

# Computer Simulation of the Asymmetric Cell Division in Early Development of *C. elegans* Embryo Using E-CELL System

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**Keywords:** computer simulation, *C. elegans* development, asymmetric cell division, MPF, DNA synthesis

## 1 Introduction

In early development, egg cleavage is a very well-coordinated process under genetic regulation. The nematode worm *Caenorhabditis elegans* is one of the leading organisms for study of the embryogenesis [4]. During early development of the worm, asymmetric cell divisions produce different type of cells with asynchronous cell cycle time and these cells are essential for determining the subsequent developmental fates. In 1998, the genome of *C. elegans* has been sequenced [5], and a set of refined genetic tools are becoming available. We have constructed a computer model of the cell cycle in the *C. elegans* development using E-CELL simulation system. In the simulation environment, unreplicated DNA content of each cell is a key to determine accurate timing of cell division. Combination of the both simulations, cell cycle and DNA synthesis in the early development may explain the asymmetric cell divisions in *C. elegans*.

## 2 Methods

In the previous work, Novak, B. and Tyson, J.J. reported a model for the cell cycle based on the biochemistry of M-phase promoting factor (MPF) in *Xenopus* oocyte extracts [3]. We have reconstructed the cell cycle model of *Xenopus* oocyte by adapting their model into the E-CELL system, a software environment for whole cell simulation [6]. MPF oscillations are also observed in our system. Next, we have confirmed the most of the homologous factors involving in the regulation of *Xenopus* oocyte cell cycle (Figure 1) are found in the genome of *C. elegans*. A possible model of the asymmetric cell division is constructed by considering the data from both papers, DNA synthesis [1] and cell division mutants in *C. elegans* [2].

## 3 Results and Discussions

We have constructed a model of the cell cycle in the E-CELL system based on the model of *Xenopus* oocyte [3]. To obtain some insight into the early development of *C. elegans*, we have expanded the model using the experimental data of the worm. Sequential oscillations of activated MPF were observed in the simulation experiments. The cycle time was increased depending on the content of

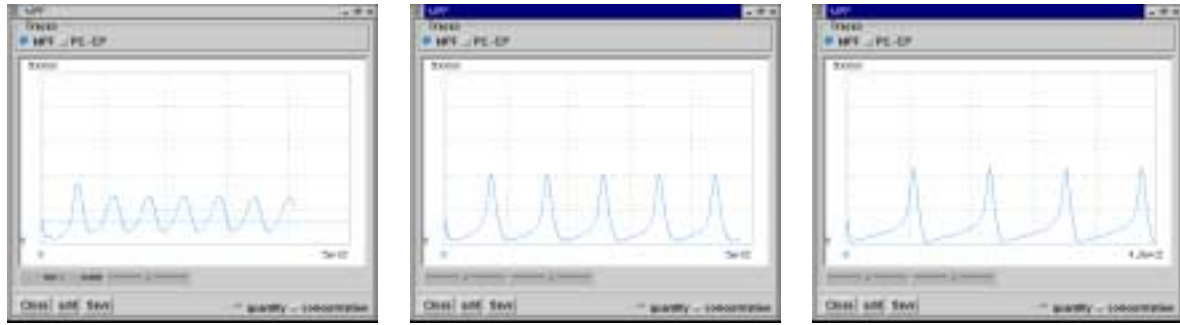


Figure 2: The increase of MPF oscillations. This simulation was carried out using the carried out using the alternative parameter values in Figure 1, depending on unreplicated DNA.

unreplicated DNA (Figure 2). The experimental data, the various time course of DNA synthesis in each cell lineage [1], is well fit to explain the results of our simulation of the asymmetric cell divisions. Recently, it was reported that DNA replication mutants in *C. elegans* exhibit delayed embryonic cell divisions and losses of asymmetry during early embryonic cleavage [2]. These data also provided the suitability of our simulations. On the other hand, our model did not explain the first asymmetric cell division in *C. elegans*. Other mechanisms determining the position of mitotic apparatus such as centrosomes and microtubule in the cell should be mounted on the E-CELL system in the future.

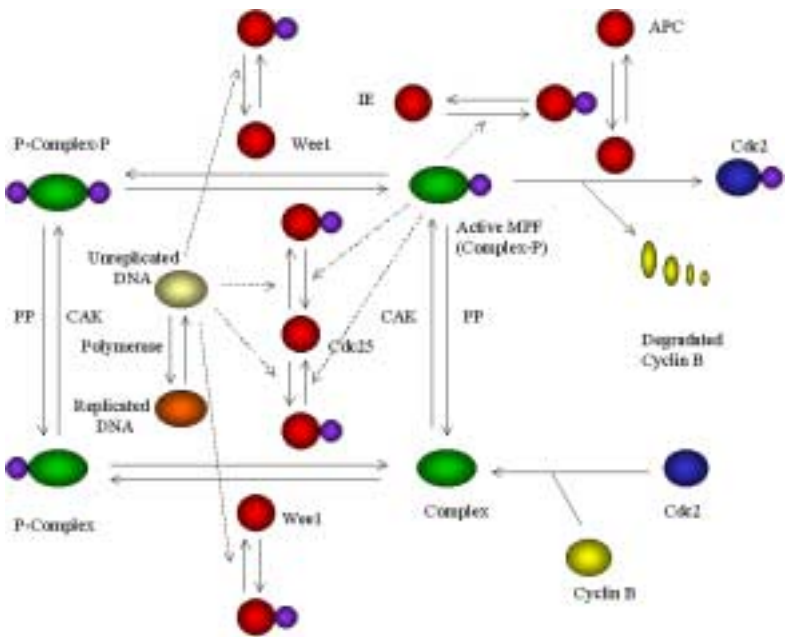


Figure 1: Pathway involved in cell cycle regulation.

### Acknowledgments

This work was supported in part by Japan Science and Technology Corporation.

### References

- [1] Edgar, L.G. and McGhee, J.D., DNA synthesis and the control of embryonic gene expression in *C. elegans*, *Cell*, 53(4):589–599, 1988.
- [2] Encalada, S.E., Martin, P.R., Phillips, J.B., Lyczak, R., Hamill, D.R., Swan, K.A., and Bowerman, B., DNA replication defects delay cell division and disrupt cell polarity in early *Caenorhabditis elegans* embryos, *Dev. Biol.*, 228(2):225–238, 2000.
- [3] Novak, B. and Tyson, J.J., Numerical analysis of a comprehensive model of M-phase control in *Xenopus* oocyte extracts and intact embryos, *J. Cell Sci.*, 106:1153–1168, 1993.
- [4] Sulston, J.E., Schierenberg, E., White, J.G., and Thomson, J.N., The embryonic cell lineage of the nematode *Caenorhabditis elegans*, *Dev. Biol.*, 100(1):64–119, 1983.
- [5] The *C. elegans* Sequencing Consortium, Genome sequence of the nematode *C. elegans*: a platform for investigating biology, *Science*, 282:2012–2018, 1998.
- [6] Tomita, M., Hashimoto, K., Takahashi, K., Shimizu, T.S., Matsuzaki, Y., Miyoshi, F., Saito, K., Tanida, S., Yugi, K., Venter, J.C., and Hutchison C.A. 3rd, E-CELL: software environment for whole-cell simulation, *Bioinformatics*, 15(1):72–84, 1999.