A LIAPUNOV FUNCTION FOR FOUR-DIMENSIONAL POSITIVE FEEDBACK SYSTEMS*

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Abstract. In this paper, we use elementary symmetric polynomials in parameters to construct a Liapunov function for four-dimensional positive feedback systems. By applying it, we give a sufficient condition for every positive-time trajectory to converge to an equilibrium.

1. Introduction. The biochemical feedback loops may be modeled by the following system:

$$\begin{aligned}\dot{x}_1 &= f(x_n) - a_1 x_1, \\ \dot{x}_i &= x_{i-1} - a_i x_i, \quad 2 \leq i \leq n,\end{aligned}\tag{1}$$

where $a_i > 0$ for $i = 1, 2, \dots, n$, and f is a C^1 function with $f(x_n) > 0$ for $x_n > 0$. The x_i represent chemical concentrations so the natural domain is the positive orthant $\mathbb{R}_+^n$. If $f' \geq 0$, the system describes a positive feedback loop [1, 2, 6, 7]. For the positive feedback system with $n = 2$ or $n = 3$, Selgrade [1, 2] shows that every positive-time trajectory converges to an equilibrium under appropriate conditions. Hirsch [5] provides another proof of Selgrade's result under slightly different assumptions. In earlier work [9], the author presents a criterion for convergence of solutions of (1) with $n = 3$. By applying it to positive feedback loops, we can easily prove that every bounded solution of (1) is convergent. This criterion can also be applied to negative feedback loops and other systems. For higher dimensions, Hirsch [4] verifies that the positive-time trajectory of almost every point in $\mathbb{R}_+^n$ is asymptotic to the equilibria. Moreover, Hirsch [5, p. 105] points out: "It is not known if the stronger results in dimension three can be generalized to n dimensions." Because Selgrade [3] shows that a Hopf bifurcation can occur in the n -dimensional positive feedback system (1) for $n \geq 5$, the stronger result which holds for $n = 2$ and $n = 3$ is not possible for $n \geq 5$; meanwhile, he points out: "The existence of periodic solutions is not clear" in four dimensions (see [3, p. 348]). Therefore, the convergence question in four-dimensional positive feedback systems is still open.

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The aim of this article is to construct a Liapunov function [8, 9, 10, 11] for four-dimensional positive feedback loops by using elementary symmetric polynomials in parameters a_1, a_2, a_3 , and a_4 . By applying it, we shall give a sufficient condition for every solution of (1) for $n = 4$ to approach an equilibrium; furthermore, if the equilibrium set is not a singleton, then the equilibrium is not the same for all solutions.

Henceforth, we assume $n = 4$ and replace a_1, a_2, a_3 , and a_4 by a, b, c , and d respectively.

2. The main results. Let $A = a + b + c + d$, $B = ab + ac + ad + bc + bd + cd$, $C = abc + abd + acd + bcd$, and $D = abcd$. Therefore, A, B, C , and D are elementary symmetric polynomials in the parameters a, b, c , and d .

Define a function g for $x_4 \geq 0$ by

$$g(x_4) = f(x_4) - Dx_4.$$

The zeros of g determine the equilibria of (1). To be more precise, the equilibrium set of (1) is

$$E = \{x_4 \Phi : g(x_4) = 0\},$$

where $\Phi = (bcd, cd, d, 1)$. Therefore, E is bounded if and only if the zero set of g is bounded. In this case we denote by x_4^* and y_4^* the smallest zero and the largest zero of g respectively.

The main result is stated as follows:

THEOREM 1. Suppose that f is a C^1 function with $f(x_4) > 0$ for $x_4 > 0$. If there exist sequences $w_k \rightarrow \infty$ such that $f(w_k) \leq Dw_k$ for $k = 1, 2, \dots$, and

$$0 \leq f'(x_4) < 4A(ABC - C^2 - A^2D)/C \quad (2)$$

for $x_4 > 0$, then every solution of (1) converges to an equilibrium. In particular, if the equilibrium set of (1) is bounded and the right inequality of (2) holds for $x_4^* \leq x_4 \leq y_4^*$, then every solution of (1) converges to an equilibrium.

For the Griffith model [6] we have

$$f(x_4) = x_4^p / (1 + x_4^p),$$

where p is a positive integer. For the Tyson-Othmer model [7] we have

$$f(x_4) = (1 + x_4^p) / (K + x_4^p),$$

where p is a positive integer and $K > 1$.

