

## A PASSIVITY-BASED STABILITY CRITERION FOR A CLASS OF BIOCHEMICAL REACTION NETWORKS

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**ABSTRACT.** This paper presents a stability test for a class of interconnected nonlinear systems motivated by biochemical reaction networks. The main result determines global asymptotic stability of the network from the diagonal stability of a *dissipativity matrix* which incorporates information about the passivity properties of the subsystems, the interconnection structure of the network, and the signs of the interconnection terms. This stability test encompasses the *secant criterion* for cyclic networks presented in [1], and extends it to a general interconnection structure represented by a graph. The new stability test is illustrated on a mitogen-activated protein kinase (MAPK) cascade model, and on a branched interconnection structure motivated by metabolic networks. The next problem addressed is the robustness of stability in the presence of diffusion terms. A compartmental model is used to represent the localization of the reactions, and conditions are presented under which stability is preserved despite the diffusion terms between the compartments.

**1. Introduction.** This paper continues the development of passivity-based stability criteria for interconnected systems motivated by classes of biochemical reaction networks. In [1,2] the authors studied a cyclic interconnection

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structure in which the first subsystem of a cascade is driven by a negative feedback from the last subsystem downstream. This cyclic feedback structure is ubiquitous in gene regulation networks [3–14], cellular signaling pathways [15, 16], and has also been noted in metabolic pathways [17, 18]. In [1, 2] the authors first presented a passivity interpretation of the “secant criterion” developed earlier in [8, 14] for the stability of linear cyclic systems, and next used this passivity insight to extend the secant criterion to nonlinear systems. The dynamic system

$$\dot{x} = f(x, u) \quad y = h(x, u), \quad (1)$$

$u, y \in \mathbb{R}$  is said to be *output strictly passive* (OSP) if there exists a  $C^1$  storage function  $S(x) \geq 0$  such that

$$\dot{S} = \nabla S(x)f(x, u) \leq -y^2 + \gamma uy \quad (2)$$

for some constant  $\gamma > 0$ . The notion of *passivity* evolved from an abstraction of energy conservation and dissipation in electrical and mechanical systems [19, 20], into a fundamental tool routinely used for nonlinear system design and analysis [21, 22].

The first contribution of this paper is to expand the analysis tool of [1] to a general interconnection structure, thus obtaining a broadly applicable stability criterion that encompasses the secant criterion for cyclic systems as a special case. As in [1], our approach is to exploit the OSP properties and the corresponding storage functions for smaller components that comprise the network, and to construct a composite Lyapunov function for the interconnection using these storage functions. The idea of using composite Lyapunov functions has been explored extensively in the literature of large-scale systems as surveyed in [23, 24], and led to several network small-gain criteria [25, 26] that restrict the strength of the interconnection terms. A distinguishing feature of our passivity-based criterion, however, is that we take advantage of the sign properties of the interconnection terms to obtain less conservative stability conditions than the small-gain approach.

To determine the stability of the resulting network of OSP subsystems we follow the formalism of [27, 28], and construct a *dissipativity matrix* (denoted by  $E$  below) that incorporates information about the OSP properties of the subsystems, the interconnection structure of the network, and the signs of the interconnection terms. As a stability test for the interconnected system, we check the *diagonal stability* [29] of this dissipativity matrix, that is, the existence of a diagonal solution  $D > 0$  to the Lyapunov equation  $E^T D + DE < 0$  which, if feasible, proves that the network is indeed stable. In particular, the diagonal entries of  $D$  serve as the weights of the storage functions in our composite Lyapunov function. Although similar results can be proven by combining the pure input/output approach in [27, 28] with appropriate detectability and controllability conditions, the direct Lyapunov approach employed in this paper allows us to formulate verifiable state-space

conditions that guarantee the desired passivity properties for the subsystems. These conditions are particularly suitable for systems of biological interest because they are applicable to models with nonnegative state variables, and do not rely on the knowledge of the location of the equilibrium.

The second contribution of this paper is to accommodate state products which are disallowed in the nonlinear model studied in [1]. This is achieved with a new storage function construction for each subsystem which, in the absence of state products, coincides with the construction in [1]. Thanks to this extension, our stability criterion is now applicable to a broader class of models, even in the case of cyclic systems. This class encompasses a mitogen activated protein kinase (MAPK) cascade model with inhibitory feedback proposed in [15,16], which is studied in Example 1 as an illustration of our main result. The final result in the paper employs a compartmental model to describe the spatial localization of the reactions, and proves that, if the passivity-based stability criterion holds for each compartment and if the storage functions satisfy an additional convexity property, then stability is preserved in the presence of diffusion terms between the compartments.

The paper is organized as follows: Section 2 gives an overview of the main results in [1]. Section 3 presents a general interconnection structure represented by a graph and gives the main stability result of the paper. Section 4 illustrates this result on biologically motivated examples. Section 5 studies robustness of stability in the presence of diffusion terms in a compartmental model. Section 6 gives the conclusions.

**2. Overview of the secant criterion for cyclic systems.** To evaluate stability properties of negative feedback cyclic systems, references [8,14] analyzed the Jacobian linearization at the equilibrium, which is of the form

$$A = \begin{bmatrix} -a_1 & 0 & \cdots & 0 & -b_n \\ b_1 & -a_2 & \ddots & & 0 \\ 0 & b_2 & -a_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -a_n \end{bmatrix} \quad (3)$$

$a_i > 0$ ,  $b_i > 0$ ,  $i = 1, \dots, n$ , and showed that  $A$  is Hurwitz if the following sufficient condition holds:

$$\frac{b_1 \cdots b_n}{a_1 \cdots a_n} < \sec(\pi/n)^n. \quad (4)$$

Unlike a *small-gain* condition which would restrict the right-hand side of (4) to be 1, the “secant criterion” (4) also exploits the phase of the loop and allows the right-hand side to be as high as 8 (when  $n = 3$ ). The secant criterion is also necessary for stability when the  $a_i$ ’s are identical.

Local stability of the equilibrium proven in [8,14], however, does not rule out the possibility of periodic orbits. Indeed, the Poincaré-Bendixson Theorem of Mallet-Paret and Smith for cyclic systems [30,31] allows such periodic

orbits to coexist with stable equilibria, as we illustrate on the system<sup>1</sup> :

$$\begin{aligned}\dot{x}_1 &= -x_1 + \varphi(x_3) \\ \dot{x}_2 &= -x_2 + x_1 \\ \dot{x}_3 &= -x_3 + x_2\end{aligned}\tag{5}$$

where

$$\varphi(x_3) = e^{-10(x_3-1)} + 0.1\text{sat}(25(x_3 - 1)),\tag{6}$$

and  $\text{sat}(\cdot) := \text{sgn}(\cdot) \min\{1, |\cdot|\}$  is a saturation<sup>2</sup> function. The function (6) is decreasing, and its slope has magnitude  $b_3 = 7.5$  at the equilibrium  $x_1 = x_2 = x_3 = 1$ . With  $a_1 = a_2 = a_3 = b_1 = b_2 = 1$  and  $n = 3$ , the secant criterion (4) is satisfied and, thus, the equilibrium is asymptotically stable. However, simulations in Figure 1 show the existence of a periodic orbit in addition to this stable equilibrium.

