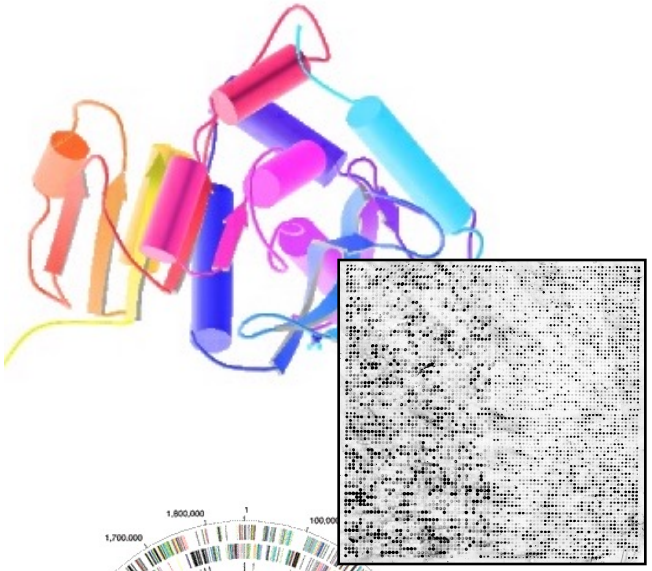
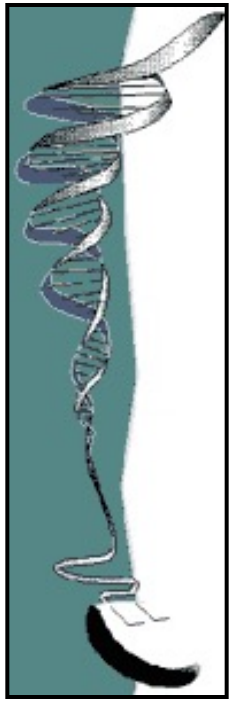
Biomedical Data Science:

Analysis of Network Topology D – Central Network Points





Mark Gerstein, Yale University

gersteinlab.org/courses/452

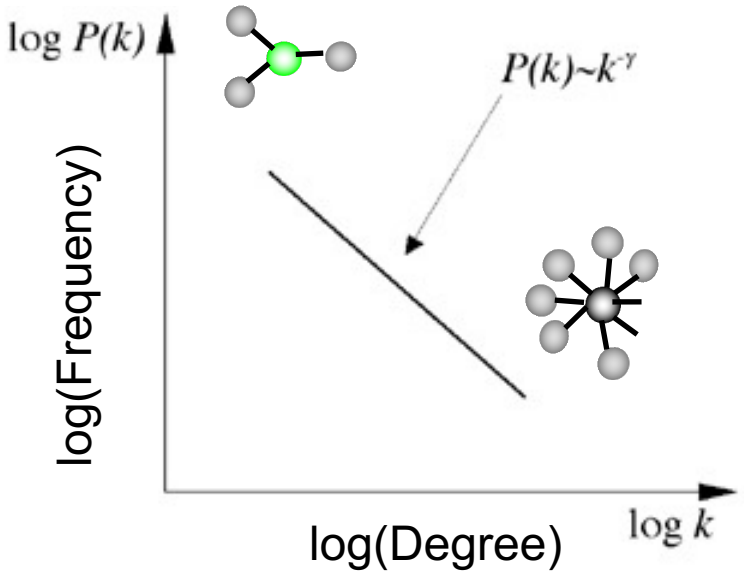
(last edit in spring ‘21)

