{ee'} + R_{ed'} + R_{de'} + R_{dd'}$$

Rewriting R in matrix form

- Let A be a matrix with $|V_1|*|V_2|$ rows and $|V_1|*|V_2|$ columns
- Each row of $A[i,j]$ corresponds to a pair of nodes (i,j) where i is from V_1 and j is from V_2
- Each column of A corresponds to a pair of nodes (u,v) where u is from V_1 and v is from V_2

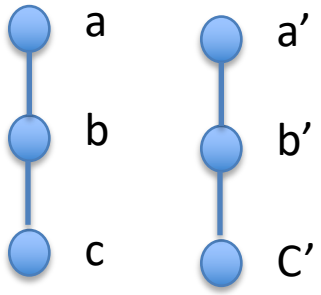
$$A[i,j][u,v] = \begin{cases} \frac{1}{|N(u)||N(v)|}, & \text{if}(i,u) \in E_1, (j,v) \in E_2 \\ 0 \text{ otherwise} \end{cases}$$

- In matrix form we have

$$R = AR$$

- Thus R is the eigen vector of A, with eigen value 1

$\boldsymbol{R}$ is the eigen vector of a specific matrix



$$A[i,j][u,v] = \begin{cases} \frac{1}{|N(u)||N(v)|}, & \text{if}(i,u) \in E_1, (j,v) \in E_2 \\ 0 \text{ otherwise} \end{cases}$$

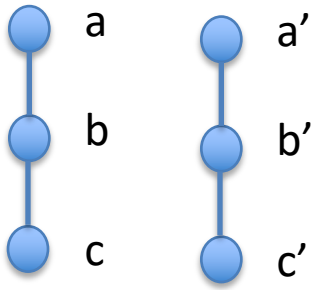
$\boldsymbol{A}$

$\boldsymbol{R}$

	$R_{aa'}$
a a'	
a b'	$R_{ab'}$
a c'	$R_{ac'}$
b a'	$R_{ba'}$
b b'	$R_{bb'}$
b c'	$R_{bc'}$
c a'	$R_{ca'}$
c b'	$R_{cb'}$
c c'	$R_{cc'}$

	a a'	a b'	a c'	b a'	b b'	b c'	c a'	c b'	c c'
a a'	0	0	0	0	0.25	0	0	0	0
a b'	0	0	0	0.5	0	0.5	0	0	0
a c'	0	0	0	0	0.25	0	0	0	0
b a'	0	0.5	0	0	0	0	0	0.5	0
b b'	1	0	1	0	0	0	1	0	1
b c'	0	0.5	0	0	0	0	0	0.5	0
c a'	0	0	0	0	0.25	0	0	0	0
c b'	0	0	0	0.5	0	0.5	0	0	0
c c'	0	0	0	0	0.25	0	0	0	0

R is the eigen vector of A



$$R_{bb'} = \frac{1}{|N(a)||N(a')|}R_{aa'} + \frac{1}{|N(a)||N(c')|}R_{ac'} + \frac{1}{|N(c)||N(a')|}R_{ca'} + \frac{1}{|N(c)||N(c')|}R_{cc'}$$

$$R_{bb'} = R_{aa'} + R_{ac'} + R_{ca'} + R_{cc'}$$

$R_{bb'}$ from the matrix form

- Let's check if we get the same answers

	R^{new}
a a'	$R_{aa'}$
a b'	$R_{ab'}$
a c'	$R_{ac'}$
b a'	$R_{ba'}$
b b'	$R_{bb'}$
b c'	$R_{bc'}$
c a'	$R_{ca'}$
c b'	$R_{cb'}$
c c'	$R_{cc'}$

	a a'	a b'	a c'	b a'	b b'	b c'	c a'	c b'	c c'	R^{old}
a a'	0	0	0	0	0.25	0	0	0	0	$R_{aa'}$
a b'	0	0	0	0.5	0	0.5	0	0	0	$R_{ab'}$
a c'	0	0	0	0	0.25	0	0	0	0	$R_{ac'}$
b a'	0	0.5	0	0	0	0	0	0.5	0	$R_{ba'}$
b b'	1	0	1	0	0	0	1	0	1	$R_{bb'}$
b c'	0	0.5	0	0	0	0	0	0.5	0	$R_{bc'}$
c a'	0	0	0	0	0.25	0	0	0	0	$R_{ca'}$
c b'	0	0	0	0.5	0	0.5	0	0	0	$R_{cb'}$
c c'	0	0	0	0	0.25	0	0	0	0	$R_{cc'}$

$$R^{new}_{bb'} = R^{old}_{aa'} + R^{old}_{ac'} + R^{old}_{ca'} + R^{old}_{cc'}$$

