Systems Biology: A Personal View
X. Intra-cellular Systems II: Protein-Protein Interaction

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Intra-cellular biochemical networks

- Metabolic networks

  Nodes: metabolites (substrates & products of metabolism)

  Links: chemical reactions (directed)

- Genetic regulatory networks

  Nodes: Genes & Proteins

  Links: regulatory interactions (directed)

- **Protein-Protein interaction network**

  Nodes: Proteins

  Links: physical binding and formation of protein complex (undirected)

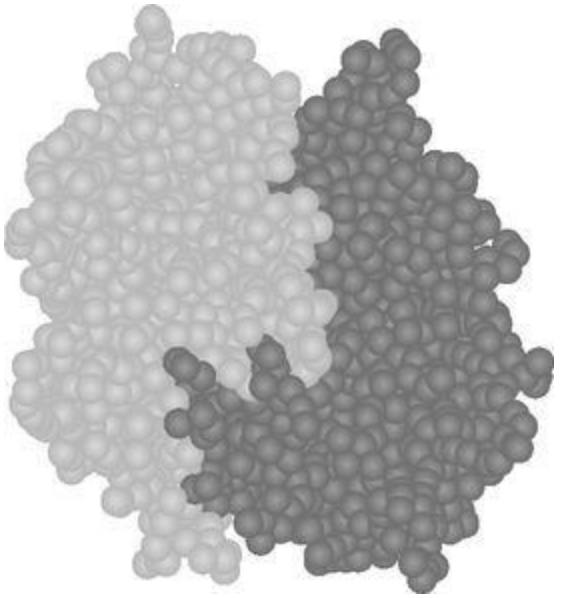
- Signaling network

  Nodes: Signaling molecules e.g., kinase, cyclicAMP, Ca

  Links: chemical reactions (directed)

Protein-Protein Interaction

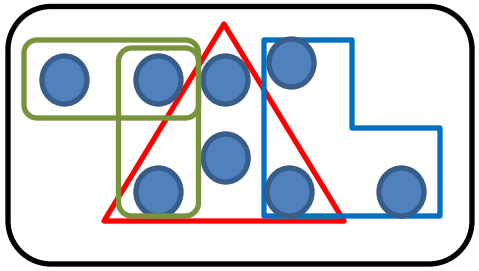
Proteins interact with other proteins primarily through physical binding – locking of 3-D shapes creating *protein complexes*



Newman, *Networks: An Introduction*

[Other modes of interaction include chemical – e.g., in signaling networks – where small subgroups such as a phosphate group (in phosophorylation) is exchanged.]

Interactions involving more than 2 proteins should ideally be represented using hypergraphs – but usually conveyed approximately by a number of pairwise interactions

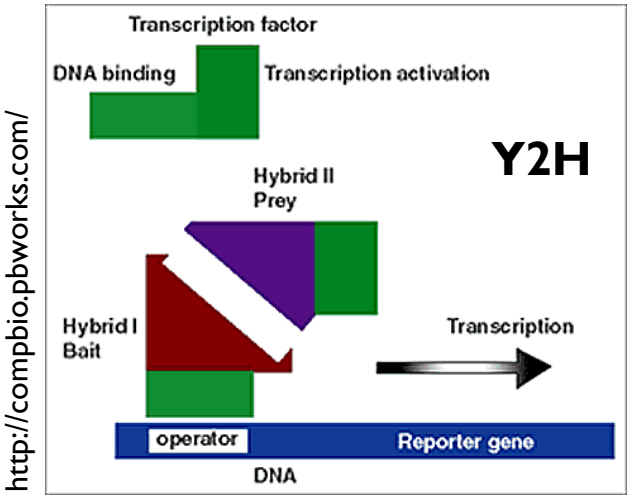


Set of all such undirected pairwise interactions constitute the Protein-Protein Interaction Network (PPIN)

Experimental techniques for PPI

http://compbio.pbworks.com/

Methods have different sensitivity and specificity
high sensitivity ⇒ many interactions that occur in reality are detected by the screen.
high specificity ⇒ most of the interactions detected are also occurring in reality.



Yeast two-hybrid screen investigates interaction between artificial fusion proteins inside the nucleus of yeast - can fish out binding partners of a protein
But has a high false-positive rate
Necessary to verify identified interactions by co-immunoprecipitation

Co-immunoprecipitation (gold standard assay for protein-protein interactions) Protein of interest is fished out of the cells with a specific antibody. Interaction partners sticking to this protein are subsequently identified by western blot
Interactions detected by this approach considered to be real - but can only verify interactions between suspected interaction partners – NOT a screening approach.

Tandem affinity purification (TAP) detects interactions within the correct cellular environment (e.g. in the cytosol of a mammalian cell) (Rigaut et al., 1999) – advantage compared to Y2H approach.
But requires 2 successive steps of protein purification – cannot readily detect transient PPI

Yeast protein interaction network

N = 1870 nodes, L = 2240 links

PPIs determined by Y2H method

Largest connected cluster (78% of all proteins)