COROLLARY 2. (i) If

$$\frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p} C < 4A(ABC - C^2 - A^2D), \quad (3)$$

then every solution of the Griffith equations converges to an equilibrium.

(ii) If

$$\frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p} (K-1)K^{-(p+1)/p} C < 4A(ABC - C^2 - A^2D), \quad (4)$$

then every solution of the Tyson-Othmer equations converges to an equilibrium.

REMARK 1. For fixed p , $\lim_{K \rightarrow \infty} (K-1)K^{-(p+1)/p} = 0$, which means that for fixed parameters a, b, c , and d , (4) holds for sufficiently large K .

3. The proof of results. In order to show that Theorem 1 has meaning, it is necessary to prove the following lemma.

LEMMA 1. $F = ABC - C^2 - A^2D > 0$.

Proof. A long calculation gives

$$\begin{aligned} F = & 2(C^2 + a^3bcd + b^3acd + c^3abd + d^3abc) \\ & + a^3b^2c + a^3c^2b + b^3a^2c + b^3c^2a + c^3a^2b + c^3b^2a \\ & + a^3b^2d + a^3d^2b + b^3a^2d + b^3d^2a + d^3a^2b + d^3b^2a \\ & + a^3c^2d + a^3d^2c + c^3a^2d + c^3d^2a + d^3a^2c + d^3c^2a \\ & + b^3c^2d + b^3d^2c + c^3b^2d + c^3d^2b + d^3b^2c + d^3c^2b. \end{aligned}$$

Since a, b, c , and d are positive, $F > 0$.

LEMMA 2. If $f(x_4) > 0$ and $f'(x_4) \geq 0$ for $x_4 > 0$, and there exist sequences $w_k \rightarrow \infty$ such that $f(w_k) \leq Dw_k$ for $k = 1, 2, \dots$, then every solution of (1) is bounded.

This lemma is (b) of [4, Theorem 5.1].

It remains to prove that under the condition (2) every bounded solution of (1) converges to an equilibrium.

Let $L = \{t\Phi : t \geq 0\}$. Then $E \subset L$. We shall make a rotation transformation such that all equilibria lie on the x -axis. For this goal, the following transformation suffices:

$$\begin{aligned} x &= x_4, \\ y &= x_3 - dx_4, \\ z &= x_2 - (c+d)x_3 + d^2x_4, \\ u &= x_1 + ax_2 - (B-ab)x_3 + (A-d)d^2x_4. \end{aligned} \tag{5}$$

Transforming (1) by (5), we have

$$\begin{aligned} \dot{x} &= y, \\ \dot{y} &= z, \\ \dot{z} &= u - Az, \\ \dot{u} &= -Dx - Cy - Bz + f(x). \end{aligned} \tag{6}$$

Since (1) and (6) are equivalent, we only have to construct a Liapunov function for (6).

Analysing the characteristic of the Liapunov function for three-dimensional feedback systems constructed in [9], we find that the Liapunov function is the sum of three classes of functions. One is a quadratic form, another is a product of the feedback function f and a linear homogeneous function for variables, and the third is a

product of a constant and the integral of the feedback function f . Enlightened by this idea, we shall try to construct a Liapunov function for (6) that has the form:

$$V = a_{11}x^2 + a_{22}y^2 + a_{33}z^2 + a_{44}u^2 + 2a_{12}xy + 2a_{13}xz + 2a_{14}xu \\ + 2a_{23}yz + 2a_{24}yu + 2a_{34}zu + (b_1x + b_2y + b_3z + b_4u)f(x) + c_1 \int_0^x f(t) dt.$$

Choosing the coefficients a_{ij} , b_k , c_1 suitably so that V decreases along the solutions of (6) with increasing time, we obtain that

$$V(x, y, z, u) = \frac{1}{2}AD^2x^2 + \frac{1}{2}(AC^2 + ABD - CD)y^2 + \frac{1}{2}(BC - AD)z^2 \\ + \frac{1}{2}Cu^2 + ACDxy + CDxz + C^2yz + ADyu \\ - (ACy + Cz)f(x) - AD \int_0^x f(t) dt. \quad (7)$$

Proof of Theorem 1. If one differentiates V in (7) along a solution of (6), one finds

$$\frac{dV}{dt} = -(ABC - C^2 - A^2D)z^2 - ACf'(x)(y^2 + yz/A) \\ = -(ABC - C^2 - A^2D - Cf'(x)/4A)z^2 - ACf'(x)(y + z/2A)^2 \\ \leq -(ABC - C^2 - A^2D - Cf'(x)/4A)z^2, \quad (8)$$

where the last inequality follows from (2). By (2) and (8), $\frac{dV}{dt} \leq 0$, and $\frac{dV}{dt} = 0$ implies that $z = 0$. Since the systems (1) and (6) are equivalent, it follows from Lemma 2 that every solution of (6) is bounded.

