Periodic Control of Circadian Rhythms in Drosophila Based on Speed Gradient Algorithm

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Abstract

Recently,developing molecuar biology and system biology, the mechanism of the circadian rhythm in which the inside of the body rhythm of the living thing is ruled is being clarified at the cell level. On the other hand, it is thought that various sicknesses are related in the medicine and pharmacology to the disorder of the circadian rhythm. To control the disease caused by such an abnormality the rhythm syndrome, it proposes the method of controlling the cycle by using Speed Gradient Algorithm that is one of the nonlinear control techniques for the circadian rhythm with an abnormal rhythm.

Key words : Circadian rhythm, Speed Gradient Algorithm, Periodic control

1.Introduction

Recently, the circadian rhythm with about 24 cycles of the hour from the viewpoint of the system biology is actively researched. This rhythm mechanism controls the rhythm of the entire body like not only bureau lives, sleep, the blood pressure, and the temperature but also the hormone and the internal secretion systems, etc. to the suprachiasmatic nucleus in hypothalamus of the living body in the peculiarity. The existence of the circadian rhythm is proven by all almost the living thing kinds, and the mechanism at the cell level is being clarified on some seeds because of the development of a molecular biology approach. Especially, the mathematics model of the mechanism is proposed by Goldbeter as for the circadian rhythm in Drosophila treated by this research.

On the other hand, the disorder of the circadian rhythm, that is, abnormality the rhythm syndrome is observed under special conditions of cancer, sleeplessness, and a mental disease, etc. in the medicine and pharmacology. The research to make the sickness controlled by recovering the rhythm to man under such a condition is done.

In this research, it proposes the technique for achieving this rhythm recovery by using a circadian rhythm in Drosophila expressed by nonlinear state equation proposed by Goldbeter. The circadian rhythm with an abnormal rhythm is considered to be a plant system and the circadian rhythm with an normal rhythm is considered to be a reference system, the recovery to the normal rhythm is achieved by syhchronozing the rhythm of the plant system with the rhythm of the reference system . By using Speed Gradient Algorythm that is one of the nonlinear control techniques, it is shown that the control system only dependent on per mRNA concentration that can be only observed in circadian rhythm is possible.

2.Molecular model of Circadian rhythm in Drosophila

Fig.1 shows a molecular model of circadian rhythm proposed by Goldbeter. [1]

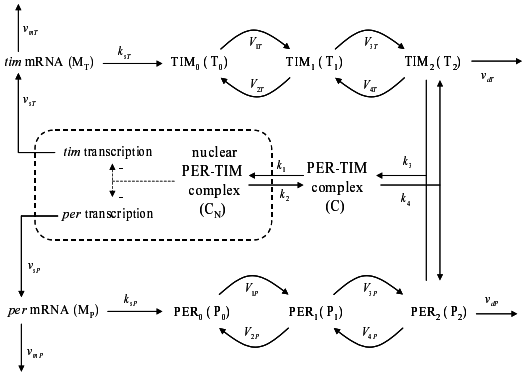

Fig.1 : Molecular model [1]

First of all, the genetic information on the *per* gene is transcribed in *per* mRNA(M_{P}) in the cell nucleus. *per* mRNA moves from the nucleus to the cytoplasm, translates genetic information and generates protein $\mathrm{PER}_0(P_0)$ with the ribosome of the cytoplasm. Then, protein PER_0 is phosphorylated in reversible manner into the forms $\mathrm{PER}_1(P_1)$ and $\mathrm{PER}_2(P_2)$. On the other hand, the *tim* gene operate in symmetry. That is, the genetic information is transcribed to *tim* mRAN(M_{T}) in the cell nucleus, after moves to the cytoplasm, it generates protein $\mathrm{TIM}_0(T_0)$, then, protein TIM_0 is monophosphorylated into $\mathrm{TIM}_1(T_1)$ and bisphosphorylated

into $\mathrm{TIM}_2(T_2)$ in reversible manner. The fully phosphorylated forms of protein PER and TIM becomes a PER-TIM complex(C). Then, the PER-TIM comlex is transported into the nucleus. The PER-TIM complex in the nucleus(C_N) exerts a negative feedback on the production of *per* and *tim* mRNAs.

