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Stochastic Simulation of *P53, MDM2* Interaction

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ABSTRACT

It is vital to get the daughter cell with complete genetic information during the cell division. The cell has the DNA damage check and repairing mechanisms; and proteins, *P53 and MDM2*, play important role in these mechanisms. If there found any DNA damages the cell cycle should be stopped for a while to repair. If the damage cannot repair the P53 (*P53*, tumor suppressor), *MDM2* (Mouse Double Minute) proteins regulation failed and develops cancer. We purposed to study the P53-MDM2 interaction stochastic model and its regulation mechanisms of the eukaryote cell with the DNA damage. There are totally 10 reactions between *P53, MDM2*. We wrote down the propensities and construct the 4x10 type changing matrix. The simulation model was computed on MATLAB 7, FORTRAN 95 programs by four-step Gillespie algorithm.

INTRODUCTION

DNA is a nucleic acid that contains most of the genetic instructions needed for the all known live organisms' growth, development, functioning and reproduction.

MDM2 protein intensifies the *P53* degradation and regulates p53 protein level down [1-3].

DNA damage is mainly caused by stresses like ultraviolet gamma rays, heating, chemical reactions and oxygen deficiency [4].

The inverse correlation between *P53 and MDM2* regulates the cellular senescence, cell cycle arrest and apoptosis and DNA damage repairing processes in response to DNA damage, hypoxia and nutrition deprivation [5-7].

In 60 % of tumor, cases were revealed p53 protein mutation[8]. Under the mutation, the non-functioning p53 proteins are synthesized, and the cells with damaged DNA begin to uncontrolled multiple forming the tumor [9].

The DNA damage causes the *MDM2 and P53* proteins interaction: the MDM2 downregulating process.

MDM2 inactiveness leads to the death of mice fetus, it means that if there is no *MDM2* protein regulation the *P53* protein getting more causing the tumor. [10, 11]. In other hand, the high level *MDM2* protein suppresses the *P53* and form the tumor too [12].

The DNA damage induces the P53 protein through the *Chk1* (Chk1, Checkpoint kinase 1), *Chk2* (Chk2, Checkpoint kinase 2), *ATM* (ATM, Ataxia Telangiectasia Mutated), *ATR* (AtaxiaTelangiectasia). Alongside it P53 protein activation is regulated by the interaction of *P53* and *MDM2*. Activated *P53* is main regulating agent to generate the cellular senescence, cell cycle arrest, and apoptosis selecting and activating the transcriptions *P21, Bax, P48*[4]. Thus it is not only theoretically, but practically important to understand and explain the *P53, MDM2* proteins interactions

In the framework of the study purpose to express the *P53 and MDM2* proteins interactions' stochastic and regulation models we aimed to get the codes by the Gillespie algorithm.

MATERIALS AND METHODS

Eukaryote cell is any organism whose 10-100 mkm diameter cells contain a nucleus and organelles enclosed within membranes [13]. It contains DNA that has inherited and protein synthesis information, and variety of proteins, ferments, nutrition substances and ions.

Modeling process:

- Based on experimental and stochastic model studies we wrote the reaction equitation using the law of mass action. [14].

- All proteins' first meaning was expressed by 1. The reaction speed constants were selected by comparing other models with reactions constants [4].

- The stochastic model computed on MATLAB 7, FORTRAN 95 programs by four-step Gillespie algorithm. [15-18].

In stochastic model, state/constant space is transited from N to deterministic system $S=(S_1, ..., S_N)$. And there is possible to have the reaction R_μ. The system state is expressed by the number of molecules. It can be different depending on the moments of certain reactions.

The reaction is determined by the reaction probability (probability per unit time) [19].

R_μ Equation probability in state S at t moment in less unlimited interval $(t+\tau, t+\tau+d\tau)$:

$$P(\mu,\tau)d\tau = a_\mu e^{-a^*\cdot\tau}d\tau \qquad (2.1)$$

During this time there is possible to have one of the M numbers of reactions:

$$a^* = \sum_{\mu=1}^{M} a_\mu \ (2.2)$$

a_μ- μ Probability of possible reaction. a^*- Total probability. Find randomly r_1 times the next reaction time interval τ.

$$\tau = -\frac{1}{a^*} lnr_1 (2.3)$$

The μ reaction probability in the given time interval τ:

$$P^2(\mu|\tau) = \frac{P(\mu,\tau)}{P(\tau)} = \frac{a_\mu}{a^*} (2.4)$$

Determine the reaction that probably to hold randomly r_2.

$$\sum_{j=1}^{\mu-1} \frac{a_j}{a^*} \leq r_2 < \sum_{j=1}^{\mu} \frac{a_j}{a^*} \qquad (2.5)$$

