Revisiting Date and Party Hubs: Novel Approaches to Role Assignment in Protein Interaction Networks

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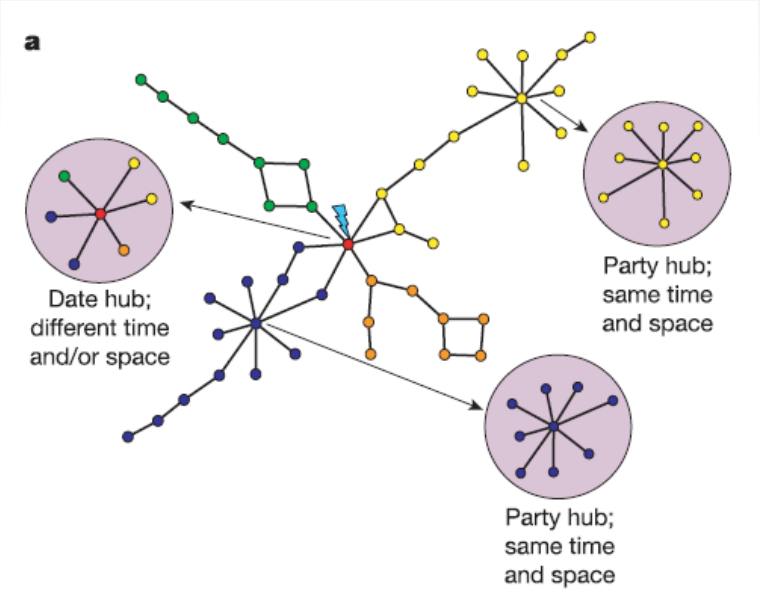
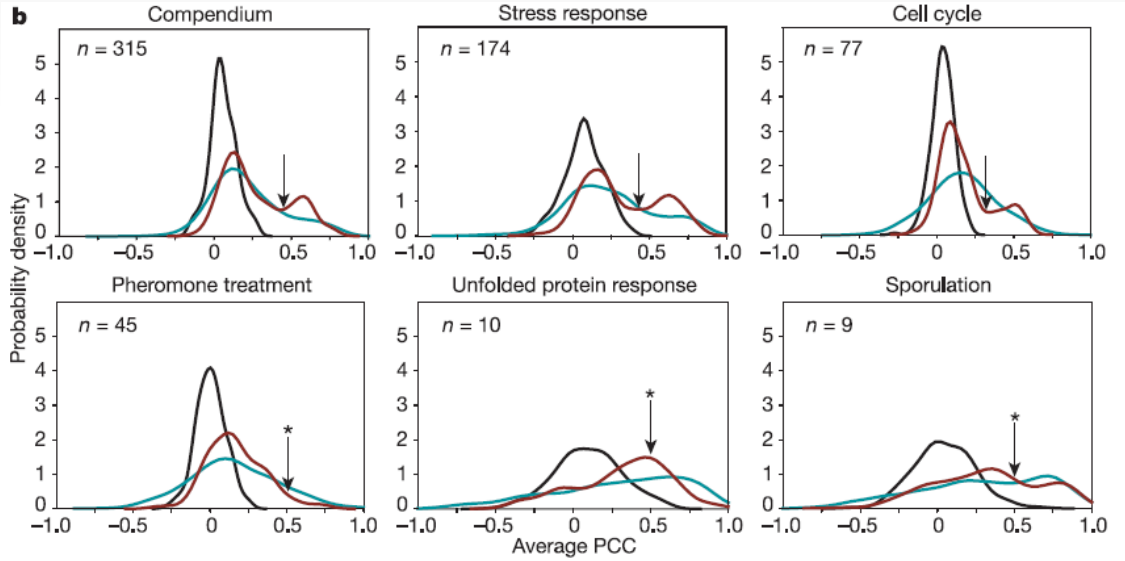
Date and Party Hubs in the Interactome