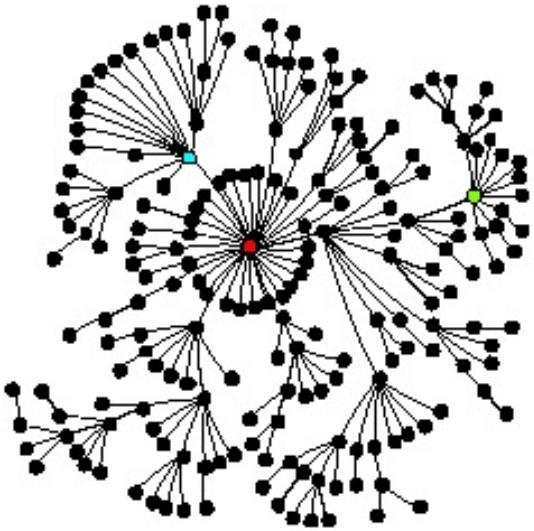
Network Topology

Measures of Centrality: Hubs

Scale-free networks in Biology

Power-law distribution

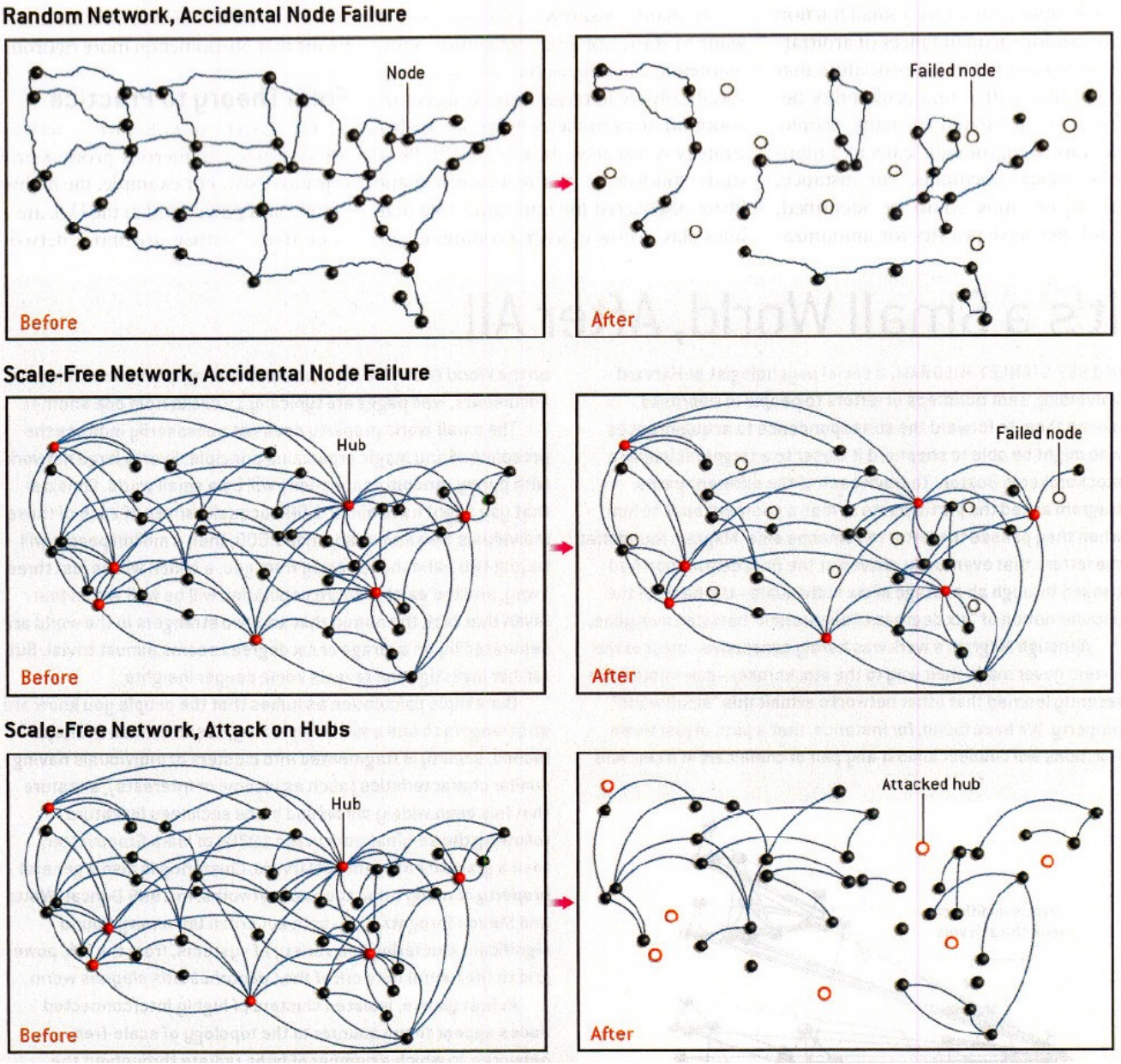




Hubs dictate the structure of the network

[Barabasi]

Knocking Out Nodes in Scale-free and Random Networks

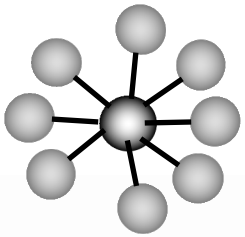


[From Barabasi & Bonabeau, *Sci. Am.,* May '03]

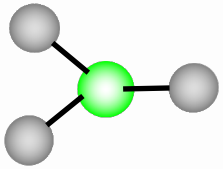
Hubs tend to be Essential

Integrate gene essentiality data with protein interaction network. Perhaps hubs represent vulnerable points?

[Lauffenburger, Barabasi]



"hubbiness"



[Yu et al., 2003, TIG]

- **Notably, the most highly conserved proteins were highly connected in *E.coli* protein interaction network. (*E.coli*)**

  - Butland et al. 2004, Nature

- **Connectivity of well-conserved proteins in network is negatively correlated with their rate of evolution. (*Saccharomyces cerevisiae*)**

  - Fraser et al. 2002, Science
  - Fraser et al. BMC Evol. Biol. (2003)

- **Proteins that have a more central position evolve more slowly and are more likely to be essential for survival. (*Saccharomyces cerevisiae; C. elegans; Drosophila*)**

  - Hahn et al. 2005, Mol Biol Evol

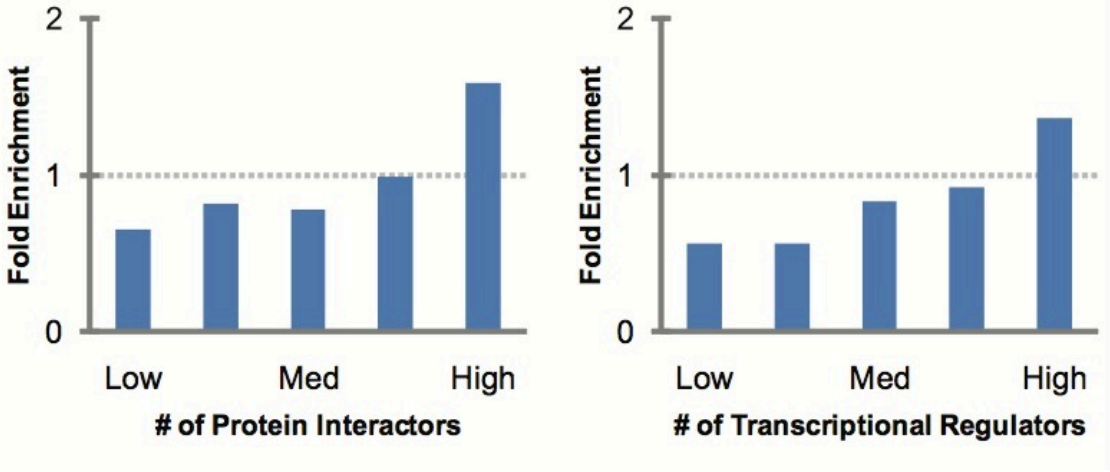
- **More miRNA regulation of a target gene associated with lower dN/dS (r = -.21) *(M. musculus)***

  - Cheng et al. 2009, BMC Genomics

- **Slowly evolving proteins tend to have more interaction partners. (*Saccharomyces cerevisiae*)**