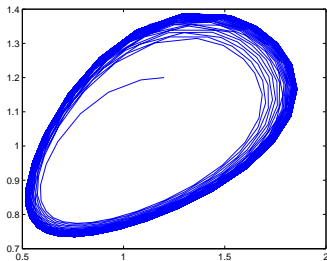


FIGURE 1. Trajectory of (5) starting from initial condition  $x = [1.2 \ 1.2 \ 1.2]^T$ , projected onto the  $x_1$ - $x_2$  plane.

To study *global* stability properties of cyclic systems with negative feedback, in [1, 2] the authors first developed a passivity interpretation of the secant criterion (4), and next used this passivity insight to extend the secant criterion to the nonlinear model:

$$\begin{aligned}\dot{x}_1 &= -f_1(x_1) + h_n(x_n) \\ \dot{x}_2 &= -f_2(x_2) + h_1(x_1) \\ &\vdots \\ \dot{x}_n &= -f_n(x_n) + h_{n-1}(x_{n-1})\end{aligned}\tag{7}$$

in which  $x_i \in \mathbb{R}_{\geq 0}$ ,  $f_i(\cdot)$ ,  $i = 1, \dots, n$  and  $h_i(\cdot)$ ,  $i = 1, \dots, n - 1$  are increasing functions, and  $h_n(\cdot)$  is a decreasing function which represents the inhibition of the formation of  $x_1$  by the end product  $x_n$ . When an

<sup>1</sup> Other authors have also noted the existence of such examples [32].

<sup>2</sup> One can easily modify this example to make  $\varphi(\cdot)$  smooth while retaining the same stability properties.

equilibrium  $x^*$  exists, [1] proves its global asymptotic stability under the following condition:

$$\left| \frac{\frac{\partial h_i(x_i)}{\partial x_i}}{\frac{\partial f_i(x_i)}{\partial x_i}} \right| \leq \gamma_i \quad \forall x_i \in \mathbb{R}_{\geq 0}, \quad i = 1, \dots, n, \quad (8)$$

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n, \quad (9)$$

which encompasses the linear secant criterion (4) with  $\gamma_i = b_i/a_i$ .

The first step in the global asymptotic stability proof of [1] is to represent (7) as the interconnection of  $n$  subsystems, each of which is OSP as in (2), thanks to the property (8). The next step is to show that the interconnected system is globally asymptotically stable if the matrix

$$E_{cyclic} = \begin{bmatrix} -1/\gamma_1 & 0 & \cdots & 0 & -1 \\ 1 & -1/\gamma_2 & \ddots & & 0 \\ 0 & 1 & -1/\gamma_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & 1 & -1/\gamma_n \end{bmatrix} \quad (10)$$

is *diagonally stable*; that is, if there exists a diagonal matrix  $D > 0$  such that

$$E_{cyclic}^T D + D E_{cyclic} < 0. \quad (11)$$

In particular, the diagonal entries of  $D$  constitute the weights of the storage functions in a composite Lyapunov function for (7), and (11) guarantees that the time derivative of this composite Lyapunov function is negative definite. Finally, [1] proves that the secant condition (9) is a necessary and sufficient condition for the diagonal stability of (10), thus connecting the secant condition to the global asymptotic stability of (7).

**3. From the cyclic structure to general graphs.** We now extend the diagonal stability procedure outlined above for cyclic systems to a general interconnection structure, described by a directed graph without self-loops. If a link is directed from node  $i$  to node  $j$ , we refer to node  $i$  as the *source* and to node  $j$  as the *sink* of the link. The nodes represent subsystems with possibly multiple outputs, and a separate link is used for each output. For the nodes  $i = 1, \dots, N$  and links  $l = 1, \dots, M$ , we denote by  $\mathcal{L}_i^+ \subseteq \{1, \dots, M\}$  the subset of links for which node  $i$  is the sink, and by  $\mathcal{L}_i^-$  the subset of links for which node  $i$  is the source. We write  $i = \text{source}(l)$  if  $l \in \mathcal{L}_i^-$ , and  $i = \text{sink}(l)$  if  $l \in \mathcal{L}_i^+$ . Using this graph we introduce the dynamic system:

$$\dot{x}_i = -f_i(x_i) + g_i(x_i) \sum_{l \in \mathcal{L}_i^+} h_l(x_{\text{source}(l)}) \quad i = 1, \dots, N \quad (12)$$

where  $x_i \in \mathbb{R}_{\geq 0}$ , and  $f_i(\cdot)$ ,  $g_i(\cdot)$ ,  $i = 1, \dots, N$ ,  $h_l(\cdot)$ ,  $l = 1, \dots, M$  are locally Lipschitz functions further restricted by the following assumptions:

A1:  $f_i(0) = 0$  and, for all  $\sigma \geq 0$ ,  $g_i(\sigma) > 0$ ,  $h_l(\sigma) \geq 0$ .

Assumption A1 guarantees that the nonnegative orthant  $\mathbb{R}_{\geq 0}^N$  is forward invariant for (12). The strict positivity of  $g_i(x_i)$  is also essential for our analysis since we exploit the sign properties of  $h_l(x_{\text{source}(l)})$  which are multiplied by  $g_i(x_i)$  in (12).

A2: There exists an equilibrium  $x^* \in \mathbb{R}_{\geq 0}^N$  for (12).

A3: For each node  $i$ , the function  $f_i(x_i)/g_i(x_i)$  satisfies the *sector* property:

$$(x_i - x_i^*) \left( \frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right) > 0 \quad \forall x_i \in \mathbb{R}_{\geq 0} - \{x_i^*\}. \quad (13)$$

A4: For each node  $i$ , and for each link  $l \in \mathcal{L}_i^-$ , the function  $h_l(x_i)$  satisfies one of the following sector properties for all  $x_i \in \mathbb{R}_{\geq 0} - \{x_i^*\}$ :

$$(x_i - x_i^*)[h_l(x_i) - h_l(x_i^*)] > 0 \quad (14)$$

$$(x_i - x_i^*)[h_l(x_i) - h_l(x_i^*)] < 0. \quad (15)$$

To distinguish between positive and negative feedback signals we assign to each link  $l$  a positive sign if (14) holds, and a negative sign if (15) holds, and rewrite (14)-(15) as

$$\text{sign}(\text{link } l)(x_i - x_i^*)[h_l(x_i) - h_l(x_i^*)] > 0 \quad (16)$$

$\forall x_i \in \mathbb{R}_{\geq 0} - \{x_i^*\}$ .

