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On the Conditions of Hopf Bifurcation for ATM Protein and DNA Damage Signal Model; Cuts off the DNA Healing Process

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Abstract

In this paper, we consider some available models and then introduce a model which simulates the interaction between ATM protein and DNA damage signal, which motivated biologically. Next we find a Hopf bifurcation for this system. Biologically we find a region for the DNA damage signal and ATM protein where solutions in this region are not of those solutions that DNA healing process occurs on these. In fact entering solutions in this region aren't biologically appropriate solutions.

Keywords: Hopf bifurcation; ATM protein; damage signal; limit cycle.
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1 Introduction

Once a DNA damage occurs, the damage signal begins to scintillate and then the level of ATM-p, activated ATM, increases in a cell, which in turn activates some proteins which are interfered in DNA repair, by phosphorylating these proteins. One of these proteins is p53, which play a very important role in DNA repairing process, such that p53 is called the tumor suppressor protein [1].

In normal cells p53 protein usually maintains at a low level and has a short half-life due to the degradation by ubiquitination and proteolysis [2]. The inhibitor is Mdm2 protein, in fact Mdm2 is a p53 binding protein that possesses potent inhibitory effects on p53 transcription [3].

Indeed, when a cell is stressed by DNA damage signal, such as ionizing radiation (IR), ATM will add phosphate group to p53. Thus the p53 level will be raised and activated to perform its major functions [2]. All the above introductions can be summarized in Figure 1 [2].

When DNA damage is repaired, ATM cannot phosphorylate p53, then the network of transcription is shut down. ATM shows switch characteristics for p53 network [4]. In fact the ATM kinase exhibits bistable switch-like behavior. The network dynamics essentially consists of the core p53 oscillator, which is turned ON/OFF by the ATM switch, which is in turn activated by DNA damage [5]. Experimental

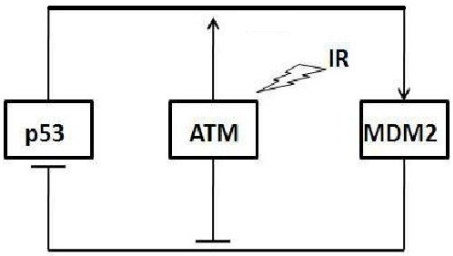

Figure 1: Schematic diagram to illustrate p53, Mdm2 and ATM core regulation. Arrows represents activation, while arrow-bar means inhibition. IR is short for ionizing radiation.

observations show that the amount of ATM and ATM-p holds for the conservative equation $[ATM](t)+[ATM-p](t) = \mu$, for a positive real constant μ. Also, they are in a reaction for which the phosphorylated form ATM-p promotes further phosphorylation of ATM, hence, once a small amount of ATM-p is produced, it leads to further increase in ATM-p, until all the ATM is converted into its phosphorylated form. This should happen only when a significant DNA damage occurs.

Upon DNA damage, ATM-p accumulates rapidly in the nucleus [6]. We assume that the effect of ionizing radiation is to reduce the ability of phosphatases to bind ATM. The preceding discussion motivates a simple model for ATM into which is built a positive feedback loop wherein the phosphorylated form of ATM-p promotes further phosphorylation of ATM. Hence once a small amount of ATM-p is produced, it leads to further increase in ATM-p, until all the ATM is converted into its phosphorylated form. This process can be modeled by the following equation [5]

$$z' = \alpha_{1s}\frac{z(\mu - z)}{k_{1s} + \mu - z} + \alpha_{2s}\frac{z}{(k_{0d} + w)(k_{2s} + z)}.$$

Where $z(t)$ is the level of ATM-p and $w(t)$ simulates DNA damage signal, the first term of the above equation, with coefficient α_{1s} and the second term, with coefficient α_{2s} show phosphorylation and dephosphorization rates of ATM protein, respectively. The parameter k_{1s} controls dependence of dephosphorization rate of ATM protein to the level of ATM. Similarly, parameters k_{2s} and k_{0d} control dependence of dephosphorylation rate of ATM protein to the level of ATM-p and damage signal, respectively.

