# Graph theory and biological networks

November 26, 2013

# Hybrid system

## Graph theory
graphlet representation

## Biological discoveries
Infer protein functions

Understand underlying mechanisms of disease

*http://www.toyota.ca/toyota/en/vehicles/prius/gallery*

# Outline

- Introduction
- Network properties
- An example of relationship between network properties and disease
- Biological network comparisons
- Uncovering biological network function
- Conclusion

# Introduction

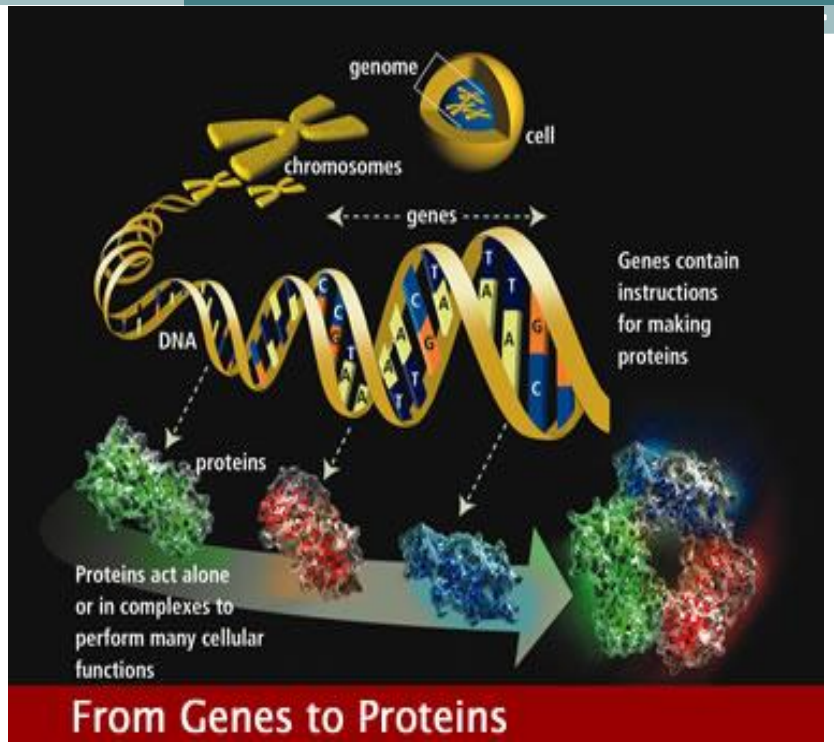
# Biological networks

**Vertices: proteins**
**Edges: physical interactions**

- Traditionally, individual cellular components and their functions are studied
- most biological functions are due to interactions between different cellular constituents
- various networks have emerged including protein-protein interactions networks.

*(H. Jeong et al., 2001) Lethality and centrality in protein networks, H.Jeong et al., 2001*

# Central dogma




http://www.ornl.gov/sci/techresources/Human_Genome/project/info.shtml

**DNA (segments of DNA, 'genes')**

**Transcription**

**mRNA (mRNA abundance detected using microarrays)**

**Translation**

**Protein**

(H. C. Causton et al., 2003) *Figure 1.2 (partial) from Ch 1 of Microarray Gene Expression Data Analysis*

# Definitions

- **Definition 1:**
  Let G(V,E) denotes a graph where V is the set of vertices, and E, $E \subseteq V \times V$, is the set of edges in G

- **Definition 2:**
  Let x and y be vertices from G. y is adjacent to x if there is an edge between x and y, and y is a neighbor of x. Let N(x) denote the set of vertices that are adjacent to x, and N(x) is the neighborhood of x

- **Definition 3:**
  A degree of a vertex, x, d(x) is the number of incident edges to x

- **Definition 4:**
  An induced subgraph, H, is a subgraph such that E(H) consists of all edges that are connected to V(H) in G

# Network properties

# Global network properties versus local network properties

**Global network properties**

- Look at the overall network
- PPI networks are incomplete, and contain bias

**Local network properties**

- Focus on local structures or patterns
- Can measure properties in local regions even though networks are incomplete

# Global network properties

- Degree distribution, P(k)
  - is the probability in which any randomly selected vertex has degree k
- Diameter
  - the maximum shortest path length between any pair of vertices. Often, it is the average shortest path length between all pairs of vertices
- Centrality measures

# Centrality measures – degree centrality

**degree centrality of vertex $u$:**

$$C_d(u) = d(u)$$

# Centrality measures – closeness centrality

**center of $G$:**

$$Cen(G) = \{x \in V | e(x) = r(G)\}$$

**excentricity of $x$:**

$$e(x) = \max_{y \in V} d(x, y)$$

**radius of $G$:**

$$r(G) = \min_{x \in V} e(x)$$

# Centrality measures – betweenness centrality

**betweenness centrality of vertex $w$:**

$$\{u, v, w \in V | u \neq v, v \neq w\}$$

$$BC(w) = \sum_{u,v \in V} \frac{S_{uv}(w)}{S_{uv}}$$

**$S_{uv}(w)$ is the number of geodesic paths between $u$ and $v$ that pass through $w$**

**$S_{uv}$ is the number of geodesic paths between $u$ and $v$**

# Local network properties

**Motifs**

- Small subgraphs in a network whose patterns appear significantly more than in randomized networks
- Do not take into account patterns that appear with average or low frequency
- Depend on randomization scheme

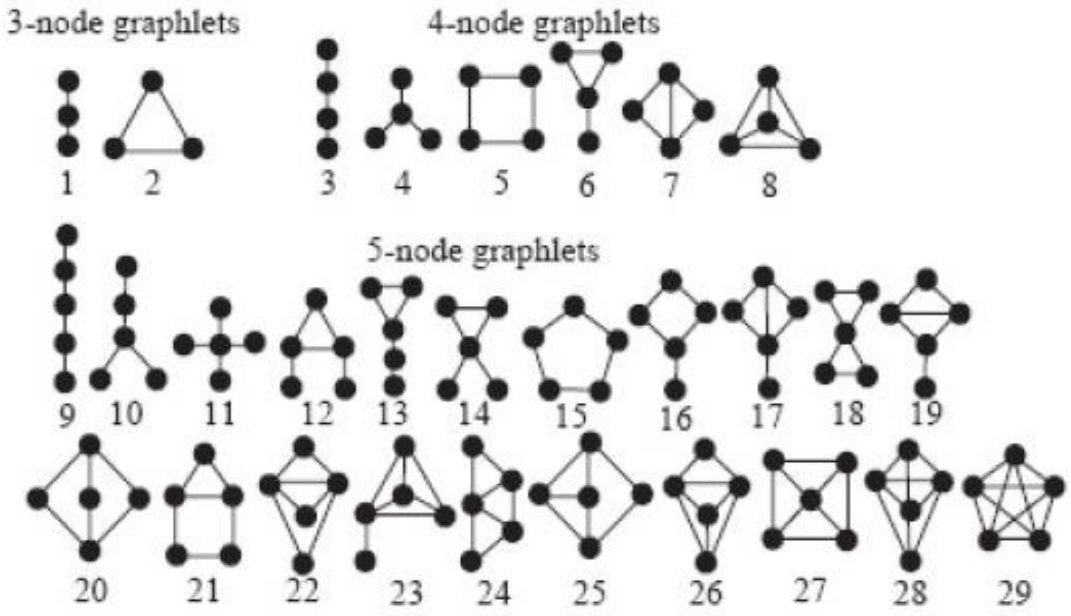
*(R. Milo et al, 2002)*

**Graphlets**

- All non-isomorphic connected induced graphs on a certain number of vertices
- Identify all structures, not only the over-represented ones

*(N. Pržulj et al. 2004b)*

# Graphlets




**Not limited to 3-5 node graphlets!**

All 3 to 5 node graphlets, graphlet No. 1 to 29. Fig. 1 of Modeling interactome: scale-free or geometric.