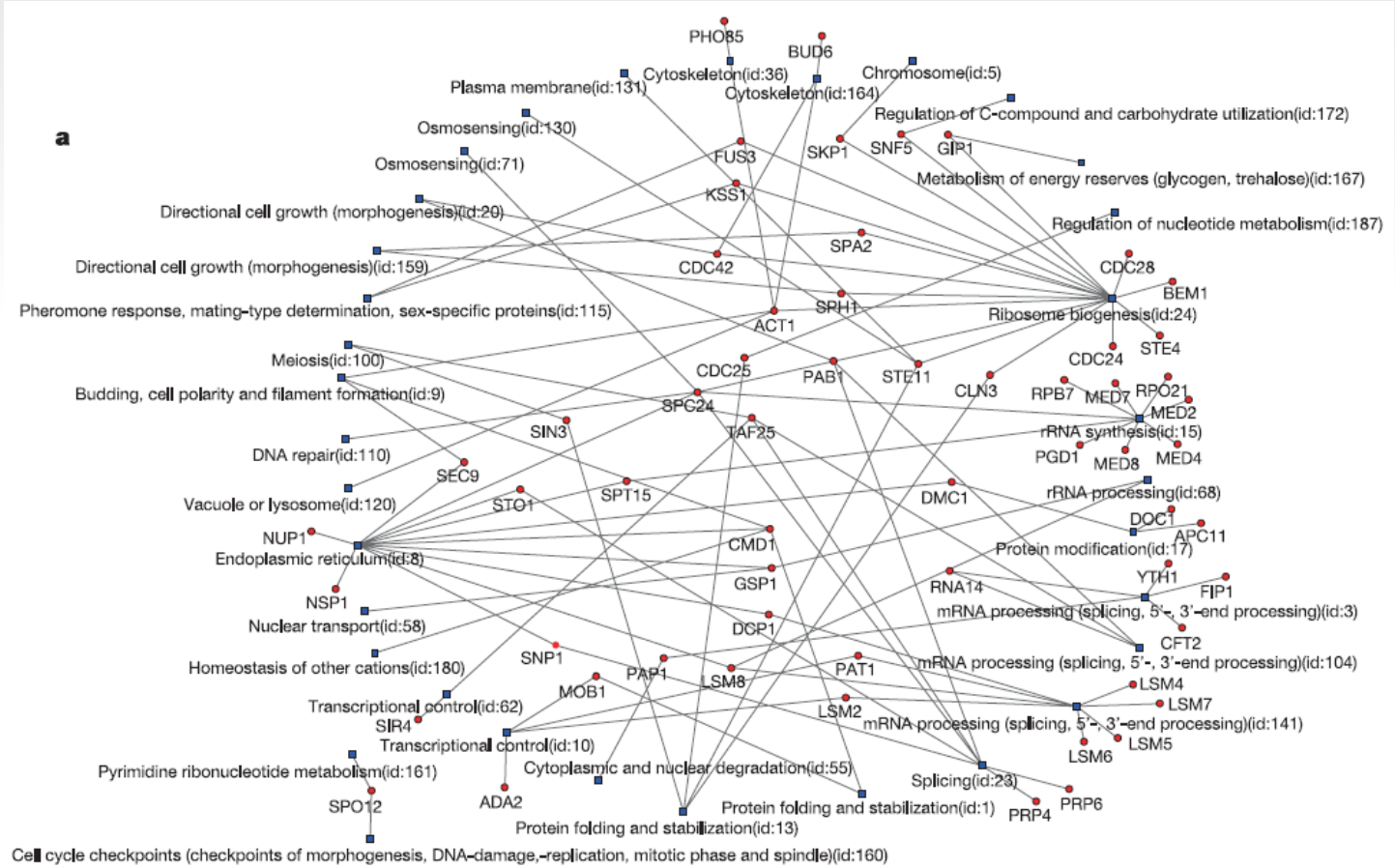
- The Interactome is the set of all physical protein-protein interactions inside a cell, which can be represented as a network
- Hubs, defined as nodes with degree 5 or greater, were found to fall into two classes based on average co-expression with their interaction partners (Han *et al*. 2004)

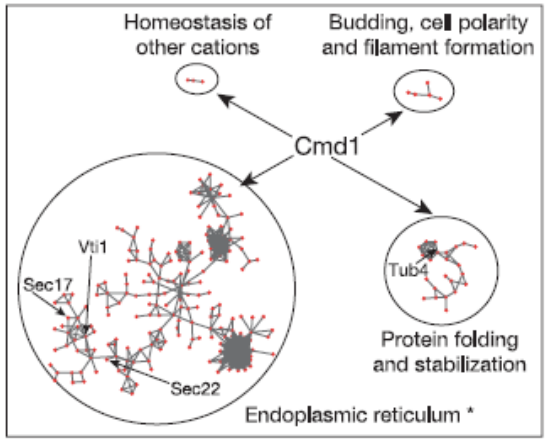




Modular Organisation

- It was proposed that date and party hubs play a key role in organising the interactome into modules with specific functions, with party hubs coordinating single modules and date hubs serving as inter-module linkers (Han *et al*. 2004)



