Thesis Abstract

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Title of Thesis:

Comprehensive Understanding of Gene Regulatory Networks
Based on Evolutionary Systems Biology

Summary of Thesis:

In this study, I developed novel evolutionary analysis methods contributing to the new field of evolutionary systems biology. I successfully applied these methods to analyze several important factors related to transcription or translation, such as upstream Open Reading Frames (uORFs) (Chapter 2) and transcription factors (TFs) (Chapters 3 and 4).

First, I reviewed changes in the approaches to understanding life in the history of biology; then, I showed that evolutionary systems biology is a particularly effective approach to reconstructing possible evolutionary scenarios of gene regulatory networks based on various large-scale datasets (Chapter 1). Next, I performed comprehensive analysis of uORFs, which act as *cis* regulators of mRNA, by using microarray data on humans and mice. Comparison of transcriptional expression level and RNA decay ratio of mRNAs in a number of different tissues suggested that uORF controlled not only translation efficiency but also mRNA decay rate in a wide range of tissues and species (Chapter 2). In chapter 3, I developed a novel evolutionary analysis method, the TOP-DOWN approach, by integrating step-wise spectral clustering techniques into network theory to solve highly complex structures of sequence similarity networks. The TOP-DOWN approach was applied to the large-scale analysis of the CRP/FNR superfamily, which is one of the major TF families in the bacterial domain, and clarified its comprehensive evolutionary processes in a wide range of bacterial species (Chapter 3). Moreover, I applied the method to analyze all *Escherichia coli* TFs and all well-annotated bacterial TFs. As a result, I proposed a novel evolutionary model for TF-TF regulatory networks and transcriptional regulatory interactions between TFs and their target genes (Chapter 4). Finally, I discussed the contribution of my method to furthering the research of multi-hierarchical biological networks (Chapter 5).

Key words: Post-transcriptional control; Transcription factor; upstream ORF; Phylogenetics; Network analysis