Suppose $(x(t), y(t), z(t), u(t))$ is an arbitrary solution of (6). Then $\lim_{t \rightarrow \infty} z(t) = 0$ by LaSalle's invariance principle (see [8, Theorem 2]). Denote by Ω the limit set of this solution. Therefore, Ω is a compact, connected subset of the plane $\{z = 0\}$. For any $(x_0, y_0, z_0, u_0) \in \Omega$, (6) has one solution $(x_0(t), y_0(t), z_0(t), u_0(t))$ with initial point (x_0, y_0, z_0, u_0) defined on $\mathbb{R}$ such that $(x_0(t), y_0(t), z_0(t), u_0(t)) \in \Omega$ for any $t \in \mathbb{R}$. So $z_0(t) \equiv 0$, $u_0(t) \equiv 0$, $y_0(t) \equiv y_0$, and $x_0(t) = y_0t + x_0$. Since $(x_0(t), y_0(t), z_0(t), u_0(t)) \in \Omega$ for any t and Ω is compact, $y_0 = 0$. This proves $(x_0, y_0, z_0, u_0) = (x_0, 0, 0, 0)$ is an equilibrium of (6); that is, Ω consists of equilibria of (6). Equivalently, every solution of (1) approaches the set of equilibria E . The nature of equilibria shows that E is simply ordered; by the corollary to Theorem 2.3 of [4] this implies that in fact every solution of (1) converges to an equilibrium.

We write $p \leq q$ ($p < q$), where p and q are vectors in $\mathbb{R}^4$, in case the specified inequality holds component-wise. If p and q are two vectors with $p \leq q$ ($p < q$), let $[p, q] = \{r : p \leq r \leq q\}$ ($[[p, q]] = \{r : p < r < q\}$). If $r \in \mathbb{R}_+^4$, we denote by $\omega(r)$ the omega limit set of r and by $r(t)$ the solution of (1) with initial point r .

Now suppose the equilibrium set of (1) is bounded. Let $p^* = x_4^*\Phi$ and $q^* = y_4^*\Phi$. We shall prove that $\omega(r) \subset [p^*, q^*]$ for any $r \in \mathbb{R}_+^4$.

Since x_4^* and y_4^* are the smallest zero and the largest zero of g , respectively, $g(x_4) < 0$ for $x_4 > y_4^*$, and if $x_4^* > 0$ then $g(x_4) > 0$ for $0 \leq x_4 \leq x_4^*$. It

follows from [2, Lemma 5.1] that $\omega(p) = p^*$ for any $p \in L$ with $0 \leq p \leq p^*$ and $\omega(q) = q^*$ for any $q \in L$ with $q > q^*$. For any $r \in \mathbb{R}_+^4$, there exists $p \in L$ with $p > q^*$ such that $0 \leq r < p$. From the Kamke theorem [2, Theorem 2.2] we obtain that $\omega(r) \subset [p^*, q^*]$. Because (2) holds for $x_4^* \leq x_4 \leq y_4^*$ and f is a C^1 function, there exist $\varepsilon_1 \geq 0$ and $\varepsilon_2 > 0$ such that (2) also holds for $x_4^* - \varepsilon_1 \leq x_4 \leq y_4^* + \varepsilon_2$. We note that if $x_4^* = 0$ then $\varepsilon_1 = 0$ and otherwise $\varepsilon_1 > 0$. Let $p_1 = (x_4^* - \varepsilon_1)\Phi$ and $q_1 = (y_4^* + \varepsilon_2)\Phi$. For any $r \in \mathbb{R}_+^4$, we have $\omega(r) \subset [p^*, q^*] \subset [p_1, q_1]$; hence there exists $t_0 > 0$ such that $r(t) \in [p_1, q_1]$ for $t > t_0$. By arguing as in the previous paragraphs we obtain that $\omega(r)$ is a singleton. This completes the proof.