  - Xia et al. 2009, Plos Comput Biol

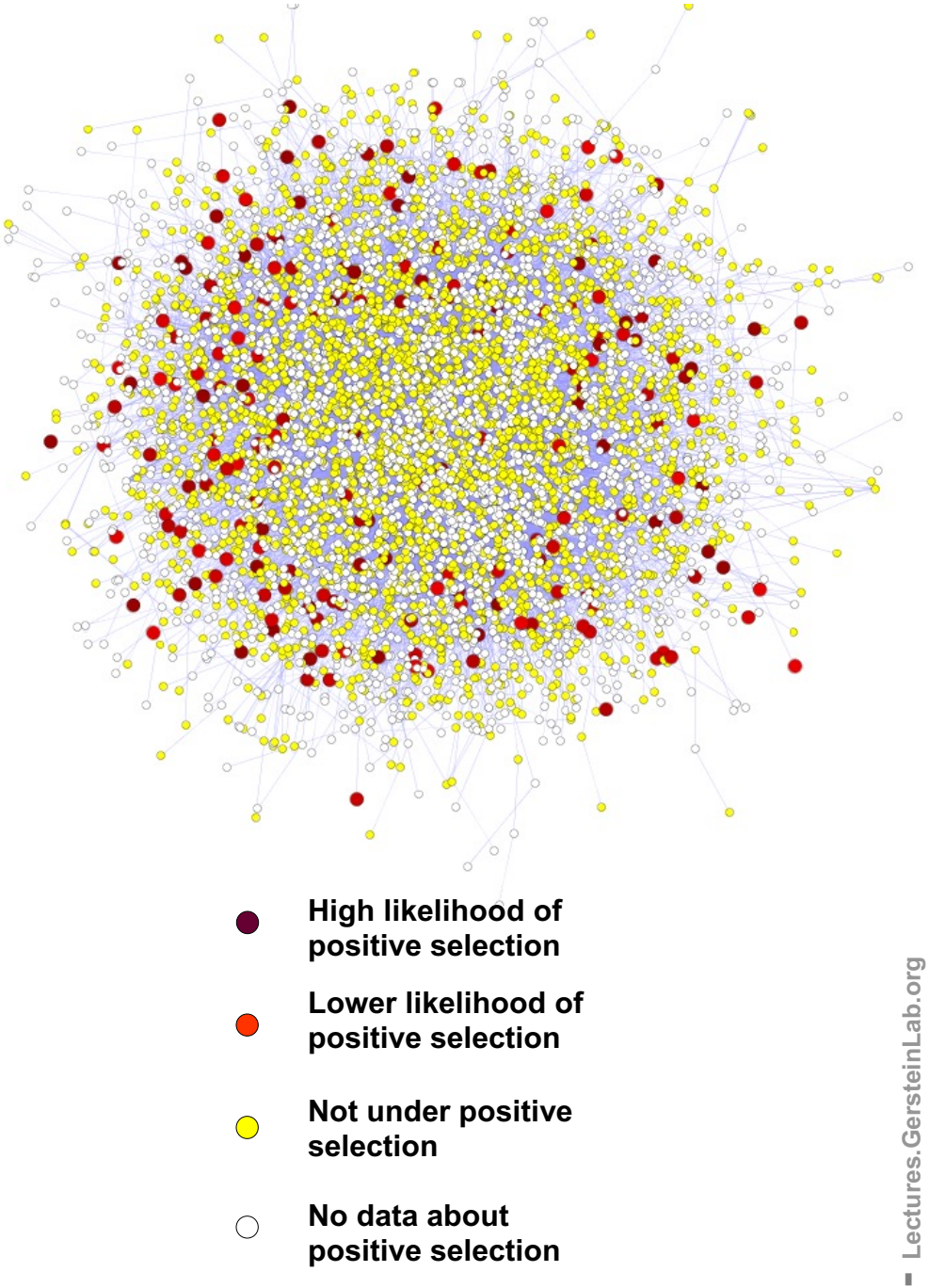
More Connectivity, More Constraint : A theme borne out in many studies



Fold Enrichment of slowly evolved proteins - *Xia et al.*

Rapid Evolution in the interaction network takes place at the periphery

- **Pos. sel. v. deg. centrality:**
  ρ = -.06, P < 1.2e-6
  - Effect is independent of any bias due to gene expression differences
  - Update w. 1000G Phase I
    SNP dens. v. centrality:
    ρ = -.1, p< 2.2e-16



Source: Nielsen et al. *PLoS Biol.* (2005), HPRD, and Kim et al. PNAS (2007)

Network Topology

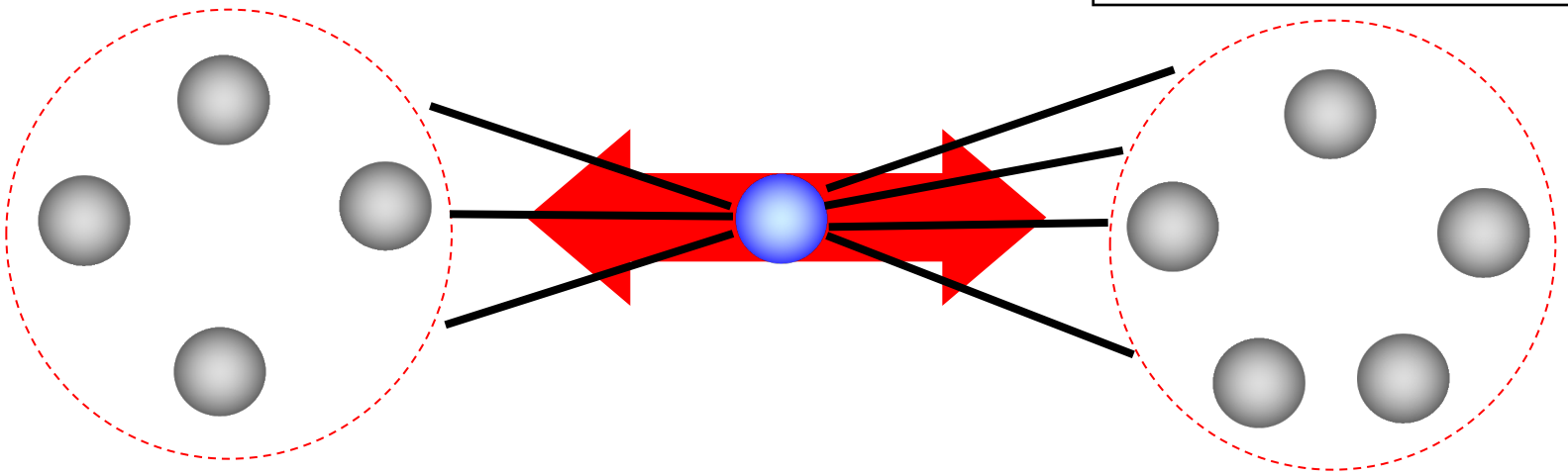
Other Measures of Centrality besides Hubs: Bottlenecks

