Modeling a Complex Gene Regulation Network Using the E-CELL System

Kenta Hashimoto[1,2]
kem@sfc.keio.ac.jp
Sae Seno[1,3]
t98536ss@sfc.keio.ac.jp
Fumihiko Miyoshi[1,2]
fumi@sfc.keio.ac.jp
Masaru Tomita[1,3]
mt@sfc.keio.ac.jp

[1] Laboratory for Bioinformatics
[2] Graduate School of Media and Governance
[3] Department of Environmental Information, Keio University,
5322 Endo, Fujisawa, Kanagawa 252-8502, Japan

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1 Introduction

We present a general framework for modeling gene expression by using the E-CELL system, a general purpose cell simulator developed at Keio University. Using this framework, we modeled and simulated the following two gene regulation systems: the *lac* operon in *E. coli*, and the lytic-lysogenic switch network in bacteriophage λ.

We previously constructed a detailed model [1] of the gene expression system as part of a "virtual" cell with 127 genes [4]. The previous model accurately reflected the gene expression system of *M. genitalium*, involving more than 100 objects including various subunits, factors, amino acids, nucleotides, tRNAs, and their ligases. However, in order to simulate complex gene regulation systems with a large number of genes, a more abstract and simpler model is desired for the sake of efficiency. The gene expression system used in this work consists of the following four basic elements. 1) Production of RNAs and proteins, 2) Regulation of expression by various factors, 3) Time delay between regulation and production, and 4) Sigmoidal curve of product increase over time. All gene expressions are reduced to these four elements.

2 *lac* Operon in *E. coli*

Based on the framework described above, we modeled gene regulation systems of the *lac* operon in *E. coli*. We are currently integrating the *lac* operon model with the glycolysis pathway (Fig. 1-a), so that we can simulate *E. coli*'s sugar metabolism and regulation with lactose and glucose.

The results of the simulation are shown in Figures 1-b and 1-c. It was observed that, expected, glucose was consumed first, then, after glucose had been exhausted, lactose began to be consumed (Fig1-b).

3 Lytic-lysogenic switch network of bacteriophage λ

To attempt a more complex gene regulation system, we are modeling the lytic-lysogenic switch network of bacteriophage λ (Fig. 2-a). The model of the lytic-lysogenic switch network includes the effects of glucose deprivation and ultraviolet light.

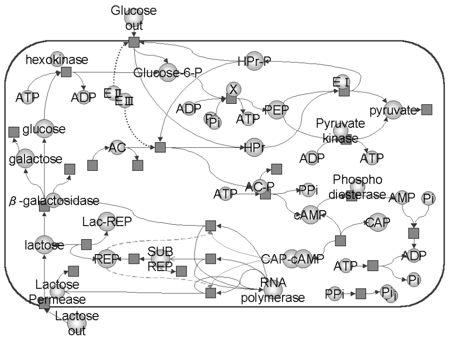
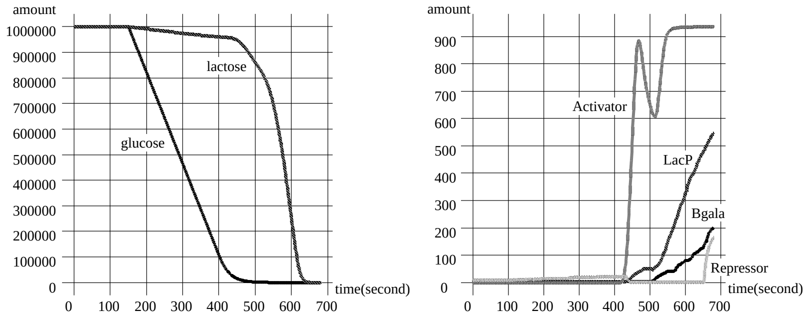


Figure 1-a: The integrated model of the *lac* operon and glycolysis



Figures 1-b, 1-c: results of simulation

The results of the simulation are shown in Figures 2-b and 2-c. Under glucose deprived conditions and with irradiation by ultraviolet light, the lysogenization process was activated (Fig. 2-b). This is shown by the generation of Integrase (Int protein), and the suppression of the production of parts involved in head and tail construction. Under other conditions, lytic growth was activated. An example of lytic growth under conditions contrasting with those of the lysogenization process is shown in Figure 2-c.

With regard to future investigation, given that the E-CELL system allows the user to easily substitute individual reactions, several variations of gene expression models of bacteriophage λ reported in the current literature [2, 3] could be constructed and compared by using this system.

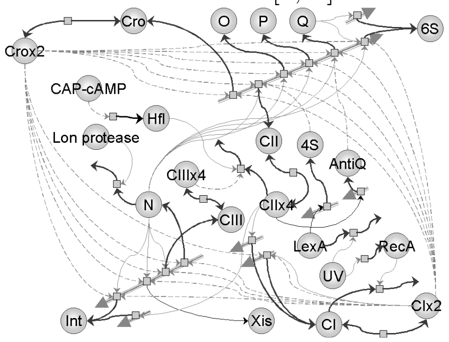
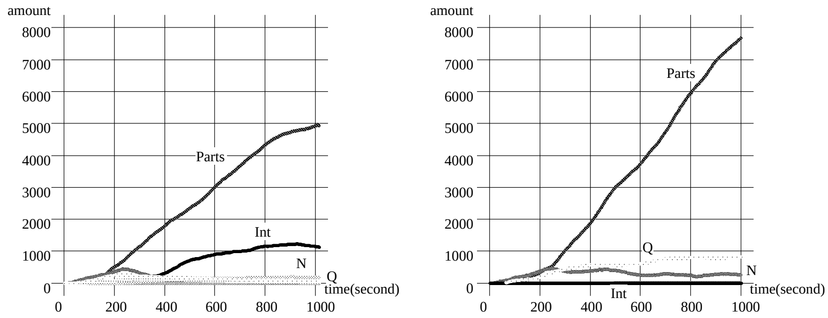


Figure 2-a: The lytic-lysogenic switch network of bacteriophage λ



Figures 2-b, 2-c: results of simulation

References

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