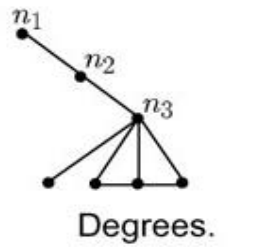
*(N. Pržulj et al. 2004b)*

# An example of relationship between network properties and disease

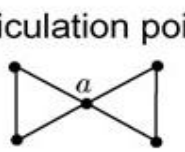
# Protein essentiality

*Minimum spanning tree (MST)*: an acyclic connected subgraph that contains all the vertices of the graph, and the edges that give the minimum sum of edge weights

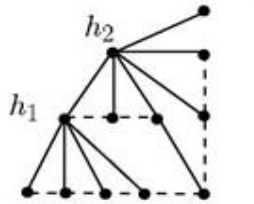
*Hubs*: highly connected vertices in the MST



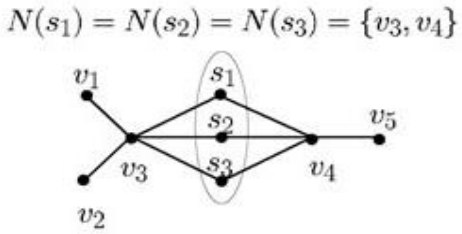

Degrees.




*Articulation point* is a vertex that, if removed, results in a disconnected graph




Hubs: $h_1$ and $h_2$.



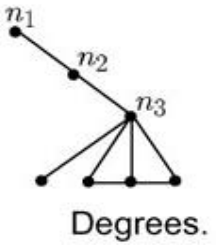

Siblings: $s_1, s_2$, and $s_3$.

If 2 vertices have the same neighborhood, then they are *siblings*

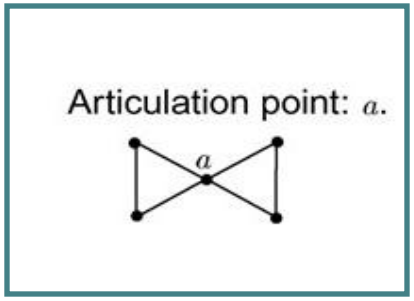
*(N. Pržulj et al., 2004)* Graph theoretic properties. Partial Fig. 1B of Functional topology in a network of protein interactions

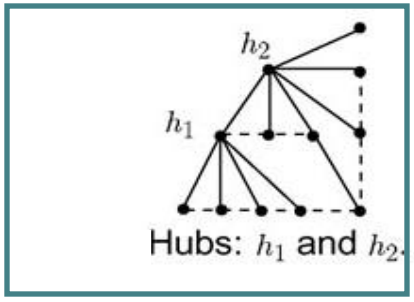
# Protein essentiality

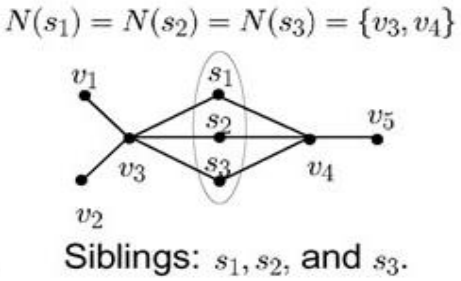
Lethal proteins: more frequent in the top 3% of degree vertices
Viable proteins: more frequent in the vertices with degree 1




Degrees.




Lethal proteins were not only hubs, but they were articulation points

Viable proteins were more frequent in the group of vertices that belonged to the sibling group

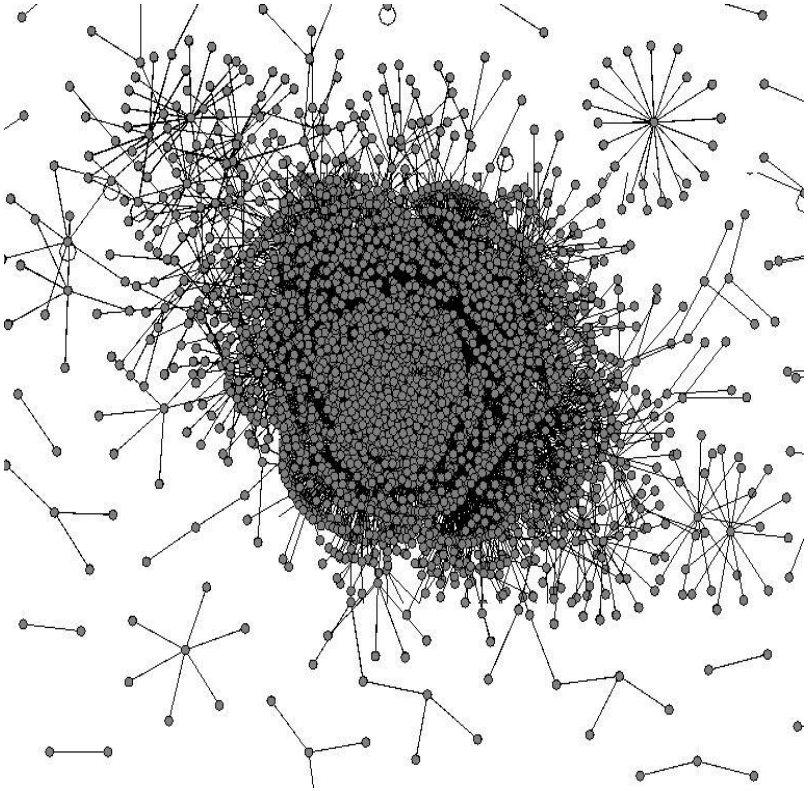
Graph theoretic properties. Partial Fig. 1B of Functional topology in a network of protein interactions

