数理解析研究所講究録 1372 巻 2004 年 51-57

時間遅れをもつネガティブフィードバックを含む体内時計モデルの安定性解析
Stability Analysis for a physiological clock model with delayed negative feedback loop

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1 Introduction

Organism has several autonomous rhythms such as respiration, blood cycle, cell cycle and so on. The rhythm that has a roughly 24 hours period is called "circadian rhythm". Recent studies of molecular biology have revealed that circadian rhythm is generated through complicated interactions among genes and proteins; a clock gene is transcribed to a clock mRNA which in turn is translated to an enzyme and it in turn is translated to another enzyme and so on until an end product protein is produced. This end product enters a nucleus through some modifications and it finally suppress the transcription of own gene. This negative feedback loop is suggested to cause circadian rhythm.

Several mathematical models are proposed to investigate the mechanism of physiological clock. The periodic solution of the model can be interpreted as a physiological clock. Some of studies are by numerical simulations ([2], [7]), others are theoretical studies in terms of biology ([4], [5]). In this paper, we study physiological clock model in terms of mathematical analysis with the help of numerical simulations.

The derivation of the model is as follows. Let $x(t)$, $y(t)$ and $z(t)$ be concentrations of clock mRNA, clock protein, and protein complex respectively. The protein complex is assumed to suppress the transcription of the clock mRNA after time delay σ. This suppression is described by the form $b/(1+az^n)$. Then the total amount of produced proteins until the protein complex suppresses the transcription of the clock mRNA is described by

$$P(t)=\int_{t-\sigma}^{t}\frac{be^{-\gamma_1(t-s)}}{1+az^n(s)}ds. \tag{1.1}$$

The clock gene is transcribed to the clock mRNA and it in turn produce the clock protein in proportion to the amount of the clock mRNA with constant rate c. ρ represents the time which the clock gene needs to produce the clock protein. Then, in the same manner, the total amount of produced enzymes until the clock protein is produced is

$$E(t)=\int_{t-\rho}^{t}ce^{-\gamma_2(t-s)}x(s)\,ds. \tag{1.2}$$

Each clock mRNA, clock protein and protein complex is also assumed to lose itself proportionally with the per unit respective loss rate μ_1, μ_2 and μ_3 instantaneously. Two clock proteins unite to become a protein complex with constant rate d. Thus, the model for physiological clock is described by the following system of integro-differential equations (1.1), (1.2) and

$$\begin{cases} x'(t) = -\mu_1 x(t) + \dfrac{be^{-\gamma_1\sigma}}{1+az^n(t-\sigma)}, \\ y'(t) = -\mu_2 y(t) + ce^{-\gamma_2\rho}x(t-\rho) - dy^2(t), \\ z'(t) = -\mu_3 z(t) + dy^2(t). \end{cases} \tag{E}$$

Here a, b, c, d and μ_i $(i = 1,2,3)$ are positive constants. σ, ρ and γ_j $(j = 1,2)$ are nonnegative constants. n is a positive integer.

We impose the following initial condition for $-\max[\sigma,\rho] \le s \le 0$:

$$\begin{cases} x(s) = \phi_1(s) \ge 0, \quad y(s) = \phi_2(s) \ge 0, \quad z(s) = \phi_3(s) \ge 0, \\ P(0) = \displaystyle\int_{-\sigma}^{0} \frac{be^{\gamma_1 s}}{1+a\phi_3^n(s)} ds, \quad E(0) = \int_{-\rho}^{0} ce^{\gamma_2 s}\phi_1(s)\, ds. \end{cases} \tag{I}$$

Note that since (1.1), (1.2) and (E) is closed only in (E), throughout the reminder of this paper, the dynamics of physiological clock is considered by (E) with initial condition (I).

The organization of this paper is as follows: In the next section, several basic properties are given for (E) with (I). In section 3, we introduce the result for geometric stability switch criteria obtained by Beretta and Kuang [1] which is applicable to the characteristic equations with delay dependent parameters. In section 4, we study the asymptotic behavior of (E) around the positive equilibrium and observe that a family of periodic solutions of (E) occurs though the Hopf bifurcation.

2 basic properties

In this section, some basic properties are given for (E) such as uniqueness of the nonnegative solution and existence of the unique positive equilibrium. The definition of the solution of functional differential equation is due to Hale [6].