Node color represents phenotypic effect of removing corresponding protein

Red: lethal

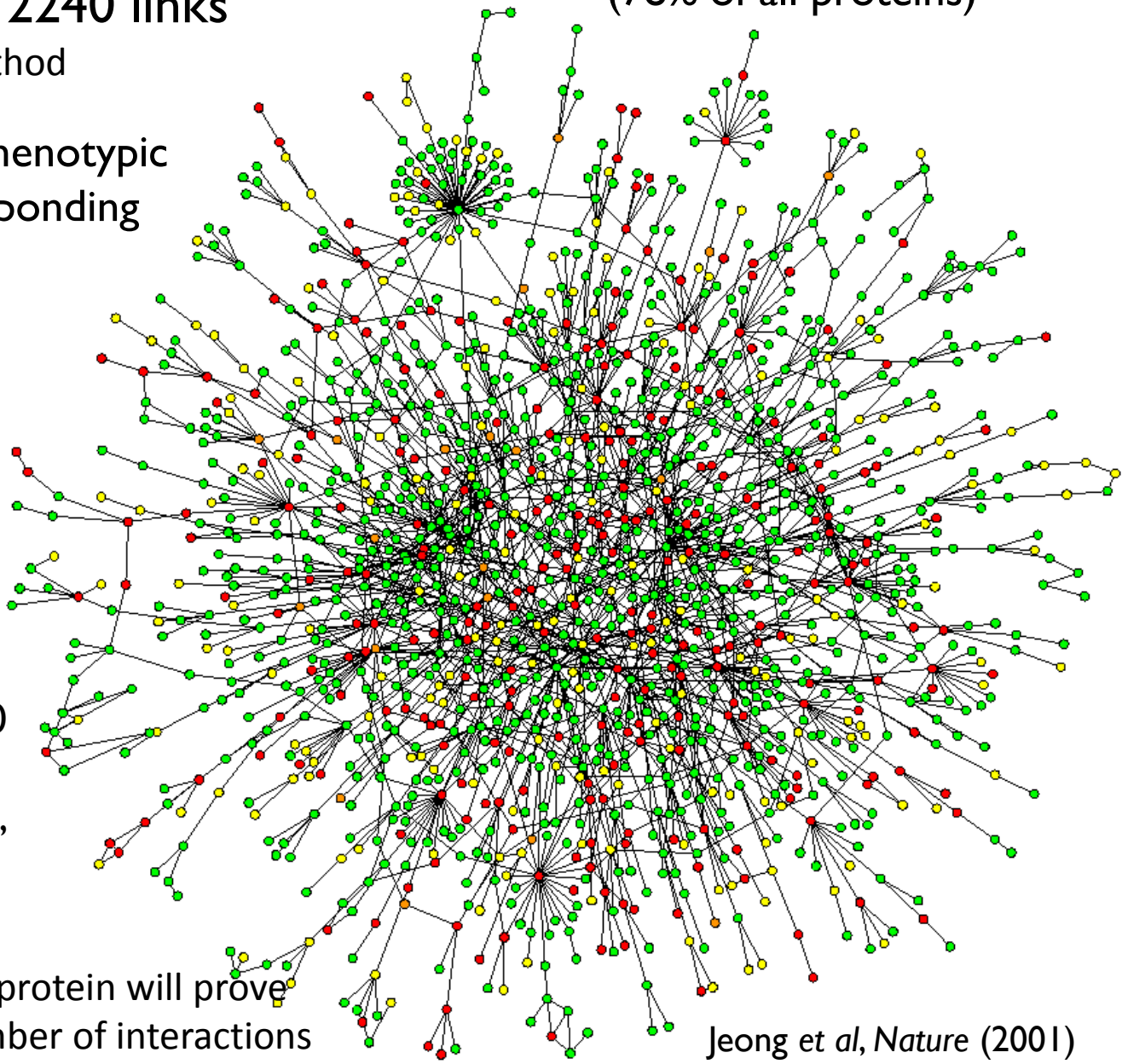
Green: nonlethal

Orange: slow growth

Yellow: unknown

Degree distribution P(k) is power-law having exponent ~2.4 over a limited range – exponential cut-off at k = 20

Tolerance to random errors, fragility w.r.t. removal of most connected nodes



Likelihood that removal of a protein will prove lethal correlates with its number of interactions

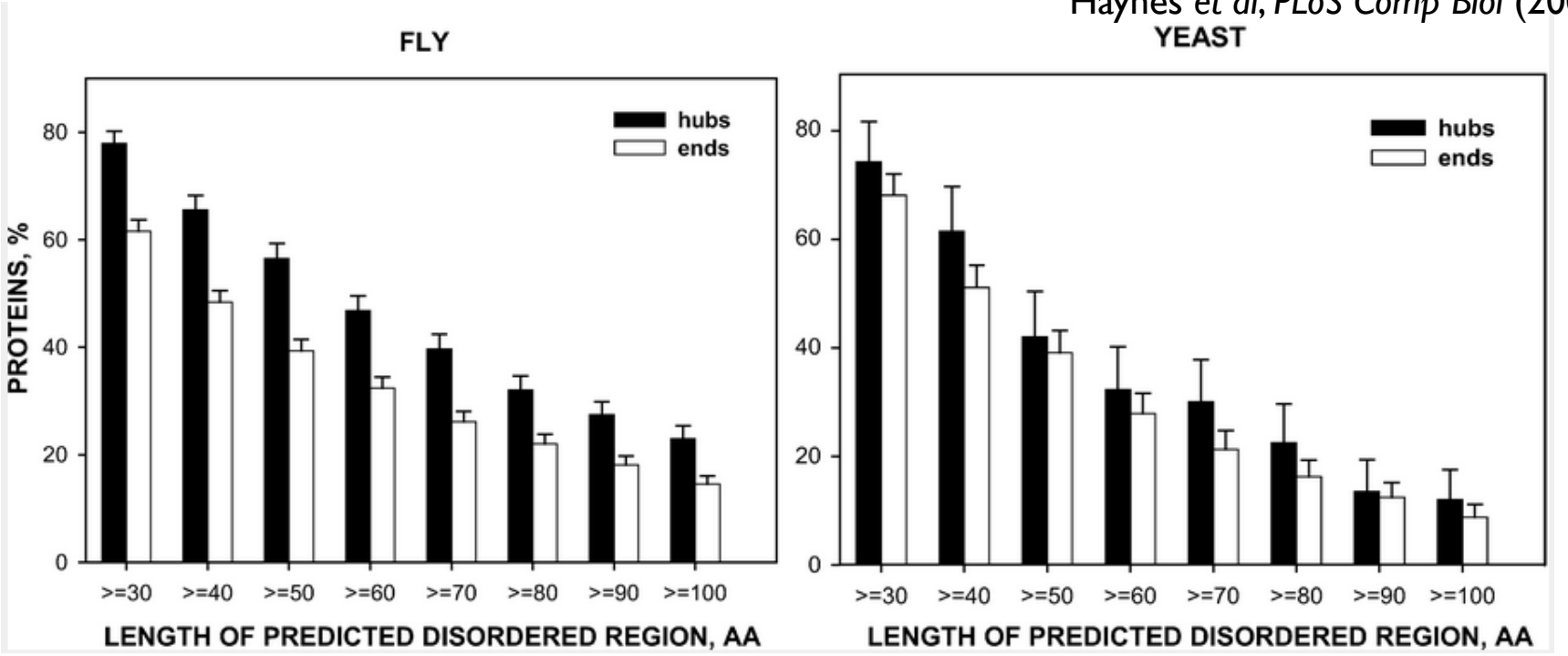
Jeong *et al*, *Nature* (2001)

Are hub proteins special ?

