Master Module
Proteinbiochemistry and Bioinformatics
March 2022

Session: Protein interaction networks

4. Graph-theoretical aspects of protein interaction networks

How can I use protein interaction data in biological research?

What is the function of my gene of interest?

Is the protein of my interest part of a protein complex?

Can I find new protein complexes?

I found 20 genes in my screen that rescued phenotype X:

- do these genes work in the same biological process?
- are these genes part of the same protein complex?

-> do these proteins (tend to) interact with each other?

My protein has many interaction partners,
does it mean that it is of functional importance?

How can I use protein interaction data in biological research?

Resources for protein interactions ✓

How can I use protein interaction data in biological research?

Resources for protein interactions ✓

Methods to analyze protein interaction data ✗

How can I use protein interaction data in biological research?

Resources for protein interactions ✓

Methods to analyze protein interaction data ✗

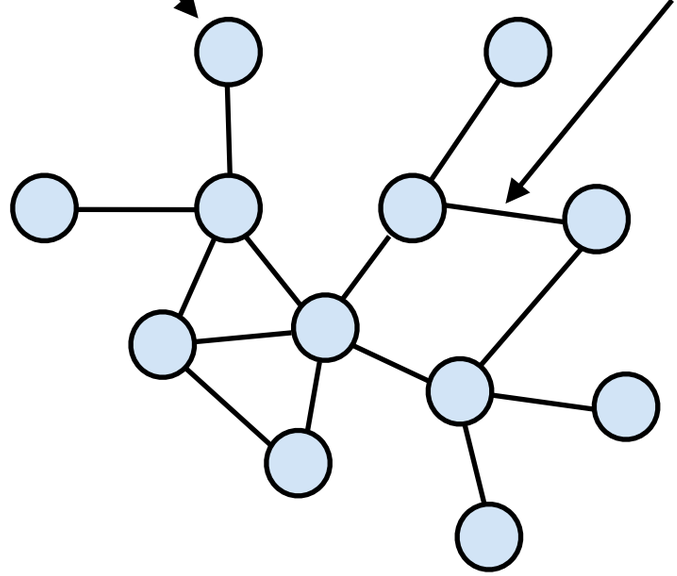
↓

Graph theory

Protein interaction data as a graph

Actual data
Network
Graph

Protein
Node
Vertex



Interaction
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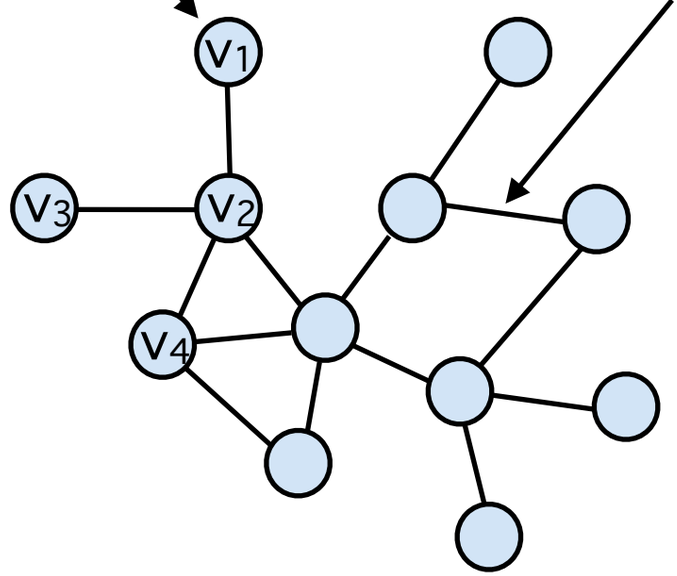

$V = \{v_1, v_2, v_3, v_4, \ldots\}$

$E = \{(v_1, v_2), (v_2, v_3), (v_2, v_4), \ldots\}$

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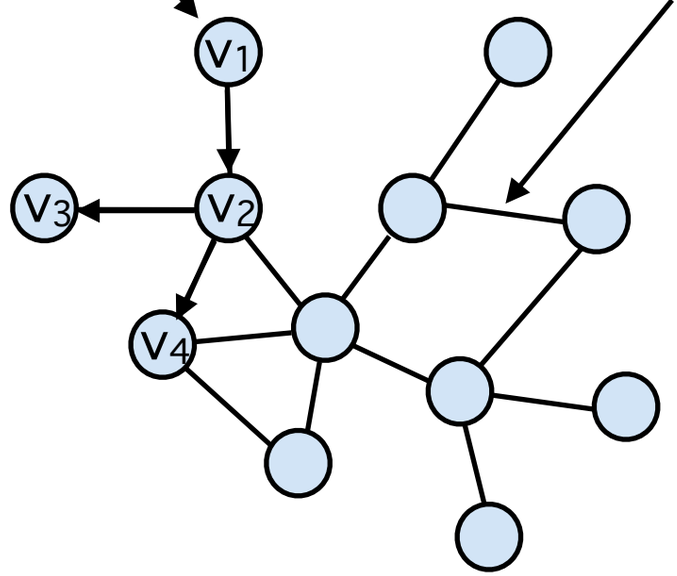

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- undirected vs directed graph

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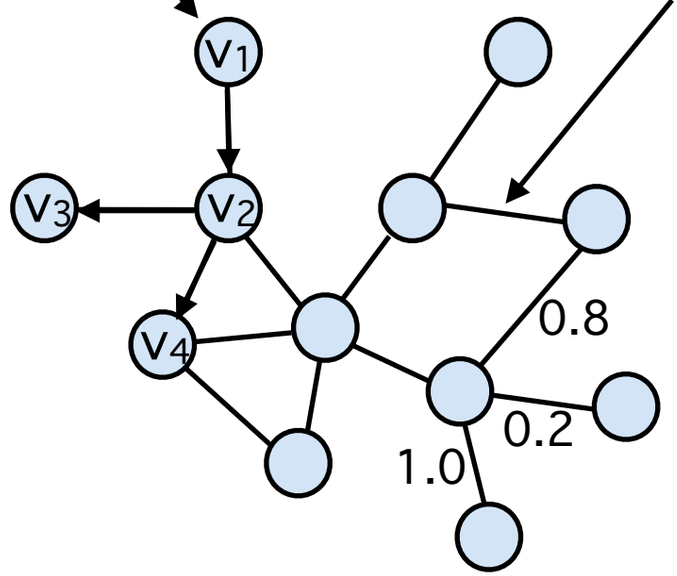

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- undirected vs directed graph
- weighted vs unweighted graph

Degree, average degree, and degree distribution

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- Degree: number of edges of a vertex
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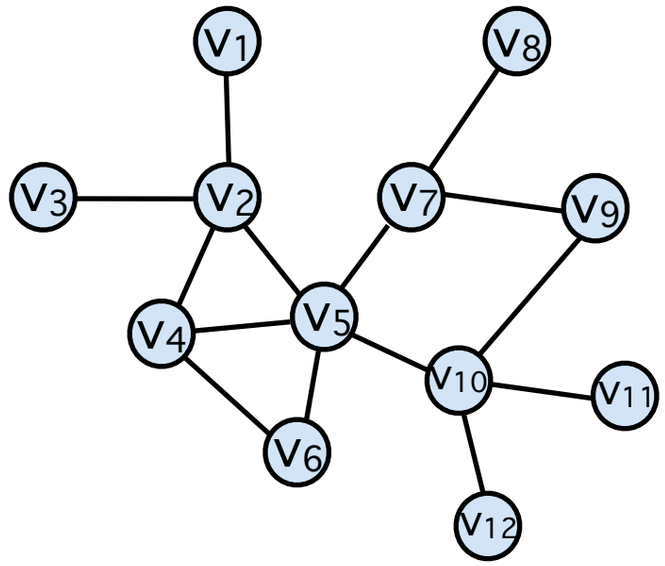

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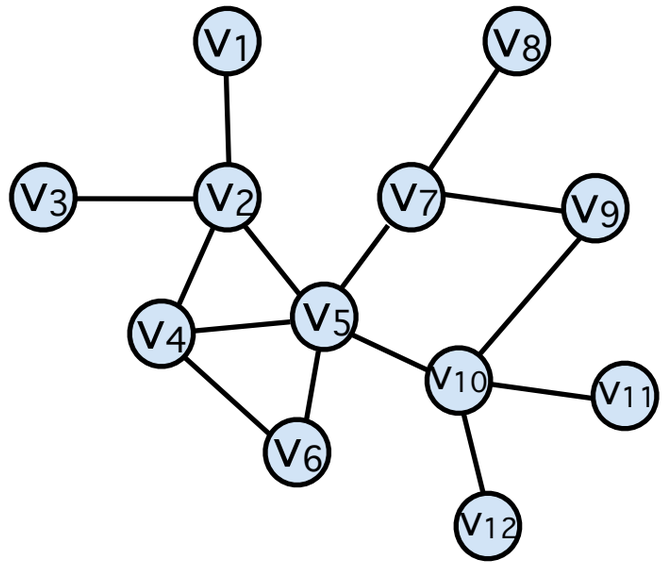

- Average degree
  -> network property

$$\langle k \rangle = \frac{1}{N} \sum_{i=1}^{N} k_i \qquad N = \text{number of vertices in graph}$$

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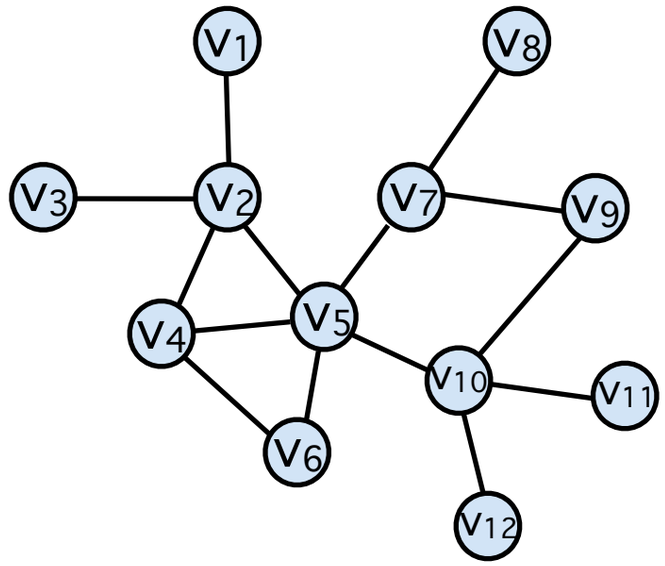

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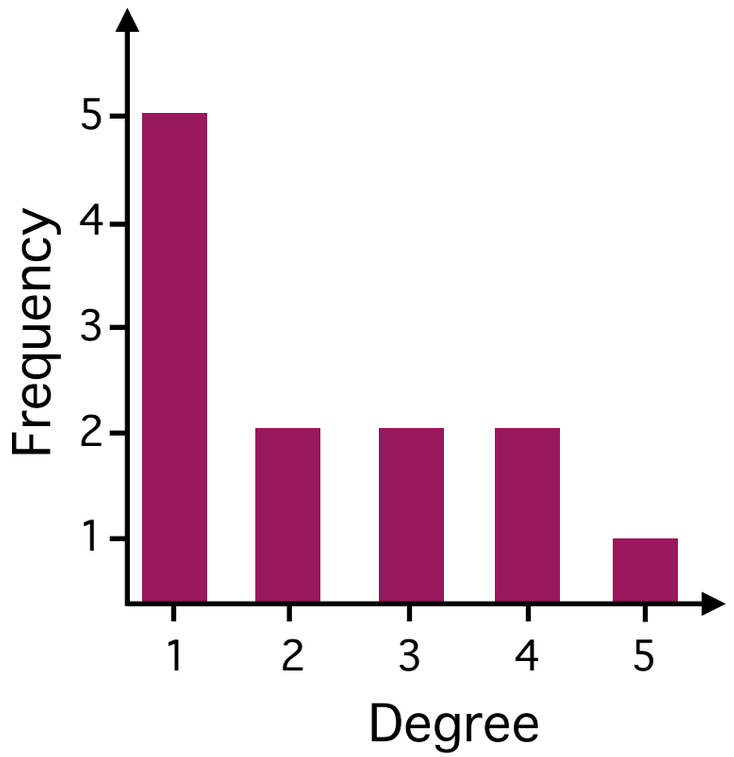

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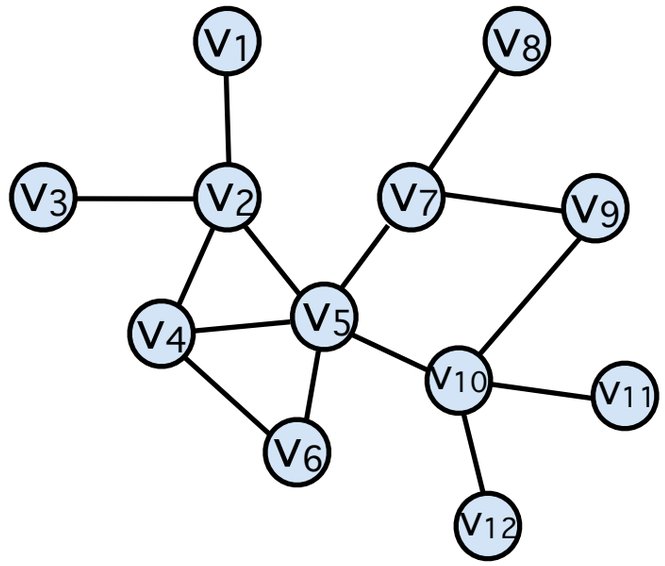

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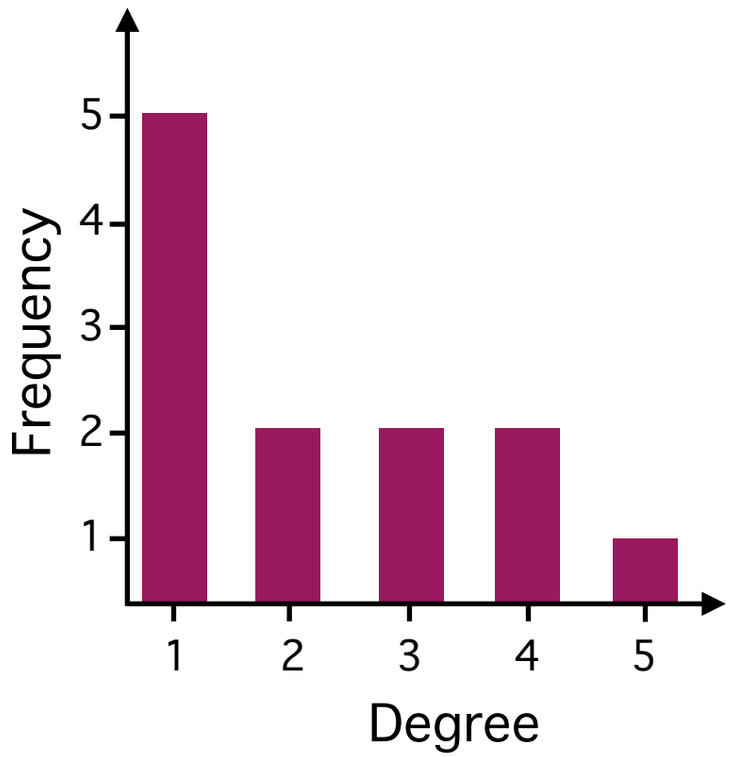

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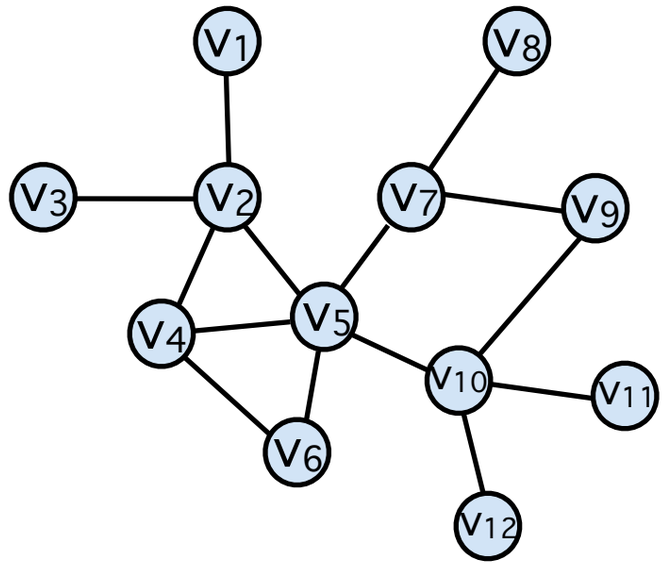

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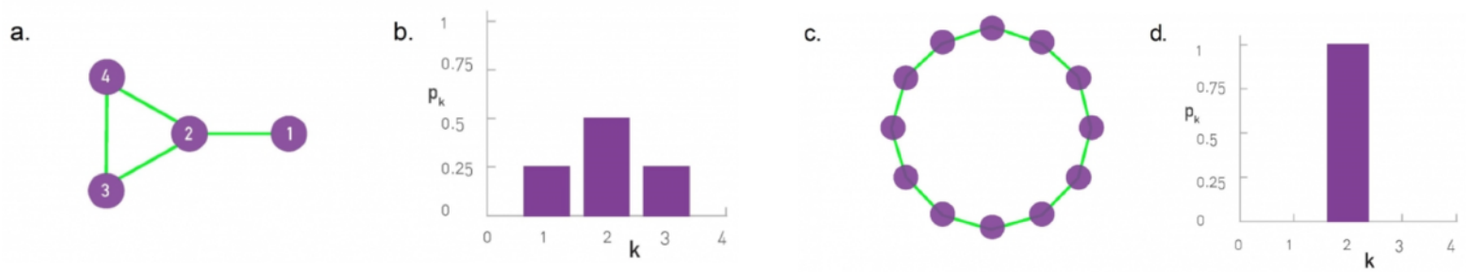

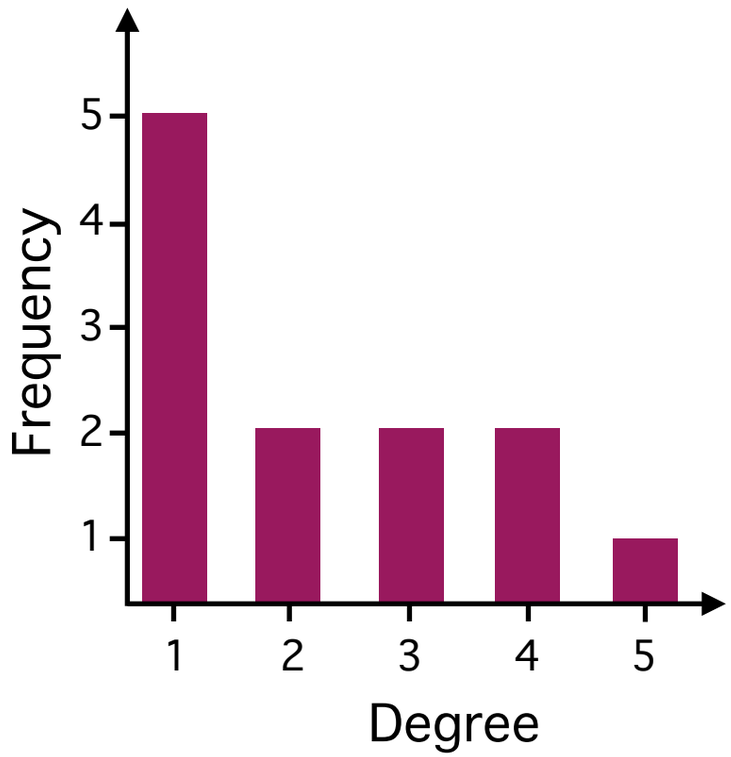

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Protein interaction networks are scale-free

Yeast protein interaction network

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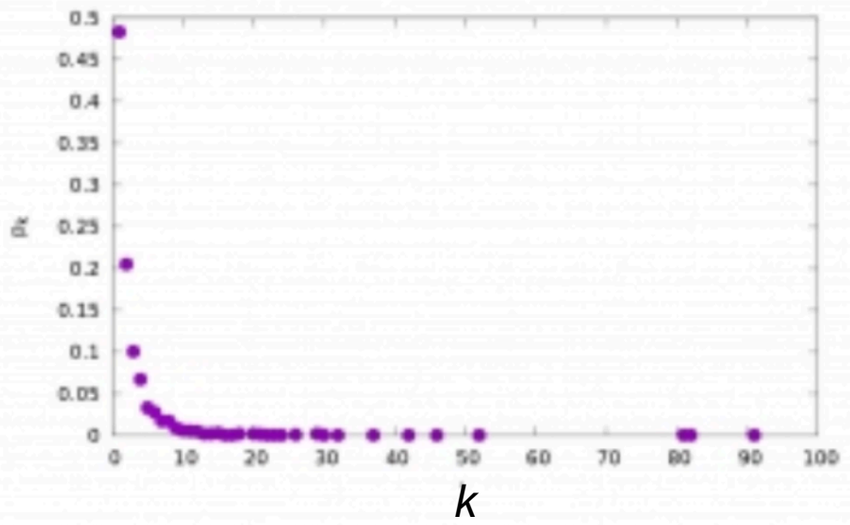
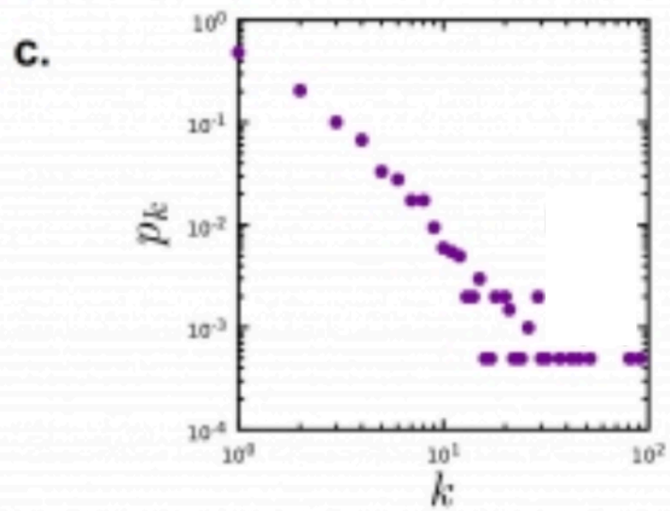
Degree distribution - normal scale

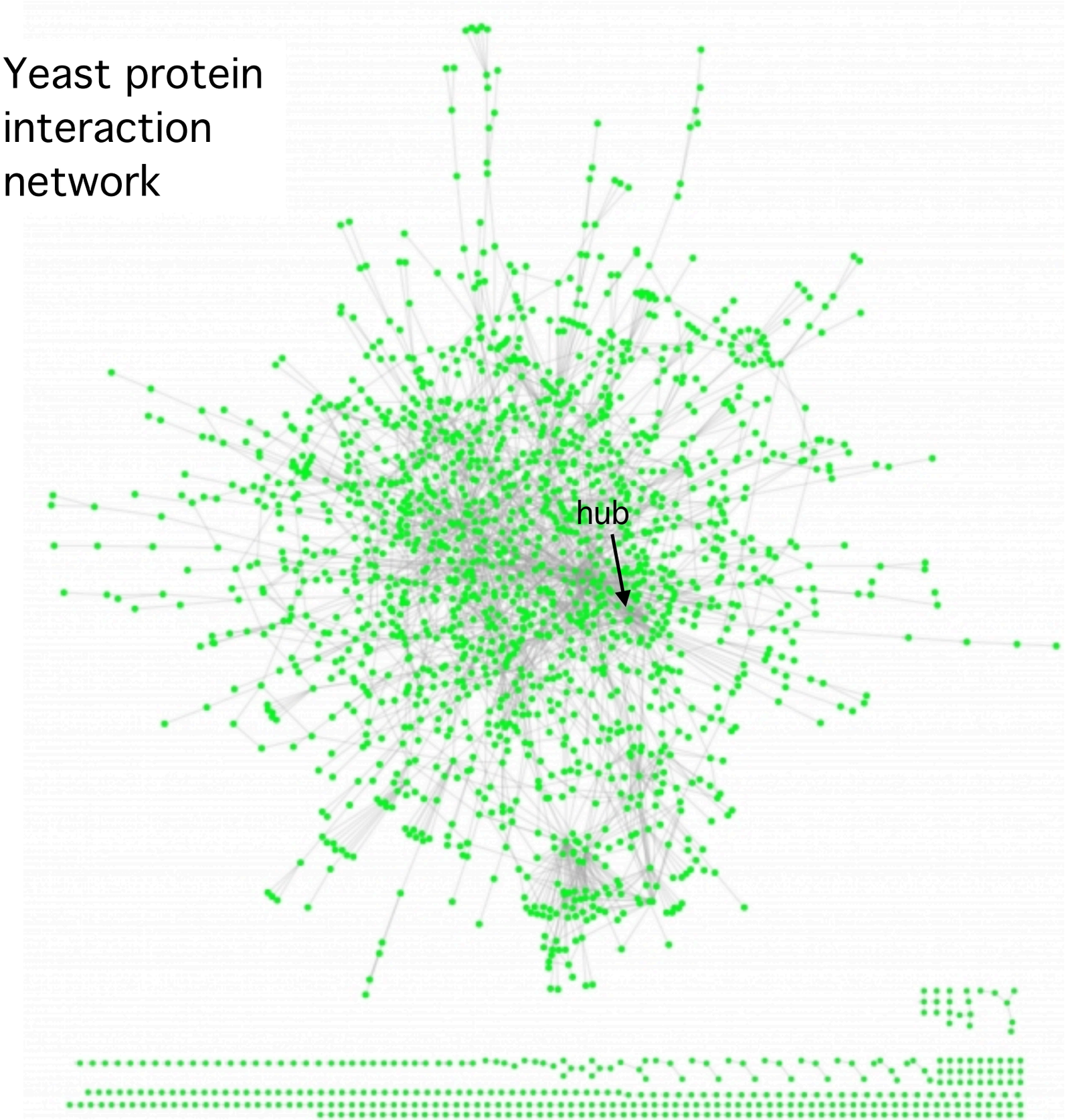


Degree distribution - log-log scale



Protein interaction networks are scale-free

Yeast protein interaction network



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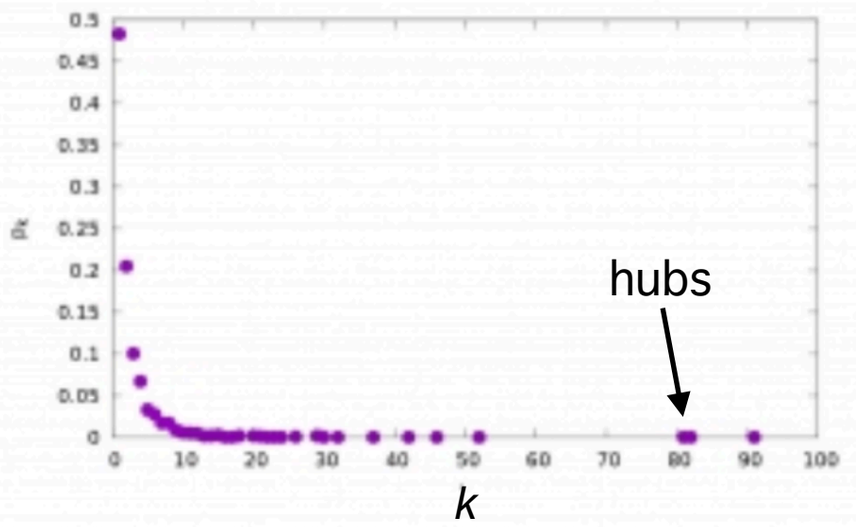

