Synthesis and Analysis of a Biological System

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1 Background

Genome sequencing and further systematic functional analyses of complete gene sets will enable a mathematical framework model to synthesize specific biological systems and to analyze them at a molecular interaction level. Computational system analysis will clarify some of the design principles underlying a biological architecture.

Barkai and Leibler [1] demonstrated a robust property of adaptation behavior in bacterial chemotaxis, indicating that the robust adaptation was a consequence of the network's connectivity and the chemotaxis system did not require the fine-tuning of biochemical parameters. However, they did not answer the crucial question on whether it is possible to isolate such a subsystem from the whole system composed of heterogeneous and interactive networks and to analyze it separately. To address this issue, Kurata [2] established a numerical framework model of the *E. coli* heat shock response, and showed how complexity in regulation generates the robustness of the factors interconnected among subsystems.

2 Objective

Biological systems can be understood at different levels such as molecular, cellular, tissue, and organ levels and can be divided into different categories such as prokaryotes, eukaryotes (fungi, plants, animals). The design principles depend on such levels or categories. We would try to analyze an individual system belonging to different categories at molecular levels rather than pursue the general principles common to all the biological systems.

At the first step, we focus on a bacterial system at a molecular level and try to extract its design principles. In bacteria, all reactions including cell division, metabolism, and stress responses are performed in the cytosol, different from eukaryotes that consist of many organelles. Our aim is to elucidate the principle of how the biochemical networks are coordinated without any serious confliction.

3 Hypothesis of Design principle

Bacteria are complex systems composed of heterogeneous and interactive subsystems. Complexity seems to impede isolating a smaller subsystem out of a whole biological system. However, our hypothesis is that complexity generates robustness among subsystems, thereby making the subsystems function without serious confliction. A biological system may be a collective body of mosaic-like subsystems rather than a melting pot of subsystems.

4 Strategy

4.1 Mathematical model

Biochemical networks in bacteria can be regarded to consist of chemical reactions, such as association, dissociation, degradation, and synthesis. Biochemical networks can be divided into a binding phase and a reaction phase. Binding association/dissociation rates among components are assumed to be quite fast compared with the rates of synthesis/degradation of their complex, thus all of the fractions of the complexes are at equilibrium. This assumption greatly increases the calculation rate.

4.2 Simulator

We develop the simulator that automatically describes the differential equations and simultaneous equations and can search the large space of parameter combinations. Calculations involving differential equations and those involving simultaneous nonlinear equations were performed by the Runge-Kutta method and by the Newton-Raphson method, respectively. Computer programs in C language and Message-Passing Interface were executed on 1024 CPUs of a super parallel computer SR2201 (Hitachi, Tokyo) or the Beowulf, a PC cluster machine (33×Pentinum III).

4.3 System analysis

We analyze biological systems in comparison with control theory of artificial substances, and apply modern theory regarding system science to them. Key words are complexity and robustness. We focus on the robustness of the factors interconnected among subsystems and show how complexity in biochemical networks generates the robustness. Two systems of heat shock response [2] and ammonia assimilation [3] have been investigated, supporting our hypothesis that complexity generates robustness among subsystems.

5 Discussion

The problem for synthesizing/analyzing a biological system using numerical models is that it is quite difficult to determine all of the biochemical parameters. Since the parameters vary with intracellular or extracellular conditions, it is hard to measure them by means of experiments and they will remain unknown. However, an important approach to understanding a biological system would be to extract some of the design principles underlying the biological architecture rather than to obtain full knowledge of the molecular details. Computational system analysis with modern control theory and subsequent verification through biological experiments are expected to become a novel methodology, what is called "systems biology", for describing the design principles of biological systems.

References

[1] Barkai, N. and Leibler, S., Robustness in simple biochemical networks, *Nature*, 387:913–917, 1997.

[2] Kurata, H., Complexity generates robustness and high performance in *E. coli* heat shock response, *The Proceedings of the 13th Meeting of Japanese Society for Artificial Intelligence*, 1999.

[3] Kurata, H. and Seki, M., The algorithm for controlling the ratio of C/N in the ammonia assimilation system of *E. coli*, *The Proceedings of the 32th Fall Meeting of the Society of Chemical Engineers*, Japan, 1999.