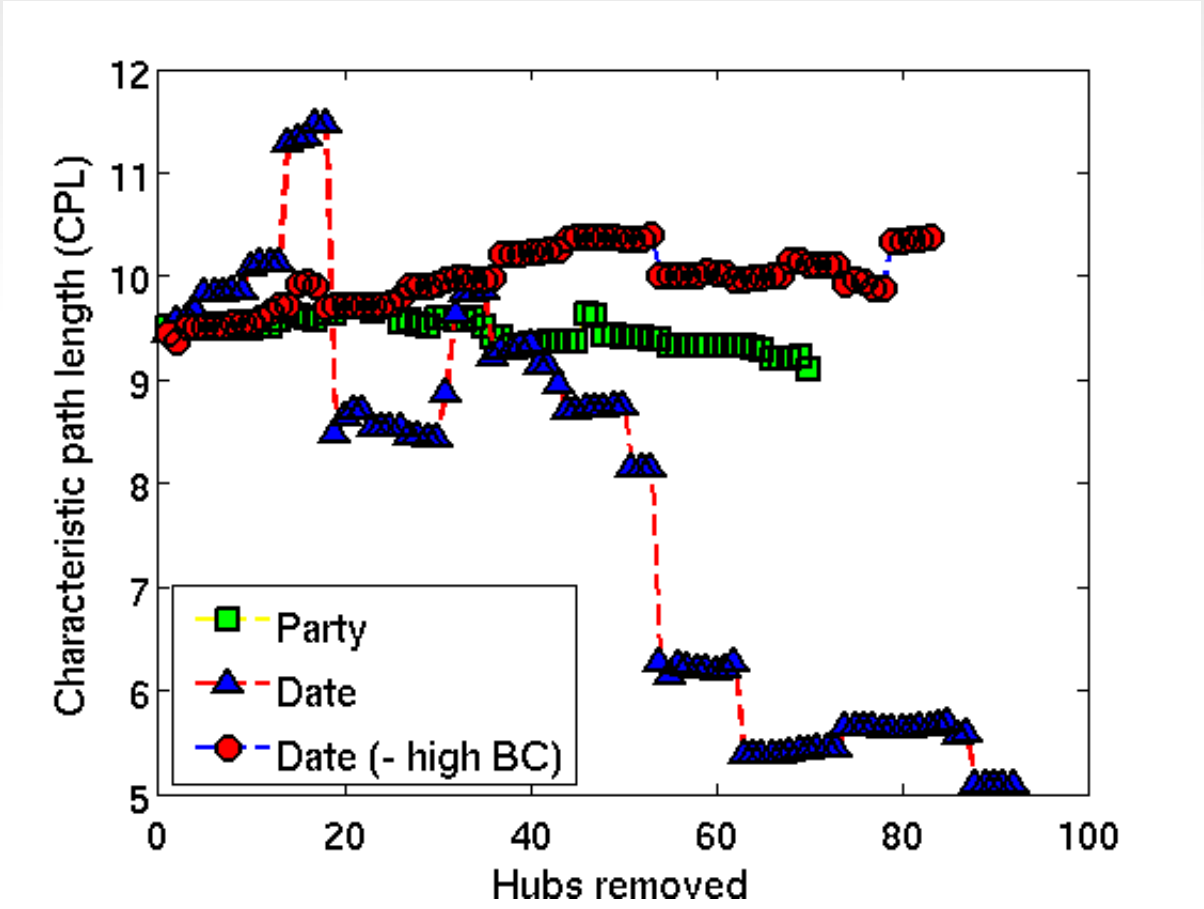


A Controversial Idea

- Marc Vidal group (Harvard): First proposed date and party hubs for the yeast interactome – *Nature* 2004
- Mike Tyers group (Toronto): Disputed date/party observation, saying it resulted from incomplete data and flawed analysis – *PLoS Biology* 2006
- Vidal group: Re-asserted existence of date/party hubs in expanded yeast network – *PLoS Biology* 2007
- Tyers group: Responded with further analysis once again suggesting invalidity of the date/party distinction – *PLoS Biology* 2007
- Vidal group: Reiterated the idea in the context of newer protein interaction data from different kinds of experimental procedures – *Science* 2008
- Jeffrey Wrana group (Toronto): Suggested existence of intermodular and intramodular hubs in humans, using the same methodology as for date/party hubs – *Nature Biotechnology* 2009