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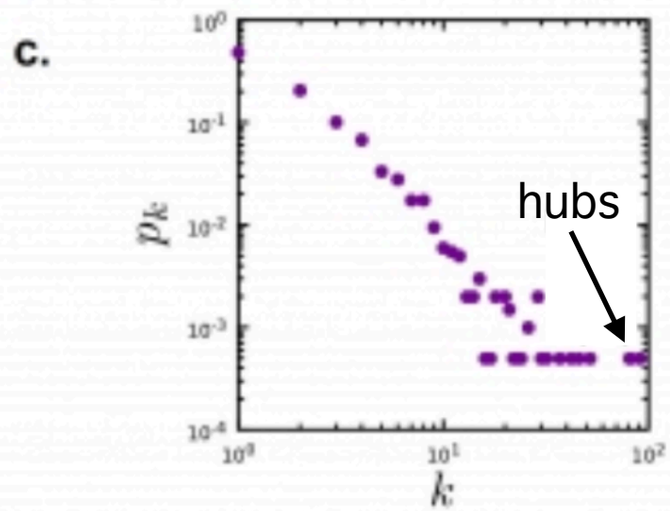

Degree distribution and scale-free networks

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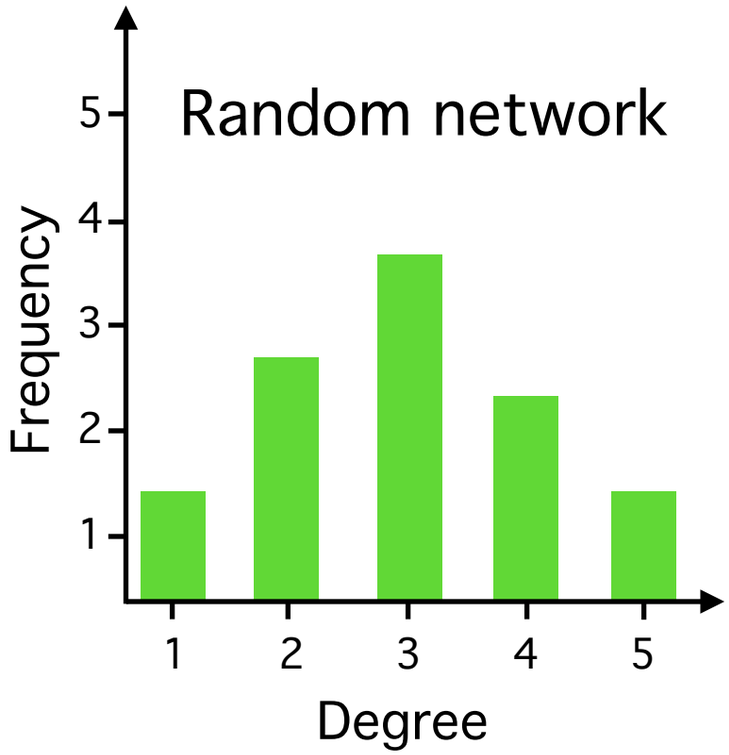

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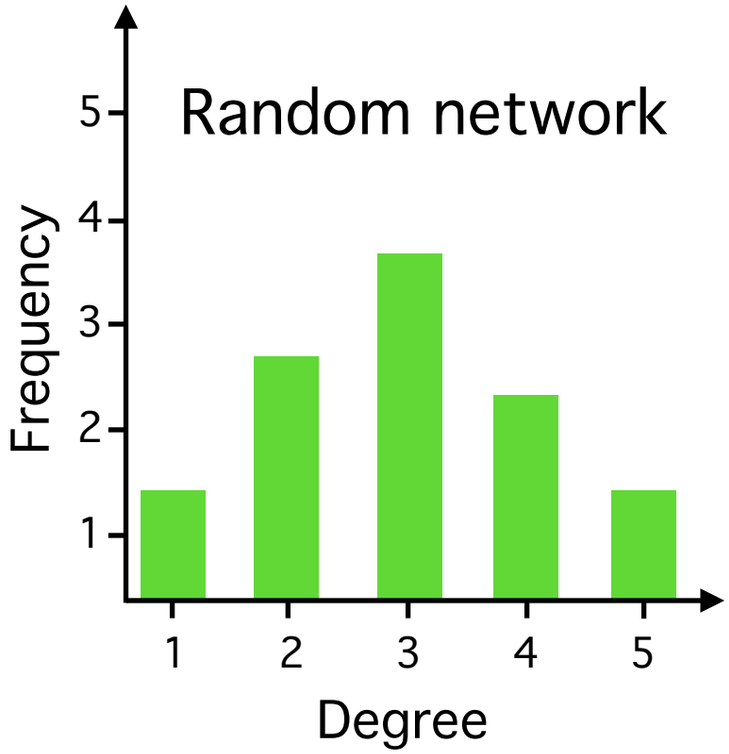
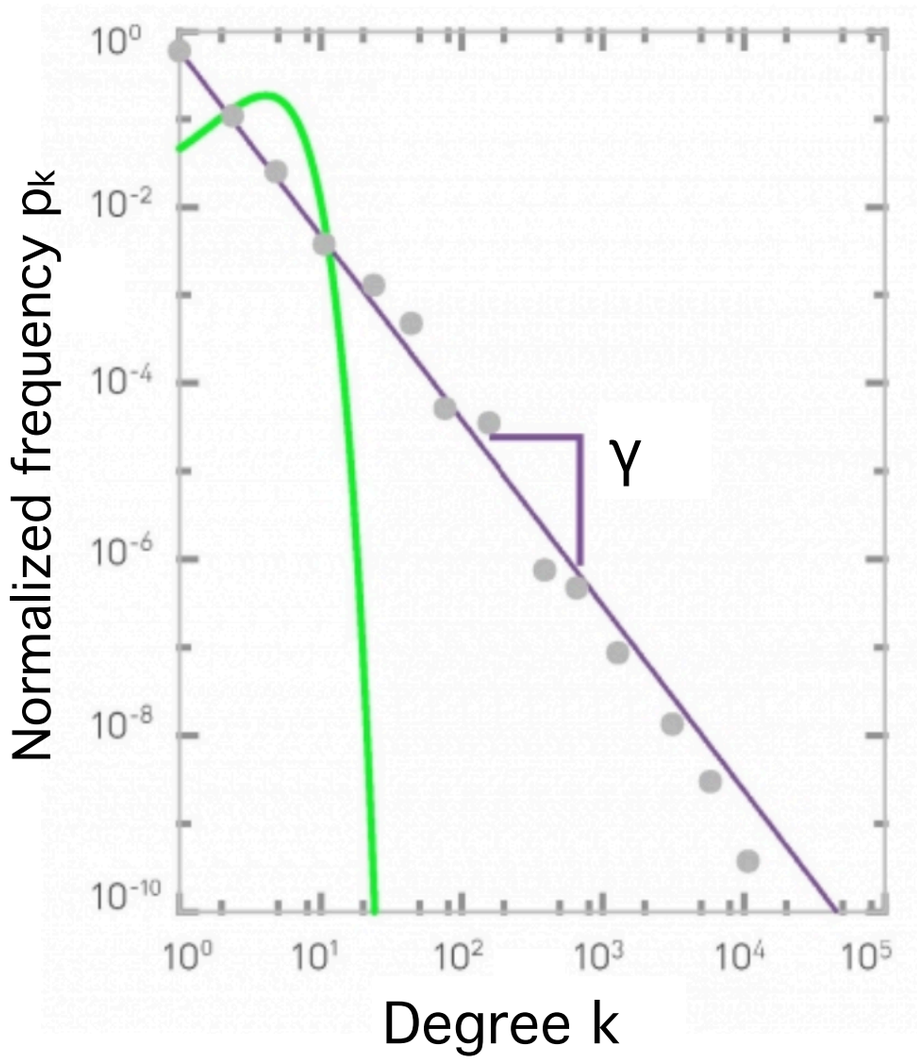
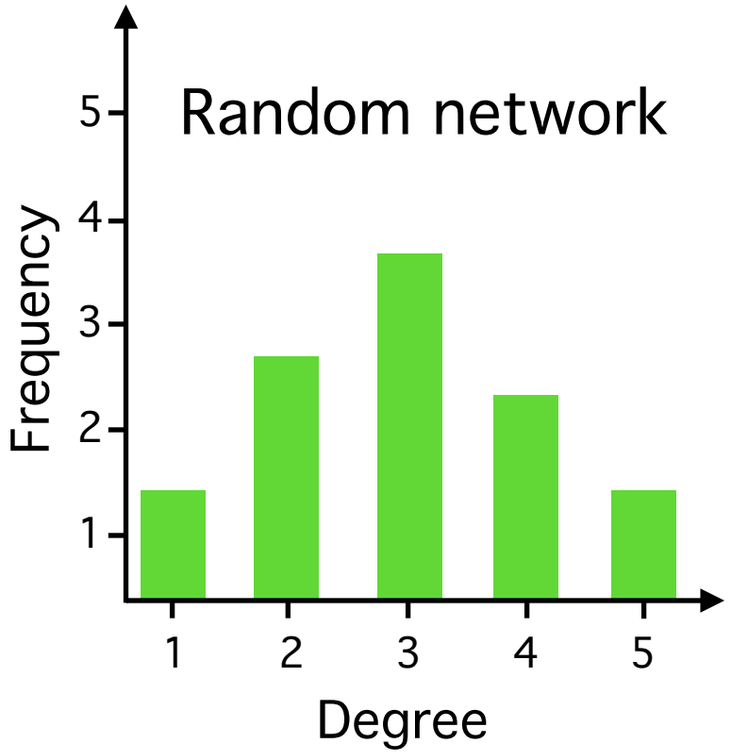
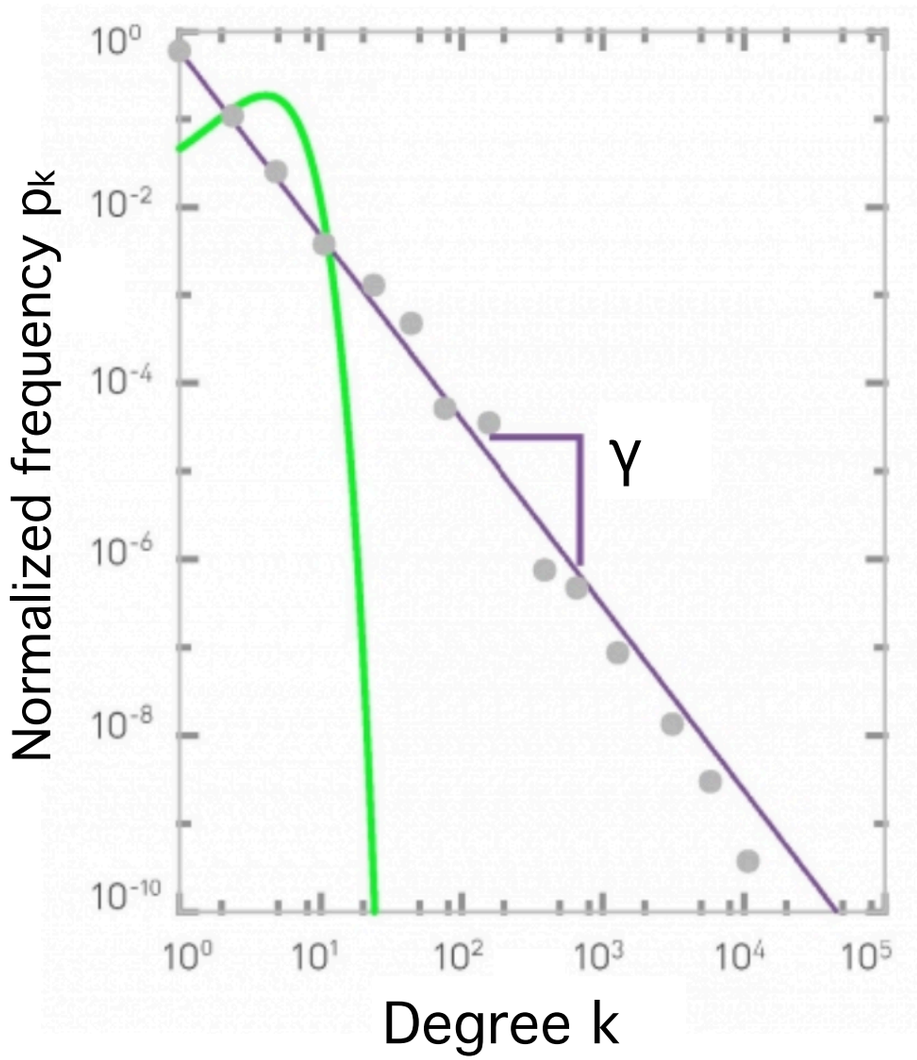




Degree distribution and scale-free networks

Degree distributions of many real world networks follow a power law distribution in log-log scale





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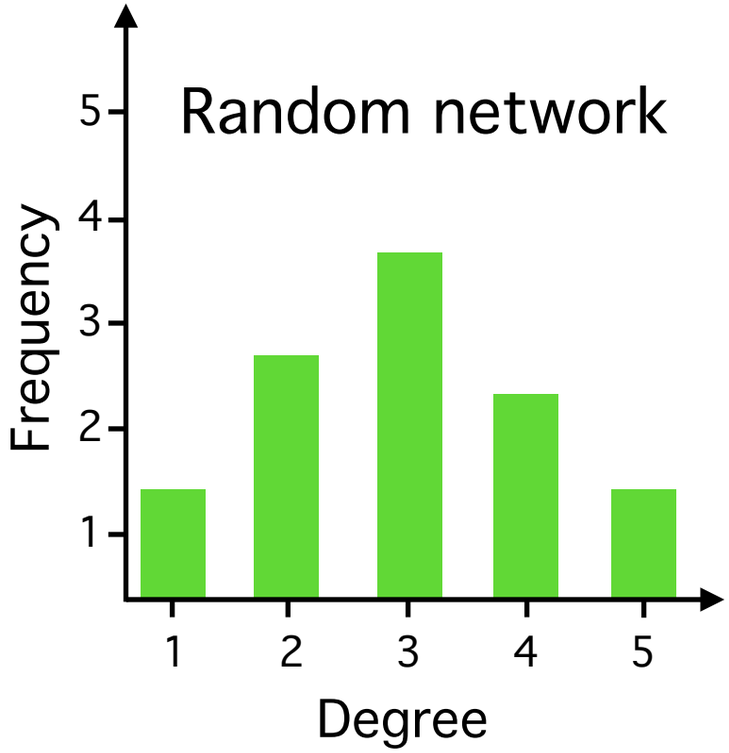

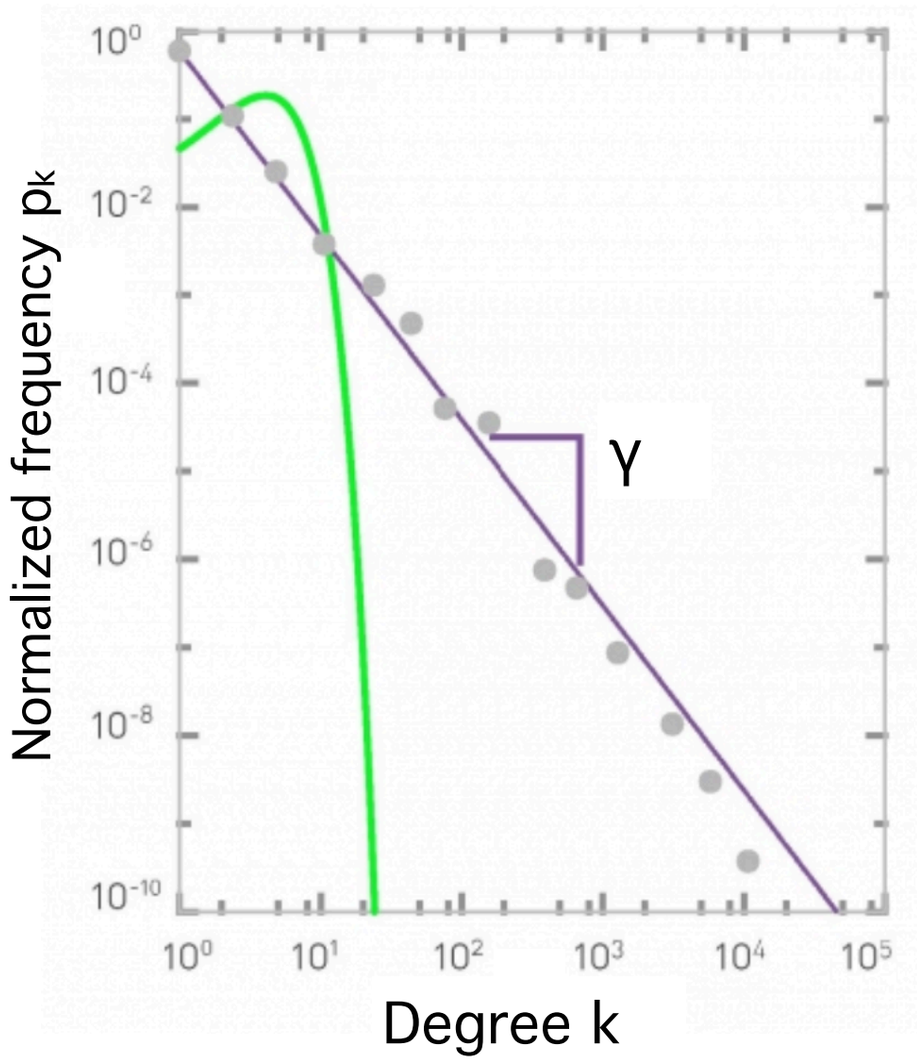

Power law distribution

$p_k \sim k^{-\gamma}$

$\log p_k \sim -\gamma \log k$

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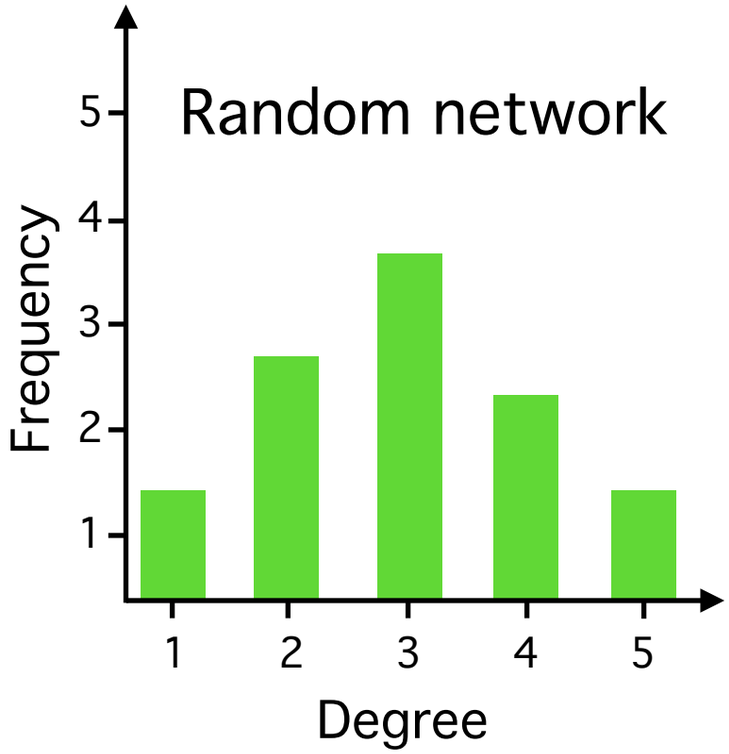

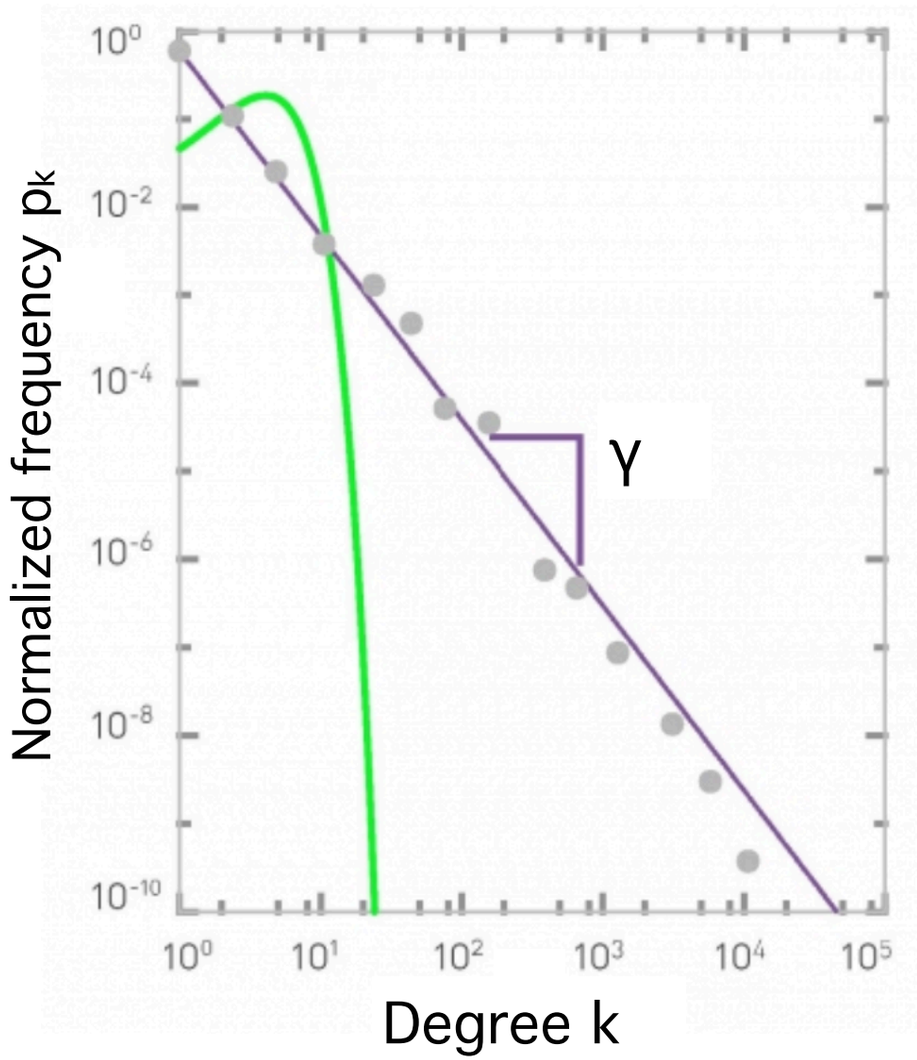

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Networks whose degree distribution follows a power law, are called scale-free.

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Lethality and centrality in protein networks

The most highly connected proteins in the cell are the most important for its survival.

Proteins are traditionally identified on the basis of their individual actions as catalysts, signalling molecules, or building blocks in cells and microorganisms. But our post-genomic view is expanding the protein's role into an element in a network of protein–protein interactions as well, in which it has a contextual or cellular function within functional modules[1,2]. Here we provide quantitative support for this idea by demonstrating that the phenotypic consequence of a single gene deletion in the yeast *Saccharomyces cerevisiae* is affected to a large extent by the topological position of its protein product in the complex hierarchical web of molecular interactions.

The *S. cerevisiae* protein–protein interaction network we investigate has 1,870 proteins as nodes, connected by 2,240 identified direct physical interactions, and is derived from combined, non-overlapping data[3,4], obtained mostly by systematic two-hybrid analyses[3]. Owing to its size, a complete map of the network (Fig. 1a), although informative, in itself offers little insight into its large-scale characteristics. Our first goal was therefore to identify the architecture of this network, determining whether it is best described by an inherently uniform exponential topology, with proteins on average possessing the same number of links, or by a highly heterogeneous

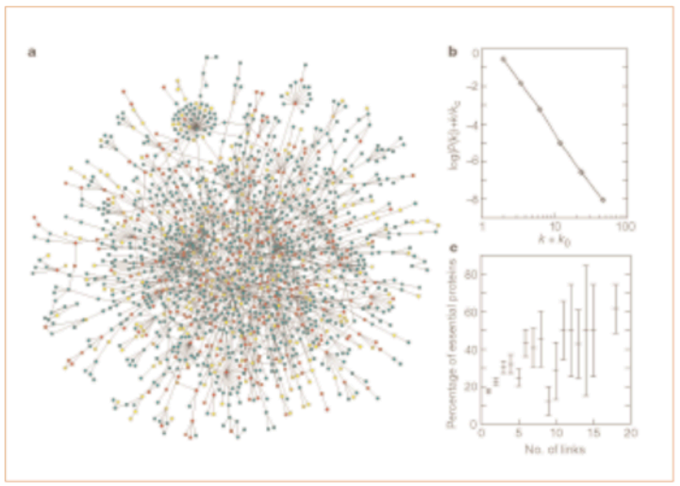

Figure 1 Characteristics of the yeast proteome. **a**, Map of protein–protein interactions. The largest cluster, which contains ~78% of all proteins, is shown. The colour of a node signifies the phenotypic effect of removing the corresponding protein (red, lethal; green, non-lethal; orange, slow growth; yellow, unknown). **b**, Connectivity distribution $P(k)$ of interacting yeast proteins, giving the probability that a given protein interacts with k other proteins. The exponential cut-off[6] indicates that the number of proteins with more than 20 interactions is slightly less than expected for pure scale-free networks. In the absence of data on the link directions, all interactions have been considered as bidirectional. The parameter controlling the short-length scale correction has value $k_0=1$. **c**, The fraction of essential proteins with exactly k links versus their connectivity, k, in the yeast proteome. The list of 1,572 mutants with known phenotypic profile was obtained from the Proteome database[13]. Detailed statistical analysis, including $r=0.75$ for Pearson's linear correlation coefficient, demonstrates a positive correlation between lethality and connectivity. For additional details, see http://www.nd.edu/~networks/cell.