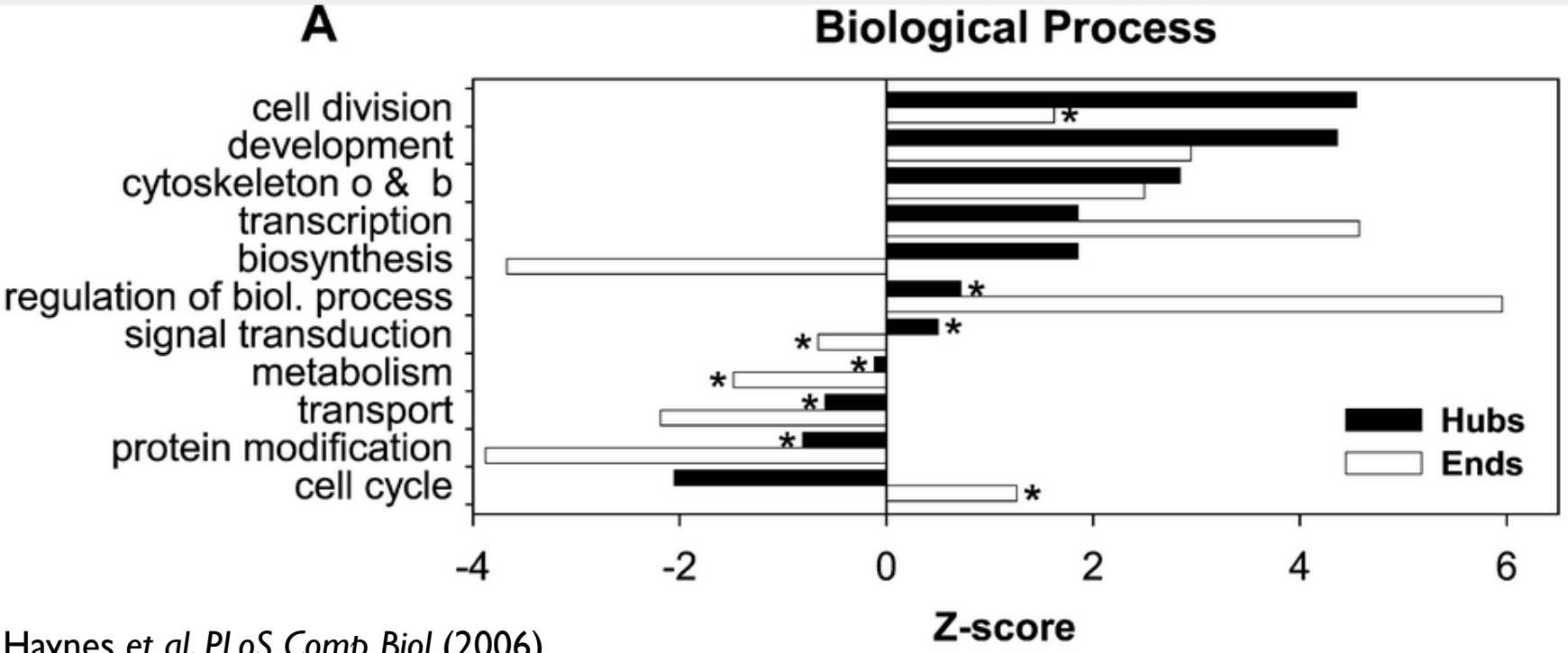
Hub proteins are more likely to be intrinsically disordered (ID)

ID proteins and protein regions lack a unique 3-D structure and exist in a dynamic ensemble of conformations. Many ID proteins shown to mediate interactions via disorder-to-order transition on binding to their biological targets
Ability to recognize multiple binding partners with distinct interaction surfaces ⇒ more efficient hubs relative to ordered proteins

Haynes *et al*, *PLoS Comp Biol* (2006)



What processes are they involved in?



Haynes *et al*, *PLoS Comp Biol* (2006)

A positive (negative) *Z*-score indicates that more (less) disorder is associated with the indicated biological process than would be expected by chance

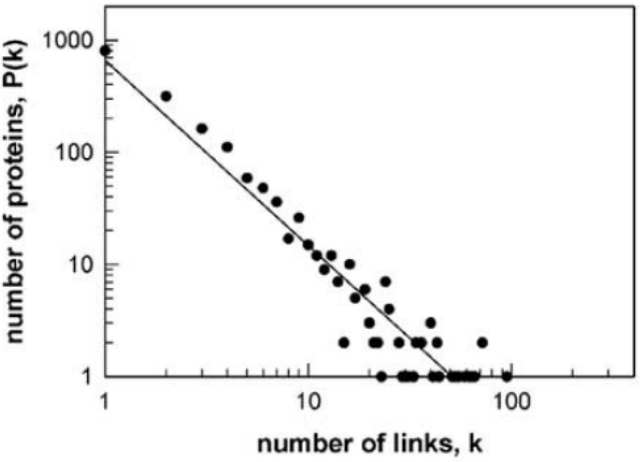
Disorder is enriched in both hubs and ends for several processes including development, cytoskeleton organization and biogenesis, and transcription: consistent with the hypothesis that disorder is highly involved in functions specific to eukaryotes. Hubs are only significantly depleted for cell cycle, whereas the ends are significantly depleted for biosynthesis

