Vulval Development Modeling Using Hybrid Functional Petri Net with extension and its Simulation-based Formal Model Validation

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Abstract

The key motivation of this poster is to establish a quantitative methodology to model and analyze *in silico* models incorporating the use of model checking approach. We propose a novel method of modeling and simulating biological systems with the use of model checking approach based on the hybrid functional Petri net with extension (HFPNe) as the framework dealing with both discrete and continuous events. We considered two rules for the quantitative model of the VPC fate specification from two viewpoints. We conducted 10,000 simulations for each of 48 sets of different genetic conditions, and investigated their variations as well as validating the two rules by comparing three simulation targets consisting of fate patterns obtained from *in silico* and *in vivo* experiments. In particular, an evaluation was successfully done by using our *in silico* model for one target which is derived from the biological experiments involving hybrid lineage observations, whereas such understandings are hard to make on a discrete model because these hybrid lineages occur when a system comes close to certain threshold as discussed by Sternberg and Horvitz in 1986. Our simulation results suggest that the rule on the fate-sustaining capacity is more reasonable than the other rule owing to the high coverage of predicted fate patterns (except for the *lin-15ko; lin-12ko* genetic condition).

Keywords: model checking, Petri net, simulation, cell fate, vulval development

1 Introduction

Model checking is a successful method for verifying system requirements. It is a high speed technique for automatic verification of software and reactive systems [1]. The pioneering work of using the model checking approach for validating biological systems with biological experiments was initiated by Fisher *et al.* in 2007 [2]. They took a discrete and state-based approach to explore all possible states of the system underlying vulval precursor cell (VPC) fate specification for the desired properties. However, both discrete and continuous features appear to be an indispensable part of fundamental biological processes, it is more appropriate to use quantitative models to capture the dynamics of biological systems. Thus, it is crucial to establish a quantitative methodology to model and analyze *in silico* models incorporating the use of model checking approach.

2 Method and Results

The mechanism of *C. elegans* vulval development involves multiple regulatory signaling pathways consisting of EGFR/Ras/MAPK cascades, LIN-12/Notch-mediated lateral signaling events, and signaling

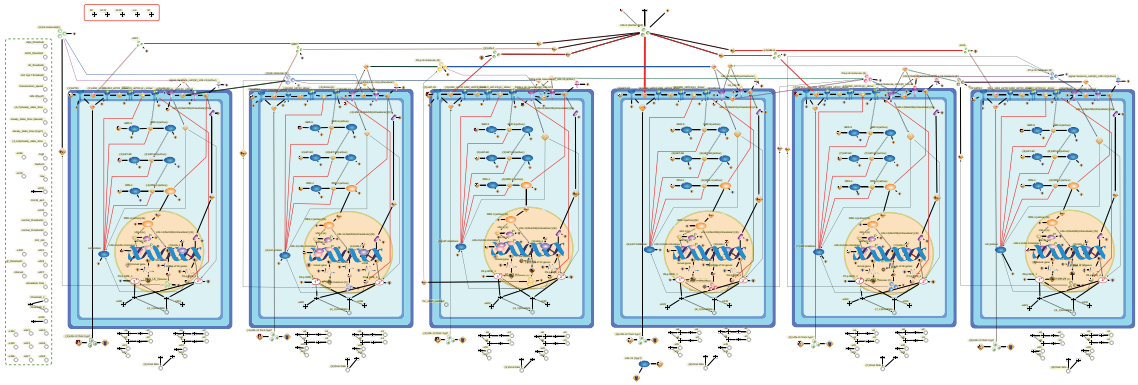

Figure 1: The whole HFPNe model underlying the fate specification mechanisms involving six equivalent VPCs.

pathways induced by the hypodermal syncytium hyp7. In order to quantitatively model this biological systems, we use *hybrid functional Petri net with extension* (HFPNe) [4] that is an enhanced Petri net architecture which best meets the features of biological processes. Figure 1 exhibits a whole HFPNe model constructed by compiling and interpreting the information appeared in the literature.

In order to deal with the quantitative model, we define two rules of fate specification from the following viewpoints: (i) The fate-sustaining capacity of the fate candidates, i.e., the cell fate satisfies the condition that the fate can sustain the behaviors at a certain over-threshold state within a given length of time; and (ii) the temporal order of the fate candidates, i.e., the cell fate will be priorly adopted according to the temporal sequence of the events inducing an over-threshold state. Three simulation targets of this model have been considered: The first one is the fate patterns obtained by improving the qualitative method of Fisher *et al.* [2]; the second target is the fate patterns summarized by Sternberg and Horvitz [3]; and the last one is derived from the biological experiments in [3] including the hybrid lineage data.

We conduct 10,000 simulations for each of 48 sets of different genetic conditions which is the combination of four mutants and the anchor cell, and we investigated their variations as well as validating the two rules by comparing three simulation targets on Cell Illustrator. Our simulation results suggest that the rule on the fate-sustaining capacity is more reasonable than the other rule owing to the high coverage of predicted fate patterns (except for the *lin-15ko; lin-12ko* genetic condition), (ii) for the *lin-15ko; lin-12ko*, the coverage will be considerably augmented, if the number of animal population is increased in the *in vivo* experiments, and (iii) the fate patterns in the *lin-15ko* and the *ac-; lin-15ko* genetic conditions not covered by prediction have a possibility to be examined with biological experiments by enlarging the animal numbers. We consider that this computational experiment and the biological evaluation could not be easily put into practice without the HFPNe modeling method and the functions of Cell Illustrator, especially, the "High-Speed Simulation Module".

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