Another measure of Centrality: Betweenness centrality

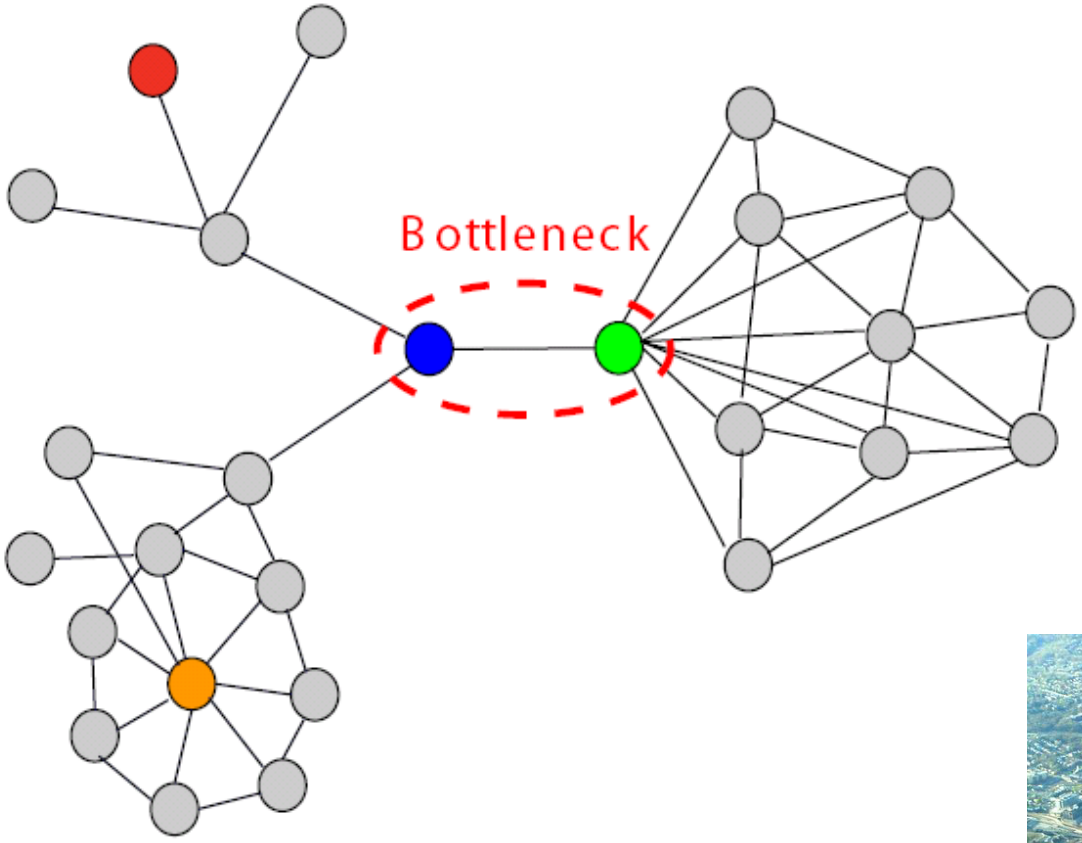
Betweenness of a node is the number of shortest paths of pairs of vertices that run through it -- a measure of information flow.

Freeman LC (1977) Set of measures of centrality based on betweenness. Sociometry 40: 35–41.

Girvan & Newman (2002) PNAS 99: 7821.



Bottlenecks & Hubs



Hub-bottleneck **node**

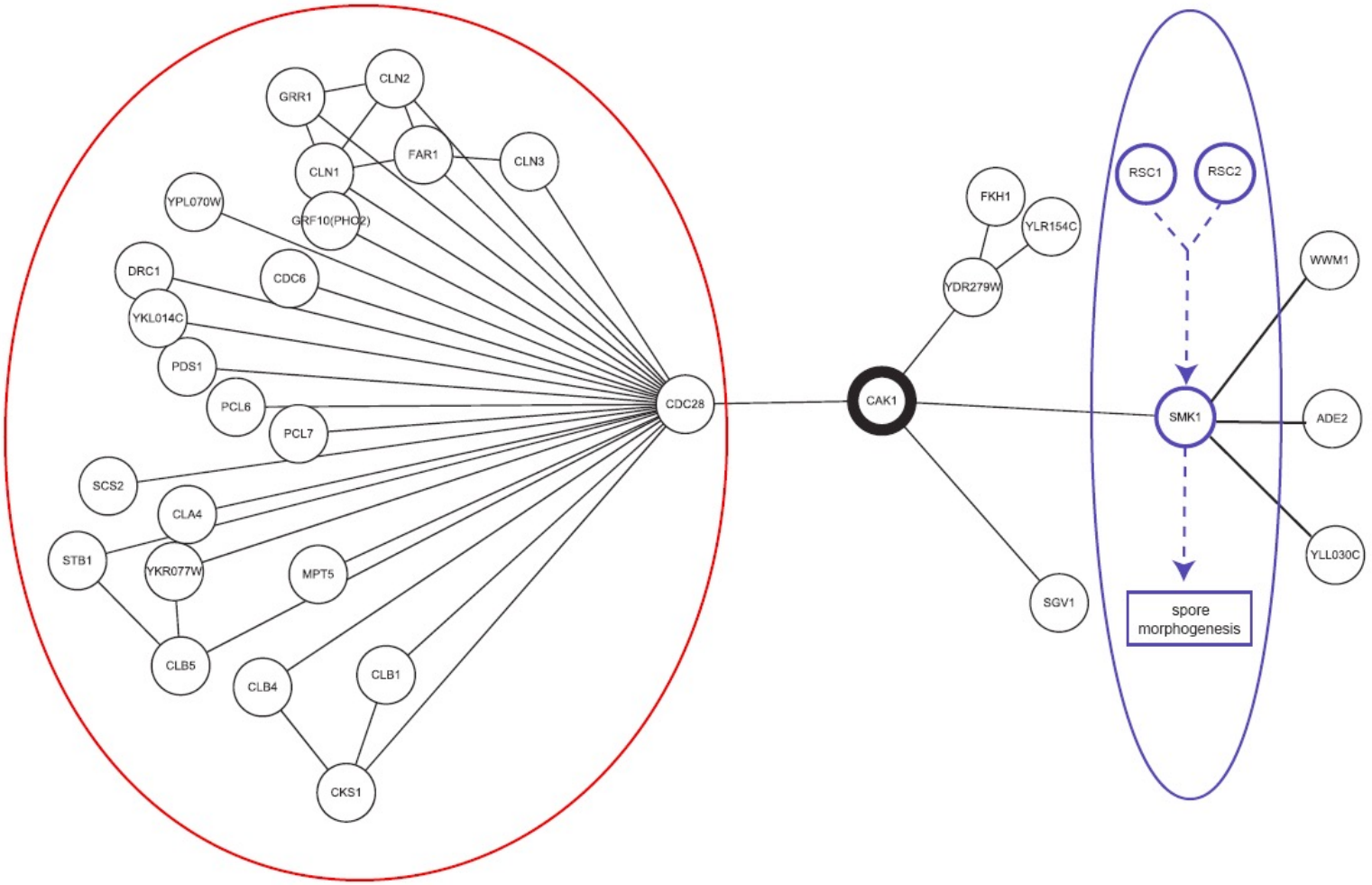
Non-hub-bottleneck **node**

Hub-non-bottleneck **node**

Non-hub-non-bottleneck **node**

[Yu et al., PLOS CB (2007)]