*(N. Pržulj et al., 2004)*

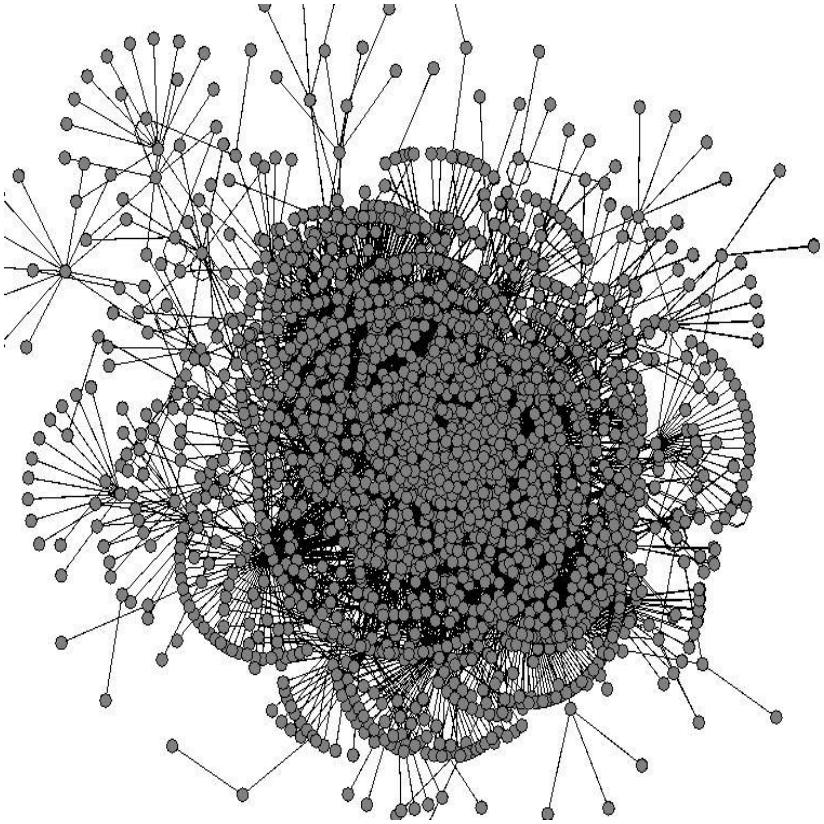
# Grahplets

# Biological network comparisons

# Biological network comparisons



Network 1



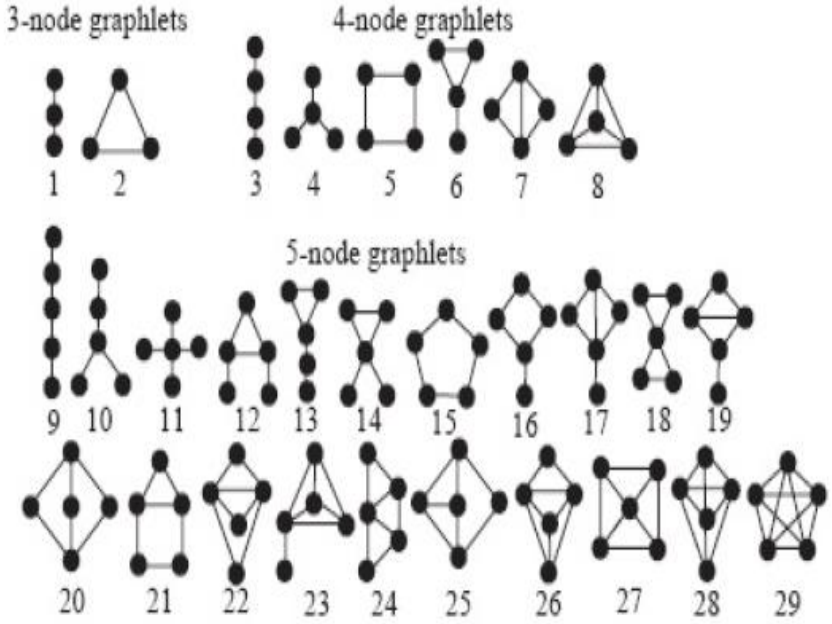
Network 2

# Graphlets

- 2 local measures based on graphlets have developed
  - Relative graphlet frequency distance (RGF-distance)
  - Graphlet degree distribution agreement (GDD-agreement)

*(N. Pr˘zulj et al. 2004b, N. Pr˘zulj 2007 )*

# Graphlet frequency




All 3 to 5 node graphlets, graphlet No. 1 to 29. Fig. 1 of Modeling interactome: scale-free or geometric

- The count of how many graphlets of each type (ranging from 1 to 29)
- Not limited to 3 to 5 node graphlets
- If more graphlets can be computed, a greater number of local constrains are imposed on similarity measures

*(N. Pržulj et al. 2004b)*

# Relative graphlet frequency

**relative frequency of graphlets is defined to be:** $\frac{N_i(G)}{T(G)}$

$N_i(G)$ is the number of graphlets of type $i$, $i \in [1, ..., 29]$ in graph $G$

$T(G) = \sum_{i=1}^{29} N_i(G)$

*(N. Pržulj et al. 2004b)*

# Relative graphlet frequency distance (RGF – distance)

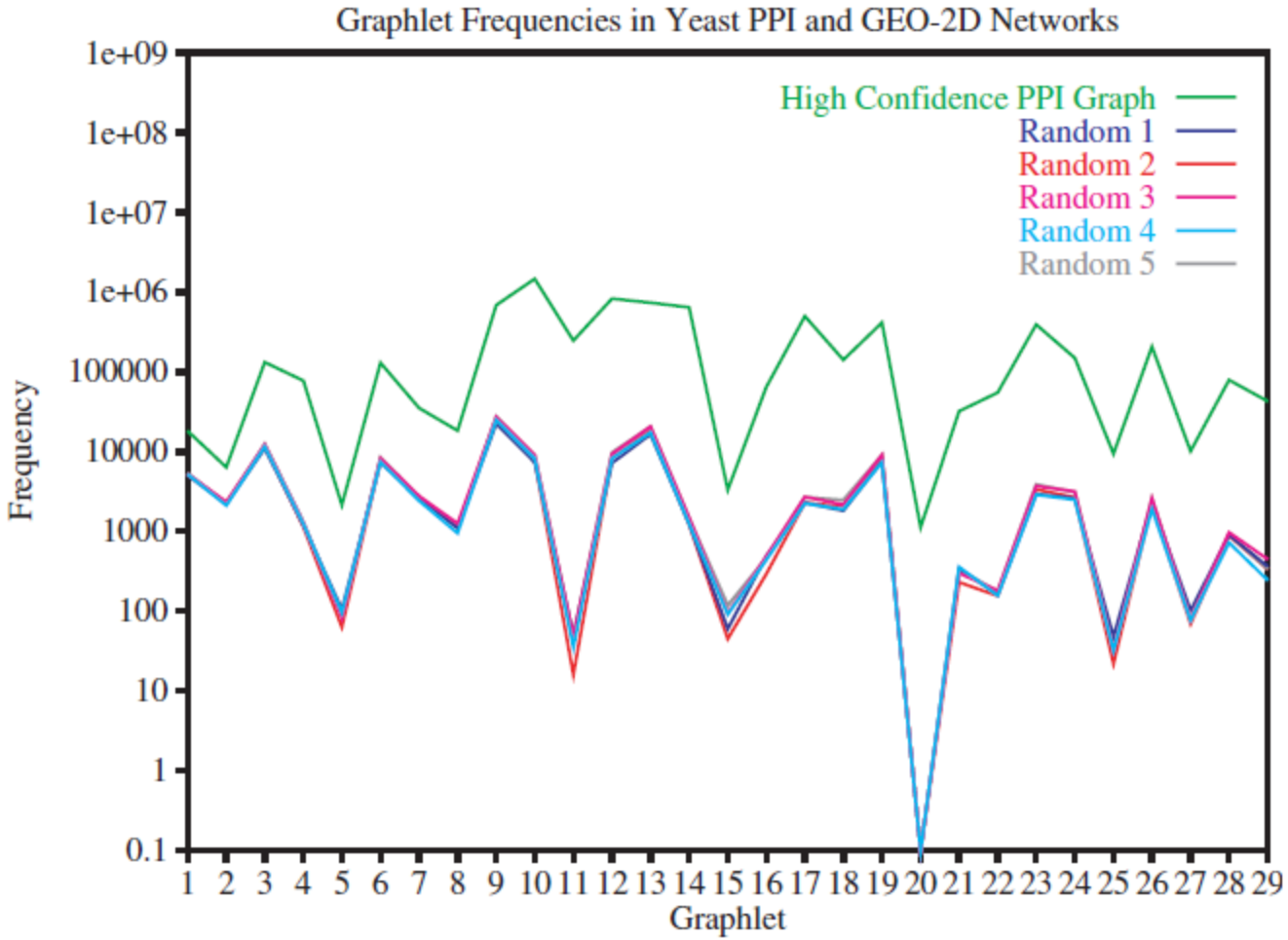
**relative graphlet frequency distance between graphs *G* and *H*, *D(G,H)*:**