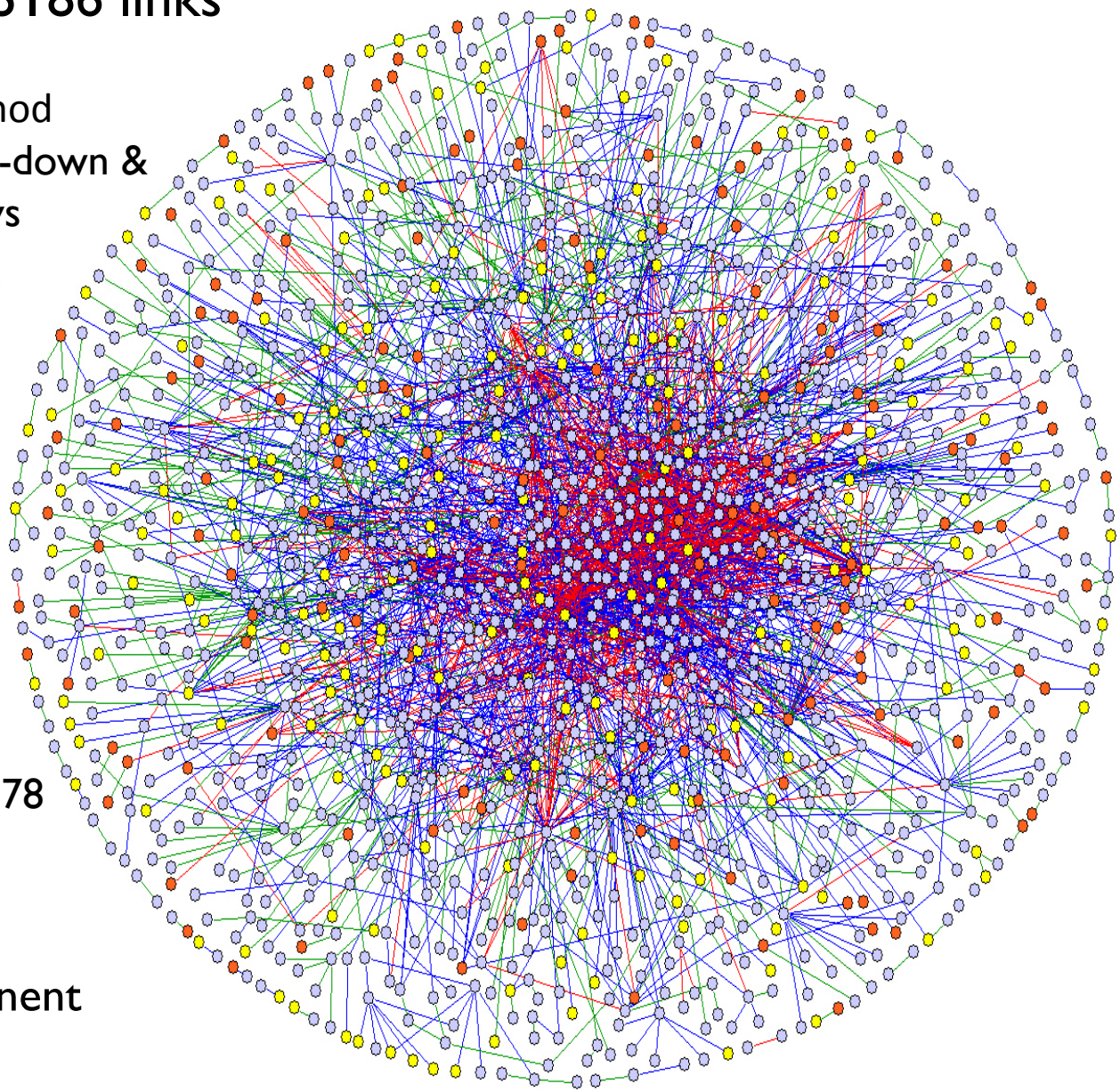
Human protein interaction network

N = 1705 nodes, *L* = 3186 links

Stelzl *et al, Cell* (2005)

PPIs determined by Y2H method
Validated by independent pull-down & co-immunoprecipitation assays





Degree distribution P(k) is power-law with exponent ~1.78
Avg degree ~ 1.87
24 hubs with > 30 links

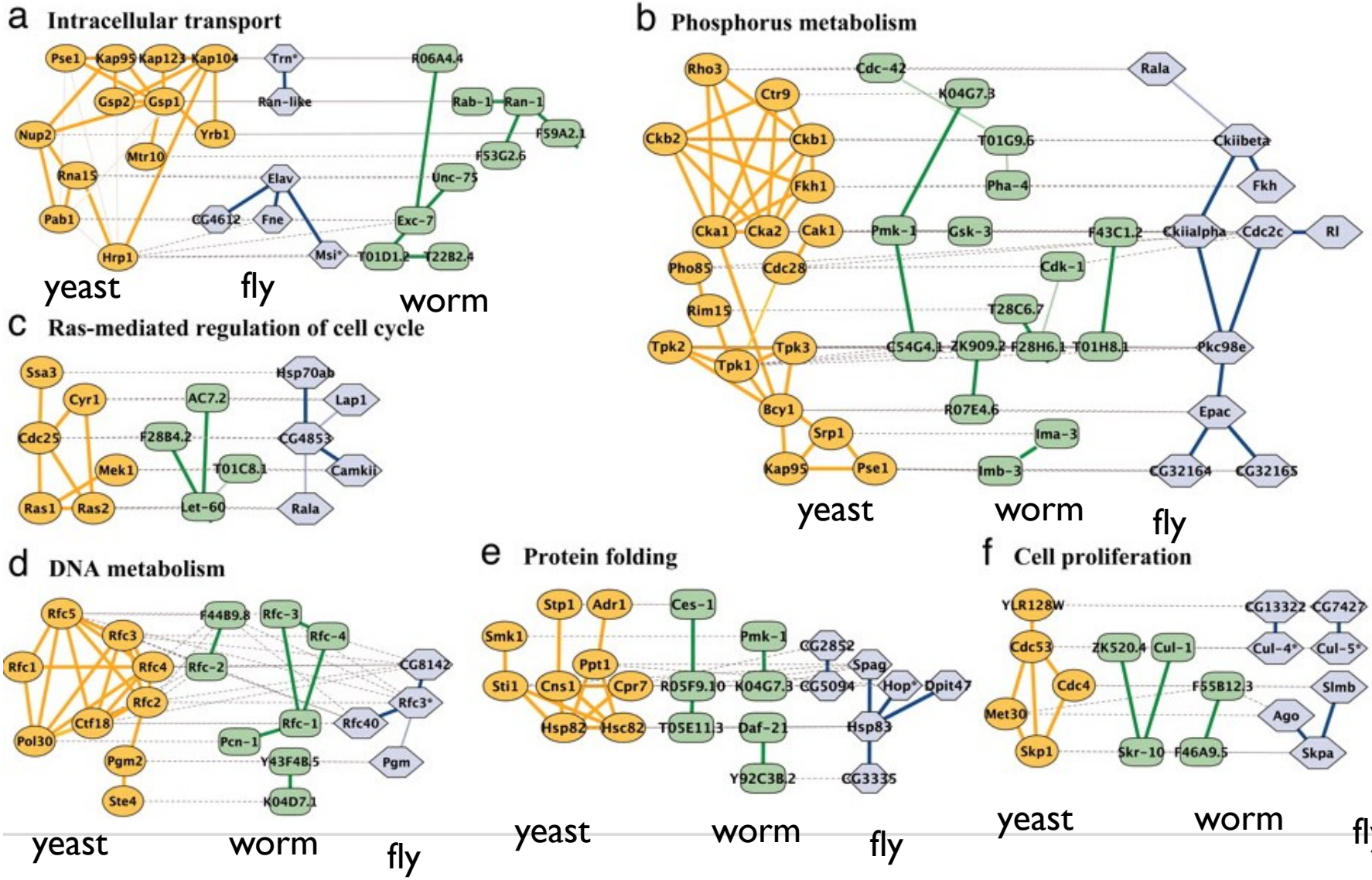
Largest connected component comprises 1613 proteins

