Lethality and Isolation in the Yeast Transcriptional Network

Sara E. Dempster[1]

***Short Abstract* — Transcriptional regulatory networks are the fundamental information processing networks of the cell, yet fewer than ten percent of transcription factor (TF) knockouts prove lethal in single gene deletion studies in yeast. To gain insight into this robustness, I analyze the network position of yeast TFs in relation to data on the phenotypic effects of single knockouts of TFs. I develop a new measure of network disruption, CL_{comp}, that successfully discriminates among sets of TFs grouped by their knockout phenotype and demonstrates that knockout of TFs that mediate pathways with more in-degree branching is less likely to be lethal.**

I. Introduction

Elucidation of the sources of biological network robustness is crucial to connecting genomic data to the mechanistic basis of complex disease [1], choosing more effective drug targets [2], and clarifying the constraints on biological network topologies during molecular evolution [3]. What characterizes cellular network structures that are robust versus sensitive to node removal? Much work has shown that analysis of network topology provides new insights into network behavior [4-6] even when such approaches do not explicitly treat network dynamics.

Robustness derived from network properties in the cell [7] has been studied by comparing network measures to results from genome-wide knockout experiments in model organisms. For example, highly connected hub genes are integral to efficient network communication [8] and previous analysis of biological networks argued that removal of hub genes is associated with lethality [9]. It is increasingly clear, however, that in addition to the amount of connectivity of a gene, higher order aspects of the network structure surrounding a gene's network position influence the cellular response to gene perturbation [10].

Here I focus on robustness to deletion of transcription factors (TFs) in the yeast transcriptional network.

II. Results

I ask what features of a TF's position in the network best reflect the disruption to information flow caused by their removal. Due to their directed and two-component nature, TFs have different types of network interactions, posing challenges for network analysis. I provide a framework to examine whether or not the types of connections that a TF is involved in have different relationships to phenotypic impact of TF knockout.

I show that examining a TF's amount of connectivity alone obscures features of a TF's network position important for understanding its knockout phenotype. For example, the independent removal of two TFs may sever the same number of connections, but in very different ways. One TF may directly regulate many downstream targets, but be influenced by only one or two upstream signals. Another TF may regulate fewer downstream events, but have many upstream signals converging upon it. Furthermore, the pathways in which a TF participates may be on average more linear or branched. Using these insights, I then develop a new measure of network disruption, CL_{comp}, that successfully discriminates among sets of TFs grouped by their knockout phenotype and demonstrates that knockout of TFs that mediate pathways with more in-degree branching is less likely to be lethal.

III. Conclusion

I find evidence that among TFs with overall similar total amounts of connectivity, the yeast cell is less sensitive to removal of TFs embedded in more connected topologies with surrounding TFs. This insight refines a common premise in the study of biological networks that the more connected a node, the more detrimental its removal, and instead reveals that greater connectivity within a pathway can reduce sensitivity to removal of any given node within the pathway.

References

[1] Chen YQ et al. (2008) Variations in DNA elucidate molecular networks that cause disease. *Nature* **452**: 429-435.

[2] Hopkins AL (2008) Network pharmacology: the next paradigm in drug discovery. *Nature Chemical Biology* **4**:682-690.

[3] Hartwell LH, Hopfield, JJ, Leibler S, Murray AW (1999) From molecular to modular cell biology. *Nature* **402**:C47-C52.

[4] Watts DJ, Strogatz SH (1998) Collective dynamics of 'small-world' networks. *Nature* **393**:440-442.

[5] Maslov S, Sneppen K (2002) Specificity and stability in topology of protein networks. *Science* **296**:910-913.

[6] Ma'ayan A, et al. (2005) Formation of regulatory patterns during signal propagation in a mammalian cellular network. *Science* 309:1078-1083.

[7] Wagner A (2005) Distributed robustness versus redundancy as causes of mutational robustness, Bioessays 27:176-188.

[8] Albert R, Jeong N, Barabasi AL (2000) Error and attack tolerance of complex networks. Nature 406:378-402.

[9] Jeong H, Mason SP, Barabasi AL, Oltvai ZN (2001) Lethality and centrality in protein networks. Nature 411:41-42.

[10] Guimera R, Amaral LAN (2005) Functional cartography of complex metabolic networks. *Nature* **433**:895-900.

[1]Department of Molecular and Cellular Biology, Harvard University. E-mail: saradempster@alum.mit.edu