REMARK 2. If E contains no more than two equilibria, then every positive-time trajectory of (1) converges towards one of them.

When E is a singleton, the conclusion follows immediately from [2, Theorem 5.4]. Suppose E only has two points p^* and q^* with $p^* < q^*$. From the proof of Theorem 1 it follows that $\omega(r) \subset [p^*, q^*]$ for any $r \in \mathbb{R}_+^4$. Let J denote the open line segment with endpoints p^* and q^* . Then [2, Lemma 5.1] tells us that either $\omega(r) = p^*$ for every $r \in J$ or $\omega(r) = q^*$ for every $r \in J$. The Kamke theorem implies that $\omega(r)$ is a singleton for $r \in [[p^*, q^*]]$. If there exists $r \in \mathbb{R}_+^4$ such that $\omega(r)$ is not a singleton, then $\omega(r)$ is contained in $\partial[p^*, q^*]$, where $\partial[p^*, q^*]$ denotes the boundary of $[p^*, q^*]$. Suppose $r^0 \in \omega(r) \setminus \{p^*, q^*\}$; then, by the invariance of $\omega(r)$, $r^0(t) \in \omega(r)$ for any $t \in \mathbb{R}$. Using the Kamke theorem and the technique in [12], we can prove that either $r^0(t) \in p^* + \pi^i$ for any $t \in \mathbb{R}$ or $r^0(t) \in q^* - \pi^j$ for any $t \in \mathbb{R}$, where $\pi^k = \{p \in \mathbb{R}_+^4 : p_k = 0\}$. This implies that there is at least one component of $r^0(t)$ such that it is constant. Without loss of generality we assume that $r_4^0 = p_4^*$ (the other cases can be proved in quite the same manner). Therefore, $(r_1^0(t), r_2^0(t), r_3^0(t))$ is the solution of the following linear system:

$$\begin{aligned}\dot{x}_1 &= -ax_1 + p_4^*, \\ \dot{x}_2 &= x_1 - bx_2, \\ \dot{x}_3 &= x_2 - cx_3.\end{aligned}\tag{9}$$

Since the unique equilibrium of (9) is globally asymptotically stable in $\mathbb{R}_+^3$, $(r_1^0(t), r_2^0(t), r_3^0(t))$ is unbounded for $-\infty < t < 0$. But $\omega(r)$ is compact and $(r_1^0(t), r_2^0(t), r_3^0(t), p_4^*) \in \omega(r)$ for any t , a contradiction. This proves $\omega(r)$ is a singleton.

Proof of Corollary 2. In the Griffith equations, we have

$$\begin{aligned}f(x_4) &= x_4^p(1 + x_4^p)^{-1}, \\ f'(x_4) &= px_4^{p-1}(1 + x_4^p)^{-2}, \\ f''(x_4) &= px_4^{p-2}(1 + x_4^p)^{-3}(p - 1 - (p + 1)x_4^p).\end{aligned}$$

Hence, when $x_4 = (\frac{p-1}{p+1})^{1/p}$, $f'(x_4)$ has maximum value, i.e.,

$$f'(x_4) < f'\left(p\sqrt{\frac{p-1}{p+1}}\right) = \frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1}\right)^{(p-1)/p} \quad \text{for } x_4 \neq \left(\frac{p-1}{p+1}\right)^{1/p}.$$

This shows that if (3) holds then (2) is true. By Theorem 1, every solution of the Griffith equations converges to an equilibrium. This proves (i).

In the Tyson-Othmer equations, we have

$$\begin{aligned} f(x_4) &= (1 + x_4^p)(K + x_4^p)^{-1}, \\ f'(x_4) &= p(K - 1)x_4^{p-1}(K + x_4^p)^{-2} \\ &= (K - 1)K^{-(p+1)/p} p(x_4 K^{-1/p})^{p-1} [1 + (x_4 K^{-1/p})]^{-2}. \end{aligned}$$

In the same manner as the proof of (i), we can prove that

$$f'(x_4) < (K - 1)K^{-(p+1)/p} \frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p} \quad \text{for } x_4 \neq \left(\frac{K(p-1)}{p+1} \right)^{1/p}.$$

This shows that (4) implies (2). The conclusion of (ii) follows immediately from Theorem 1.

4. Applications. In order to illustrate the usefulness of Theorem 1, we shall provide some idea about the size of the parameter set where inequality (2) may hold and present several examples.