A5: For each link  $l \in \mathcal{L}_i^-$  there exists a constant  $\gamma_l > 0$  such that,  $\forall x_i \in \mathbb{R}_{\geq 0} - \{x_i^*\}$ ,

$$\text{sign}(\text{link } l) \frac{h_l(x_i) - h_l(x_i^*)}{\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)}} \leq \gamma_l. \quad (17)$$

**THEOREM 1.** *Consider the system (12), and suppose assumptions A1-A5 hold. If the  $M \times M$  dissipativity matrix*

$$E_{lk} = \begin{cases} -1/\gamma_l & \text{if } k = l \\ \text{sign}(\text{link } k) & \text{if } \text{source}(l) = \text{sink}(k) \\ 0 & \text{otherwise} \end{cases} \quad (18)$$

*is diagonally stable; that is, if there exists a diagonal matrix  $D > 0$  such that*

$$E^T D + D E < 0, \quad (19)$$

*then the equilibrium  $x^*$  is asymptotically stable. If, further, for each node  $i$  one of the following two conditions holds, then  $x^*$  is globally asymptotically stable in  $\mathbb{R}_{\geq 0}^N$ :*

a)  $\mathcal{L}_i^-$  is nonempty and there exists at least one link  $l \in \mathcal{L}_i^-$  such that

$$\lim_{x_i \rightarrow \infty} \int_{x_i^*}^{x_i} \frac{h_l(\sigma) - h_l(x_i^*)}{g_i(\sigma)} d\sigma = \infty, \quad (20)$$

b)  $\mathcal{L}_i^-$  is empty; that is, the outdegree of node  $i$  is zero;

$$\lim_{x_i \rightarrow \infty} \int_{x_i^*}^{x_i} \frac{\sigma - x_i^*}{g_i(\sigma)} d\sigma = \infty, \quad (21)$$

and there exists a class- $\mathcal{K}_\infty$  function<sup>3</sup>  $\omega(\cdot)$  such that

$$(x_i - x_i^*) \left( \frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right) \geq |x_i - x_i^*| \omega(|x_i - x_i^*|) \quad \forall x_i \geq 0. \quad (22)$$

*Proof.* We first prove the theorem for the case when  $\mathcal{L}_i^-$  is nonempty for all  $i = 1, \dots, N$ ; that is, when there are no nodes with outdegree equal to zero. In this case we construct a composite Lyapunov function of the form

$$V(x - x^*) = \sum_{l=1}^M d_l V_l(x_{\text{source}(l)} - x_{\text{source}(l)}^*) \quad (23)$$

in which the components are

$$V_l(x_{\text{source}(l)} - x_{\text{source}(l)}^*) = \text{sign}(\text{link } l) \int_{x_{\text{source}(l)}^*}^{x_{\text{source}(l)}} \frac{h_l(\sigma) - h_l(x_{\text{source}(l)}^*)}{g_{\text{source}(l)}(\sigma)} d\sigma \quad (24)$$

and the coefficients  $d_l > 0$  are to be determined. The function (23) is positive definite because each component  $V_l$  is a positive definite function of  $(x_{\text{source}(l)} - x_{\text{source}(l)}^*)$  due to the sign property (16) of the integrand in (24), and because  $(x_{\text{source}(l)} - x_{\text{source}(l)}^*) = 0$ ,  $l = 1, \dots, M$ , guarantees  $x - x^* = 0$  by virtue of the fact that each node is the source for at least one link.

We now claim that the function  $V_l$  in (24) satisfies the dissipativity property

$$\dot{V}_l \leq y_l \sum_{k=1}^M E_{lk} y_k \quad (25)$$

where

$$y_l := \text{sign}(\text{link } l) [h_l(x_{\text{source}(l)}) - h_l(x_{\text{source}(l)}^*)] \quad (26)$$

$l = 1, \dots, M$ , and the coefficients  $E_{lk}$  are as in (18). Before we prove this claim, we first note that the diagonal stability property (19) and the estimate (25) together imply that the Lyapunov function (23), with coefficients  $d_l$  obtained from the diagonal elements of  $D$ , yields a negative definite derivative because

$$\dot{V} = \sum_{l=1}^M d_l \dot{V}_l \leq \sum_{l=1}^M d_l y_l \sum_{k=1}^M E_{lk} y_k = \frac{1}{2} y^T (E^T D + D E) y. \quad (27)$$

Asymptotic stability of  $x^*$  thus follows from (19). If, further, for each node  $i$  there exists at least one link  $l \in \mathcal{L}_i^-$  such that (20) holds, then the Lyapunov

<sup>3</sup>  $\mathcal{K}$  is the class of functions  $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$  which are zero at zero, strictly increasing and continuous.  $\mathcal{K}_\infty$  is the subset of class- $\mathcal{K}$  functions that are unbounded.

function (23) grows unbounded as  $|x| \rightarrow \infty$ , thus proving global asymptotic stability.

We now show that the claim (25) is indeed true. To this end we compute from (24) and (12) the derivative

$$\dot{V}_l = \text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)] \left( -\frac{f_i(x_i)}{g_i(x_i)} + u_i \right) \quad (28)$$

where  $i = \text{source}(l)$ , and

$$u_i := \sum_{k \in \mathcal{L}_i^+} h_k(x_{\text{source}(k)}). \quad (29)$$

Adding and subtracting

$$u_i^* := \sum_{k \in \mathcal{L}_i^+} h_k(x_{\text{source}(k)}^*) = \frac{f_i(x_i^*)}{g_i(x_i^*)} \quad (30)$$

within the bracketed term in (28), we obtain

$$\dot{V}_l = \text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)] \left( -\frac{f_i(x_i)}{g_i(x_i)} + \frac{f_i(x_i^*)}{g_i(x_i^*)} + u_i - u_i^* \right). \quad (31)$$

Next, we note that  $\text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)]$  and  $\left( \frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right)$  possess the same signs due to (13) and (16), and thus, the left-hand side of the inequality (17) is positive. This means that we can rewrite (17), by taking reciprocals of both sides, as

$$-\text{sign}(\text{link } l) \frac{\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)}}{h_l(x_i) - h_l(x_i^*)} \leq -\frac{1}{\gamma_l}, \quad (32)$$

and multiply each side by  $[h_l(x_i) - h_l(x_i^*)]^2$  to obtain:

$$-\text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)] \left( \frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right) \leq -\frac{1}{\gamma_l} [h_l(x_i) - h_l(x_i^*)]^2. \quad (33)$$

Substituting (33) in (31), and using the variables  $y_l$  defined in (26), we get

$$\dot{V}_l \leq -\frac{1}{\gamma_l} y_l^2 + y_l(u_i - u_i^*) \quad (34)$$

which is an OSP property as in (2) with respect to input  $(u_i - u_i^*)$ . Finally, noting from (29) and (30) that

$$u_i - u_i^* = \sum_{k \in \mathcal{L}_i^+} \text{sign}(\text{link } k) y_k, \quad (35)$$

we rewrite (34) as

$$\dot{V}_l \leq -\frac{1}{\gamma_l} y_l^2 + y_l \sum_{k \in \mathcal{L}_i^+} \text{sign}(\text{link } k) y_k, \quad (36)$$

which is equivalent to (25) by the definition of the coefficients  $E_{kl}$  in (18).



