Comments and Corrections on "Stability of Genetic Regulatory Networks With Time Delay"

Masaaki Takada, Yutaka Hori, Member, IEEE, and Shinji Hara, Fellow, IEEE

Abstract—This paper shows that the necessary and sufficient condition for the local stability of gene regulatory networks with time delay (Theorem 2) presented in the highly cited paper [L. Chen and K. Aihara, IEEE TCAS-I, vol. 49, No. 5, pp. 602–608, 2002] is erroneous. An illustrative counterexample is presented, and it is pointed out that there are essentially two errors in their derivation. A corrected theorem is then derived using the approach shown in the aforementioned paper. It turns out that the corrected theorem provides only a sufficient condition for the local stability. Finally, a necessary and sufficient condition that was recently presented by the authors' of this paper is presented. Both the sufficient and the necessary and sufficient conditions are demonstrated using the Repressilator, the oscillatory gene regulatory network, which was also used for the illustration of the Chen and Aihara's original result.

Index Terms—Gene regulatory networks, local stability analysis, time delay.

I. INTRODUCTION

C HEN and Aihara [2] presented a necessary and sufficient condition for the local stability of gene regulatory networks with time delay. In this correspondence, we show that Theorem 2 of [2], which is a key result that delivers most of the results presented in [2], is erroneous. In particular, it is shown that the approach proposed in [2] can yield only a sufficient condition for the local stability after appropriate corrections to the proof. We then present the necessary and sufficient condition that was recently derived in the papers contributed by some of the authors of this correspondence [4], [5].

We use the following notations: $\mathbb{C}_+ := \{s \in \mathbb{C} \mid \operatorname{Re}[s] \ge 0\},\$ $\mathbb{R}_+ := \{c \in \mathbb{R} \mid c > 0\}$ and j is the imaginary unit.

II. DYNAMICS OF GENE REGULATORY NETWORKS WITH TIME DELAY

In this section, we briefly review the dynamics of gene regulatory networks with time delay introduced in [2].

Let n denote the number of genes in the network. We denote the concentrations of mRNAs and proteins

Manuscript received November 20, 2013; revised February 11, 2014; accepted February 15, 2014. Date of publication July 09, 2014; date of current version August 26, 2014. The work of Y. Hori was supported in part by JSPS Fellowship for Research Abroad. This paper was recommended by Associate Editor F. Bizzarri.

M. Takada is with NS Solutions Corporation, Tokyo 104-8280, Japan (e-mail: takada.masaaki@ns-sol.co.jp).

Y. Hori is with the Department of Computing and Mathematical Sciences, California Institute of Technology, Pasadena, CA 91125 USA (e-mail: yhori@caltech.edu).

S. Hara is with the Department of Information Physics and Computing, The University of Tokyo, Tokyo 113-8656, Japan (e-mail: Shinji_Hara@ipc.i.u-tokyo.ac.jp).

Color versions of one or more of the figures in this paper are available online at http://ieeexplore.ieee.org.

Digital Object Identifier 10.1109/TCSI.2014.2332245

by $\boldsymbol{m}(t) := [m_1(t), m_2(t), \cdots, m_n(t)]^T$ and $\boldsymbol{p}(t) := [p_1(t), p_2(t), \cdots, p_n(t)]^T$, respectively. The dynamics of gene regulatory networks is then given by

$$\dot{\boldsymbol{m}}(t) = -K_m \boldsymbol{m}(t) + \boldsymbol{c} \left(\boldsymbol{p}(t, \boldsymbol{\tau}_p) \right)$$

$$\dot{\boldsymbol{p}}(t) = -K_p \boldsymbol{p}(t) + \boldsymbol{d} \left(\boldsymbol{m}(t, \boldsymbol{\tau}_m) \right)$$
(1)