Jeong et al *Nature* 2001

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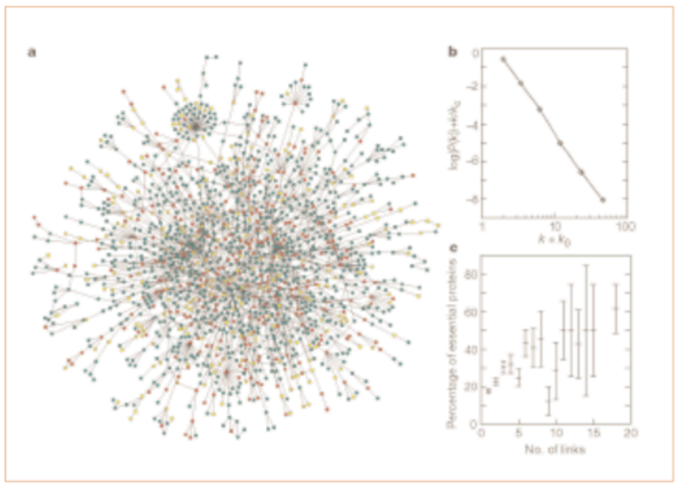

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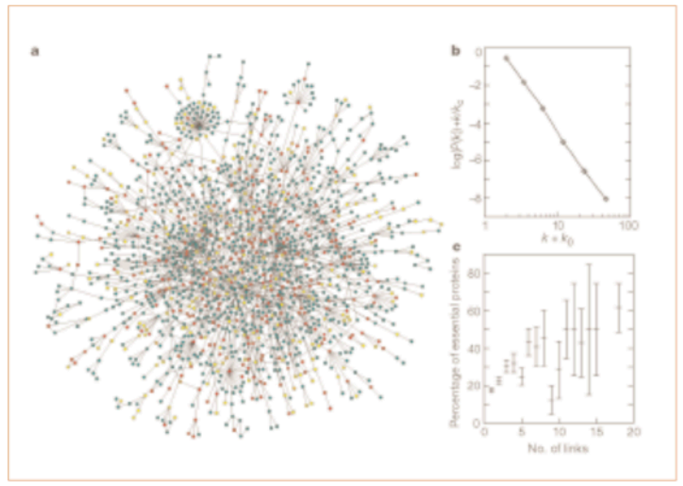

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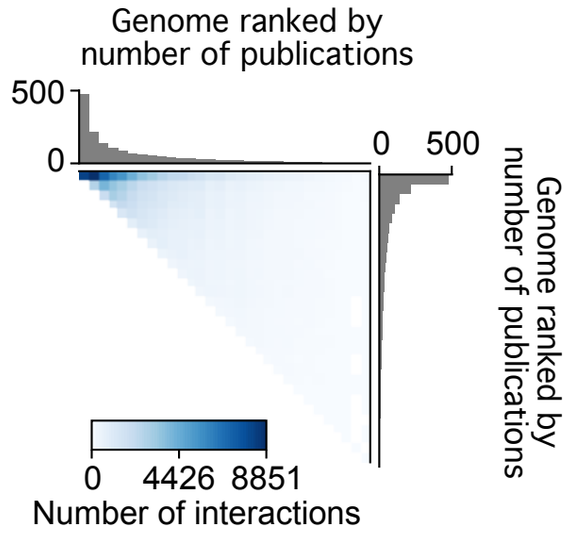
Jeong et al *Nature* 2001

Are essential genes more highly studied?



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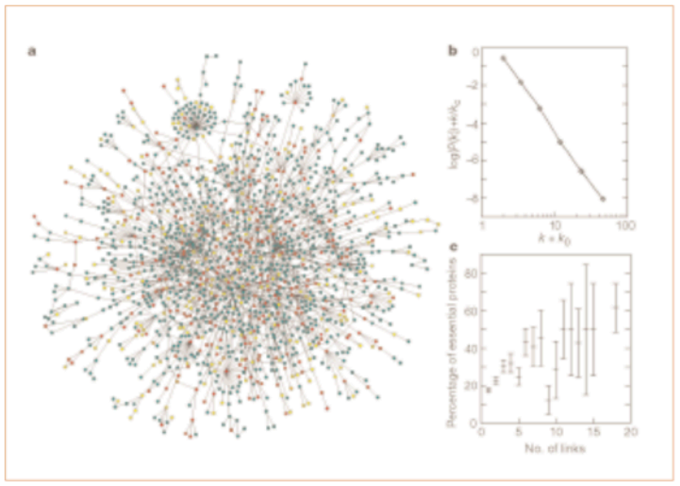

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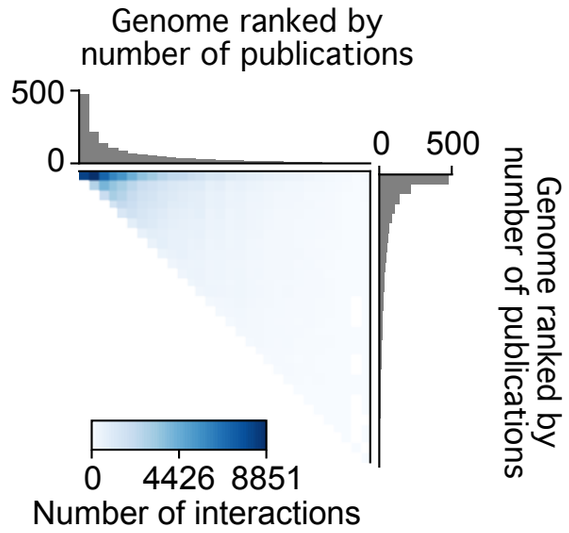
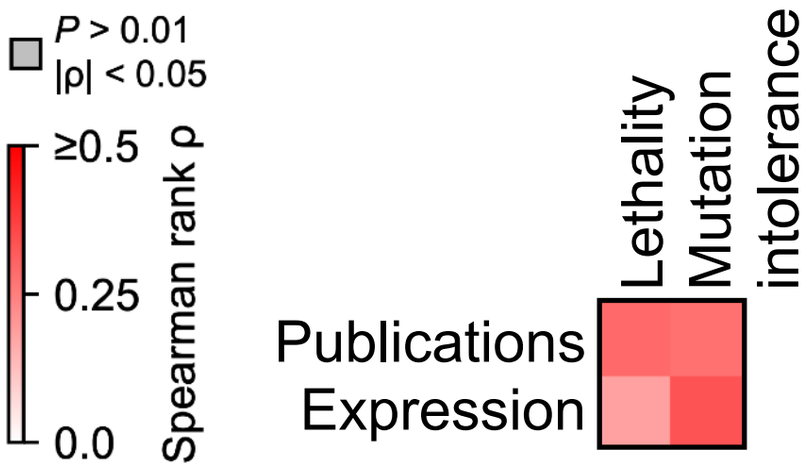


Degree distributions are influenced by technical assay biases



Luck et al *Nature* 2020

My protein has many interaction partners, does it mean that it is of functional importance?

Lethality and centrality in protein networks

The most highly connected proteins in the cell are the most important for its survival.

Proteins are traditionally identified on the basis of their individual actions as catalysts, signalling molecules, or building blocks in cells and microorganisms. But our post-genomic view is expanding the protein's role into an element in a network of protein–protein interactions as well, in which it has a contextual or cellular function within functional modules[1,2]. Here we provide quantitative support for this idea by demonstrating that the phenotypic consequence of a single gene deletion in the yeast *Saccharomyces cerevisiae* is affected to a large extent by the topological position of its protein product in the complex hierarchical web of molecular interactions.

The *S. cerevisiae* protein–protein interaction network we investigate has 1,870 proteins as nodes, connected by 2,240 identified direct physical interactions, and is derived from combined, non-overlapping data[3,4], obtained mostly by systematic two-hybrid analyses[3]. Owing to its size, a complete map of the network (Fig. 1a), although informative, in itself offers little insight into

Our first g
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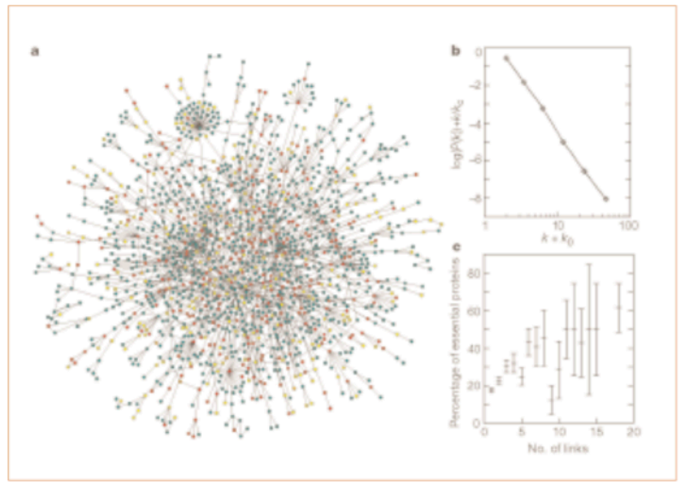

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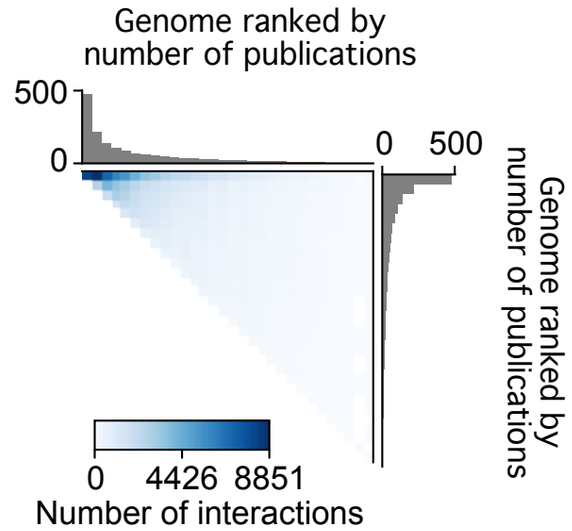
Cited 3,266 times!

Jeong et al *Nature* 2001

Are essential genes more highly studied?



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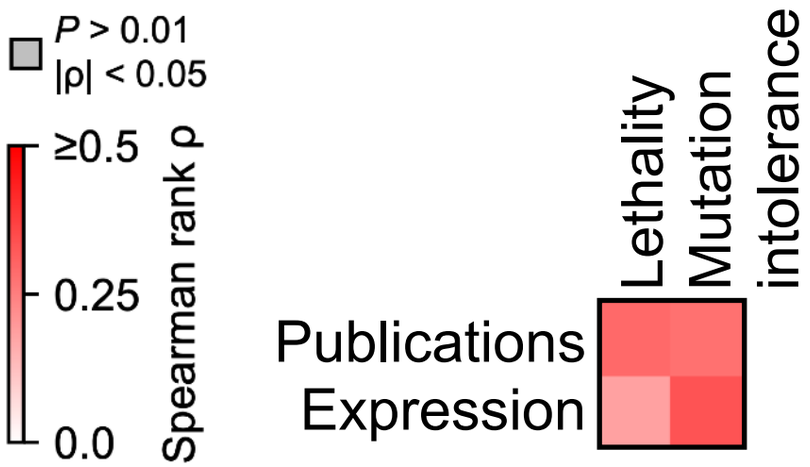

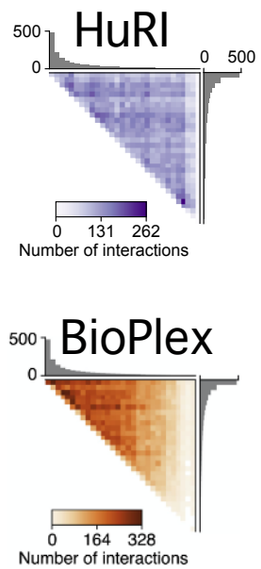

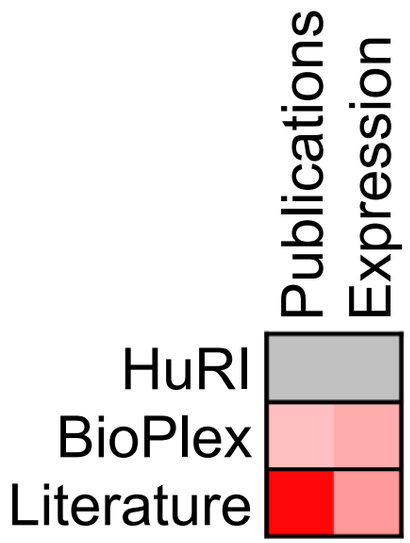

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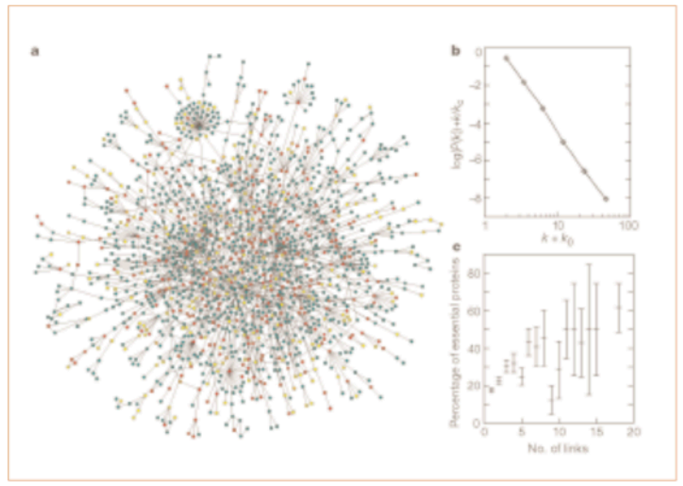

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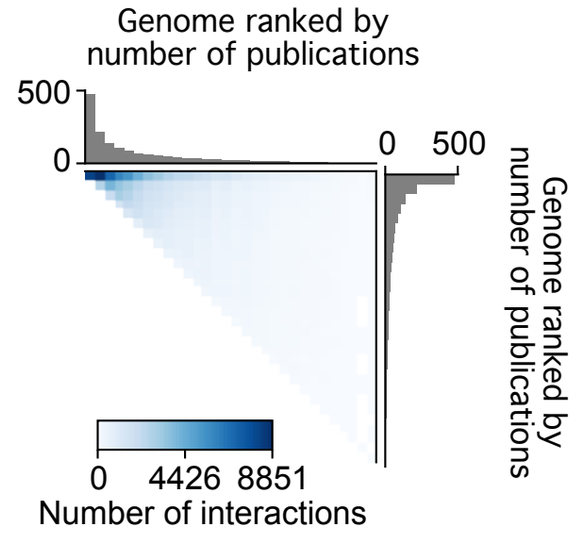

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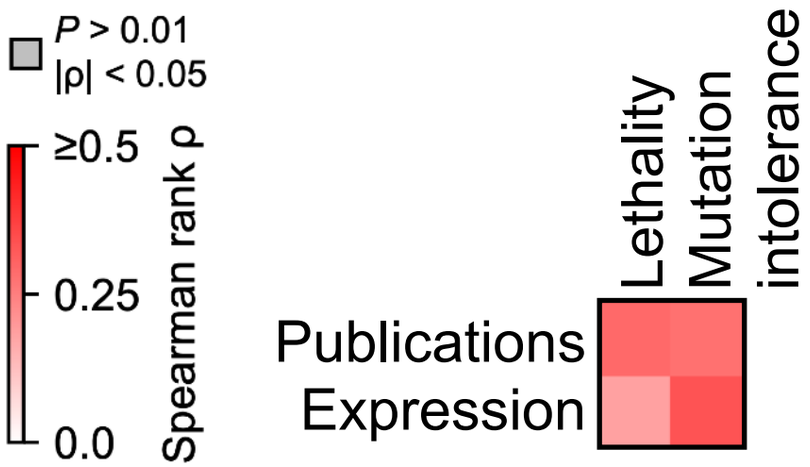
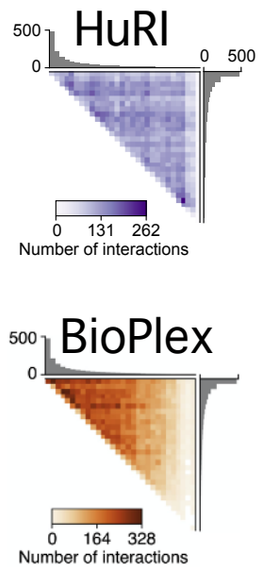
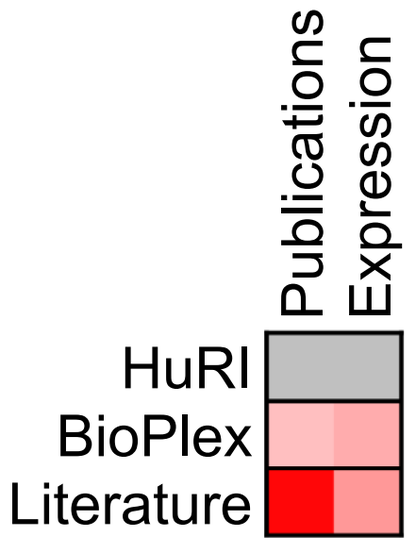
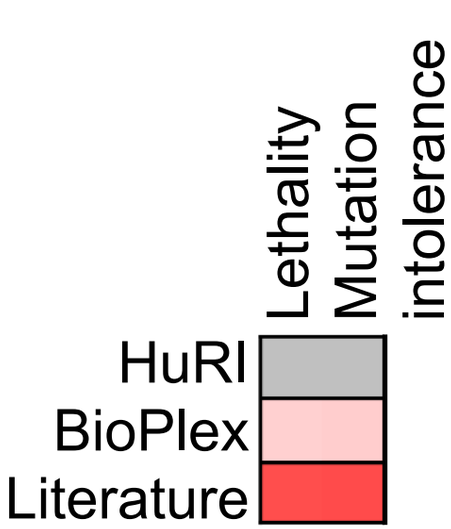


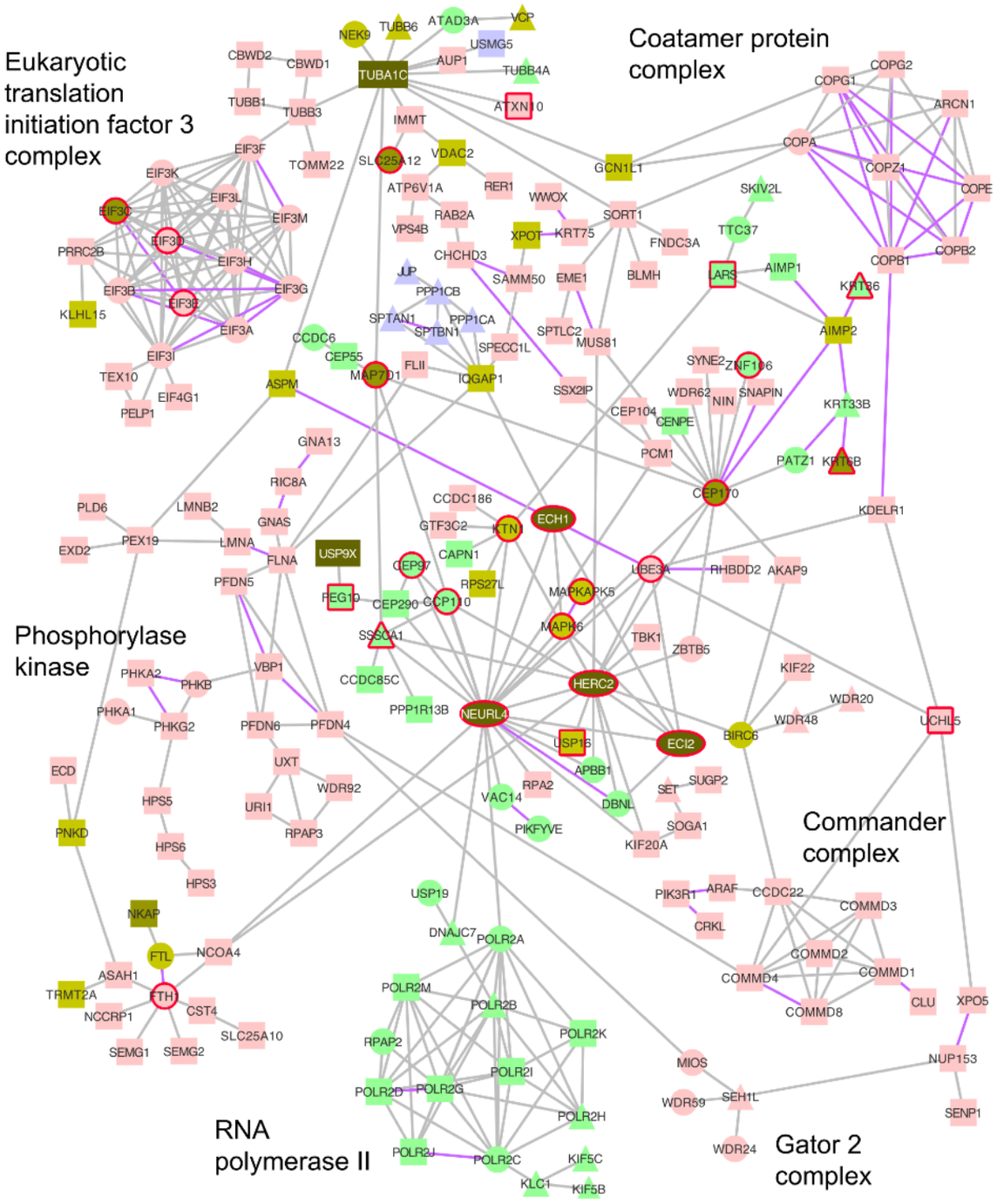






Luck et al *Nature* 2020

Finding communities in graphs



Martinez-Noel et al *JMB* 2018, networksciencebook.com

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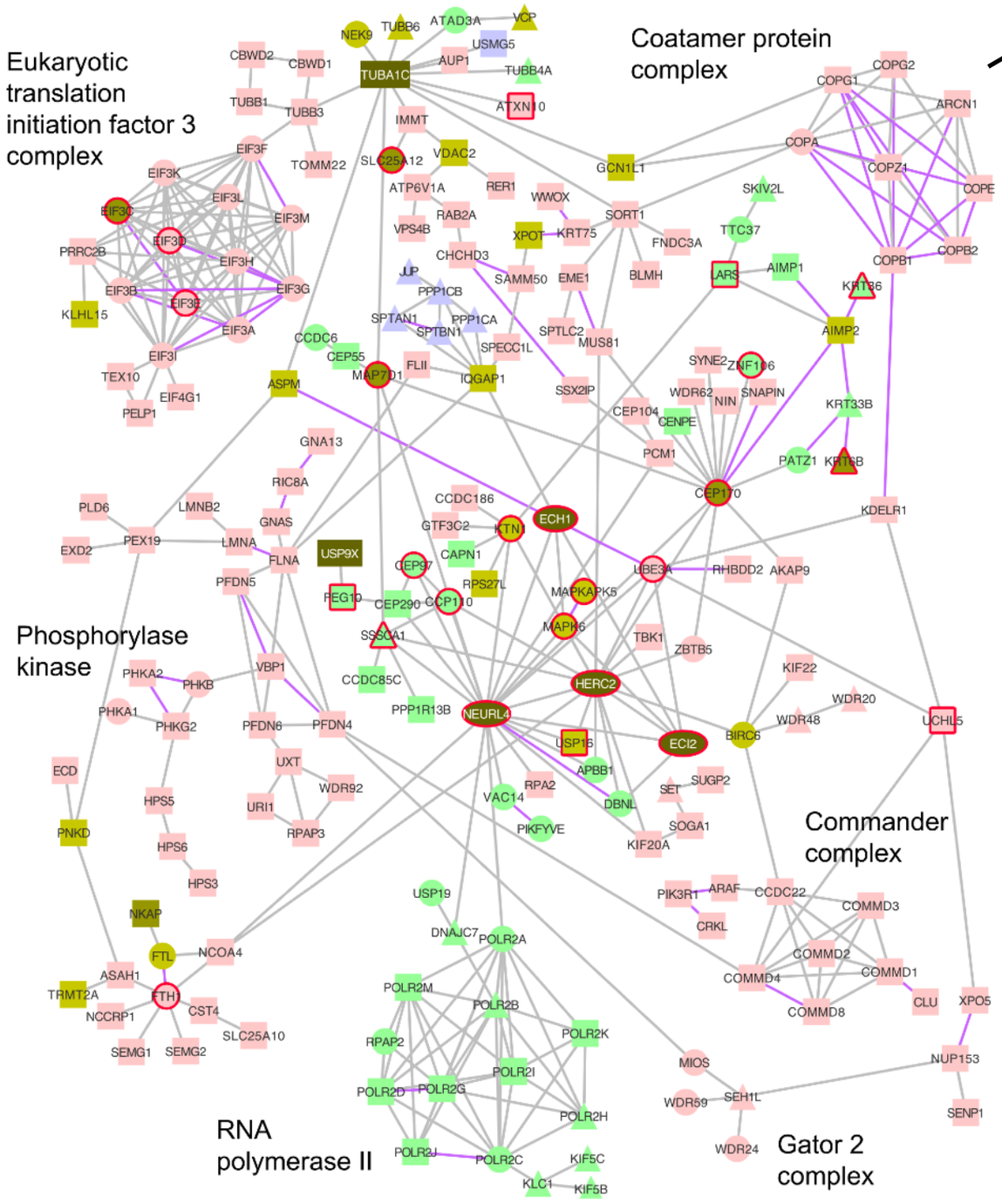
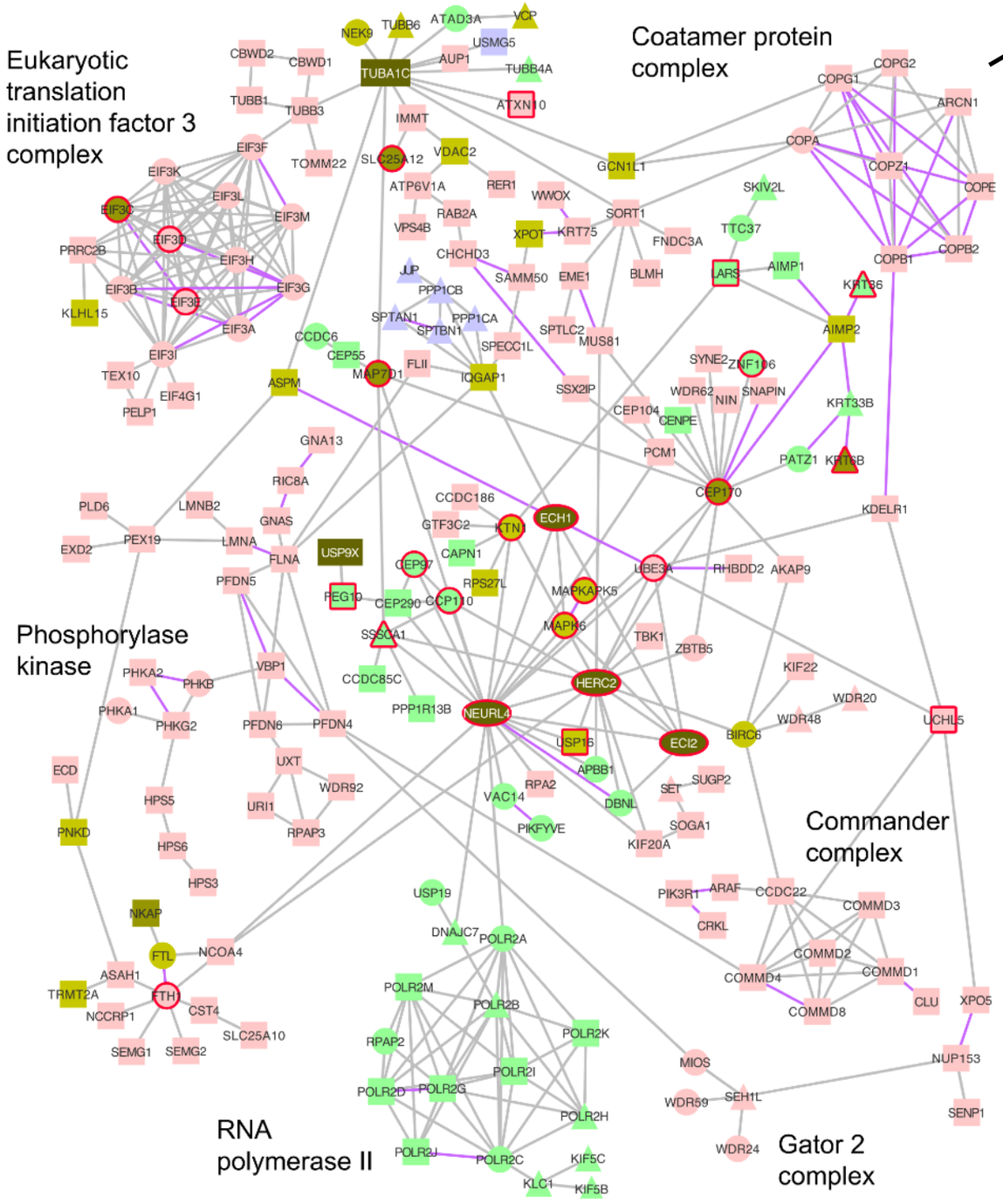