Bottleneck bridging between processes

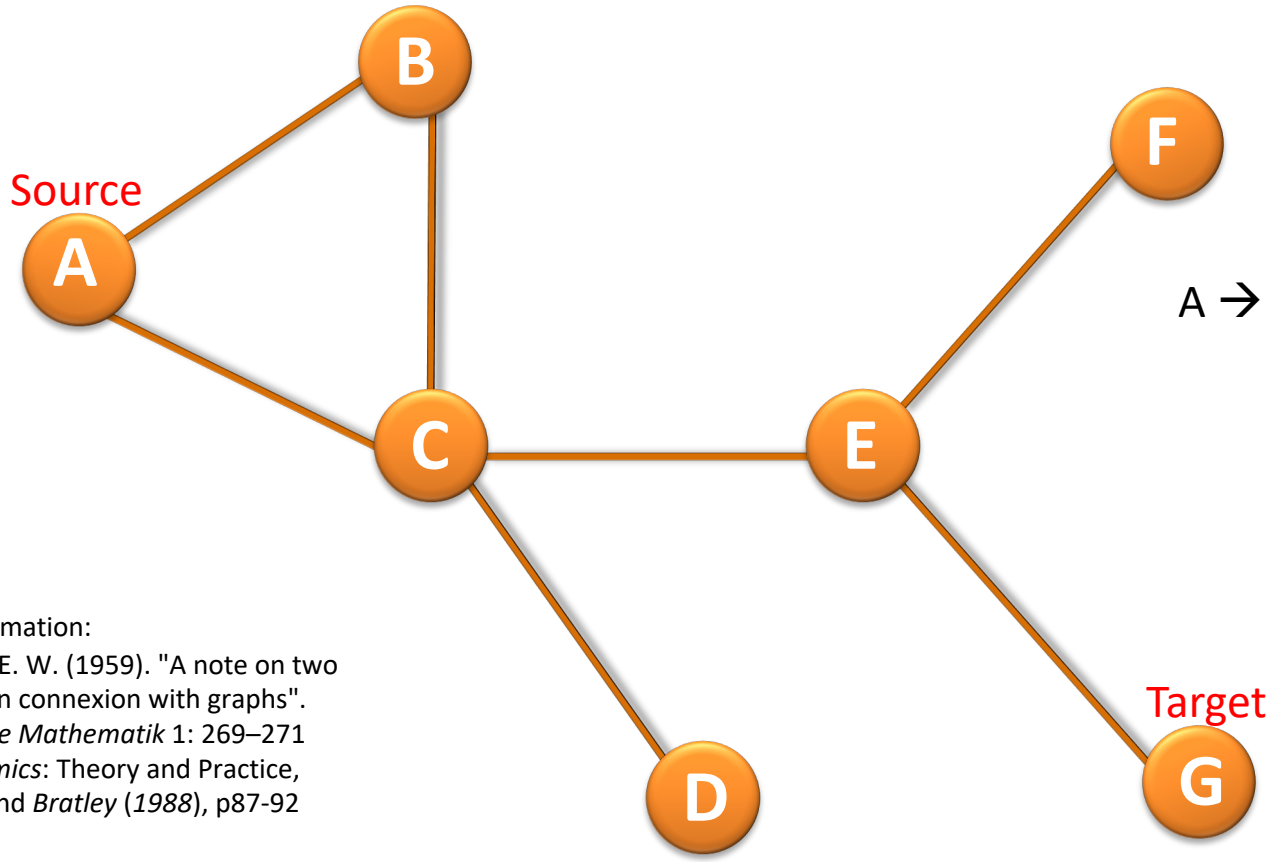


Regulation of mitotic cell cycle

MAP Kinase pathway regulating spore morphogenesis

[Yu et al., PLOS CB (2007)]

Shortest Paths: The Dijkstra Algorithm



More information:

