Stability and Bifurcation Analysis in a Model of Hes1 Selfregulation with Time Delay

Kejun Zhuang, Hailong Zhu

Abstract—The dynamics of a delayed mathematical model for Hes1 oscillatory expression are investigated. The linear stability of positive equilibrium and existence of local Hopf bifurcation are studied. Moreover, the global existence of large periodic solutions has been established due to the global bifurcation theorem.

Keywords—Hes1, Hopf bifurcation, time delay, transcriptional repression loop

I. INTRODUCTION

SINCE the oscillatory gene expression driven by negative feedback loops was first predicted by Goodwin [1], variants of this model have been proposed, see [2–4] and the references cited therein. In those delayed models, oscillations are generated if the delays surpass a critical value; in such cases, the delays can be regarded as driving the oscillations. From the viewpoint of mathematics, this kind of oscillations are exactly periodic solutions of delay differential equations due to Hopf bifurcation [5–7].

Oscillatory expression of members of the Hes/Her family of basic helix–loop–helix transcription factors have been shown to be involved in the segmentation clock [8]. The Hes/Her family members that oscillate during somitogenesis are involved in direct negative feedback loops, since they are capable of repressing their own transcription. Especially, Hes1 represses the transcription of its own gene through direct binding to regulatory sequences in the Hes1 promoter. Then Bernard considered the influence of an additional factor known to be involved in the Hes1 repression loop, namely Gro/TLE1. Protein Gro/TLE1 is activated through Hes1–induced hyper–phosphorylation. This activation is described by a Hill function that is a monotonically increasing function of Hes1 with Hill coefficient. The associated equations are written as [2]:

$$\begin{cases} \frac{dH(t)}{dt} = \frac{f_0 k^n}{k^n + G^n(t-\tau)} - \alpha H(t), \\ \frac{dG(t)}{dt} = \frac{g_0 H^m(t)}{l^m + H^m(t)} - \sigma G(t), \end{cases} \quad (1)$$

where $H(t)$ and $G(t)$ are the relative concentrations of Hes1 protein and of the TLE1/Groucho–Hes1. All the coefficients are positive constants, f_0 and g_0 are the production rates of Hes1 protein and of the TLE1/Groucho–Hes1, respectively. σ is the linear degradation rate of GroH, m and l_0 are parameters representing the sensitivity and scale of the rate of formation of the GroH complex. In this model, Hes1 mRNA is not explicitly

Kejun Zhuang is with the Institute of Applied Mathematics, School of Statistics and Applied Mathematics, Anhui University of Finance and Economics, Bengbu 233030, P.R.China, e-mail: zhkj123@163.com

Hailong Zhu is with the Institute of Applied Mathematics, School of Statistics and Applied Mathematics, Anhui University of Finance and Economics, Bengbu 233030, P.R.China, e-mail: mmyddk@163.com

modeled, but protein complex formation between Hes1 and its transcriptional co–repressor TLE1/Groucho is incorporated explicitly. Detailed numerical analysis was given to describe the stability and local Hopf bifurcation in [2].

The aim of this paper is to give the explicitly mathematical analysis for stability and periodicity of system (1). The remainder of the paper is organized as follows. In next section, existence of small amplitude periodic solutions will be proved by analyzing the distribution of roots for the transcendental characteristic equation. In Section 3, the global Hopf bifurcation is established.

II. LINEAR STABILITY ANALYSIS

Assume that system (1) has the unique positive equilibrium $E_*(H_*, G_*)$, then the corresponding linear system at E^* is in the form

$$\begin{cases} \frac{dH(t)}{dt} = a_{11} G(t-\tau) - \alpha H(t), \\ \frac{dG(t)}{dt} = a_{21} H(t) - \sigma G(t), \end{cases} \quad (2)$$

where $a_{11} = -\frac{n\alpha H_* G_*^{n-1}}{k^n + G_*^n} < 0$ and $a_{21} = \frac{m\sigma l^m G_*}{H_*(l^m + H_*^m)} > 0$. Then the characteristic equation is

$$\lambda^2 + (\alpha + \sigma)\lambda + \alpha\sigma - a_{11}a_{21}e^{-\lambda\tau} = 0. \quad (3)$$

When $\tau = 0$, equation (3) can be reduced to $\lambda^2 + (\alpha + \sigma)\lambda + \alpha\sigma - a_{11}a_{21} = 0$, which has two roots with negative real parts. Next we shall explore the distribution of characteristic roots when $\tau > 0$. Let $\lambda = i\omega(\omega > 0)$ be a root of (3). Then

$$-\omega^2 + i(\alpha + \sigma)\omega + \alpha\sigma - a_{11}a_{21}(\cos\omega\tau - i\sin\omega\tau) = 0.$$

Separation of the real and imaginary parts yields

$$\begin{cases} \omega^2 - \alpha\sigma = -a_{11}a_{21}\cos\omega\tau, \\ (\alpha + \sigma)\omega = -a_{11}a_{21}\sin\omega\tau, \end{cases}$$

and

$$\omega^4 + (\alpha^2 + \sigma^2)\omega^2 + (\alpha\sigma + a_{11}a_{21})(\alpha\sigma - a_{11}a_{21}) = 0. \quad (4)$$

It is easy to verify that equation (4) has the unique positive root when $\alpha\sigma + a_{11}a_{21} < 0$. This means that the characteristic equation only has a pair of purely imaginary roots.

