Phenotypic Effects of Network Rewiring in Regulatory Hierarchies

Nitin Bhardwaj\textsuperscript{1}, Philip M. Kim\textsuperscript{2,3,4,5} and Mark B. Gerstein\textsuperscript{1,6,7}

\textsuperscript{1}Program in Computational Biology and Bioinformatics, \textsuperscript{6}Department of Molecular Biophysics and Biochemistry, and \textsuperscript{7}Department of Computer Science, Yale University, Bass 432, 266 Whitney Avenue, New Haven, CT 06520.
\textsuperscript{2}Terrence Donnelly Centre for Cellular and Biomolecular Research, \textsuperscript{3}Banting and Best Department of Medical Research, \textsuperscript{4}Department of Molecular Genetics, \textsuperscript{5}Department of Computer Science, University of Toronto, Toronto, ON M5S 3E1, Canada.

Abstract

Tinkering with biological networks, including transcriptional regulatory networks, has been used as a tool in the post-genome era to measure the tolerance of the cell in response to different kinds of perturbations. This tampering may include constructing synthetic model networks, knocking out and over-expression of genes. To obtain further insights into the organizational architecture of these networks, they have been rearranged into more intuitive structures like pyramidal hierarchies. In this study, we carry out a comprehensive analysis of the phenotypic effects of various kinds of network rewiring events in regulatory hierarchies in two species: \textit{E. coli} and Yeast. To study first order effects, we build intuitive pyramidal hierarchies with the ‘chain-of-command’ pointing downward and superimpose the phenotypic effects of tampering with nodes and edges related to various levels of the hierarchy. We find that rewiring events that affect the upper levels have more dramatic effect on cell growth than those affecting lower level ones. Extending it further, second order effects involve allowing the hierarchies to change upon deletions and insertions of nodes/edges in the network. To study these effects, we reconstruct modified hierarchies in response to various perturbations that change the arrangement of genes in different levels. From this analysis, we find that more than the absolute number of changes in the altered hierarchies, it is the location and type of change that more accurately reflects the phenotypic effect of rewiring; upper level changes more adversely affect the cell fitness than lower level ones. Since, connectivity of regulators is not linearly related with its position in the hierarchy, these results show that approaches based on the position of regulators in hierarchies can give better predictions about their importance for cell fitness than those just based on their in- or out-degrees.

Figure 1. Analysis of 1\textsuperscript{st} and 2\textsuperscript{nd} order effects. First, the network is arranged in a hierarchy with the regulation edges only pointing down. Next, the phenotypic effects of tinkering with various nodes are overlaid onto the hierarchy. In the subsequent step, these hierarchies are changed in response to the perturbations in the network and correlate the phenotypic effects of these changes.