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Stochastic simulation of cell cycle

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ABSTRACT

Dynamic model of cell cycle from G_1 to S stage is described by a system of six ordinary differential equations. These equations display the rate of changes in concentrations of proteins, cyclin E, *CycE*, cyclin dependent kinase, *CDK2* and protein phosphatase, *CDC25*. We have developed a stochastic model of $G_1 \rightarrow S$ transition of cell cycle on the basis of the above mentioned dynamic model. The model is realized by the Gillespie algorithm of stochastic simulation using the Matlab 7.0 and FORTRAN 95. Scaling factor converts the normalized concentration of the dynamic model to the number of molecules of the stochastic model. The increase of scaling factor is related to the increasing number of the molecules of *CycE*, inactive *CycE/CDK2* complex, active *CycE/CDK2* complex, and mono and dephosphorylated *CDC25*. Solutions of this model show limit cycle depending on the time. When scaling factor is small the solution shows drastic random fluctuations. The solutions of the stochastic model is approached to the solutions of dynamic model, especially, when the scaling factor is more than two hundred (Ω=200). In this case, fluctuations of periods of limit cycle are stabilized.

Key words: Cell cycle, regulator proteins of cell cycle, stochastic model, Gillespie algorithm

1. INTRODUCTION

Cell division is conducted by four stages. In each stage there is a fine coordination. Stages are carried out in strict sequence, when one stage finishes the other one starts, it is the law (1). When molecular reaction occurs, the process of cell division is coordinated. In this coordination molecular unknown have stochastic symptom of which reaction occurs (2). In one cell there are 10^4 ferments and these come through more than 2000 various reactions into catalyzing. Nowadays more than 5600 ferments is known. Dynamic model of cell division is expressed by differential equation system of protein concentration change. In general it is impossible to reveal influence of unexpected factor of nature by dynamic model. In other words position of material point and speed are known at certain time, further movement of that point is defined by differential equation with one meaning. For example: if we see the movement of bullet which is shooting, its way may be different for each shooting, because many factors such as the first speed of bullet, wind direction, air, wet influences it. Therefore by the outer and inner there are many unexpected factors such as influence of condition of cell division protein concentration which takes part in cell division is different at each time and minute. Therefore roe aimed at transmitting dynamic model to stochastic model from G_1 stage to S stage of cell division cycle and to do simulation of mammals. Stochastic model of cell division $G_1 \rightarrow$S stage was shown in Figure 1. In each stage of cell division one complex proteins participate in these proteins called Cyclin and *CDK* ferment are involved. *CDK* has comparatively constant concentration in the period of cycle. But Cyclin is formed before that stage and come untied at the end of the stage. Cyclin is connected with *CDK* and activates in the phosphorisation of the proteins which are participated in the cycle. Far this model CDK protein is *CDK2* (3). *CDK* activity is controlled by Cyclin synthesis and degradation. In this figure 1 shown the $G_1 \rightarrow$S transition dynamic model scheme (4).