Theorem 2.1. *There exists a unique solution of* (E) *with* (I) *for* $t \in [0,\infty)$ *and all solutions of* (E) *are nonnegative, that is,* $x(t) \ge 0$, $y(t) \ge 0$ *and* $z(t) \ge 0$ *for* $t \in [0,\infty)$. *Furthermore,* $x(t) > 0$, $y(t) > 0$ *and* $z(t) > 0$ *for* $t \in (\rho,\infty)$.

Theorem 2.2. *There exists a unique positive equilibrium* (x^*, y^*, z^*) *of system* (E).

The proof of Theorem 2.1 and 2.2 are omitted.

3 Geometric stability switch criteria (third order)

Consider the third order characteristic equation with delay dependent coefficients:

$$P(\lambda,\tau)+Q(\lambda,\tau)e^{-\lambda\tau}=0. \tag{3.1}$$

$P(\lambda,\tau)$ and $Q(\lambda,\tau)$ denote analytic functions in λ and differentiable in τ of the form:

$$P(\lambda,\tau)=\lambda^3+p_1(\tau)\lambda^2+p_2(\tau)\lambda+p_3(\tau), \quad Q(\lambda,\tau)=q_1(\tau)\lambda^2+q_2(\tau)\lambda+q_3(\tau),$$

where $p_k(\cdot)$, $q_k(\cdot):\mathbf{R}_{+0}\equiv[0,+\infty)\to\mathbf{R}$ are continuous and differentiable functions in τ.

Let us impose the following assumptions for (3.1):

(B1) $P(0,\tau)+Q(0,\tau)=p_3(\tau)+q_3(\tau)\neq 0$, $^\forall\tau\in\mathbf{R}_{+0}$.

(B2) if $\lambda=i\omega$, $\omega\in\mathbf{R}$, then $P(i\omega,\tau)+Q(i\omega,\tau)\neq 0$, $^\forall\tau\in\mathbf{R}_{+0}$.

(B3) $F(\omega,\tau)=|P(i\omega,\tau)|^2-|Q(i\omega,\tau)|^2$ for each τ has at most a finite number of real zeroes and each positive root $\omega(\tau)$ of $F(\omega,\tau)=0$ is continuous and differentiable in τ whenever it exists.

Assumption (B1) asserts that the imaginary axis cannot be crossed by $\lambda(\tau)=0$ for some $\tau>0$ with increasing the value of τ. Furthermore, assumption (B2) asserts that there are no common imaginary roots. Hence we look for the occurrence of a pair of simple and conjugate imaginary roots $\lambda=\pm i\omega(\tau)$ which cross the imaginary axis at some positive τ. Hereafter, we consider just $\lambda=i\omega(\tau)$, $\omega(\tau)>0$, and the possibility that it is a root of characteristic equation (3.1). Then $\omega(\tau)$ must satisfy the following:

$$P_R+Q_R\cos\omega\tau+Q_I\sin\omega\tau=0, \quad P_I+Q_I\cos\omega\tau-Q_R\sin\omega\tau=0,$$

where $P_R(\lambda,\tau)$ and $P_I(\lambda,\tau)$ (or $Q_R(\lambda,\tau)$ and $Q_I(\lambda,\tau)$) are real functions in λ and τ which represent the real part and the imaginary part of $P(\lambda,\tau)$ (or $Q(\lambda,\tau)$), respectively.

Direct calculations give

$$\cos\omega\tau=\frac{P_RQ_R+P_IQ_I}{|Q(i\omega,\tau)|^2}, \quad \sin\omega\tau=-\frac{P_RQ_I-P_IQ_R}{|Q(i\omega,\tau)|^2}. \tag{3.2}$$

If ω satisfies (3.2), then ω must satisfy

$$|P(i\omega,\tau)|^2=|Q(i\omega,\tau)|^2 \tag{3.3}$$

Let us define $F(\omega,\tau)$ as follows:

$$F(\omega,\tau)=|P(i\omega,\tau)|^2-|Q(i\omega,\tau)|^2=0. \tag{3.4}$$

Assume that $I \subset \mathbf{R}_{+0}$ denotes the set where $\omega(\tau)$ is a positive root of (3.4) and for $\tau \notin I$, $\omega(\tau)$ is not definite. Then for all $\tau \in I$, $\omega(\tau)$ satisfies $F(\omega, \tau) = 0$. It is also important to notice that if $\tau \notin I$, then there are no positive solutions of (3.4) and we cannot have stability switches. Further, for any $\tau \in I$ where $\omega(\tau)$ is a positive solution of (3.4), we can define the angle $\theta(\tau) \in [0, 2\pi]$, as the solution of (3.2). Then the relation between the arguments $\omega\tau$ and θ must be $\omega\tau = \theta + 2m\pi$, $m \in \mathbf{N}_0 \equiv \{0, 1, 2, \cdots, \}$.