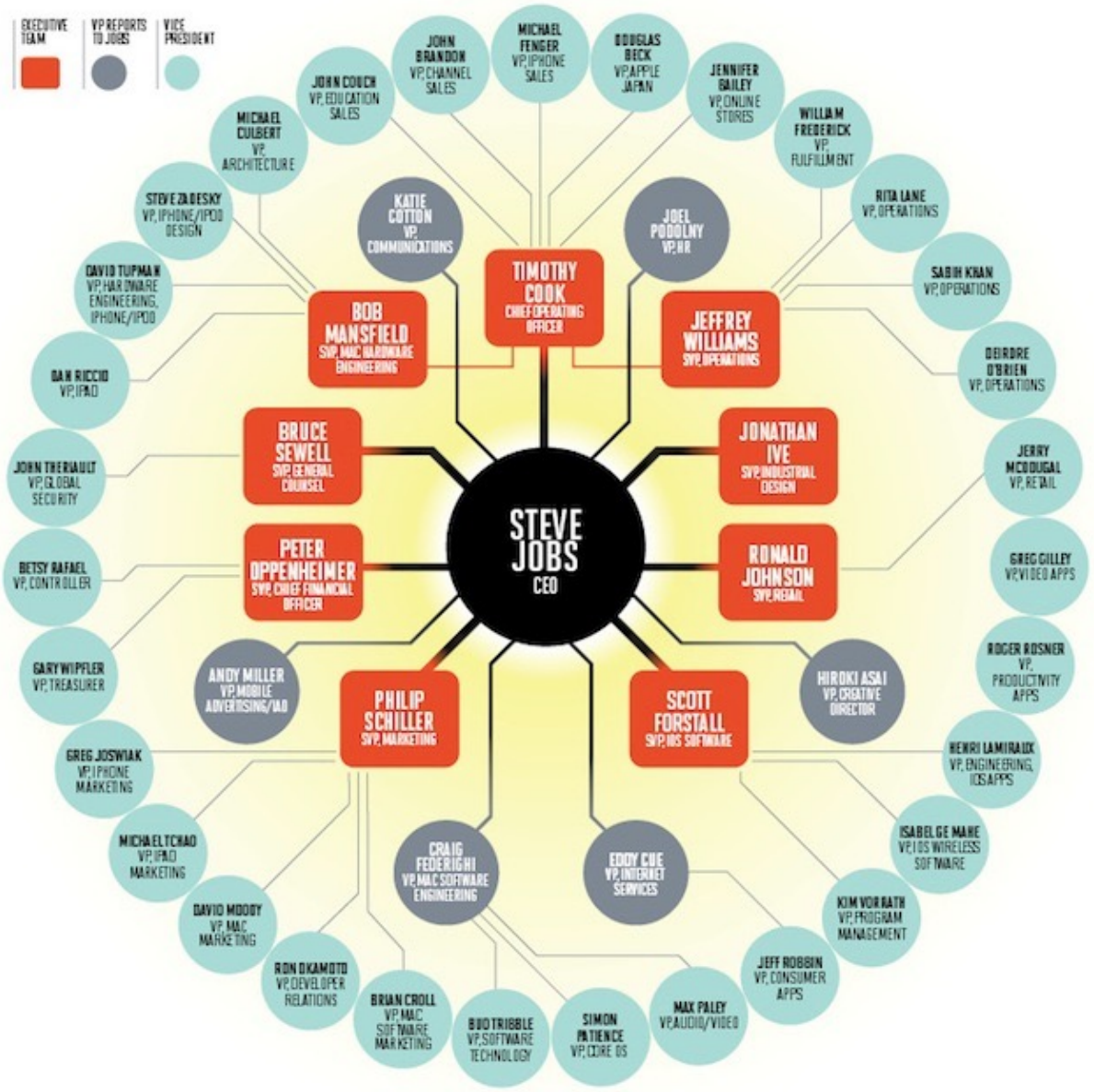
1.Dijkstra, E. W. (1959). "A note on two problems in connexion with graphs". *Numerische Mathematik* 1: 269–271

2.Algorithmics: Theory and Practice, *Brassard* and *Bratley* (*1988*), p87-92

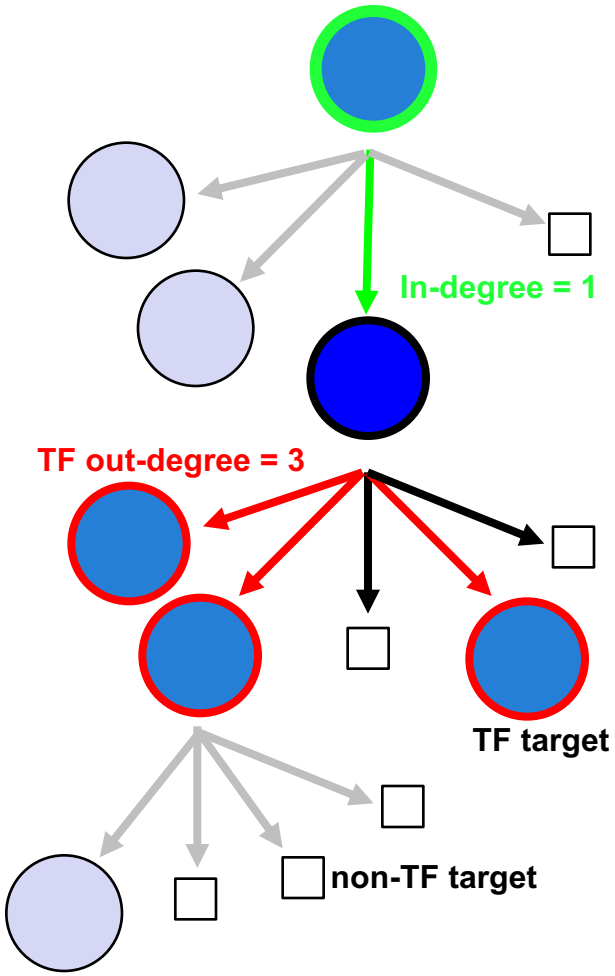
Network Topology

Other Measures of Centrality besides Hubs: Hierarchy

Network Hierarchy



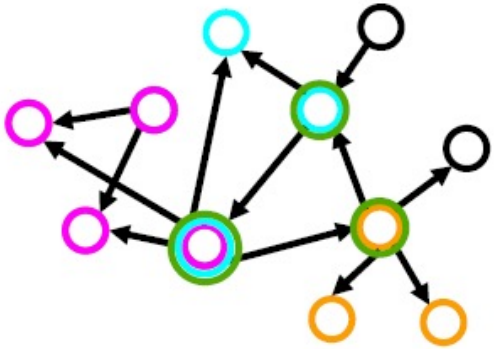
Network Stats to Identify Hierarchy



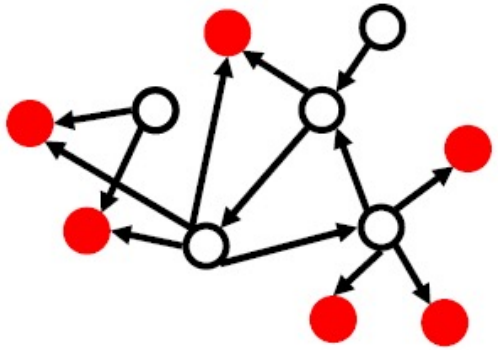
Hierarchy Height Statistic =
(normalized TF Out deg. – In deg.)

