Circadian Oscillations in Systems of Biochemical Oscillators Coupled to Stationary Systems

Masaji Watanabe *

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Abstract

According to previous studies, we may expect that slow oscillations can occur in dynamics of a parameterized family of systems in which a biochemical oscillator is coupled to a stationary systems. We introduce some numerical results that confirm our expectation. The results suggest that it is possible for slow oscillations to occur in dynamics of a system in which an active oscillatory unit is coupled to a passive medium, and that it is possible for circadian oscillations to arise from fast glycolytic oscillations in such a coupled system.

KEYWORDS: circadian rhythm, glycolytic oscillation, nonlinear oscillator.

1. Introduction

24-hour physiological cycles endogenous to living systems are called circadian rhythms, and they have been studied extensively in the past half century. Mathematical studies of circadian rhythms have also been undertaken, and their models include interacting oscillators, each of which corresponds to a biochemical oscillator [4]. A result in [4] suggests a possible mechanism for generating slow oscillations in circadian rhythms from fast biochemical oscillations whose period is typically a few minutes. In this paper, we introduce some numerical results that also suggest a possibility for slow circadian oscillations to arise from fast biochemical oscillations.

In previous studies, we analyzed a parameterized family of systems in which a planar oscillator is coupled to a stationary system [6, 7]. We analyzed the systems in the limit where one of the parameters approaches a certain value. Our results suggest that it is possible for slow oscillations to arise in their dynamics. Those systems were also analyzed numerically. The numerical results show that it is possible for periodic solution with arbitrarily large period to exist. We expect that these properties can hold even when an biochemical oscillator is coupled to a stationary system. In the following sections, we introduce some numerical result which confirm our expectation. Suppose that there is a transport of a substance between a cell and its medium through the cell membrane. In such a situation, a model in which a system is coupled to stationary system can be vied as a governing system [3]. In this view point, our numerical results which we introduce in the following sections suggest a possibility for slow oscillations of circadian rhythms to arise from fast biochemical oscillations via coupling between a cell and a medium.

In Section 2, we introduce a parameterized family of systems in which a biochemical oscillator is coupled to a stationary system. In particular, we consider a biochemical oscillator is a planar system that model dynamics in glycolysis. We also introduce the transformation to take those systems into the framework of the previous studies. In Sections 3, we introduce some numerical results. When one of the parameter approaches 0, it is expected that the asymptotic period of any periodic solution is essentially different in each of two cases determined by another parameter. The parameter value which determines those two case is computed numerically, and these two cases are analyzed numerically. One result shows that the period approaches some finite value, whereas another result shows that the period becomes arbitrarily large.

*Department of Environmental and Mathematical Sciences, Faculty of Environmental Science and Technology, Okayama University, Okayama 700, Japan. Supported by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports, and Culture.
2. Parameterized Systems of Biochemical Oscillators Coupled to Stationary Systems

In mathematical studies of glycolytic oscillations in [1,3,5], systems of the following form are analyzed.

\[ \frac{dp}{dt} = \Phi(p,q) - \Psi(p), \]

\[ \frac{dq}{dt} = \mu - \Phi(p,q). \]

(1)

Particular examples of the functions \( \Phi(p,q) \) and \( \Psi(p) \) introduced in [1] can be written in the following equations:

\[ \Phi(p,q) = \frac{\sigma q (1+q)(1+p)^2}{l + (1+q)^2(1+p)^2}, \]

\[ \Psi(p) = \chi p. \]

(2)

Here, \( p \) and \( q \) represent the dimensionless concentrations of product and substrate, respectively. Suppose that (1) governs the reaction which takes place in a unit with no transport of substances between the unit and its medium. Now suppose that there is a transport of the second component between the unit and its medium. Then the temporal change in the concentrations of substances is modeled by the following system.

\[ \frac{dp}{dt} = \Phi(p,q) - \Psi(p), \]

\[ \frac{dq}{dt} = \mu - \Phi(p,q) + \delta (r-q), \]

\[ \frac{dr}{dt} = -\epsilon \delta (r-q). \]

(3)

This model is introduced in [3] as a governing system of the temporal change of substances in a cell and its medium. Here, \( r \) denotes the dimensionless concentrations of the substance in the medium.