Conserved patterns of protein interaction across species

Sharan et al, *PNAS* (2005)

Representative conserved network clusters

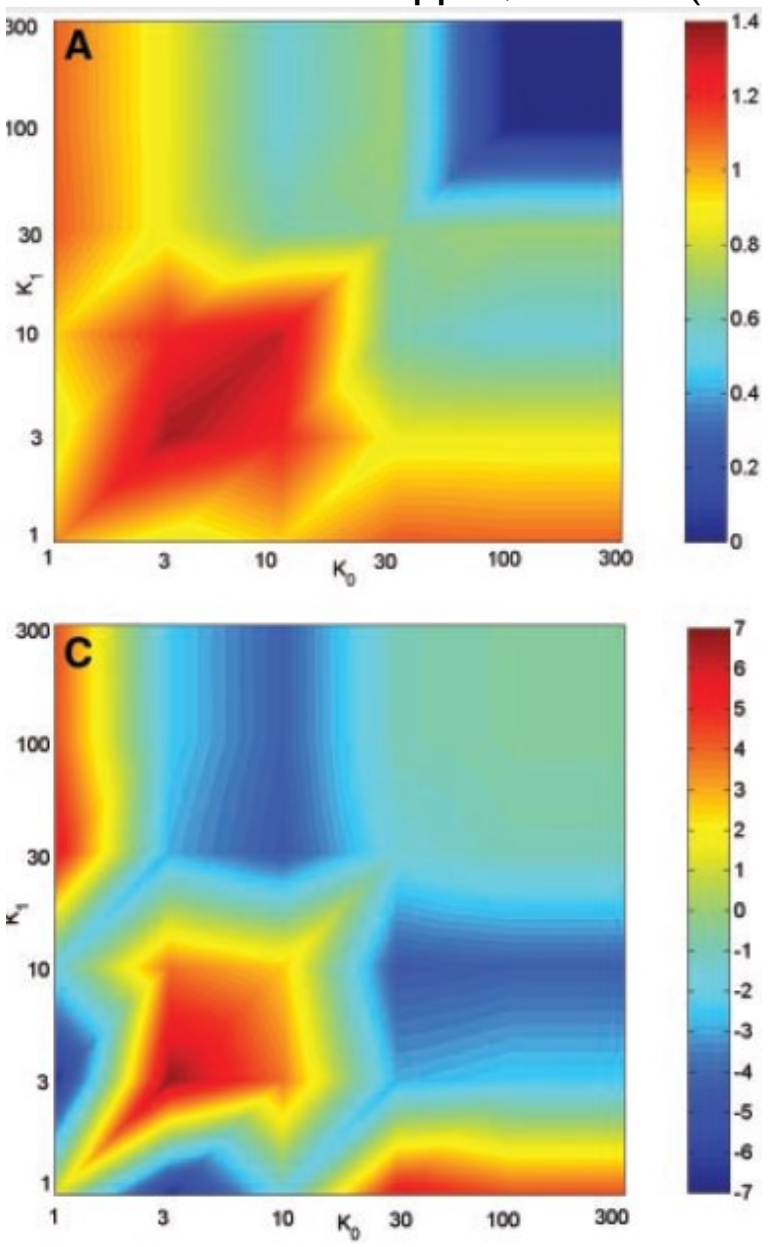
Horizontal dotted gray links → cross-species sequence similarity between proteins



Yeast PPIN is disassortative

Maslov & Sneppen, *Science* (2002)

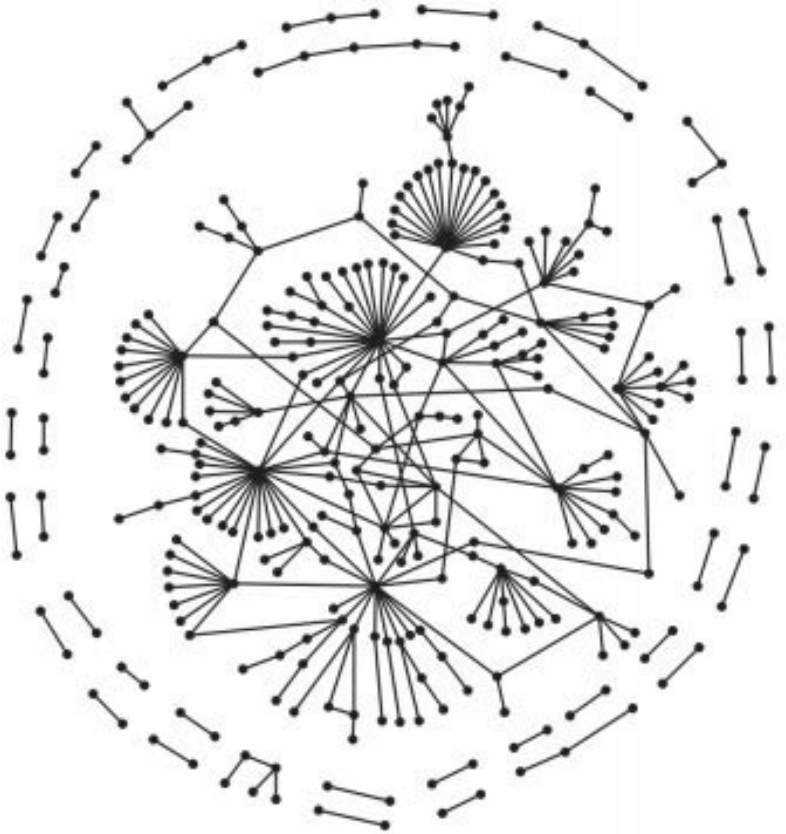
"links between highly connected proteins are systematically suppressed, whereas those between a highly connected and low-connected pairs of proteins are favored … decreases the likelihood of cross talk between different functional modules of the cell and increases the overall robustness of a network by localizing effects of deleterious perturbations."

