3000788 Intro to Comp Molec Biol

Lecture 18: Biological networks

October 18, 2022

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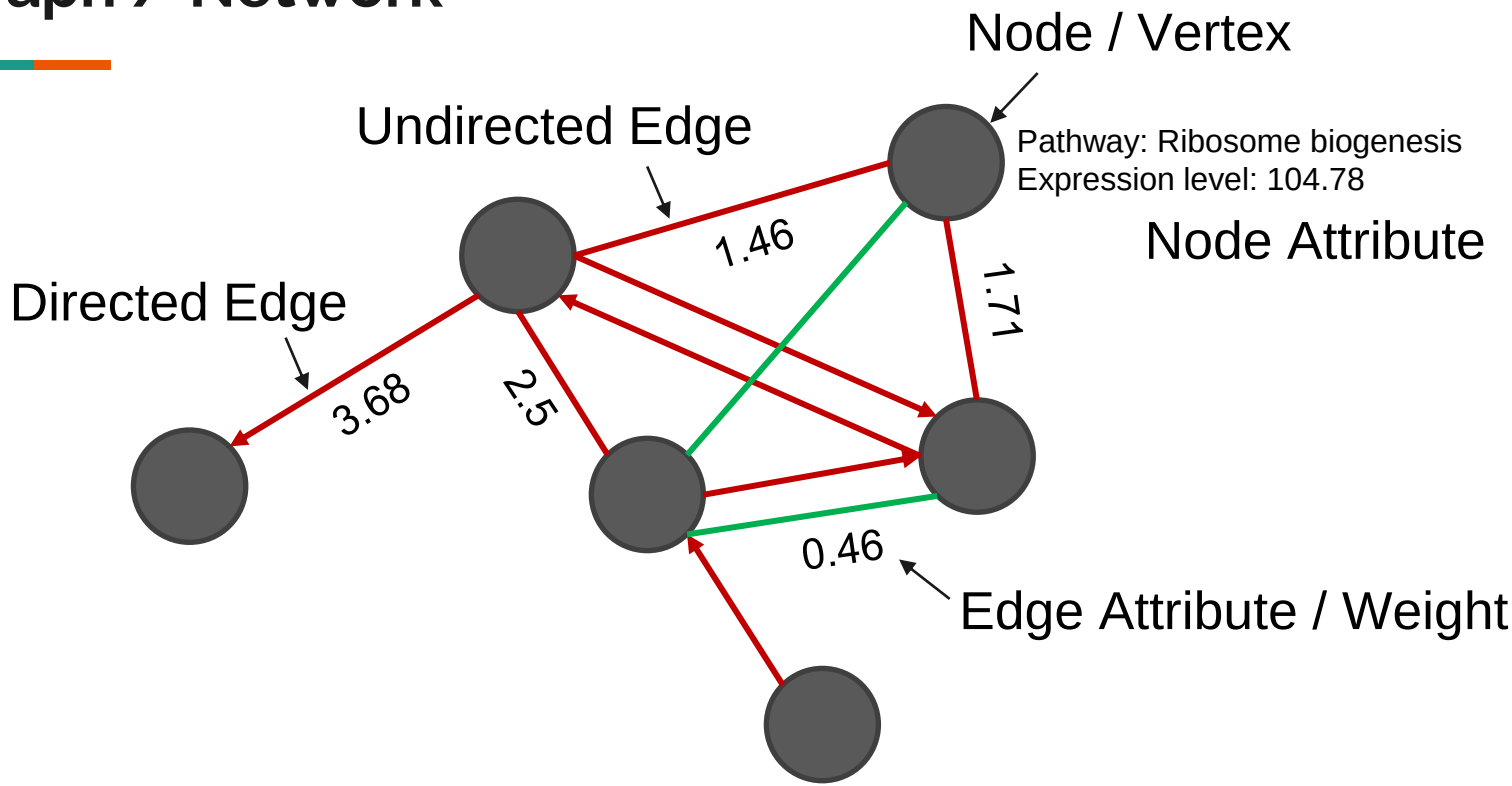
- Research Affairs
- Center of Excellence in Computational Molecular Biology (CMB)
- Center for Artificial Intelligence in Medicine (CU-AIM)

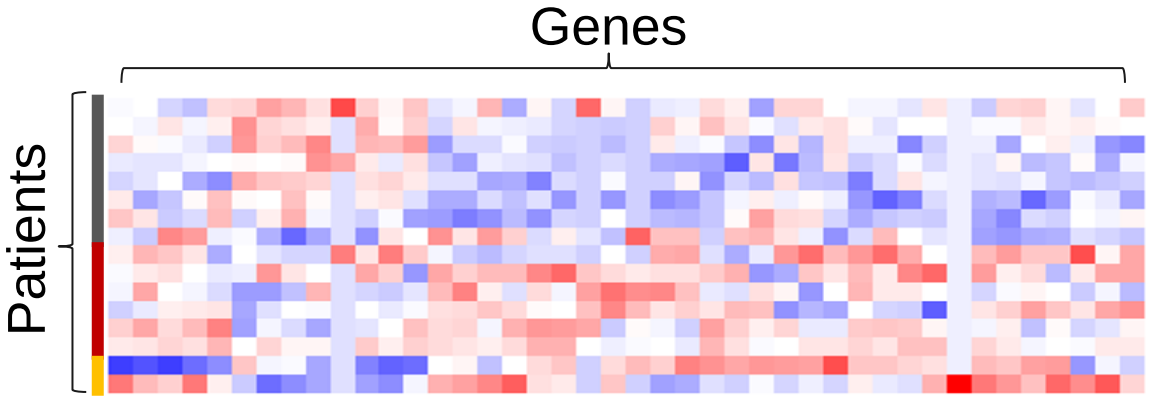
Network data

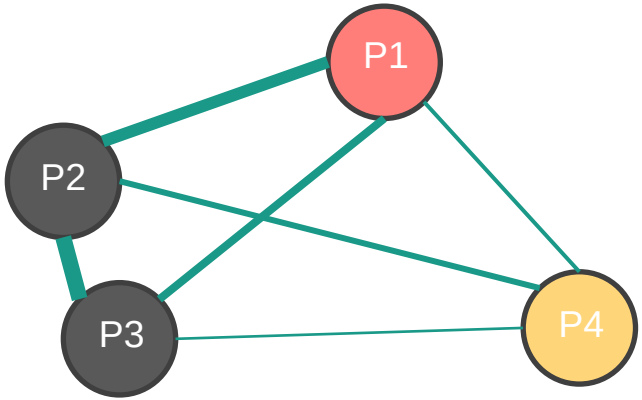
Graph / Network



- Connection & relationship between entities

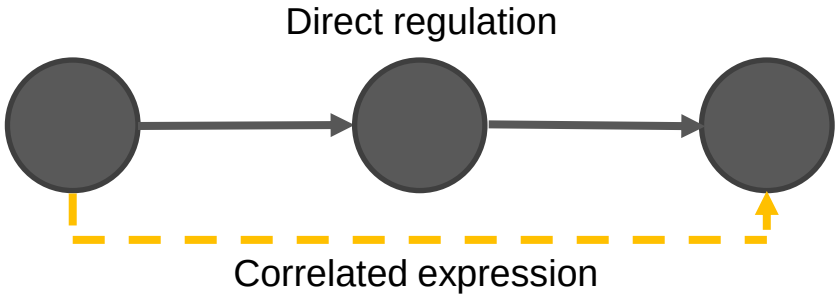
Distance network

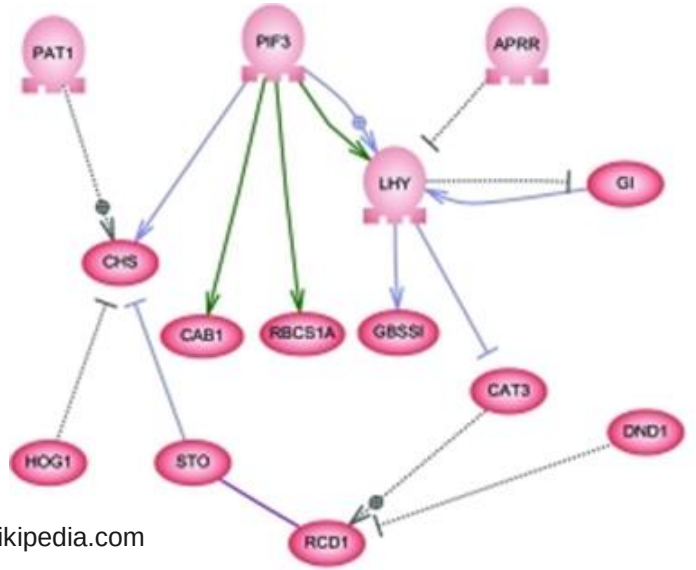




- Node = sample
- Edge weight = similarity / distance between samples
- Node attribute = sample metadata

Causal inference from network





Source: Wikipedia.com

- Causation = direct interaction: protein binding, TF-DNA binding, etc.
- Type of interaction: activation, repression

Real-world networks

- Computer network
- City-street
- Internet webpages
- Co-authorship
- Friendship
- River & sewage

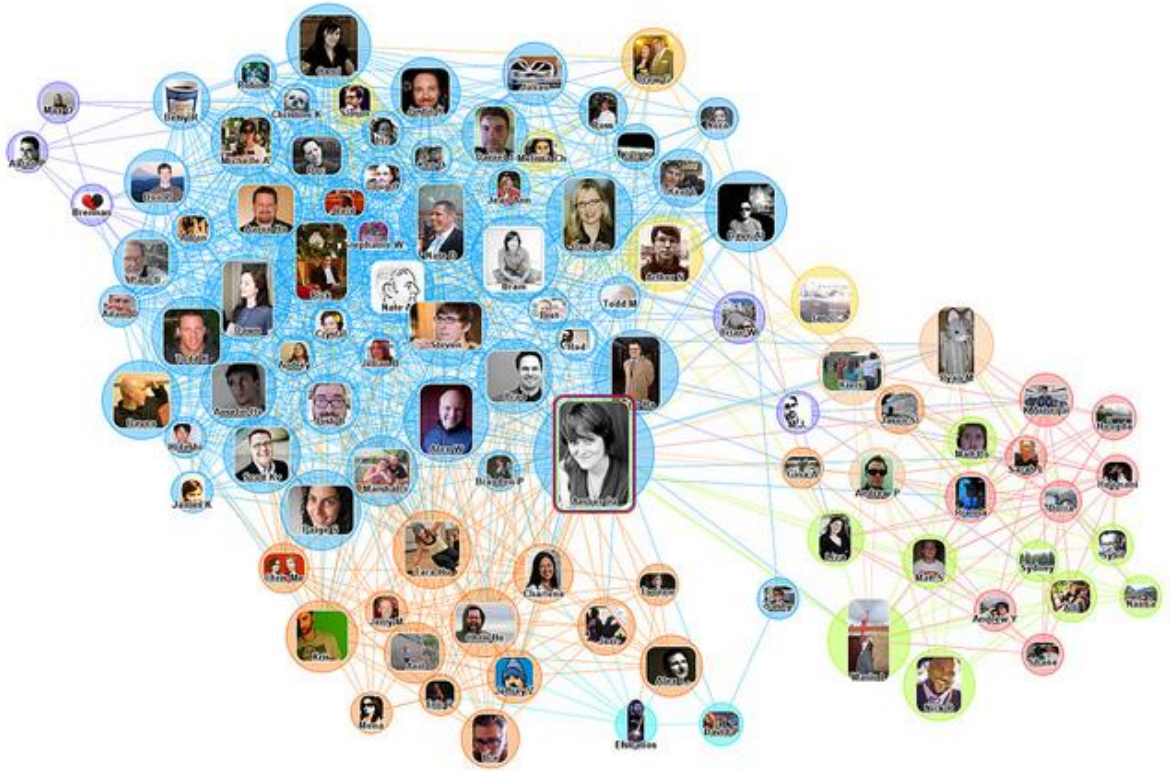
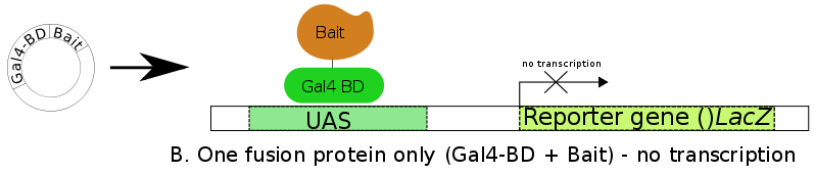