This molecular model was expressed by Goldbeter by the following chemical reaction equations.

$$\dot{M}_\mathrm{P} = v_\mathrm{sP}\frac{{K_\mathrm{IP}}^\mathrm{n}}{{K_\mathrm{IP}}^\mathrm{n}+{C_\mathrm{N}}^\mathrm{n}} - v_\mathrm{mP}\frac{M_\mathrm{P}}{K_\mathrm{mP}+M_\mathrm{P}} - k_\mathrm{d}M_\mathrm{P} \quad (1)$$

$$\dot{P}_0 = k_\mathrm{sP}M_\mathrm{P} - V_\mathrm{1P}\frac{P_0}{K_\mathrm{1P}+P_0} + V_\mathrm{2P}\frac{P_1}{K_\mathrm{2P}+P_1} - k_\mathrm{d}P_0 \quad (2)$$

$$\dot{P}_1 = V_\mathrm{1P}\frac{P_0}{K_\mathrm{1P}+P_0} - V_\mathrm{2P}\frac{P_1}{K_\mathrm{2P}+P_1} - V_\mathrm{3P}\frac{P_1}{K_\mathrm{3P}+P_1} + V_\mathrm{4P}\frac{P_2}{K_\mathrm{4P}+P_2} - k_\mathrm{d}P_1 \quad (3)$$

$$\dot{P}_2 = V_\mathrm{3P}\frac{P_1}{K_\mathrm{3P}+P_1} - V_\mathrm{4P}\frac{P_2}{K_\mathrm{4P}+P_2} - k_3P_2T_2 + k_4C - v_\mathrm{dP}\frac{P_2}{K_\mathrm{dP}+P_2} - k_\mathrm{d}P_2 \quad (4)$$

$$\dot{M}_\mathrm{T} = v_\mathrm{sT}\frac{{K_\mathrm{IT}}^\mathrm{n}}{{K_\mathrm{IT}}^\mathrm{n}+{C_\mathrm{N}}^\mathrm{n}} - v_\mathrm{mT}\frac{M_\mathrm{T}}{K_\mathrm{mT}+M_\mathrm{T}} - k_\mathrm{d}M_\mathrm{T} \quad (5)$$

$$\dot{T}_0 = k_\mathrm{sT}M_\mathrm{T} - V_\mathrm{1T}\frac{T_0}{K_\mathrm{1T}+T_0} + V_\mathrm{2T}\frac{T_1}{K_\mathrm{2T}+T_1} - k_\mathrm{d}T_0 \quad (6)$$

$$\dot{T}_1 = V_\mathrm{1T}\frac{T_0}{K_\mathrm{1T}+T_0} - V_\mathrm{2T}\frac{T_1}{K_\mathrm{2T}+T_1} - V_\mathrm{3T}\frac{T_1}{K_\mathrm{3T}+T_1} + V_\mathrm{4T}\frac{T_2}{K_\mathrm{4T}+T_2} - k_\mathrm{d}T_1 \quad (7)$$

$$\dot{T}_2 = V_\mathrm{3T}\frac{T_1}{K_\mathrm{3T}+T_1} - V_\mathrm{4T}\frac{T_2}{K_\mathrm{4T}+T_2} - k_3P_2T_2 + k_4C - v_\mathrm{dT}\frac{T_2}{K_\mathrm{dT}+T_2} - k_\mathrm{d}T_2 \quad (8)$$

$$\dot{C} = k_3P_2T_2 - k_4C - k_1C + k_2C_\mathrm{N} - k_\mathrm{dc}C \quad (9)$$

$$\dot{C}_\mathrm{N} = k_1C - k_2C_\mathrm{N} - k_\mathrm{dN}C_\mathrm{N} \quad (10)$$

3. Mutant model

The cycle of the circadian rhythm in the Drosophila shortened and the phenomenon were observed long. that understands this is related to the mutant of the gene of the drosophila and cuts it . The model of this mutant can be reproduced according to the Goldbeter model. In document , it specifies which parameter is related to the mutant by changing the parameter of the model, and the observation of the change in the cycle of that time. As for short mutant *per*^{s}at the cycle, it is understood that maximum collapse speed $k_{dN}$of compound protein (C_N) in the cell nucleus is related. It is shown that *per*^{s}mutant appears by improving the resolution ability of the adjustment factor of the gene expression in the cell nucleus , and this responds to the fact of increasing k_dN of Goldbete molecular model. The cycle becomes hour when assuming $k_{dN} = 0.5$, and the behavior of the rhythm of day with *per*^{s}mutant is reproduced by the simulation. Moreover, generation speed k_3 of complex protein (C) of the cytoplasm is related to long mutant *per*^{l}at the cycle. It is shown that the PER-PER complex is formed in *per*^{l}mutant and the cycle of day rhythm becomes long by obstructing the appearance of the PER-TIM complex. This responds to the fact of decreasing generation speed k_3 of the PER-TIM complex. It comes to indicate 28 hours at the cycle when assuming $k_3 = 0.4$, and the behavior of the day of of *per*^{l}mutant rhythm is reproduced by the simulation. Figure. shows this.