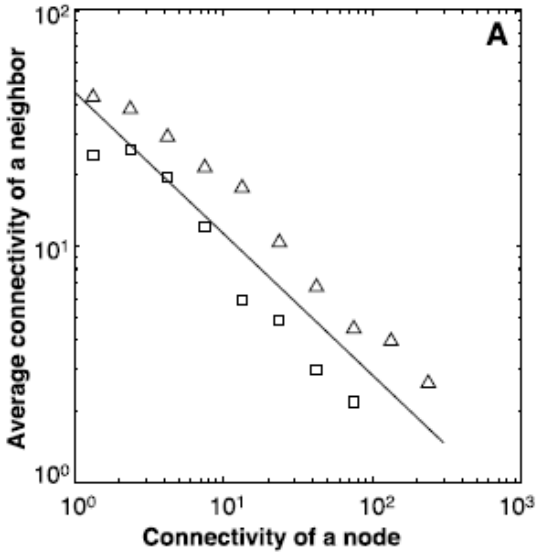


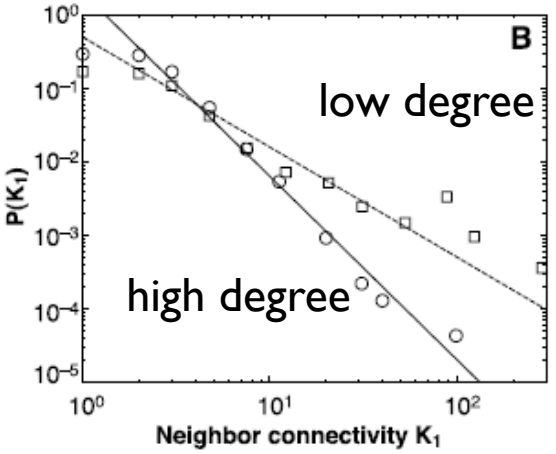
Ratio of probability of connection between pairs of proteins with degree k0,k1 compared to that of a randomized network (top) and the corresponding z-score (bottom)

Hub-and-spoke formations

Functional modules clustered around individual hubs







The average degree <k1> of nearest neighbors of a node, as a function of its own degree k0 shows a power-law decay with exponent 0.6

Interaction network between 329 proteins localized in the yeast nucleus that interact with at least one other protein in the nucleus.

Most neighbors of highly connected nodes have low degree → hub-and-spoke topology

probability distribution of nearest-neighbor degree k1 shown separately for nodes with low degree k0<4 and for high degree k0>100 (For uncorrelated networks, this should decay as k1/k1^degree distrn exponent i.e., $1/k1^{1.5}$) For the latter it decays as $1/k1^{2.5}$.

"Date" hubs and "Party" hubs

Han et al, *Nature* (2004)

Filtered Yeast Interactome
Network of 1379 proteins
LCC: 778 proteins

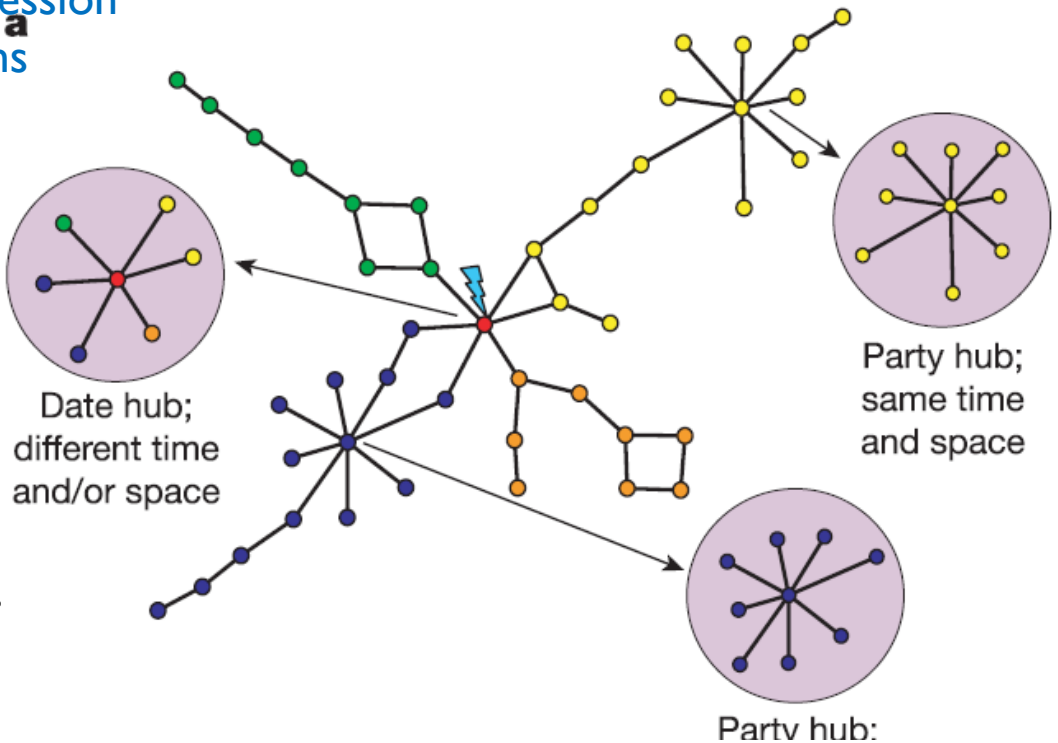
Considering the temporal structure of PPIs