where $K_m := \operatorname{diag}(k_{m1}, k_{m2}, \cdots, k_{mn}) \in \mathbb{R}_+^{n \times n}$ and $K_p := \operatorname{diag}(k_{p1}, k_{p2}, \cdots, k_{pn}) \in \mathbb{R}_+^{n \times n}$ represent the degradation rates of mRNAs and proteins, respectively. The vectors $\boldsymbol{\tau}_m := [\tau_{m1}, \tau_{m2}, \cdots, \tau_{mn}]^T \in \mathbb{R}_+^n$ and $\boldsymbol{\tau}_p := [\tau_{p1}, \tau_{p2}, \cdots, \tau_{pn}]^T \in \mathbb{R}_+^n$ denote the time delays of translation and transcription process, respectively. We define $\boldsymbol{m}(t, \boldsymbol{\tau}_m) := [m_1(t - \tau_{m1}), m_2(t - \tau_{m2}), \cdots, m_n(t - \tau_{mn})]^T$ and $\boldsymbol{p}(t, \boldsymbol{\tau}_p) := [p_1(t - \tau_{p1}), p_2(t - \tau_{p2}), \cdots, p_n(t - \tau_{pn})]^T$. The functions $\boldsymbol{c}(\boldsymbol{p}) := [c_1(\boldsymbol{p}), c_2(\boldsymbol{p}), \cdots, c_n(\boldsymbol{p})]^T$ and $\boldsymbol{d}(\boldsymbol{m}) := [d_1(m_1), d_2(m_2), \cdots, d_n(m_n)]^T$ are nonlinear functions.

The following assumption was imposed in [2] for simplifying the analysis.

Assumption 1: Assume that the total delay time τ of the transcription and translation processes for each gene product has the same value, i.e., $\tau := \tau_{m1} + \tau_{p1} = \tau_{m2} + \tau_{p2} = \cdots = \tau_{mn} + \tau_{pn}$. Assume that all mRNAs and proteins have the same degradation rates k_m and k_p , respectively, i.e., $k_m := k_{m1} = k_{m2} = \cdots = k_{mn}$ and $k_p := k_{p1} = k_{p2} = \cdots = k_{pn}$.

Let $(\bar{\boldsymbol{m}}, \bar{\boldsymbol{p}})$ denote an equilibrium of (1). Theorem 1 of [2] implies that all roots of the *n* equations

$$\gamma_i = (\lambda + k_m)(\lambda + k_p)e^{\lambda\tau} \tag{2}$$

have negative real parts, if and only if (1) is asymptotically stable at the equilibrium, where γ_i ($i = 1, 2, \dots, n$) are the eigenvalues of $J := J_d J_c$, and J_d and J_c are the Jacobian of $\boldsymbol{d}(\cdot)$ and $\boldsymbol{c}(\cdot)$ at the equilibrium, respectively.

Theorem 2 of [2], which is the main result of the paper, was then derived under the following assumption.

Assumption 2: Assume the degradation rates of mRNA and proteins are the same, i.e., $k := k_m = k_p$.

In what follows, we show that Theorem 2 of [2] is erroneous.

III. A COUNTEREXAMPLE TO THEOREM 2 IN [2]

We illustrate a counterexample by using the numerical example shown in Section IV of [2]. We use the same notations as those in [2] throughout this section.

The dynamics of Repressialtor [3] is expressed as

$$\dot{m}_i(t) = -m_i(t) + \frac{\alpha}{1 + p_k^2(t - \tau_p)} + \alpha_0$$
(3)

$$\dot{p}_i(t) = -\beta p_i(t) + \beta m_i(t - \tau_m) \tag{4}$$

1549-8328 © 2014 IEEE. Personal use is permitted, but republication/redistribution requires IEEE permission. See http://www.ieee.org/publications standards/publications/rights/index.html for more information.



Fig. 1. A counterexample to Theorem 2 in [2]. (a) The stability region shown in Theorem 2 of [2] and Theorem A. (b) The solution trajectory starting in the vicinity of the equilibrium.