From above, we have the following lemma.

Lemma 2.1. If $\alpha\sigma + a_{11}a_{21} < 0$, then equation (3) has a pair of purely imaginary roots $\pm i\omega_0$ when $\tau = \tau_j$, where

$$\omega_0 = \sqrt{\frac{\sqrt{(\alpha^2 - \sigma^2)^2 + 4a_{11}^2 a_{21}^2} - (\alpha^2 + \sigma^2)}{2}},$$

$$\tau_j = \frac{1}{\omega_0}\left(\arccos\frac{\alpha\sigma - \omega^2}{a_{11}a_{21}} + 2j\pi\right), \quad j = 0, 1, 2, \ldots.$$

World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:4, No:7, 2010

Let $\lambda(\tau) = \beta(\tau) + \mathrm{i}\omega(\tau)$ be a root of (3) satisfying $\beta(\tau_j) = 0$ and $\omega(\tau_j) = \omega_0$, $j = 0, 1, 2, \ldots$.

Lemma 2.2. If $\alpha\sigma + a_{11}a_{21} < 0$, then $\beta'(\tau_j) > 0$.

Proof. By substituting $\lambda(\tau)$ into equation (3) and differentiating both sides of the equation with respect to τ, we obtain

$$
\left.\frac{\mathrm{d}\lambda(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau_j}
$$

$$
= \left.\frac{-a_{11}a_{21}\lambda e^{-\lambda\tau}}{2\lambda + (\alpha + \sigma) + a_{11}a_{21}\tau e^{-\lambda\tau}}\right|_{\tau=\tau_j}
$$

$$
= \left.\frac{-a_{11}a_{21}\lambda}{e^{\lambda\tau}(2\lambda + \alpha + \sigma) + a_{11}a_{21}\tau}\right|_{\tau=\tau_j}
$$

$$
= \frac{-a_{11}a_{21}\omega_0\mathrm{i}}{(\cos\omega_0\tau_j + \mathrm{i}\sin\omega_0\tau_j)(\alpha + \sigma + 2\mathrm{i}\omega_0) + a_{11}a_{21}\tau_j},
$$

and

$$
\left.\frac{\mathrm{d}\beta(\tau)}{\mathrm{d}\tau}\right|_{\tau=\tau_j} = \frac{\omega_0^2(2\omega_0^2 + \alpha^2 + \sigma^2)}{A}
$$
$$
> 0,
$$

where $A = [(\alpha + \sigma)\cos\omega_0\tau_j - 2\omega_0\sin\omega_0\tau_j + a_{11}a_{21}\tau_j]^2 + [(\alpha + \sigma)\sin\omega_0\tau_j + 2\omega_0\cos\omega_0\tau_j]^2$. The conclusion follows.

According to Corollary 2.4 in [9], it is easy to verify the distribution of characteristic roots.

Lemma 2.3. (i) If $\alpha\sigma + a_{11}a_{21} > 0$, then all roots of (3) have strictly negative real parts.

(ii) If $\alpha\sigma + a_{11}a_{21} < 0$, then there exist $\tau_0 < \tau_1 < \tau_2 < \cdots$ such that all roots of (3) have negative real parts when $\tau \in [0, \tau_0)$, and equation (3) has $2(j + 1)$ roots with positive real parts when $\tau \in (\tau_j, \tau_{j+1})$.

From Lemma 2.2–2.3 and the Hopf bifurcation theorem [10], we have the following results.

Theorem 2.4. (i) If $\alpha\sigma + a_{11}a_{21} > 0$, then positive equilibrium E_* of (1) is locally asymptotically stable for any $\tau > 0$.

(ii) If $\alpha\sigma + a_{11}a_{21} < 0$, then E_* is asymptotically stable for $\tau \in [0, \tau_0)$, and unstable for $\tau > \tau_0$. System (1) undergoes a Hopf bifurcation at E_* when $\tau = \tau_j$, $j = 0, 1, 2, \ldots$.