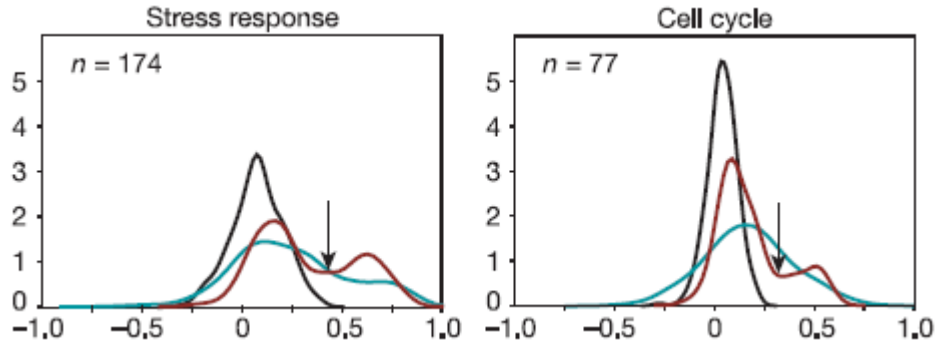
Interactome hubs characterized by expression profiling across different exptl conditions

Pearson correlation coefficient (PCC) for mRNA expression of each hub and its partners calculated

PCCs of hubs, defined as nodes (proteins) with degree k >5 follow a bimodal distribution (red curve) in contrast to non-hub nodes with k<5 (cyan curve) or in randomized networks (black curve)

Bimodal distribution suggests that hubs can be split into two distinct populations:
Party hubs : relatively high avg PCCs
Date hubs: relatively low avg PCCs



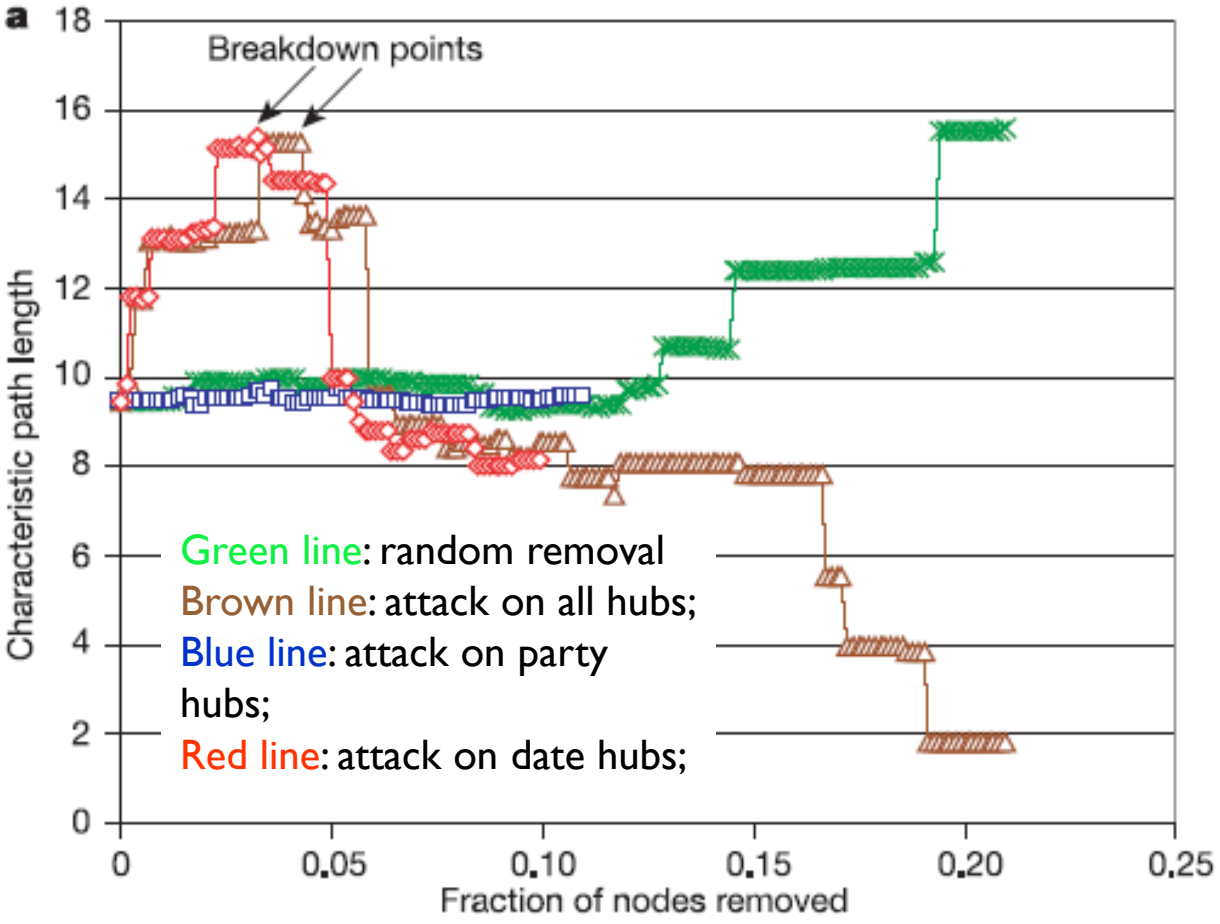


"Date" hubs and "Party" hubs

Han et al, *Nature* (2004)