Let us introduce functions $S_m : I \to \mathbf{R}$ be

$$S_m(\tau) \equiv \tau - \frac{\theta + 2m\pi}{\omega}, \quad m \in \mathbf{N}_0. \tag{3.5}$$

Theorem 3.1. *[1, Beretta, Kuang] Assume that $\omega(\tau)$ is a positive real root of (3.4) defined for $\tau \in I$, $I \subset \mathbf{R}_{+0}$ and at some $\tau \in I$,*

$$S_m(\tau^*) = 0, \quad m \in \mathbf{N}_0.$$

Then a pair of simple conjugate pure imaginary roots $\lambda_+(\tau^*) = i\omega(\tau^*)$, $\lambda_-(\tau^*) = -i\omega(\tau^*)$ of (3.1) exists at $\tau = \tau^*$ which crosses the imaginary axis from left to right if $\delta(\tau^*) > 0$ and crosses the imaginary axis from right to left if $\delta(\tau^*) < 0$, where

$$\delta(\tau^*) \equiv \mathrm{sgnRe}\left[\left.\frac{d\lambda}{d\tau}\right|_{\lambda = i\omega(\tau^*)}\right] = \mathrm{sgn}[\mathrm{F}'_\omega(\omega(\tau^*), \tau^*)]\mathrm{sgn}\left[\left.\frac{dS_m(\tau)}{d\tau}\right|_{\tau=\tau^*}\right]$$

and $F'_\omega(\omega, \tau)$ denotes the partial derivative of $F(\omega, \tau)$ with respect to ω.

4 Hopf bifurcation

The linearized system of (E) around the positive equilibrium is given by

$$\begin{cases} x'(t) = -\mu_1 x(t) - \dfrac{abne^{-\gamma_1\sigma}(z^*)^{n-1}}{(1 + a(z^*)^n)^2} z(t - \sigma), \\ y'(t) = ce^{-\gamma_2\rho}x(t - \rho) - (\mu_2 + 2dy^*)y(t), \\ z'(t) = 2dy^*y(t) - \mu_3 z(t). \end{cases} \tag{4.1}$$

Then characteristic equation $p(\lambda; \sigma, \rho) = 0$ of (4.1) is defined by

$$p(\lambda; \sigma, \rho) = \lambda^3 + a_1(\sigma, \rho)\lambda^2 + a_2(\sigma, \rho)\lambda + a_3(\sigma, \rho) + a_4(\sigma, \rho)e^{-\tau\lambda} = 0, \tag{4.2}$$

where $a_1(\sigma, \rho) \equiv \mu_1 + \mu_3 + \mu_2 + 2dy^*(\sigma, \rho)$, $a_2(\sigma, \rho) \equiv (\mu_1 + \mu_3)(\mu_2 + 2dy^*(\sigma, \rho)) + \mu_1\mu_3$, $a_3(\sigma, \rho) \equiv \mu_1\mu_3(\mu_2 + 2dy^*(\sigma, \rho))$, $a_4(\sigma, \rho) \equiv \frac{2abcdny^*(\sigma,\rho)(z^*(\sigma,\rho))^{n-1}}{(1+a(z^*(\sigma,\rho))^n)^2} e^{-\gamma_1\sigma - \gamma_2\rho}$ and $\tau = \sigma + \rho$. Note that all coefficients of (4.2) depend on σ and ρ since $y^*(\sigma, \rho)$ is a positive root of $2n + 2$-th polynomial equation with delay dependent parameters

$$ad\mu_1 \left(\frac{d}{\mu_3}\right)^n y^{2n+2} + a\mu_1\mu_2 \left(\frac{d}{\mu_3}\right)^n y^{2n+1} + d\mu_1 y^2 + \mu_1\mu_2 y - bce^{-\gamma_1\sigma - \gamma_2\rho} = 0.$$

Let us give the necessary and sufficient condition for the origin of system (4.1) to be uniformly asymptotically stable for $\sigma = \rho = 0$. The following result is a consequence of applying the well known Hurwitz criterion to characteristic equation (4.2).

Lemma 4.1. *The zero solution of linearized system* (4.1) *is uniformly asymptotically stable for* $\sigma = \rho = 0$ *if and only if* $a_1 a_2 > a_3 + a_4$.

