SUMMARY OF Ph.D. DISSERTATION

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Title

SYSTEMS BIOLOGICAL APPROACHES FOR UNDERSTANDING SPORULATION MECHANISM OF *BACILLUS SUBTILIS*

Abstract

Systems biology is an emergent field that aims at system-level understanding of biological systems. The approach of systems biology can be categorized into two; that is, 1) omics data driven research, and 2) theory/model driven research. In this thesis, I utilized those approaches to understand sporulation mechanism in *Bacillus subtilis*.

In Chapter 1, systems biology field was broadly overviewed, particularly from computational analysis standpoint. Recent advances in this field were discussed, and issues I solved in this thesis are addressed.

In Chapter 2, a genetic and biochemical network editor CellDesigner is described. So far, there are issues in computational modeling, such as 1) ambiguity in network pathway semantics, 2) difference between computational model and pathway drawing, and 3) model representation is different among analysis tools. To solve these issues, I developed a network editor called CellDesigner. Owing to the development of CellDesigner, drawing pathway models are easily possible because of its rigid definition of semantics. Besides, employing SBML (Systems Biology Markup Language) enables users to interact easily with other analysis tools and database. CellDesigner was applied to metabolome analysis in Chapter 4.

In Chapter 3, I propose a methodology to compare between computational models, using "robustness" as a qualitative measure. Using two comparative biochemical models of *Xenopus*, we investigated the system characteristics in detail. As a model is improved owing to obtaining massive experimental data, this methodology could be applied to see if newer model is more plausible, which is mentioned in Chapter 5.

In Chapter 4, I describe a metabolome data processing method. Using metabolome data obtained from CE-MS (capillary electrophoresis mass spectrometry), noise reduction is a significant step toward extracting quantitatively and qualitatively reliable data. I thus developed a filtering method called P-BOSS (Peak filter Based on Orphan Survival Strategy), which enables user 1) to set objective measure of threshold level, and 2) to process data in different manner depending on data characteristics. Using real data obtained from various *E. coli* mutants, I confirmed that P-BOSS is superior in screening efficiency that it removed 65% of peaks without removing significant peaks.

In Chapter 5, I describe the analysis for sporulation mechanism of *Bacillus subtilis*, utilizing tools as developed in previous chapters. I modeled a minimal model of Spo0A consisting of positive/negative feedback pathway. The system analysis revealed that negative feedback primarily modulates the system behavior, and the simulation results were confirmed to be consistent with experimental data. To understand sporulation from molecular viewpoint, I conducted metabolome analysis. As the results, metabolome profiles were found yield distinct characteristics among both time points and strains. In addition to finding data characteristics being consistent with past studies, I found several interesting metabolome characteristics upon sporulation, such as dramatic increase in ATP level.

In Chapter 6, I summarize the results obtained from previous chapters, and discuss current issues and future perspectives.