In order to analyze the systems (1) and (3) in the framework of previous studies, we let \( v = p \) and \( w = c - q \), where \( c \) is a constant. Then (1) leads to the system:

\[ \frac{dv}{dt} = g(v,w), \]

\[ \frac{dw}{dt} = h(v,w), \]

(4)

where

\[ g(v,w) = \Phi(v,c-w) - \Psi(v), \]

\[ h(v,w) = \Phi(v,c-w) - \mu. \]

(5)

We also let \( x = c - r \). Then (3) leads to the system:

\[ \frac{dv}{dt} = g(v,w), \]

\[ \frac{dw}{dt} = h(v,w) + \delta (x-w), \]

\[ \frac{dx}{dt} = -\epsilon \delta (x-w). \]

(6)

This system can be viewed as a system in which the planar system (4) is coupled to the stationary system

\[ \frac{dx}{dt} = 0. \]

(7)

In Section 3, we focus on the case in which \( \Phi(p,q) \) and \( \Psi(p) \) are those functions given at (2). According to previous studies, we expect that there is a \( \delta^* \) with the following properties: for \( 0 < \delta < \delta^* \), the period of
Figure 1: The nullclines of the planar system. The nullclines \( g(v, w) = 0 \) and \( h(v, w) = 0 \) are shown. Here \( g(v, w) = 0 \) and \( h(v, w) = 0 \) are given by (2) and (5), and the following parameter values are set: \( l = 1000000, \mu = 50, \sigma = 200, \chi = 10, c = 160 \).

Periodic solutions approaches a finite value as \( \epsilon \to 0 \), and that, for \( \delta > \delta^* \), the period diverges to infinity as \( \epsilon \to 0 \). We introduce some numerical results that confirm these expectations.

3. Results from Numerical Analysis of Parameterized Systems

In this section, we introduce some results from numerical analysis of the systems (4) and (6) in which \( \Phi(p, q) \) and \( \Psi(p, q) \) are those functions given at (2). It is shown in [1] that there are some parameter values for which (1), and consequently (4) can have periodic solutions. On the other hand, the existence of periodic solutions of (4) for small \( \kappa > 0 \) are guaranteed under the following conditions.

(i) The nullcline \( g(v, w) = 0 \) is given by a smooth function \( w = \alpha(v) \) that satisfies the following properties.

\[
\begin{align*}
\alpha'(v) &< 0, \quad v < v_l, \\
\alpha'(v) &> 0, \quad v_l < v < v_r, \\
\alpha'(v) &< 0, \quad v > v_r, \\
g_w(v, \alpha(v)) &< 0 \quad \text{for all } v \in \mathbb{R}, \\
g_{vv}(v_l, \alpha(v_l)) &\neq 0 \quad w_l = \alpha(v_l), \\
g_{vv}(v_r, \alpha(v_r)) &\neq 0 \quad w_r = \alpha(v_r).
\end{align*}
\]

(ii) \( h_v(v, w) > 0 \) for all \( v \in \mathbb{R}^2 \).

(iii) the nullcline \( h(v, w) = 0 \) is a smooth curve that intersects the \( v \) nullcline exactly at one point \( (v_0, w_0) \) with \( v_l < v_0 < v_r \).

Under these conditions, (4) has periodic solutions for all sufficiently small \( \kappa > 0 \) [2]. Figure 1 shows the nullclines for a possible candidate for parameter values for which these conditions are satisfied. Of course, these conditions should be verified analytically in order to guarantee the existence of periodic solutions of (4) for small \( \kappa > 0 \). In stead, we analyzed the system numerically for the set of parameter values taken to
Figure 2: Periodic solutions of the glycolytic oscillator. The closed orbits of periodic solutions of (4) for $\kappa = 0.11$, $\kappa = 0.06$, and $\kappa = 0.01$ are numerically generated, and the results are shown. Here $g(v,w)$ and $h(v,w)$ are the same functions as those used to generated nullclines in Figure (2). We also computed the approximate period $T$ for each periodic solution: $T = 1.359260$ ($\kappa = 0.11$), $T = 1.193459$ ($\kappa = 0.06$), $T = 0.944704$ ($\kappa = 0.01$).

generate the nullclines in Figure 1. The result is shown in Figure 2 where closed orbits for three different values of $\kappa$ are shown.