Image from https://www.flickr.com/photos/caseorganic/4935751455

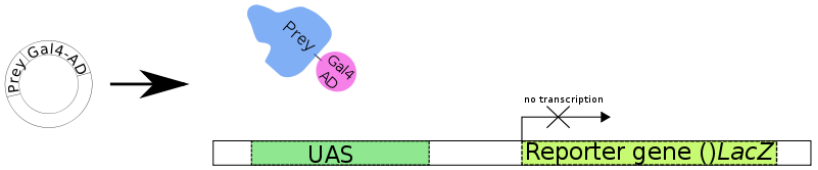
Biological networks

Networks from omics data

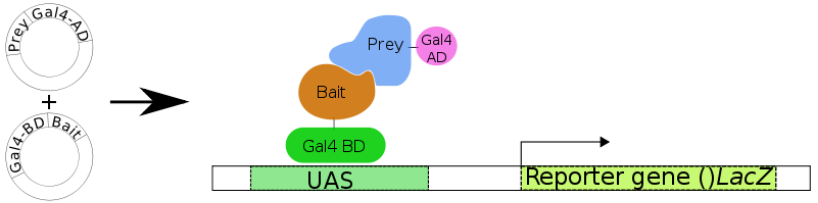
- Yeast-2-hybrid → protein-protein interaction networks
- Immunoprecipitation-MS → protein complex
- ChIP-seq → TF-gene regulatory network
- RNA-seq → gene co-expression network



B. One fusion protein only (Gal4-BD + Bait) - no transcription



C. One fusion protein only (Gal4-AD + Prey) - no transcription

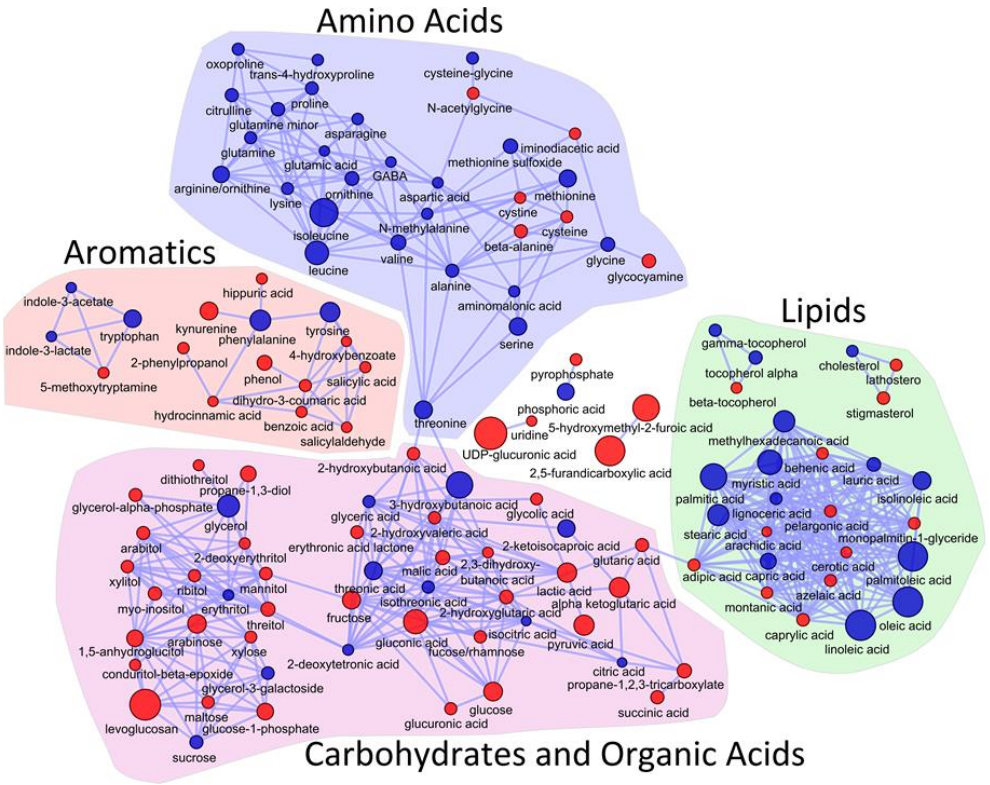


D. Two fusion proteins with interacting Bait and Prey

Source: Wikipedia.com

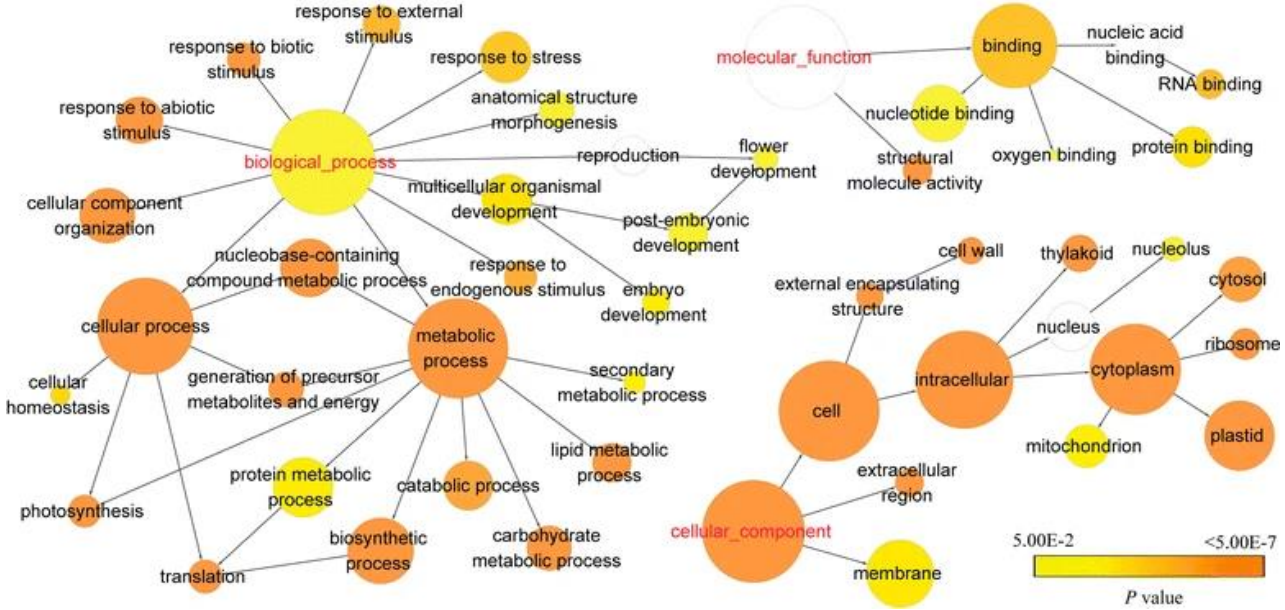
More examples

- Structural / physicochemical similarity network
- Cell-cell similarity network
- Multi-omics networks
  - Drug-gene-disease
  - RNA + ATAC + Bisulfite



Source: imdevsoftware.wordpress.com

Gene ontology network



Gao, B. et al. BMC Genomics 16:416 (2015)

- Generate a concise summary based on connected terms

CLUE.IO

The Connectivity Map

The Connectivity Map (CMap) at the Broad Institute is creating a genome-scale library of cellular signatures that catalogs transcriptional responses to chemical, genetic, and disease perturbation. To date, the library contains more than 1 Million profiles resulting from perturbations of multiple cell types.

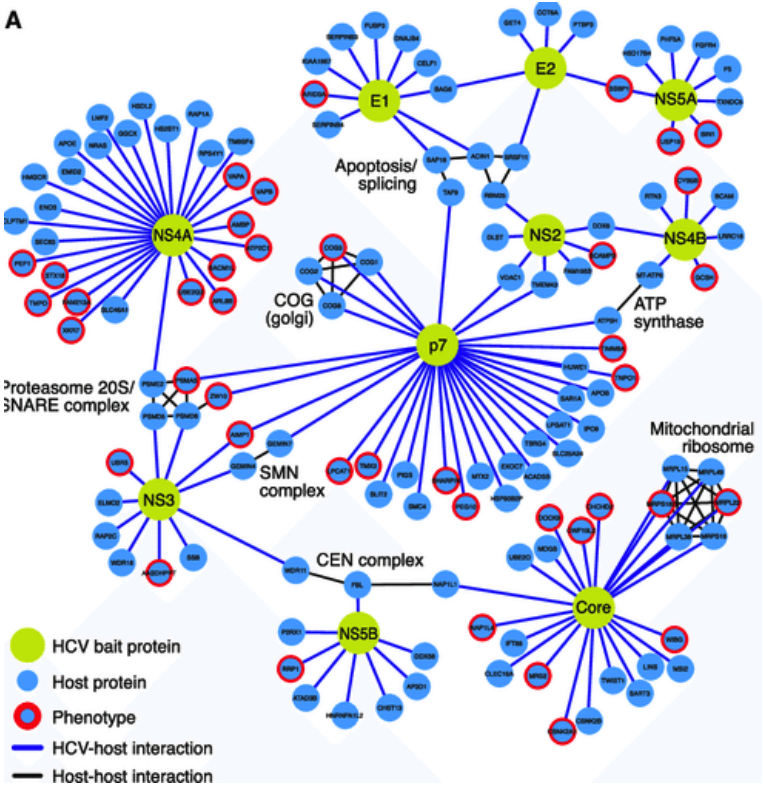
- More than 1M gene expression profiles of cell lines with various disease states and treated with various small molecules
- Network of transcriptome similarity → characterize effect of new drugs

Host-viral protein interaction

- Two node types: human, HIV
- Two edge types
- Node attribute: affected by infection

- Propose mechanisms underlying the effect of infection

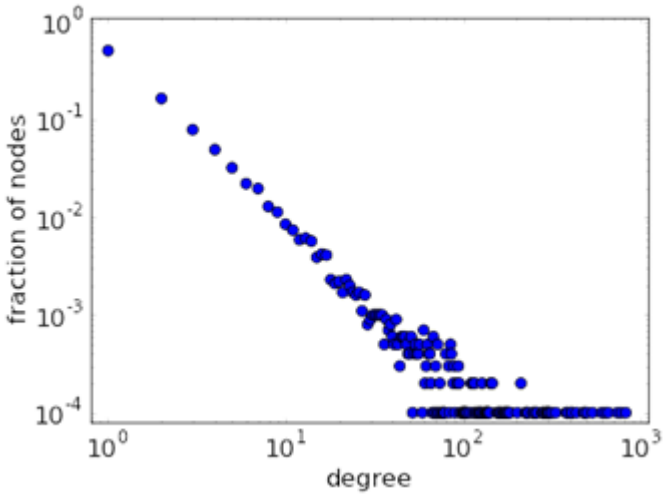
- Prioritize targets for antibody design



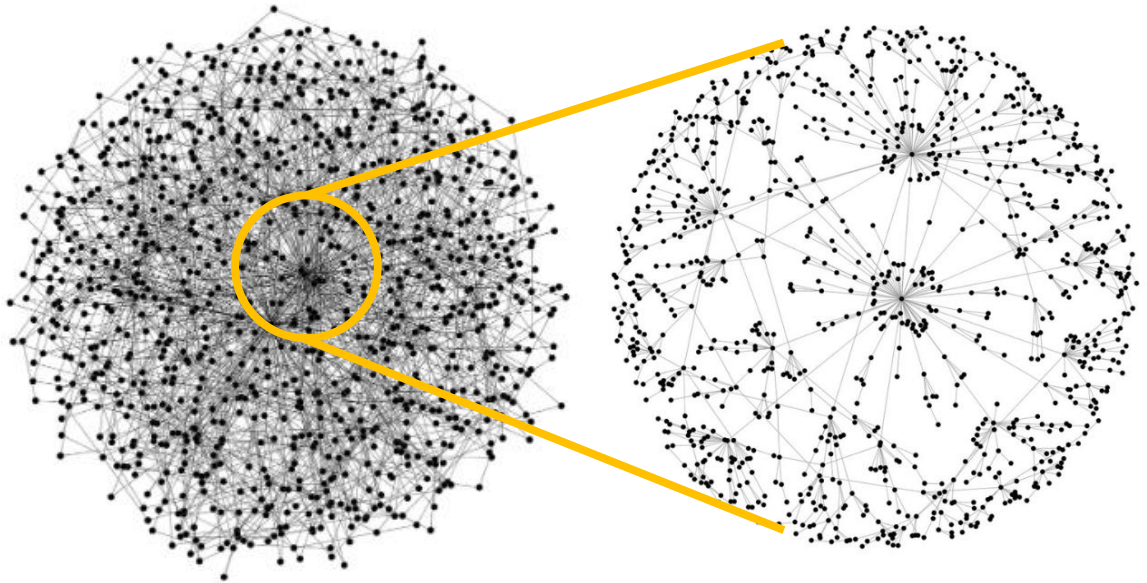
Source: Ramage et al. Mol Cell (2015)