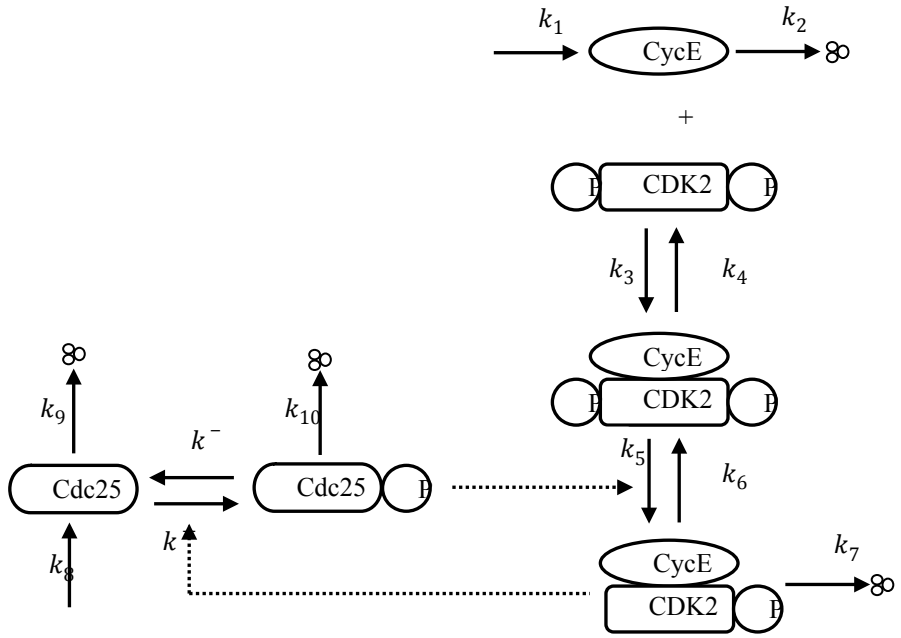

Figure 1. G1→S transition dynamic model scheme

k_1-to synthesize free CycE, k_2-to untied CycE, k_3-CycE protein connected with CDK2 and formed inactive CycE/CDK2 pair of protein, k_4-is inactive CycE/CDK2 pair is div separated as CycE protein and CDK2 protein, k_5-inactive CycE/CDK2 pair protein and formed active pair protein, k_6 active CycE/CDK2 pair protein becomes inactive, k_7-active CycE/CDK2 pair protein is untied, k_8-Cdc25 protein synthesized, k_9 Cdc25 protein untied, k_{10}-Cdc25 protein with phosphate unties, k_Z^+-Cdc25 protein is phosphate, k_Z^--Cdc25 protein without phosphate, these are Constance of reaction.

Here, constant volume system is $x=(x_1,\ldots,x_N)$ condition consists of N part these parts have possibility of conducting R_1 number reaction between each other (5). In *CycE* cell, inactive *CycE/CDK2* pair protein, active *CycE/CDK2* pair protein, *Cdc25* without phosphate, *Cdc25* with one or two phosphate they have possibility of conducting 14 types of reaction between each other. A calculates probability of these reactions. Reactions and probability of each reaction is shown by the following tables (Table 1, Table 2).

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Table 1. Probability of each reaction

Number of reaction	Reaction	Reaction probability - $a_\mu = c_\mu \cdot h_\mu$
1	$0 \rightarrow CycE$	c_1*Ω
2	$CycE \rightarrow 0$	$c_2 * CycE$
3	$CycE \rightarrow (CycE/CDK2)PP$	$c_3 * CycE$
4	$(CycE/CDK2)PP \rightarrow CycE$	$c_4 * (CycE/CDK2)\mathrm{PP}$
5	$(CycE/CDK2)PP \rightarrow (CycE/CDK2)P$	$\left(c_5 + \frac{(Cdc25)\mathrm{PP}}{\Omega}\right) * (CycE/CDK2)PP$
6	$(CycE/CDK2)P \rightarrow (CycE/CDK2)PP$	$c_6 * (CycE/CDK2)P$
7	$(CycE/CDK2)P \rightarrow 0$	$c_7 * (CycE/CDK2)P$
8	$0 \rightarrow Cdc25$	c_8*Ω
9	$Cdc25 \rightarrow 0$	$c_9 * (Cdc25)P$
10	$(Cdc25)PP \rightarrow 0$	$c_{10} * (Cdc25)PP$
11	$Cdc25 \rightarrow (Cdc25)P$	$\left(1 + 1 * \frac{(CycE/CDK2)\mathrm{P}}{\Omega}\right) * Cdc25$
12	$(Cdc25)P \rightarrow Cdc25$	$c_{11} * (Cdc25)P$

13	*(Cdc25)P* $\rightarrow$ *(Cdc25)PP*	$\left(1+1*\frac{(CycE/CDK2)\mathrm{P}}{\Omega}\right)*(Cdc25)P$
14	*(Cdc25)PP* $\rightarrow$ *(Cdc25)P*	$c_{12}*(Cdc25)PP$

Table 2. Correlation of rate constant, *k* and stochastic constant, *c*

Number	*Reaction type*	*Correlation of rate constant, k and stochastic constant, c*
1	$s_1+s_2\rightarrow s_3$	$\frac{k}{\Omega}$
2	$s_1\rightarrow 0$	k
3	$0\rightarrow s_1$	$k*\Omega$

In Table 3 is multiplicand of parameter which converts concentration of dynamic model into molecular number of stochastic model (5-8).

