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The Affection of L-D Cycle to Complicated Drosophila Circadian Oscillation

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Abstract: In most organisms, the circadian oscillation existed. The circadian oscillation of drosophila is about 24 hours, with the analysis of drosophila 10 dimensional model, and the linear method to prove the existence of equilibrium point and the stability. Moreover, the condition of stability is obtained.The stability of the drosophila under the L-D cycle was also analyzed by using the perturbation theory. The numerical simulation results demonstrate the veracity of the condition obtained.

Key words: circadian oscillation; stability; perturbation theory

1 Introduction

In most organisms, from mammals to fungi and even some prokaryotes, the circadian oscillation is about 24 hours, which was decided by the clock genes in organisms [1, 2, 3]. The circadian oscillations of organisms are not only decided by the clock genes in the organisms, but also the environment, such as temperature, humidity, light and so on. To date, the research has proved that the light plays the most important part in the cycle of the circadian oscillation.

Over the past decades, many models have been used to describe the circadian oscillation. The Van der Pol model was first used to describe the circadian oscillation of human by Prof. Wever [4] With different organisms, the coefficients of Van der Pol model are different. In 1995, Goldbeter first proposed a five dimensional drosophila model which was based on the per clock genes, but there is no consideration of light and other environmental influences affections. With the development of system biology[5], in 1998, Goldbeter and Leloup proposed a ten dimensional drosophila model which was based on per and tim clock genes. In this model, not only the circadian oscillation was analyzed, but also the phenomena of chaos was proposed under unsymmetrical conditions[6].

With the linear method, the drosophila's ten dimensional model in this article is analyzed, also the influences of L-D cycle. Firstly, we introduce the ten dimensions of Goldbeter model. Secondly, based on the linear method, the existence and stability of equilibrium point of the drosophila model are analyzed and proved. Finally, with the simulation, the validity of the conclusion is proved.

2 Goldbeter drosophila model

The drosophila ten dimensional model is shown in Fig.1, in which M_p and M_T denote the cytosolic concentration of per messenger and tim messenger.P_0,P_1,P_2,T_0,T_1 and T_2 denote the degree of per and tim messenger phosphorylated. P_0 and T_0 denote the unphosphorylated per and tim messenger, P_1 and T_1

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denote the monophosphorylated per and tim messenger. P_2 and T_2 denote the bisphosphorylated per and tim messenger. V_{iP} and V_{iT} denote the maximum rates of action(in which $i = 1, 2, 3, 4$). K_{IP} and K_{IT} denotes the Michaelis constant. The rate of synthesis of constants are k_{sP} and k_{sT}. The constants k_d, k_{dC} and k_{dN} denote the linear degradation term, n is the coefficient of Hill function and $n = 4$.

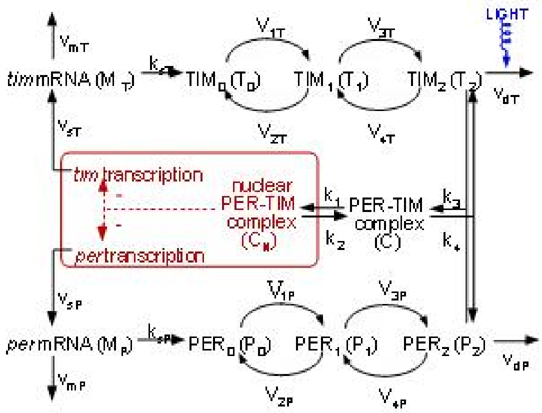

Figure 1: The per-tim drosophila model.