$$D(G,H) = \sum_{i=1}^{29} |F_i(G) - F_i(H)|,$$

$$\text{where } F_i(G) = -log\frac{N_i(G)}{T(G)}$$

*(N. Pržulj et al. 2004b)*

# Graphlet frequencies comparison in *S. cerevisiae 1*



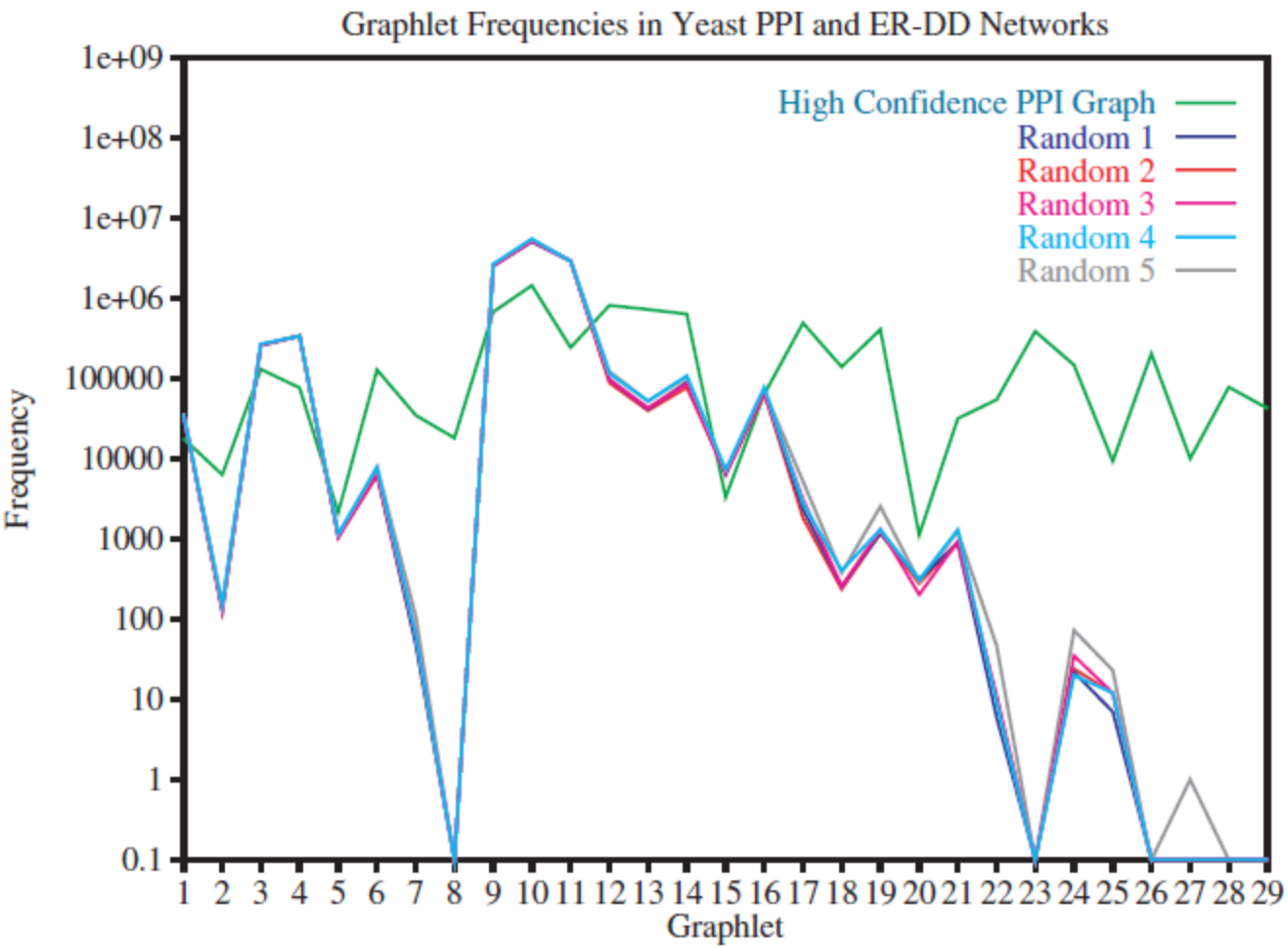

GEO-2D

Geometric graph – 2 dimensional Euclidean space

A geometric graph $G(V, r)$
*radius* $r$
$E = \{\{u, v\} | (u, v \in V) \wedge (0 < ||u - v|| \leq r)\}$
$||.||$ *any distance norm in space*

*Figure 2D of (N. Pržulj et al. 2004b)*

# Graphlet frequencies comparison in *S. cerevisiae 2*




ER-DD:

Erdös–Rényi random

Same number of nodes and edges

Same degree distribution

(as the corresponding PPI networks)

*Figure 2B of (N. Pržulj et al. 2004b)*

# Graphlet degree distribution (GDD)

- Direct generalization of degree distribution
- Imposes *73* local constraints to the structure of networks
  - When used as similarity measure between networks, increases the possibility that the networks are indeed similar

*(N. Pržulj, 2007)*

# Graphlet degree distribution (GDD)

- Direct generalization of degree distribution

Degree distribution:
How many vertices 'touch' one $G_0$?
How many vertices 'touch' two $G_0$?

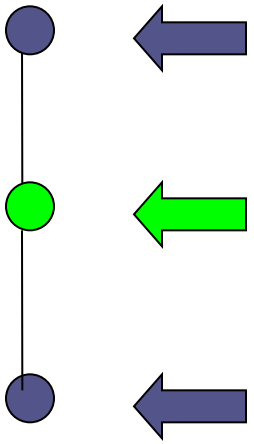
How many vertices 'touch' *k* $G_0$?

Graphlet degree distribution:
Apply the above also to the 29 graphlets $G_0$, $G_1$, ..., $G_{29}$

- Imposes *73* local constrains to the structure of networks

Topological Issue:

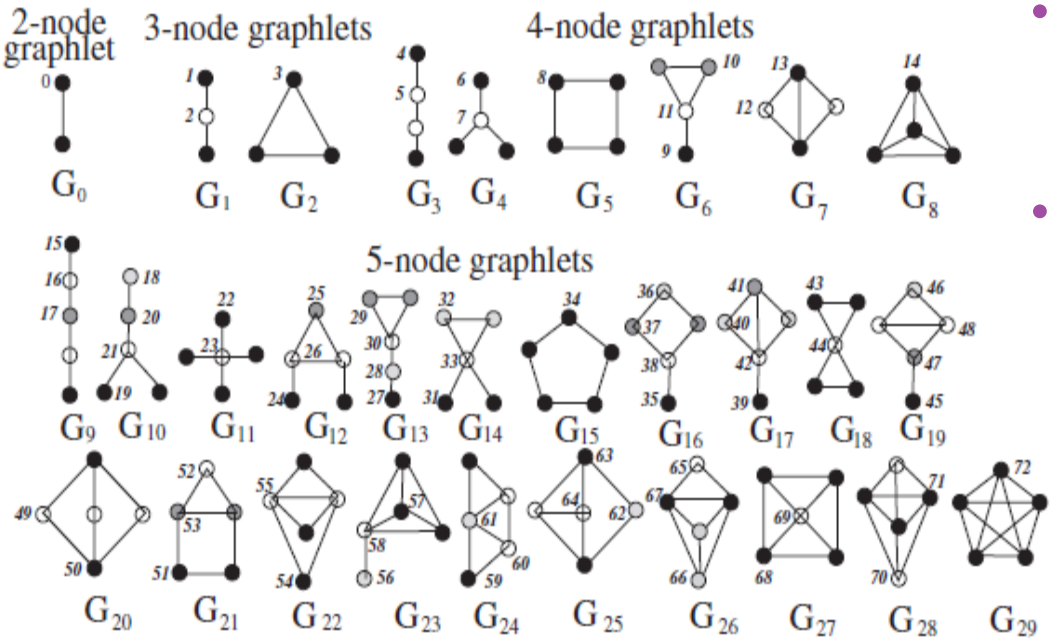
How many vertices 'touch' $G_1$?



$G_1$

*(N. Pržulj, 2007)*

# Graphlet degree distribution 2




- 73 graphlet degree distributions
- Each distributions answers questions such as
  - how many vertices touch 1 orbit 2 of $G_1$
  - How many vertices touch 2 orbit 2 of $G_1$
  - How many vertices touch k orbit 2 of $G_1$

2-5 node graphlets with automorphism orbits 0 .. 72.
Fig. 1 of Biological network comparison.