Only a Few Hubs are Critical to Connectivity

- Are date hubs really more central to network connectivity than party hubs?
- We used betweenness centrality (BC) to identify significant hubs

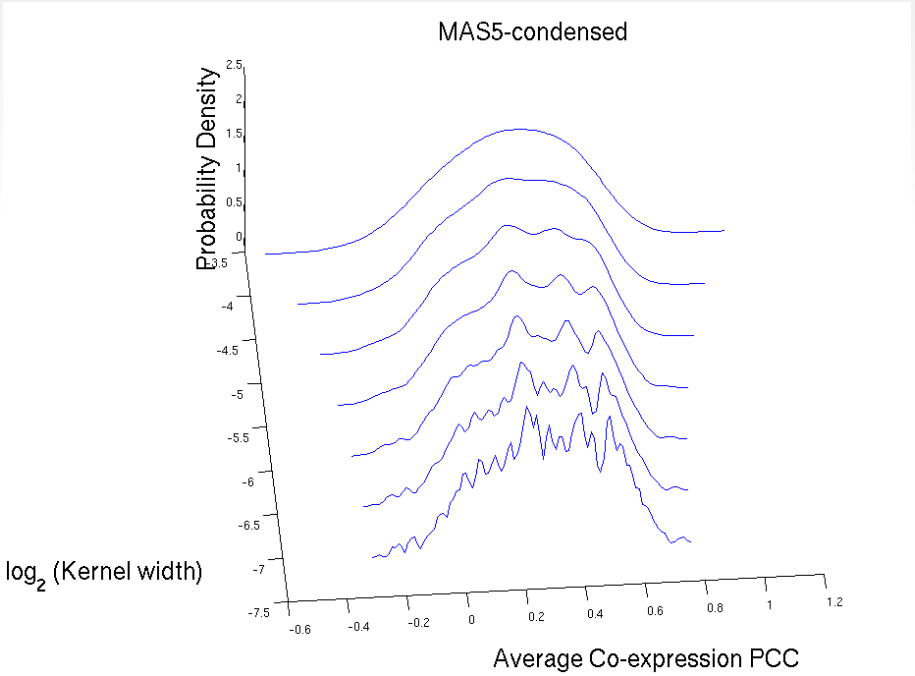


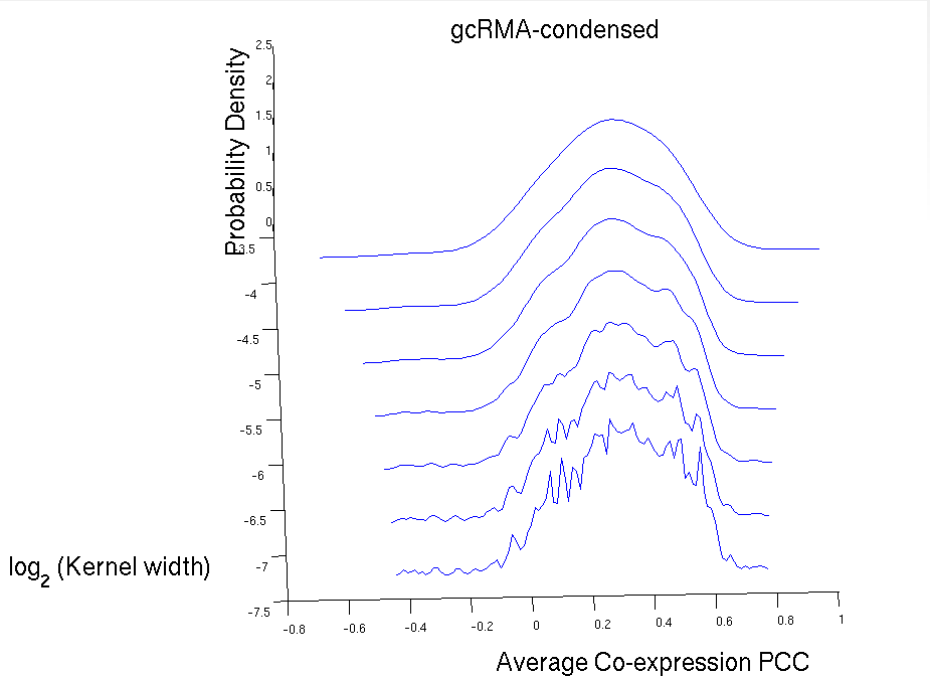
High BC Hubs

Protein	Degree	AvPCC
SPC24	18	0.02
SRP1	10	0.40
TAF25	32	0.07
TID3	6	0.15
ACT1	17	0.34
BUD6	8	0.06
NUP1	8	0.31
SPT15	10	0.10
CMD1	8	0.07