Determination of "Level" in Regulatory Network Hierarchy with Breadth-first Search

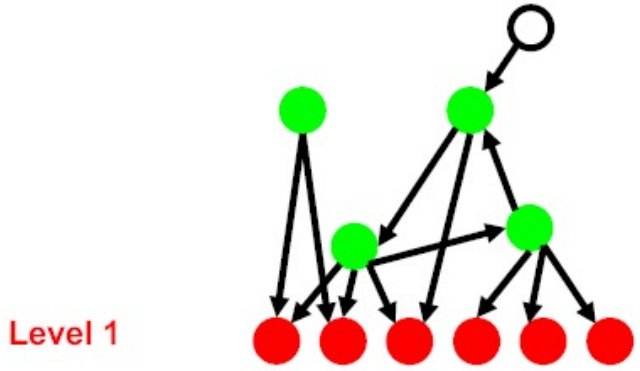
I. Example network with all 4 motifs



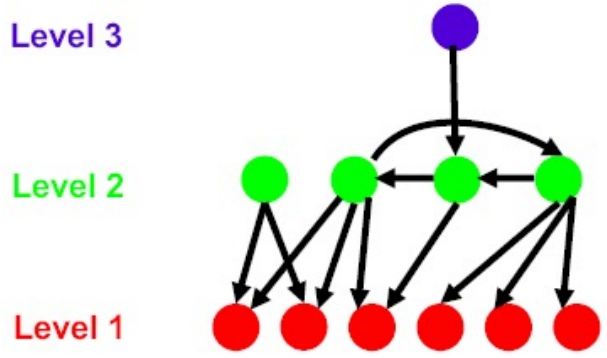
II. Finding terminal nodes (Red)



III. Finding mid-level nodes (Green)

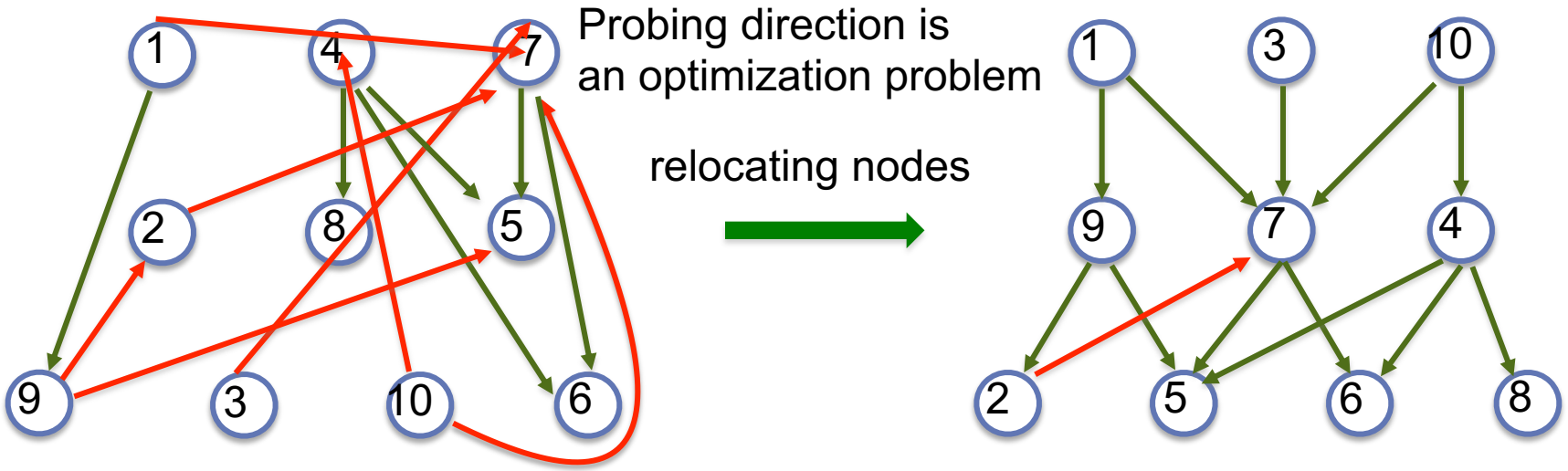


IV. Finding top-most nodes (Blue)



[Yu et al., PNAS (2006)]

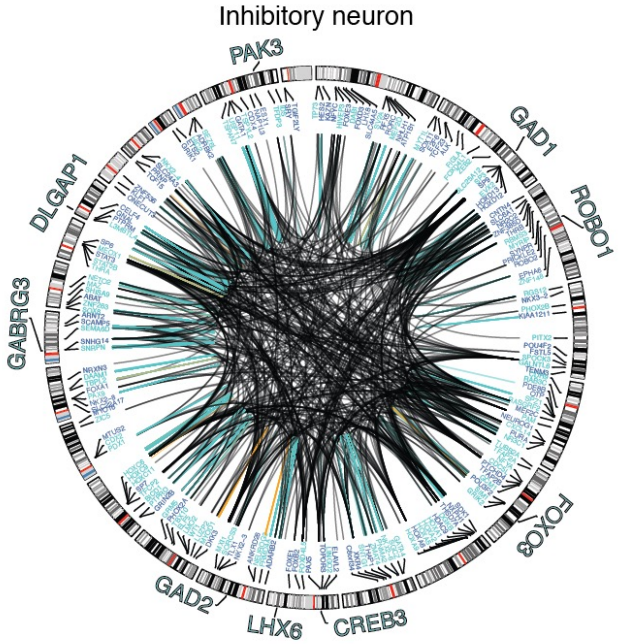
Using Simulated Annealing to Globally Minimize the Number of Upward Pointing Edges



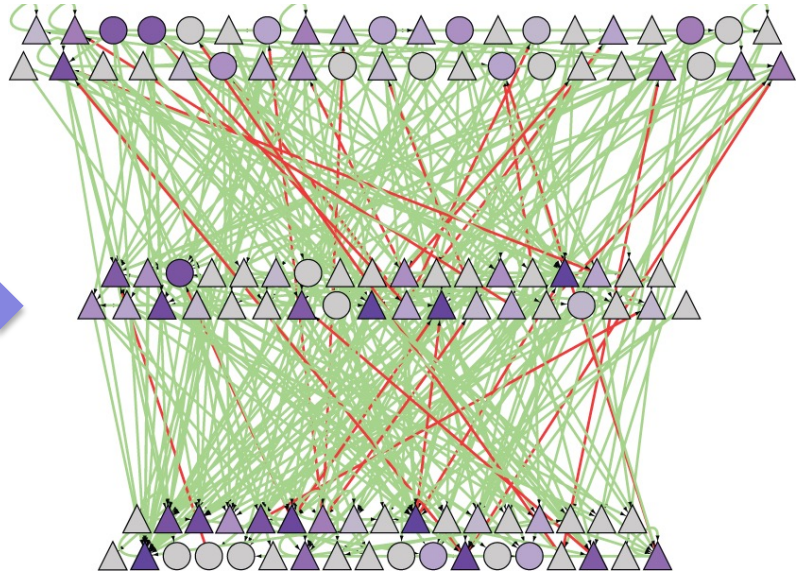
[Gerstein et al. Nature ('12)]