Throughout the reminder of this section, we assume $a_1 a_2 > a_3 + a_4$ by which it is assured that all roots of (4.2) are located on the left hand side of the complex plane for $\sigma = \rho = 0$. For the analysis of characteristic equation (4.2), we can refer to the contents of section 3. Note that we must fix either σ or ρ since Theorem 3.1 is only applicable to characteristic equations with one delay dependent parameter. Then all coefficients of (4.2) depend on τ $(k = 1, 2, 3, 4)$.

Let us set coefficients of characteristic equation (3.1) $p_k(\tau)$ and $q_k(\tau)$ by $p_k(\tau) = a_k(\tau)$ $(k = 1, 2, 3)$, $q_1(\tau) = q_2(\tau) = 0$ and $q_3(\tau) = a_4(\tau)$. Then (3.1) corresponds to (4.2). Hereafter we omit to write the dependence of τ for the convenience.

It is easy to see that basic assumptions (B1) — (B3) hold for (4.2).

(3.4) in section 3 corresponds to

$$F(\omega, \tau) = \omega^6 + (a_1^2 - 2a_2)\omega^4 + (a_2^2 - 2a_1 a_3)\omega^2 + a_3^2 - a_4^2 = 0. \tag{4.3}$$

In order to apply Theorem 3.1 to characteristic equation (4.2), the following two assumptions of Theorem 3.1 must be satisfied.

(S1) There exists a positive root of (4.3) for some $\tau \in I$, $I \subset \mathbf{R}_{+0}$.

(S2) There exists $\tau = \tau^* \in I$ such that $S_m(\tau^*) = 0$.

First, we check assumption (S1).

Lemma 4.2. *If* $a_3(\tau) < a_4(\tau)$, *then there exists a positive root of* (4.3). *On the other hand, there are no positive roots of* (4.3) *if* $a_3(\tau) \geq a_4(\tau)$. *Furthermore, all roots of characteristic equation* (4.2) *are located on the left hand side of the complex plane if* $a_3(\tau) \geq a_4(\tau)$.

Proof. Let us set $u \equiv \omega^2$ and define the function $g(u)$ as follows:

$$g(u) \equiv u^3 + (a_1^2 - 2a_2)u^2 + (a_2^2 - 2a_1 a_3)u + a_3^2 - a_4^2. \tag{4.4}$$

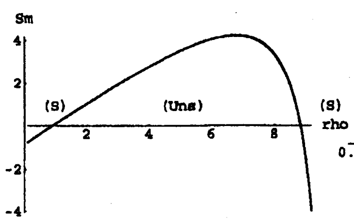
It can be shown that $a_1^2 - 2a_2 > 0$ and $a_2^2 - 2a_1 a_3 > 0$. Then $g'(u) = 3u^2 + 2(a_1^2 - 2a_2)u + (a_2^2 - 2a_1 a_3) > 0$ for $u > 0$. This implies that $g(u)$ is strictly monotonically increasing for $u > 0$. If $a_3^2 - a_4^2 < 0$, or equivalently $a_3 - a_4 < 0$, then the intermediate theorem implies that there exists $\bar{u} > 0$ such that $g(\bar{u}) = 0$. This leads the first assertion of this lemma holds true. The proof of the later part of this lemma is omitted. □

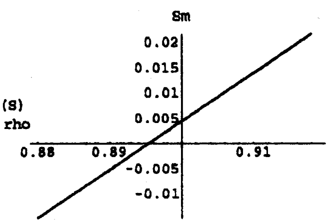
From Lemma 4.2, the interval I defined in assumption (S1) is exactly given by

$$I = \{\tau \in \mathbf{R}_{+0} | a_3(\tau) < a_4(\tau)\}$$

and hence this leads assumption (S1) holds true if $a_3(\tau) < a_4(\tau)$. Hereafter we assume interval I exists, that is, we assume $a_3(\tau) < a_4(\tau)$.