Under the conditions (i), (ii), and (iii), the results obtained in [7] imply that given a pair $(\delta, \epsilon)$, (6) has periodic solutions for all sufficiently small $\kappa > 0$. Now denote by $T$ the period of a periodic solution of (6). Then the results in [7] also suggest that a periodic solution with arbitrarily large $T$ can be found. Suppose that $v = \zeta_\ell (w)$ is the inverse function of $w = \alpha (v)$ defined for $v \leq v_\ell$, $w \geq w_\ell$, and that $v = \zeta_r$ is the inverse function of $w = \alpha (v)$ defined for $v \geq v_r$, $w \leq w_r$. Define the functions $\xi_\ell (w)$ and $\xi_r (w)$ by the following equations.

$$
\xi_\ell (w) = w - \frac{1}{\delta} h(\zeta_\ell (w), w),
$$
$$
\xi_r (w) = w - \frac{1}{\delta} h(\zeta_r (w), w).
$$

Suppose that $\xi_\ell (w_\ell) = \xi_r (w_r)$ for $\delta = \delta^*$. That is

$$
\delta^* = \frac{h(v_r, w_r) - h(v_\ell, w_\ell)}{w_r - w_\ell}.
$$

In case $\Psi (p)$ is the function given at (2), (5) leads to the equation

$$
h(v_\ell, w_\ell) = \Phi(v_\ell, c - w_\ell) - \mu = \Psi(v_\ell) - \mu = \chi v_\ell - \mu.
$$

Similarly, $h(v_r, w_r) = \chi v_r - \mu$. It follows that

$$
\delta^* = \frac{v_r - v_\ell}{w_r - w_\ell}.
$$

The value of $\delta^*$ is numerically computed, and we found

$$
\delta^* \approx 3.170912.
$$
Figure 3: The period $T$ for $\delta < \delta^*$. Some approximate values of $T$ computed for $\delta = 2.7 < \delta^*$ show that $T$ converges to a finite value as $\epsilon \to 0$. Here $g(v, w)$ and $h(v, w)$ are the same functions as those used to generated nullclines in Figure 1, and $\kappa = 0.1$.

Figure 4: The period $T$ for $\delta < \delta^*$. Some approximate values of $T$ computed for $\delta = 3.2 > \delta^*$ show that $T$ diverges to $\infty$ value as $\epsilon \to 0$. Here $g(v, w)$ and $h(v, w)$ are the same functions as those used to generated nullclines in Figure 1, and $\kappa = 0.1$. 
Results of [7] suggest what asymptotic value of the period would be in the limit $\epsilon \to 0$. We expect that the period $T$ approaches some finite value for $0 < \delta < \delta^*$ and that $T$ diverges to $\infty$ for $\delta > \delta^*$. Numerical results that confirm these expectations are shown in Figures 3 and 4. For the results shown in Figures 3 and 4, we set $\delta = 2.7$ and $\delta = 3.2$, respectively. The result in Figure 3 indicates that the period approaches a value that approximately equals 1.9 in the limit. The result in Figure 4 indicates that the period diverges to $\infty$ as $\epsilon \to 0$ as we have expected.

We recall that (4) is set as the model for a glycolytic oscillation in a unit in case there is no transport of substances between the unit and its medium, and that (7) is set as the model for the state of the medium. On the other hand, (6) is set as the model in case there is a transport of a substance between the unit and the medium. The result shown in Figure 4 suggest that it is possible for slow circadian oscillations to arise from fast glycolytic oscillations in such a system.

**Reference**