If there exist nodes with outdegree equal to zero, then the arguments above prove that the subsystem comprising of the nodes with outdegree one or more is asymptotically stable. The outputs  $h_l$  from this subsystem serve as inputs to the nodes with outdegree equal to zero. Because the dynamics of these nodes in (12) are asymptotically stable by A3, asymptotic stability for the equilibrium  $x^*$  for the full system follows from standard results on cascade interconnections of asymptotically stable systems (see *e.g.* [33, p. 275]). To insure *global* asymptotic stability, we show that when condition (b) holds, (22) and (21) imply an *input-to-state stability* (ISS) property [34] for the driven subsystem of the cascade; that is, each node  $i$  with outdegree equal to zero satisfies:

$$\sup_{t \geq 0} |x_i(t) - x_i^*| \leq \max\{\gamma_0(|x_i(0) - x_i^*|), \gamma(\sup_{t \geq 0} |u_i(t) - u_i^*|)\} \quad (37)$$

$$\limsup_{t \rightarrow \infty} |x_i(t) - x_i^*| \leq \gamma(\limsup_{t \rightarrow \infty} |u_i(t) - u_i^*|) \quad (38)$$

for some class- $\mathcal{K}$  functions  $\gamma_0(\cdot)$  and  $\gamma(\cdot)$ . As shown in [34–36], the ISS property (37)-(38) follows if there exists an *ISS Lyapunov function*  $V_{ISS}^i(x_i)$  and a class- $\mathcal{K}$  function  $\chi(\cdot)$  satisfying the property:

$$|x_i - x_i^*| > \chi(|u_i - u_i^*|) \quad \Rightarrow \quad \dot{V}_{ISS}^i < 0. \quad (39)$$

Indeed, with the choice:

$$V_{ISS}^i(x_i) = \int_{x_i}^{x_i^*} \frac{\sigma - x_i^*}{g_i(\sigma)} d\sigma, \quad (40)$$

it follows from (22) that

$$\dot{V}_{ISS}^i \leq -|x_i - x_i^*| \omega(|x_i - x_i^*|) + |x_i - x_i^*| |u_i - u_i^*| \quad (41)$$

and, thus, (39) holds with  $\chi(\cdot) = \omega^{-1}(\cdot)$ . Having proven ISS for the nodes with outdegree zero, we conclude global asymptotic stability for the full system because the cascade interconnection of an ISS system driven by a globally asymptotically stable system is globally asymptotically stable [34].  $\square$

REMARK 1. *The assumptions A3-A5 rely on the knowledge of the equilibrium  $x^*$  which may not be available in practice. When the functions  $f_i(\cdot)$ ,  $g_i(\cdot)$ , and  $h_l(\cdot)$  are  $C^1$ , the following incremental conditions guarantee A3-A5, and do not depend on  $x^*$ :*

A3': For each  $i = 1, \dots, N$ , and  $\forall x_i \geq 0$ ,

$$\frac{\partial}{\partial x_i} \left( \frac{f_i(x_i)}{g_i(x_i)} \right) > 0. \quad (42)$$

A4': For each  $l = 1, \dots, M$ , and  $\forall x_i \geq 0$ ,

$$\text{sign}(\text{link } l) \frac{\partial h_l(x_i)}{\partial x_i} > 0. \quad (43)$$

A5': For each link  $l \in \mathcal{L}_i^-$  there exists a constant  $\gamma_l > 0$  such that

$$\frac{\left| \frac{\partial h_l(x_i)}{\partial x_i} \right|}{\frac{\partial}{\partial x_i} \left( \frac{f_i(x_i)}{g_i(x_i)} \right)} \leq \gamma_l \quad \forall x_i \geq 0. \quad (44)$$

REMARK 2. Although the growth assumption (44) may appear restrictive, most biologically relevant nonlinearities satisfy this condition globally. If there exist closed intervals  $\mathcal{X}_i \subseteq \mathbb{R}_{\geq 0}$  such that  $\mathcal{X}_1 \times \cdots \times \mathcal{X}_N$  is forward invariant for (12), a less conservative  $\gamma_l$  may be obtained by evaluating (44) on  $\mathcal{X}_i$ , rather than for all  $x_i \geq 0$ . This relaxation is particularly useful in biological applications where  $x_i$  represents the amount of a substance which may be lower- and upper-bounded.

REMARK 3. The integral conditions (20) and (21) serve to insure properness of the Lyapunov function in the proof of Theorem 1, which is in turn used to guarantee global asymptotic stability. If the solutions are known to belong to a bounded set as in Remark 2, and if this set is a subset of a compact level set of the Lyapunov function, then properness of the Lyapunov function is not needed to prove a global result. Hence, if boundedness can be shown independently, the assumptions (20) and (21) can be dropped.

The dissipativity matrix  $E$  in (18) combines information about the interconnection structure of the network with the passivity properties of its components. Because the off-diagonal components of this matrix are negative for links that represent inhibitory reaction rates, diagonal stability is less restrictive than a networked small-gain condition [25, 26] which ignores the signs of the off-diagonal terms. In the case of a cyclic graph where each link  $l = 1, \dots, n$  connects source  $i = l$  to sink  $i = l + 1 \pmod{n}$ , and where only link  $n$  has a negative sign, (18) assumes the form (10). Theorem 1 thus recovers the result of [1] as a special case, and further relaxes it by accommodating the  $g_i(x_i)$  functions in (12) which are not allowed in [1].

#### 4. Examples.

EXAMPLE 1. To illustrate Theorem 1 we first study a simplified model of mitogen-activated protein kinase (MAPK) cascades with inhibitory feedback, proposed in [15, 16]:

$$\dot{x}_1 = -\frac{b_1 x_1}{c_1 + x_1} + \frac{d_1(1 - x_1)}{e_1 + (1 - x_1)} \frac{\mu}{1 + kx_3} \quad (45)$$

$$\dot{x}_2 = -\frac{b_2 x_2}{c_2 + x_2} + \frac{d_2(1 - x_2)}{e_2 + (1 - x_2)} x_1 \quad (46)$$

$$\dot{x}_3 = -\frac{b_3 x_3}{c_3 + x_3} + \frac{d_3(1 - x_3)}{e_3 + (1 - x_3)} x_2. \quad (47)$$

The variables  $x_i \in [0, 1]$  denote the active forms of the proteins, and the terms  $1 - x_i$  indicate the inactive forms (after nondimensionalization and

assuming that the total concentration of each of the proteins is 1). The second term in each equation indicates the rate at which the inactive form of the protein is being converted to active form, while the first term models the inactivation of the respective protein. For the proteins  $x_i$ ,  $i = 2, 3$ , the activation rate is proportional to the concentration of the active form of the protein  $x_{i-1}$  upstream, which facilitates the conversion. The activation of the first protein  $x_1$ , however, is inhibited by  $x_3$  as represented by the decreasing function  $\mu/(1 + kx_3)$ .

The model (45)-(47) is of the form (12) with

$$\begin{aligned} f_i(x_i) &= \frac{b_i x_i}{c_i + x_i}, \quad g_i(x_i) = \frac{d_i(1 - x_i)}{e_i + (1 - x_i)}, \quad i = 1, 2, 3, \\ h_i(x_i) &= x_i, \quad i = 1, 2, \quad h_3(x_3) = \frac{\mu}{1 + kx_3}. \end{aligned} \quad (48)$$

Because the underlying graph is cyclic with each link  $l = 1, 2, 3$  connecting source  $i = l$  to sink  $i = l + 1 \pmod{3}$ , and because  $h_3(\cdot)$  is strictly decreasing, the dissipativity matrix  $E$  in (18) is of the form (10) and, as proved in [1], its diagonal stability is equivalent to the secant criterion (9). However, unlike the model (7) of [1] which disallows state products, Theorem 1 above accommodates the functions  $g_i(x_i)$ , and is applicable to (45)-(47).