where i and k have the following three pairs of value: (i = 1, k = 2), (i = 2, k = 3) and (i = 3, k = 1). Note that this corresponds to

$$k_m = 1.0, \ k_p = \beta \tag{5}$$

$$c_i(\mathbf{p}) = \frac{\alpha}{1 + p_{i+1}^2(t - \tau_p)} + \alpha_0$$
(6)

$$l_i(m_i) = \beta m_i(t - \tau_m) \tag{7}$$

for i = 1,2,3, where $p_4(t) := p_1(t)$

(

Let $\beta = 1.0$, $\alpha = 2.8$, $\alpha_0 = 0$ and $\tau_p = \tau_m = 0.50$. Then, both Assumption 1 and 2 are satisfied, and the stability region specified in Theorem 2 of [2] can be drawn with k = 1.0 and $\tau = 1.0$ as illustrated in Fig. 1(a). The unique equilibrium is calculated as $\bar{P} := [\bar{m}_1, \bar{p}_1, \bar{m}_2, \bar{p}_2, \bar{m}_3, \bar{p}_3]^T = [1.176, 1.176, 1.176, 1.176, 1.176, 1.176, 1.176]^T$, and it follows that X = -1.160, $R_i = 1.160$ and $\theta_i = (2i-1)\pi/3$ (i = 1, 2, 3). We can then plot $(\sqrt{R_i}/k)e^{j\theta_i/2}$ and $-(\sqrt{R_i}/k)e^{j\theta_i/2}$ as shown in Fig. 1(a).

According to Theorem 2 of [2], all roots of the characteristic polynomial (2) have negative real parts, which means that the equilibrium \overline{P} is locally stable, if and only if $(\sqrt{R_i}/k)e^{j\theta_i/2}$ and $-(\sqrt{R_i}/k)e^{j\theta_i/2}$ lie inside the region shown in Fig. 1(a) for all i = 1,2,3. Therefore, Fig. 1(a) implies that the equilibrium is locally stable.

However, the trajectory starting near the unique equilibrium exhibits oscillations as shown in Fig. 1(b), where the initial values are set as $[m_1, p_1, m_2, p_2, m_3, p_3] = [1.174, 1.174, 1.176, 1$ 1.176]. In fact, the characteristic polynomial $(\lambda + 1)^2 e^{\lambda} = \gamma$ with $\gamma = R_1 e^{j\theta_1} = 1.160 e^{j\pi/3}$ has a root in the open right-half complex plane at $\lambda = 9.53 \times 10^{-3} + i3.61 \times 10^{-1}$. Moreover,



Fig. 2. Nyquist contour of the loop transfer function.

the Nyquist plot of the loop transfer function, which is defined by

$$L(s) := -\prod_{i=1}^{3} \left(\frac{\beta e^{-s(\tau_r + \tau_p)}}{(s+1)(s+\beta)} X \right) = (1.160)^3 \frac{e^{-3s}}{(s+1)^6}$$

encircles -1 + j0. These results imply that Theorem 2 of [2] is not the necessary and sufficient stability condition.

IV. MODIFICATION OF THEOREM 2 IN [2]

In this section, we clarify the errors of the mathematical proof provided in [2] and modify the statement of Theorem 2 of [2].

- There are essentially two errors in the proof.
- 1) Theorem 2.6 of [1], which is used in the proof in [2], is incorrect.

2) Theorem 2.6 of [1] was applied in a wrong way in [2]. We use the notations in [1] throughout this section.

A. Modification of Theorem 2.6 of [1]

Theorem 2.6 of [1] claims that all roots λ of

$$\lambda = -1 + be^{-\lambda\tau} \tag{8}$$

have negative real parts if and only if $b \in \mathbb{C}$ lies inside the bounded region specified by

$$R = \begin{cases} \frac{\phi - \left(\frac{\pi}{2}\right)}{\tau} & \text{for } \frac{\pi}{2} < \phi < \pi\\ \frac{\left(\frac{3\pi}{2}\right) - \phi}{\tau} & \text{for } \pi < \phi < \frac{3\pi}{2}, \end{cases}$$
(9)

where (R, ϕ) represents the radius and angle of the polar coordinate representation in complex plane.¹ However, we here show that Theorem 2.6 in [1] is not a necessary and sufficient but a sufficient condition.

Remark 1: When the authors of [1] illustrated the stability region (Fig. 2 in [1]), they somehow measured the angle ϕ from 1 + j0, although ϕ was originally defined as the angle from the origin of the complex plane. Thus, the stability region illustrated in Fig. 2 of [1] does not represent the region specified in Theorem 2.6.