$$\begin{cases} z^{'} = \alpha_{1s}\frac{z(\mu-z)}{k_{1s}+\mu-z} + \alpha_{2s}\frac{z}{(k_{0d}+w)(k_{2s}+z)} \\ w^{'} = IR - az + bw - \alpha_d wz. \end{cases} \tag{1.1}$$

The second equation describes damage generated due to ionizing radiation IR. Here α_d is the rate of repair in dimensionless unites. On the other hand, when the stress signal is withdraw, it is assumed that the repair of DNA damage will follow the process below [2].

$$w' = -az + bw - \alpha_d wz.$$

DNA damage is induced by exposure to stress and has a negative influence on the level of nuclear Mdm2, by accelerating its degradation through ATM-mediated phosphorylation and auto-ubiquitination [7]. This damage-induced Mdm2 destabilization enables p53 to accumulate and remain active which enhance the level of damage signal.

There is so many woks on Hopf bifurcation [8], [9]. Now for following our main previous works [10] here we show that Hopf bifurcation occurs in some points of system.

2 Results and Discussion

Here there is the following theorem as the main theorem.

Theorem 2.1. (Main Theorem) *For any θ, let $(z(\theta), w(\theta))$ be a fixed point of system (1.1), there is a curve such as $\nu(\theta)$ such that in system (1.1) Hopf bifurcation occurs for all θ on this curve. Thus on this curve DNA healing process does not occur and so permanence damage.*

2.1 Proof of Main Theorem

We can write system (1.1) as the following

$$\begin{cases} z^{'} = zh(z,w) \\ w^{'} = IR - az + bw - \alpha_d wz \end{cases} \tag{2.1}$$

where

$$h(z,w) = \alpha_{1s}\frac{(\mu-z)}{k_1-z} + \alpha_{2s}\frac{1}{(k_{0d}+w)(k_{2s}+z)}$$

and $k_1 = k_{1s} + \mu$. For finding fixed points of system (2.1) we must solve equation $z^{'} = zh(z,w) = 0$, so by implicit function theorem, there exists a map

$$w = \varphi(z) = \theta_2 z^2 + \theta_1 z + \theta \tag{2.2}$$

such that $h(z, \varphi(z)) = 0$, and thus $h(0, \varphi(0)) = 0$, so

$$\frac{\partial h}{\partial z}(0,\varphi(0)) + \frac{\partial h}{\partial w}(0,\varphi(0))\varphi'(0) = 0$$

and also

$$\frac{\partial^2 h}{\partial z^2}(0,\varphi(0)) + 2\frac{\partial^2 h}{\partial z \partial w}(0,\varphi(0)).\varphi'(0) + \frac{\partial^2 h}{\partial w^2}(0,\varphi(0))(\varphi'(0))^2 + \frac{\partial h}{\partial w}(0,\varphi(0))\varphi''(0) = 0.$$

Thus

$$\begin{aligned} \theta &= -\mu k_{0d} k_{2s} \alpha_{1s} - k_{1s} \alpha_{2s} \\ \theta_2 &= k_{0d} \alpha_{1s}, \\ \theta_1 &= -\mu k_{0d} \alpha_{1s} + k_{0d} k_{2s} \alpha_{1s}. \end{aligned} \tag{2.3}$$

Moreover from $w^{'} = L(z, \theta) = IR - az - \alpha_d wz + bw = 0$, by implicit function theorem, there exists a map $z(\theta)$ such that $L(z(\theta), \theta) = 0$. First we solve equation (2.3) with respect to μ, then put its solution in two other equations of (2.3), finally by (2.2) we have

$$\theta_2 = k_{0d}\alpha_{1s}, \qquad \theta_1 = k_{0d}k_{2s}\alpha_{1s} + \alpha_{2s} + \frac{\theta + k_{1s}\alpha_{2s}}{k_{2s}}.$$