From the drosophila model, we can get the kinetic equations as following[6]:

$$\begin{cases} \frac{dM_p}{dt} = \frac{v_{sP}K_{IP}^n}{K_{IP}^n + C_N^n} - \frac{v_{mP}M_P}{K_{mP}+M_P} - k_dM_P \\ \frac{dP_0}{dt} = k_{sP}M_P - \frac{V_{1P}P_0}{K_{1P}+P_0} + \frac{V_{2P}P_1}{K_{2P}+P_1} - k_dP_0 \\ \frac{dP_1}{dt} = \frac{V_{1P}P_0}{K_{1P}+P_0} - \frac{V_{2P}P_1}{K_{2P}+P_1} - \frac{V_{3P}P_1}{K_{3P}+P_1} + \frac{V_{4P}P_2}{K_{4P}+P_2} - k_dP_1 \\ \frac{dP_2}{dt} = \frac{V_{3P}P_1}{K_{3P}+P_1} - \frac{V_{4P}P_2}{K_{4P}+P_2} - k_3P_2T_2 + k_4C - \frac{v_{dP}P_2}{K_{dP}+P_2} - k_dP_2 \\ \frac{dM_T}{dt} = \frac{v_{sT}K_{IT}^n}{K_{IT}^n + C_N^n} - \frac{v_{mT}M_T}{K_{mT}+M_T} - k_dM_T \\ \frac{dT_0}{dt} = k_{sT}M_T - \frac{V_{1T}T_0}{K_{1T}+T_0} + \frac{V_{2T}T_1}{K_{2T}+T_1} - k_dT_0 \\ \frac{dT_1}{dt} = \frac{V_{1T}T_0}{K_{1T}+T_0} - \frac{V_{2T}T_1}{K_{2T}+T_1} - \frac{V_{3T}T_1}{K_{3T}+T_1} + \frac{V_{4T}T_2}{K_{4T}+T_2} - k_dT_1 \\ \frac{dT_2}{dt} = \frac{V_{3T}T_1}{K_{3T}+T_1} - \frac{V_{4T}T_2}{K_{4T}+T_2} - k_3P_2T_2 + k_4C - \frac{v_{dT}T_2}{K_{dT}+T_2} - k_dT_2 \\ \frac{dC}{dt} = k_3P_2T_2 - k_4C - k_1C + k_2C_N - k_{dC}C \\ \frac{dC_N}{dt} = k_1C - k_2C_N - k_{dN}C_N \end{cases} \quad (1)$$

The variables of the system are :

$v_{mP} = v_{mT} = 0.7, v_{dP} = v_{dT} = 2, k_{sP} = k_{sT} = 0.9, K_{nT} = K_{mP} = 0.2, K_{IP} = K_{IT} = 1, K_dP = K_dT = 0.2, k_1 = k_4 = 0.6, k_2 = 0.2, k_3 = 1.2, V_{1P} = V_{1T} = 8, V_{2P} = V_{2T} = 1, V_{3P} = V_{3T} = 8, V_{4P} = V_{4T} = 1, K_{1P} = K_{1T} = K_{2P} = K_{2T} = K_{3P} = K_{3T} = K_{4P} = K_{4T} = 2, k_d = k_{dC} = k_{dN} = 0.01.$

3 The existence and stability analysis of equilibrium points of Goldbeter drosophila model

3.1 The existence analysis of equilibrium points

From equation (1) we know, when the per system and tim system are in symmetry, and the variable $V_{iP} = V_{iT}$, $K_{iP} = K_{iT}$, $v_{iP} = v_{iT}$ and $k_d = k_{dc} = k_{dN}$ hold, dropping off the negative part from equation (1) and setting the right side as zero, we can get the follow equations.

$$\frac{v_{sP}K_{IP}^n}{K_{IP}^n + C_N^n} - \frac{v_{mP}M_P}{K_{mP} + M_P} = 0 \quad (2)$$

$$k_{sP}M_P - \frac{V_{1P}P_0}{K_{1P} + P_0} + \frac{V_{2P}P_1}{K_{2P} + P_1} = 0 \quad (3)$$

$$\frac{V_{1P}P_0}{K_{1P} + P_0} - \frac{V_{2P}P_1}{K_{2P} + P_1} - \frac{V_{3P}P_1}{K_{3P} + P_1} + \frac{V_{4P}P_2}{K_{4P} + P_2} = 0 \quad (4)$$

$$\frac{V_{3P}P_1}{K_{3P}+P_1}-\frac{V_{4P}P_2}{K_{4P}+P_2}-k_3P_2T_2+k_4C-\frac{v_{dP}P_2}{K_{dP}+P_2}=0 \tag{5}$$