If $f'(x_4)$ is bounded on $[0, \infty)$, then we define

$$M_f = \sup\{f'(x_4) : x_4 \geq 0\}.$$

When E is bounded, we only have to replace M_f by $\sup\{f'(x_4) : x_4^* \leq x_4 \leq y_4^*\}$.

Let

$$\begin{aligned} G(a, b, c, d) &= 4A(ABC - C^2 - A^2D)/C, \\ S(f) &= \{(a, b, c, d) : M_f < G\}. \end{aligned}$$

For a given C^1 function f with $f'(x_4) \geq 0$, (2) holds if and only if

$$(a, b, c, d) \in S(f).$$

Obviously, $\lim_{a+b+c+d \rightarrow \infty} G(a, b, c, d) = \infty$. Therefore, when $a + b + c + d$ is sufficiently large, every positive-time trajectory of (1) converges to an equilibrium.

Conversely, for fixed parameters a, b, c , and d , (2) holds if and only if any tangent line of the curve $y = f(x)$ does not intersect the straight line $y = Gx$ in the first quadrant. We can choose a great number of functions f satisfying such a property (see Fig. 1).

For a given M_f , it is difficult to describe the geometry of $S(f)$ completely. But if we fix two parameters, for example c and d , then we can discuss the size of $S(f)$. For simplicity, we take $c = d = 1$; the other cases are similar.

Clearly, $M_f < G$ if and only if

$$M_f C < 4AF. \quad (10)$$

When $c = d = 1$, $A = a + b + 2$, $C = 2ab + a + b$, and

$$\begin{aligned} F &= 2[2a^2b^2(a + b + 2) + 3ab(a^2 + b^2) + 2(a^3 + b^3) \\ &\quad + 6ab(a + b) + 3(a^2 + b^2) + 4ab + 2(a + b)]. \end{aligned}$$

FIG. 1

A calculation gives

$$\begin{aligned}
 4AF = & 8[2a^2b^2(a+b+2)^2 + 3ab(a+b)(a^2+b^2) + 6ab(a^2+b^2) \\
 & + 2(a+b)(a^3+b^3) + 4(a^3+b^3) + 6ab(a+b)^2 + 16ab(a+b) \\
 & + 3(a+b)(a^2+b^2) + 6(a^2+b^2) + 8ab + 2(a+b)^2 + 4(a+b)].
 \end{aligned} \quad (11)$$

This implies that

$$4AF > 64(a^2 + b^2) + 96ab + 32(a + b).$$

Define

$$H(a, b) = 64(a^2 + b^2) + (96 - 2M_f)ab + (32 - M_f)(a + b). \quad (12)$$

A sufficient condition for (10) to hold is

$$H(a, b) \geq 0; \quad (13)$$

that is, $(a, b, 1, 1) \in S(f)$. In the following, we shall decide the size of the parameters a and b where (13) may hold.

Case 1. $M_f \leq 32$.

From (12), we know that $H(a, b) > 0$ in this case; that is, (13) holds.

Case 2. $32 < M_f \leq 72$.

Changing the form of (12), we obtain that

$$H(a, b) = \frac{\lambda_1}{2} \left(a + b - \frac{M_f - 32}{112 - M_f} \right)^2 + \frac{\lambda_2}{2} (b - a)^2 - \frac{(M_f - 32)^2}{2(112 - M_f)}, \quad (14)$$

where $M_f \neq 112$, $\lambda_1 = 112 - M_f$, and $\lambda_2 = 16 + M_f$.

Let

$$\begin{aligned}
 a^* &= \frac{\sqrt{2}}{2} \left(a + b - \frac{M_f - 32}{112 - M_f} \right), \\
 b^* &= \frac{\sqrt{2}}{2} (b - a).
 \end{aligned}$$

FIG. 2

Then, in this case the curve $H(a, b) = 0$ is the ellipse

$$\lambda_1 a^{*2} + \lambda_2 b^{*2} = \frac{(M_f - 32)^2}{2(112 - M_f)},$$

whose graph Γ_{M_f} is shown in Fig. 2. Therefore, all points in the first quadrant, except those in the interior of Γ_{M_f} , satisfy (13).

Case 3. $72 < M_f \leq 117$.