Properties of real-world networks

Scale-free property



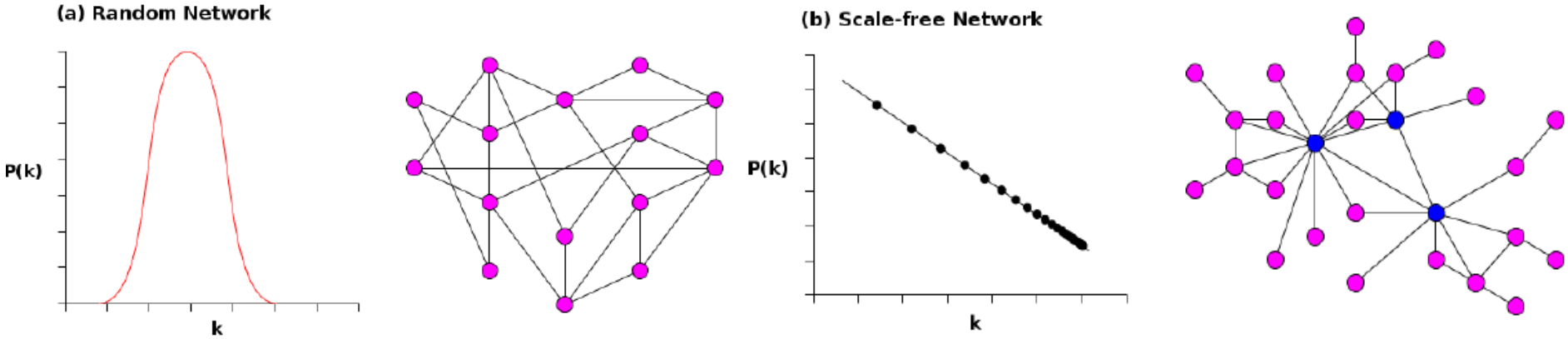
Source: mathinsight.org



Source: flickr.com & pacojariego.me

- Power law: P(node connected to k edges) ~ $1/k^n$
- Same local structure as global structure
  - Node-edge distribution

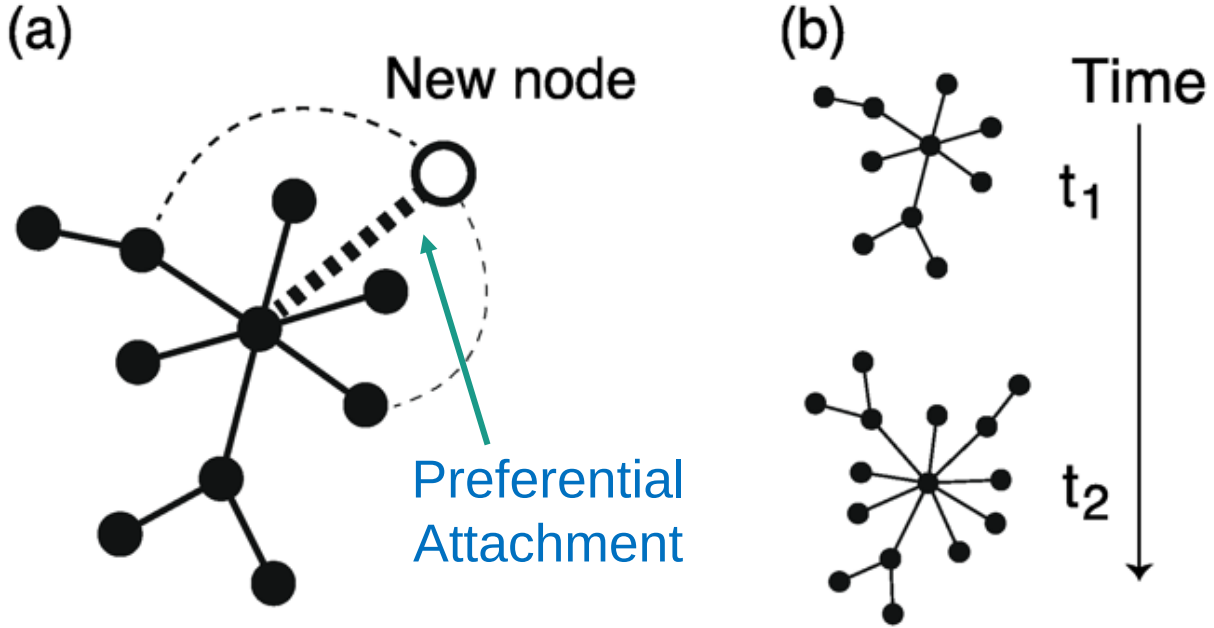
Hub and small-world propery



Source: Segura-Cebrera *et al*. Analysis of Protein Interaction Networks to Prioritize Drug Targets of Neglected-Diseases Pathogens

- Few nodes connected with many edges act as short-cut for traffic through the network
  - Transcription factors in biological networks
  - Social influencers on internet

Emergence of real-world networks



Takemoto. Metabolites, 2:429-457 (2012)

- New edges prefer to attach to existing nodes with already many edges

Implication of preferential attachment

- **Assumption**: Node connected with high number of edges will more easily attract more edges
- **Consequence 1**: There will be nodes connected to extremely high numbers of edges
- **Consequence 2**: A lot of nodes will not be connected to many edges
- Qualitatively agree with power law: P(connected to k edges) ~ $1/k^n$

The rise of power law

- Number of edges, E(t) = rt, grow linearly with time with factor r
- Node N_i is connected to $k_i(t)$ edges at time t

- Rate of increase of $k_i(t)$ is a competition with other nodes
  - $\frac{dk_i(t)}{dt} = \frac{k_i(t)}{2\,E(t)}$
  - $\frac{1}{k_i(t)}dk_i(t) = \frac{1}{2\,E(t)}dt = \frac{1}{rt}dt$

- Integrating both sides
  - $\ln\left(k_i(t)\right) = \frac{1}{r}\ln(t) + C_i$
  - $k_i(t) = C_i\, t^{1/r}$

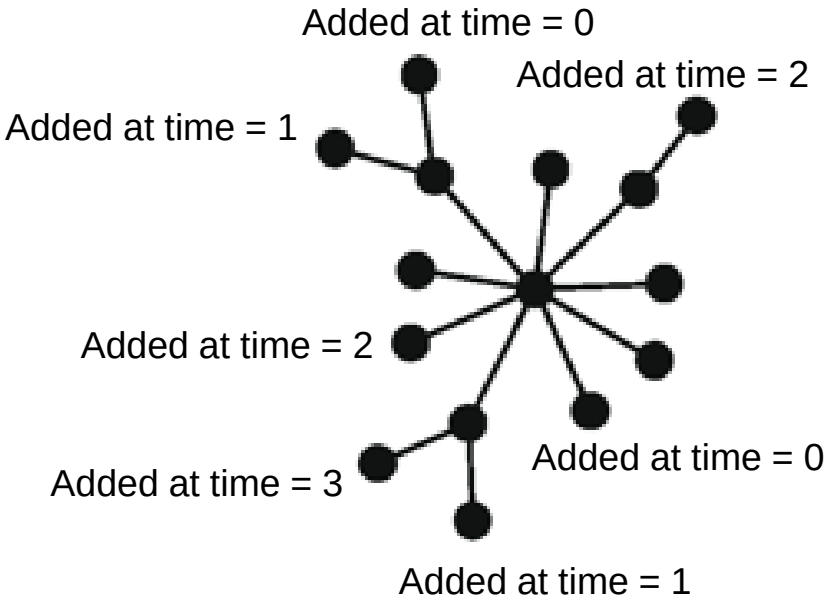
The rise of power law

- Node N_i emerge in the network at time t_i with initial edges = m_0
  - $m_0 = k_i(t_i) = C_i {t_i}^{1/r}$
  - $C_i = \frac{m_0}{{t_i}^{1/r}}$

- Let's look at the cumulative density of $k_i(t)$
  - $\mathrm{P}(k_i(t) < k) = \mathrm{P}\left(\frac{m_0}{{t_i}^{1/r}} t^{1/r} < k\right) = \mathrm{P}\left(t_i > \frac{m_0^r t}{k^r}\right) = 1 - \mathrm{P}\left(t_i \leq \frac{m_0^r t}{k^r}\right)$
  - $\mathrm{P}\left(t_i \leq \frac{m_0^r t}{k^r}\right)$ is equal to the probability of picking a node N_i that emerged in the network before time = $\frac{m_0^r t}{k^r}$

The rise of power law

- Number of nodes, $N(t)$, also grow linearly
- The probability of picking a node N_i that emerged in the network before time $\frac{m_0^r t}{k^r}$ among $N(t)$ nodes is directly proportional to $\frac{m_0^r t}{N(t)k^r}$
- $P\left(t_i \leq \frac{m_0^r t}{k^r}\right) = \frac{m_0^r t}{pN(t)k^r}$

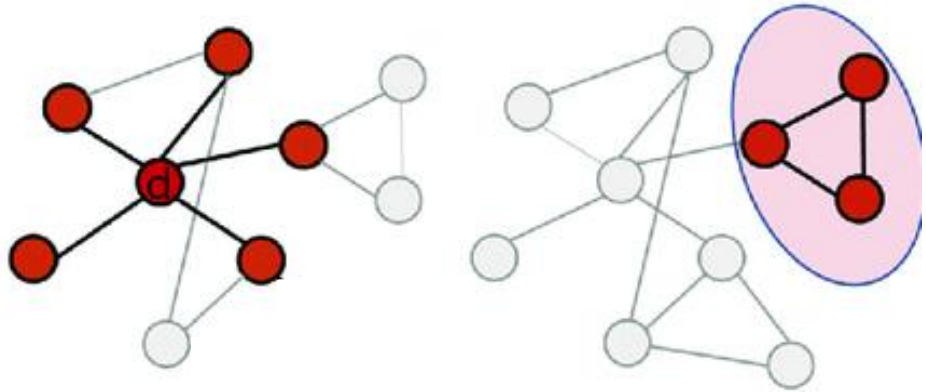


The rise of power law

- We now know the cumulative density
  - $\mathrm{P}(k_i(t) < k) = 1 - \mathrm{P}\left(t_i \leq \frac{m_0^r t}{k^r}\right) = 1 - \frac{m_0^r t}{pN(t)k^r}$
- Take derivative to get the probability density
  - $\mathrm{P}(k_i(t) = k) = \frac{d\mathrm{P}(k_i(t)<k)}{dk} = \frac{rm_0^r t}{pN(t)k^{r+1}} \propto \frac{1}{k^{r+1}}$
  - The order of the power law is linked to the growth rate of edges

Topological properties

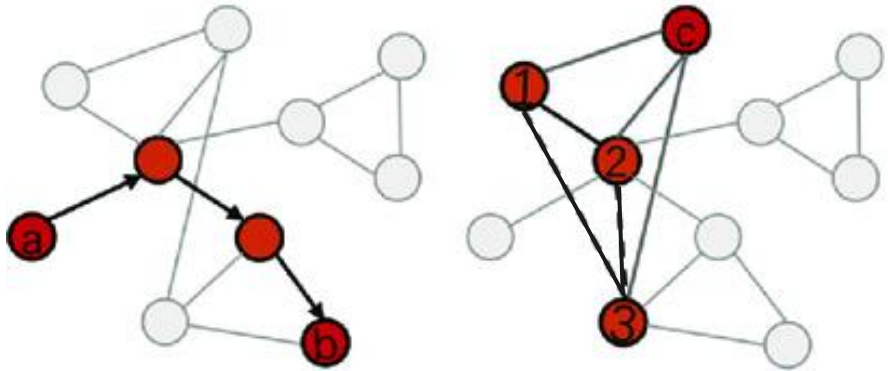
Degree and complete subgraph



Cai and Niu. Dev Cog Neuroscience (2018)

- Degree = number of edges connected to a certain node
- Clique, complete subgraph = region of a network whose nodes are fully connected with $\frac{n(n-1)}{2}$ edges

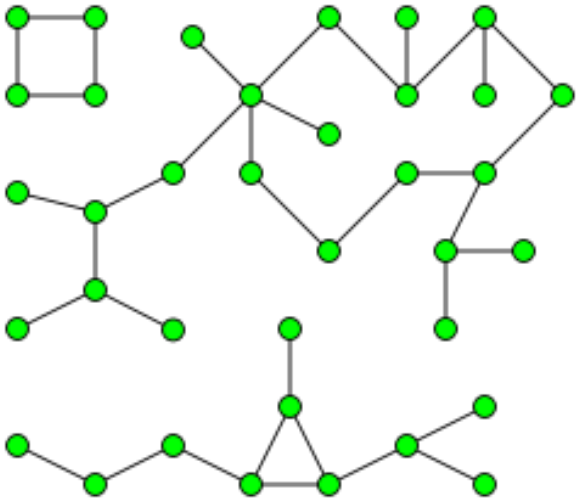
Path and clustering coefficient



Cai and Niu. Dev Cog Neuroscience (2018)