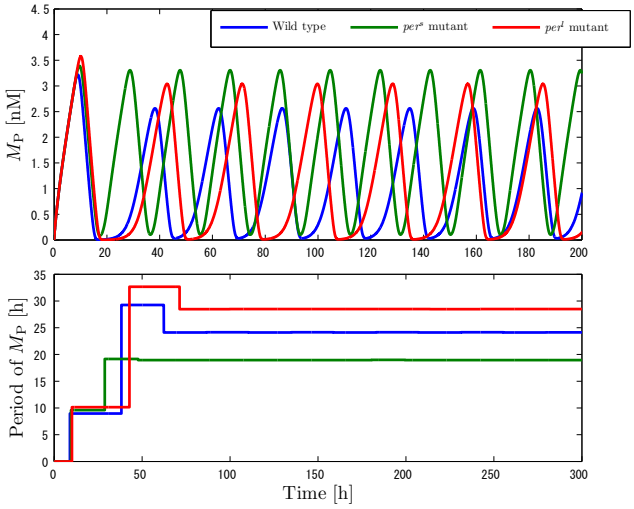

Fig.2 : Density and cycle of mRNA of mutant *per*^{s} , *per*^{l}and normal drosophila

4. Problem setting

It is assumed input $v_\mathrm{mP}(t)$that can adjust parameter $v_\mathrm{mP}$of the controlled object. Moreover, the control system based on $M_\mathrm{P}$and $M_\mathrm{Pr}$was designed as shown in figure because the signal that was able to be actually observed as day rhythm was only M_P

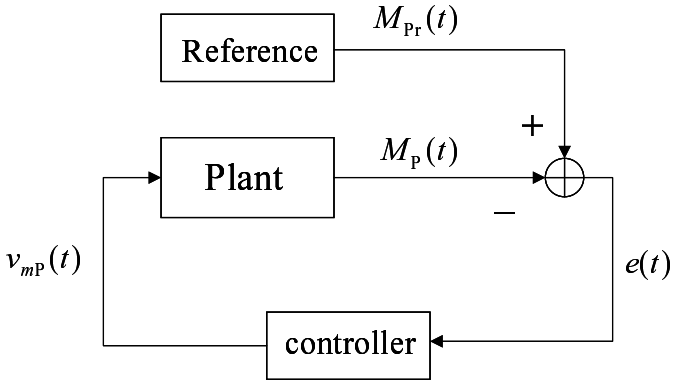

Fig.3 : controlled system

It thinks the reference model is composed, and output $M_{\mathrm{P}}(t)$of the controlled object is synchronized with the output signal $M_{\mathrm{Pr}}(t)$ Here as an evaluation function

$$Q(t) = \frac{1}{2}\left(M_P(t) - M_{Pr}(t)\right)^2 \tag{11}$$

Is introduced. This evaluation function $Q(t)$

$$Q(t) \to 0 \quad as \quad t \to \infty \tag{12}$$

When becoming it, synchronization is achieved. Input $v_{\mathrm{mP}}(t)$that achieves this is decided. Next, the method of deciding input $v_{\mathrm{mP}}(t)$that achieves (11) according to the SG algorithm is shown.

5. Speed Gradient Algorithm [2]

The Speed Gradient Algorithm that is one of the methods of solving the nonlinear control problem is described. First of all, general differential equation

$$\begin{aligned} \dot{x} &= F(x,u,t) \\ x \in R^n \quad &, \quad u \in R^m,\ t \geq 0 \end{aligned} \tag{13}$$

It is thought control object. The control purpose of this system is expressed in the form of the evaluation function.

$$Q(t) = Q\left(x,t\right) \tag{14}$$

The time along (14) of this evaluation function differentiation is requested.

$$\dot{Q} = \frac{\partial Q(x,t)}{\partial t} + \left(\nabla_x Q(x,t)\right)^T F\left(x,u,t\right) \equiv \omega\left(x,u,t\right) \tag{15}$$