III. GLOBAL EXISTENCE OF HOPF BIFURCATING PERIODIC SOLUTIONS

In this section, we focus on the global continuation of positive periodic solutions bifurcating from the equilibrium E_*. Throughout this section, we closely follow the notation in [11] and define

$X = C([-\tau, 0], \mathbf{R}^2)$,

$\Sigma = Cl\{(x, \tau, p) : (x, \tau, p) \in X \times \mathbf{R}_+ \times \mathbf{R}_+, x \text{ is a } p-\text{periodic solutions of (1)}\}$,

$N = \left\{(\hat{x}, \tau, p) : \hat{x} = (\hat{H}, \hat{G}), \frac{f_0 k^n}{k^n + \hat{G}^n} = \alpha\hat{H}, \frac{g_0\hat{H}^m}{l^m + \hat{G}^m} = \sigma\hat{G}\right\}$,

$\Delta(x_*, \tau, p)(\lambda) = \lambda^2 + (\alpha + \sigma)\lambda + \alpha\sigma - a_{11}a_{21}e^{-\lambda\tau}$,

and let $C(x_*, \tau_j, 2\pi/\omega_0)$ denote the connected component of $(x_*, \tau_j, 2\pi/\omega_0)$ in Σ, where ω_0 and τ_j are defined in Lemma 2.1.

Lemma 3.1. If m and n are even, then all periodic solutions of (1) are positive and uniformly bounded.

Proof. Let $(H(t), G(t))$ be a nonconstant periodic solution of (1), and $H(t_1) = M_1$, $H(t_2) = m_1$ be its maximum and minimum of $H(t)$, respectively. Then $H'(t_1) = H'(t_2) = 0$, namely

$$
M_1 = \frac{f_0 k^n}{\alpha(k^n + G^n(t_1 - \tau))}
$$

and

$$
m_1 = \frac{f_0 k^n}{\alpha(k^n + G^n(t_2 - \tau))}.
$$

Thus, $0 < H(t) \leq \frac{f_0}{\alpha}$.

Similarly, let $G(t_3) = M_2$, $G(t_4) = m_2$ be its maximum and minimum of $G(t)$, we get $0 < G(t) \leq \frac{g_0}{\sigma}$. Then all periodic solutions of (1) are positive and bounded for any t.

Lemma 3.2. System (1) has no nonconstant $\tau-$periodic solution.

Proof. For a contradiction, suppose that system (1) has a $\tau-$peridic solution. Then the following ordinary differential equations has nonconstant periodic solution:

$$
\begin{cases} \frac{dH(t)}{dt} = \frac{f_0 k^n}{k^n + G^n(t)} - \alpha H(t), \\ \frac{dG(t)}{dt} = \frac{g_0 H^m(t)}{l^m + H^m(t)} - \sigma G(t). \end{cases} \tag{5}
$$

If we define $P(H, G) = \frac{f_0 k^n}{k^n + G^n} - \alpha H$ and $Q(H, G) = \frac{g_0 H^m}{l^m + H^m} - \sigma G$, then $\frac{\partial P}{\partial H} + \frac{\partial Q}{\partial G} = -\alpha - \sigma < 0$. According to Bendixson–Dulac Criterion, system (5) has no nonconstant periodic solutions. This completes the proof.

Theorem 3.3. If $\alpha\sigma + a_{11}a_{21} < 0$ and m, n are even, then periodic solutions bifurcating from positive equilibrium of (1) still exist for $\tau > \tau_j$, $j = 0, 1, 2, \ldots$.

Proof. If is sufficient to prove that the projection of $C(x_*, \tau_j, 2\pi/\omega_0)$ onto $\tau-$space includes $[\tau_j, \infty)$ for each $j \geq 0$.

From Lemma 2.2 and 2.3, there exist $\varepsilon > 0$, $\delta > 0$ and a smooth curve $\lambda : (\tau_j - \delta, \tau_j + \delta) \to \mathbf{C}$, such that

$$
\Delta(\lambda(\tau)) = 0, \quad |\lambda(\tau) - \mathrm{i}\omega_0| < \varepsilon,
$$

for all $\tau \in [\tau_j - \delta, \tau_j + \delta]$ and

$$
\lambda(\tau_j) = \mathrm{i}\omega_0, \quad \left.\frac{\mathrm{dRe}(\lambda(\tau))}{\mathrm{d}\tau}\right|_{\tau=\tau_j} > 0.
$$

Define $\Omega_\varepsilon = \{(u, p) : 0 < u < \varepsilon, |p - 2\pi/\omega_0| < \varepsilon\}$. It is not difficult to show that if $|\tau - \tau_j| \leq \delta$ and $(u, p) \in \Omega_\varepsilon$, then $\Delta(x_*, \tau, p)(u + 2\mathrm{i}m\pi/p) = 0$ if and only if $u = 0, \tau = \tau_j, p = 2\pi/\omega_0$. This verifies the assumptions (A1)–(A4) in [11] for $m = 1$.