$$\frac{v_{sT}K_{IT}^n}{K_{IT}^n+C_N^n}-\frac{v_{mT}M_T}{K_{mT}+M_T}=0 \tag{6}$$

$$k_{sT}M_T-\frac{V_{1T}T_0}{K_{1T}+T_0}+\frac{V_{2T}T_1}{K_{2T}+T_1}=0 \tag{7}$$

$$\frac{V_{1T}T_0}{K_{1T}+T_0}-\frac{V_{2T}T_1}{K_{2T}+T_1}-\frac{V_{3T}T_1}{K_{3T}+T_1}+\frac{V_{4T}T_2}{K_{4T}+T_2}=0 \tag{8}$$

$$\frac{V_{3T}T_1}{K_{3T}+T_1}-\frac{V_{4T}T_2}{K_{4T}+T_2}-k_3P_2T_2+k_4C-\frac{v_{dT}T_2}{K_{dT}+T_2}=0 \tag{9}$$

$$k_3P_2T_2-k_4C-k_1C+k_2C_N=0 \tag{10}$$

$$k_1C-k_2C_N=0 \tag{11}$$

Let the equilibrium point of system (2)-(11) is $x_0=(\overline{M}_P,\overline{P}_0,\overline{P}_1,\overline{P}_2,\overline{M}_T,\overline{T}_0,\overline{T}_1,\overline{T}_2,\overline{C},\overline{C}_N)^T$. We can see that the point $(0,0,0,0,0,0,0,0,0,0)^T$ is not the solution of the system(2)-(11). From equation (2) and (6) we can know the following equations hold.

$$\frac{v_{sP}K_{IP}^n}{K_{IP}^n+C_N^n}=\frac{v_{mP}M_P}{K_{mP}+M_P} \tag{12}$$

$$\frac{v_{sT}K_{IT}^n}{K_{IT}^n+C_N^n}=\frac{v_{mT}M_T}{K_{mT}+M_T} \tag{13}$$

From equation (12),(13) and the symmetry of the parameters we get M_P=M_T. So, we can know P_0=T_0,P_1=T_1,P_2=T_2. From the equation(3),(4),(5),(10) and (11) we can know the follow equation hold.

$$M_P=\frac{v_{dP}P_2}{k_{dP}(K_{dP}+P_2)} \tag{14}$$

With equation (11) we know:$k_1C=k_2C_N$, from (10) and $P_2=T_2$ we can get the following equation.

$$P_2^2=k_4C=\frac{k_4k_2C_N}{k_3k_1} \tag{15}$$

So $P_2=\alpha\sqrt{C_N}$,where $\alpha=\frac{k_4k_2}{k_3k_1}$. Substituting equation (14) into the equation (12) we get

$$\frac{v_{sP}K_{IP}^n}{K_{IP}^n+C_N^n}=\frac{v_{mP}\frac{v_{dP}P_2}{k_{dP}(K_{dP}+P_2)}}{K_{mP}+\frac{v_{dP}P_2}{k_{dP}(K_{dP}+P_2)}} \tag{16}$$

Simplify the equation (16) we can get the following equation.

$$v_{sP}K_{IP}^n(K_{mP}k_{sP}K_{dP}+K_{mP}k_{sP}P_2+v_{dP}P_2)=v_{mP}v_{dP}P_2(K_{IP}^n+C_N^n) \tag{17}$$

Setting $v_{sP}K_{IP}^nK_{mP}k_{sP}K_{dP}=\delta$,$v_{sP}K_{IP}^n(K_{mP}k_{sP}+v_dP)-v_{mP}v_{dP}K_{IP}^n=\beta$, $v_{mP}v_{dP}=\gamma$ and then substituting into equation (17), we can get

$$\alpha\gamma C_N^{n+\frac{1}{2}}-\alpha\beta C_N^{\frac{1}{2}}-\delta=0 \tag{18}$$