- Path = connection from one node to another through several edges
  - Serve as distance between nodes on the network
- Clustering coefficient = proportion of neighbors that are also connected
  - Indicate the extent of local connectivity / redundancy of the network

Connected components

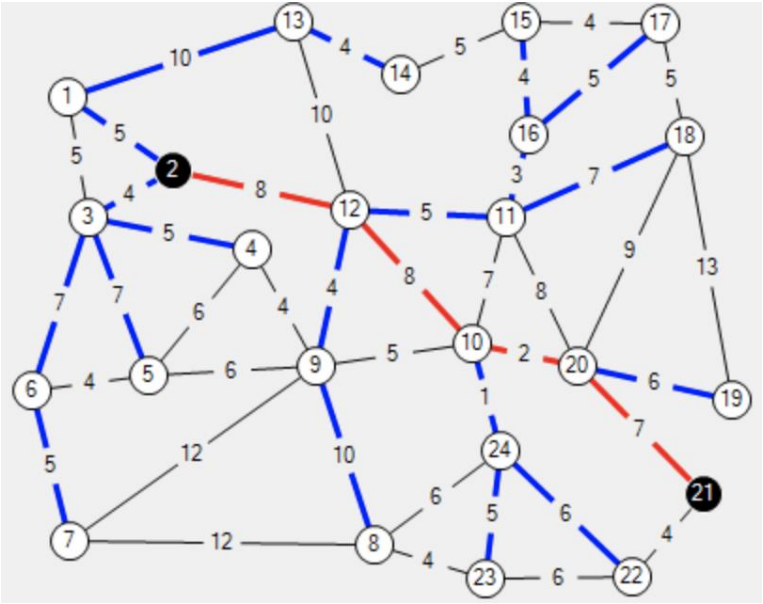


Source: Wikipedia.com

- Some network might consist of small disconnected subnetworks
- Number of connected components can indicate the complexity and organization of the whole network
- Can be caused by incomplete data
  - Missing edges in biological networks

Connectivity measures and interpretation

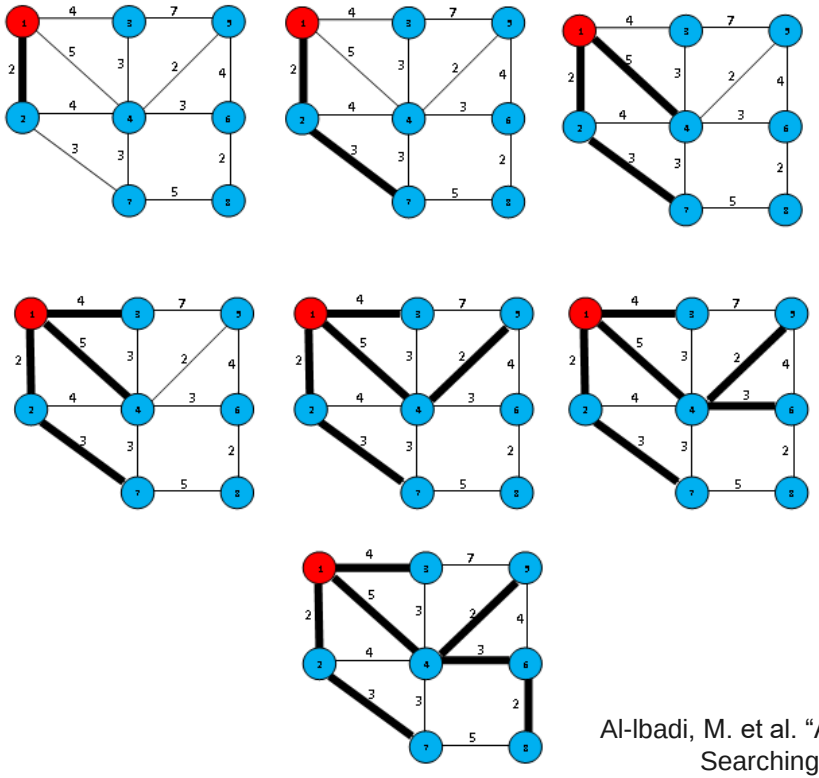
Importance of of path and path length



Source: Csharphelper.com

- Network operates by transmitting signals from one node to another
- Nodes frequently involved in the transmission are important
- **Model 1**: Shortest paths only
- **Model 2**: Weighted across all paths

Dijkstra algorithm



- Dynamic programming
- From a start node, traverse the edges and record current distances for visited nodes
- Update distance d(i, j) if a shorter path is found

Al-Ibadi, M. et al. “A New Hardware Architecture for Parallel Shortest Path Searching Processor Based-on FPGA Technology” 2012

Network as flows

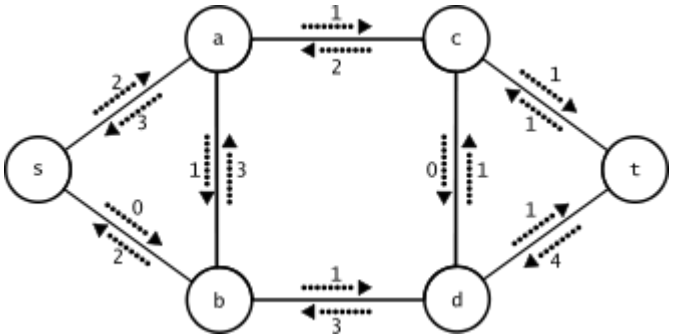


Image from https://en.wikipedia.org/wiki/Flow_network

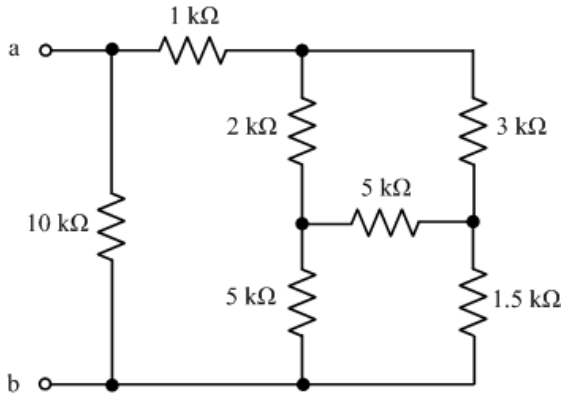
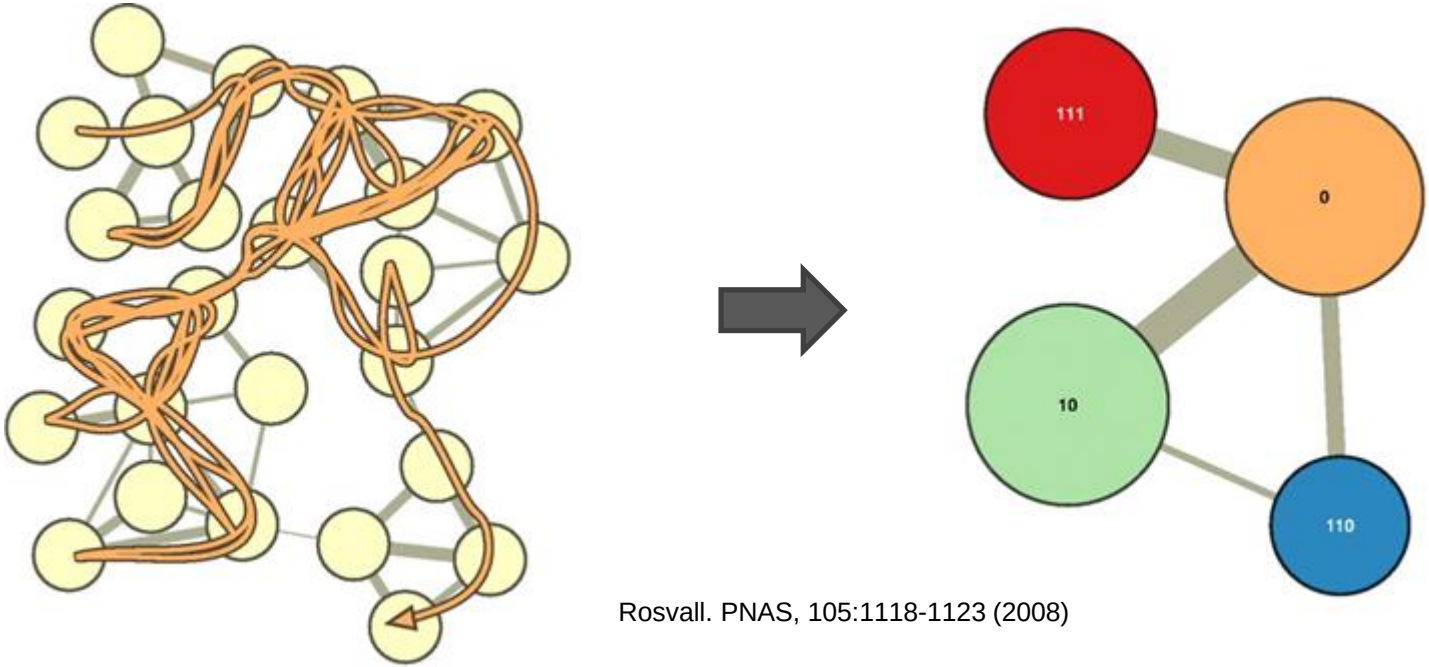


Image from http://www.rose-hulman.edu/CLEO/browse/?path=1/2/79/91/92/19

- Signal as fluid flowing through pipes with various diameters
- Signal as electric current flowing through circuit with various resistances
- Study the dynamics and stationary states with simulations

Network as random walks

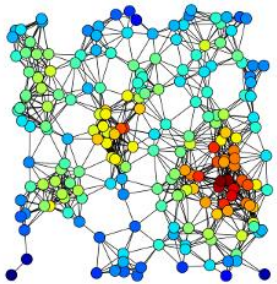


Rosvall. PNAS, 105:1118-1123 (2008)

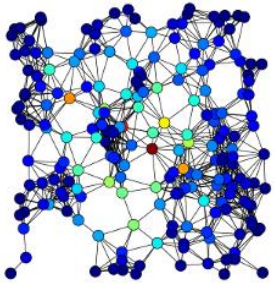
- Discrete particles travel from node to node with probability (edge weight)