A counterexample to Theorem 2.6 of [1] is obtained as follows. We consider the roots of

$$\lambda + 1 = 0.5e^{-\lambda} \tag{10}$$

¹We point out minor errors in [1] to avoid confusion. (i) Equation (2.4) in [1] should be corrected as $\lambda = -1 + be^{-\lambda \tau}$. (ii) The definition of the Archimedean spiral is not stated correctly in Theorem 2.6 of [1]. ϕ should be defined for $\phi \in (\pi/2, 3\pi/2)$ as shown in (9), which follows from (2.10) and (2.11) of [1].

by letting b = 0.5 and $\tau = 1$. We see that b is written as $(R, \phi) = (0.5, 0)$, and b is not located in the stability region specified by (9). However, no roots of the polynomial (10) lie in the right-half complex plane, because $|\lambda + 1| > |0.5e^{-\lambda}|$ for $\operatorname{Re}[\lambda] \ge 0$. This implies Theorem 2.6 in [1] is inaccurate.

We now point out an error in the proof of Theorem 2.6 of [1]. In the proof, the complex number b was expressed by the polar coordinate as $b = Re^{j\phi}$ with $R \ge 0$ and $0 \le \phi < 2\pi$. Then, the set of parameters (R, ϕ) for which all roots of λ have their real parts negative was explored. More specifically, it follows from the first paragraph of the proof of Theorem 2.6 that all roots λ of (8) have negative real parts if and only if $b \in \mathbb{C}$ lies inside the region

$$\Pi := \{ (R, \phi) \in [0, \infty) \times [0, 2\pi) \mid r < 1 \\ \text{for all } \rho \ge 0 \text{ and } 0 \le \theta < 2\pi \text{ s.t. (a) and (b)} \}$$
(11)

where (a) and (b) are

$$R = \rho e^{(r-1)\tau} \tag{a}$$

$$\phi = \theta + Re^{(1-r)\tau}\tau\sin\theta.$$
 (b)

Note that $r := \text{Re}[\lambda + 1]$ can be viewed as a function of ρ and θ , since $r = \text{Re}[\rho e^{j\theta}]$. We also note that (a) and (b) correspond to (2.7a) and (2.8) of [1], respectively.

Then, the stability region was derived by specifying the region Π . It follows that

$$\{(R,\phi) \in [0,\infty) \times [0,2\pi) \mid r < 1$$

for all $\rho \ge 0$ and $0 \le \theta < 2\pi$ s.t. (a) and (b)
$$\}$$
(12)

$$\begin{array}{l}
\bigcirc \left\{ (R,\phi) \in [0,\infty) \times [0,2\pi) \mid r < 1 \\
\text{for all } \rho \ge 0 \text{ and } 0 \le \theta < 2\pi \text{ s.t. (b)} \right\} \\
= \overline{\left\{ (R,\phi) \in [0,\infty) \times [0,2\pi) \mid r \ge 1 \\
\end{array}$$
(13)

$$\{(R, \phi) \in [0, \infty) \times [0, 2\pi) \mid r \ge 1$$

for some $\rho \ge 0$ and $0 \le \theta < 2\pi$ s.t. (b)} (14)

where $\{\cdot\}$ denotes a complementary set. In [1], the set (14) was characterized in the second paragraph of the proof as

$$(14) = \overline{\left\{ (R,\phi) \in [0,\infty) \times [0,2\pi) \mid \phi \leq \frac{\pi}{2} + R\tau \text{ or } \phi \geq \frac{3\pi}{2} - R\tau \right\}}$$

= $\left\{ (R,\phi) \in [0,\infty) \times [0,2\pi) \mid \phi > \frac{\pi}{2} + R\tau \text{ and } \phi < \frac{3\pi}{2} - R\tau \right\}.$ (15)

The set (15) is "the interior of the triangular region with vertices $(0, \pi/2)$, $(0, 3\pi/2)$ and $(\pi/2, \pi)$ in the (R, ϕ) plane" described in the second paragraph of Theorem 2.6, and it was concluded in Theorem 2.6 that (15) is the stability region.

However, (13) was not treated as a subset but as an equivalent set of (12) in [1]. In fact, the equation (2.7a) was not used throughout the proof of Theorem 2.6 in [1]. This implies that the conclusion that all roots of (8) have negative real parts if and only if $b \in \mathbb{C}$ lies inside the region bounded by (15) is erroneous, because (13) is actually a subset of (12). Instead, Theorem 2.6 of [1] is only a sufficient condition, but not a necessary condition, for all roots of (8) to have negative real parts.