Proposition 1 *If the condition* $v_{sP}K_{IP}^n(K_{mP}k_{sP}+v_{dP})-v_{mP}v_{dP}K_{IP}^n\geq 0$ *holds, then the drosophila circadian oscillation system (2)-(11) must have an equilibrium point.*

Proof. Assuming $f(C_N) = \alpha\gamma C_N^{n+\frac{1}{2}} - \alpha\beta C_N^{\frac{1}{2}} - \delta$, when $f(\overline{C}_N) = 0$, then we can get $\overline{C}_N^n = \frac{\beta}{(2n+1)\gamma}$, and also the following equation hold.

$$f''(C_N) = [(\frac{2n+1}{2})\alpha\gamma C_N^{n-\frac{1}{2}} - \frac{\alpha\beta}{2} C_N^{-\frac{1}{2}}]' = (\frac{2n+1}{2})(\frac{2n-1}{2})\alpha\gamma C_N^{n-\frac{3}{2}} + \frac{\alpha\beta}{4} C_N^{\frac{3}{2}} \tag{19}$$

It is obvious that when $f'(\overline{C}_N) = 0$, $f''(\overline{C}_N) > 0$. So we can know that the point $\overline{C}_N = [\frac{\beta}{(2n+1)\gamma}]^{\frac{1}{n}}$ and $f(C_N)$ gets the minimum value. Substituting the point $\overline{C}_N$ into $f(C_N)$,then we can get $f(\overline{C}_N) = \overline{C}_N^{\frac{1}{2}}(\frac{\alpha\beta}{2n+1} - \beta) - \delta < 0$. When $C_N > \overline{C}_N$,$f'(C_N) > f'(\overline{C}_N) = 0$, it means $f'(C_N) > 0$, so the function $f(C_N)$ is increasing. In contrast, if $0 < C_N < \overline{C}_N$, then $f'(C_N) < f'(\overline{C}_N) = 0$, which means $f'(C_N) < 0$. So the function $f(C_N)$ is decreasing. For the function $f(0) = -\delta < 0$, the function $f(C_N) = \alpha\gamma C_N^{n+\frac{1}{2}} - \alpha\beta C_N^{\frac{1}{2}} - \delta$ must have the only equilibrium point. □

The system (2)-(11) had the only equilibrium stable point, so with the theory of concealed function the system (1) also had an exclusive equilibrium point. The condition $v_{sP}K_{IP}^n(K_{mP}k_{sP}+v_{dP}) - v_{mP}v_{dP}K_{IP}^n \geq 0$ must hold.

3.2 The stability analysis of equilibrium point

With Proposition 1 and the complex drosophila circadian oscillation model parameters, Proposition 1 holds when $1.09v_{sP} \geq v_{mP}$. From the symmetry, $1.09vsT \geq v_{mT}$ must hold, too.

From Proposition 1, let the equilibrium as $x_0 = (\overline{M}_P, \overline{P}_0, \overline{P}_1, \overline{P}_2, \overline{M}_T, \overline{T}_0, \overline{T}_1, \overline{T}_2, \overline{C}, \overline{C}_N)^T$, and the formation of the system is $\frac{dx}{dt} = f(x)$, where x describes the vectors of the variables, $f(x)$ corresponds to the ten equations in the right hand of system (1). The system had the equilibrium point at x_0, so the system (1) can be unfolded to Taylor series at the point x_0 and the following equation holds.

$$f(x) = A(x - x_0) + \varepsilon B(x) \tag{20}$$

The coefficient $A = f'(x_0)$. ε is a positive number arbitrary. B is a nonlinear term, which is high-rank infinitesimal. So we can get the following equation approximately.