Centrality scores

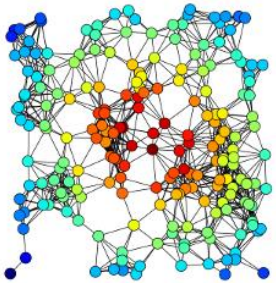
Degree



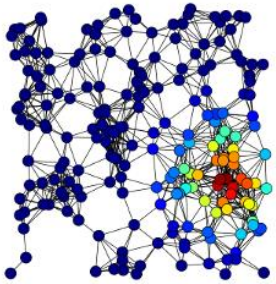
Betweenness



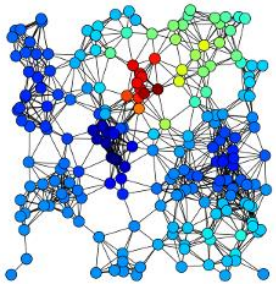
Closeness



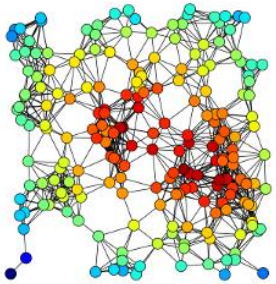
Eigenvector



Katz



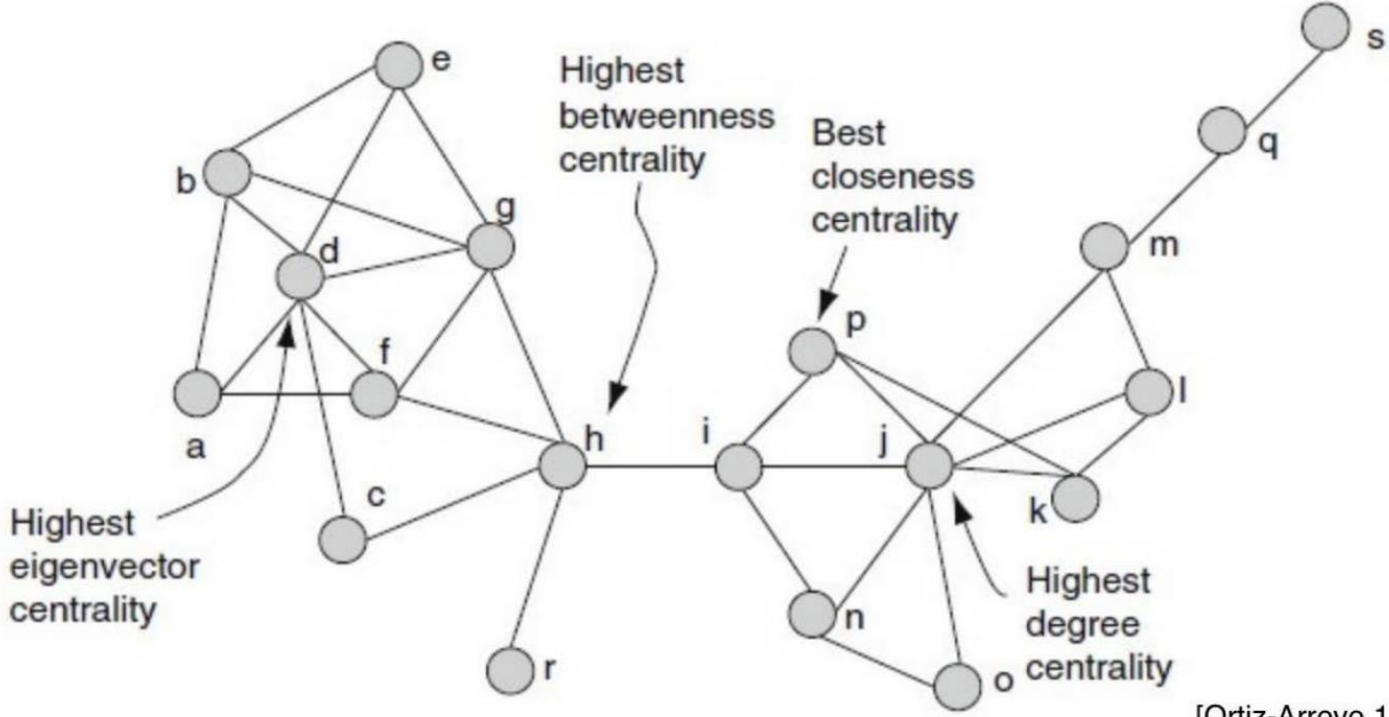
Harmonic



- Indicate the importance of a node in the context of the connectivity of the network
- Degree = local connectivity
- Betweenness = fraction of shortest paths
- Closeness = inverse distance to other nodes

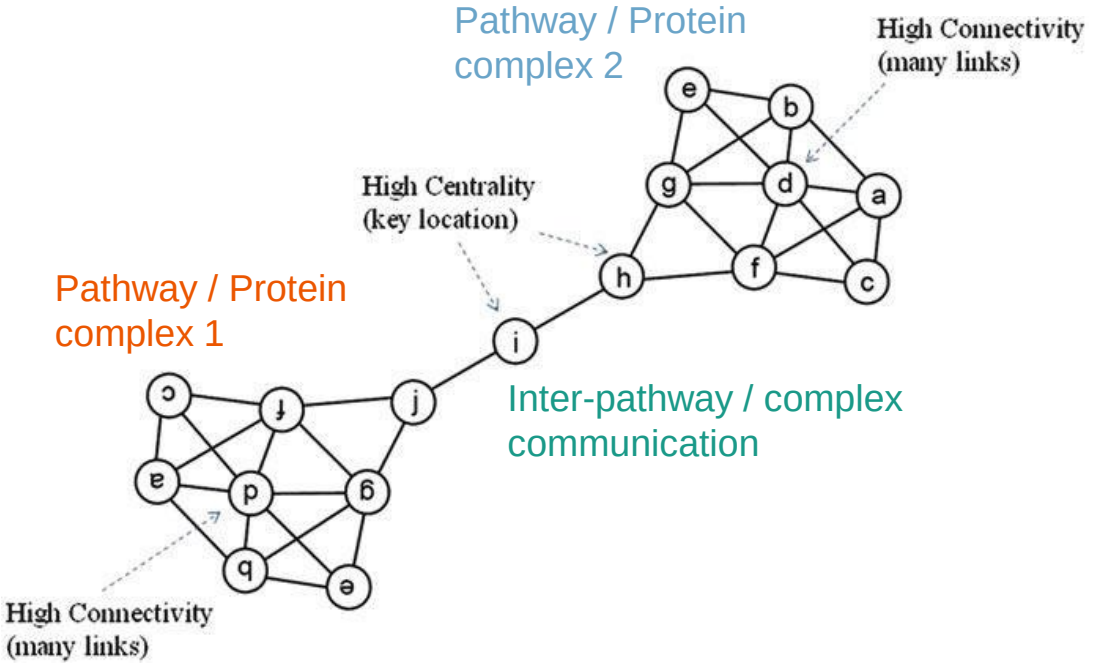
Image from https://en.wikipedia.org/wiki/Centrality

Different scores, different meaning



[Ortiz-Arroyo 10]

Biological interpretation

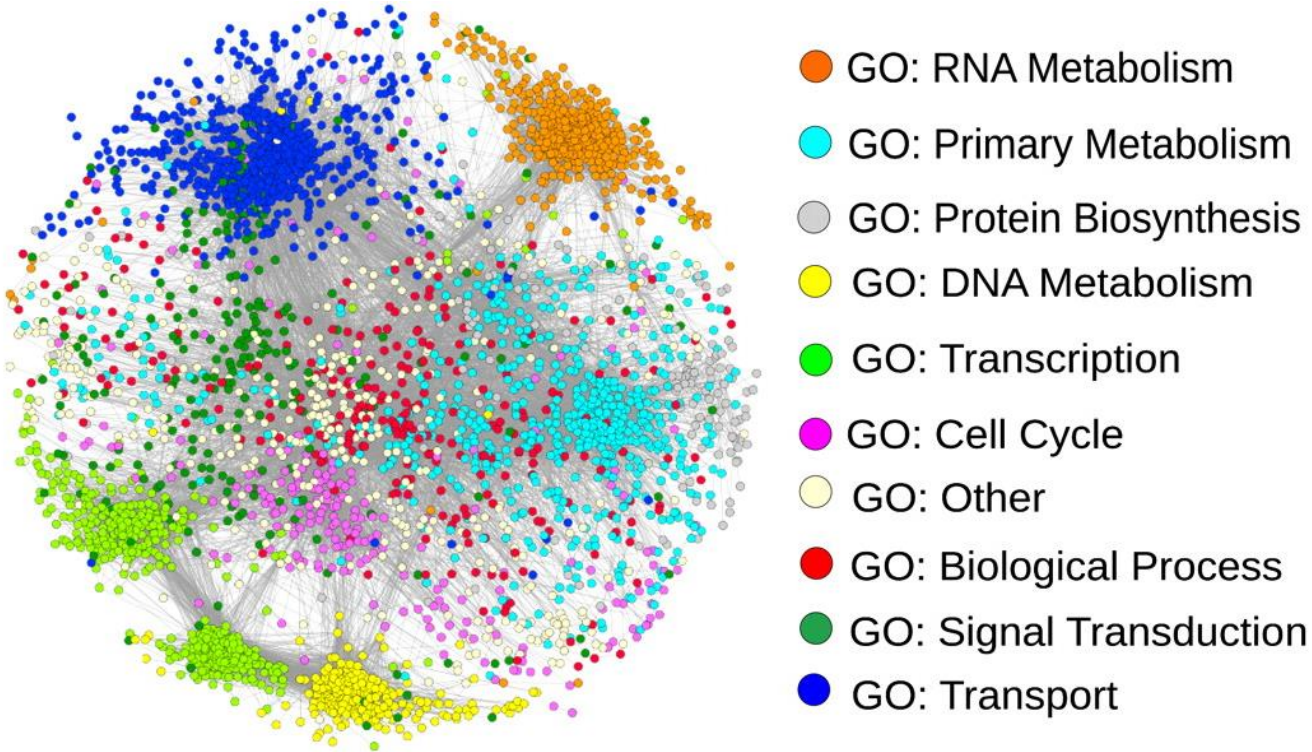


Natapov and Fisher-Gewirtzman. Smart City Networks (2017)

- **Low degree, High betweenness** = connect multiple functional pathways
- **High degree, Low betweenness** = core protein of a complex, transcription factor with multiple downstream targets

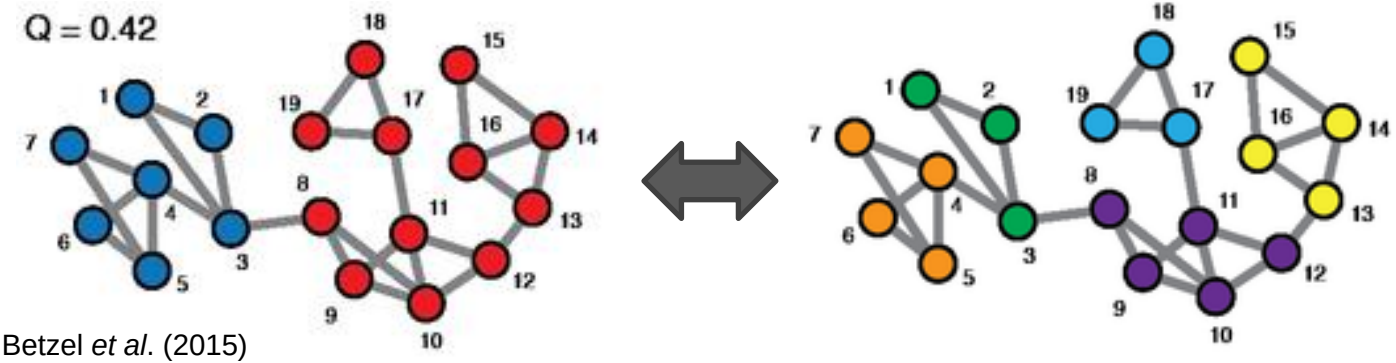
Network clustering

Dissect local characteristics

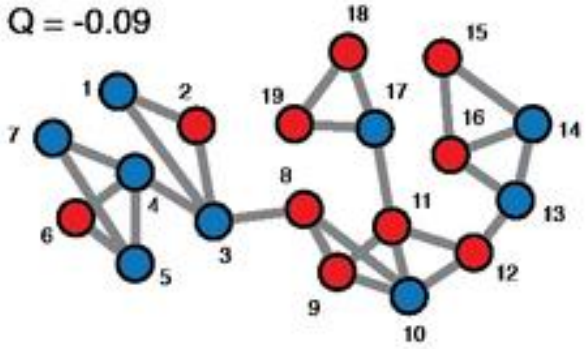


Pancaldi *et al*. G3: Genes, Genomics, Genetics, 2:453-497 (2012)

Modularity score



Betzel *et al*. (2015)



- Number of within-cluster edges compared to expectation (based on number of nodes and global number of edges)
- Multiple resolutions

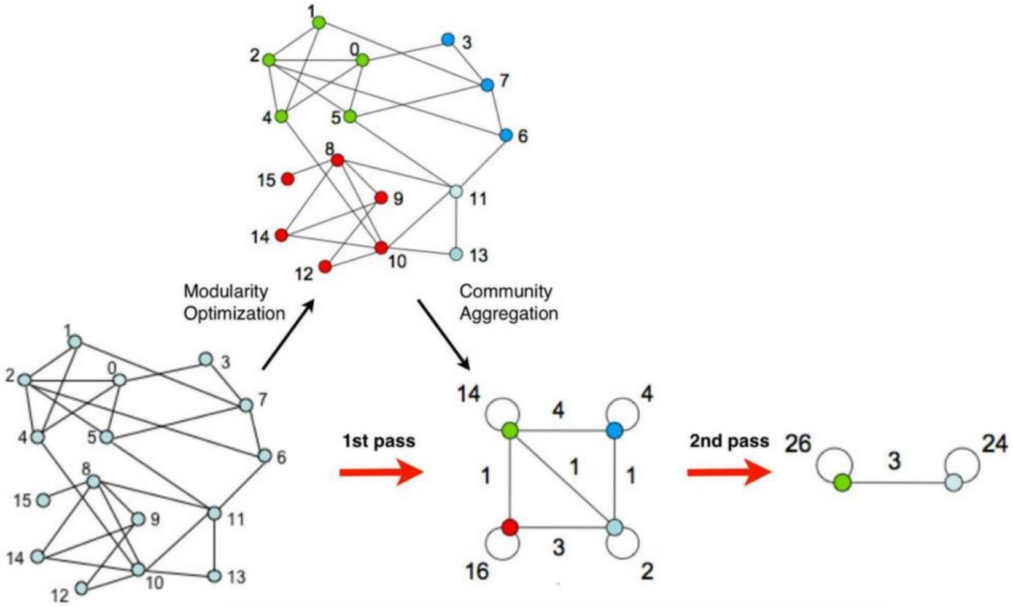
A simple modularity score

- Node N_i with degree d_i
- Node N_j with degree d_j

- Edge weights are all 1
- P(edge between N_i and N_j by chance) ~ d_i d_j / 2 x # edges

- Modularity score of a cluster of nodes (N_1, N_2, ..., N_n) is then:
  - Q = # within-cluster edges $- \sum_{i,j} \frac{d_i d_j}{2e}$