Moreover, putting

$$
H^{\pm}\left(x_*, \tau_j, \frac{2\pi}{\omega_0}\right)(u, p) = \Delta(x_*, \tau_j \pm \delta, p)\left(u + i\frac{2\pi}{p}\right),
$$

then we can compute the crossing number of the isolated center $(x_*, \tau_j, 2\pi/\omega_0)$ as follows

$$
\gamma\left(x_*, \tau_j, \frac{2\pi}{\omega_0}\right) = \deg_B\left(H^-\left(x_*, \tau_j, \frac{2\pi}{\omega_0}\right), \Omega_\varepsilon\right)
$$
$$
-\deg_B\left(H^+\left(x_*, \tau_j, \frac{2\pi}{\omega_0}\right), \Omega_\varepsilon\right)
$$
$$
= -1,
$$

World Academy of Science, Engineering and Technology
International Journal of Mathematical and Computational Sciences
Vol:4, No:7, 2010

where $\deg_B$ denotes the Brouwer degree. Then we have

$$\sum_{(\hat{x},\tau,p)\in C(x_*,\tau_j,2\pi/\omega_0)} \gamma(\hat{x},\tau,p) < 0.$$

Therefore, from Theorem 3.3 in [11], the connected component $C(x_*,\tau_j,2\pi/\omega_0)$ in Σ is unbounded.

Lemma 3.1 implies that the projection of $C(x_*,\tau_j,2\pi/\omega_0)$ onto $x-$space is bounded. From the definition of τ_j, we know that $0 < 2\pi/\omega_0 < \tau_j$ when $j > 0$. Then the projection onto $p-$space is also bounded.

Besides, the projection of $C(x_*,\tau_j,2\pi/\omega_0)$ onto $\tau-$space is bounded below due to Lemma 3.2. This means that the projection of $C(x_*,\tau_j,2\pi/\omega_0)$ onto $\tau-$space must be unbounded and includes $[\tau_j,\infty)$. As a result, bifurcating periodic solutions of (1) still exist when τ is far away from the first critical value τ_0.

IV. CONCLUSION

In this paper, we analyze the Hes1 oscillatory expression model by regarding time delay τ as bifurcation parameter. We conclude that periodic oscillation may occur when τ passes through some critical values, and the amplitude of oscillation is small. Moreover, the amplitude of oscillation may increase with τ when Hill coefficient is an even number, which can be explained by existence of global Hopf bifurcation.

ACKNOWLEDGMENT

REFERENCES

[1] B.C. Goodwin. Oscillatory behavior in enzymatic control processes. *Adv. Enzyme Regul.* **3** (1965), 425–439.

[2] Samuel Bernard, Branka Cajavec, Laurent Pujo–Menjouet, Michael C Mackey, Hanspeter Herzel. Modelling transcriptional feedback loops: the role of Gro/TLE1 in Hes1 oscillations. *Phil. Trans. R. Soc. A* **364** (2006), 1155–1170.

[3] Hiroshi Momiji, Nicholas A.M. Monk. Dissecting the dynamics of the Hes1 genetic oscillator. *J. Theor. Biol.* **254** (2008), 784–798.

[4] Nicholas A.M. Monk. Oscillatory expression of Hes1, p53, and NF–κB deriven by transcriptional time delays. *Curr. Biol.* **13** (2003), 1409–1413.

[5] Anael Verdugo, Richard Rand. Hopf bifurcation in a DDE model of gene expression. *Commun. Nonlinear Sci. Numer. Simul.* **13** (2008), 235–242.

[6] Min Xiao, Jinde Cao. Genetic oscillation deduced from Hopf bifurcation in a genetic regulatory network with delays. *Math. Biosci.* **215** (2008), 55–63.

[7] Junjie Wei, Chunbo Yu. Hopf bifurcation analysis in a model of oscillatory gene expression with delay. *P. Roy. Soc. Edinb. A* **139** (2009), 879–895.

[8] H. Hirata, S. Yoshiura, T. Ohtsuka etal. Oscillatory expression of the bHLH factor Hes1 regulated by a negative feedback loop. *Science* **298** (2002), 840–843.

[9] Shigui Ruan, Junjie Wei. On the zeros of transcendental function with applications to stability of delayed differential equations with two delays. *Dynam. Cont. Discrete Impuls. Syst. A* **10** (2003), 863–874.

[10] B.D. Hassard, N.D. Kazarinoff, Y.H. Wan. Theory and Applications of Hopf bifurcation. Cambridge: Cambridge University Press, 1981.

[11] Jianhong Wu. Symmetric functional differential equations and neural networks with memory. *Transactions of the AMS* **350** (1998), 4799–4838.