Estimating R

- This is an eigen value problem
- A is a stochastic matrix (columns of A sum to 1)
- R can be found using the *power method*
- The power method repeatedly updates R at iteration $k+1$ as follows

$$R(k+1) = AR(k)/|AR(k)|$$

Adding sequence similarity to R

- We can integrate other types of information in the same framework
- Let B be a $|V_1|*|V_2|$ matrix where each entry B_{ij} is the sequence similarity of i and j
- Let E be the normalized version of B, E=B/BB|
- R can be redefined as

$$R = \alpha AR + (1-\alpha)E$$

- This too can be solved with an eigen value problem

$$R = \alpha AR + (1-\alpha)E\mathbf{1}^T R$$

$\mathbf{1}^{\mathrm{T}}$ is a vector of all ones

$$R = (\alpha A + (1-\alpha)E\mathbf{1}^T)R$$

Multiple GNA

- Extension to more than two networks is straightforward
- For every pair of graphs G_m, G_n, estimate R^{mn}

Two Key steps IsoRank algorithm

- Estimate the functional similarity score R that is based on network and sequence similarity for all pairs of networks
- Use R to define node mappings and to identify subgraphs that represents the aligned parts of the network

Extracting the aligned parts

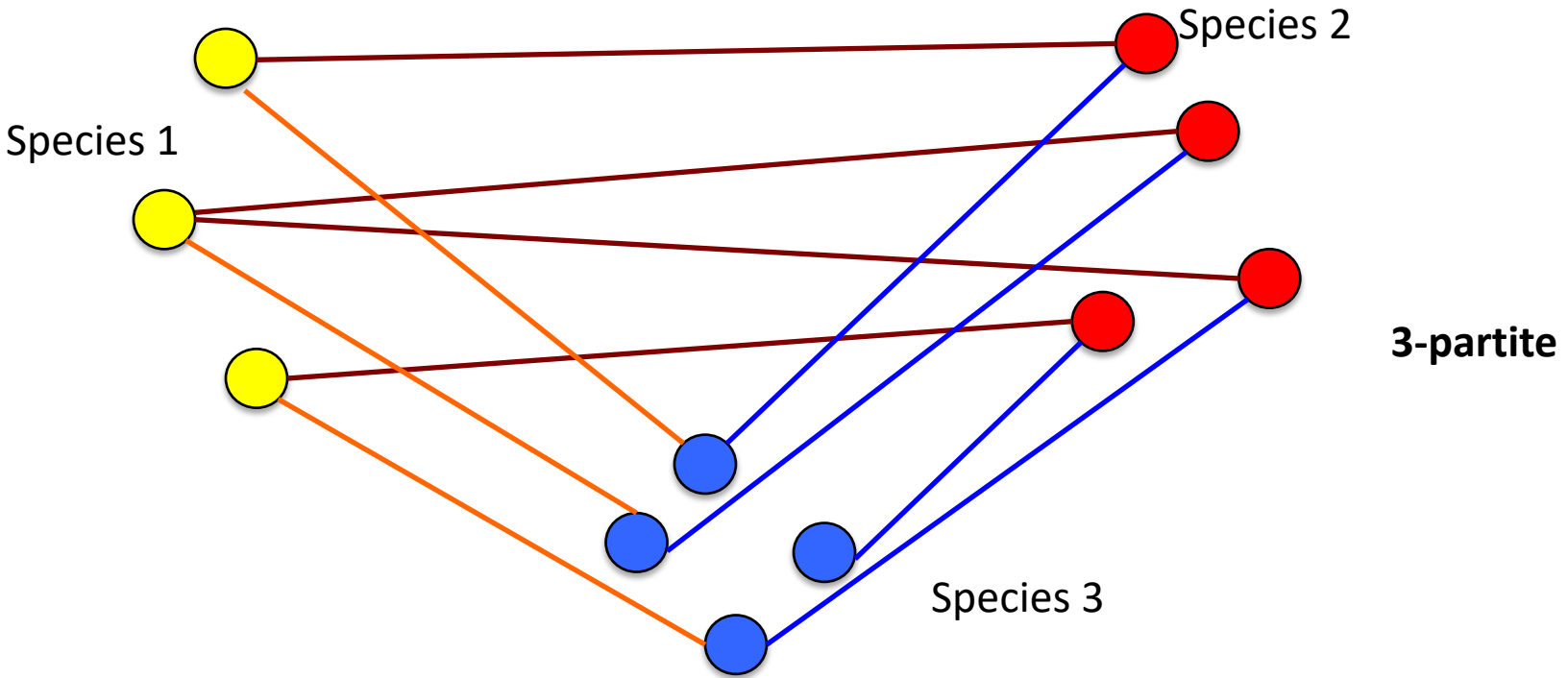
- Once R is estimated for all pairs of networks, we need to extract out node pairs with the highest values
  - 99% of the entries of R will be zero
- Two ways to do this
  - One to One mapping
    - For each node, map it to at most one other node
    - Computationally efficient but ignores gene duplications
  - Many to Many mapping