Protein complexes show as clusters in a network

Martinez-Noel et al *JMB* 2018, networksciencebook.com

Finding communities in graphs



Protein complexes show as clusters in a network

↓

Communities are locally dense connected subgraphs in a network

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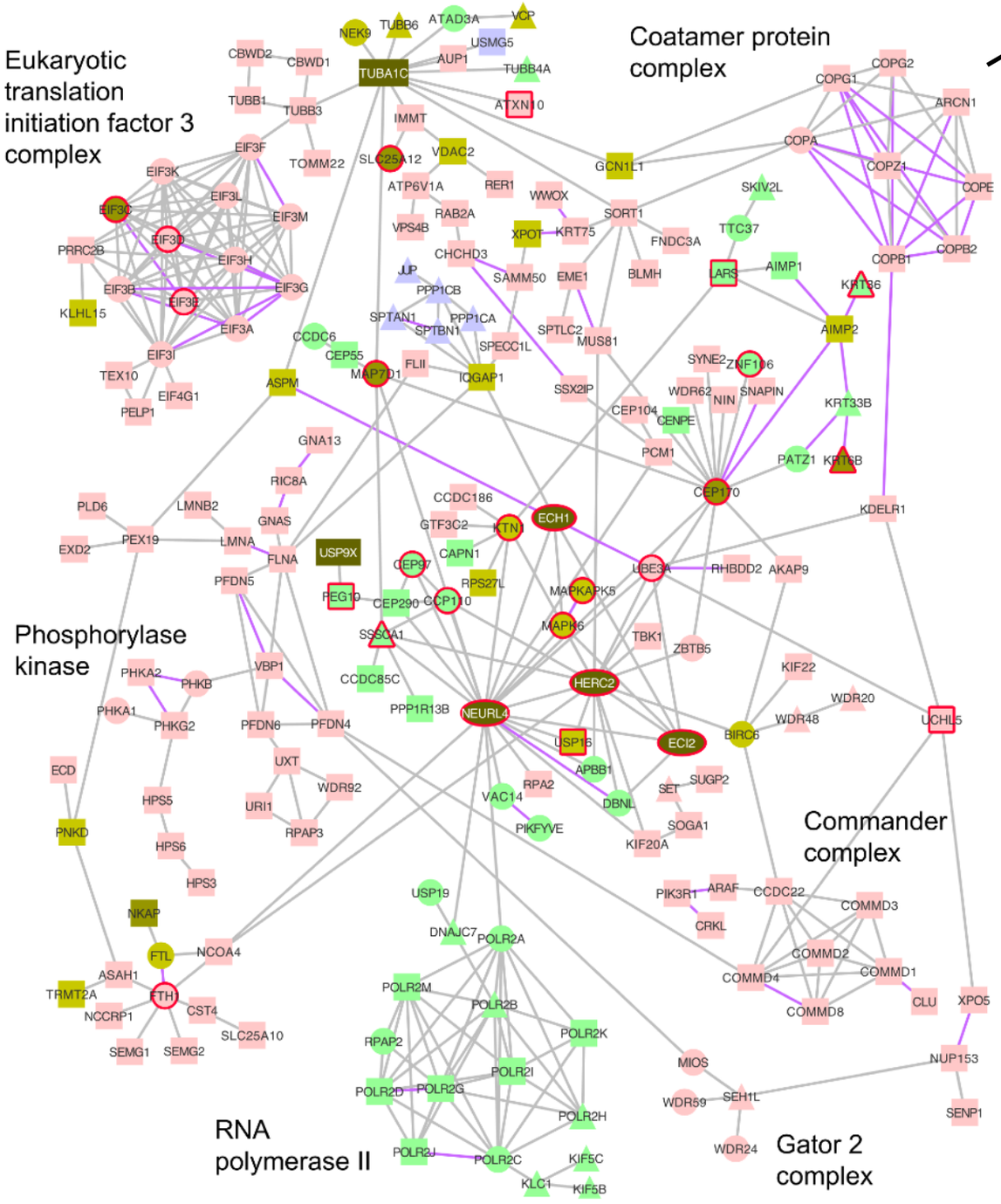
Finding communities in graphs



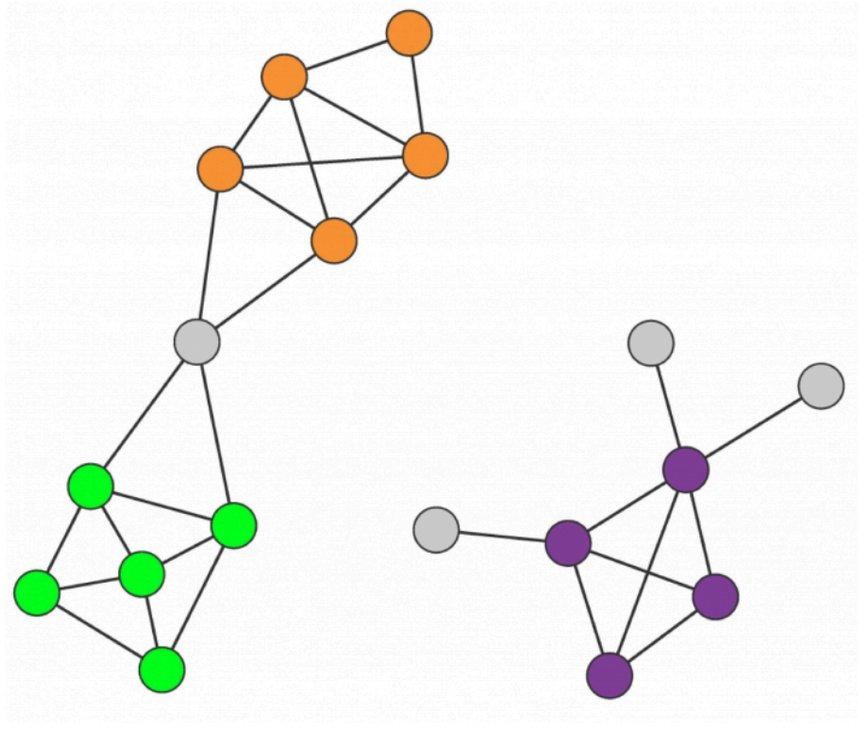
Protein complexes show as clusters in a network

↓

Communities are locally dense connected subgraphs in a network

↓

Vertex of a community is more linked to other vertices of that community than to vertices outside



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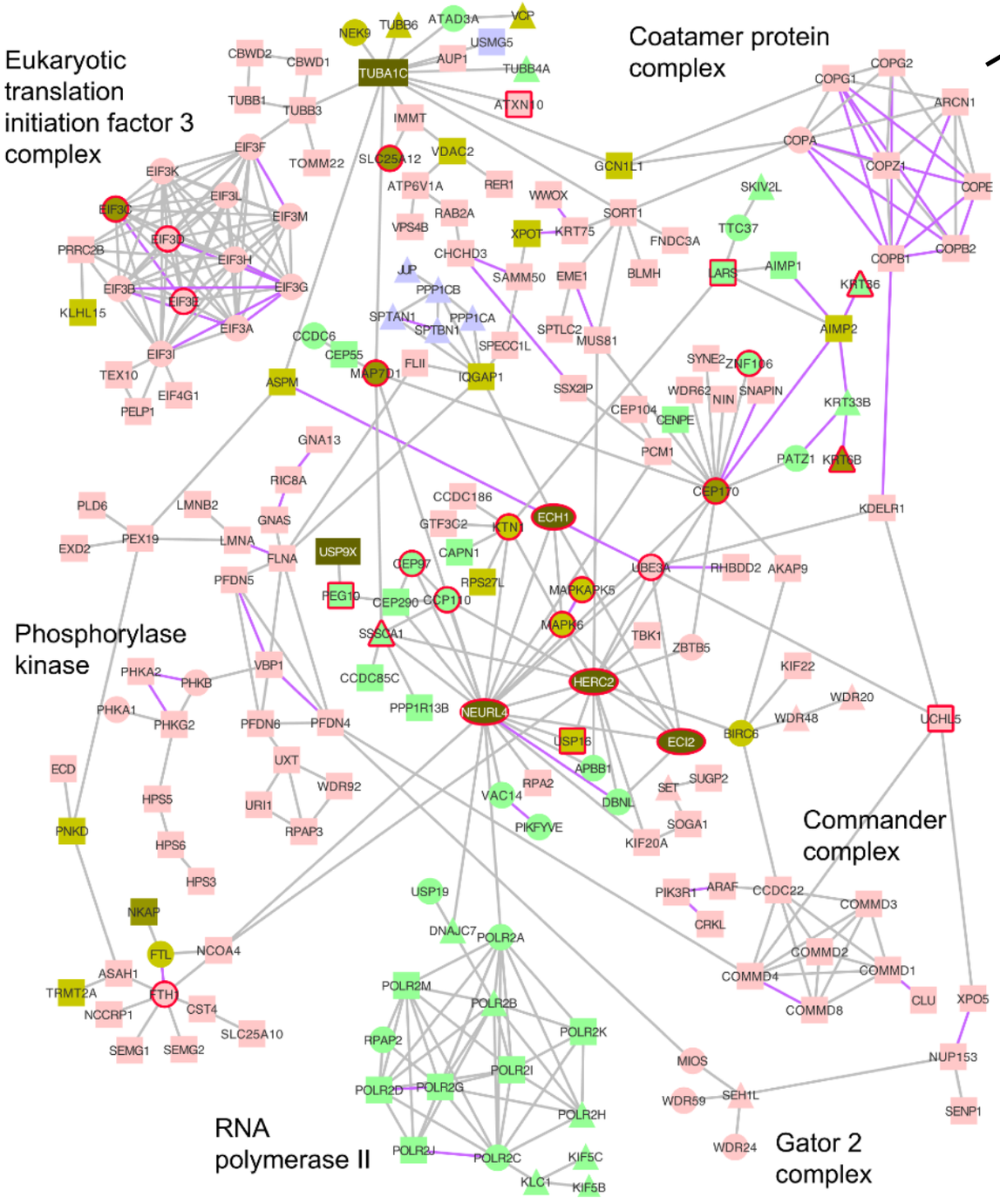
Finding communities in graphs



Numerous algorithms exist to find communities in a graph

Protein complexes show as clusters in a network

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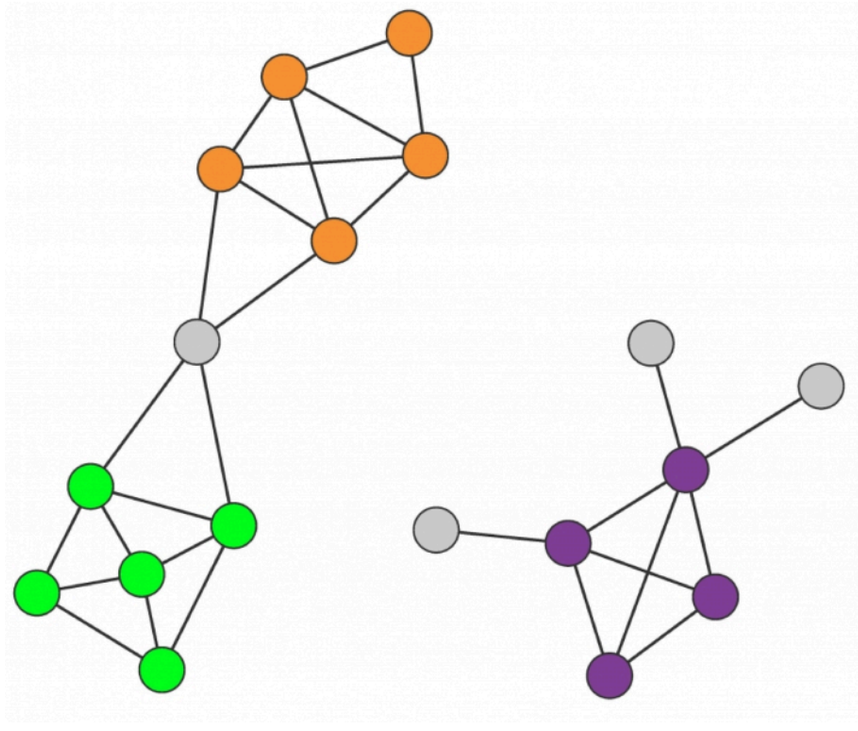

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Can I find new protein complexes or complex members?

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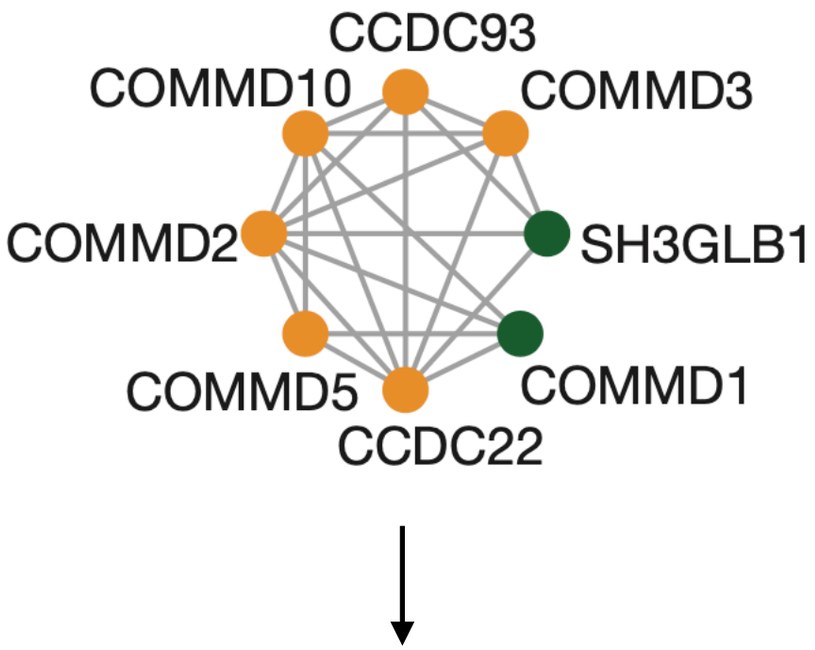
Identification of Commander complex



Role in embryonic development

Wan et al *Science* 2015

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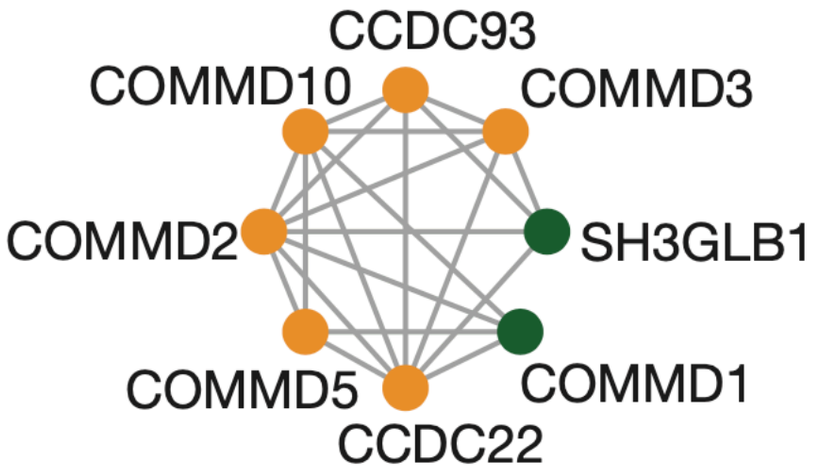
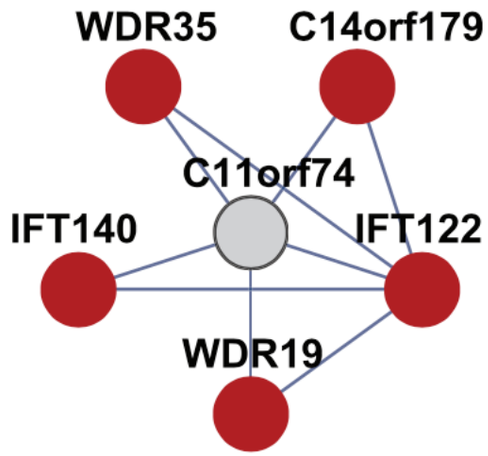


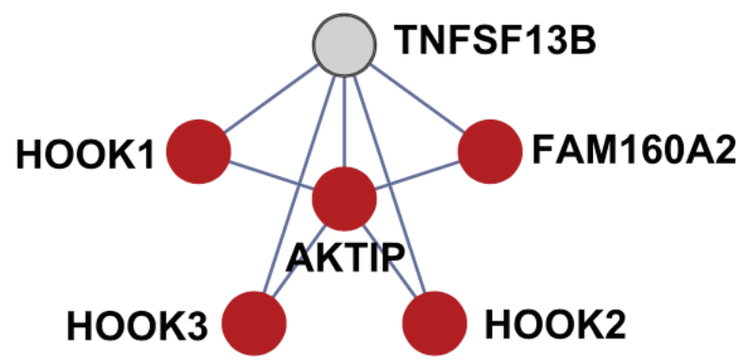
Role in embryonic development

Identification of new complex members

Intraciliary Transport Particle A



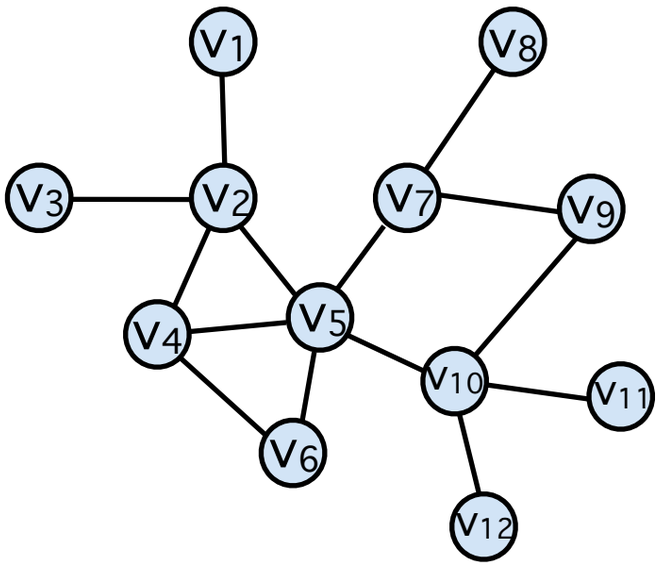
FHF complex



Wan et al *Science* 2015

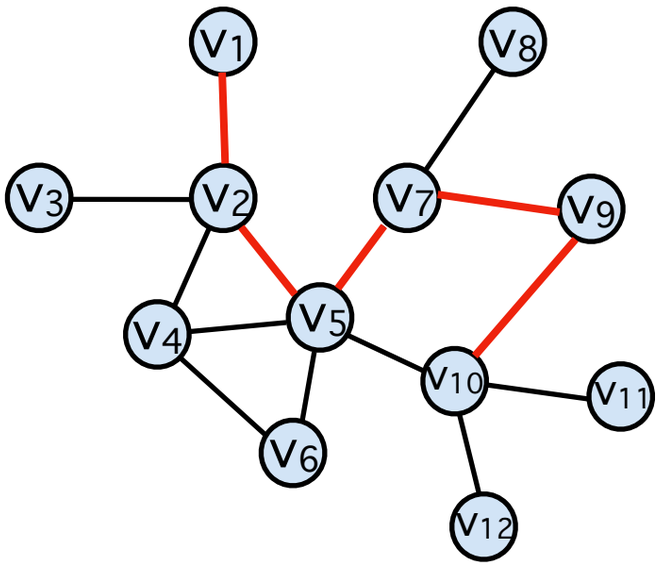
Huttlin et al *Cell* 2015

Shortest paths in graphs and betweenness centrality



A path between two vertices is formed by
the edges that lead from one vertex to the other.

Shortest paths in graphs and betweenness centrality



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A path from v_1 to v_{10}

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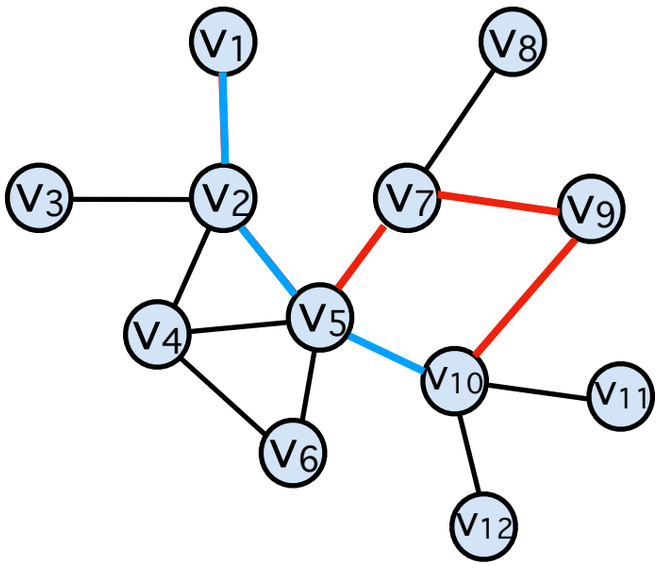

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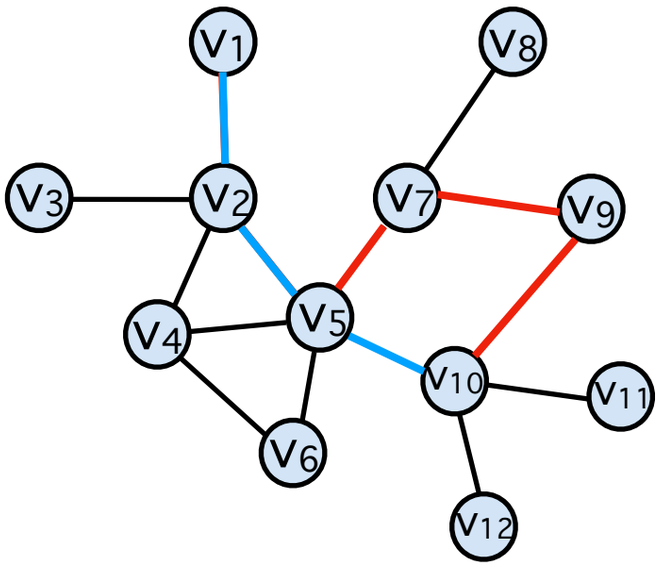

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-> a path can represent information flow in a graph

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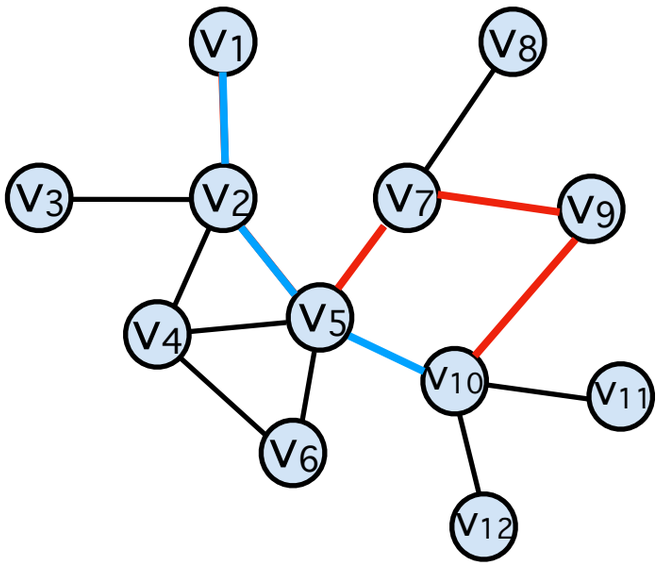

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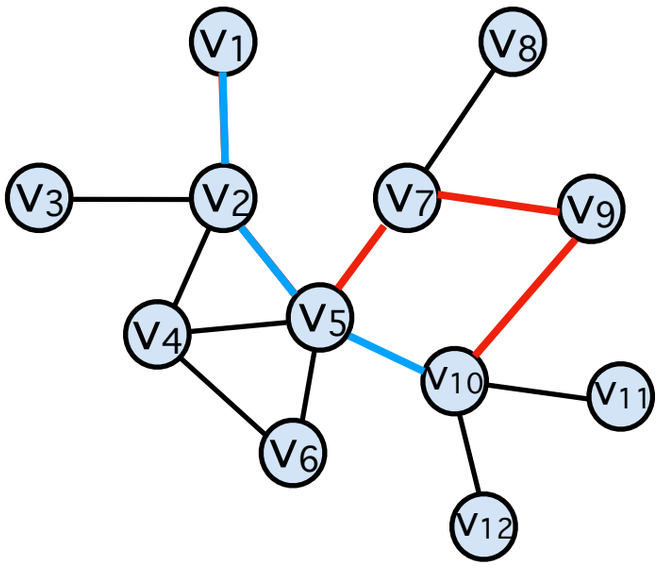
How many shortest paths cross a vertex?