To reduce conservatism in the estimates for  $\gamma_i$  in Theorem 1 we follow Remark 2 and further restrict the intervals  $[0, 1]$  in which  $x_i$ 's evolve by noting that  $h_3(x_3)$  takes values within the interval  $[\frac{\mu}{1+k}, \mu]$ . Because  $h_3(x_3)$  is the input to the  $x_1$ -subsystem, and because the function  $\theta_i : [0, 1] \rightarrow [0, \infty)$  defined by

$$\theta_i(x_i) := \frac{f_i(x_i)}{g_i(x_i)}, \quad (49)$$

is strictly increasing, it follows from the bounds on the input signal that the interval  $\mathcal{X}_1 = [x_{1,min}, x_{1,max}] := [\theta_1^{-1}(\mu/(1+k)), \theta_1^{-1}(\mu)]$  is an invariant and attractive set for the  $x_1$ -subsystem. Since  $x_1$  and  $x_2$  serve as inputs to the  $x_2$ - and  $x_3$ -subsystems respectively, the same conclusion holds for the intervals  $\mathcal{X}_2 = [x_{2,min}, x_{2,max}]$  and  $\mathcal{X}_3 = [x_{3,min}, x_{3,max}]$ , where

$$x_{i,min} := \theta_i^{-1}(x_{i-1,min}) \quad x_{i,max} := \theta_i^{-1}(x_{i-1,max}) \quad (50)$$

$i = 2, 3$ . With the following coefficients from [37]:

$$\begin{aligned} b_1 = e_1 = c_1 = b_2 = 0.1, \quad c_2 = e_2 = c_3 = e_3 = 0.01, \\ b_3 = 0.5, \quad d_1 = d_2 = d_3 = 1, \quad \mu = 0.3, \end{aligned}$$

we obtained  $\gamma_i$ 's numerically by maximizing the left-hand side of (44) on  $\mathcal{X}_i$  for various values of the parameter  $k$ . This numerical experiment showed that the secant condition  $\gamma_1 \gamma_2 \gamma_3 < 8$  is satisfied in the range  $k \leq 4.35$  (for  $k = 4.36$  we get  $\gamma_1 \gamma_2 \gamma_3 = 11.03$ ). Reference [37] gives a small-gain estimate  $k \leq 3.9$  for stability, and shows that a Hopf bifurcation occurs at around  $k = 5.1$ . The estimate  $k \leq 4.35$  obtained from Theorem 1 thus reduces the gap between the unstable range and the small-gain estimate.

EXAMPLE 2. The recent paper [38] presents topological differences in the MAPK network for PC-12 cells depending on whether the cells are activated with epidermal or neuronal growth factors (see Figure 2), and relates the resulting difference in the dynamic behavior to the change in functionality (proliferation or differentiation). Theorem 1 is applicable to appropriate extensions of the model (45)-(47) to the topologies in Figure 2 assuming that multiple inputs can be synthesized additively in this model (see Section 6 for a further discussion of this assumption) so that, for example, the second term in the  $x_2$ -subsystem (46) may be modified as

$$\frac{d_2(1-x_2)}{e_2+(1-x_2)} \left( x_1 + \frac{\mu_2}{1+k_2x_3} \right) \quad (51)$$

to account for the new inhibitory feedback from  $x_3$ . For the feedback configu-

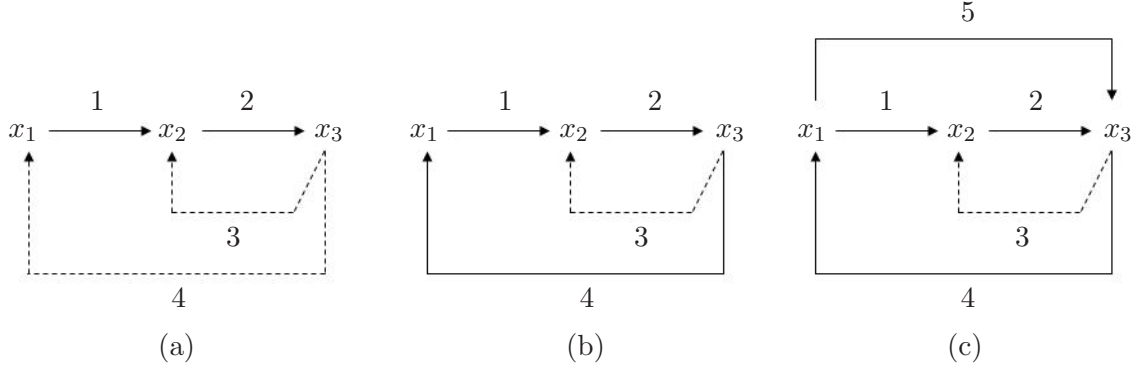


FIGURE 2. Feedback configurations observed in [38] for MAPK networks in PC-12 cells. The nodes  $x_1$ ,  $x_2$ , and  $x_3$  represent Raf-1, Mek1/2, and Erk1/2, respectively. The dashed links indicate negative feedback signals. Depending on whether the cells are activated with (a) epidermal or (b) neuronal growth factors, the feedback from Erk1/2 to Raf-1 changes sign. (c) An increased connectivity from Raf-1 to Erk1/2 is noted in [38] when neuronal growth factor activation is observed over a longer period.

rations (a) and (b) in Figure 2, the dissipativity matrices obtained according to (18) are:

$$E_a = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix} \quad E_b = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix}. \quad (52)$$

The following lemma derives necessary and sufficient conditions for their diagonal stability:

LEMMA 1. *The matrix  $E_a$  in (52) is diagonally stable iff  $\gamma_1\gamma_2\gamma_4 < 8$ , and  $E_b$  is diagonally stable iff  $\gamma_1\gamma_2\gamma_4 < 1$ .*

*Proof.* Note that the  $3 \times 3$  principal submatrix  $\tilde{E}_a$  obtained by deleting the third row and column of  $E_a$  exhibits the cyclic form (10) for which diagonal stability is equivalent to  $\gamma_1\gamma_2\gamma_4 < 8$  from the secant criterion. Likewise, the corresponding submatrix  $\tilde{E}_b$  of  $E_b$  is of the form (10) with the upper right element  $-1$  replaced by  $+1$ . Because all diagonal entries of  $\tilde{E}_b$  are negative and off-diagonal entries are nonnegative, it follows from [39, Theorem 2.3] that this submatrix is diagonally stable iff the principal minors of  $-\tilde{E}_b$  are all positive. Checking the positivity of these principal minors, we obtain the diagonal stability condition  $\gamma_1\gamma_2\gamma_4 < 1$ . Because principal submatrices of a diagonally stable matrix are also diagonally stable we conclude that the conditions  $\gamma_1\gamma_2\gamma_4 < 8$  and  $\gamma_1\gamma_2\gamma_4 < 1$  for the diagonal stability of  $\tilde{E}_a$  and  $\tilde{E}_b$  are necessary for the diagonal stability of the full matrices  $E_a$  and  $E_b$ , respectively. To prove that they are also sufficient, we note that both  $E_a$  and  $E_b$  possess the property that their entries (2, 3) and (3, 2) are of opposite sign, and all other off-diagonal entries in the third row and column are zero. This means that, if the principal submatrix obtained by deleting the third row and column is diagonally stable then so is the full matrix. (To see this, let the diagonal Lyapunov solution for the submatrix be  $\tilde{D} = \text{diag}\{d_1, d_2, d_4\}$ , and choose  $d_3 = d_2$  in  $D = \text{diag}\{d_1, d_2, d_3, d_4\}$  for the full matrix so that all off-diagonal entries in the third rows and columns of  $DE_a + E_a^T D$  and  $DE_b + E_b^T D$  are zero.)  $\square$

