Robustness and adaptation reveal plausible cell cycle controlling subnetwork in Saccharomyces cerevisiae

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Abstract

Biological systems are often organized spatially and temporally by multi-scale functional subsystems (modules). A specific subcellular process often corresponds to a subsystem composed of some of these interconnected modules. Accurate identification of system-level modularity organization from the large scale networks can provide valuable information on subsystem models of subcellular processes or physiological phenomena. Computational identification of functional modules from the large scale network is the key approach to solve the complexity of modularity in the past decade, but the overlapping and multi-scale nature of modules often renders unsatisfactory results in these methods. Most current methods for modularity detection are optimization-based and suffered from the drawback of size resolution limit. It is difficult to trace the origin of the unsatisfactory results, which may be due to poor data, inappropriate objective function selection or simply resulted from natural evolution, and hence no system-level accurate modular models for subcellular processes can be offered. Motivated by the idea of evolution with robustness and adaption as guiding principles, we propose a novel approach that can identify significant multi-scale overlapping modules that are sufficiently accurate at the system and subsystem levels, giving biological insights for subcellular processes. The success of our evolution strategy method is demonstrated by

applying to the yeast proteinprotein
interaction network. Functional subsystems of important physiological phenomena can be revealed.
In particular, the cell cycle controlling network is selected for detailed discussion. The cell cycle subcellular
processes in yeast can be successfully dissected into functional modules of cell cycle control, cell size check
point, spindle assembly checkpoint, and DNA damage check point in G2/M and S phases. The interconnections
between check points and cell cycle control modules provide clues on the signal stimulus entries of check
points into the cell cycle, which are consistent with experimental findings. This evolution strategy method
can be applied adequately to extract the plausible yeast cell cycle subnetworks from the whole network.
Connections between modules in the obtained cell cycle subnetworks reveal significant cell cycle control
mechanisms. This method can also be useful when applied to other biological systems at various temporal
and spatial scales for example, the gene transcription networks, and biological systems from mesoscopic
scale, e.g cortical network in brain, to subcellular molecular networks.

Keyword：modularity, protein-protein interaction, cell cycle, Sacharomyces cerevisiae, robustness