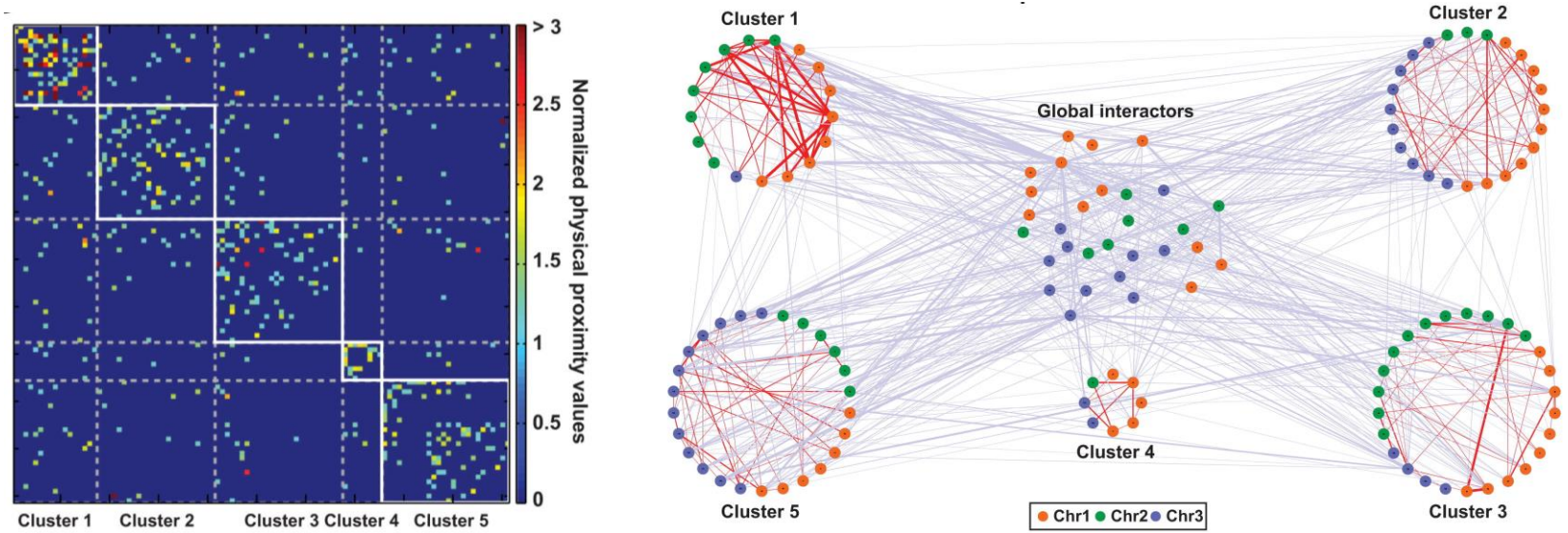
Louvain / Leiden algorithm



https://towardsdatascience.com/louvain-algorithm-93fde589f58c

- Iteratively find clusters of node that maximize modularity score
- Collapse nodes of a cluster into a representative node to speed up refinement

Application on chromatin interaction

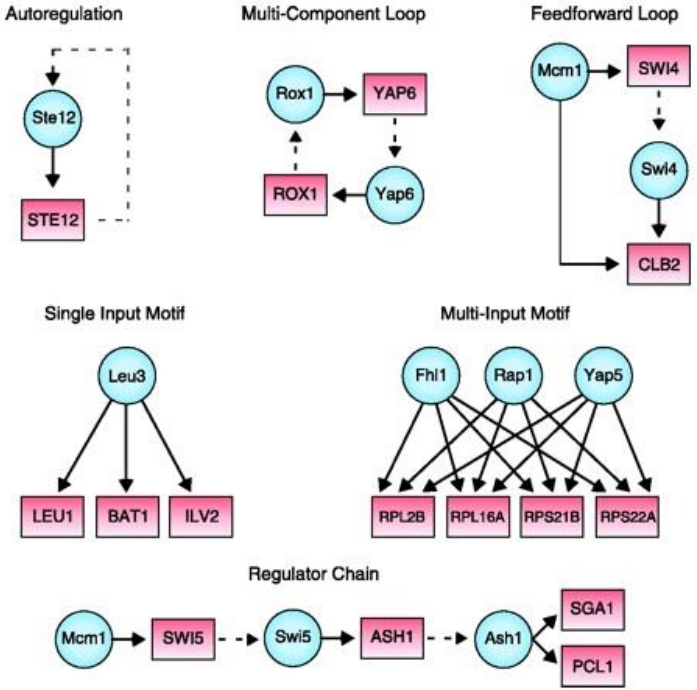


Tanaka *et al*. Molecular Cell, 48:532-46 (2012)

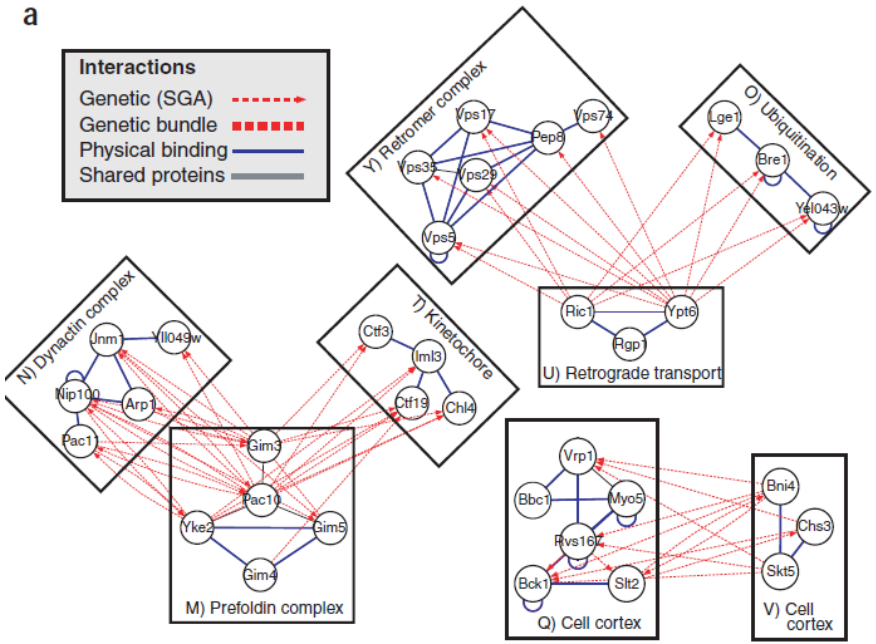
- Identify clusters of genomic loci that are nearby in 3D + global interactors

Network motifs and homology

Motif = recurring patterns

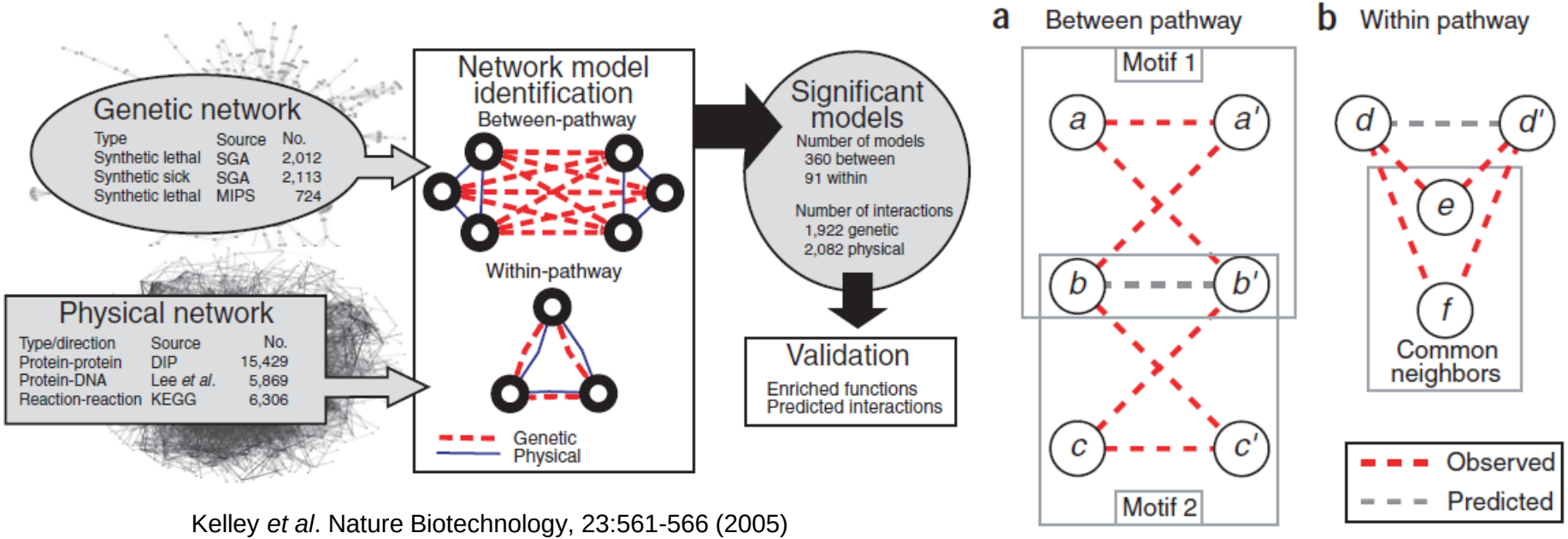


Lee *et al*. Science. 298:799-804 (2002)



Kelley *et al*. Nature Biotechnology, 23:561-566 (2005)

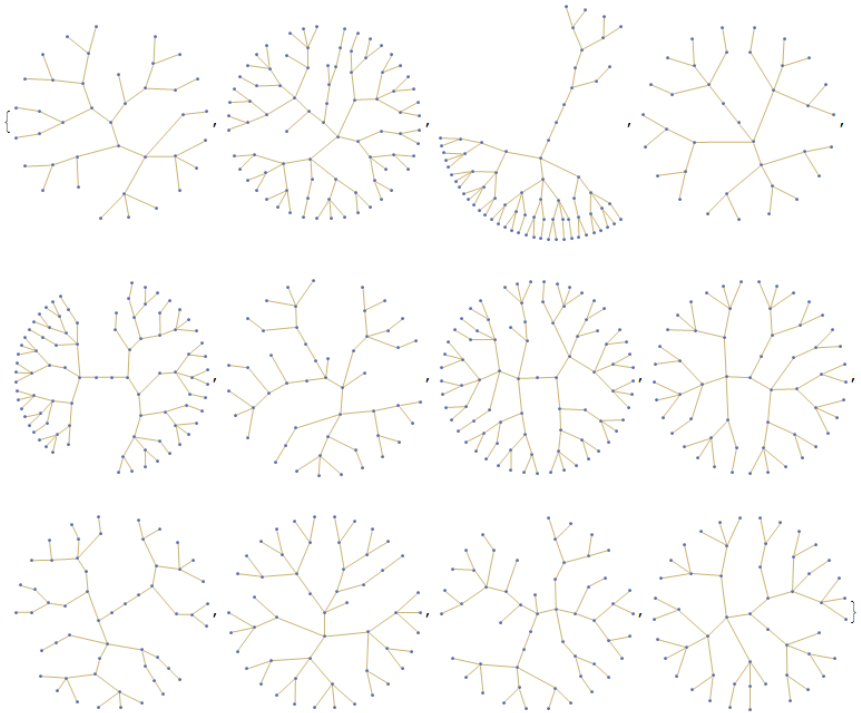
Incomplete motif indicates missing data

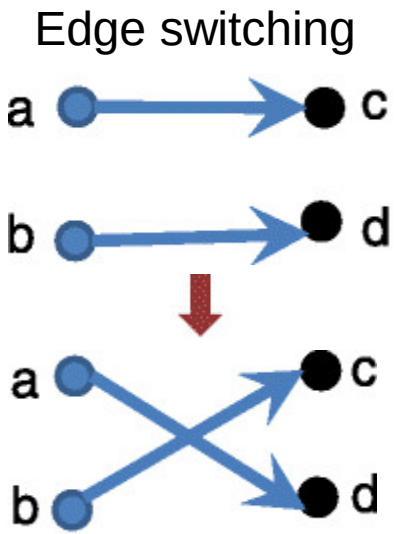


Kelley *et al*. Nature Biotechnology, 23:561-566 (2005)