Many to many mapping

- The goal here is to extract groups with multiple genes from the same species
- Each group represents an functional similarity between genes of one species to genes of another species
- Each set has the following property
  - Each gene in the set has high pairwise R scores with most other genes in the set
  - there are no genes outside each set with this property
  - there are a limited number of genes from each species
- Identified via greedy algorithm

Greedy algorithm for finding aligned parts

- Construct a k-partite graph.
  - Each part k has nodes from each species
  - Allow nodes to interact between different parts
- Extract a high confidence edge expand to connected neighbors



Greedy algorithm to find many-many node mappings

- Input k-partite graph H, b_1, b_2, r
- Repeat until no more edges are in H
  - Select an edge with the highest score (i,j), where i is G_1 and j is in G_2 to initialize a match-set
  - Grow (i,j) to create the primary match-set. This is the max k-partite matching
  - Primary match set is a set of nodes with at most 1 node from a species using b_1 to control the similarity
    - For all other graphs G_3.. G_k, add a node l if two conditions hold

      (*i*) R_{il} and R_{jl} are the highest scores between l and any node in G_1 and G_2, respectively and,

      (*ii*) the scores $R_{il} \geq b_1 R_{ij}$, and $R_{jl} \geq b_1 R_{ij}$,

- Add upto $(r-1)$ nodes v based on b_2, such that there exists u, w in the primary set and $R_{vw} \geq b_2 R_{uw}$
- Remove this set from H

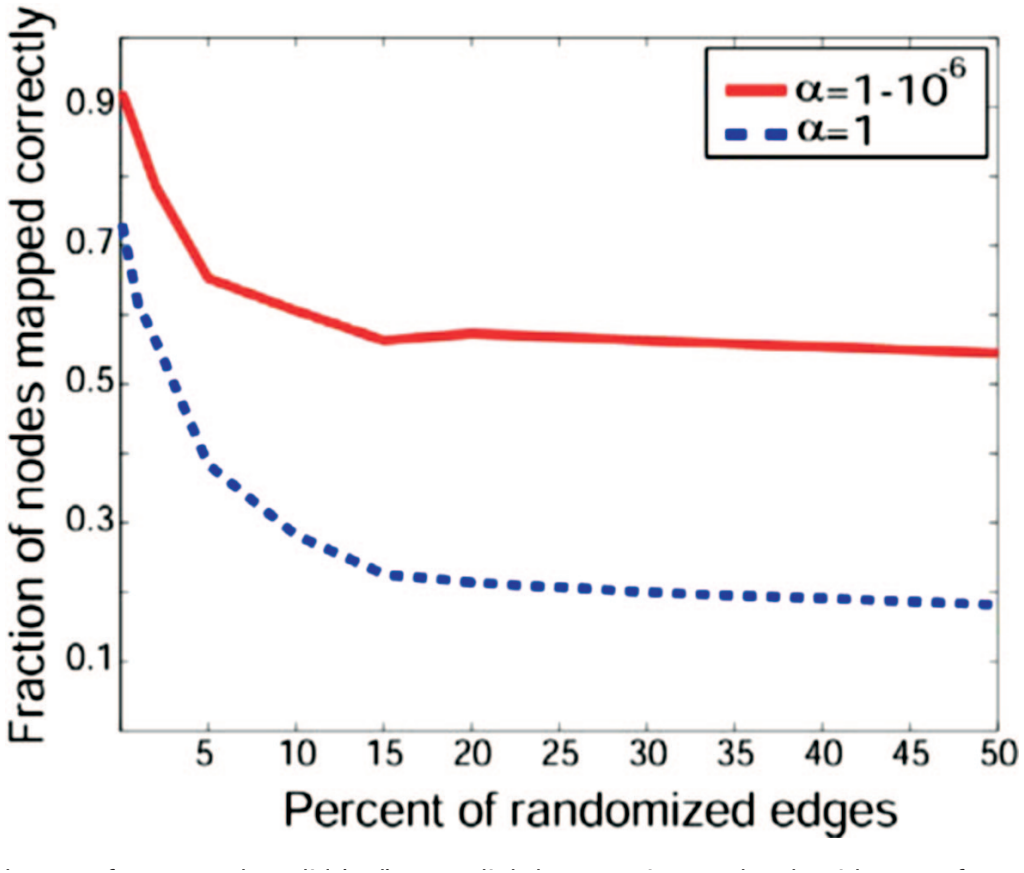
Results

- Global alignment of multiple protein-protein interaction networks
  - Yeast, human, fly, mouse, worm
- Assess functional coherence of predicted functional orthologs