*(N. Pržulj, 2007)*

# GDD agreement measure

- To compare network similarity
- Reduce the 73 graphlet degree distributions into a scalar agreement between [0,1]
  - 0 – networks are far apart
  - 1 - the distributions of the 2 graphs are identical

*(N. Pržulj, 2007)*

# GDD agreement

$$S_G^j(k) = \frac{d_G^j(k)}{k}$$

Is scaled in order to decrease the effect on large *k*s

$$T_G^j = \sum_{k=1}^{\infty} S_G^j(k)$$

Total area

$$N_G^j(k) = \frac{S_G^j(k)}{T_G^j}$$

Is normalized with respect to total area

*(N. Pržulj, 2007)*

# Distance

Let *H* be another graph. The distance of the *j* orbit between two graphs, *G* and *H* is defined to be:

$$D^j(G,\ H) = \frac{1}{\sqrt{2}} \left( \sum_{k=1}^{\infty} \left[ N_G^j(k) - N_H^j(k) \right]^2 \right)^{\frac{1}{2}}$$

The *j*th GDD *agreement* is defined to be:

$$A^j(G,\ H) = 1 - D^j(G,\ H)\ ,\ for\ j \in \{0, 1, \ldots, 72\}$$

*(N. Pržulj, 2007)*

# GDD Agreement

The *agreement* for graph *G* and *H* can be defined as the arithmetic mean over $A^j(G;H)$ for all *j*:

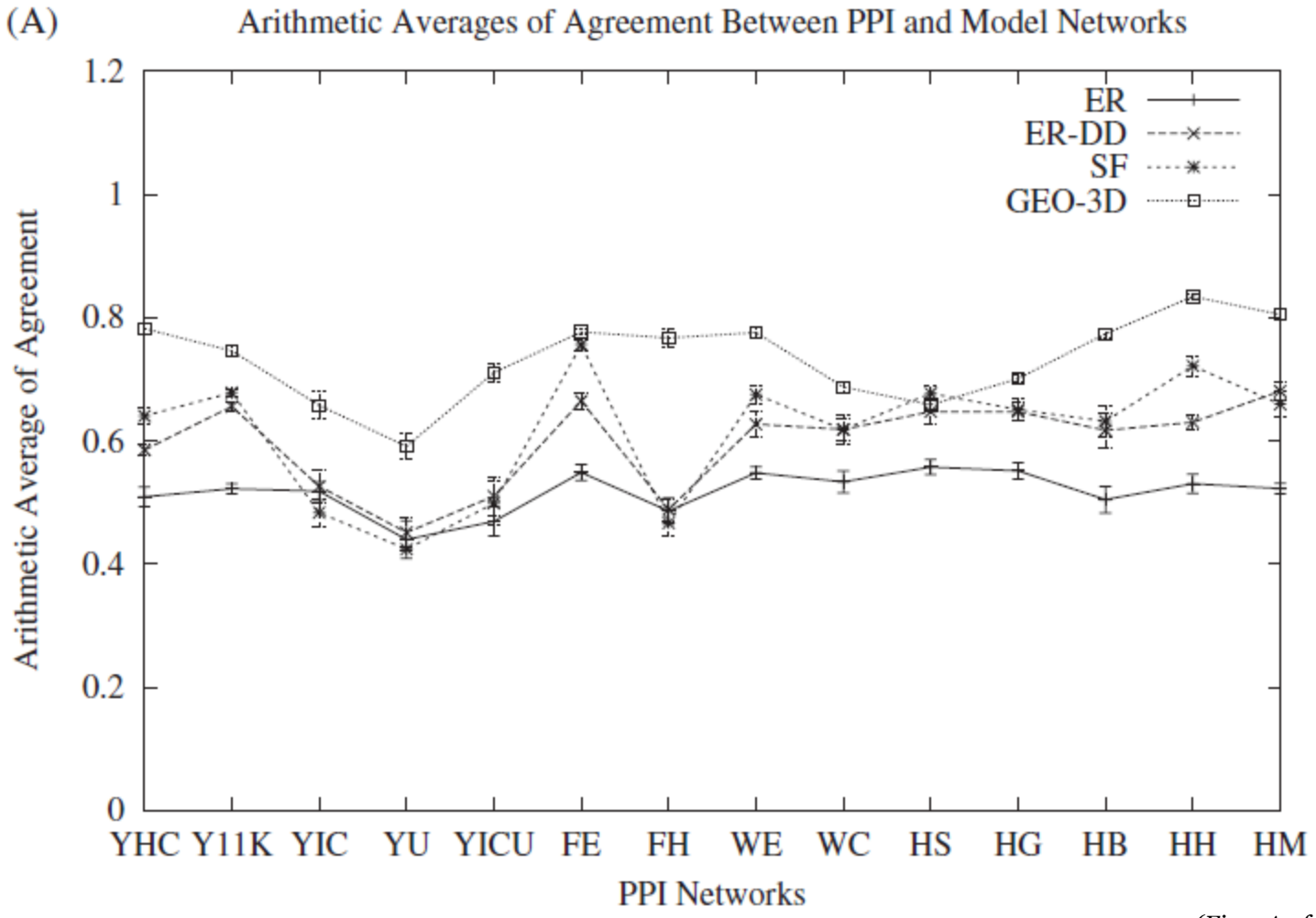
$$A_{arith}(G,H) = \frac{1}{73}\sum_{j=0}^{72} A^j(G,H)$$

or the geometric mean over $A^j(G;H)$ for all *j*:

$$A_{geo}(G,H) = (\prod_{j=0}^{72} A^j(G,H))^{1/73}$$

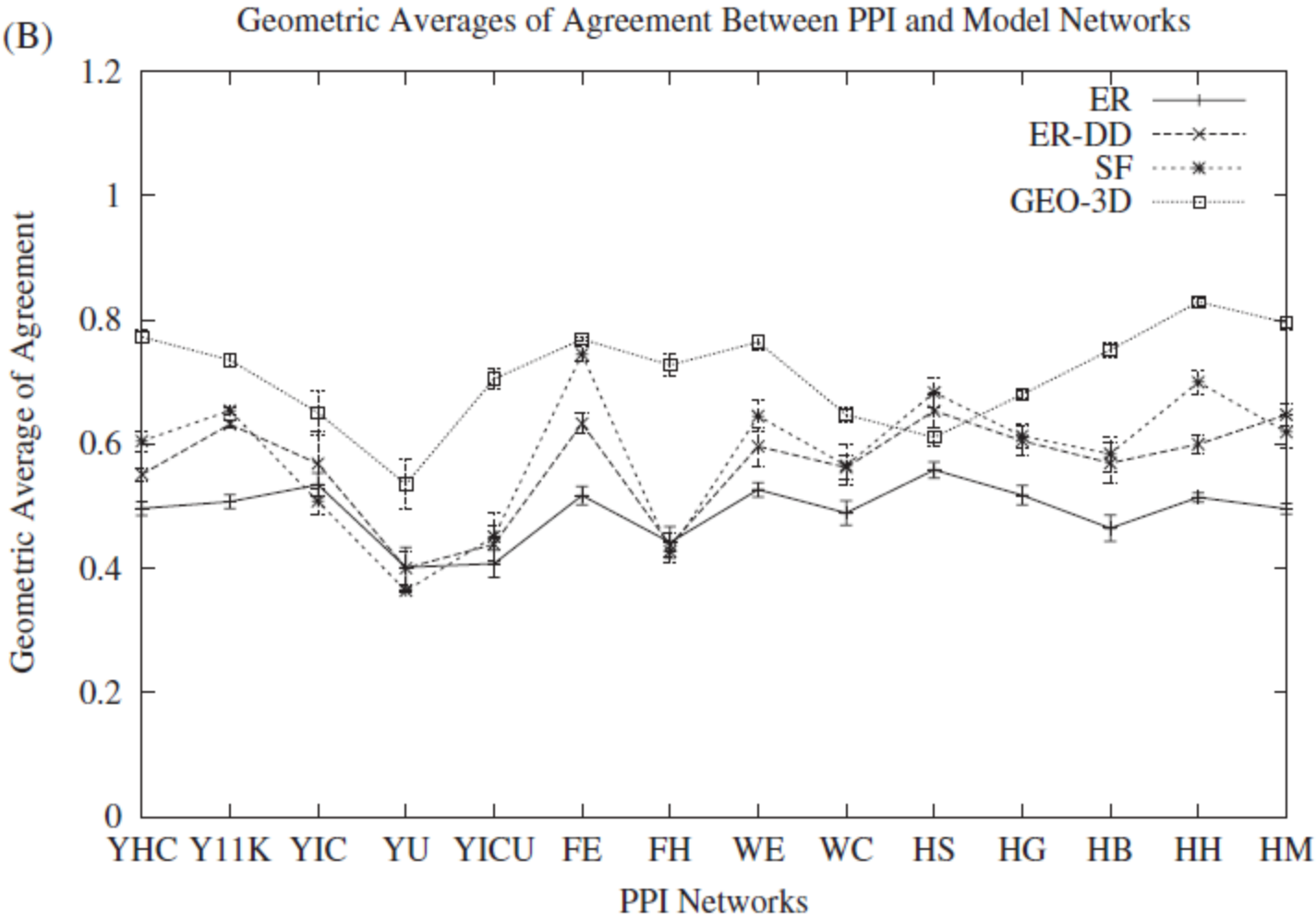
*(N. Pržulj, 2010)*

# Example of graphlet degree distribution & agreement




*(Fig. 3A of N. Pržulj, 2007)*

# Example of graphlet degree distribution & agreement




*(Fig. 3B of N. Pržulj, 2007)*

# Uncovering biological network function

# Uncovering Biological Network Function

- Using neighborhood of proteins to infer protein functions
  - Majority rules
- Graphlets
  - Clustering method on node signatures
  - Nodes in a cluster do not need to be connected or in the same neighborhood