Table 3. Meaning of stochastic constant and meaning of the first action of protein molecule

Number	***c- stochastic constant***	***Number***	***c- stochastic constant***	***The first meaning of protein molecule***
1	$c_1=200$	7	$c_7=7$	*CycE(0)=1*
2	$c_2=1$	8	$c_8=100$	*CycE/CDK2P(0)=1*
3	$c_3=50$	9	$c_9=1$	*CycE/CDK2PP(0)=1*
4	$c_4=50$	10	$c_{10}=0$	*Cdc25(0)=1*
5	$c_5=0.1$	11	$c_{11}=100$	*Cdc25P(0)=1*
6	$c_6=1$	12	$c_{12}=100$	*Cdc25PP(0)=1*

2. MATERIALS AND METHODS

2.1. Gillespie Algorithm

Determine the Gillespie algorithm state means to find \set\ a next reaction time and which reaction will take place. Reaction probability R_μ with endless low time interval *(t+τ, t+τ+dτ)* in *X* state at *t* moment:

$$P(\mu,\tau)=a_\mu e^{-S_M\cdot\tau}, \qquad S_M=\sum_{\mu=1}^{M}a_\mu$$

From this the next reaction time τ :

$$\tau=-\frac{1}{S_M}\ln r_1$$

The next reaction time is determined by random number - r_1 and accumulative S_M. Monte Carlo is a method to set the realization of random process by random numbers. If mark the probability of 14 reactions on S line with the meaning [0, 1]:

$S_1=a_1$
$S_2=a_1+a_2$
$S_3=a_1+a_2+a_3$
…
$S_M=\sum_{\mu=1}^{M}a_\mu$

S_1, S_2, S_3 … S_M are accumulative probability. Reaction number μ will be chosen in case of the falling random number r_2, located on line S, on the interval [$S_{\mu-1}$, S_μ]

Finally, the type of reaction is determined by generating a second random number r_2 in the unit interval. Then the type of reaction that occurs at time τ corresponds to that value of which μ satisfies the inequality

$$\sum_{j=1}^{\mu-1}a_j\le r_2*S_M<\sum_{j=1}^{\mu}a_j$$

In other words the reaction number is found by random numbers and accumulative probabilities.

Steps of Gillespie algorithm:
I step: Find the first meaning
-Initialize the concentration of molecule at t=0

II step: Find probability of each and all possible reactions.
$a_\mu=h_\mu\cdot c_\mu \qquad \mu=1,....M.$
h_μ- The protein molecule of the μ□ reaction (Table-1), c_μ - stochastic constant □μ.

$$S_M=\sum_{\mu=1}^{M}a_\mu$$

S_M- Accumulative probability.

III step: Find what reaction will take place after what time interval will use the random numbers r_1, r_2

$$\tau=\frac{1}{S_M}\ln\left(\frac{1}{r_1}\right)=-\frac{1}{S_M}\ln r_1$$

$$\sum_{j=1}^{M-1}a_j\le r_2\cdot S_M<\sum_{j=1}^{M}a_j$$

IV step:

-Find the changing of the molecule number by the reaction R_μ

$$X \leftarrow X + \alpha_{\mu,j}$$

$\alpha_{\mu,j}$- changed state vector.