Alignment results of five PPI networks

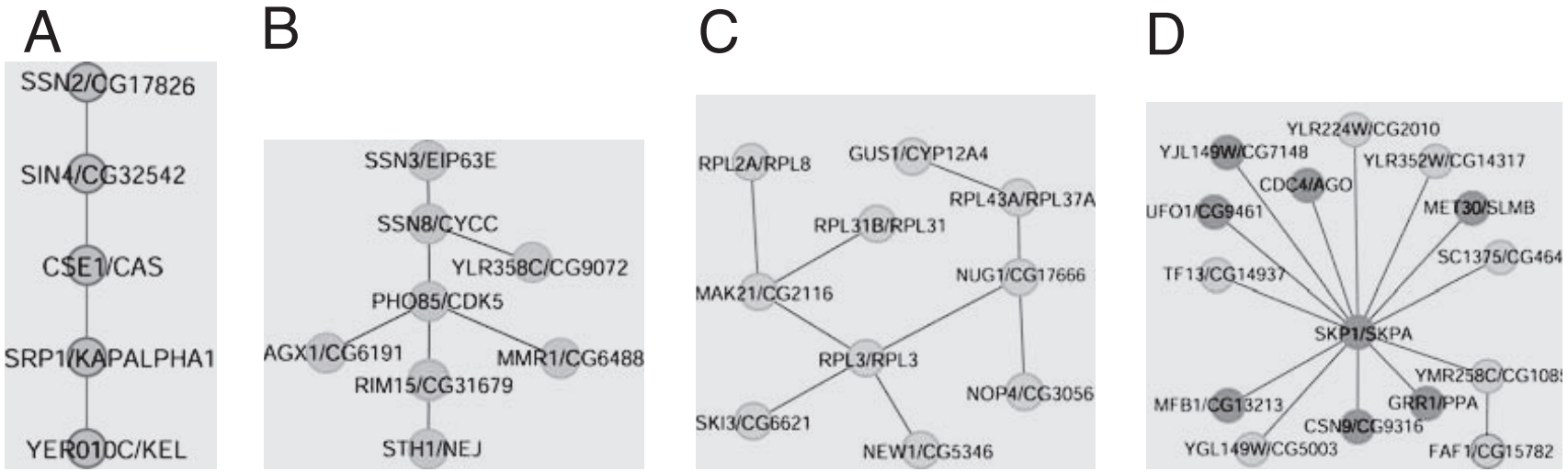
- Common subgraph has 1,663 edges supported by at least 2 networks and 157 edges by at least 3
- Very few edges from all species
  - It is possible that the networks are too noisy and incomplete
- But this is much better than a pure sequence only mapping
  - 509 edges would be identified in two or more species with 40 in three species

IsoRank framework is robust to noisy data



Experiments done on a PPI network of 200 nodes. Randomized graphs obtained by swapping pairs of edges

Yeast-fly GNA exhibit subgraphs of different topologies



IsoRank predictions of functional orthology

- The output of IsoRank can be used to define “functional orthologs”(FO)
- Of the 86,932 proteins from the five species, 59,539 (68.5%) of the proteins were matched to at least one protein in another species (i.e., had at least one FO).
- In contrast, sequence orthology maps only 38.5% of the proteins.

How good are functional orthologs?

- Use functional coherence measure
  - Obtain sets of orthologous proteins (each set is made up of proteins from different species) and select sets with the majority(80%) of the proteins with a GO annotation
  - For each such set P,
    - Collect all GO terms associated with the proteins in P.
    - Compute a similarity between each pair of GO terms based on the similarity of the gene content of each term (this is the Jaccard coefficient of the annotated proteins)
    - Take a median of all pairs of similarity
  - Functional coherence for the input ortholog list is the mean of the coherence per set

Functional orthologs from IsoRank are comparable to sequence based orthology

- Functional coherence for IsoRank: 0.22
- Functional coherence for Homologene: 0.223
- Functional coherence for InParanoid: 0.206

Summary

- IsoRank is a global alignment algorithm
- How does it differ from PATHBLAST?
  - Identifies different types of subnetworks
  - Uses a global alignment
  - Applicable to multiple networks
- How is it similar Sharan 2004?
  - Search and score of subnetworks is done similarly