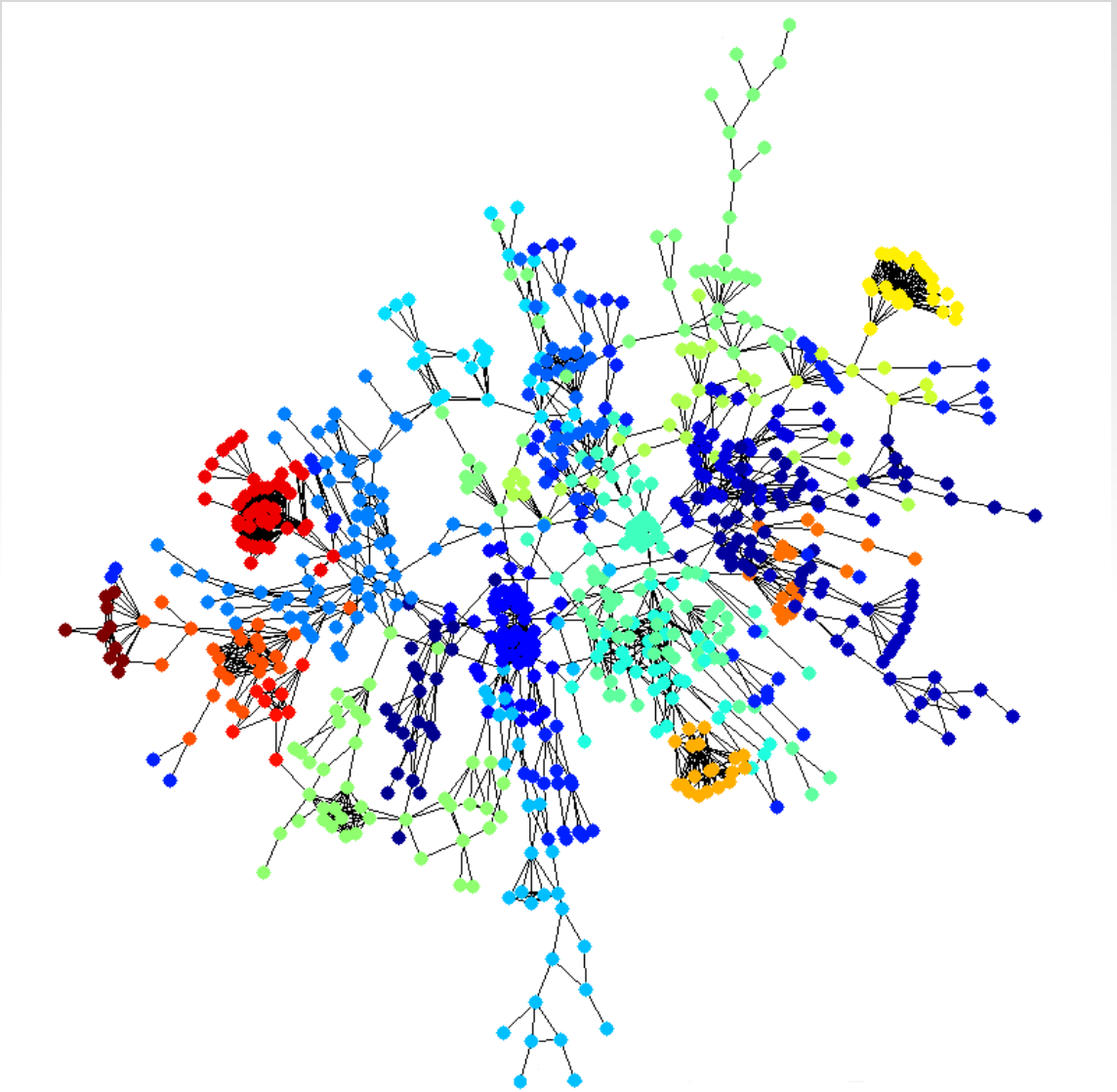
Bimodality of Hub Co-expression Distributions is not Robust

- Recent work by Taylor *et al*. (2009) suggests the existence of date and party hubs in humans as well; we looked at how robust this observation is to changes in methodology, varying the smoothing kernel width as well as the method used to process raw expression data