$\alpha_{\mu,j}$=[1 0 0 0 0 0
-1 0 0 0 0 0
-1 0 1 0 0 0
1 0 -1 0 0 0
0 1 -1 0 0 0
0 -1 1 0 0 0
0 -1 0 0 0 0
0 0 0 1 0 0
0 0 0 -1 0 0
0 0 0 0 0 -1
0 0 0 -1 1 0
0 0 0 1 -1 0
0 0 0 0 -1 1
0 0 0 0 1 -1]

-Compute adding the next reaction time. $t = t + \tau$

-Transfer to II step.

We code this 4 steps algorithm using the Matlab 7.0, FORTRAN 95 software.

3. RESULTS AND DISCUSSION

In accordance with this study we have the molecule number changing with phased solution of the stochastic model proteins such as *CycE*, inactive *CycE/CDK2* complex, active *CycE/CDK2* complex, and mono and dephosphorylated *Cdc25*, on the transition stage S. The active *CycE/CDK2* complex and free CycE proteins changing was shown in the Figure 1. The grading scale factors were in figure 1: Ω=1(A); Ω=10 (B); Ω=50(C); Ω=200(D). Resolutions were calculated in first meaning of proteins molecule, *CycE* and *CycE/CDK2P*, and other stochastic constants ($c_1 \ldots . c_{12}$). It is presented in Table 3. According to the resolution the cell successfully past the stage G_1 and ready to the stage S when the number of *CycE* molecules were gone down when it reached the maximum meaning whereas *CycE/CDK2P* protein molecule number had direct rising and reach maximum point. Maximum meanings have their randomized meanings. (Fig. A, B) Molecules numbers are constantly changed as the Ω parameters ups. (Fig. C, D). It approves that random factor is decreasing. Figure 3 have showed proteins phase, *CycE* active *CycE/CDK2P*. Figure 2.A shows that if the meaning of Ω goes up the diagram filling goes down. A parameter increases phase diagram filling is decreasing. (Fig 3 B, C, D).