We restrict a and b with

$$a + b \geq \frac{1}{2}. \quad (15)$$

It follows from (11) and (15) that

$$\begin{aligned} 4AF &\geq 8[2ab + a + b + 8(a^2 + b^2) + 12ab + 4(a + b)] \\ &= 8C + 64(a^2 + b^2) + 96ab + 32(a + b). \end{aligned}$$

Hence, a sufficient condition for (10) to hold is

$$64(a^2 + b^2) + 96ab + 32(a + b) \geq 2(M_f - 8)ab + (M_f - 8)(a + b). \quad (16)$$

Let

$$\bar{H}(a, b) = 64(a^2 + b^2) + (96 - 2\bar{M}_f)ab + (32 - \bar{M}_f)(a + b),$$

where $\bar{M}_f = M_f - 8$. Then (16) is equivalent to

$$\bar{H}(a, b) \geq 0. \quad (17)$$

Replacing M_f by $\bar{M}_f$ in Case 2, we know that $\bar{H}(a, b) = 0$ is the ellipse $\Gamma_{\bar{M}_f}$ whose graph is similar to Fig. 2. It is easy to prove that $a + b \geq \frac{1}{2}$ outside of $\Gamma_{\bar{M}_f}$. Hence, all points in the first quadrant, except those in the interior of $\Gamma_{\bar{M}_f}$, satisfy (17).

Case 4. $M_f > 117$.

In this case, $\lambda_1 < 0$. This implies that $H(a, b) = 0$ is a hyperbola indicated in Fig. 3. All points in I satisfy (13). Moreover, if $a + b$ is sufficiently large, then the point (a, b) in II also satisfies (13).

FIG. 3

Note that in the above discussion we have determined that (10) holds for many values of the parameters a and b .

From (3) and (4), we can prove that

$$M_f \leq \frac{(p+1)^2}{4p} = \frac{1}{4} \left(\sqrt{p} + \frac{1}{\sqrt{p}} \right)^2$$

for the Griffith model and the Tyson-Othmer model. Therefore, for integer p , $\frac{1}{4}(\sqrt{p} + \frac{1}{\sqrt{p}})^2 \leq i$ if and only if $p \leq (\sqrt{i} + \sqrt{i-4})^2$; that is, p is not larger than the integer part of $(\sqrt{i} + \sqrt{i-4})^2$. For example, if $i = 32$, then $p \leq 125$.

Fixing $c = d = 1$ in these models and applying the above results to them, we obtain that every positive-time trajectory of either the Griffith equations or the Tyson-Othmer equations converges to an equilibrium if any of the following conditions hold:

- (i) $p \leq 125$,
- (ii) $125 < p \leq 285$ and (a, b) is in the exterior of $\Gamma_{(p+1)^2/4p}$,
- (iii) $285 < p \leq 465$ and (a, b) is in the exterior of $\Gamma_{((p+1)^2/4p)-8}$,
- (iv) $p > 465$ and $(a, b) \in I$.

In order to make the Griffith model and the Tyson-Othmer model feasible in biochemistry, we require that the value of p is not too large. The above-mentioned results show that our method is good if p is not too large.

Finally, we present several examples to show the applications of Theorem 1.

EXAMPLE 1.

$$\begin{aligned} \dot{x}_1 &= -ax_1 + Dx_4 + \sin x_4, \\ \dot{x}_2 &= x_1 - bx_2, \\ \dot{x}_3 &= x_2 - cx_3, \\ \dot{x}_4 &= x_3 - dx_4, \end{aligned} \tag{18}$$

where $D = abcd \geq 1$.

Let $f(x_4) = Dx_4 + \sin x_4$. Then $f'(x_4) = D + \cos x_4 \geq 0$. This proves that (18) is a positive feedback system. $g(x_4) = f(x_4) - Dx_4 = \sin x_4$. Therefore, the equilibrium set of (18) is $E = \{n\pi\Phi : n = 0, 1, 2, \dots\}$, which is countably infinite. Applying Lemma 2, we know that every positive-time trajectory of (18) is bounded.

Obviously, $M_f = D + 1$. By Lemma 1,

$$F > 2C^2 > 2(a^2b^2c^2 + a^2b^2d^2 + b^2c^2d^2 + a^2c^2d^2),$$

which implies that

$$\begin{aligned} 4AF &> 8(a^2b^2c^2d + a^2b^2d^2c + a^2c^2d^2b + b^2c^2d^2a) \\ &= 8DC > 2DC \geq DC + C, \end{aligned}$$

where the last inequality follows from $D \geq 1$. Hence, (10) holds. From Theorem 1, we conclude that every positive-time trajectory of (18) tends to an equilibrium.