Shortest paths in graphs and betweenness centrality



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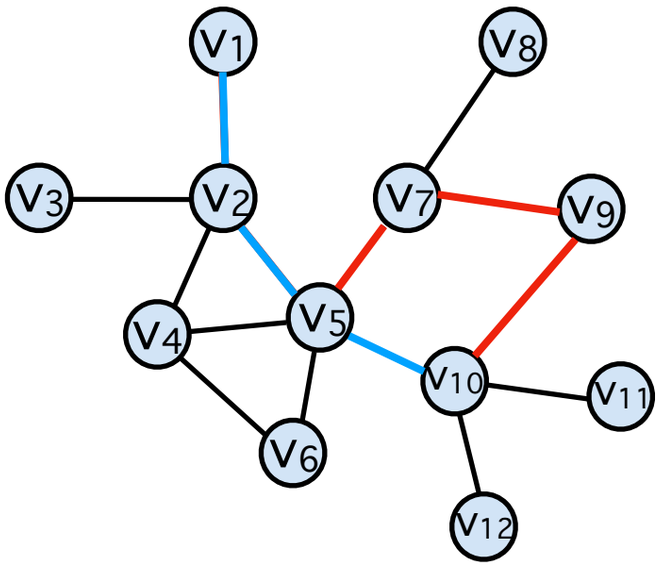
How many shortest paths cross a vertex? ⟶ Node betweenness

Shortest paths in graphs and betweenness centrality



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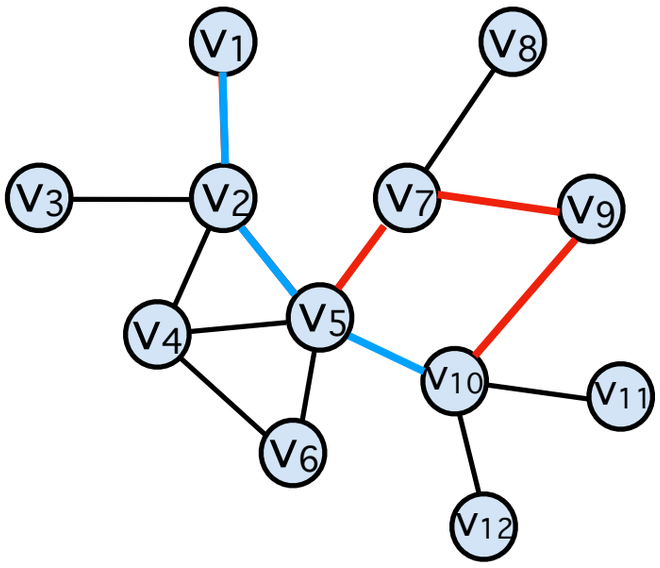

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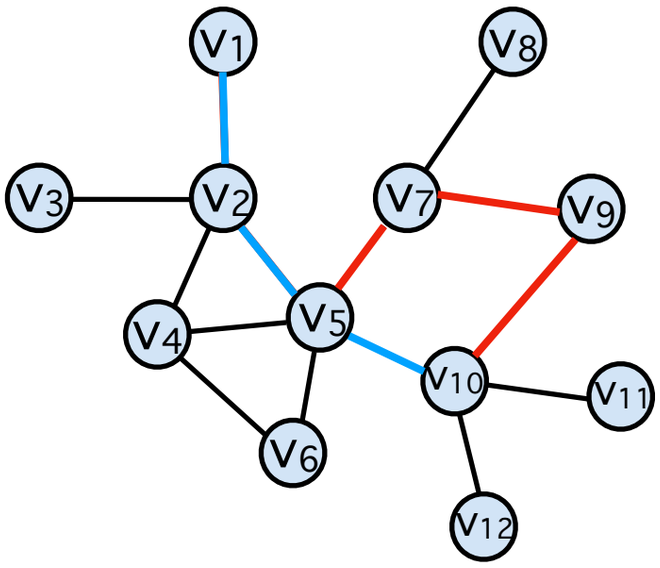

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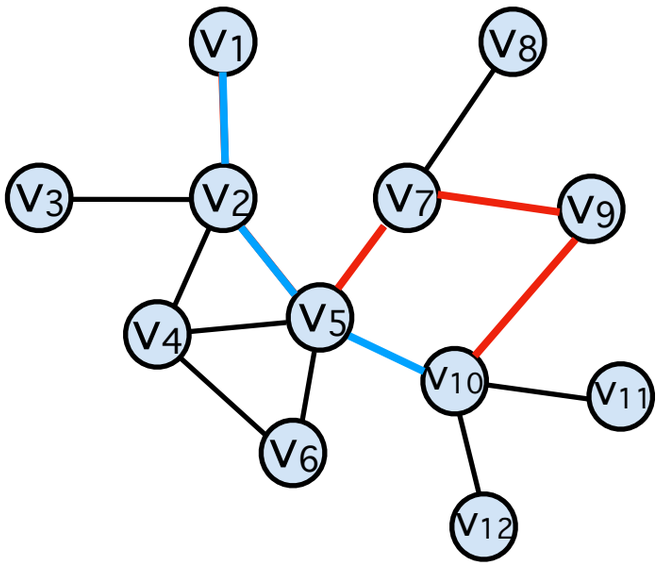
How many shortest paths go over an edge? ⟶ Edge betweenness

High betweenness

↓

Important for system

Shortest paths in graphs and betweenness centrality



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High betweenness

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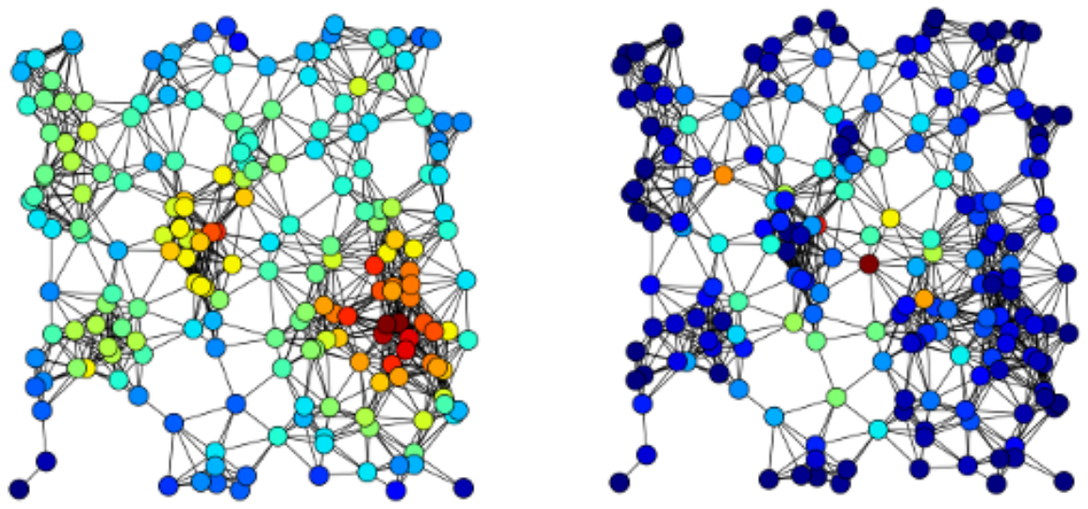
Important for system

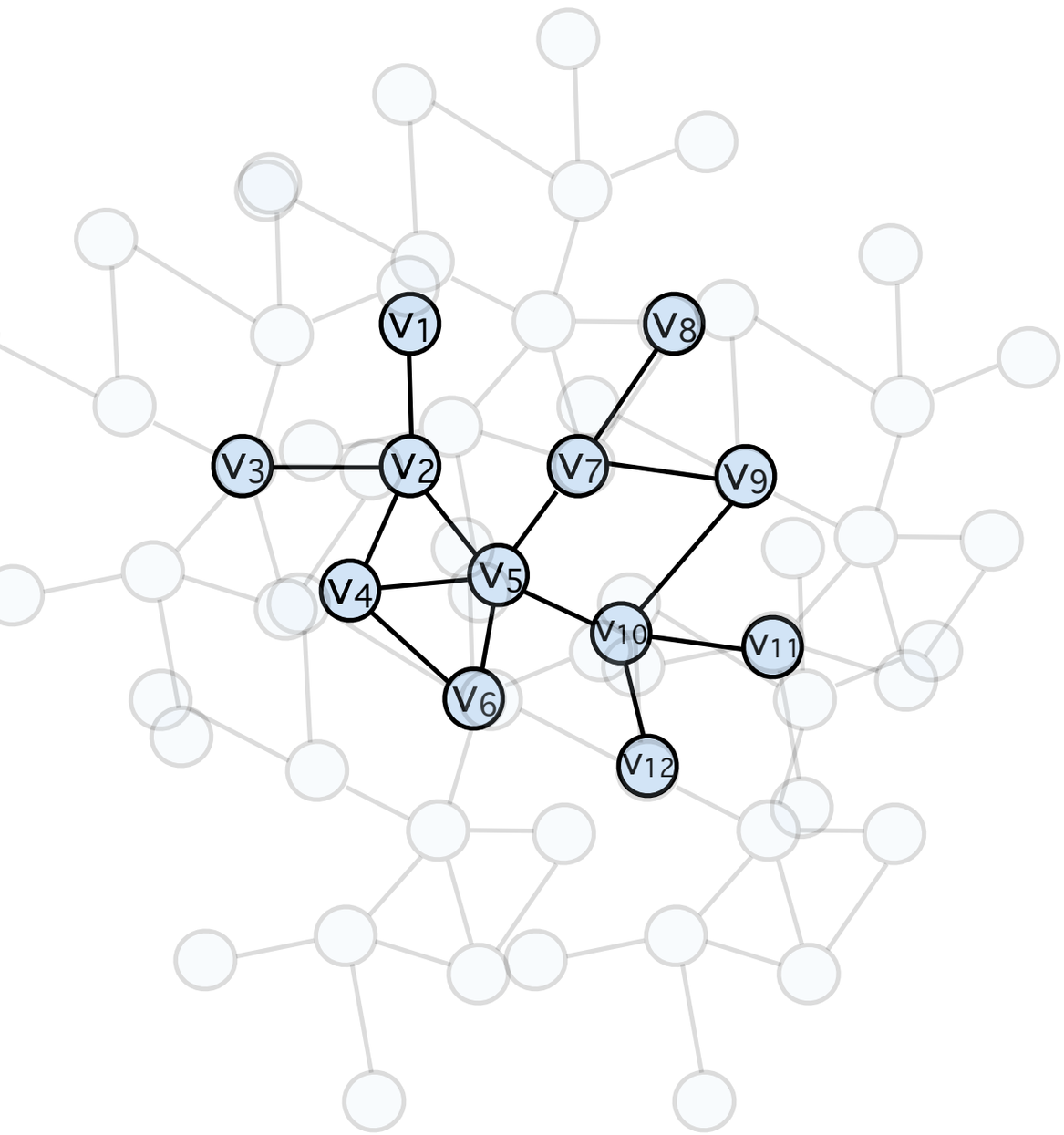
High degree ≠ high betweenness



Tapiocozzo, https://commons.wikimedia.org/w/index.php?curid=39064835

Measuring closeness in networks

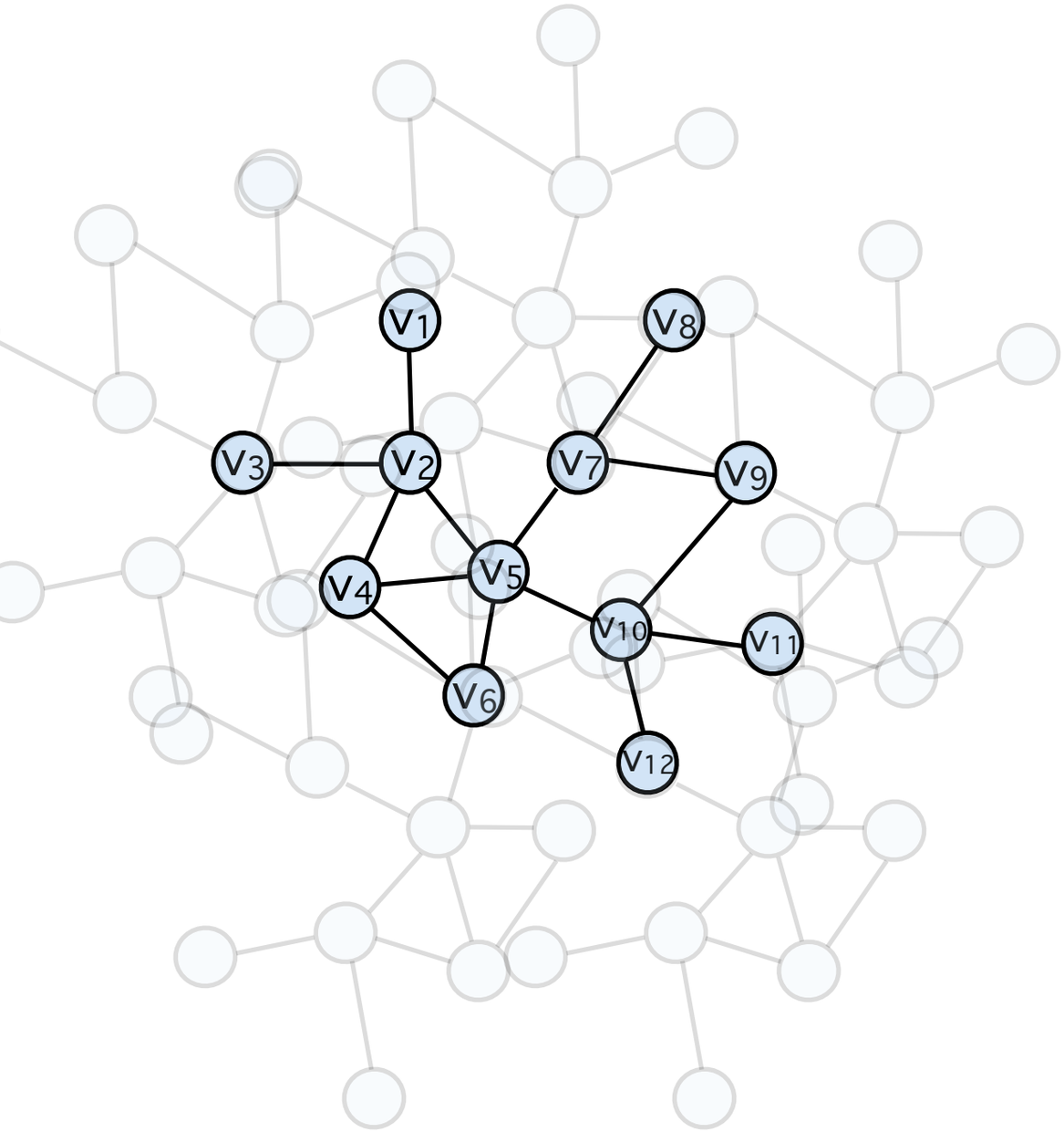
Do candidate proteins from my screen tend to interact with each other?



Measuring closeness in networks

Do candidate proteins from my screen tend to interact with each other?

-> count number of edges between vertices that are candidate proteins
or
calculate average shortest path between them:



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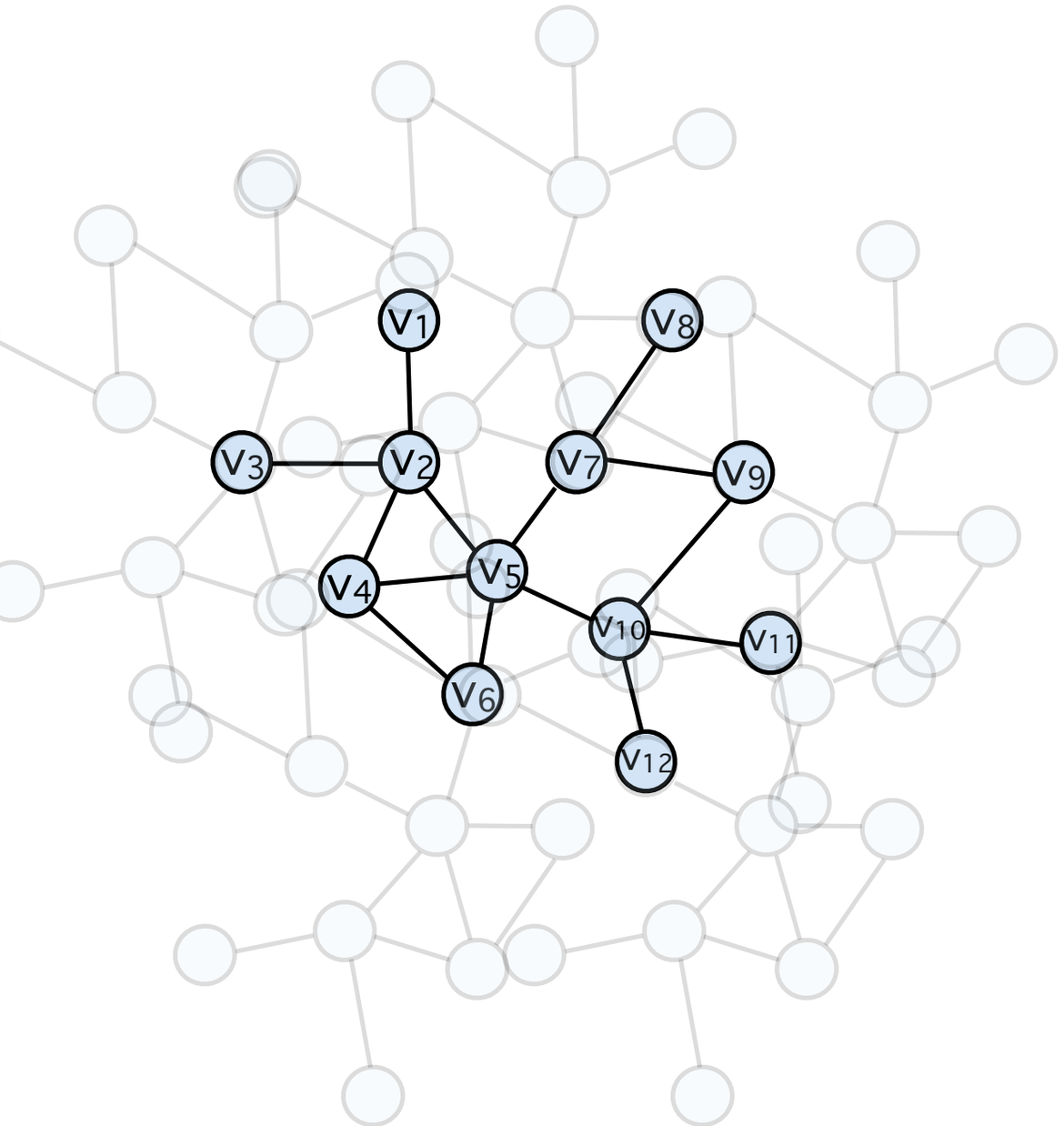


How close are all the vertices v_1 to v_{12} to each other?

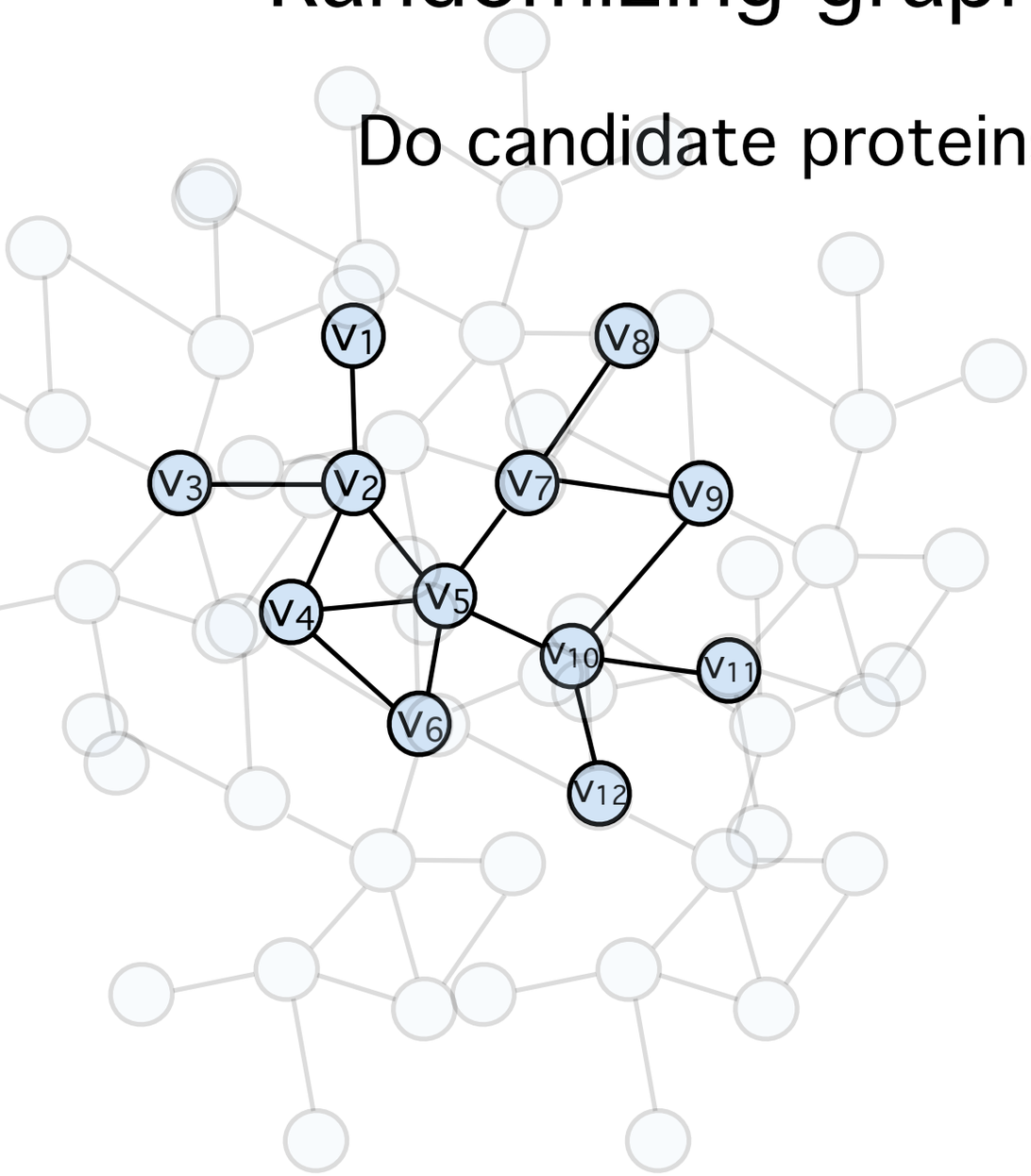
↓

Calculate the average shortest path:

$$L_G = \frac{1}{N \cdot (N-1)} \sum_{\substack{i,j=1 \\ i \neq j}}^{N} d_{i,j} \qquad N = 12$$

Randomizing graphs to compute significances

Do candidate proteins tend to interact with each other?



Number of edges: 14
Average shortest path: 2.17

Randomizing graphs to compute significances

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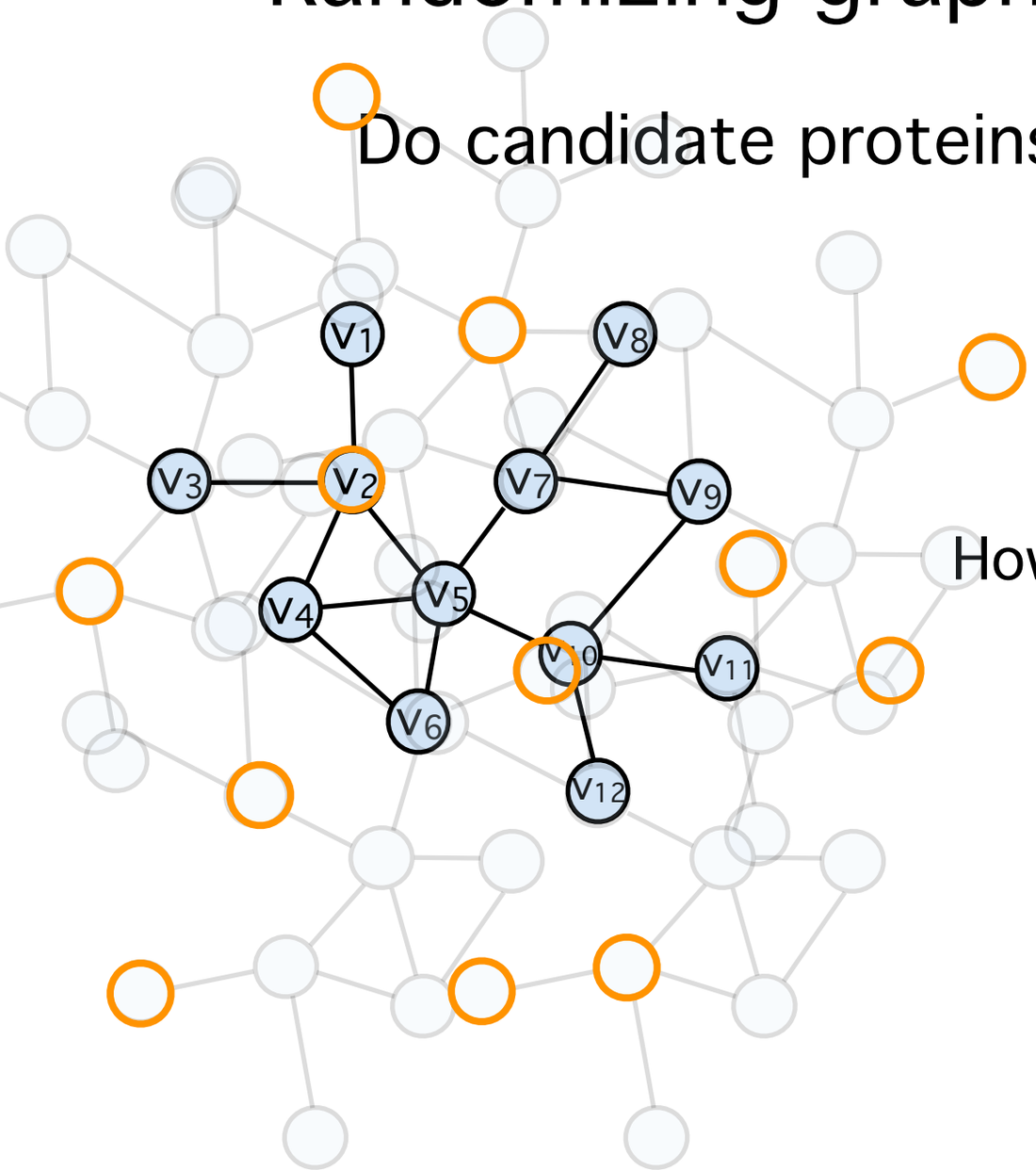

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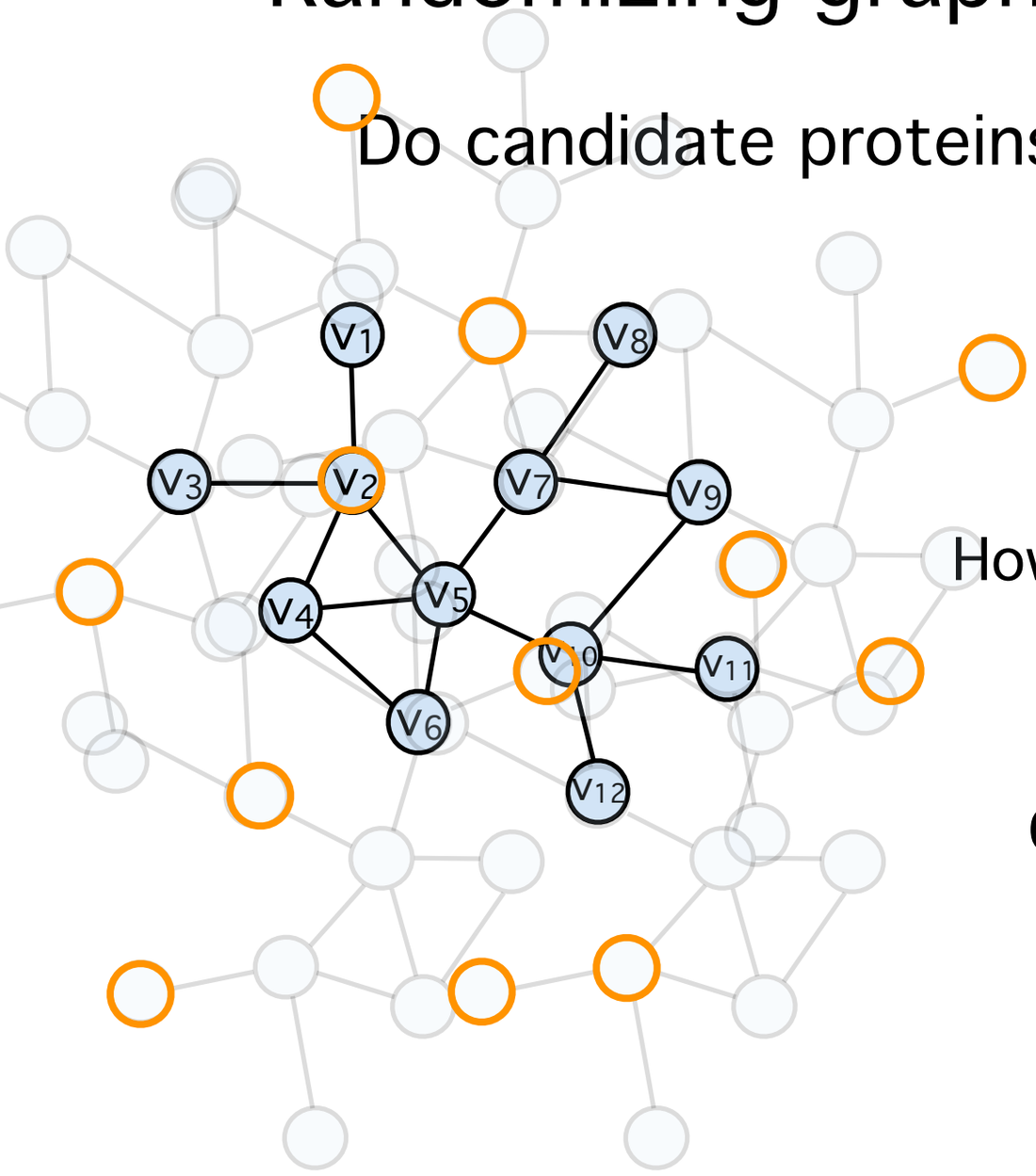
How close would be 12 randomly selected proteins in the network?