*(T. Milenkovic, 2008)*

# 1 objective

- Look for proteins with common biological processes, cellular components, tissue expressions in a cluster

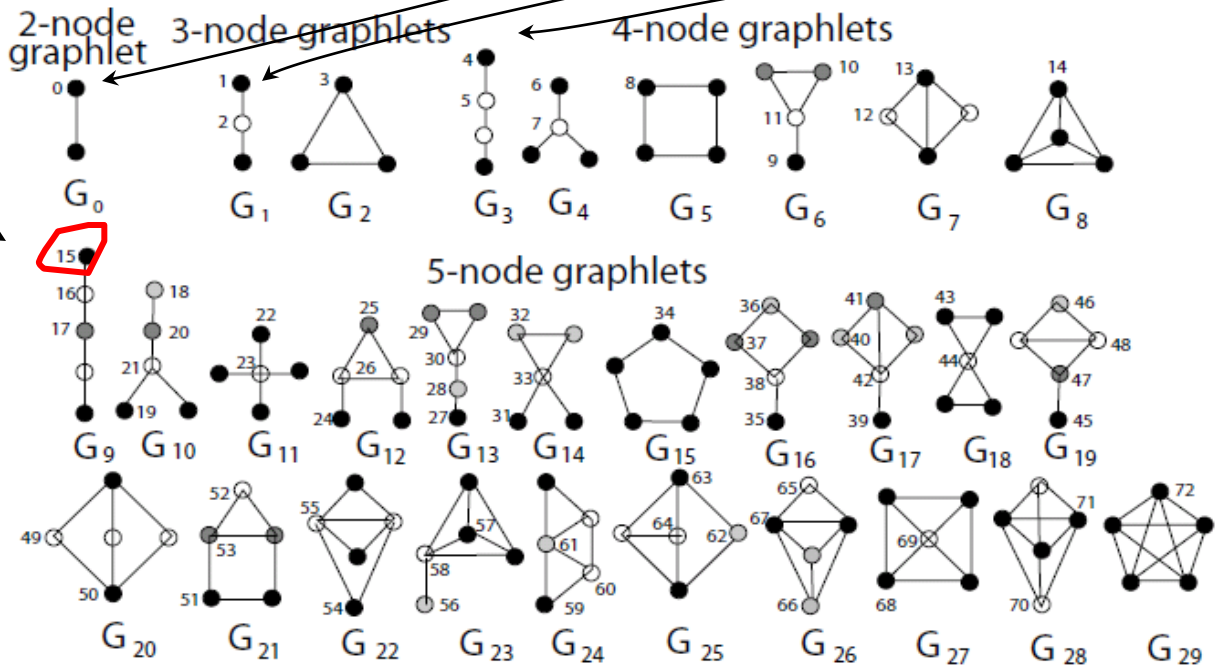
*(T. Milenkovic, 2008)*

# Clustering

- For each vertex $u$ in the network
  - Vertex $v$ belongs to the cluster if the signature similarity metric for $u$, $v$ > threshold

*(T. Milenkovic, 2008)*

# Signature of a node




*(Fig. 1 of T. Milenkovic, 2008)*

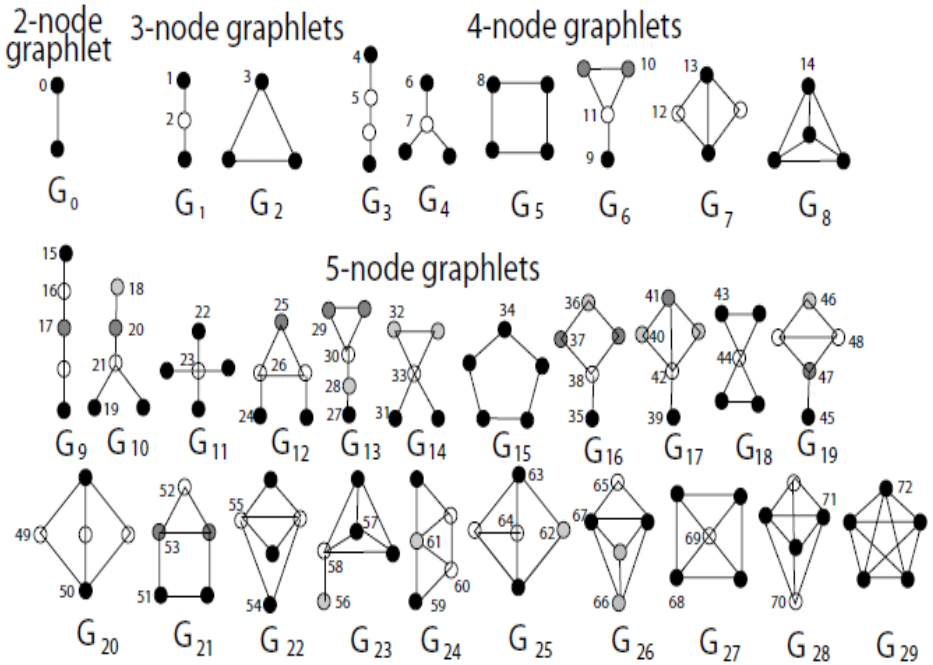
0 .. 72

| | |
|---|---|
| 0 | 1 |
| 1 | 1 |
| 2 | 0 |
| 3 | 0 |
| 4 | 1 |
| 5 | 0 |
| 6 | 0 |
| 7 | 0 |
| 8 | 0 |
| 9 | 0 |
| 10 | 0 |
| 11 | 0 |
| 12 | 0 |
| 13 | 0 |
| 14 | 0 |
| 15 | 1 |
| 16 | 0 |
| ⋮ | |
| ⋮ | |
| ⋮ | |
| 72 | 0 |

0

*(T. Milenkovic, 2008)*

# Weight vector

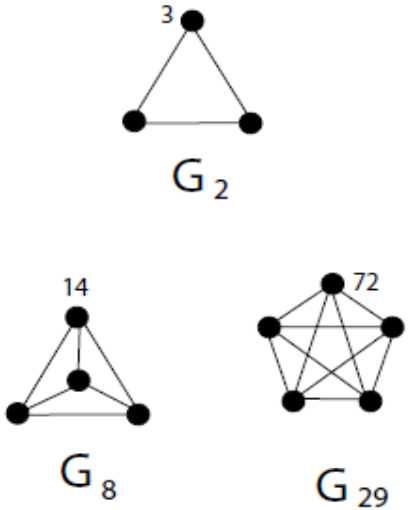



weight vector

$i \in \{0, \ldots, 72\}$

| $i$ | $w_i$ |
|---|---|
| 0 | |
| 1 | |
| 2 | |
| 3 | |
| 4 | |
| 5 | |
| 6 | |
| 7 | |
| 8 | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| | |
| 72 | |

- Remove redundancy




E.g. difference in orbit 3 will affect difference in orbits such as 14, 72

*(T. Milenkovic, 2008)*

# Weight

- Weight ($w_i \in [0, 1]$)
  - higher to important orbits (orbits that do not depend on a lot  on other orbits)
  - lower to less important orbits (orbits that depend on lots of other orbits)
- Computed as

$$w_i = 1 - \frac{log(o_i)}{log(73)}.$$

where $o_i$ is the count of orbits that affect $i$

  - E.g. $o_{15}$ =4, orbit 15 is affected by 0, 1, 4, 15

*(T. Milenkovic, 2008)*

# Distance

- Distance for orbit $i$ between node $u$ and $v$

$$D_i(u,v) = w_i \times \frac{\left|log(u_i+1) - log(v_i+1)\right|}{log(max\{u_i, v_i\}+2)}.$$