EXAMPLE 2.

$$\begin{aligned} \dot{x}_1 &= \frac{1 + x_4^2}{K + x_4^2} - ax_1, \\ \dot{x}_i &= x_{i-1} - ax_i, \quad 2 \leq i \leq 4. \end{aligned} \quad (19)$$

We claim that every solution of (19) converges towards an equilibrium if one of the following conditions holds:

- (i) $1 < K \leq 524245$;
- (ii) $K > 524245$ and $a^4 > 0.000003504$.

Clearly, $D = a^4$ and $G = 256a^4$. For (19), (4) becomes

$$\frac{3\sqrt{3}}{2048}(K-1)K^{-3/2} < D. \quad (20)$$

If $K > 524245$, then

$$\frac{3\sqrt{3}}{2048}(K-1)K^{-3/2} < \frac{3\sqrt{3}}{2048\sqrt{524245}} \doteq 0.000003504.$$

Therefore, (ii) implies (20). Applying Corollary 2, we obtain that every solution of (19) converges to an equilibrium.

It follows from Remark 2 that if (19) has no more than two equilibria, then every positive-time trajectory of (19) converges towards one of them. In the following, we shall prove that (19) has at least three equilibria. Therefore, in order to prove that our claim holds under condition (i), we only have to prove that if (19) has three equilibria then (20) is true. The proof of this statement is given below.

For (19),

$$g(x_4) = \frac{1 + x_4^2}{K + x_4^2} - Dx_4 = -\frac{Dx_4^3 + DKx_4 - x_4^2 - 1}{K + x_4^2}.$$

Let $F(x) = Dx^3 + DKx - x^2 - 1$. Then the zeros of $F(x)$ determine the equilibria of (19). Hence, (19) has at most three equilibria. Furthermore, the following conclusions can be proved:

If $1 < K \leq 9$, (19) has no more than two equilibria.

If $K > 9$, then (19) has three equilibria if and only if

$$\begin{aligned} \frac{1}{3K} \left[1 - \frac{K-9}{8K} \left(\frac{K-9}{K} + \sqrt{\left(\frac{K-9}{K} \right)^2 + \frac{8(K-9)}{K} + 4} \right) \right] &< D^2 \\ &< \frac{1}{3K} \left[1 - \frac{K-9}{8K} \left(4 + \frac{K-9}{K} - \sqrt{\left(\frac{K-9}{K} \right)^2 + \frac{8(K-9)}{K}} \right) \right]. \end{aligned} \quad (21)$$

In order to prove that (20) is true under (i), it suffices to prove that

$$\frac{1}{3K} \left[1 - \frac{K-9}{8K} \left(4 + \frac{K-9}{K} + \sqrt{\left(\frac{K-9}{K} \right)^2 + \frac{8(K-9)}{K}} \right) \right] \geq \frac{27(K-1)^2}{2048^2 K^3},$$

which is equivalent to

$$H(K) = \frac{81}{2048^2} \left(1 - \frac{1}{K} \right)^2 + \frac{1}{8} \left(1 - \frac{9}{K} \right) \left[5 - \frac{9}{K} + \sqrt{\left(1 - \frac{9}{K} \right)^2 + 8 \left(1 - \frac{9}{K} \right)} \right] \leq 1. \quad (22)$$

Obviously,

$$H(K) < \frac{81}{2048^2} + \frac{1}{8} \left(1 - \frac{9}{K} \right) \left(8 - \frac{9}{K} \right).$$

A sufficient condition for (22) to hold is

$$\frac{81}{2048^2} + \frac{1}{8} \left(1 - \frac{9}{K} \right) \left(8 - \frac{9}{K} \right) < 1. \quad (23)$$

For $K > 9$, (23) holds if and only if

$$K \leq \frac{2}{1 - \sqrt{1 - 131072^{-1}}}.$$

It is not difficult to prove that

$$\frac{2}{1 - \sqrt{1 - 131072^{-1}}} \geq 524245.$$

So far, we have proved that if $1 < K \leq 524245$, and (19) has three equilibria, then (20) is true. Our claim follows immediately from Corollary 2 and Remark 2.