Randomizing graphs to compute significances

Do candidate proteins tend to interact with each other?



Number of edges: 14
Average shortest path: 2.17

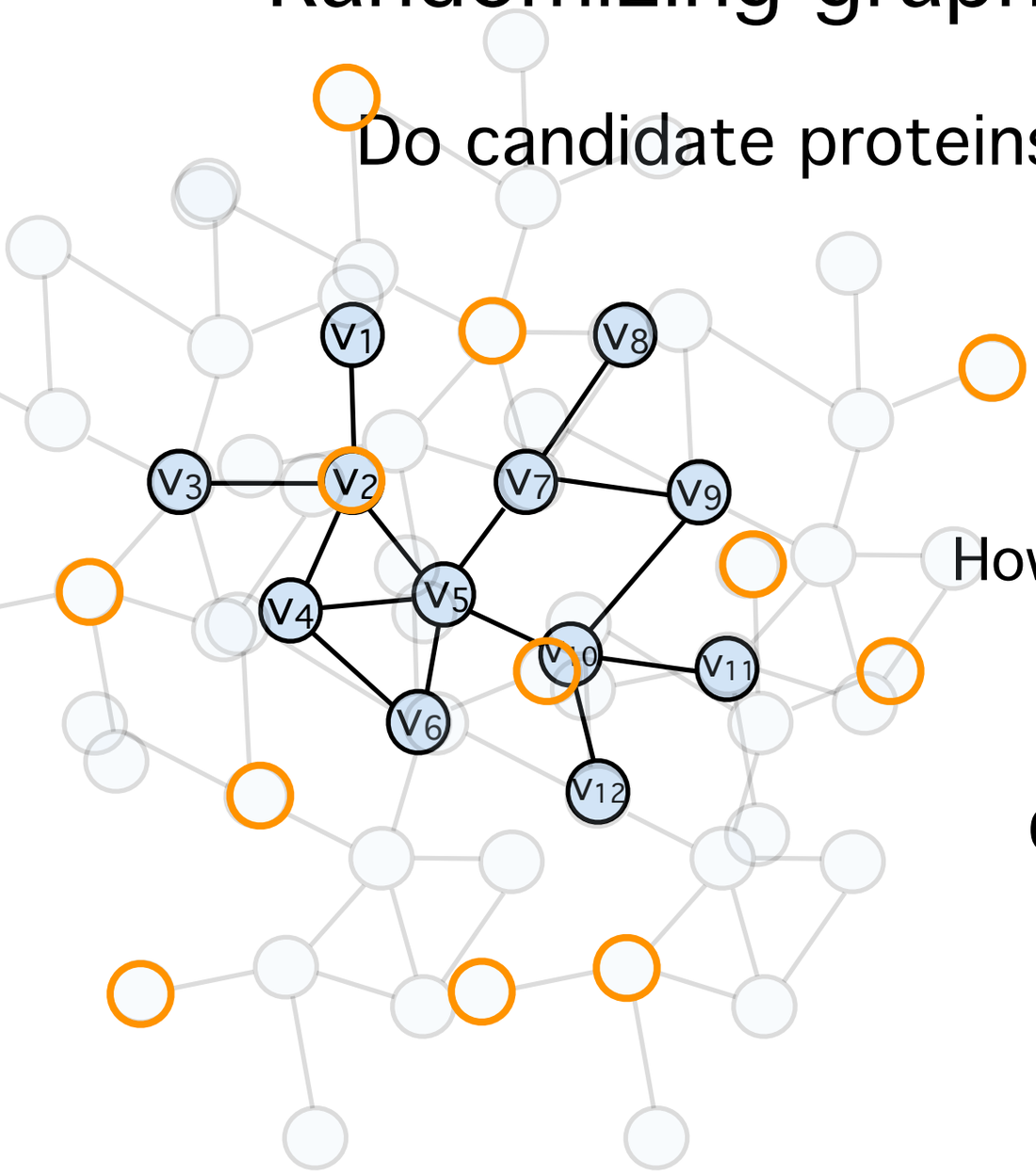
↓

How close would be 12 randomly selected proteins in the network?

↓

Can I randomly choose any 12 proteins in the network?

Randomizing graphs to compute significances



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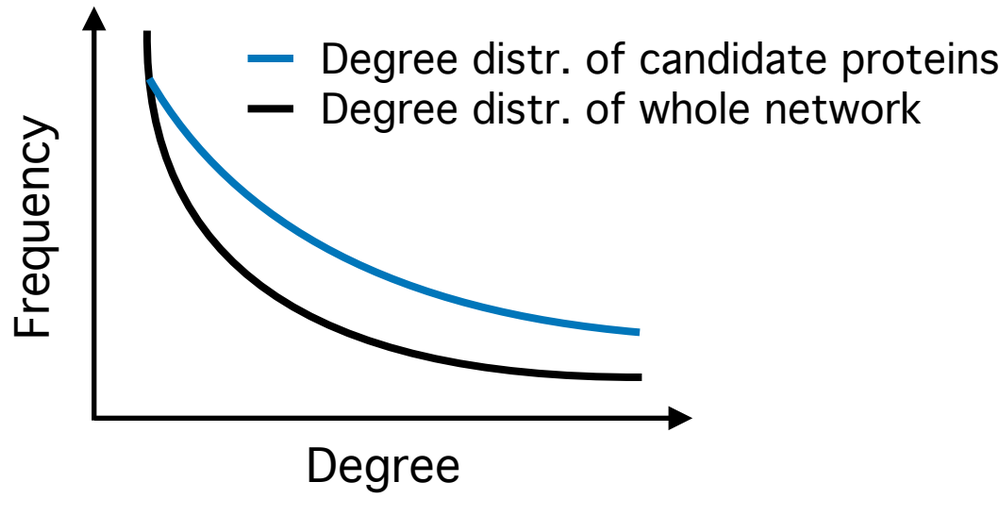

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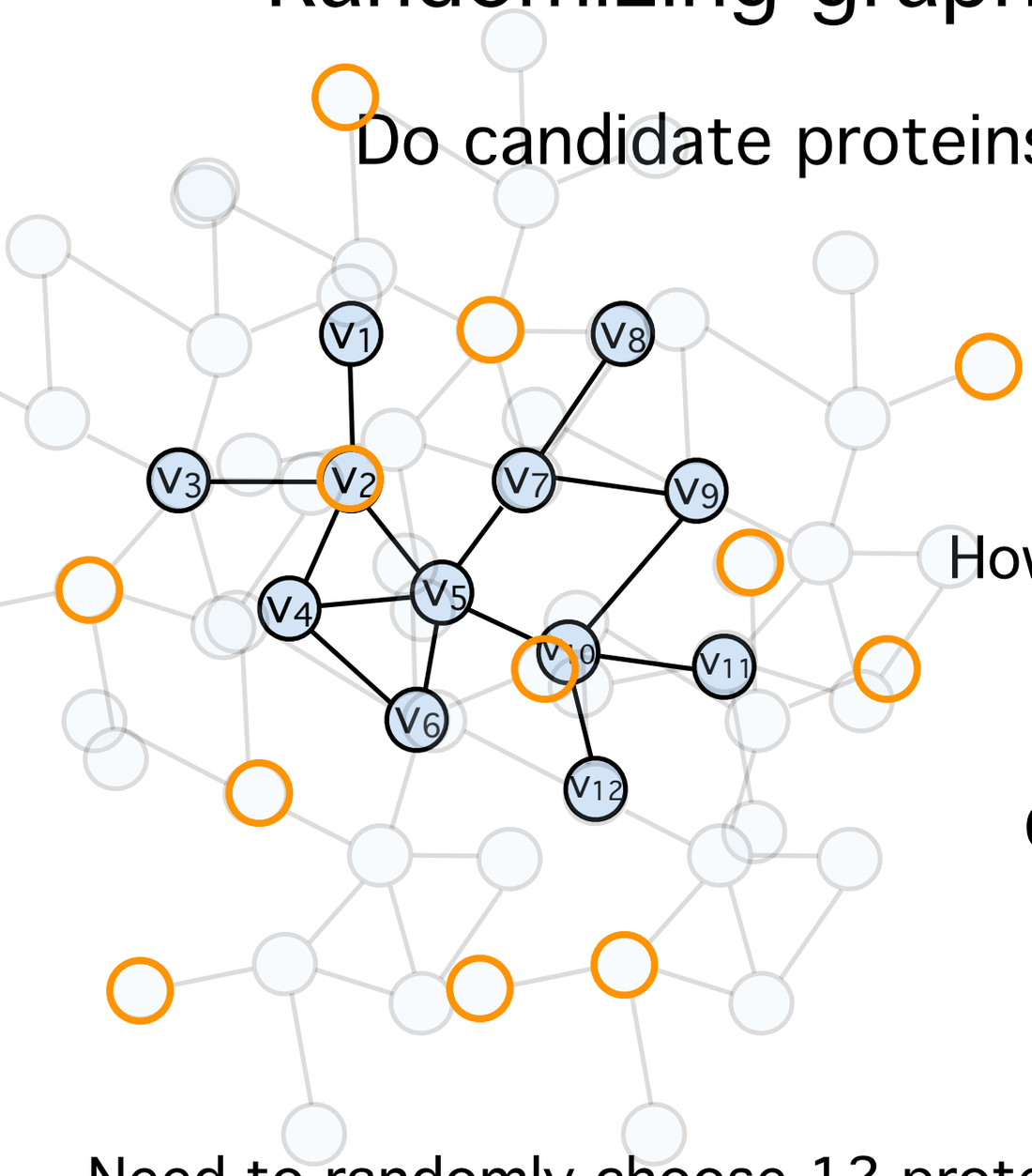

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Can I randomly choose any 12 proteins in the network?

Need to randomly choose 12 proteins with the same degree distribution like candidate proteins

←

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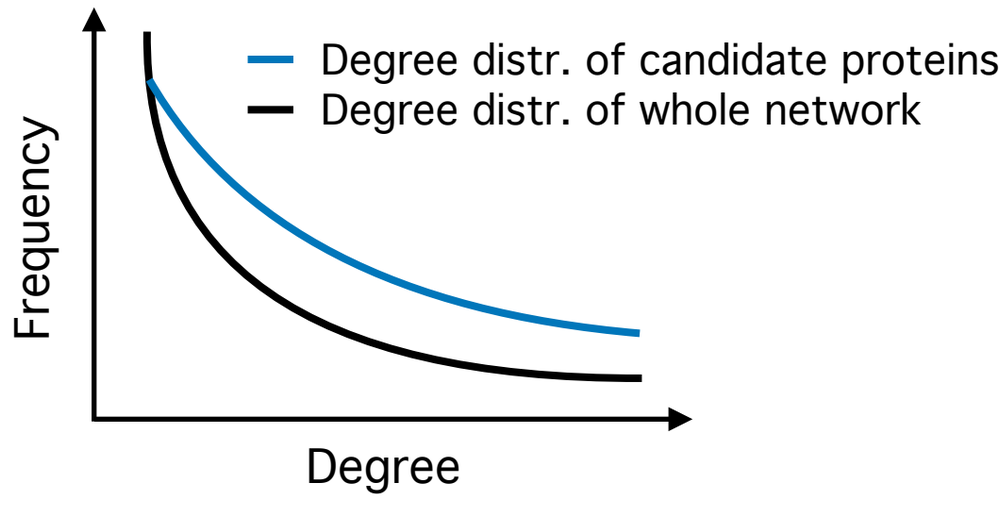

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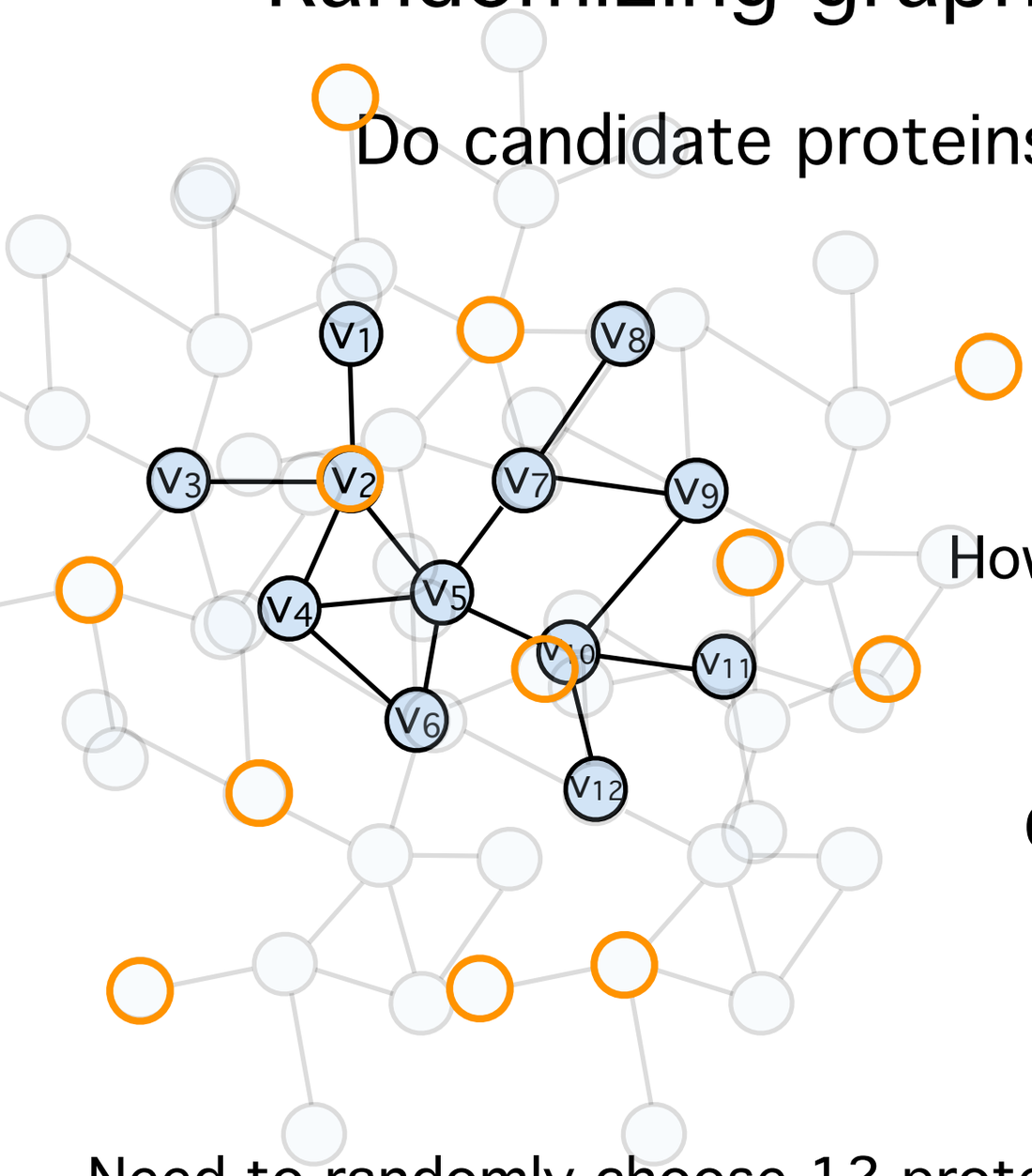

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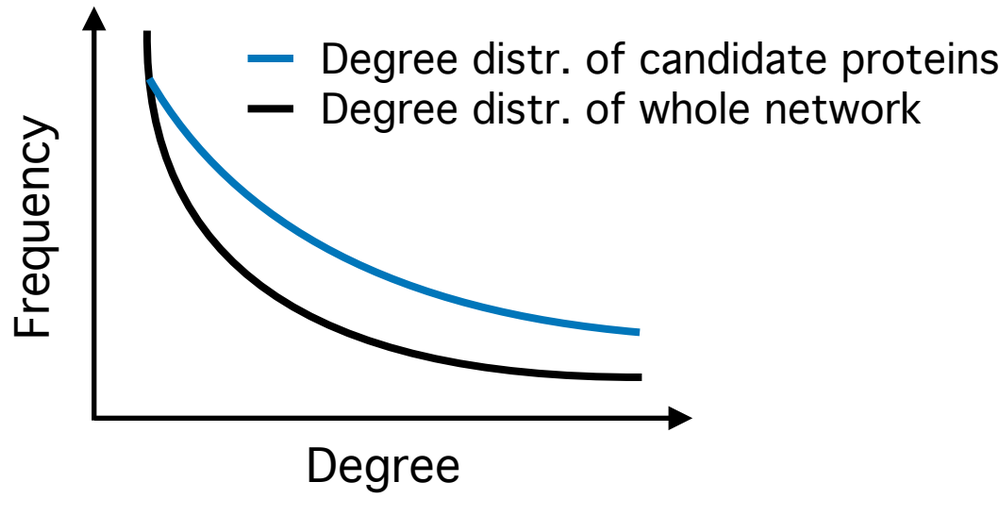


←

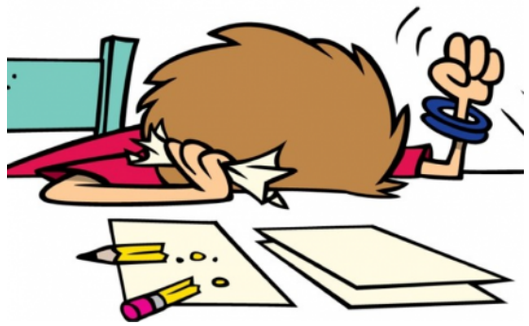
Need to randomly choose 12 proteins with the same degree distribution like candidate proteins

Hard

Randomizing graphs to compute significances

Need to randomly choose 12 proteins with the same degree distribution like candidate proteins

Hard



Randomizing graphs to compute significances

Need to randomly choose 12 proteins with the same degree distribution like candidate proteins

Hard

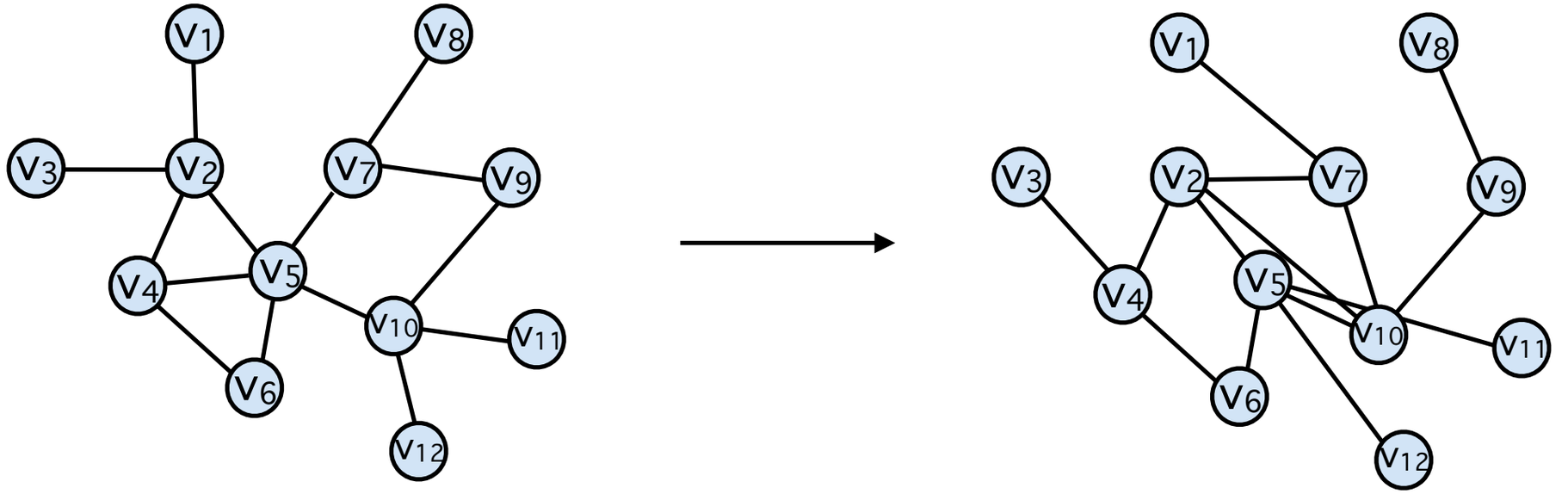
↓

Solution: Randomize network instead - in a degree-controlled way

Randomizing graphs to compute significances

Need to randomly choose 12 proteins with the same degree distribution like candidate proteins

Hard



Edges are shuffled such that every vertex maintains its degree

Randomizing graphs to compute significances

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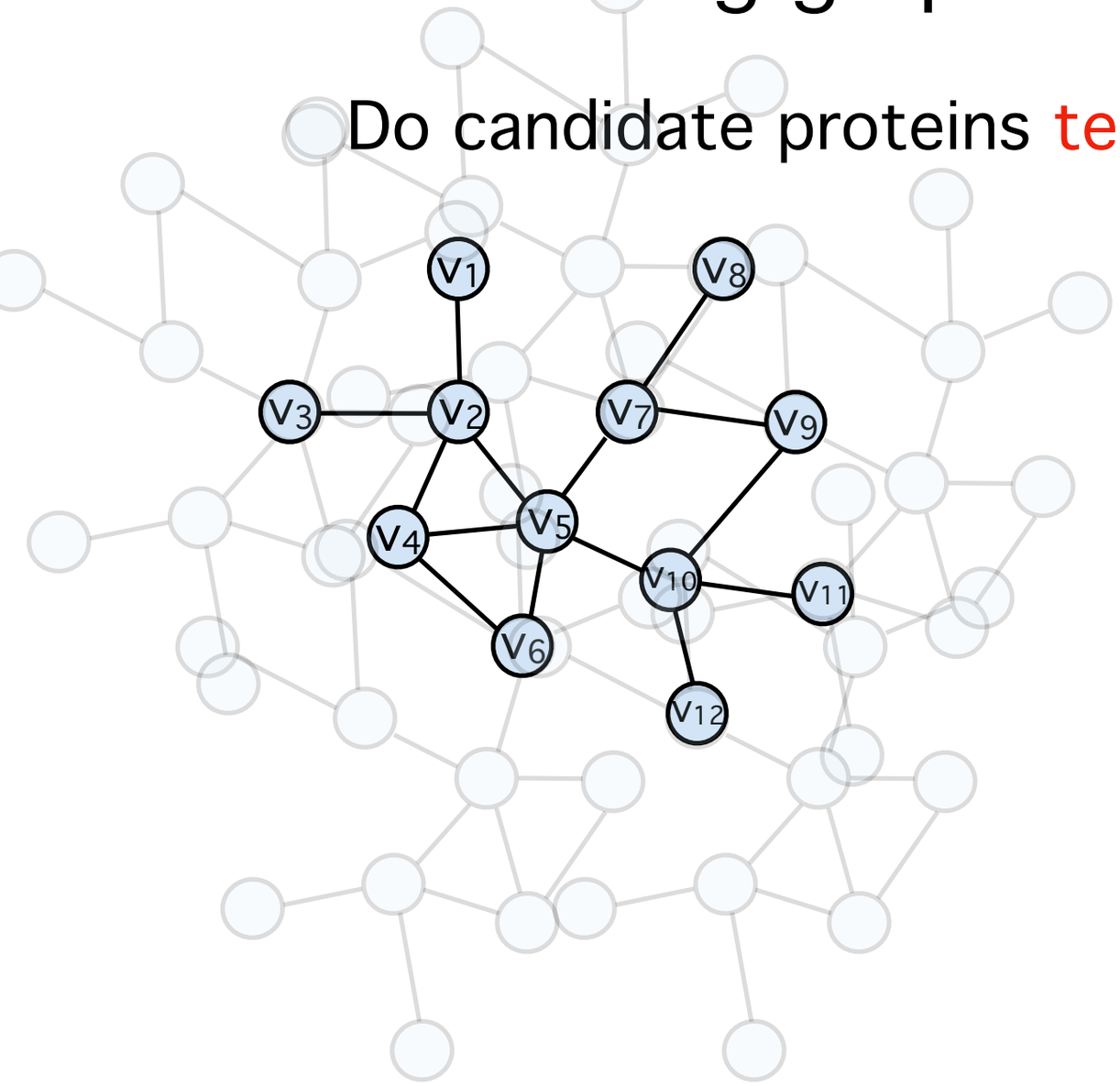

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Randomizing graphs to compute significances