The speed inclination of ω along input u is calculated.

$$\begin{aligned} \nabla_u \omega\left(x,u,t\right) &= \left(\frac{\partial \omega(x,u,t)}{\partial u}\right)^T \\ &= \left(\frac{\partial}{\partial u}\left(\frac{\partial Q}{\partial t}(x,t) + \left(\nabla_x Q(x,t)\right)^T F(x,u,t)\right)\right)^T \\ &= \left(\frac{\partial F\left(x,u,t\right)}{\partial u}\right)^T \nabla_x Q(x,t) \end{aligned} \tag{16}$$

The following control algorithms are obtained by using the speed inclination of this objective function.

5.1 Simple Speed Gradient Algorithm

$$\frac{du}{dt} = -\Gamma \nabla_u \omega\left(x,u,t\right) \quad , \qquad \Gamma = \Gamma^T > 0 \tag{17}$$

However, Γ is assumed to be a positive definit value symmetric matrix. The above expression is a control rule that moves in the direction where the objective function decreases by the speed inclination of the objective function at time, and this is called a simple Speed Gradient algorithm.

5.2 Finite Form Speed Gradient Algorithm

Speed Gradient Algorithm with shape of limited

$$u(t) = u_0 - \Gamma \nabla_u \omega\left(x,u,t\right) \quad , \qquad \Gamma = \Gamma^T > 0 \tag{18}$$

It is said Finite Form SG algorithm.

6. Decision of v_{mP} according to Speed Gradient Algorithm

When you differentiate objective function $Q(t)$at time

$$\begin{aligned} \dot{Q}(t) &= \left(M_{\mathrm{P}}(t) - M_{\mathrm{Pr}}(t)\right)\left[v_{\mathrm{sP}} \frac{{K_{\mathrm{IP}}}^{\mathrm{n}}}{{K_{\mathrm{IP}}}^{\mathrm{n}} + {P_{\mathrm{N}}}^{\mathrm{n}}(t)}\right. \\ &\quad \left. - v_{\mathrm{mP}} \frac{M_{\mathrm{P}}(t)}{K_{\mathrm{mP}} + M_{\mathrm{P}}(t)} - k_{\mathrm{d}} M_{\mathrm{P}}(t) - \dot{M}_{\mathrm{Pr}}(t)\right] \end{aligned} \tag{19}$$

Is obtained. Next, this is requested and speed inclination $\nabla_{v_{\mathrm{mP}}} \dot{Q}(t)$of partial differential target function is requested by input v_{mP}

$$\nabla_{v_{\mathrm{mP}}} \dot{Q}(t) = -\left(M_{\mathrm{P}}(t) - M_{\mathrm{Pr}}(t)\right) \frac{M_{\mathrm{P}}(t)}{K_{\mathrm{mP}} + M_{\mathrm{P}}(t)} \tag{20}$$

It proposes two SG algorithms based on the expression.

$$\frac{du}{dt} = -\gamma \nabla_u \dot{Q}, \quad \gamma > 0 \quad \text{(Basic type)} \tag{21}$$

$$\frac{dv_{mP}}{dt}(t) = \gamma\left(M_P(t) - M_{Pr}(t)\right) \frac{M_P(t)}{K_{mP} + M_P(t)} \tag{22}$$

$$u(t) = u_0 - \gamma \nabla_u \dot{Q}_t, \quad \gamma > 0 \quad \text{(Basictype)} \tag{23}$$

$$v_{mP}(t) = v_{mP0} + \gamma\left(M_P(t) - M_{Pr}(t)\right) \frac{M_P(t)}{K_{mP} + M_P(t)} \tag{24}$$

However, v_{mP0} nominal value 0.7 of v_{mP} by an initial value of input v_{mP} Moreover, γ was assumed to be 0.5 here.