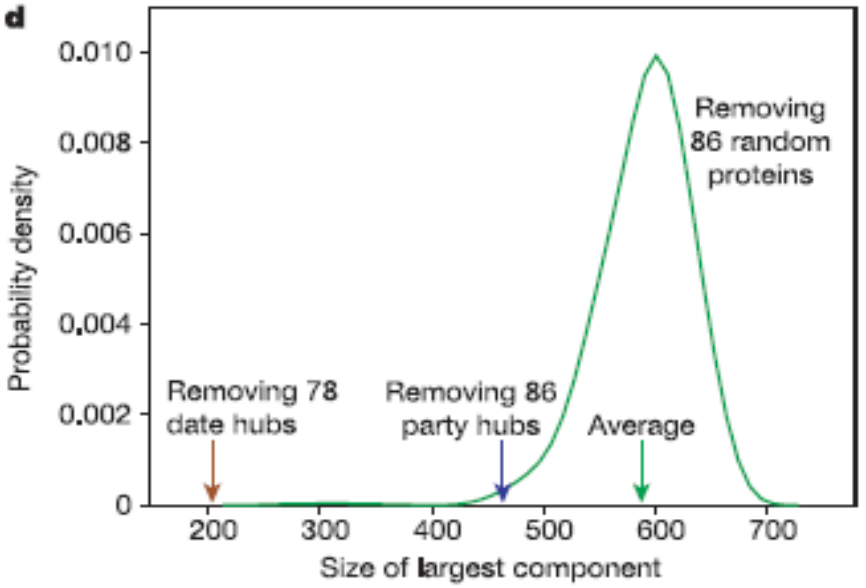
Considering the temporal structure of PPIs

When removed from interactome network, party and date hubs have distinct effects on the overall topology.



Can be observed from an *in silico* strategy that simulates the effect of specifically removing hubs in the network on the characteristic path length of the main component of the network.

LCC of FYI network



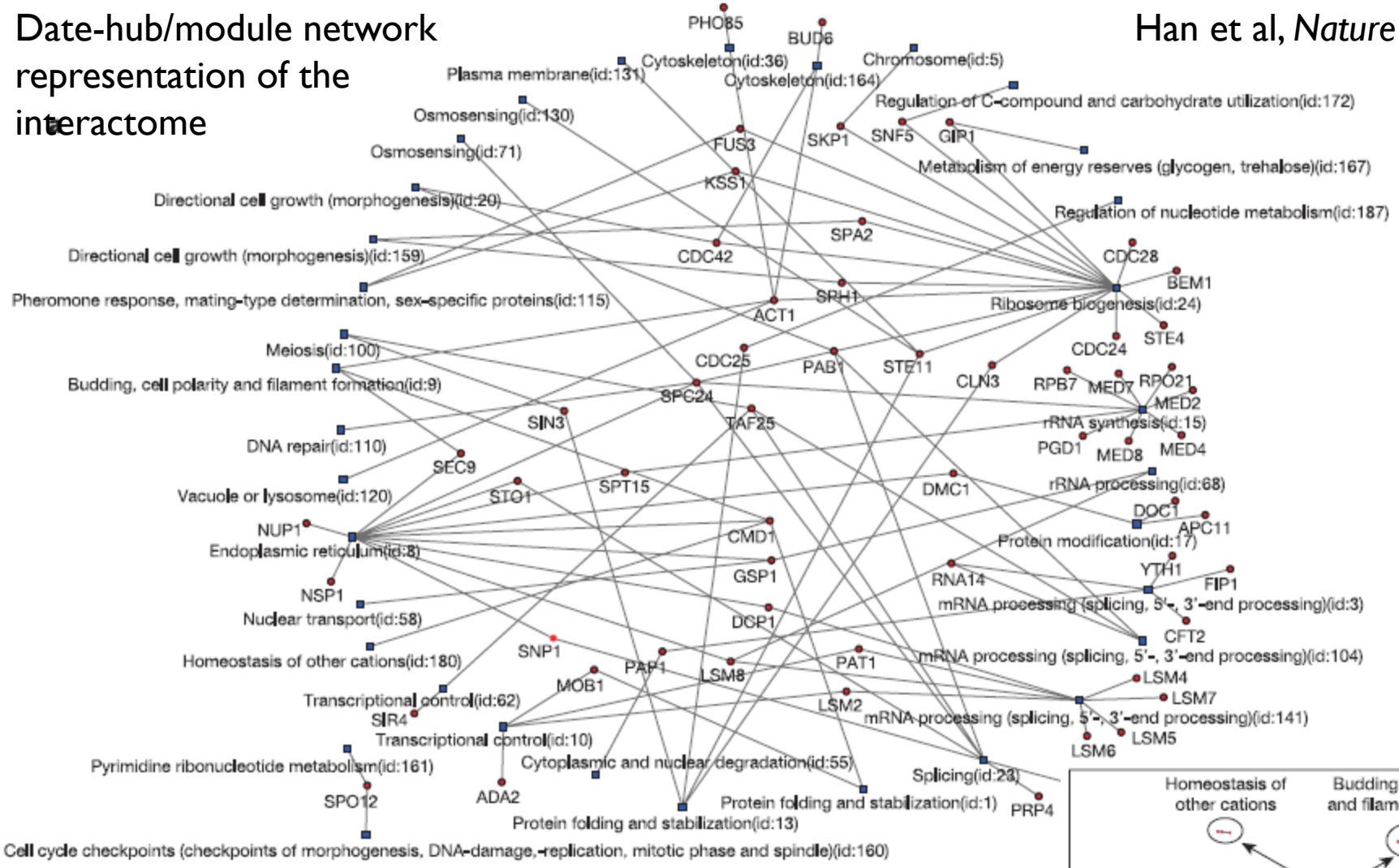
Removal of date hubs

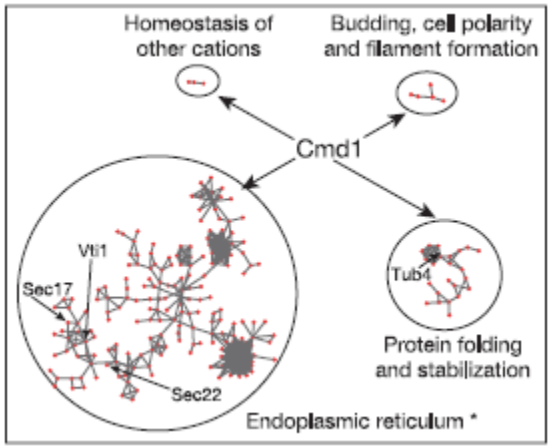
Removal of party hubs

Han et al, *Nature* (2004)

Date-hub/module network representation of the interactome

Han et al, *Nature* (2004)





Date hubs represent global, or 'higher level, connectors between modules (red circles)

Party hubs function inside modules, at a 'lower level' of the organization of the proteome (blue squares)