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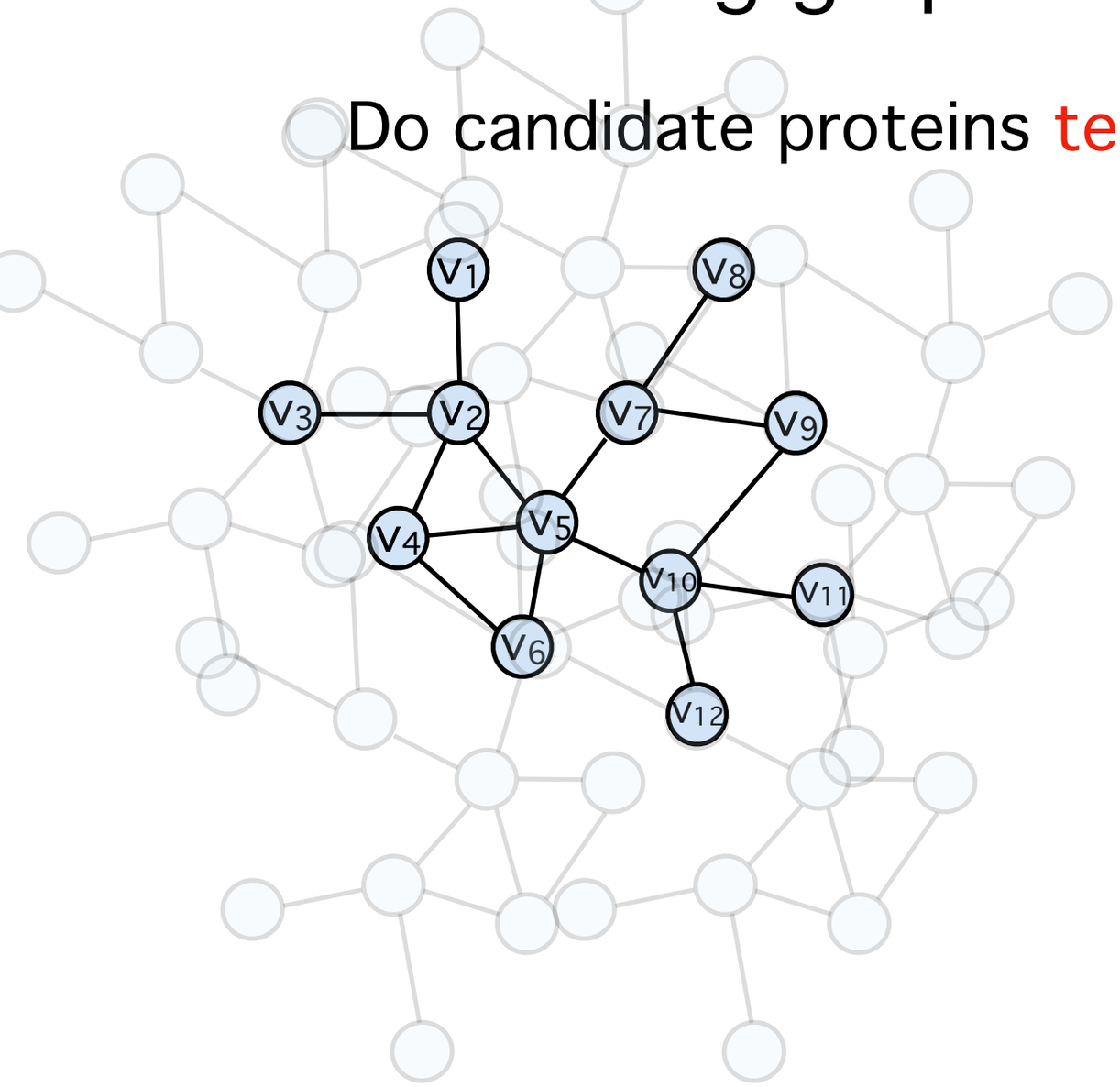

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Generate a high number of degree-controlled randomized networks

Randomizing graphs to compute significances

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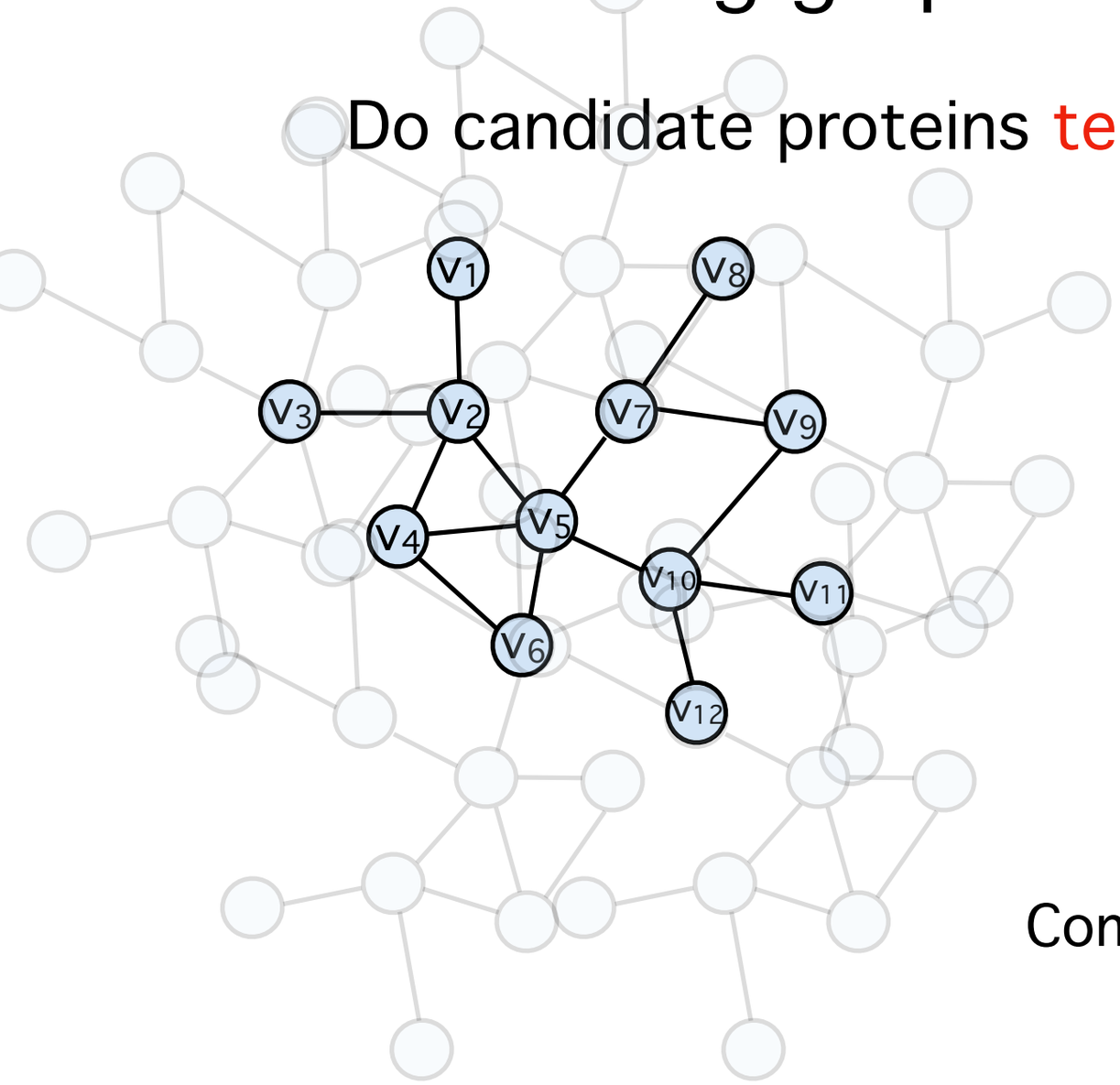

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Compute closeness of candidate proteins in each of them

Randomizing graphs to compute significances

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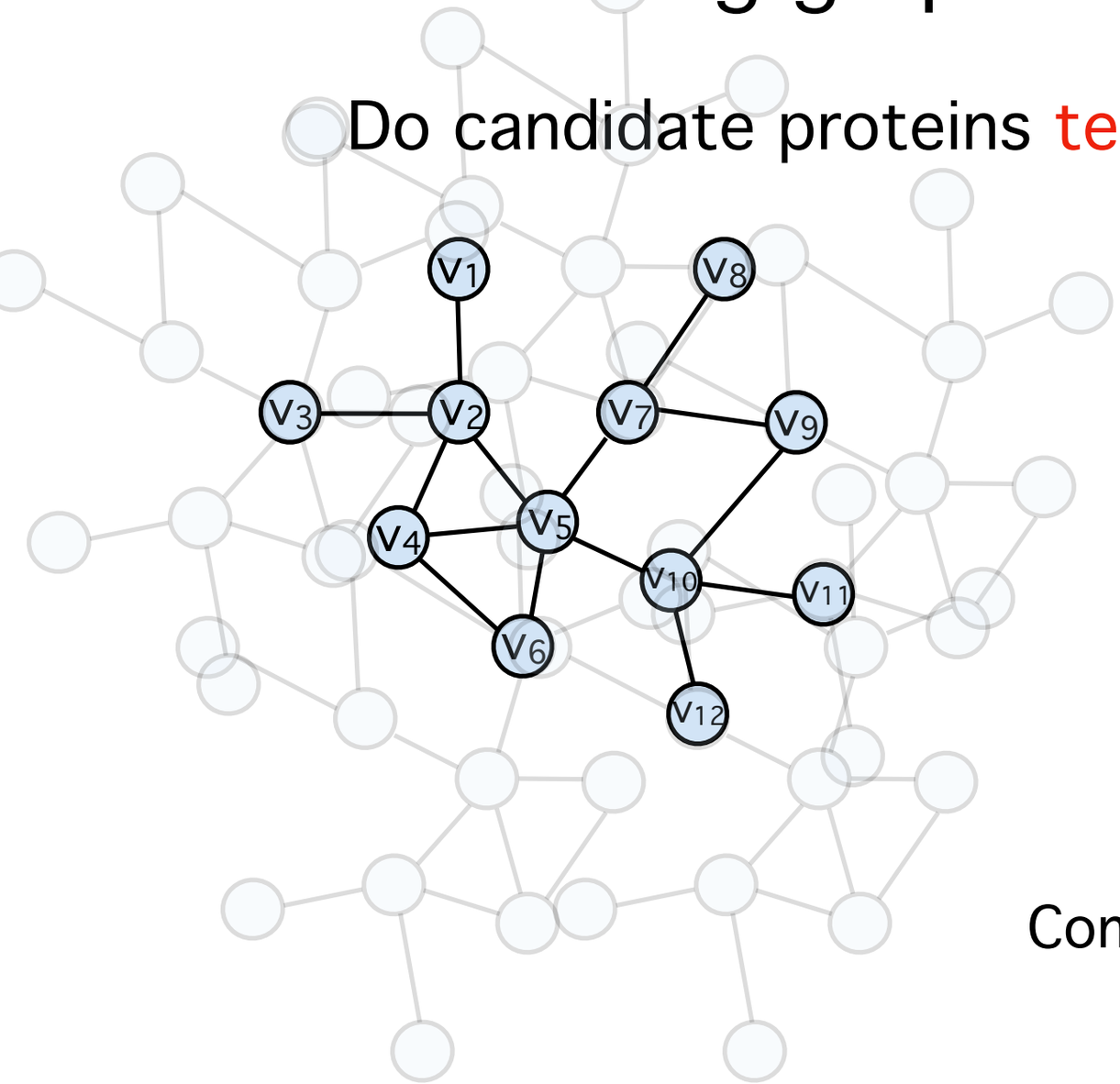

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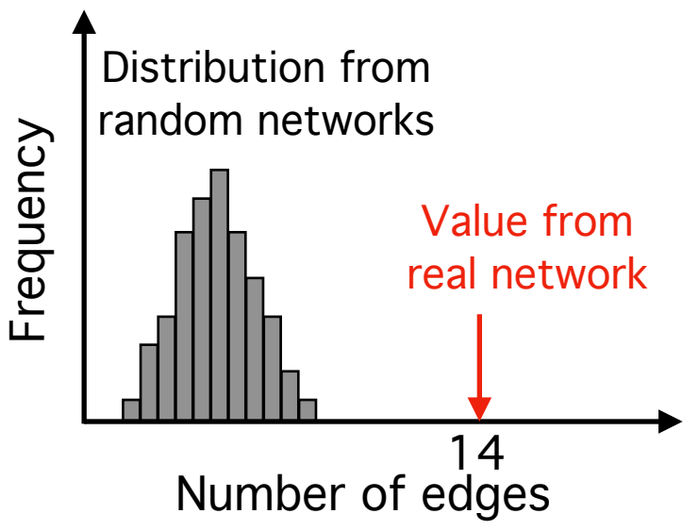

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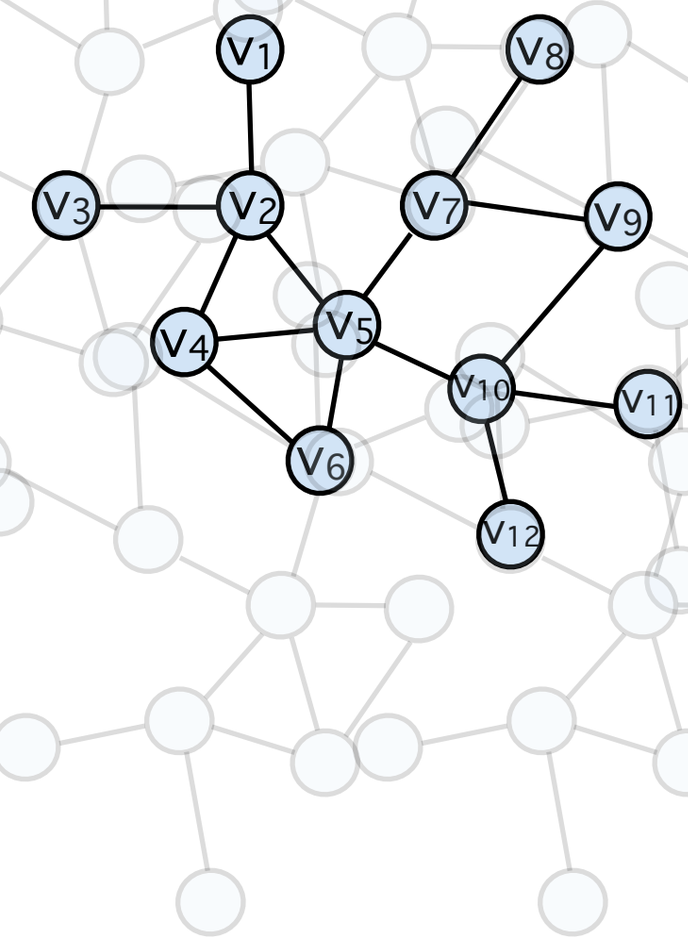

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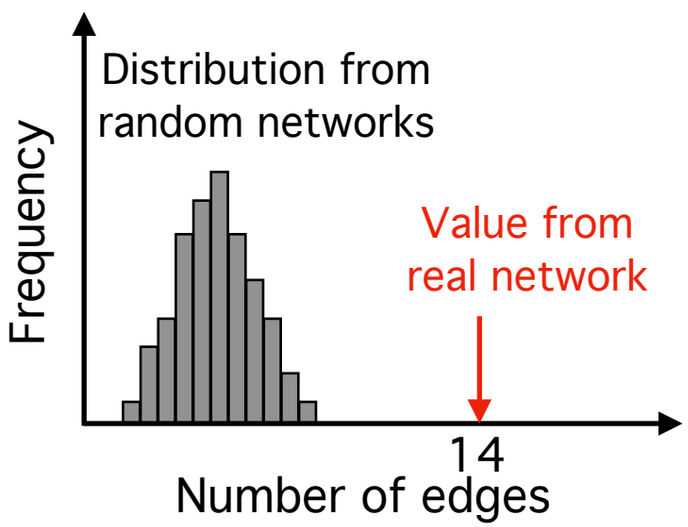
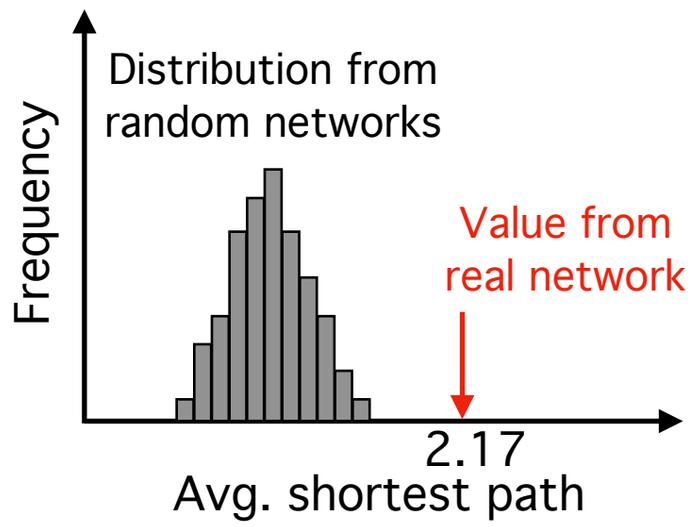


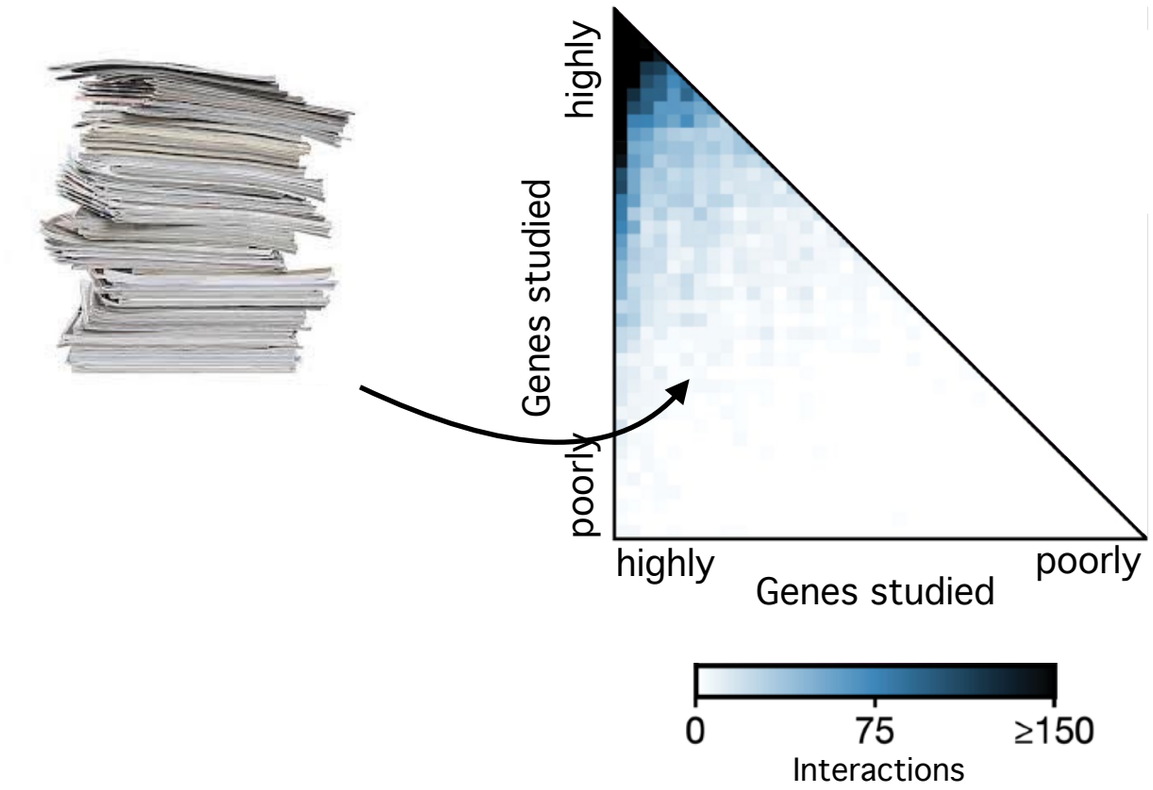


Study bias in curated protein interaction data can falsify network analyses

Luck et al *Nature* 2020

Study bias in curated protein interaction data can falsify network analyses

Literature curation



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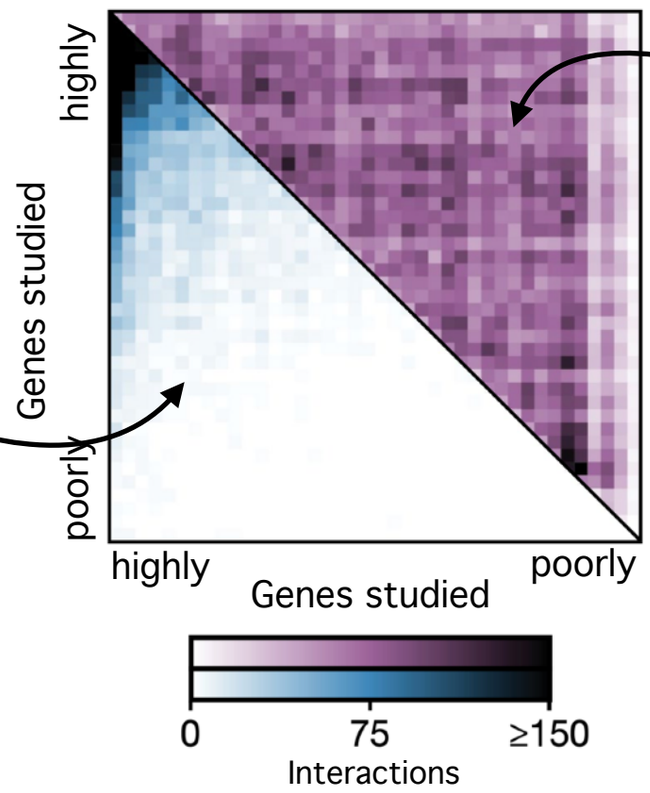
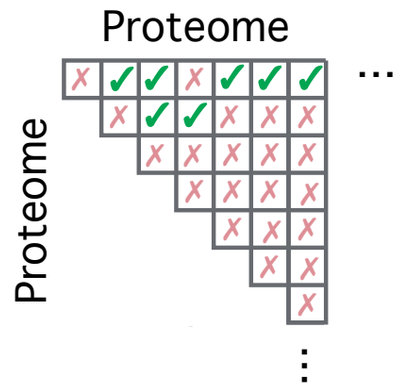


Systematic mapping



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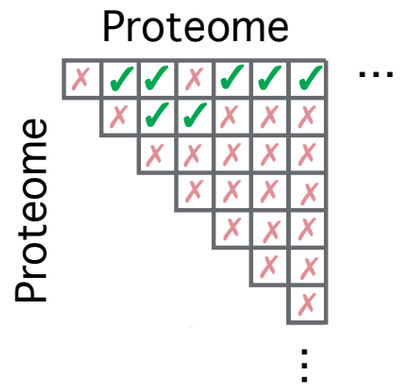

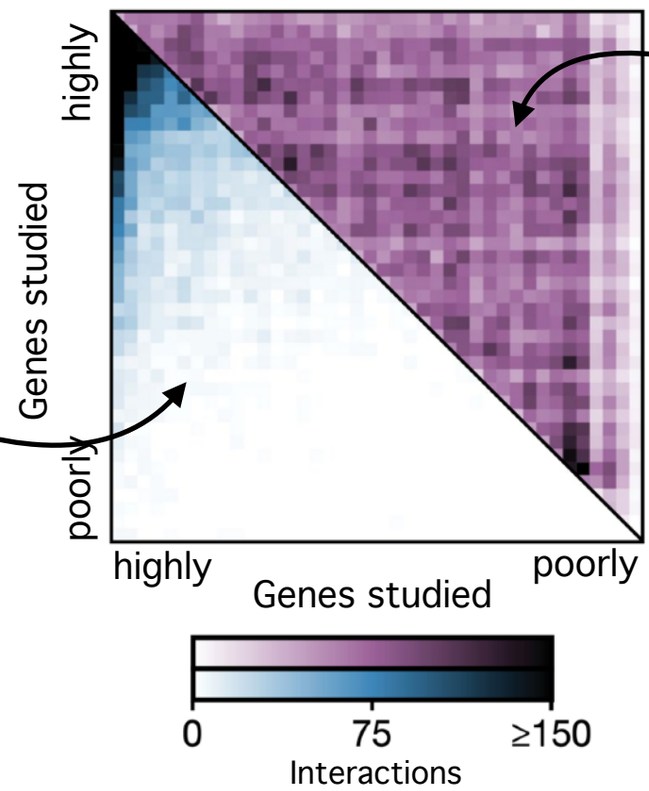

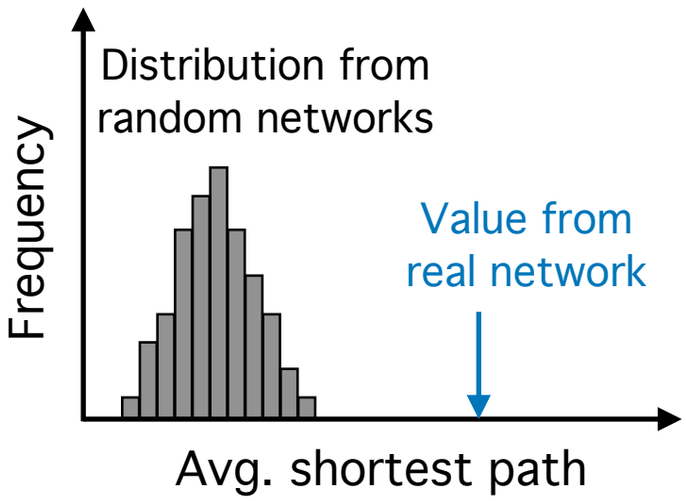

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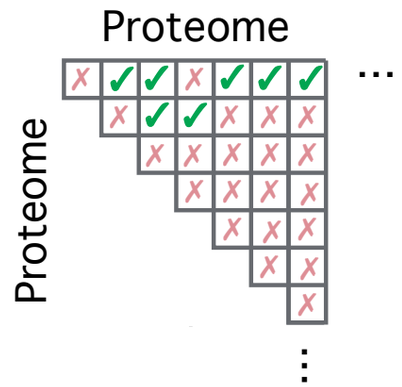
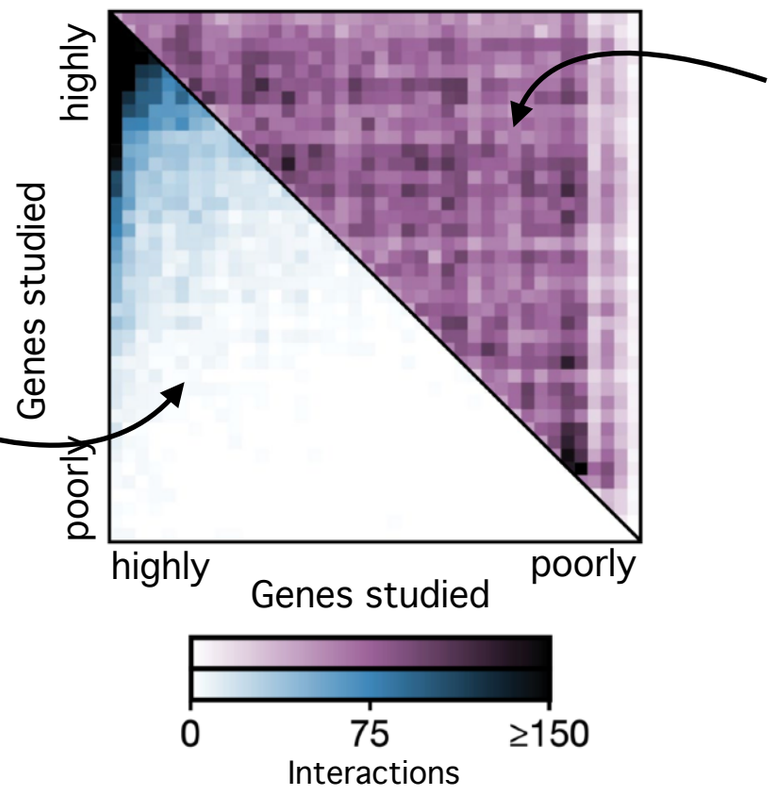
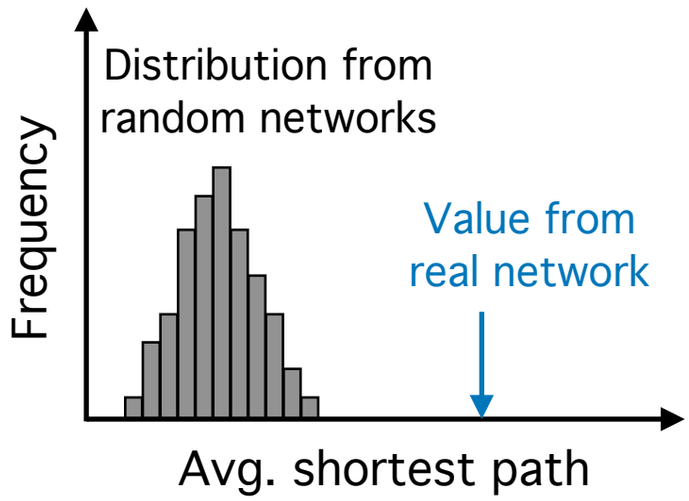
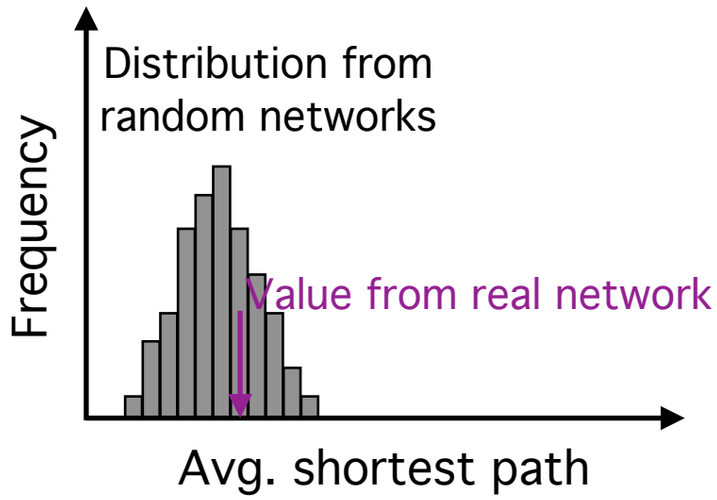