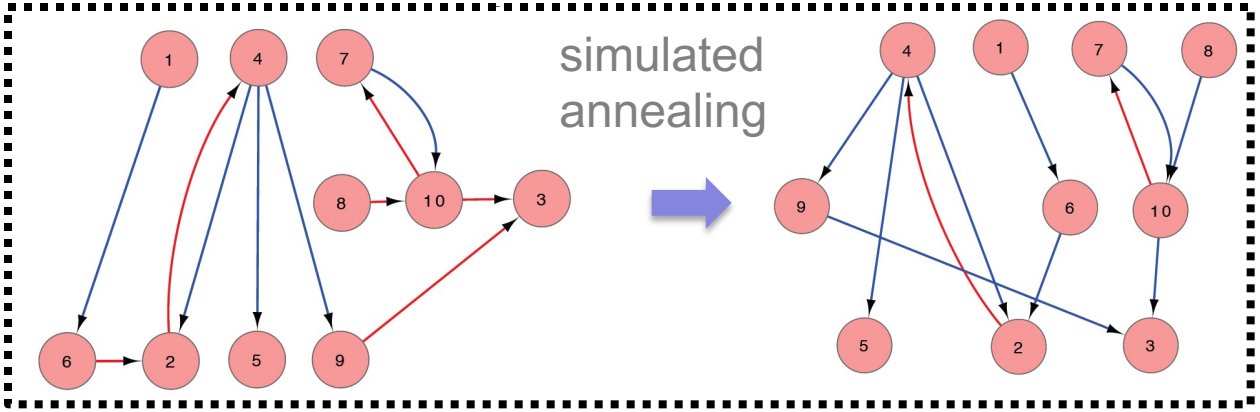
Transforming a Regulatory Network into a Hierachy

Regulatory Network



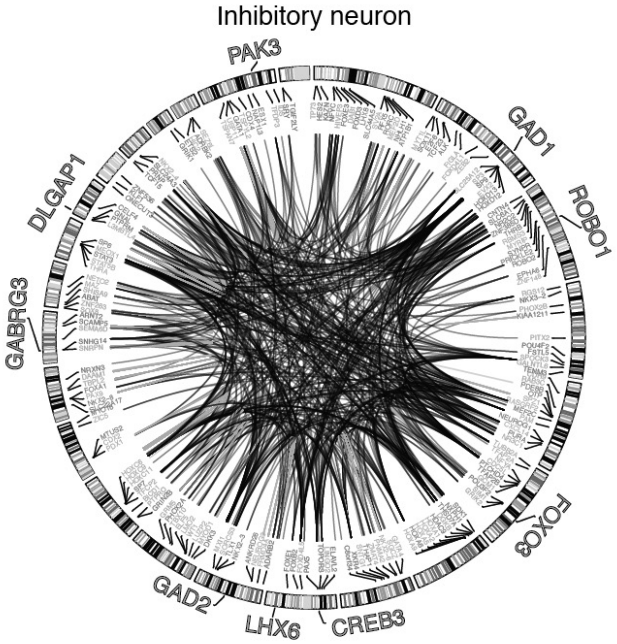
Network Hierarchy

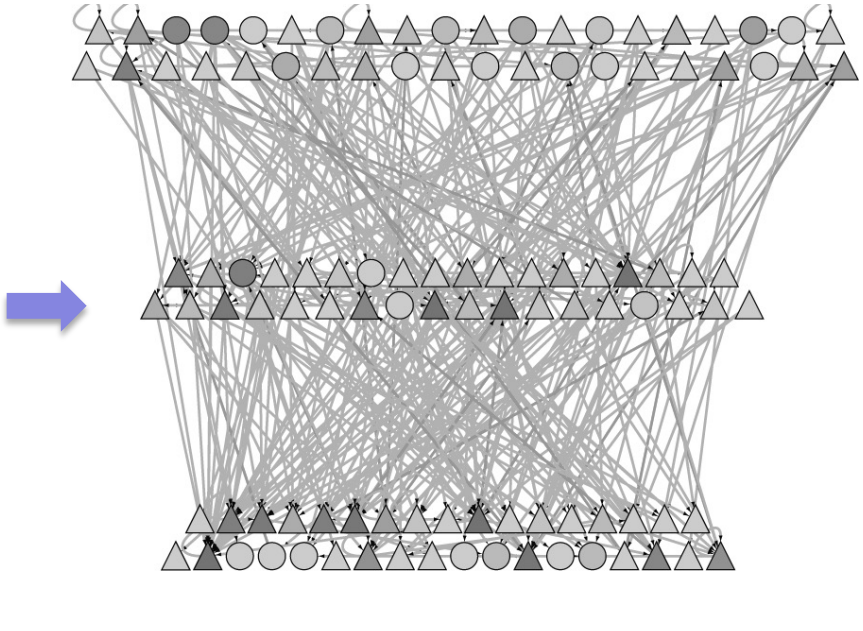


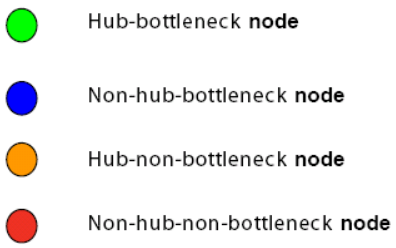


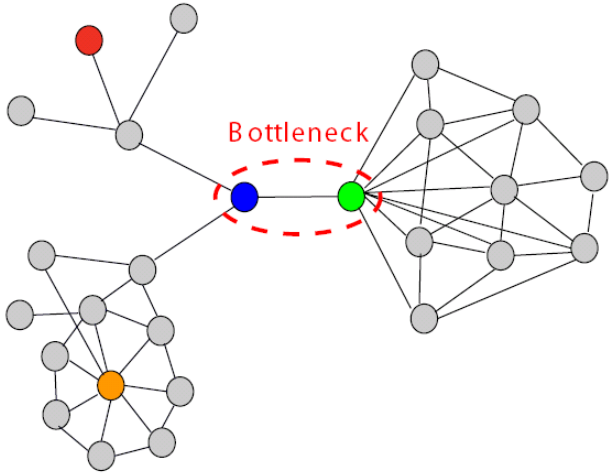
[Wang et al. ('18) Science, Gerstein et al. Nature ('12)]

Mid-level of the hierarchy has many high-connectivity bottlenecks









[Wang et al. ('18) Science, Gerstein et al. Nature ('12)]