- Predict missing data and prioritize for validation

Finding motif with permutation test



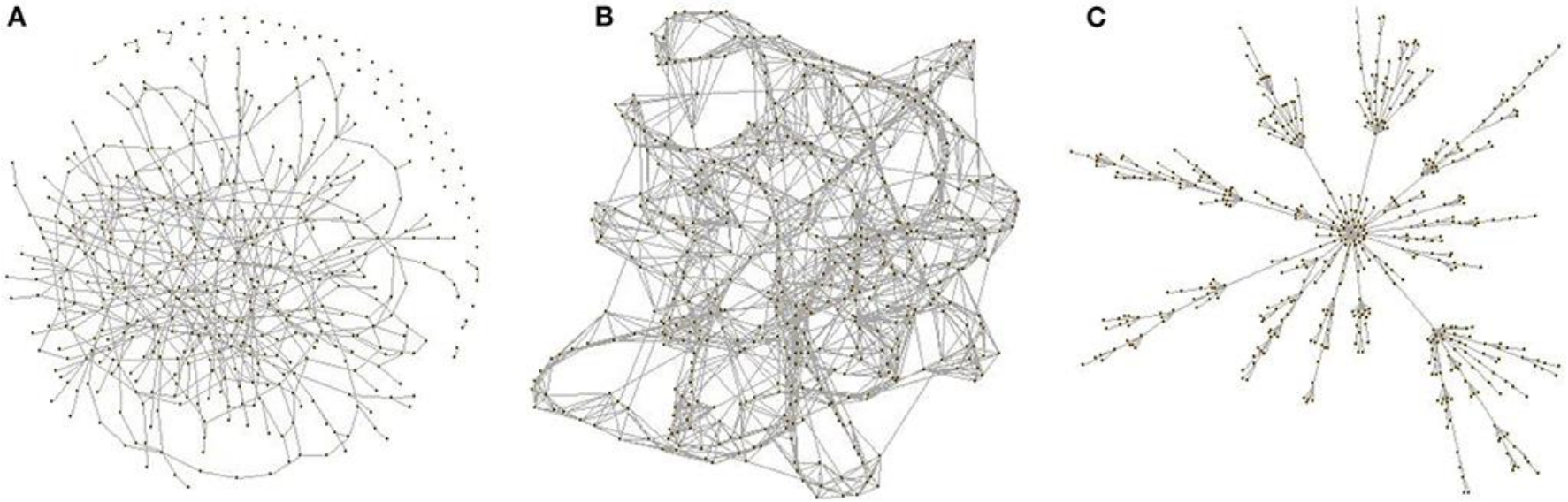


Temate-Tiageru *et al*. BMC Genomics, 17:542 (2016)

Preserve degree distribution!

Source: https://mathematica.stackexchange.com/questions/11632/how-to-generate-a-random-tree

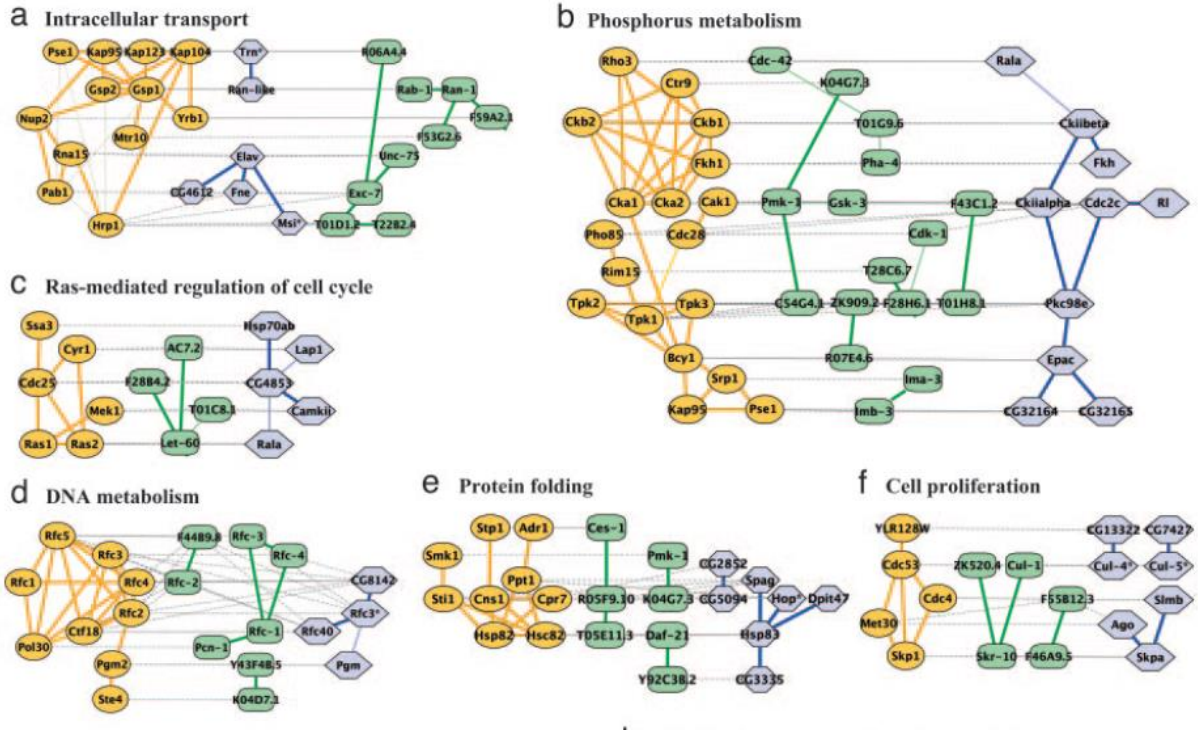
Random network models



Koutrouli, M. et al. Front. Bioeng. Biotechnol. 31 (2020)

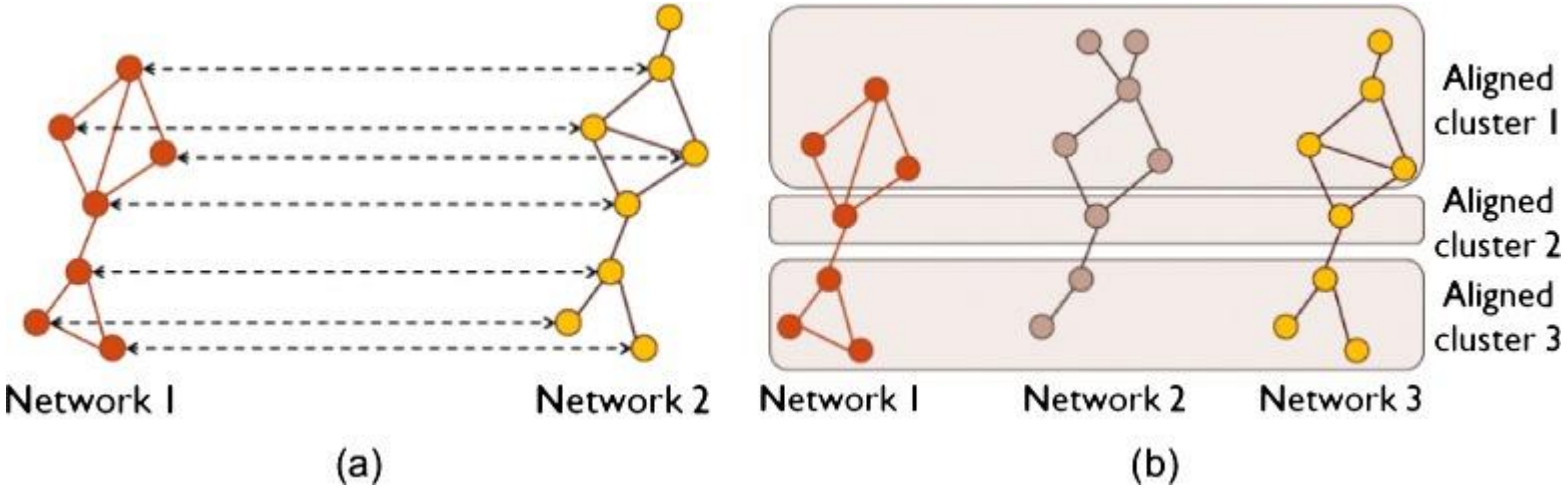
- A) Erdos-Renyi, B) Watts-Strogatz, C) Barabasi-Albert

Homology between nodes and network structures



Sharan *et al*. PNAS, 102:1974-1979 (2005)

Evolution as change in networks

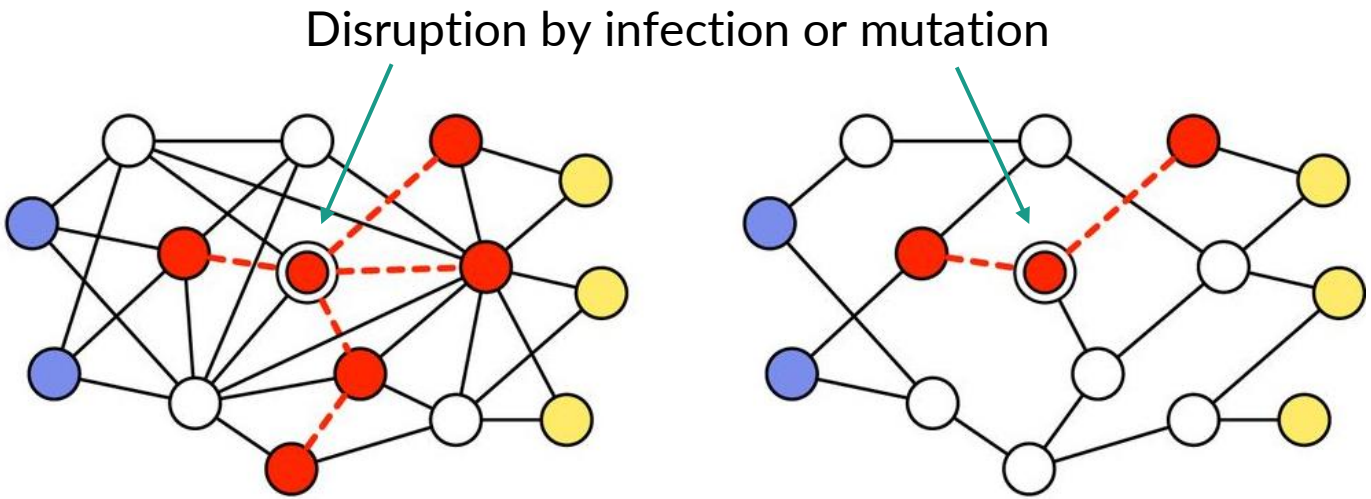


Faisal *et al*. EURASIP J Bioinform Syst Biol (2015)

- Identify gene expansion and emergence of new interactions
- Predict missing interactions for validation

Applications of network analyses

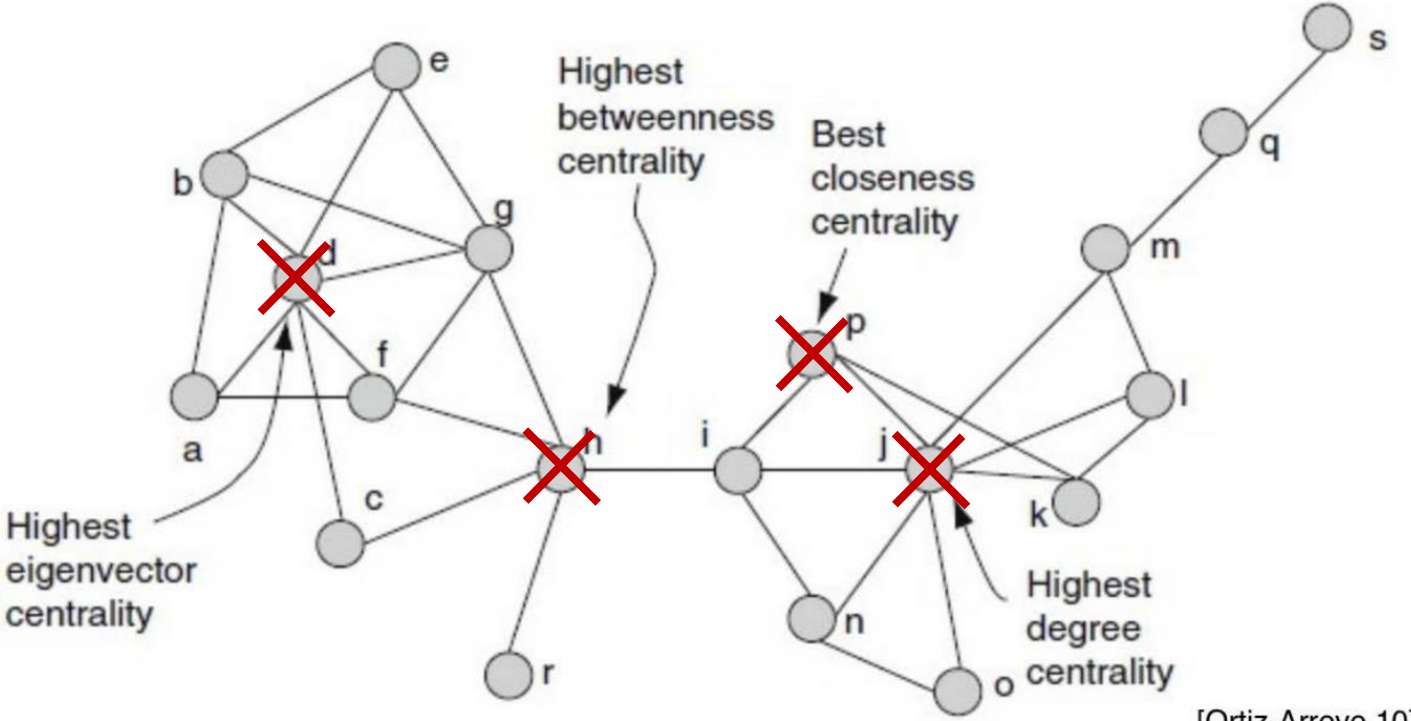
What if nodes/edges were removed?