$$\frac{dx}{dt} \approx A(x - x_0) \tag{21}$$

For $1.09v_{sP} \geq v_{mP}$ and $1.09v_{sT} \geq v_{mT}$ hold, the system (1) had the only equilibrium point. Let the parameters $v_{sP} = v_{sT}$ change. With the system parameter $v_{mP} = v_{mT} = 0.7$ we can get the condition $v_{sP} = v_{sT} \geq 0.64$. When $v_{sP} = v_{sT} = 0.80$, the eigenvalues of system (1) are -4.18, -4.03, -2.87,$-2.26, 0.07 \pm 0.35i, -0.06, -1.36 \pm 0.48i, -0.97$. When $v_{sP} = v_{sT} = 0.65$, the eigenvalues of system(1) are -4.41, -4.26, -2.92, -2.47, $-0.02 \pm 0.21i$,-0.07,$-1.38 \pm 0.05i$,-1.23. We can see that there are two group conjugate complex numbers, with the change of $v_{sP} = v_{sT}$ from 0.65 to 0.8. The real part of one conjugate complex number changed from positive to negative, so there exists a Hopf bifurcation. As a result , when parameters $v_{sP} = v_{sT} > 0.65$,the system will be at oscillation state; when $v_{sP} = v_{sT} \leq 0.65$ the system will be at asymptotic stable state.

4 The influence of L-D cycle on the drosophila circadian oscillation

In the environment, the drosophila circadian oscillation is affected by the light[7,8]. With the influence of the light, the clock genes of the drosophila will be changed. Let the variable of L-D cycle as $L(t)$. It can be shown as the following equation.

$$L(t) = L_0 \sin(\frac{2\pi t}{\tau}) \tag{22}$$

So, the drosophila model can be changed into equation (23) under L-D cycle.

$$\frac{dx}{dt} = f(x) + \varepsilon p(t) \tag{23}$$

where $p(t) = (0,0,0,\sin(\frac{\pi t}{12}),0,0,0,\sin(\frac{\pi t}{12}),0,0)^T$, $\varepsilon = L_0$ and $0 < \varepsilon = L_0 < 1$. With the perturbation theory, the solution format of equation (23) can be written in the following way:

$$x = x_0 + \epsilon x_1 + \epsilon^2 x_2 + \epsilon^3 x_3 + \cdots$$

Then unfolding the equation (23) as Taylor series, we can get the following equation.

$$\dot{x_0} + \varepsilon\dot{x_1} + \varepsilon^2\dot{x_2} + \varepsilon^3\dot{(x-3)} + \ldots = f(x_0) + f'(x_0)(\varepsilon x_1 + \varepsilon^2 x_2 + \varepsilon^3 x_3 + \ldots) + f''(x_0)(\varepsilon x_1 + \varepsilon^2 x_2 + \varepsilon^3 x_3 + \ldots)^2 + \ldots + \varepsilon p(t)$$

Since $f(x_0) = 0$, we simplify both sides with the item ε, and the following equations hold.

$$\begin{cases} \varepsilon\dot{x}_1 = f'(x_0)\varepsilon x_1 + \varepsilon p(t) \\ \varepsilon^2\dot{x}_2 = f'(x_0)\varepsilon^2 x_2 + \frac{f''(x_0)}{2!}\varepsilon^2 x_1^2 \\ \ldots \\ \varepsilon^n\dot{x}_n = f'(x_0)\varepsilon^n x_n + g(x_0,x_1,x_2,\ldots,x_{n-1})\varepsilon^n \end{cases} \tag{24}$$

So the equaitons (25),(26)and(27)hold.

$$\dot{x}_1 = Ax_1 + p(t) \tag{25}$$

$$\dot{x}_2 = Ax_2 + \frac{1}{2}x_1^T D^2 f(x_0)x_1 \tag{26}$$

$$\cdots$$

$$\dot{x}_n = Ax_n + g(x_0,x_1,x_2,\ldots,x_n-1) \tag{27}$$

where $A = f'(x_0)$ and $g(x_0,x_1,x_2,\ldots,x_n-1)$ is the polynome of $x_0,x_1,x_2,\ldots,x_n-1$. With equation (25), we can get the following equation hold.

$$\begin{aligned} x_1 &= ce^{At} + e^{At}\int e^{-As}p(s)ds \\ &= ce^{At} - (\frac{1}{A}\sin\frac{\pi t}{12} + \frac{\pi}{12A^2}\cos\frac{\pi t}{12})(1 + (\frac{\pi}{12A})^2)^{-1} \end{aligned} \tag{28}$$

In equation (28), it is obviously that ce^{At} is asymptotic converge to zero, and $(\frac{1}{A}\sin\frac{\pi t}{12} + \frac{\pi}{12A^2}\cos\frac{\pi t}{12})(1 + (\frac{\pi}{12A})^2)^{-1}$ is obviously oscillation periodical. Similarly, $x_2,x_3,\ldots,x_n$ are all oscillation periodically. So we can know that the drosophila circadian oscillation can maintain oscillation under L-D cycle when it is asymptotic stable without L-D cycle.