7.1 Recovery to 24 hour of mutant *per*^{s}

$k_{\mathrm{dN}} = 0.5$ nM and an *per*^{s} mutant rhythm occur. The value of other parameters and reference model's parameters uses the following values.

$$
\begin{aligned}
&v_{\mathrm{mP}} = v_{\mathrm{mT}} = 0.7\ \mathrm{nMh}^{-1},\ v_{\mathrm{sP}} = v_{\mathrm{sT}} = 1\ \mathrm{nMh}^{-1},\\
&K_{\mathrm{mP}} = K_{\mathrm{mT}} = 0.2\ \mathrm{nM},\ k_{\mathrm{sP}} = k_{\mathrm{sT}} = 0.9\ \mathrm{h}^{-1},\\
&v_{\mathrm{dP}} = v_{\mathrm{dT}} = 2\ \mathrm{nMh}^{-1},\ k_1 = 0.6\ \mathrm{h}^{-1},\ k_2 = 0.2\ \mathrm{h}^{-1},\\
&K_{\mathrm{dP}} = K_{\mathrm{dT}} = 0.2\ \mathrm{nM},\ \mathrm{n} = 4,\\
&k_3 = 1.2\ \mathrm{h}^{-1},\ k_4 = 0.6\ \mathrm{h}^{-1},\ K_{\mathrm{IP}} = K_{\mathrm{IT}} = 1\ \mathrm{nM},\\
&K_{1\mathrm{P}} = K_{1\mathrm{T}} = K_{2\mathrm{P}} = K_{2\mathrm{T}} = K_{3\mathrm{P}} = K_{3\mathrm{T}} =\\
&K_{4\mathrm{P}} = K_{4\mathrm{T}} = 2\ \mathrm{nM},\ k_{\mathrm{d}} = k_{\mathrm{dc}} = k_{\mathrm{dN}} = 0.01\ \mathrm{h}^{-1},\\
&V_{1\mathrm{P}} = V_{1\mathrm{T}} = 8\ \mathrm{nMh}^{-1},\ V_{2\mathrm{P}} = V_{2\mathrm{T}} = 1\ \mathrm{nMh}^{-1},\\
&V_{3\mathrm{P}} = V_{3\mathrm{T}} = 8\ \mathrm{nMh}^{-1},\ V_{4\mathrm{P}} = V_{4\mathrm{T}} = 1\ \mathrm{nMh}^{-1}
\end{aligned}
$$

The beginning time of the control was assumed to be 300 hours.

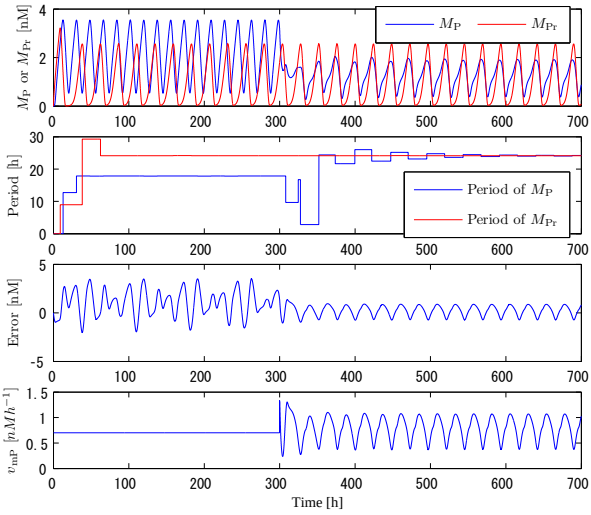

Fig.4 : Recovery at *per*^{s} mutant rhythm cycle

7.2 Recovery to 24 hour of mutant *per*^{l}

$k_3 = 0.4$ nM and an *per*^{l} mutant rhythm occur. The value of other parameters and reference model's parameters uses the nominal values. The beginning time of the control was assumed to be 300 hours.

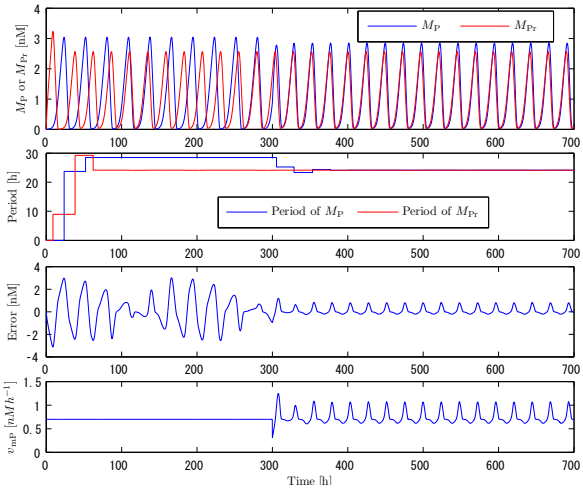

Fig.5 : Recovery at *per*^{l} mutant rhythm cycle

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