$u_i$ – number of times node $u$ touches orbit $i$

- Distance between node $u$ and $v$

$$D(u,v) = \frac{\sum_{i=0}^{72} D_i}{\sum_{i=0}^{72} w_i}.$$

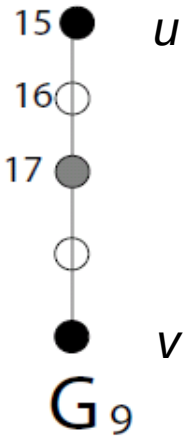
*(T. Milenković, 2008)*

# Distance 2

- Signature similarity

$$S(u, v) = 1 - D(u, v).$$

- For example




- D($u$,$v$)= 0 (same signatures)
- S($u$,$v$) = 1

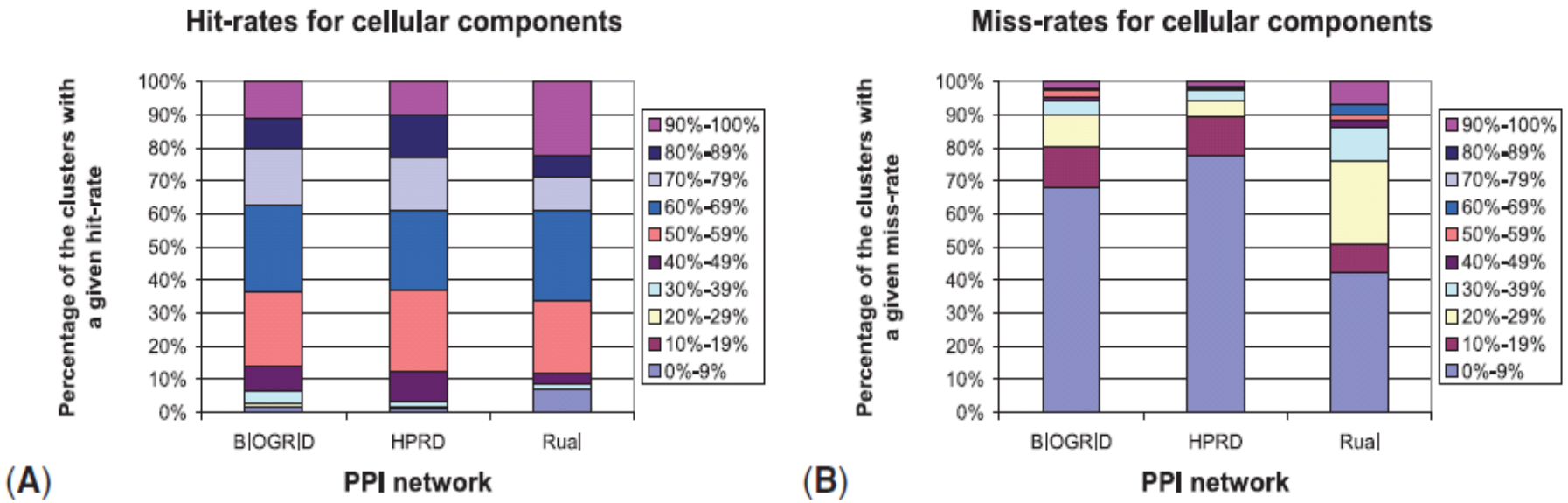
*(T. Milenkovic, 2008)*

# Evaluation method

- Hit-rate of cluster *C*
  $Hit(C) = max\ N_p/N$
  - *Np - number of vertices in C with protein property p*
  - *N - number of vertices in C*
- Miss-rate of cluster *C*
  $Miss(C) = U_p/N$
  - *Up - number of vertices in C that do not have any protein properties p in common with any other vertices in C*
  - *N - number of vertices in C*

*(T. Milenkovic, 2008)*

# Results




*(Fig. 5A, B. of T. Milenkovic, 2008)*

- Cellular components
  - Hit-rates
    - All 3 networks, 86% of clusters have hit-rates > 50%
  - Miss-rates
    - BIOGRID, HPRD, 68% of clusters have miss-rates < 10%
    - Rual, 76% of clusters have miss-rates < 29%

*(T. Milenkovic, 2008)*

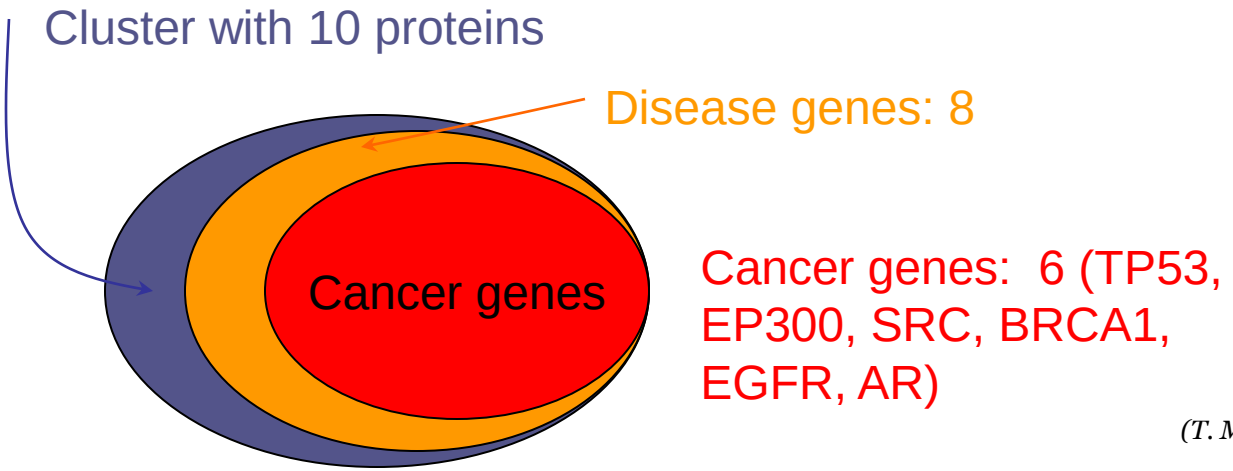
# Disease genes

- Hypothesis:
  - If the topology of a network is related to function, then cancer genes might have similar graphlet degree signatures

*(T. Milenkovic, 2008)*

# Cancer genes

- Protein of interest
  - TP53
- Look for proteins with signature similarity >= 0.95
- Resulting cluster