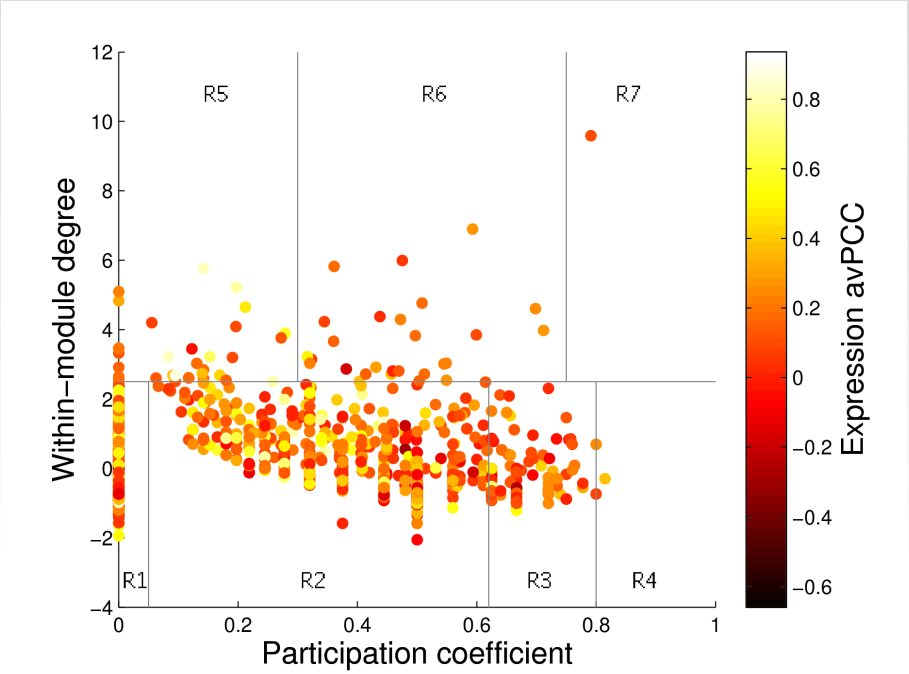


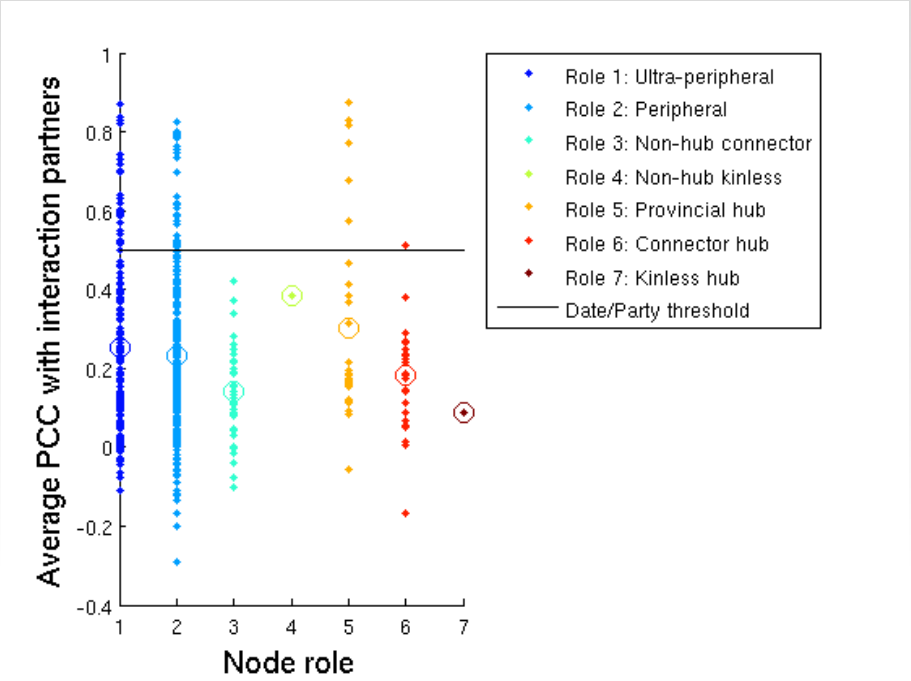


Modules in the Yeast Interactome



Node Roles do not Correspond to Date/Party Hubs

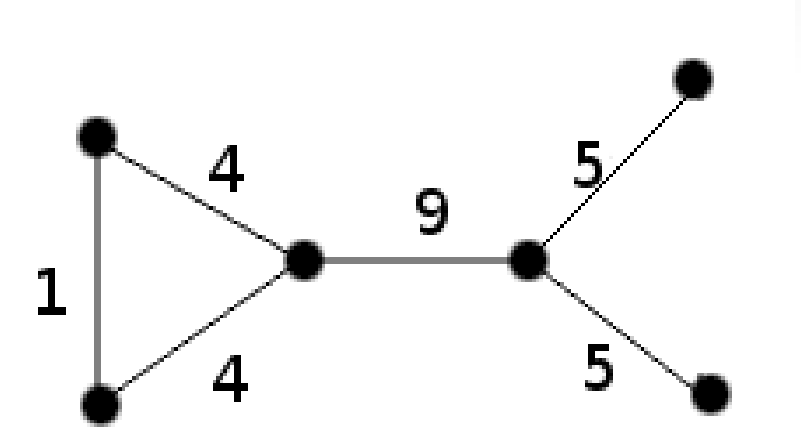




Nodes are assigned roles in the network based on two metrics: within-module degree and participation coefficient, as per Guimerà & Amaral (2005). These roles are then examined for their distribution in terms of the date/party metric, which is based on a threshold on the average expression correlation with partners. There is no clear relation between the expression correlation and the topological role, as one would expect if the date/party hypothesis were valid.