We next study the dissipativity matrix

$$E_c = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 & 0 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 1 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} & 1 \\ 0 & 0 & 0 & 1 & -\frac{1}{\gamma_5} \end{bmatrix} \quad (53)$$

for the feedback configuration in Figure 2(c). The principal submatrix  $\tilde{E}_c$  obtained by deleting the third row and column exhibits nonnegative off-diagonal entries and, thus, its diagonal stability is equivalent [39, Theorem 2.3] to the positivity of the principal minors of  $-\tilde{E}_c$ , which results in the condition:

$$\gamma_1\gamma_2\gamma_4 + \gamma_4\gamma_5 < 1. \quad (54)$$

Because principal submatrices of a diagonally stable matrix are also diagonally stable, (54) is necessary for the diagonal stability of the full matrix  $E_c$ . In contrast to our analysis for  $E_a$  and  $E_b$  however, we cannot conclude sufficiency of this condition for the diagonal stability of  $E_c$  because the entries (3, 5) and (5, 3) of the deleted row and column do not have opposite signs (*cf.* proof of Lemma ??). In fact, in Figure 3 we demonstrate the gap between the necessary condition (54) and the exact diagonal stability

region in the parameter space by fixing  $\gamma_1 = 1$ ,  $\gamma_2 = \gamma_5 = 0.5$  (so that (54) becomes  $\gamma_4 < 1$ ) and by plotting the region in the  $(\gamma_3, \gamma_4)$ -plane in which diagonal stability is confirmed numerically by a linear matrix inequality (LMI) solver. This feasibility region is indeed narrower than  $\gamma_4 < 1$  which means that, unlike the feedback configurations (a) and (b), diagonal stability for the configuration in Figure 2(c) is affected by the magnitude of the gain  $\gamma_3$ .

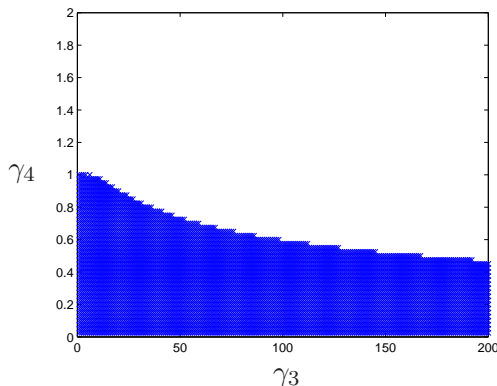


FIGURE 3. Diagonal stability region for (53) in the  $(\gamma_3, \gamma_4)$ -plane when the other gains are fixed at  $\gamma_1 = 1$ ,  $\gamma_2 = \gamma_5 = 0.5$ . With these values the necessary condition (54) is  $\gamma_4 < 1$  which is wider than the exact region (shaded).

EXAMPLE 3. A common form of feedback inhibition in metabolic networks occurs when several end metabolites in different branches of a pathway inhibit a reaction located before the branch point [18, 40]. As an example of this situation we consider the network in Figure 4 where the end metabolites with concentrations  $x_4$  and  $x_6$  inhibit the formation of  $x_1$  from an initial substrate  $x_0$ . Assuming that  $x_0$  is kept constant, and that its conversion to  $x_1$  is regulated by two isofunctional enzymes each of which is selectively sensitive to  $x_4$  or  $x_6$ , we represent this network as in (12):

$$\begin{aligned}
 \dot{x}_1 &= -f_1(x_1) + h_4(x_4) + h_7(x_6) \\
 \dot{x}_2 &= -f_2(x_2) + h_1(x_1) \\
 \dot{x}_3 &= -f_3(x_3) + h_2(x_2) \\
 \dot{x}_4 &= -f_4(x_4) + h_3(x_3) \\
 \dot{x}_5 &= -f_5(x_5) + h_5(x_2) \\
 \dot{x}_6 &= -f_6(x_6) + h_6(x_5),
 \end{aligned} \tag{55}$$

where the functions  $h_4(x_4)$  and  $h_7(x_6)$  are decreasing due to the inhibitory effect of  $x_4$  and  $x_6$ , while  $h_l(\cdot)$ ,  $l = 1, 2, 3, 5, 6$  and  $f_i(\cdot)$ ,  $i = 1, \dots, 6$  are increasing.

Rather than study specific forms for these functions, we assume that A1 and A2 hold, and that  $\gamma_l$ 's exist as in (44). An application of Theorem 1

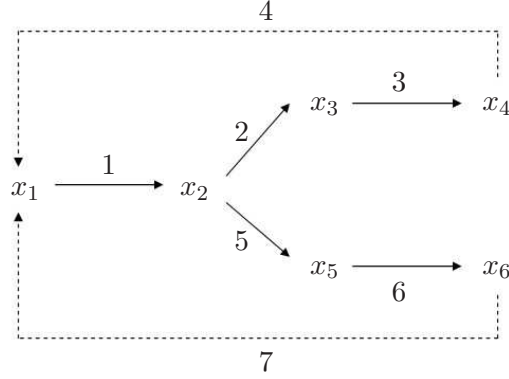


FIGURE 4. Feedback inhibition in a branched network. The dashed links 4 and 7 indicate negative (inhibitory) feedback signals. The dissipativity matrix obtained from (18) for this network is (56).

then proves global asymptotic stability of the equilibrium if the dissipativity matrix

$$E = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -\frac{1}{\gamma_4} & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -\frac{1}{\gamma_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_7} \end{bmatrix} \quad (56)$$

is diagonally stable. Note that the  $4 \times 4$  principal submatrices obtained by deleting row-column pairs  $\{5, 6, 7\}$  and  $\{2, 3, 4\}$  each exhibit a cyclic structure for which, as shown in [1], diagonal stability is equivalent to the secant criteria

$$\gamma_1\gamma_2\gamma_3\gamma_4 < \sec(\pi/4)^4 = 4 \quad \text{and} \quad \gamma_1\gamma_5\gamma_6\gamma_7 < 4, \quad (57)$$

respectively. Because principal submatrices of a diagonally stable matrix are also diagonally stable, we conclude that (57) is a necessary condition for the diagonal stability of (56). In fact, we prove the following necessary and sufficient condition:

