A Design Method of Artificial Genetic Circuits on Effective Search of These Logical Structures

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1 Introduction

In the context of synthetic biology, artificial genetic circuits are designed in the following way: after setting a biological target phenomenon to be investigated, reaction parameter estimations among related molecules are conducted based on the dynamic analyses with mathematical models, finally a system of biological reactions is developed with these molecules *in vivo* or *in vitro*. It is desired to develop an effective method to select the suitable circuits for realizing the target phenomenon, because not a few models are possible as candidates for the target phenomenon.

We propose a new procedure to effectively design a mathematical model by the following two steps. The first step is the process creating possible structures of the mathematical by a logical technique. The second step is the process creating dynamic models in two ways; a system of differential equations for the analysis of dynamics in the model and a model of hybrid functional Petri net as a common platform for knowledge sharing between biologists and computer scientists.

2 Method and Results

2.1 2-state genetic toggle switch

The key of our proposed method is to separate the design process of a mathematical model into two steps. Our proposed method enables us to realize a suitable artificial genetic circuit in more reduced time and cost than existing methods.

Figure 1 shows the 2-state genetic toggle switch [1]. The biological model consists of two genes A and B being led by prompter regions for each. Repressors A and B are produced from these two genes A and B, which are initiated by two promoter regions B and A, respectively, and repressors A and B inhibit the expressions of promoters A and B, respectively (biological model). This 2-state gene toggle switch is finally transformed into either of two stable states, where either of two genes (target phenomenon) is expressed depending on an initial amount of repressors A and B. A kinetic model is given as a system of differential equations as shown in Figure 1.

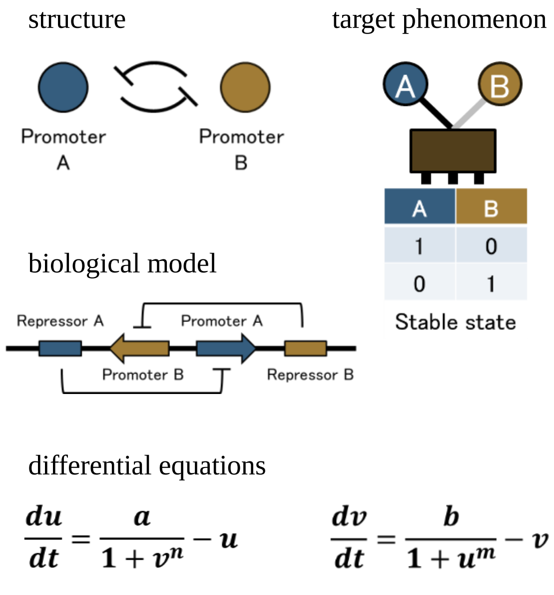

Figure 1: 2-state genetic toggle switch

2.2 Extension to 3-state toggle switch

3-state toggle switch has three stable states as shown in Figure 2. Among many possible logical structure models, three models are presented in Figure 2. State transitions, which are produced from GINSim [2], are given as well. Model 3 can be eliminated from the candidates because of the complicated state transitions, in which more states are used than Models 1 and 2 and cycle behaviors are found. Possible structures of artificial genetic circuit to be selected in this way will be sent to the next step, where dynamic parameters are incorporated in the selected structures. Resulting dynamical models shall be a system of differential equations and a hybrid functional Petri net model, which can be executed on the tools such as MATLAB and Cell Illustrator, respectively.

2.3 Simulation of dynamic models

Two different types of simulations are conducted. One is for the analysis of dynamic behavior of the obtained artificial genetic circuit model on a system of differential equations, and the other is for acquiring biologically important behavior for the designing genetic circuit *in vivo* and/or *in vitro*. Experts in microbiology need to be participated in the process of parameter determination of these models in order to choose appropriate values from biological aspects.

2.4 Realization by biological experiments

E.coli will be used for the realization of the artificial genetic circuits. Selection of condition for expression inductions and selection of expression vector need to be considered.

3 Discussions

Besides the 3-state toggle switch, many biological behaviors such as oscillation and flip-flop can be considered as the candidate targets for artificial genetic circuits. In order to see the availability of our proposed method, these behaviors will be applied in our future work.

References

[1] Gardner, T.S., Cantor, C.R., Collins, J.J., Construction of genetic toggle switch in *Escherichia coli*, Nature 403:339-342, 2000.

[2] Fauré, A., Thieffry, D., Logical modeling of cell cycle control in eukaryotes: a comparative study, Molecular Biosystems, 5:1769-81, 2009.

[3] Cell Illustrator: http://www.cellillustrator.com/home

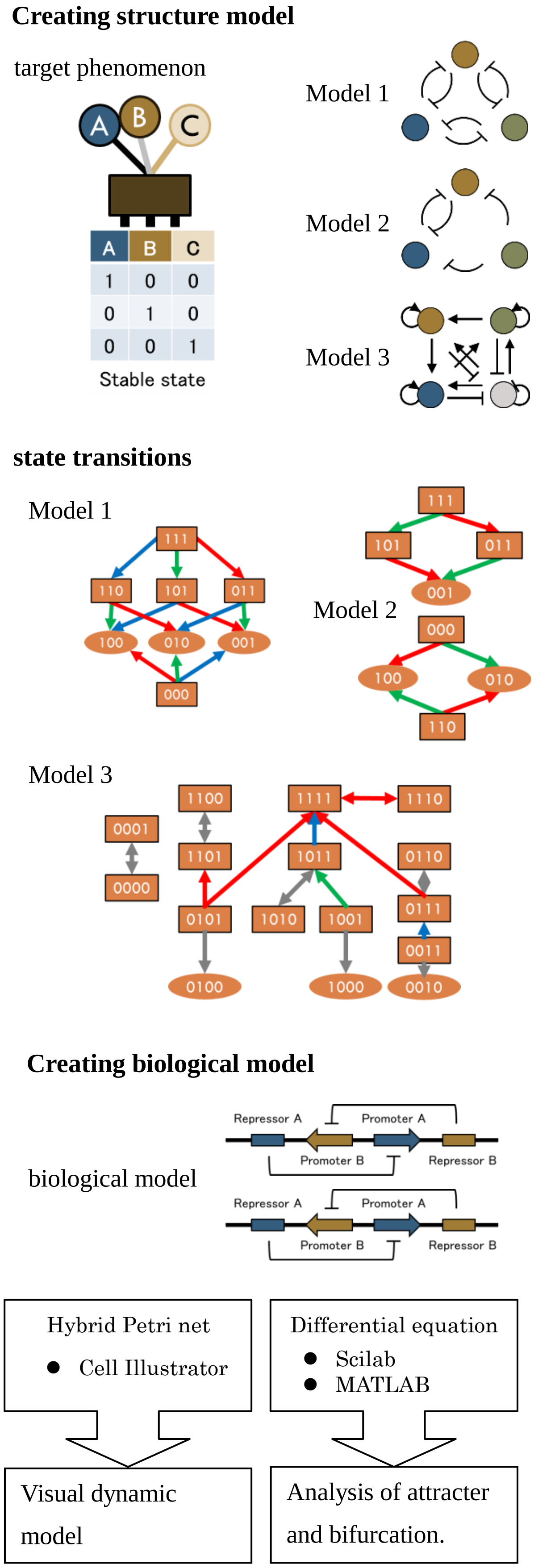

Figure 2: Process of the proposed method