$\theta = 0$ happen when $\alpha_{1s} = \alpha_{2s} = 0$. This implies that

$$z(\theta) = -b/a\theta + \frac{zb(b - k_{2s}\alpha_d)}{a^2 k_{2s}}\theta^2 + o(\theta^3),$$

so by (2.2) we have

$$\begin{aligned} w(\theta) &= \theta\Big(1 - \frac{bk_{0d}k_{2s}\alpha_{1s} - b\alpha_{2s}}{a} - \frac{bk_1\alpha_{2s}}{ak_{2s}}\Big) \\ &+ \theta^2\Big(\frac{-bak_{2s} + b^2k_{2s}^2k_{0d}\alpha_{1s}}{a^2k_{2s}} \\ &+ \frac{(2bk_{2s}^2k_0\alpha_{1s} + 2bk_1\alpha_{2s} + 2b\alpha_{2s}k_{2s})(b - k_{2s}\alpha_d)}{a^2k_{2s}}\Big). \end{aligned}$$

It is easy to see that the matrix of linear part of system at this critical point has one zero eigenvalue, so the system has a one dimensional center manifold.

Now we suppose that

$$T(\theta) = a_0 + a_1\theta + a_2\theta^2 + o(\theta^3),$$
$$\Delta(\theta) = b_0 + b_1\theta + b_2\theta^2 + o(\theta^3)$$

and

$$\lambda(\theta) = c_0 + c_1\theta + c_2\theta^2 + o(\theta^3),$$

in this notations the characteristic polynomial is

$$\Lambda(\theta) = \lambda(\theta)^2 - T(\theta)\lambda(\theta) + \Delta(\theta).$$

And thus $Re(\lambda(\theta)) = 1/2(T(\theta))$. Put $t(a_0, \theta) = a_0 + a_1\theta + a_2\theta^2$ since $t(0,0) = 0$ and $\frac{\partial t}{\partial \theta}(0,0) = a_1 \neq 0$, so by implicit function theorem there exists a map $\nu(\theta)$ such that $t(\nu(\theta), \theta) = 0$ and so $Re(\lambda(\theta)) = 0$ on $a_0 = \nu(\theta)$. Thus Hopf bifurcation occurs on the curve $a_0 = \nu(\theta)$.

Also the origin is another critical point; the linear part of system at the origin is as the following

$$\begin{pmatrix} h(0,0) & z\frac{\partial h}{\partial w}(0,0) \\ -a & b \end{pmatrix} = \begin{pmatrix} \frac{\alpha_{1s}\mu}{k_1} + \frac{\alpha_{2s}}{k_{0d}k_{2s}} & -\frac{\alpha_{2s}}{k_{0d}^2k_{2s}} \\ -a & b \end{pmatrix}$$

Remark 2.1. Note that by theorem 20.2.3 in [11] a necessary condition for occurring Hopf bifurcation in a system is that $dRe\lambda(\mu)/d\mu \mid_{\mu=0} \neq 0$ where μ is the parameter of system. If we consider $\alpha_{1s}, k_{0d}, k_{2s}, \alpha_d$ as parameters of system then system (2.1) transform to the following system

$$\begin{cases} z^{'} = zh(z, w, \delta, \eta, \nu, \beta) \\ w^{'} = IR - az + bw - (\alpha_d + \epsilon)wz \end{cases} \tag{2.4}$$

where

$$h(z,w,\delta,\eta,\nu,\beta)=\frac{(\alpha_{1s}+\delta)(\mu-z)}{k_1+\eta-z}+\frac{\alpha_{2s}}{(k_{0d}+\nu+w)(k_{2s}+\beta+z)}.$$

For this system

$$Re(\lambda)=\frac{1}{2ak_{2d}}\Big(-b\epsilon\theta^2+k_{2d}(a-a^2+\epsilon w+\epsilon\theta)+\alpha_d(b\theta^2-a(w+\theta)k_{2d})\Big)$$

so α_d can be the only parameter of Hopf bifurcation.

3 Conclusions

If we consider the origin as fixed point of system (1.1) then

$$\lambda=1/2\Big(-a\pm\sqrt{a^2+\frac{4b\mu\alpha_1}{\mu+k_1}+\frac{4b\alpha_2}{k_0k_2}}\Big)$$

and since $a>0$ then the origin is of saddle type. Thus that solutions those attracted to the origin are acceptable for DNA healing.

But on curve $\nu(\theta)$ system (1.1) may have some limit cycle. Thus the healing zone is the outside region of this limit cycle. Therefore for achieving DNA healing process we must choose parameters of system (1.1) such that the solution be out of the interior of that limit cycles.

Competing Interests

The authors declare that no competing interests exist.

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