RESULTS

Reaction:	**Probabilities of the above mentioned reactions:**	**Explanation:**
$\emptyset \xrightarrow{\sigma} P53$	$a_1 = \sigma \cdot \Omega$	*P53* protein synthesis
$P53 \xrightarrow{\alpha} \emptyset$	$a_2 = \alpha \cdot n_{P53}$	*P53* protein degradation
$P53 + MDM2 \xrightarrow{k_f} P53/MDM2$	$a_3 = \frac{k_f}{\Omega} \cdot n_{P53}$	*53* and *MDM2* proteins are reacted and form the pair *P53/MDM2*
$P53/MDM2 \xrightarrow{k_b} P53 + MDM2$	$a_4 = \frac{k_b}{\Omega} \cdot C$	Bifurcation of pair *P53/MDM2* into *MDM2, P53*
$\emptyset \xrightarrow{C \cdot \gamma} P53$	$a_5 = C \cdot \gamma \cdot \Omega$	Synthesize pair *P53/MDM2* with *P53 protein*
$P53 \xrightarrow{k_t \cdot n_{P53}} mdm2$	$a_6 = k_t \cdot n_{P53} \cdot \Omega$	*mdm2, mRNA* transcription
$mdm2 \xrightarrow{\beta} \emptyset$	$a_7 = \beta \cdot n_{Mdm2}$	*mdm2,mRNA* transcription degradation constant
$\emptyset \xrightarrow{C \cdot \delta} MDM2$	$a_8 = C \cdot \delta \cdot \Omega$	*P53/MDM2* synthesize the protein *MDM2*
$mdm2 \xrightarrow{n_{Mdm2} \cdot k_{tl}} MDM2$	$a_9 = n_{Mdm2} \cdot k_{tl} \cdot \Omega$	*MDM2* translation
$MDM2 \xrightarrow{\gamma} \emptyset$	$a_{10} = \gamma \cdot n_{MDM2}$	*MDM2* degradation

The *P53, MDM2* pair of proteins is noted *C*.

The matrix of the DNA damaged *P53, MDM2* molecules behavior changing is showed in table 1.

Table 1. Matrix of behavior

Reactions	n_{P53}	n_{MDM2}	n_{Mdm2}	n_C
1	1	0	0	0
2	-1	-1	0	1
3	1	0	0	-1
4	1	1	0	-1
5	0	1	0	-1
6	0	0	1	0
7	-1	0	0	0
8	0	1	0	0
9	0	0	-1	0
10	0	-1	0	0

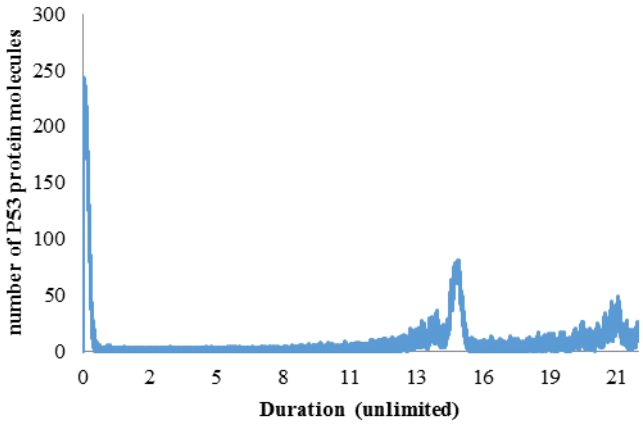

Figure 1. P53 protein molecules changing in number.

$$Firts\ quantity\ meaning\ for\ n_{mdm2}\ n_{P53}, n_{MDM2}\ is\ 1,$$
$$\beta = 0.6, \alpha = 0.1, \gamma = 0.2, \delta = 11, \sigma = 1000, k_t = 0.03, k_{tl} = 1.4, k_b = 7200, k_f = 4067.8$$

The reaction and its duration are defined using the four-step Gillespie algorithm and were coded by the FORTRAN 95 (**Figure 1**). In figure 4 there is shown the changing of P53 protein molecules number.

Figure 1. According to the simulation model, the molecules number changing was similar to dynamic model. But the dynamics were different. However, the stochastic model, the molecules maximum meaning and duration, differed from the dynamic model.

CONCLUSION

1. We made *P53, MDM2* proteins interaction stochastic model. For this model, we wrote 10 interaction equations and probabilities of each equation.

2. We construct *P53, MDM2* proteins behavior changing matrix. According to the four-step Gillespie algorithm, we coded on program Fortran 95, the number of *P53* molecules was different in every second. It means the stochastic model is more realistic/ reasonable than the dynamic one.

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