Navlakha *et al*. J of the Royal Society Interface, 11 (2014)

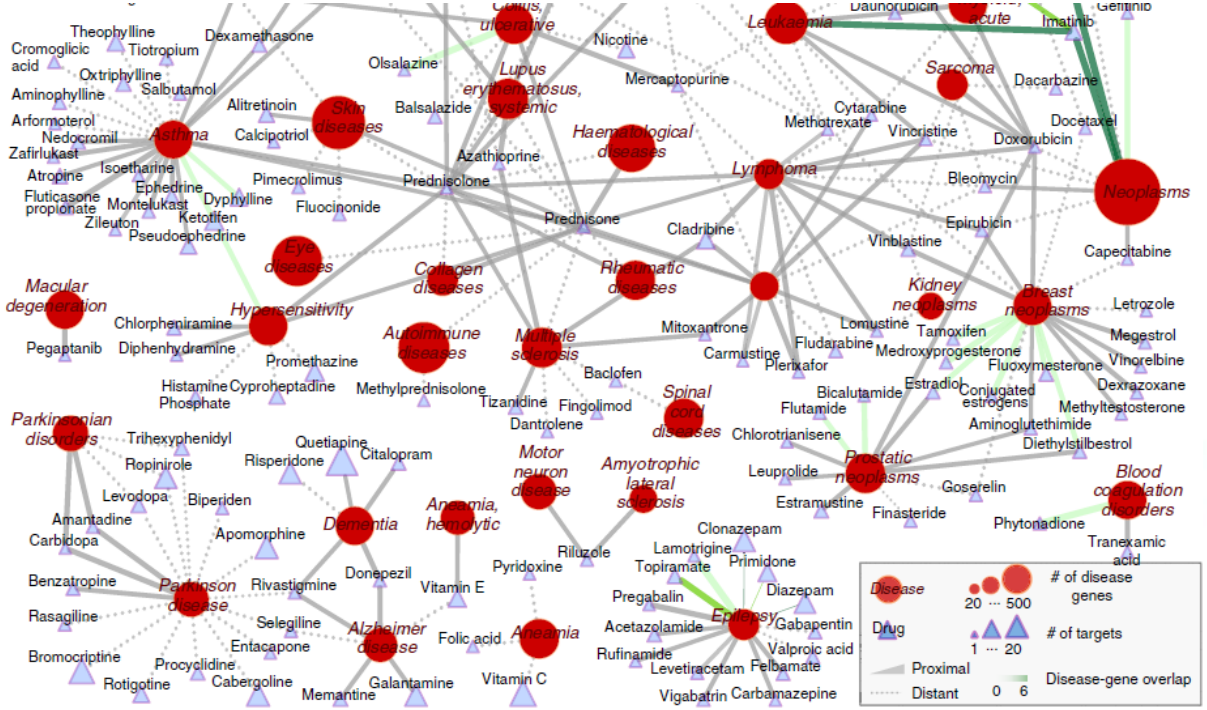
- Analysis of network-level changes induced by node/edge-level changes
- Complement centrality scores

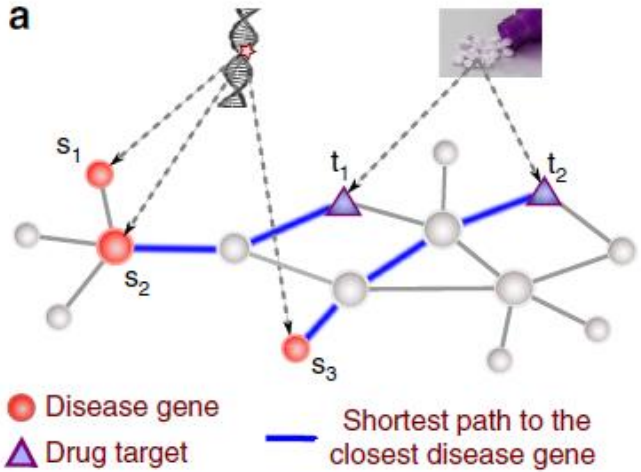
Variety of expected impacts



[Ortiz-Arroyo 10]

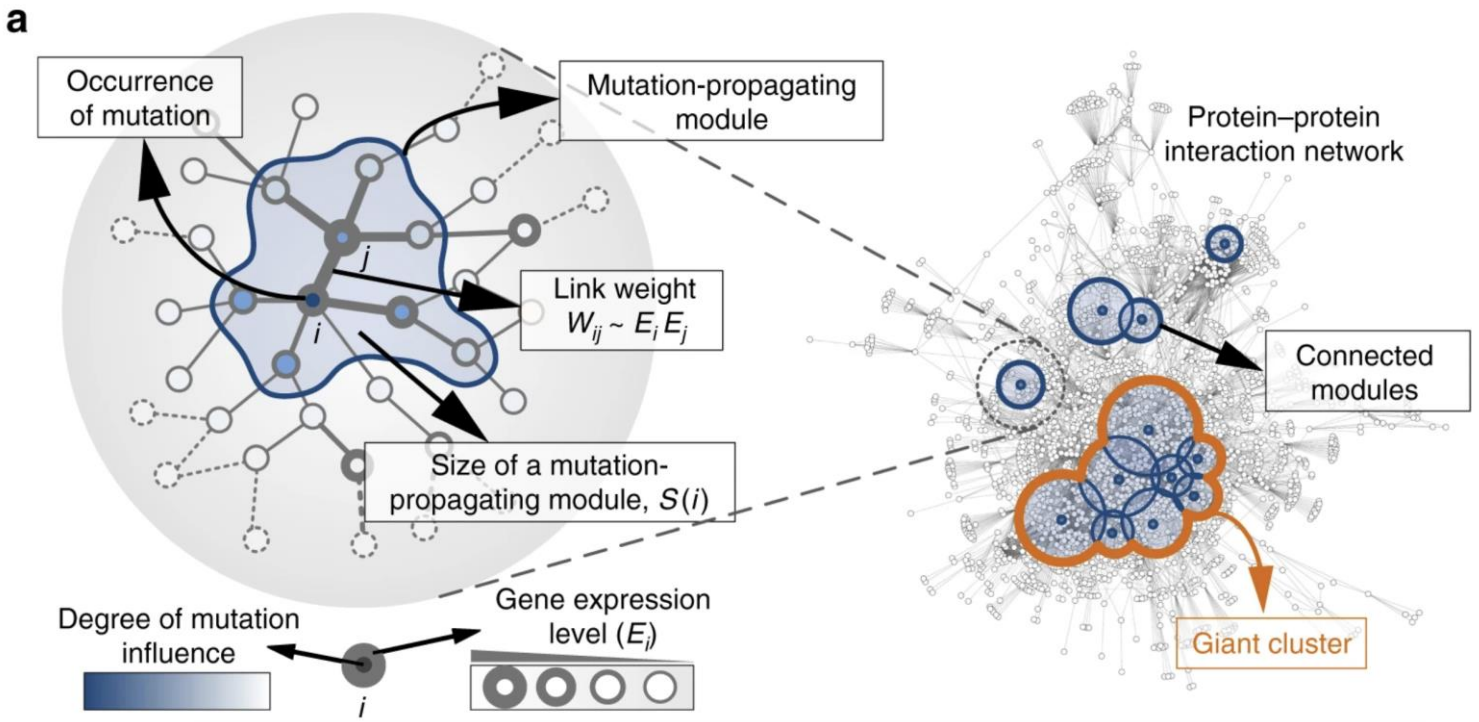
Linking drug to disease via gene network





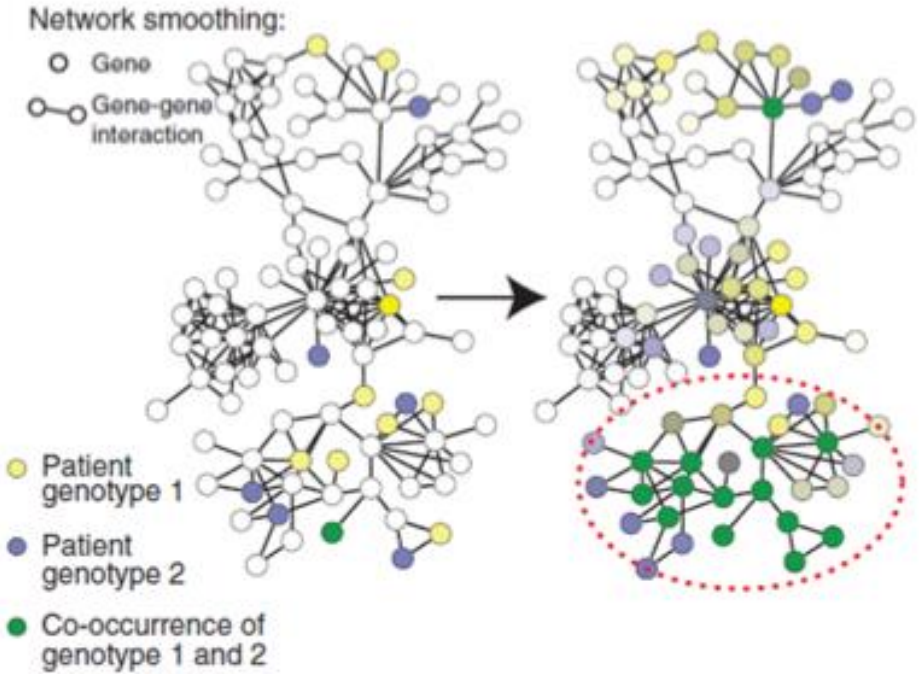
Guney *et al*. Nature Comm, 7:10331 (2016)

Propagate effect of mutations through network



Shin *et al*. Nature Comm, 8:1270 (2017)

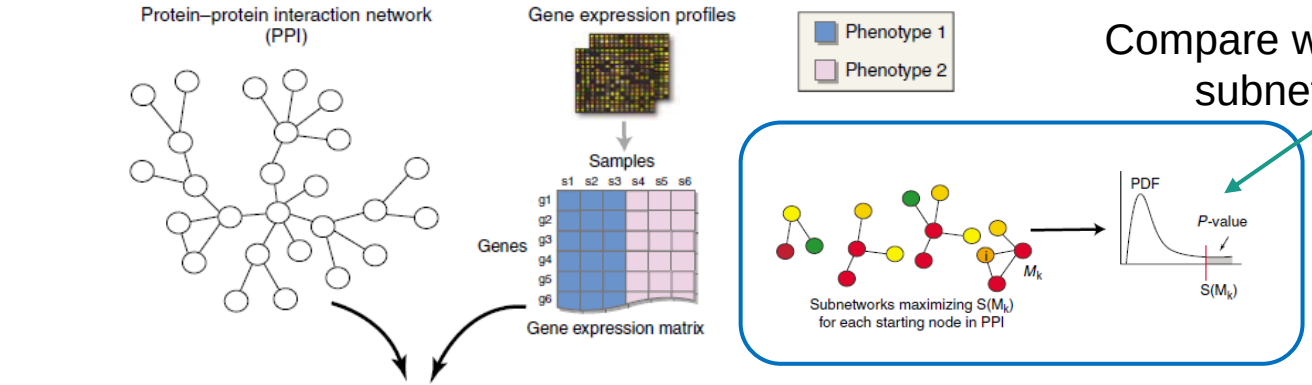
Network-based patient stratification



- Different patients have different mutation profiles
- Different mutation profiles may have similar impacts on gene-gene network
- Identify commonly affected gene subnetworks

Hofree *et al*. Nature Methods, 10:1108-1115 (2013)

Network-based differential expression



Compare with random subnetworks

- Identify differentially expressed subnetwork

Chuang *et al*. Mol Syst Biol, 3:140 (2007)

Summary

- Network data capture interaction information
  - Provide a bird-eye view of the biological systems
  - Lead to mechanistic understanding
- Connectivity analysis can reveal important components and interactions
  - Path & flow techniques
  - Perturbation
- Motif and homology analysis can help us discover missing data

Any question?

- See you on Thursday October 20th