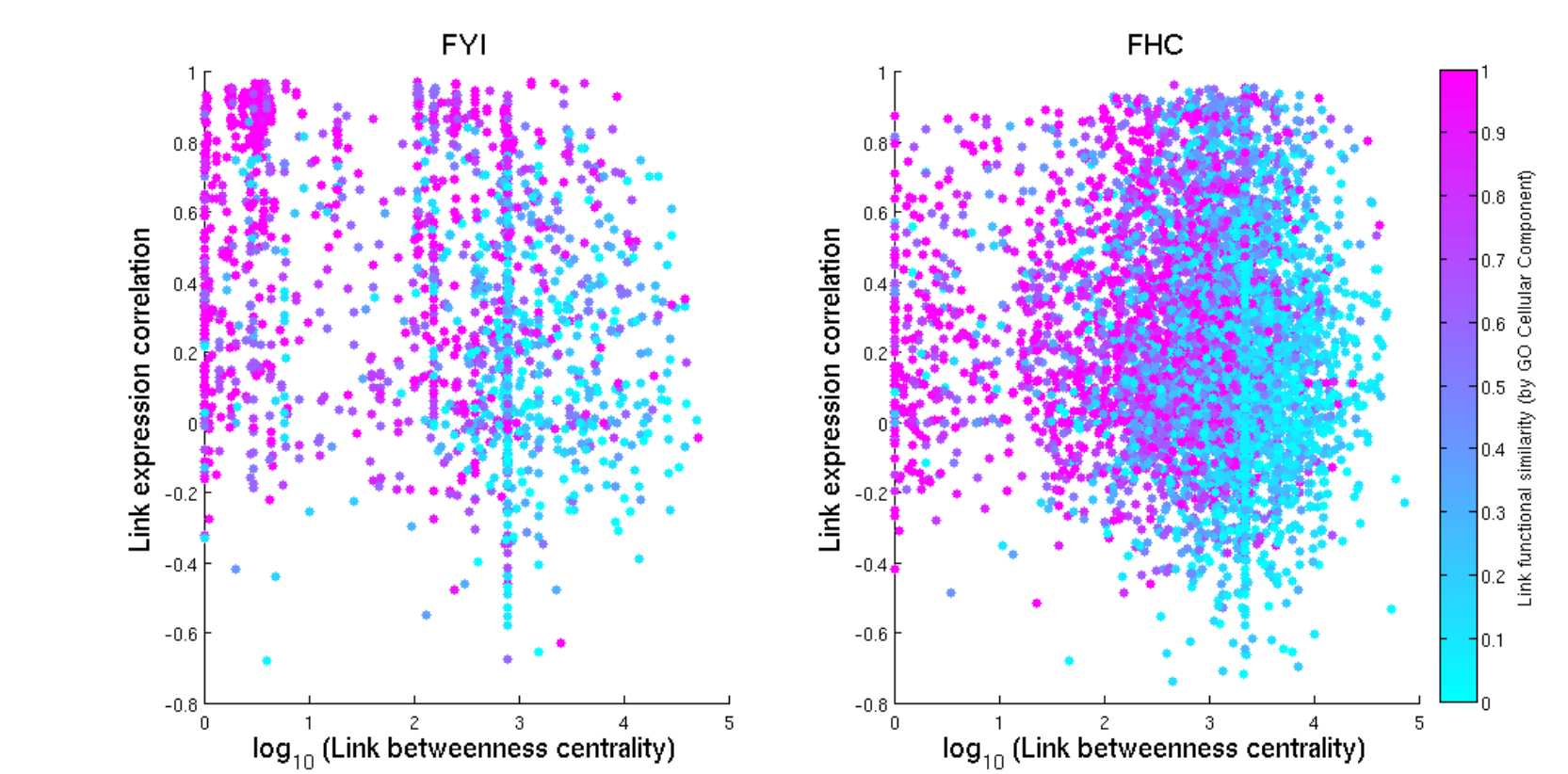
Link Betweenness Centrality

- A way of looking at roles of links rather than nodes
- Defined as number of pairwise shortest paths a link is part of
- Note that links emanating from degree-1 nodes always have betweenness = N-1, where N is the number of nodes in the network



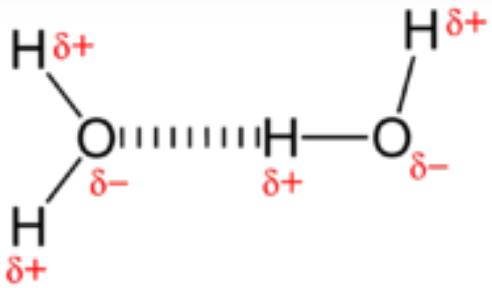
Link Betweenness is Correlated with Functional Similarity

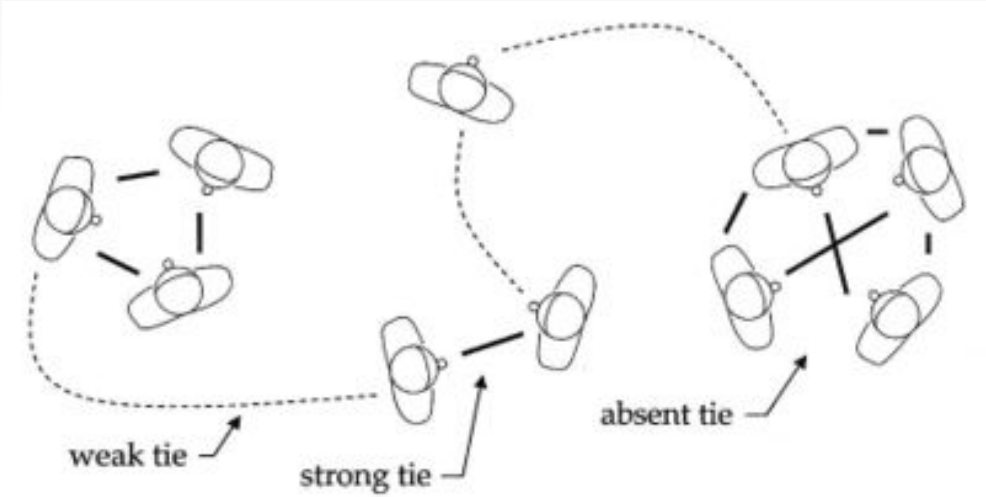
- We look at GO (Cellular Component) similarity for each interaction in two datasets
- Fairly strong correlation of betweenness centrality with functional similarity of the interactors, though little correlation with expression correlation. Also, N-1 value of betweenness seems to act approximately as a threshold



Analogy with Weak/Strong Ties in Social Networks

Sociologist Mark Granovetter interviewed people to find out how social networks are used to land new jobs. Granovetter found that most jobs were found through "weak" acquaintances. This pattern reminded him of his freshman chemistry lesson that demonstrated how "weak" hydrogen bonds hold huge water molecules together, which are themselves held together by "strong" covalent bonds.





Figures from Wikipedia

Conclusions

- Small number of date hubs responsible for holding network together; date/party distinction not very robust to methodological variations
- Node roles derived from network topology do not match up with hub co-expression values
- Link betweenness shows negative correlation to functional similarity, with a thresholding behaviour suggesting an analogy to strong/weak ties

References

- Jing-Dong J. Han *et al*. Evidence for dynamically organized modularity in the yeast protein-protein interaction network. *Nature* **430**:88–93, 2004.
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- Roger Guimerà and Luís A. Nunes Amaral. Functional cartography of complex metabolic networks. *Nature* **433**:895–900, 2005.
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