B. Modification of Theorem 2 in [2]: A Sufficient Condition

Another error in the derivation of Theorem 2 in [2] is the mis-application of Theorem 2.6 in [1]. The region (R, ϕ) had been defined as the radius and angle from the origin in [1], but the authors of [2] measured the angle ϕ from 1 + j0.

In view of all the corrections above, Theorem 2 of [2] can be amended as follows.

Theorem A: Suppose Assumptions 1 and 2 hold. Let the eigenvalues of J be denoted by $\gamma_i = R_i e^{j\theta_i}$ for $i = 1, 2, \dots, n$. Then, all roots of (2) have negative real parts at $(\bar{\boldsymbol{m}}, \bar{\boldsymbol{p}})$, if $(\sqrt{R_i}/k)e^{(j\theta_i/2)}$ and $-(\sqrt{R_i}/k)e^{(j\theta_i/2)}$ lie inside the region bounded by the arcs of Archimedean spirals

$$R = \begin{cases} \frac{2\theta - \pi}{k\tau} & \text{for } \frac{\pi}{2} < \theta < \pi\\ \frac{3\pi - 2\theta}{k\tau} & \text{for } \pi < \theta < \frac{3\pi}{2} \end{cases}$$
(16)

for all $i = 1, 2, \dots, n$, where the tuple (R, θ) defines the distance and the angle of the boundary measured from the origin.

Remark 2: It should be noted that Theorem A is only a sufficient condition for local stability. Corollary 1 and Theorem 3 of [2] should also be corrected as sufficient conditions accordingly, since the derivation of these results are based on Theorem 2 of [2].

The stability region obtained from Theorem B is illustrated with the dashed line in Fig. 1(a).

V. NECESSARY AND SUFFICIENT CONDITION

The necessary and sufficient condition for the local stability of the gene regulatory networks with time delay was recently derived in [5] based on the idea presented in [4]. We here briefly review the condition.

Theorem B (Lemma 2 of [5]): Suppose Assumption 1 holds. All roots of (2) have negative real parts if and only if all the eigenvalues γ_i ($i = 1, 2, \dots, n$) of J lie inside the region Ω_+^c , i.e., $\gamma_i \in \Omega_+^c$ ($i = 1, 2, \dots, n$), where

$$\Omega_{+}^{c} := \{ \lambda \in \mathbb{C} \mid \phi(s)e^{s\tau} \neq \lambda; \quad \forall s \in \mathbb{C}_{+} \}$$
(17)

and $\phi(s) := (s + k_p)(s + k_m)$.

The region Ω_+^c is the smallest open set that is bounded by $\{\phi(j\omega)e^{j\omega\tau} \ \omega \in \mathbb{R}\}$ and includes the origin as illustrated in Fig. 3. In particular, $\{\phi(j\omega)e^{j\omega\tau} \ \omega \in \mathbb{R}\}$ can be specifically written as

$$\{x + jy | x = (-\omega^2 + k_p k_m) \cos(\omega\tau) - (k_p + k_m)\omega \sin(\omega\tau) y = (-\omega^2 + k_p k_m) \sin(\omega\tau) + (k_p + k_m)\omega \cos(\omega\tau); \omega \in \mathbb{R} \}.$$

It should be emphasized that Theorem B is more general than Theorem A in that (i) it is the necessary and sufficient condition, and (ii) it does not require Assumption 2, which is restrictive when applied to existing biological applications.

Remark 3: The idea of Lemma 2 of [5] comes from Proposition 5.1 of [4], in which the stability condition for $\tau = 0$ was presented. We note that Lemma 2 in [5] was shown for the case where the genes interact in a cyclic way (the matrix K defined in [5] has a cyclic structure), but it can be easily generalized for any interaction structure, since the information of the interaction structure was not used in the proof of Lemma 2 of [5].

The stability region Ω_+^c and the eigenvalues of J for the numerical example illustrated in Section III are plotted in Fig. 3.



Fig. 3. Necessary and sufficient stability region shown in Theorem B.