Second, we check assumption (S2) numerically. Let us fix the values of parameter for $a = 2.6$, $b = 2.9$, $c = 2.3$, $d = 2.9$, $\mu_1 = 0.3$, $\mu_2 = 0.4$, $\mu_3 = 0.2$, $n = 3$, $\gamma_1 = 0.3$, $\gamma_2 = 0.4$ and $\sigma = 2$. Then the relation between τ and ρ must be $\tau = \rho+2$. ρ is exploited as a control parameter and is changed from 0 to 9. Fig. 1 shows the graph of $S_0(\rho) = 0$ with respect to ρ. On Fig. 1, two points at which the graph of $S_0(\rho)$ intersects ρ axis are observed around $\rho = 1$ and $\rho = 9$. Figs 2 and 3 show the graph of $S_0(\rho)$ around $\rho = 1$ and $\rho = 9$, respectively. From Figs 2 and 3, the exact values of $S_0(\rho) = 0$ can be approximated about $\rho_1^* = 0.896$ and $\rho_2^* = 8.85$. It is also found from Figs 2 and 3 that $S_0'(\rho_1^*) > 0$ and $S_0'(\rho_2^*) < 0$. Further, we can show that $F_\omega'(\omega(\tau), \tau) = 2[\omega^5 + (a_1^2 - 2a_2)w^3 + (a_2^2 - 2a_1a_3)\omega] > 0$ for any $\tau \in I$. Hence $\delta(\rho_1^*) > 0$ and $\delta(\rho_2^*) < 0$. Then Theorem 3.1 implies the stability of linearized system (4.1) switches. It suggests that the positive equilibrium is destabilized to become unstable for ρ near ρ_1^* and is stabilized to become stable for ρ near ρ_2^*.





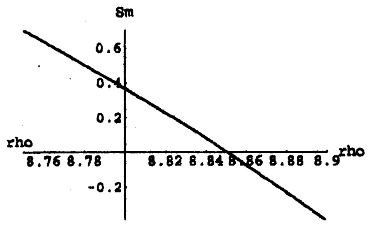


Figure 1: $S_0(\rho)$ Figure 2: $\rho_1^* = 0.896$ Figure 3: $\rho_2^* = 8.85$

Finally, we discuss the possibility of Hopf bifurcation. It is necessary to check the following three hypotheses for occurrence of Hopf bifurcation.

(H1) For $\tau \in [0, \tau^*)$, all the eigenvalues of (4.2) have negative real parts.

(H2) For τ near τ^*, there exists a pair of complex simple and conjugate eigenvalues $\lambda(\tau)$ and $\bar{\lambda}(\tau)$ of (4.2) such that $\mathrm{Re}\,(\lambda(\tau)) = 0$, $\mathrm{Im}\,(\lambda(\tau)) > 0$ and $\mathrm{Re}\,(\partial\lambda(\tau)/\partial\tau) > 0$ at $\tau = \tau^*$.

(H3) All the other eigenvalues of (4.2) at $\tau = \tau^*$ have negative real parts.

Theorem 4.1. *[6, p. 332, Theorem 1.1.] Assume that conditions (H1)— (H3) are satisfied. Then a family of periodic solutions of* (E) *bifurcates from the positive equilibrium for τ near τ^*. Further, the period of periodic solution is approximately $2\pi/\omega$, where ω is a positive root of* (4.3).

It is observed that conditions (H1)— (H3) are satisfied in terms of numerical calculations for the above parameters. From Fig. 2, the critical value τ^* is approximately estimated as $\tau^* = 2 + \rho_1^* = 2.896$. Then Theorem 4.1 suggests that there exists a family of periodic solutions of (E) for τ near $\tau^* = 2.896$. In fact, from the observation of numerical simulation, a periodic solution of (E) exists: Fig. 4 shows the trajectory of the solution of (E) with the initial condition $(\phi_1, \phi_2, \phi_3) = (0.2, 0.3, 1.6)$. Parameters are fixed as the same value for Figs 1—3 except for ρ and $\rho = 1$ $(\tau = 3)$. It is observed that the trajectory evolves to some periodic orbit.

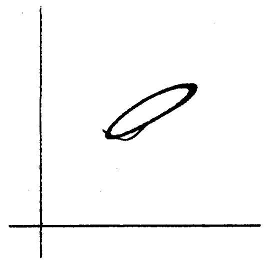


Figure 4: $\tau = 3$

Remark 4.1. *If $\gamma_1 = \gamma_2 = 0$, we can obtain mathematical analysis result. In this case, all coefficients of characteristic equation* (4.2) *are independent of time delays so that the positive root $\omega(\tau)$ of* (4.3) *is also independent of τ. Then [3, p.83, Theorem 4.1.] is applicable to* (4.2). *Hence it allows us to obtain the explicit critical value of time delay by which the positive equilibrium undergoes a Hopf bifurcation and a family of periodic solutions bifurcates as time delay increasing past the critical value. The detail is omitted.*

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