LEMMA 2. *The matrix  $E$  in (56) is diagonally stable if and only if*

$$\gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7 < \sec(\pi/4)^4 = 4. \quad (58)$$

*Proof.* We prove the sufficiency of this condition as a consequence of a more general fact. Consider the following diagonal matrix:

$$D = \text{diag} \left( 1, \frac{\gamma_3\gamma_4}{2}, \frac{\gamma_4}{\gamma_2}, \frac{2}{\gamma_2\gamma_3}, \frac{\gamma_6\gamma_7}{2}, \frac{\gamma_7}{\gamma_5}, \frac{2}{\gamma_5\gamma_6} \right) \quad (59)$$

and the matrix

$$M := E^T D + DE.$$

We will prove that condition (58) implies that  $M \leq 0$ . Diagonal stability of  $E$  follows from this claim in view of the following argument: Given any  $\gamma_i$ 's satisfying the constraint (58), we can find  $\tilde{\gamma}_i > \gamma_i$  that still satisfy the constraint, and under this transformation  $E$  gets transformed to  $\tilde{E} = E + \Delta$ , where  $\Delta$  is some positive diagonal matrix. Now let  $\tilde{D}$  be defined for  $\tilde{E}$  as in (59) with  $\gamma_i$ 's replaced by  $\tilde{\gamma}_i$ 's. Since  $E^T \tilde{D} + \tilde{D} E < \tilde{E}^T \tilde{D} + \tilde{D} \tilde{E} = \tilde{M}$ , and since  $\tilde{M} \leq 0$ , it follows that  $E^T \tilde{D} + \tilde{D} E < 0$ , which means that  $E$  is diagonally stable.

To prove that (58) implies  $M \leq 0$ , we let  $E_\varepsilon := E - \varepsilon I$  for each  $\varepsilon > 0$ , and show that  $M_\varepsilon = E_\varepsilon^T D + DE_\varepsilon$  is negative definite for small enough  $\varepsilon > 0$ . By continuity, this last property implies that  $M \leq 0$ . In order to check negative definiteness of  $M_\varepsilon$ , we consider the principal minors  $\mu_i(\varepsilon)$ ,  $i = 1, \dots, 7$  of  $M_\varepsilon$ , and ask that they all have sign  $(-1)^i$  for small  $\varepsilon > 0$ . Each  $\mu_i$  is a polynomial of degree  $\leq 7$  on  $\varepsilon$  and, upon lengthy calculations omitted here, the determinant of  $M_\varepsilon$  can be expanded as follows:

$$\mu_7(\varepsilon) = \frac{8\gamma_4\gamma_7(\gamma_5 + 2\gamma_6 + \gamma_7)(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3\gamma_5^3\gamma_6} \Delta \varepsilon^2 + O(\varepsilon^3), \quad (60)$$

where  $\Delta = \gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7 - 4$ . Similarly, we have:

$$\mu_6(\varepsilon) = \frac{-2\gamma_4\gamma_7^2(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3\gamma_5^2} \Delta \varepsilon + O(\varepsilon^2),$$

$$\mu_5(\varepsilon) = \frac{2\gamma_4\gamma_6\gamma_7(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3\gamma_5} \Delta \varepsilon + O(\varepsilon^2),$$

$$\mu_4(\varepsilon) = \frac{-2\gamma_4(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3} \Delta_1 \varepsilon + O(\varepsilon^2),$$

where  $\Delta_1 = \gamma_1\gamma_2\gamma_3\gamma_4 - 4$ ,

$$\mu_3(\varepsilon) = \frac{\gamma_4^2}{2\gamma_1\gamma_2^2} \Delta_1 + O(\varepsilon),$$

$$\mu_2(\varepsilon) = \frac{-\gamma_3\gamma_4}{4\gamma_1\gamma_2} (\Delta_1 - 4) + O(\varepsilon),$$

and

$$\mu_1(\varepsilon) = -\frac{2}{\gamma_1} - 2\varepsilon.$$

Since  $\Delta_1 < \Delta$ , we conclude that the matrix  $M_\varepsilon$  is negative definite for all small enough  $\varepsilon > 0$  if and only if  $\Delta < 0$ . In particular, condition (58) implies that  $M \leq 0$ , as claimed.

Finally, we prove the necessity of (58) for the diagonal stability of  $E$  in (56). To this end, we define  $\hat{E} = \text{diag}(\gamma_1, \dots, \gamma_7) E$  which has all diagonal components equal to  $-1$ , and characteristic polynomial equal to:

$$(s+1)^3[(s+1)^4 + k],$$



where  $k := \gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7$ . For  $k \geq 0$ , the roots of  $(s+1)^4 = -k$  have real part  $\pm\sqrt[4]{k/4} - 1$ ; hence  $k < 4$  is necessary for these real parts to be negative. Because (58) is necessary for the Hurwitz property of  $\hat{E}$ , it is also necessary for its diagonal stability. Since diagonal stability of  $\hat{E}$  is equivalent to diagonal stability of  $E$ , we conclude that (58) is necessary for the diagonal stability of  $E$ .

**5. Stability of a compartmental model with diffusion.** A compartmental model is appropriate for describing the spatial localization of processes when each of a finite set of spatial domains (“compartments”) is well-mixed, and can be described by ordinary differential equations. Instead of the lumped model (12), we now consider  $n$  compartments, and represent their interconnection structure with a new graph in which the links  $k = 1, \dots, m$  indicate the presence of diffusion between the compartments  $j = 1, \dots, n$  they interconnect. Although the graph is undirected, for notational convenience we assign an arbitrary orientation to each link and define the  $n \times m$  *incidence matrix*  $S$  as

$$s_{jk} := \begin{cases} +1 & \text{if node } j \text{ is the sink of link } k \\ -1 & \text{if node } j \text{ is the source of link } k \\ 0 & \text{otherwise.} \end{cases} \quad (61)$$

The particular choice of the orientation does not change the derivations below.

We first prove a general stability result (Theorem 2 below) for a class of compartmental models interconnected as described by the incidence matrix  $S$ . We then apply this result in Corollary 1 to the situation where the individual compartments possess dynamics of the form studied in Section 3. We let

$$X_j := (x_{j,1}, \dots, x_{j,N})^T$$

be the state vector of concentrations  $x_{j,i}$  in compartment  $j$ , and let  $\dot{X}_j = F_j(X_j)$  represent the dynamics of the  $j$ th compartment in the absence of diffusion terms. Next, for each link  $k = 1, \dots, m$ , we denote by

$$\mu_{k,i}(x_{\text{sink}(k),i} - x_{\text{source}(k),i}) \quad (62)$$

the diffusion term for the species  $i$ , flowing from  $\text{source}(k)$  to  $\text{sink}(k)$ , and assume the functions  $\mu_{k,i}(\cdot)$ ,  $k = 1, \dots, m$ ,  $i = 1, \dots, N$ , satisfy

$$\sigma \mu_{k,i}(\sigma) \leq 0, \quad \forall \sigma \in \mathbb{R}. \quad (63)$$