We see that two eigenvalues are located outside the stability region Ω_+^c , thus Theorem B implies (1) is locally unstable at the unique equilibrium. This result is consistent with the observations presented in Figs. 1(b) and 2.

When the delays due to splicing and transport are small compared to transcription and translation, one can approximately set $\tau_{m_i} = \tau_{p_i} = 0$ $(i = 1, 2, \dots, n)$. Theorem B can then be reduced to a simpler graphical condition, and we can analytically derive a necessary and sufficient stability condition in terms of reaction rates [6]. The effect of each reaction rate on oscillations was discussed in detail in [6].

ACKNOWLEDGMENT

The authors would like to thank Prof. L. Chen and Prof. K. Aihara for constructive discussions.

REFERENCES

- [1] J. Belair, "Stability in a model of a delayed neural network," J. Dynamics Differential Equations, vol. 5, no. 4, pp. 607–623, 1993.
- [2] L. Chen and K. Aihara, "Stability of genetic regulatory networks with time delay," *IEEE Trans. Circuits Syst. I, Reg. Papers*, vol. 49, no. 5, pp. 602–608, 2002.
- [3] M. B. Elowitz and S. Leibler, "A synthetic oscillatory network of transcription regulators," *Nature*, vol. 403, no. 6767, pp. 335–338, 2000.
- [4] S. Hara, T. Hayakawa, and H. Sugata, "LTI systems with generalized frequency variables: A unified frameworkfor homogeneous multiagent dynamical systems," *SICE J. Control, Meas. Syst. Integr.*, vol. 2, no. 5, pp. 299–306, 2009.
- [5] Y. Hori, M. Takada, and S. Hara, "Biochemical oscillations in delayed negative cyclic feedback: Existence and profiles," *Automatica*, vol. 49, no. 9, pp. 2581–2590, 2013.

[6] Y. Hori, T.-H. Kim, and S. Hara, "Existence criteria of periodic oscillations in cyclic gene regulatory networks," *Automatica*, vol. 47, no. 6, pp. 1203–1209, 2011.



Masaaki Takada received the B.E. and M.S. degrees in mathematical engineering and information physics from the University of Tokyo, Tokyo, Japan, in 2010 and 2012, respectively.

He is currently with NS Solutions Corporation as a researcher. His research interests include the analytical infrastructure for big data and its applications.

Mr. Takada was awarded Poster Award (Gold Prize) at the 1st International Symposium on Innovative Mathematical Modelling.



Yutaka Hori received the B.E., M.S., and Ph.D. degrees in information science and technology from the University of Tokyo, Tokyo, Japan, in 2008, 2010, and 2013, respectively.

In 2010–2011, he was a visiting student at University of California, Santa Barbara, CA, USA. He is currently with California Institute of Technology, Pasadena, CA, USA, as a postdoctoral scholar. His research interests lie in systems and synthetic biology using feedback control theory.

Dr. Hori was awarded Annual Conference Young Author's Award at 2009 ICROS-SICE International Joint Conference, Best Student Paper Award Finalist at 2010 IEEE Multi-Conference on Systems and Control and Best Paper Award Finalist at 2011 Asian Control Conference. He also received three conference awards from SICE.



Shinji Hara received the B.S., M.S., and Ph.D. degrees in engineering from Tokyo Institute of Technology, Tokyo, Japan, in 1974, 1976 and 1981, respectively.

In 1984 he joined Tokyo Institute of Technology as an Associate Professor and had served as a Full Professor for ten years. Since 2002 he has been a Full Professor of Department of Information Physics and Computing, The University of Tokyo.

Dr. Hara was the General Chair of the CCA04, the Program Co-Chair of the 17th IFAC World Congress

in Seoul, the President of SICE in 2009, the Vice President of IEEE CSS for membership activities in 2009–2010, IFAC Council member since 2011, and associate editors of several international journals including IEEE TRANS. ON AUTOMATIC CONTROL and Automatica. He is Fellow of IEEE, IFAC, and SICE. He received George S. Axelby Outstanding Paper Award from IEEE Control System Society in 2006. He also received Best Paper Awards from SICE several times. His current research interests are in robust control, decentralized control for networked dynamical systems, glocal control, systems biology, and computational aspects of control system design.