5 Simulation

When the L-D cycle was not added to the drosophila model, with the parameters in drosophila model and setting $v_{sP} = v_{sT} = 0.8$, the time evolution of M_P is shown at Fig. 2, we can see the system is obviously at oscillation state. When $v_{sP} = v_{sT} = 0.65$, the system is at asymptotic state. When the L-D cycle was added to the system, suppose $0 < \varepsilon = L_0 = 0.5 < 1$, if the parameters $v_{sP} = v_{sT} = 0.8$, then the system will at oscillation state. When the parameters $v_{sP} = v_{sT} = 0.65$, then the system will be also at oscillation state. All the simulations are shown in Fig.2 - Fig.5.

6 Conclusion

With the linear approximately method, the existence and stability of equilibrium point was proved[9]. Under the condition of symmetry and when the condition $v_{sP} = v_{sT} \geq v_c$ is satisfied (v_c is a critical point between 0.65 and 0.8 when the Hopf bifurcation happened), the system will be at oscillation state. If the condition $v_{sP} = v_{sT} \geq v_c$ doesn't hold, the system will be at asymptotic stable state. At last, the L-D cycle

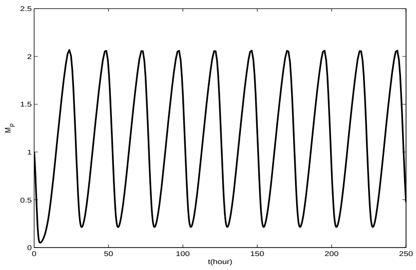

Figure 2: The time evolution of M_P without L-D cycle when $v_{sP} = v_{sT} = 0.8$.

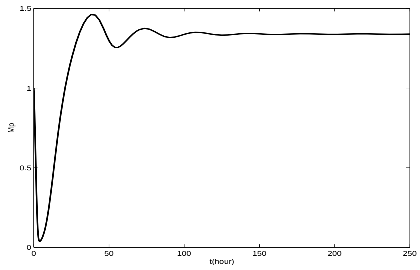

Figure 3: The time evolution of M_P without L-D cycle when v_{sP}=v_{sT}=0.65

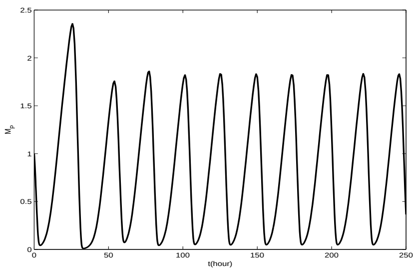

Figure 4: The time evolution of M_P under L-D cycle when $v_{sP} = v_{sT} = 0.8$

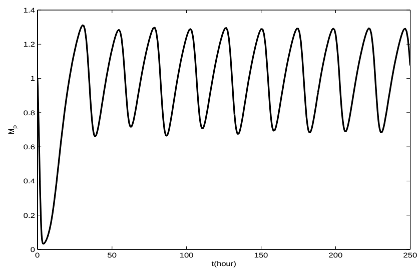

Figure 5: The time evolution of M_P under L-D cycle when $v_{sP} = v_{sT} = 0.65$.

was added to the drosophila model, with the analysis drosophila model based on the perturbation theory, the system state will be at oscillation all the time under L-D cycle, and the period is 24 hours[10].

The chaos state occurs under dissymmetry drosophila system[6,11-14]. In the symmetry drosophila, the chaos phenomenon was not found now. How to prove the condition of chaos in drosophila and when the chaos happened, even how to solve the chaos state of drosophila arestoll remain to be researched.

Acknowledgements

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