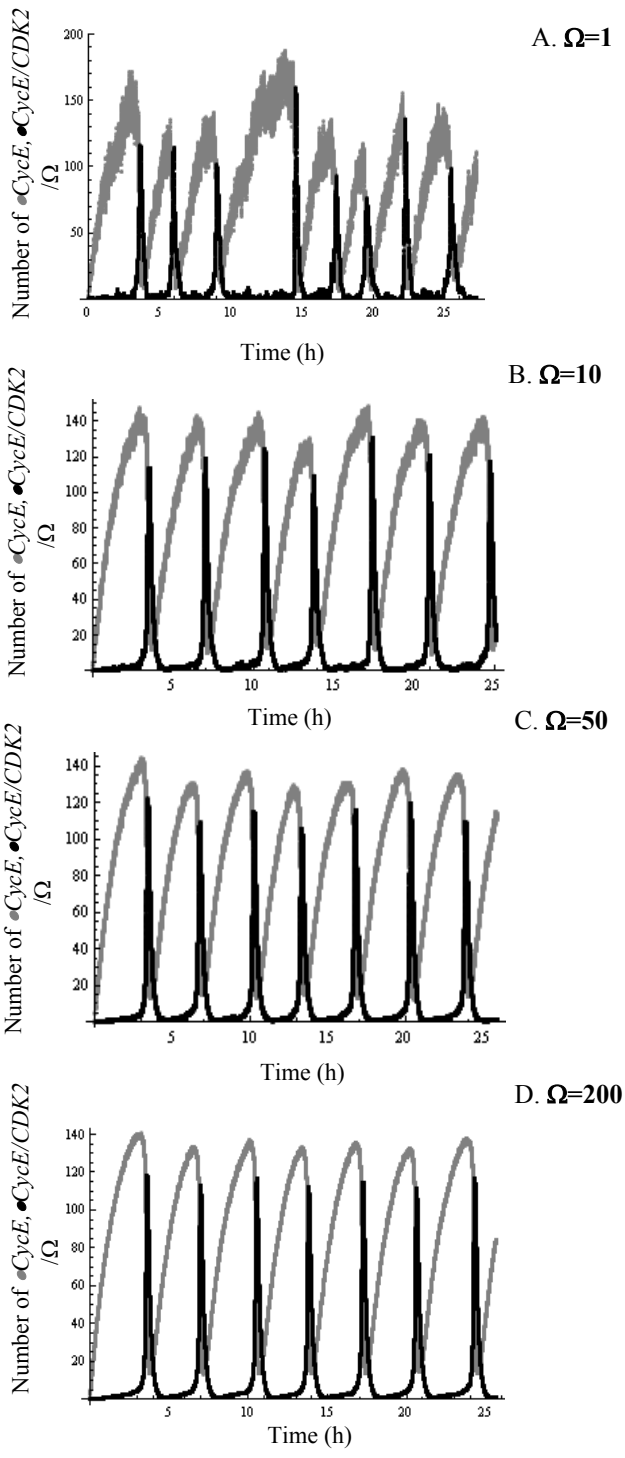

Figure 2. Change of number of *CycE* and active *CycE/CDK2P*

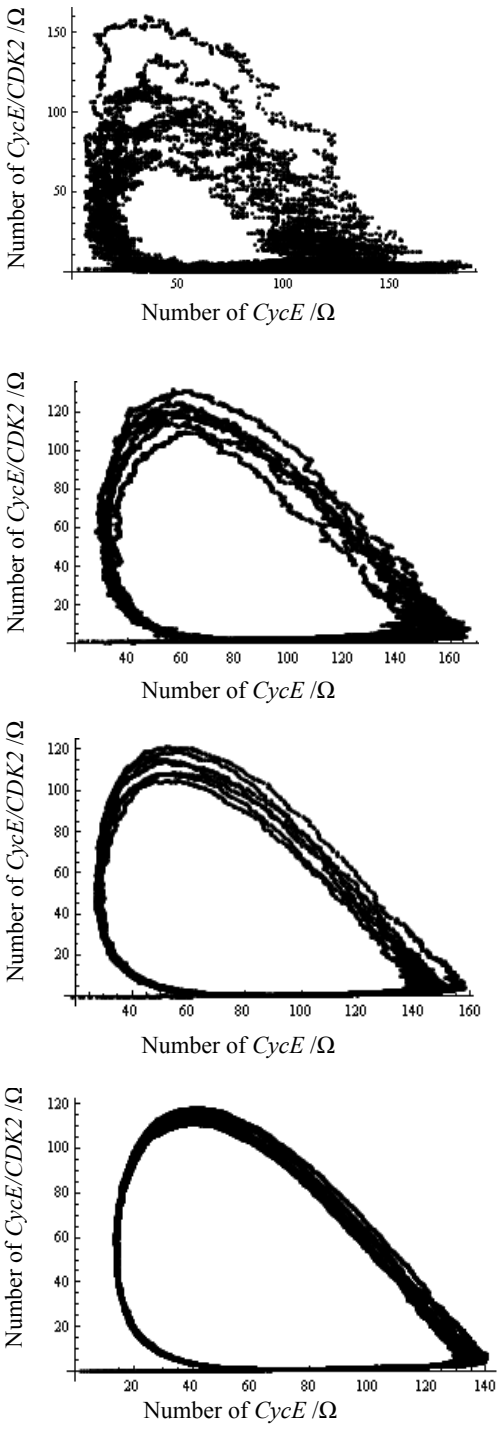

Figure 3. Phase diagram of *CycE* and *CycE/CDK2*

4. CONCLUSION

The stochastic model of $G_1 \rightarrow S$ transition of cell cycle and the model have been simulated by the Gillespie algorithm. The influences of random factors were high when the scaling factor was Ω=1. As the scaling factor rises the random factors' influences go down. Specially, the concordance of the stochastic and dynamic models' solutions were marked when the scaling factor was Ω=200.

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AUTHORS CONTRIBUTION

This work was carried out in collaboration among all

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CONFLICT OF INTEREST

The authors declared no potential conflicts of interests with respect to the authorship and/or publication of this article.

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