Then, the coupled dynamics of the compartments become:

$$\dot{X}_j = F_j(X_j) + (S_{j\cdot} \otimes I_N) \mu((S^T \otimes I_N)X) \quad j = 1, \dots, n \quad (64)$$

where  $S_{j\cdot}$  is the  $j$ th row of the incidence matrix  $S$ ,  $I_N$  is the  $N \times N$  identity matrix, “ $\otimes$ ” represents the Kronecker product,

$$X := [X_1^T \dots X_n^T]^T \quad (65)$$

and  $\mu : \mathbb{R}^{mN} \rightarrow \mathbb{R}^{mN}$  is defined as

$$\mu(z) := [\mu_{1,1}(z_1) \cdots \mu_{1,N}(z_N) \cdots \mu_{m,1}(z_{(m-1)N+1}) \cdots \mu_{m,N}(z_{mN})]^T. \quad (66)$$

We now prove stability of the coupled system (64) under the assumption that a common Lyapunov function exists for the decoupled models  $\dot{X}_j = F_j(X_j)$ ,  $j = 1, \dots, n$ , and that this common Lyapunov function consists of a sum of convex functions of individual state variables:

**THEOREM 2.** *Consider the system (64) where the function  $\mu(\cdot)$  is as in (66) and (63). If there exists a Lyapunov function  $V : \mathbb{R}^N \rightarrow \mathbb{R}$  of the form*

$$V(x) = V_1(x_1) + \cdots + V_N(x_N) \quad (67)$$

where each  $V_i(x_i)$  is a convex, differentiable and positive definite function, satisfying

$$\nabla V(x) F_j(x) \leq -\alpha(|x|) \quad j = 1, \dots, n \quad (68)$$

for some class- $\mathcal{K}$  function  $\alpha(\cdot)$ , then the origin  $X = 0$  of (64) is asymptotically stable. If, further,  $V(\cdot)$  is radially unbounded, then  $X = 0$  is globally asymptotically stable.

*Proof.* We employ the composite Lyapunov function

$$\mathcal{V}(X) = \sum_{j=1}^n V(X_j), \quad (69)$$

and obtain from (64) and (68):

$$\dot{\mathcal{V}}(X) \leq -\sum_{j=1}^n \alpha(|X_j|) + [\nabla V(X_1) \cdots \nabla V(X_n)](S \otimes I_N) \mu((S^T \otimes I_N)X). \quad (70)$$

We next rewrite the second term in the right-hand side of (70) as

$$\left( (S^T \otimes I_N) \begin{bmatrix} \nabla V^T(X_1) \\ \vdots \\ \nabla V^T(X_n) \end{bmatrix} \right)^T \mu((S^T \otimes I_N)X), \quad (71)$$

and note from (61) that (71) equals

$$\sum_{k=1}^m [\nabla V(X_{\text{sink}(k)}) - \nabla V(X_{\text{source}(k)})] \begin{bmatrix} \mu_{k,1} \\ \vdots \\ \mu_{k,N} \end{bmatrix} \quad (72)$$

where  $\mu_{k,i}$ ,  $i = 1, \dots, N$ , denotes the diffusion function (62), and the argument is dropped for brevity. Next, using (67), we rewrite (72) as

$$\sum_{k=1}^m \sum_{i=1}^N [\nabla V_i(x_{\text{sink}(k),i}) - \nabla V_i(x_{\text{source}(k),i})] \mu_{k,i}. \quad (73)$$

Because  $V_i(\cdot)$  is a convex function, its derivative  $\nabla V_i(\cdot)$  is a nondecreasing function and, hence,  $\nabla V_i(x_{\text{sink}(k),i}) - \nabla V_i(x_{\text{source}(k),i})$  possesses the same

sign as  $(x_{\text{sink}(k),i} - x_{\text{source}(k),i})$ . We next recall from the sector property (63) that the function  $\mu_{k,i}$  in (62) possesses the opposite sign of its argument  $(x_{\text{sink}(k),i} - x_{\text{source}(k),i})$ . This means that each term in the sum (73) is nonpositive and, hence, (70) becomes

$$\dot{V}(x) \leq - \sum_{j=1}^n \alpha(|X_j|), \quad (74)$$

from which the conclusions of the theorem follow.  $\square$

Theorem 2 is applicable when each compartment is as described in Section 3,  $h_l(\cdot)$  satisfies (43), and  $g_i(\cdot)$ 's,  $i = 1, \dots, N$ , are nonincreasing functions. This is because the Lyapunov construction (23) in Section 3 consists of a sum of terms as in (67), each of which is convex when the derivative of (24) is nondecreasing:

**COROLLARY 1.** *Consider the system (64) where the function  $\mu(\cdot)$  is as in (66) and (63), and  $F_j(x)$ ,  $j = 1, \dots, n$ , are identical and represent the right-hand side of (12). If all assumption of Theorem 1 hold and if, in addition,  $h_l(\cdot)$  satisfies (43), and  $g_i(\cdot)$ 's,  $i = 1, \dots, N$ , are nonincreasing functions, then the equilibrium  $X = [x^{*T}, \dots, x^{*T}]^T$  is globally asymptotically stable.*

**6. Discussion and Conclusions.** We have presented a passivity-based stability criterion for a class of interconnected systems, which encompasses the secant criterion for cyclic systems [1] as a special case. Unlike the result in [1], we have further allowed the presence of state products in our model. Our main result (Theorem 1) determines global asymptotic stability of the network from the diagonal stability of the dissipativity matrix (18) which incorporates information about the output strict passivity property (2) of the subsystems, the interconnection structure of the network, and the signs of the interconnection terms.

We wish to emphasize that our framework assumes that all subsystems are additively interconnected, thus imposing a limitation on what types of interconnections may be allowed. For example, if an enzyme  $E$  acts so as to inhibit (allosterically or competitively) the binding of another enzyme  $F$  to a substrate  $S$ , the multiplicative nature of this effect cannot be covered by our mathematical results. On the other hand, many other effects can indeed be modeled additively. In metabolic networks, for instance, the actions on a substrate  $S$  by two isofunctional enzymes  $E$  and  $F$  is additive; on the other hand, each of them may be separately influenced (positively or negatively) by a downstream metabolite  $X$  and  $Y$  respectively. The dependence of the rate of change of concentration of  $S$  upon the concentrations of  $X$  and  $Y$  may well be nonlinear, but these effects are additive. As another example, in protein signaling networks, an activating effect might be achieved through a kinase, while a negative effect may be produced by tagging  $S$  for degradation, or by an enzyme acting as a phosphatase, and such effects are again additive.

Although diagonal stability can be checked numerically with efficient linear matrix inequality (LMI) tools [41], it is of interest to derive analytical conditions that make explicit the role of the reaction rate coefficients on stability properties. Indeed our earlier paper [1] showed that the diagonal stability of negative feedback cyclic systems is equivalent to the secant criterion of [8, 14]. In Examples 2 and 3 we have derived similar analytical conditions for several other interconnection structures. Further studies for deriving analytical conditions for practically important motifs would be of great interest. Another research topic is to extend the stability result for compartmental models with diffusion in Section 5 to partial differential equation models. On this topic we have reported preliminary results applicable to cyclic systems in [42], and are currently studying more general interconnection structures.

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