*(T. Milenkovic, 2008)*

# Signature vectors

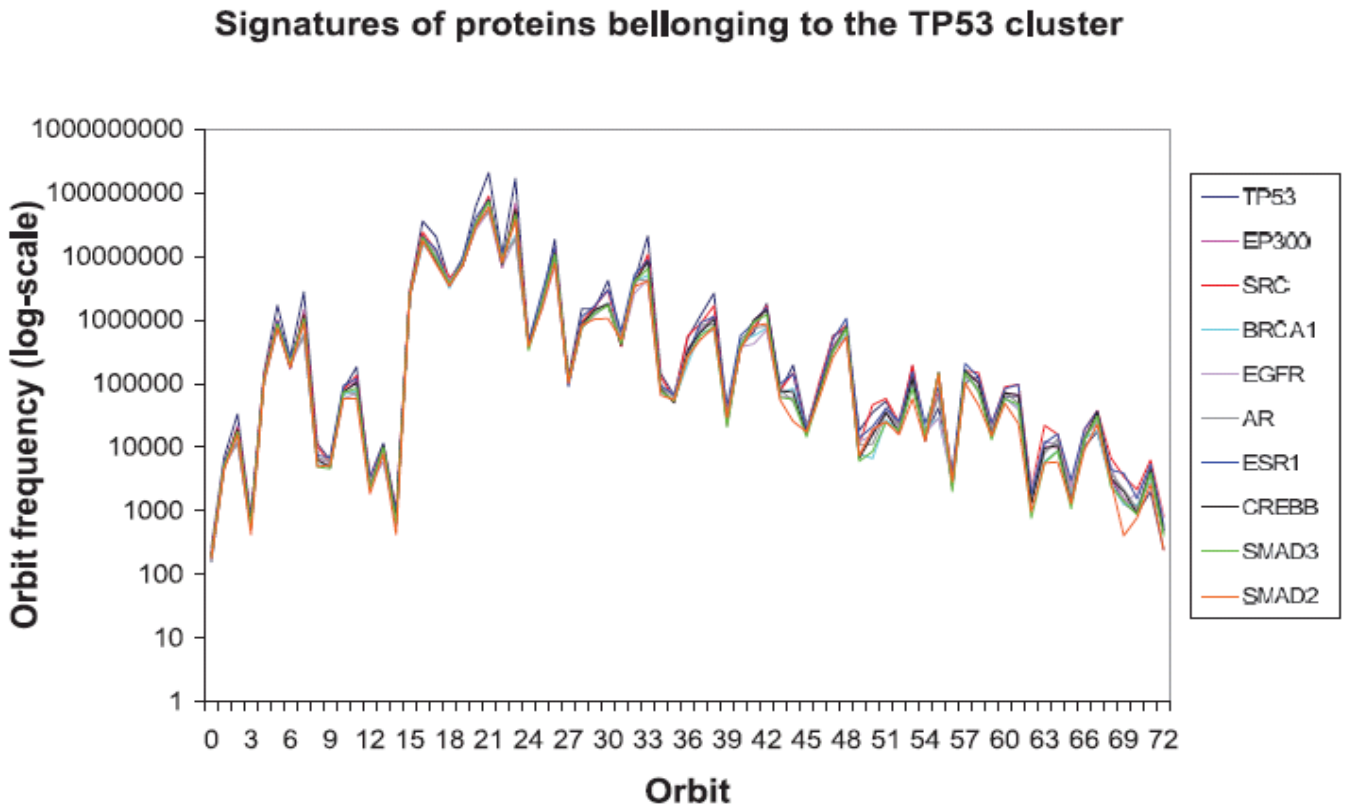


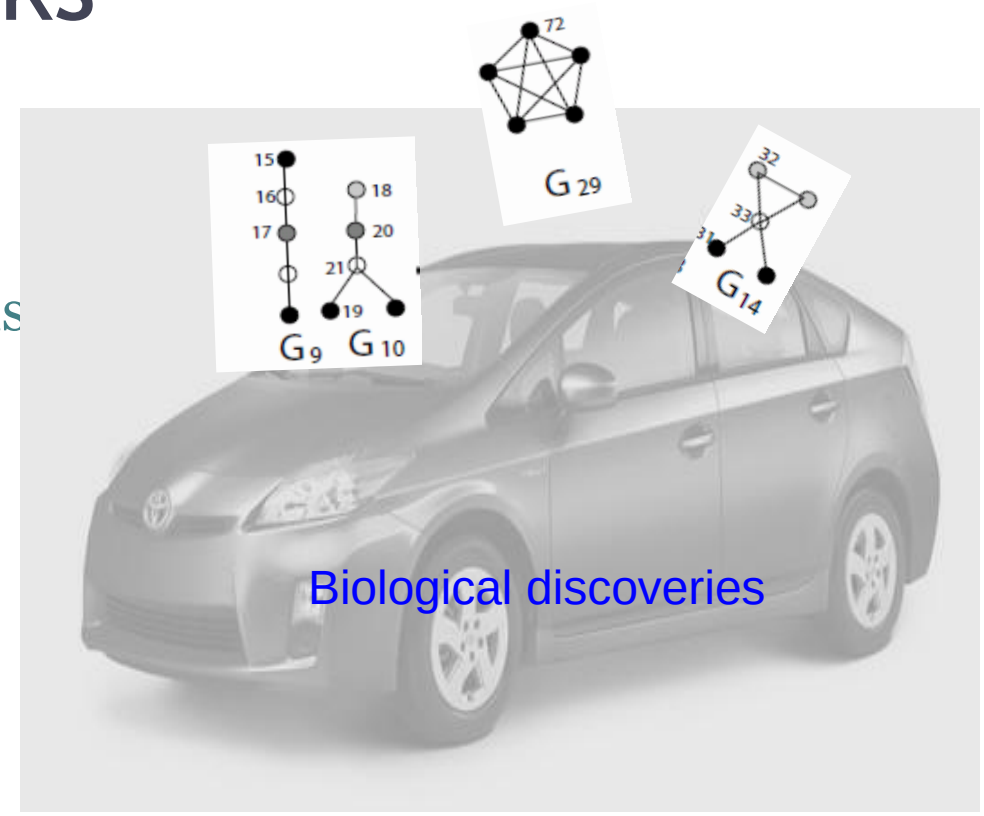

**Figure 6.** Signature vectors of proteins belonging to the TP53 cluster. The cluster is formed using the threshold of 0.95.

*(T. Milenkovic, 2008)*

# Conclusion

# Concluding remarks

- Graphlets can be used to
  - Compare networks
  - To infer protein functions
  - Characterize the relationship between disease and structure of networks




*http://www.toyota.ca/toyota/en/vehicles/prius/gallery*

# References


- (H. Jeong et al., 2001) H. Jeong, S. P. Mason, A.-L. Barab´asi, and Z. N. Oltvai. Lethality and centrality in protein networks. *Nature Brief Communications*, 411:41–42, May 2001.
- (R. Milo et al, 2002) R. Milo, S. Shen-Orr, S. Itzkovitz, N. Kashtan, D. Chklovskii, and U. Alon. Network motifs: simple building blocks of complex networks. *Science, 298* (5594):824–827, 2002.
- (H. C. Causton et al., 2003) H. C. Causton, J. Quackenbush, and A. Brazma. *Microarray Gene Expression Data Analysis, chapter Introduction. Blackwell Publishing,* 2003.
- (A.-L. Barab´asi et al., 2004) A.-L. Barab´asi and Z. N. Oltvai. Network biology: understanding the cell's functional organization. Nature Reviews Genetics, 5:101–113, February 2004.
- (N. Pr˘zulj et al., 2004) N. Pr˘zulj, D. Wigle, and I. Jurisica. Functional topology in a network of protein interactions. *Bioinformatics, 20(3):340–348, 2004.*
- (N. Pr˘zulj et al. 2004b) N. Pr˘zulj, D. G. Corneil, and I. Jurisica. Modeling interactome: scale-free or geometric? *Bioinformatics, 20(18):3508–3515, 2004.*

# References 2


- (N. Pržulj, 2005) N. Pržulj. *Analyzing large biological networks: protein-protein interactions example. PhD thesis, University of Toronto, 2005.*
- (N. Pržulj, 2006) N. Przulj. *Knowledge discovery in proteomics, chapter Graph theory* analysis of protein-protein interactions. Chapman and Hall CRC. Mathematical biology and medicine series. CRC Press Taylor and Francis. Group, 2006.
- (O. Mason et al., 2007) O. Mason and M. Verwoerd. Graph theory and networks in biology. *Systems biology, IET, 1(2):89–119, March 2007.*
- (N. Pržulj, 2007) N. Pržulj. Biological network comparison using graphlet degree distribution. *Bioinformatics, 23(2):e177–e183, 2007.*
- (N. Pržulj, 2010) N. Pržulj. Erratum Biological network comparison using graphlet degree distribution. *Bioinformatics, 26(6):853-854, 2010.*
- (M. T. Landi et al., 2008) M. T. Landi, T. Dracheva, M. Rotunno, J. D. Figueroa, H. Liu, A. Dasgupta, F. E. Mann, J. Fukuoka, M. Hames, A. W. Bergen, S. E. Murphy, P. Yang, A. C. Pesatori, D. Consonni, P. A. Bertazzi, S. Wacholder, J. H. Shih, N. E. Caporaso, and J. Jen. Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival. *PLoS one, 3(2),* 2008.

# References 3


- (T. Milenkovic, 2008) T. Milenkovic and N. Przulj . Uncovering Biological Network Function via Graphlet Degree Signatures. *Cancer Informatics, 6 257-273, 2008.*