EXAMPLE 3.

$$\begin{aligned} \dot{x}_1 &= \frac{x_4^p}{1 + x_4^p} - ax_1, \\ \dot{x}_i &= x_{i-1} - ax_i, \quad 2 \leq i \leq 4. \end{aligned} \quad (24)$$

In (24), we can calculate $D = a^4$ and $G = 256a^4$. From Corollary 2, we have

$$M_f = \frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p}.$$

Imitating [1, p. 221], we can prove that (24) has three equilibria if and only if

$$D = a^4 < \frac{1}{p}(p-1)^{(p-1)/p} := m(p).$$

The inequality

$$h(p) := \frac{(p+1)^2}{1024p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p} < a^4 \quad (25)$$

is needed for (3) to hold. Corollary 2 tells us that every positive-time trajectory of (24) converges to an equilibrium on condition that (25) holds. Moreover, even if (25) does not hold, from Remark 2, the same conclusion is true provided that $a^4 \geq m(p)$. If our result can be used, that is, (25) holds, and (24) has three equilibria, then $h(p) < a^4 < m(p)$, which means that $h(p) < m(p)$. Equivalently,

$$(p+1)^{(p+1)/p} < 1024. \quad (26)$$

The smallest integer p such that (26) is not true is 1016; that is, $h(p) < m(p)$ for $p \leq 1015$. A p -value of 1016 is too large to be biochemically feasible. For $p \leq 1015$, we conclude that if $a^4 > h(p)$, then our result can be used. Only when $h(p) < a^4 < m(p)$ does (24) have three equilibria. By numerical calculation, we give the values of $h(p)$ and $m(p)$ at $p = 1, 2, \dots, 20$, which are shown in the second and third column of Table 1. Table 1 shows that for small integer p the asymptotic behavior of solutions of (24) is not clear only in a very small parameter interval $0 < a^4 \leq h(p)$.

EXAMPLE 4.

$$\begin{aligned} \dot{x}_1 &= \frac{1 + x_4^p}{64 + x_4^p} - ax_1, \\ \dot{x}_i &= x_{i-1} - ax_i, \quad 2 \leq i \leq 4. \end{aligned} \quad (27)$$

For $p = 1, 2, \dots, 20$, we shall give the parameter interval in which (4) may hold. The calculation shows $D = a^4$, $G = 256a^4$, and

$$M_f = 63 \times 64^{-(p+1)/p} \frac{(p+1)^2}{4p} \left(\frac{p-1}{p+1} \right)^{(p-1)/p}.$$

Let $n(p) = 63 \times 64^{-(p+1)/p} h(p)$, where $h(p)$ is given in (25). Then, for (27), (4) becomes

$$a^4 > n(p). \quad (28)$$

Applying (ii) of Corollary 2, we know that if (28) holds then every solution of (27) converges to an equilibrium. As long as we know the value of $n(p)$ at p , we can decide the parameter interval in which (28) holds. The fourth column of Table 1 gives the values of $n(p)$ at $p = 1, 2, \dots, 20$.

Note that it is more difficult to give the interval of the parameter a^4 in which (27) has three equilibria than the interval in which (24) has three equilibria. But $(n(p), \infty)$ exactly contains a subinterval J_p on which (27) has three equilibria. For example, $p = 2$, J_2 can be obtained from (21). Example 2 shows that if J_p is given then our result is very effective to the Tyson-Othmer model.

TABLE 1

p	$h(p)$	$m(p)$	$n(p)$
1	0	0	0
2	0.002537184	0.5	0.000312192
3	0.003281044	0.529133684	0.000807444
4	0.004160959	0.569876764	0.001448135
5	0.005083461	0.606286627	0.002178131
6	0.006025200	0.637270409	0.002965528
7	0.006977367	0.663573060	0.003791634
8	0.007935854	0.686073742	0.004644957
9	0.008898469	0.705511579	0.005518095
10	0.009863935	0.722467406	0.006406087
11	0.010831457	0.737391664	0.007305489
12	0.011800508	0.750634836	0.008213840
13	0.012770729	0.762472091	0.009129340
14	0.013741867	0.773121827	0.010050634
15	0.014713734	0.782759308	0.010976692
16	0.015686194	0.791526706	0.011906713
17	0.016659140	0.799540512	0.012840066
18	0.017632490	0.806897078	0.013776246
19	0.018606180	0.813676794	0.014714845
20	0.019580159	0.819947272	0.015655530

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