

# Simulation for detailed mathematical model of G1-to-S cell cycle phase transition

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## 1 Introduction

Cell cycle is needed to maintain the homeostasis of a living body. The eukaryotic cell cycle is divided into four phases: G1 (Gap 1), S (Synthesis), G2 (Gap 2), and M (Mitosis) phase. This cycle is orchestrated by the expression of the cell cycle genes, which form a complex and highly integrated network [1]. The abnormality of the control mechanism of the cell cycle disturbs the regular proliferation, and results in a development of cancer. So, it is an important issue to understand the control mechanism of cell cycle, for solving development mechanism of cancer. Through the cell cycle, a transition state from G1 to S (G1-to-S transition) is one of most important process. The disruption of the control mechanism for G1-to-S transition triggers an acquisition of infinite proliferation ability which is one of the greatest features of cancer. So, last year, we reported a mathematical model of G1-to-S transition based on Aguda's model [2] and the results of a system analysis of the model [3].

In this study, we constructed an extended mathematical model of G1-to-S transition to perform more detailed system analysis and simulated it.

## 2 Mathematical model and Method

In the reaction scheme for G1-to-S transition, the central reaction is a RB protein (retinoblastoma: RB) phosphorylation. In G1 phase, RB binds E2F (E2 promoter binding factor) which is a transcription factor concerned with an induction of S phase, and represses its transcription. Mitogenic stimulation releases this repression. Next, RB is phosphorylated by kinases, and dissociates from E2F. E2F dissociated from RB transcribes some genes to induce into S phase, and a cell cycle progresses S phase. Three complexes which are related to this RB phosphorylation reaction are Cyclin D/CDK4 (a complex which are Cyclin D and Cyclin dependent kinase 4), Cyclin E/CDK2 (a complex which are Cyclin E and Cyclin dependent kinase 2) and Cyclin A/CDK2 (a complex which are Cyclin A and Cyclin dependent kinase 2) [4, 5]. Free E2F activates transcriptions of both Cyclin E and Cyclin A. CDK2 dissociates from Cyclin E and associates with Cyclin A. In addition to RB, Cyclin A/CDK2 also phosphorylates DP, which is an E2F partner, and depresses E2F transcriptional activity.

We previously constructed a mathematical model of G1-to-S transition based on Aguda's model and performed system analysis using the level of chemical species at steady state. In this study, we constructed an extended mathematical model of G1-to-S transition including this Cyclin A. Cyclin A has activity peak in early G2-M phase or the end of S phase and important role in S phase, would be utilizable as an index which shows for S phase. So we included Cyclin A into this model.

This model consisted of 19 ordinary differential equations on 19 chemical species in Table 1 and 47 kinetic parameters. In numerical simulation, we used forth-order Runge-Kutta method.

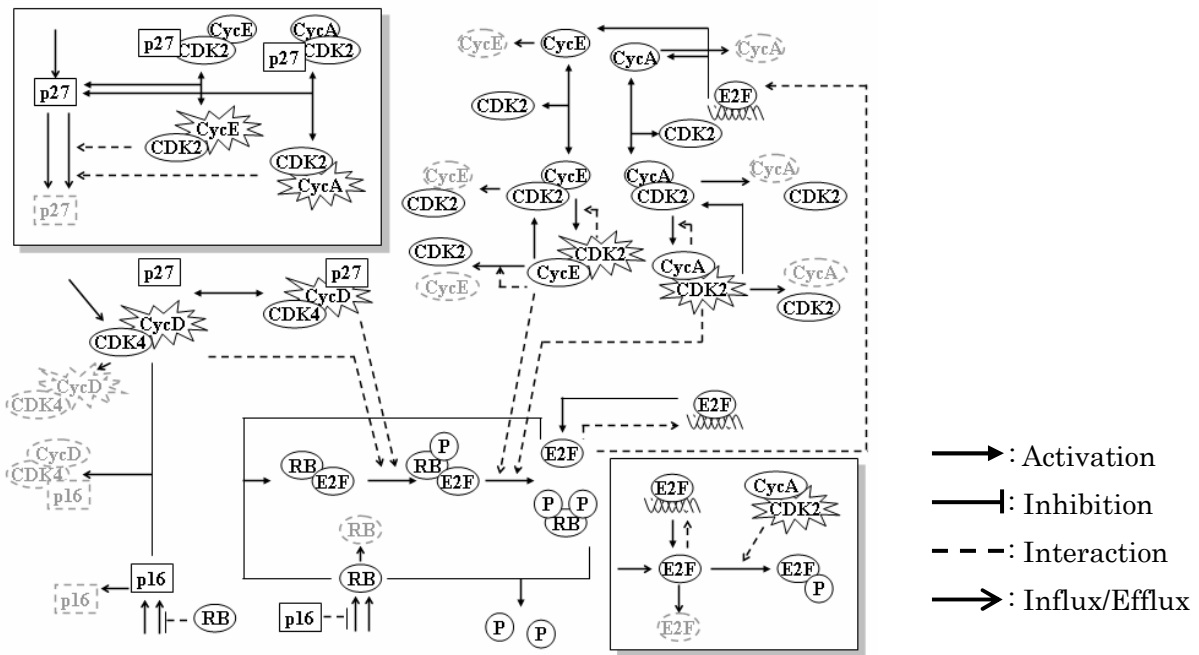


Figure 1: G1-to-S transition model proposed in this study

Table 1: Chemical species in this model

Active Cyclin E/ CDK2	Inactive Cyclin E/ CDK2	p27/Cyclin E/ CDK2	CyclinD/ CDK4	p27/Cyclin D/ CDK4
Active Cyclin A/ CDK2	Inactive Cyclin A/ CDK2	p27/Cyclin A/ CDK2	E2F	RB
Partially phosphorylated RB P/E2F	Fully phosphorylated RB PP	Phosphorylated E2F P	RB/E2F	Cyclin E
Cyclin A	p27	p16	CDK2	

### 3 Results and Discussions

The simulation results of our model agreed with the biological knowledge in previously studies qualitatively. Cyclin D and Cyclin E were central as Cyclin species in constructed mathematical models of mammalian G1-to-S transition. In this study, the concentration of Cyclin D and E had a peak in the early. Following this peak that of Cyclin A also had a peak. This result agreed with experimental result.

### References

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