Simulation of *Drosophila* Boundary Cell Formation in Forced-Expression of Notch$^{\Delta E}$

Rie Yamane[1]
yamane@ib.sci.yamaguchi-u.ac.jp
Junko Umezaki[1]
flylab@po.cc.yamaguchi-u.ac.jp
Hiroshi Matsuno[1]
matsuno@sci.yamaguchi-u.ac.jp
Ryutaro Murakami[1]
ryu@po.cc.yamaguchi-u.ac.jp
Naoyuki Yamasaki[1]
flylab@po.cc.yamaguchi-u.ac.jp
Satoru Miyano[2]
miyano@ims.u-tokyo.ac.jp

[1] Faculty of Science, Yamaguchi University, 1677-1 Yoshida, Yamaguchi 753-8512, Japan
[2] Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokane-dai, Minato-ku, Tokyo 108-8639, Japan

Keywords: Delta-Notch signaling pathway, *Drosophila* large intestine, boundary cell formation, Michaelis-Menten equation, forced-expression of Notch$^{\Delta E}$

1 Introduction

Delta-Notch signaling pathway plays an essential role in various morphogenetic systems of multicellular animal development [3]. We analyzed the mechanism of Notch-dependent boundary formation in the *Drosophila* large intestine by experimentation and computational modeling and simulation by Genomic Object Net (GON) [4]. In the last study [1], we demonstrated that several simulation patterns were obtained only by changing a few parameter values and initial conditions of a common model. In this study, we improved the parameters in order to approximate the experimental observations and tried to simulate new patterns resulting from forced-expression of Notch$^{\Delta E}$ in collaboration with biologists. As a result, we could construct the new model closer to biological phenomena and obtain several simulation patterns of forced-expression of Notch$^{\Delta E}$ only by manipulating the parameters.

2 Simulation Results and Experimental Observations

The Delta-Notch signaling pathway was modeled by Hybrid Functional Petri net (HFPN) [2], which includes the intracellular regulatory circuit as well as cell-to-cell interactions (Figure 1). Figure 2 shows the simulation model consisting of 60 cells. In addition, we introduced enzyme kinetics for parameters,

Table 1: Parameters in HFPN model.

type	V_m	K_m	K_i	Dl		nd
				d	v	
(1)	0.2	40	0.3	0	10	0
(2)	0.2	40	0.3	0	10	8
(3)	0.2	40	0.3	0	5	8
(4)	0.2	40	0.3	0	10	1.5
(5)	0.2	40	0.3	0	10	22

V_m: maximum rate, K_m: Michaelis-Menten constant, K_i: dissociation constant, Dl: the initial value of Delta, d: Delta in the dorsal domain (cell:1-36), v: Delta in the ventral domain (cell:37-60), nd: the forced-expression rate of Notch $^{\Delta E}$, (1) wild type, (2) The forced expression of Notch$^{\Delta E}$ (middle level), (3) The forced expression of Notch$^{\Delta E}$ (middle level, half level of v), (4) The forced expression of Notch$^{\Delta E}$ (small level), (5) The forced expression of Notch$^{\Delta E}$ (large level)

applying Michaelis-Menten equation to the natural degradation of each protein and the formula of competitive inhibition to the mechanism of cell-autonomous suppression of Notch signaling by Delta (Circled area in Figure 1). We also introduced random number for fluctuations. By manipulating Notch$^{\Delta E}$ expression in the large intestine, several types of disorder in boundary cell formation were observed (Figure 4) by the experimentation, and similar abnormal patterns were generated by the simulation (Figure 3). Especially, more boundary cells were expressed depending on the forced-expression rate of Notch$^{\Delta E}$ in the dorsal domain. We could explain both normal and abnormal situations only by manipulating the parameters (Refer to Table 1).

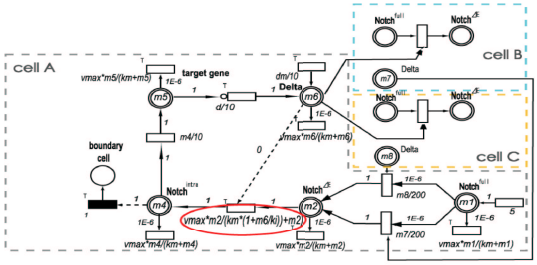

Figure 1: HFPN model of the Delta-Notch signaling pathway.

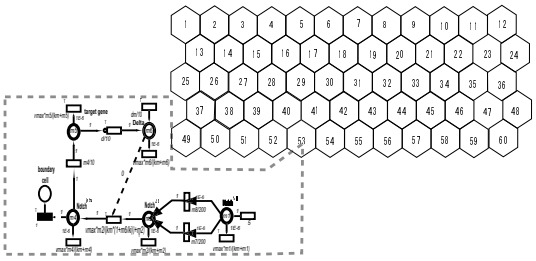

Figure 2: 60 cells model for simulation by GON. Each cell has the HFPN model in Figure 1.

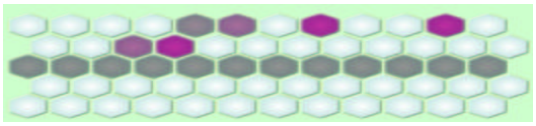

Figure 3: The simulation result of boundary cell formation in forced-expression of Notch$^{\Delta E}$.

Figure 4: The biological experiment of boundary cell formation in forced-expression of Notch$^{\Delta E}$.

Acknowledgments

This work is partially supported by the Grand-in-Aid for Scientific Research on Priority Areas "Genome Information Science" from the Ministry of Education, Culture, Sports, Science and Technology in Japan.

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