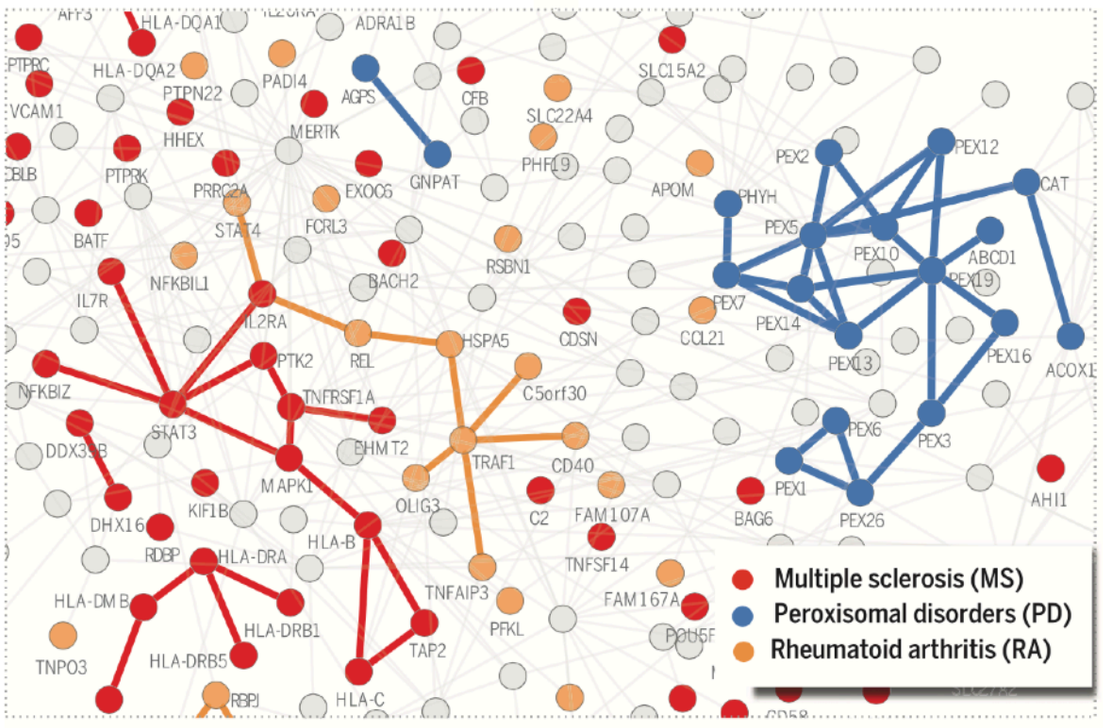


Luck et al *Nature* 2020

Network closeness of disease genes and tissue-specific proteins

Uncovering disease-disease relationships through the incomplete interactome

Jörg Menche, Amitabh Sharma, Maksim Kitsak, Susan Dina Ghiassian, Marc Vidal, Joseph Loscalzo, Albert-László Barabási*



Science 2015

A reference map of the human binary protein interactome

Katja Luck[1,2,3,33], Dae-Kyum Kim[1,4,5,6,33], Luke Lambourne[1,2,3,33], Kerstin Spirohn[1,2,3,33], David E. Hill[1,2,3]✉, Marc Vidal[1,2]✉, Frederick P. Roth[1,4,5,6,16,32]✉ & Michael A. Calderwood[1,2,3]✉

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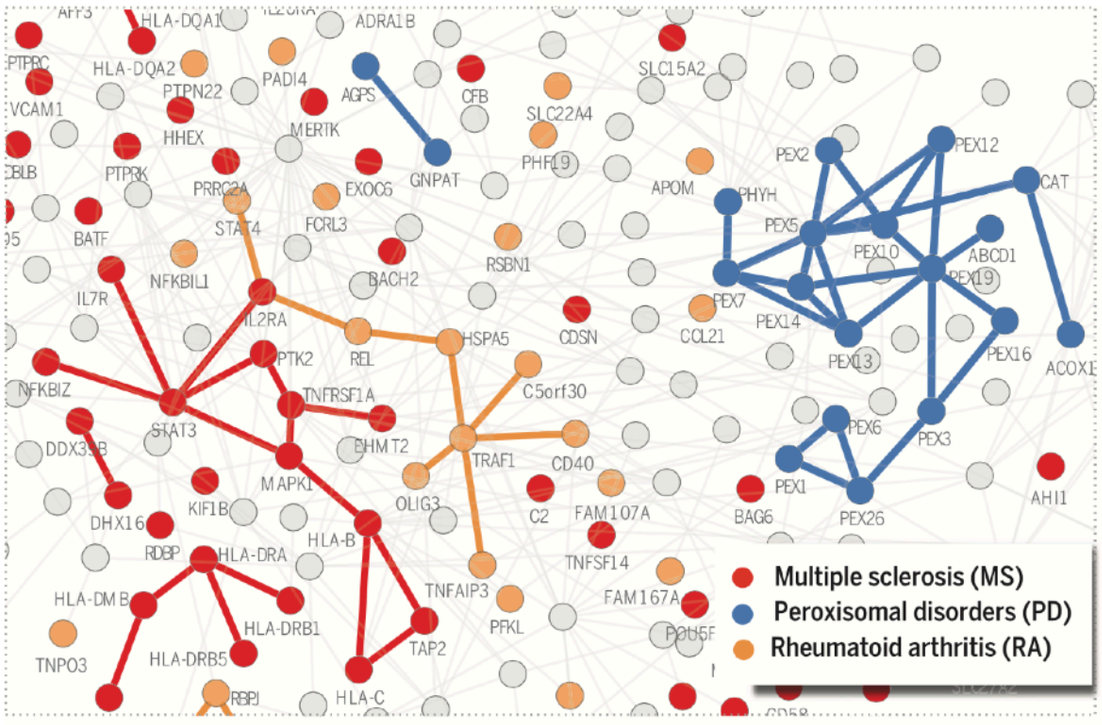

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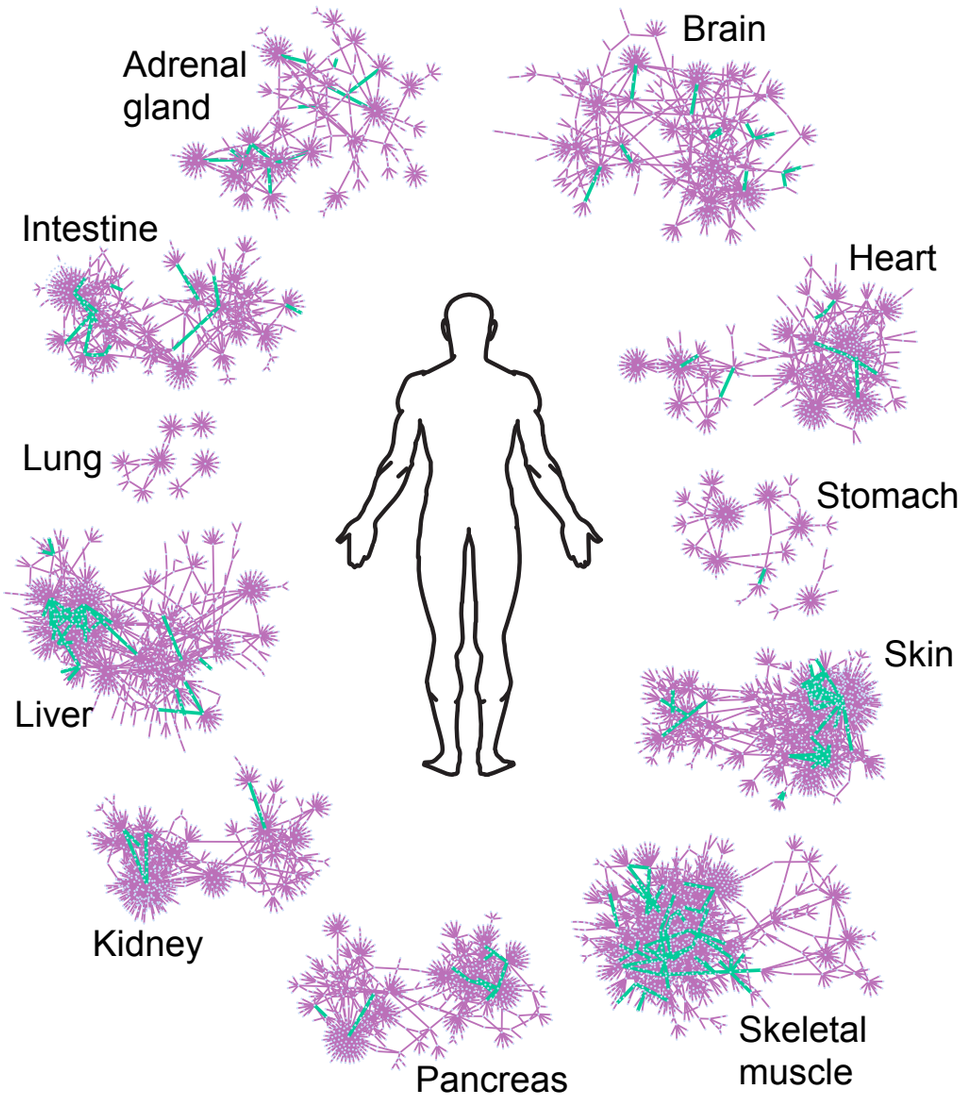
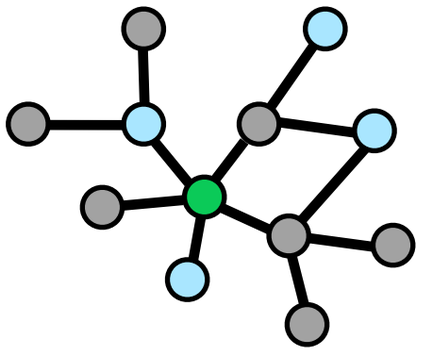


Nature 2020

What is the function of my gene of interest?

Guilt-by-association



- Candidate protein
- Known apoptosis function
- other

Fuxman Bass et al *Nature Methods* 2013, Luck et al *Nature* 2020

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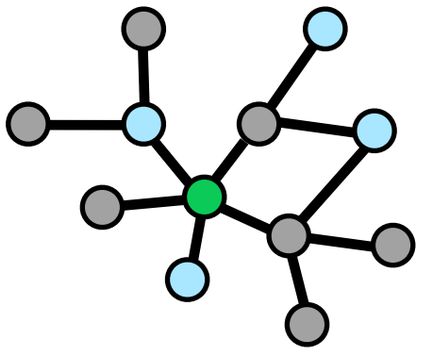

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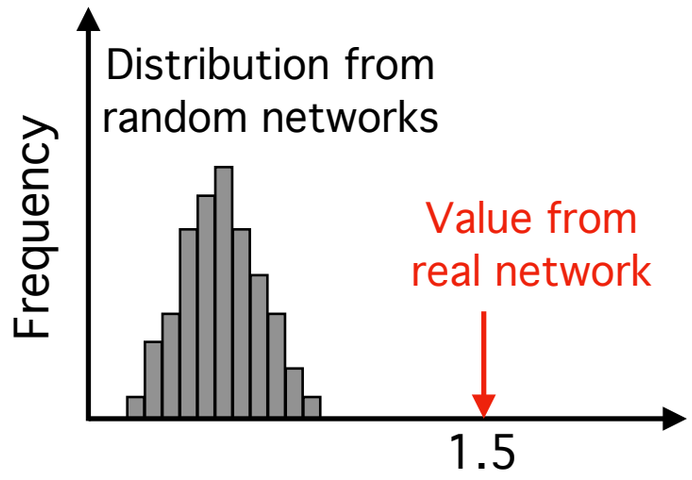

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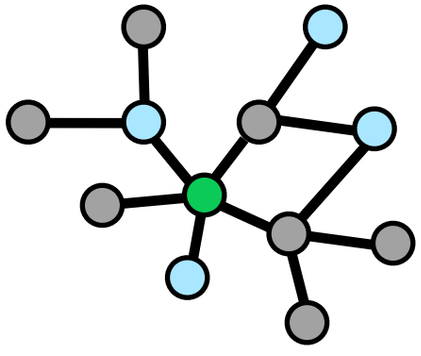

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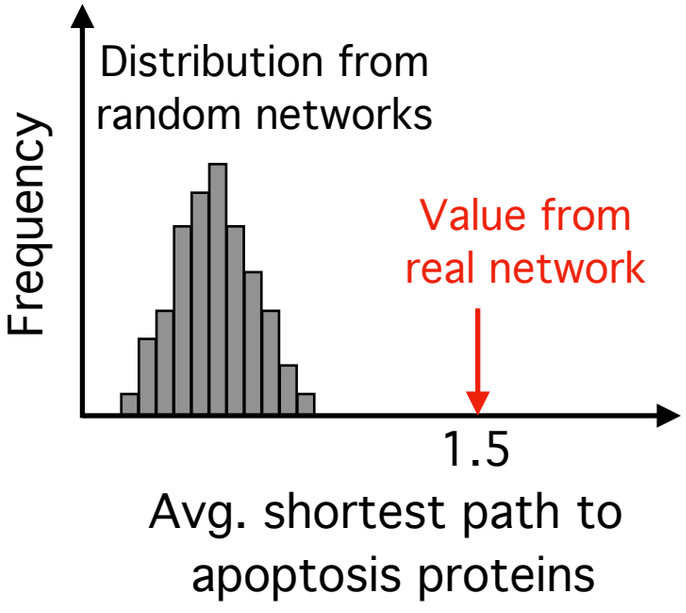

OTU deubiquitinase 6A

Fuxman Bass et al *Nature Methods* 2013, Luck et al *Nature* 2020

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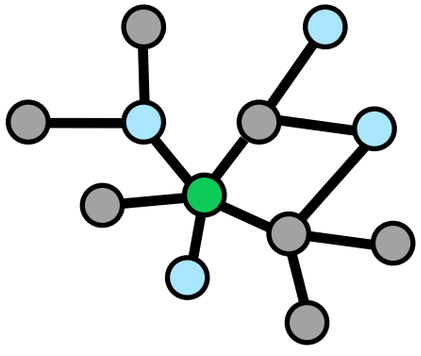

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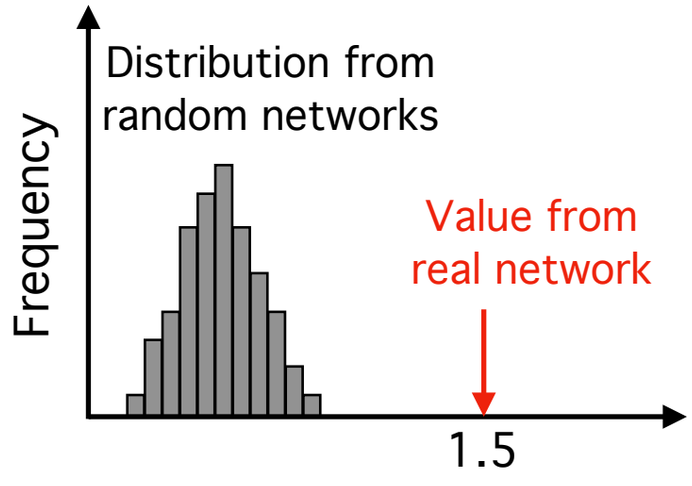

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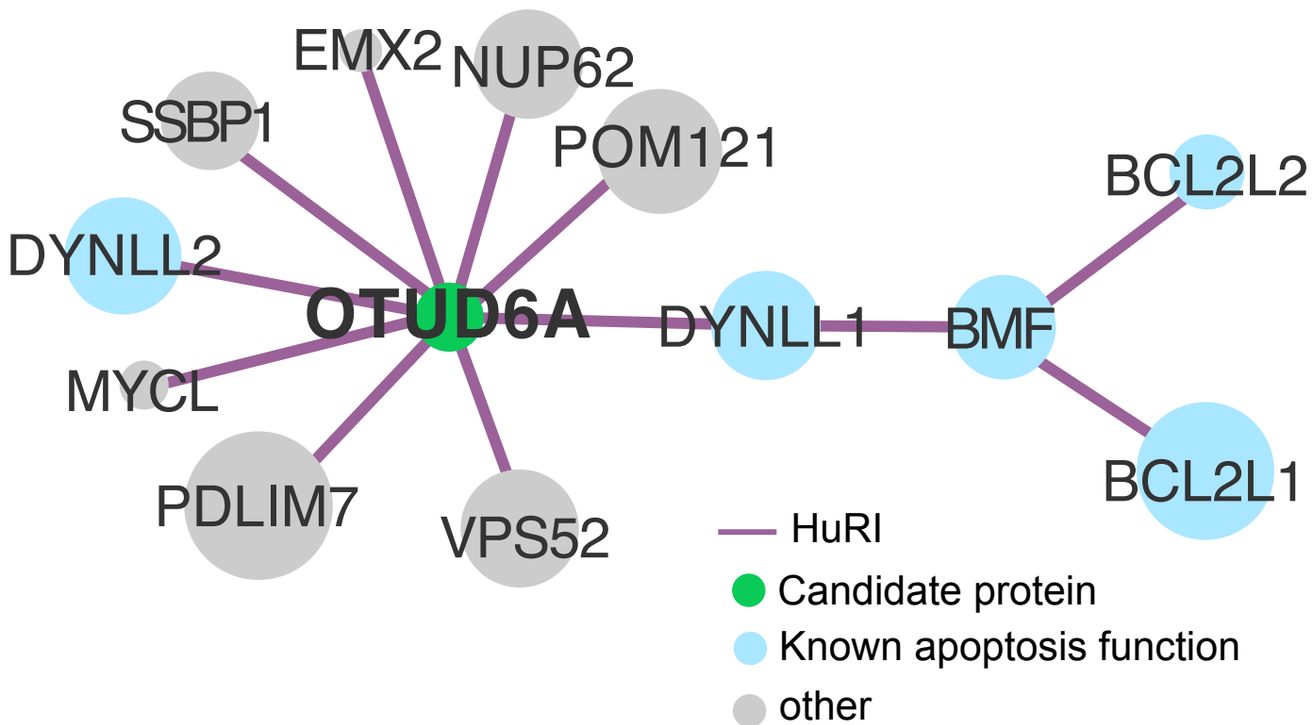

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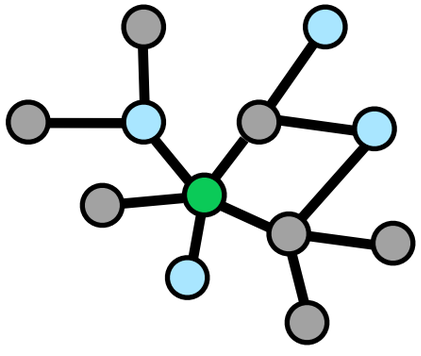

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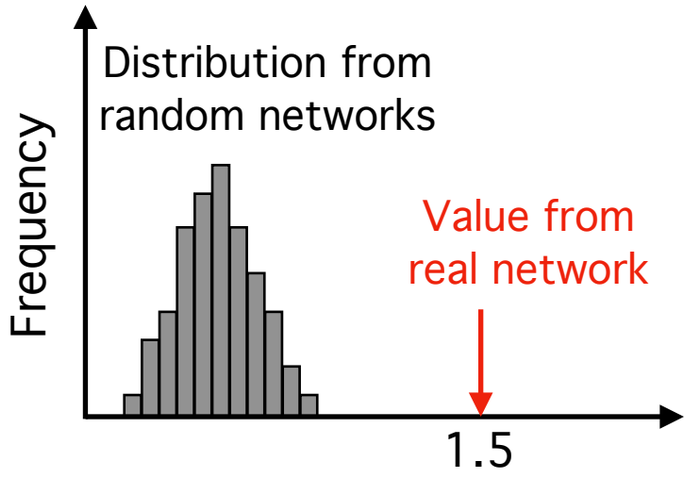

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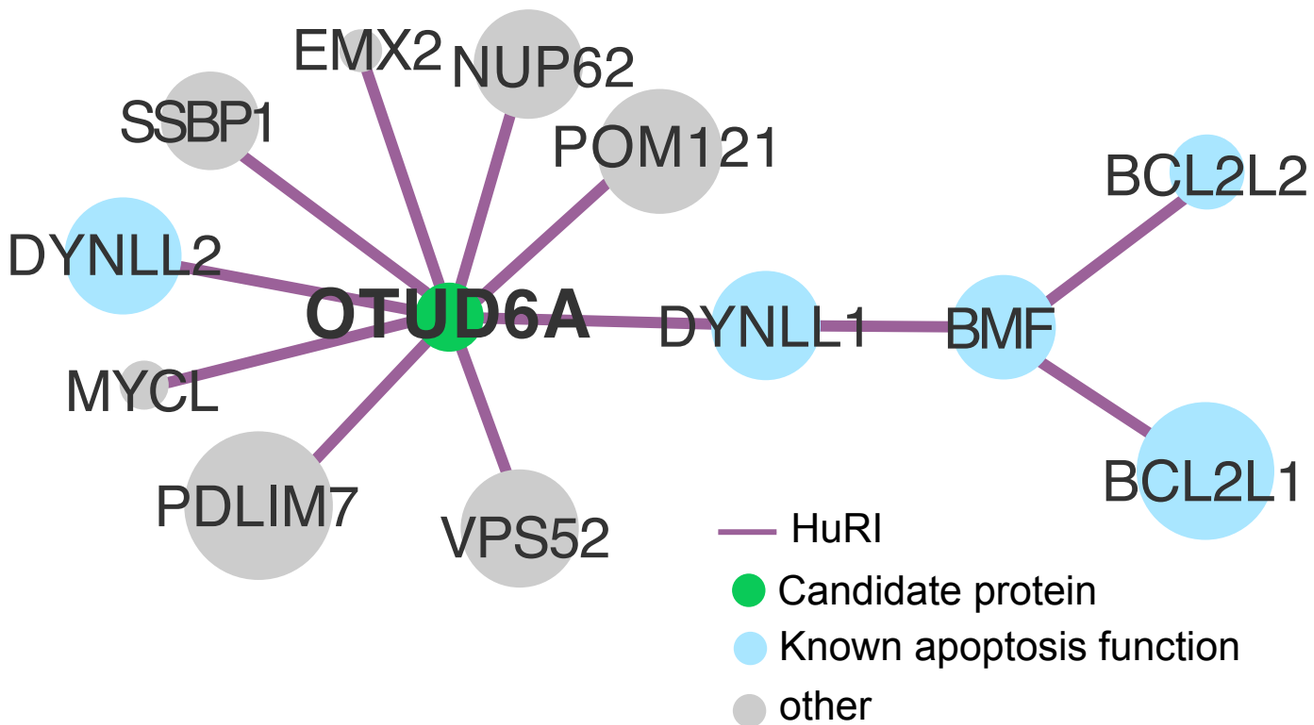
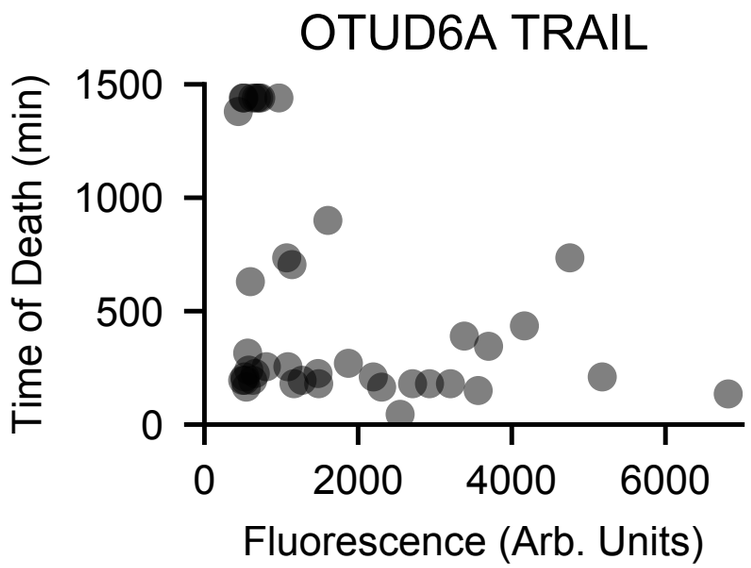


OTUD6A expression results in earlier cell death



Fuxman Bass et al *Nature Methods* 2013, Luck et al *Nature* 2020

Summary

- Molecular interaction data can be represented as graphs
- Biological networks are scale-free
- Use degree-controlled randomized networks to look for trends
- Trends in literature-curated networks can be falisified
- Guilt-by-association is a method to predict functions of proteins using interaction data