

# Functional Modules from Protein-Protein Interaction Network of Metabolite-Related Proteins in *Saccharomyces cerevisiae*

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## 1. Introduction

Proteins bind to each other to form stable complex and to contribute cellular responses. At a complex system, protein complexes interact with other proteins weakly, transiently, or conditionally to form a biological module that serves a specific function in cells and systems as well [1]. With the sufficiency of protein-protein interaction data obtained by genome projects, it is possible to create a widespread representation of the protein network of the yeast cells [2]. Protein networks are currently investigated in terms of topology, motifs, correlation structure, and modular properties that are related to function [3, 4]. A functional module is defined as a group of proteins that its function is separable from other modules. In this work, we have been constructed kinome and cell cycle networks and analyzed structural characterization and functional modules of the networks. Since large scale protein-protein interaction database contains random false positives, we employed cellular localization concept to construct highly purified metabolite-related protein network of the yeast cells in here. From functional modules of the networks, we derive tentative functions for unannotated proteins and identify several hub proteins and significant linkers regarding the lethality of the null mutants. Therefore, protein network is a useful tool for identifying unknown functions of proteins and prediction of hub or lethal proteins that highly connected with proteins to form modules.

## 2. Materials and methods

For each protein network investigated, nodes (proper proteins) and links (protein-protein interactions) were assembled and represented protein network as a graph using InterViewer program. Each link in the network was assigned a length of 1. In a basic principle, if a protein interacts with its partner, the link was designed as one. If, however, a protein does not interact with any proteins, zero was given in the link. For construction of network, the basic principle, therefore, follows adjacent matrix that is a matrix with rows and columns labeled by graph nodes with a 1 or 0 in position  $(i, j)$  according to whether  $i$  and  $j$  are adjacent or not. Protein complexes and modules are derived from clustering the protein interaction network.

## 3. Results

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We have constructed protein-protein interaction network of metabolite-related proteins from MIPS database (<http://mips.gsf.de/genre/proj/yeast/index.jsp>) in January 2005. The network (proteins: 2,755, interactions: 4,975, and clustering coefficient: 0.11181) showed characters of scale free network and hierarchical network as well. Protein-protein interaction database obtained from a yeast two hybrid screen or a composite data set includes random false positives. To filter the database, we employed cellular localization and then reconstructed metabolite-related protein network. Even if we removed largest 11 hub proteins from the reconstructed network, the largest core network (proteins: 2,254, interactions: 3,833, and clustering coefficient: 0.11248) was still remained about 80% and also revealed characters of scale free and hierarchical networks. In contrast, when removed largest 10 hub proteins of kinome network (total protein kinases, clustering coefficient: 0.06) in *S. cerevisiae*, the kinome network was mostly destroyed (clustering coefficient: 0.146). The deletion analysis indicates that metabolite-related protein network is highly robust to removal of hub proteins but kinome network is vulnerable. To find functional modules from the network, we propose a new technique that is based on multi-body correlations in the metabolite-related protein network. From the derived modules, we predicted and estimated tentative functions for unannotated proteins with high certainty. Therefore, protein network is a useful tool for identifying unknown functions of proteins and prediction of hub or lethal proteins that highly connected with proteins to form modules.

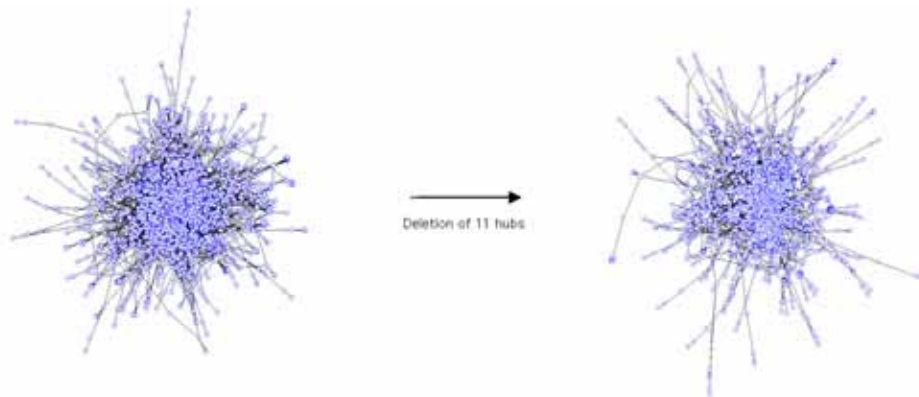


Figure 1. Largest core network (right-side) obtained from metabolite-related protein network that was removed by largest 11 hub proteins and their linkers.

## References

- [1] Hartwell, L.H., Hopfield, J.J., Leibler, S., and Murray, A.W. 1999. From molecular to modular cell biology. *Nature*, 402:C47-C52.
- [2] Schwikowski, P., Uetz, P., and Fields, S. 2000. A network of protein-protein interactions in yeast. *Nat. Biotechnol.* 18:1257-1261.
- [3] Rives, A.W. and Galitski, T. 2003. Modular organization of cellular networks. *PNAS*, 100:1128-1133.
- [4] Barabasi, A.-L. and Oltvai, Z.N. 2004. Network biology: understanding the cell's functional organization. *Nature Reviews genetics*, 5:101-113.