

A Passivity-Based Stability Criterion for a Class of Interconnected Systems and Applications to Biochemical Reaction Networks

Murat Arcak

Department of Electrical, Computer, and
Systems Engineering
Rensselaer Polytechnic Institute, Troy, NY
arcakm@rpi.edu

Eduardo D. Sontag

Department of Mathematics
Rutgers University, New Brunswick, NJ
sontag@math.rutgers.edu

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. The authors use a compartmental model to represent the localization of the reactions and present conditions 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 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 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 passivity

properties and the corresponding *storage functions* [19] 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 passive subsystems we follow the formalism of [27, 28], and construct a *dissipativity matrix* (denoted by E below) that incorporates information about the passivity 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 (see the discussion in Section 6 below), 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 develops an extension of the purely input/output-based proof in [2] of the secant criterion to the general graphs studied in this paper. In doing so, it adapts a lemma from [27, 28] and compares the input/output approach with the state-space results derived earlier in the paper. Section 7 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

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

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

$$\frac{b_1 \cdots b_n}{a_1 \cdots a_n} < \sec(\pi/n)^n. \quad (2)$$

Unlike a *small-gain* condition which would restrict the right-hand side of (2) to be 1, the “secant criterion” (2) 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:

$$\begin{aligned} \dot{x}_1 &= -x_1 + \varphi(x_3) \\ \dot{x}_2 &= -x_2 + x_1 \\ \dot{x}_3 &= -x_3 + x_2 \end{aligned} \quad (3)$$

where

$$\varphi(x_3) = e^{-10(x_3-1)} + 0.1\text{sat}(25(x_3 - 1)), \quad (4)$$

and $\text{sat}(\cdot) := \text{sgn}(\cdot) \min\{1, |\cdot|\}$ is a saturation¹ function. The function (4) 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 (2) 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.

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 (2), and next used this passivity

¹One can easily modify this example to make $\varphi(\cdot)$ smooth while retaining the same stability properties.

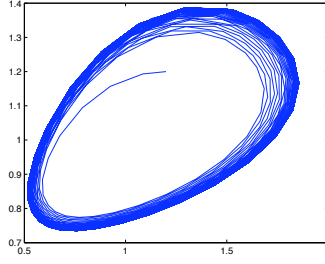


Figure 1: Trajectory of (3) starting from initial condition $x = [1.2 \ 1.2 \ 1.2]^T$, projected onto the x_1 - x_2 plane.

insight to extend the secant criterion to the nonlinear model:

$$\begin{aligned}
 \dot{x}_1 &= -f_1(x_1) + h_n(x_n) \\
 \dot{x}_2 &= -f_2(x_2) + h_1(x_1) \\
 &\vdots \\
 \dot{x}_n &= -f_n(x_n) + h_{n-1}(x_{n-1})
 \end{aligned} \tag{5}$$

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

$$\left| \frac{\frac{\partial h_i(x_i)}{\partial x_i}}{\frac{\partial f_i(x_i)}{\partial x_i}} \right| \leq \gamma_i \quad \forall x_i \in \mathbb{R}_{\geq 0}, \quad i = 1, \dots, n, \tag{6}$$

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n, \tag{7}$$

which encompasses the linear secant criterion (2) with $\gamma_i = b_i/a_i$.

A crucial ingredient in the global asymptotic stability proof of [1] is the observation that the secant condition (7) is necessary and sufficient for the *diagonal stability* of the matrix

$$E_{cyclic} = \begin{bmatrix} -1/\gamma_1 & 0 & \cdots & 0 & -1 \\ 1 & -1/\gamma_2 & \ddots & & 0 \\ 0 & 1 & -1/\gamma_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & 1 & -1/\gamma_n \end{bmatrix} \tag{8}$$

that is, for the existence of a diagonal matrix $D > 0$ such that

$$E_{cyclic}^T D + D E_{cyclic} < 0. \tag{9}$$

The authors of [1] connect this diagonal stability property to the global asymptotic stability of (5) by first noting that the assumption (6) guarantees an *output strict passivity* property, where $1/\gamma_i$ quantifies the excess of passivity in each x_i -subsystem. They then incorporate this passivity information in the diagonal terms of the *dissipativity matrix* (8), and represents the interconnection structure with the off-diagonal terms. Finally, they use the diagonal stability condition (9), which is equivalent to the secant criterion (7), to check whether the excess of passivity in each subsystem overcomes the loss of passivity in the interconnection. In particular, the diagonal entries of D constitute the weights of the storage functions in a composite Lyapunov function for (5).

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. The nodes represent subsystems with possibly vector outputs, and a separate link is used for each output channel. 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:

$$\dot{x}_i = -f_i(x_i) + g_i(x_i) \sum_{l \in \mathcal{L}_i^+} h_l(x_{\text{source}(l)}) \quad i = 1, \dots, N \quad (10)$$

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 (10). 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 (10).

A2: There exists an equilibrium $x^* \in \mathbb{R}_{\geq 0}^N$ for (10).

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

$$(x_i - x_i^*) \left(\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right) > 0 \quad \forall x_i \in \mathbb{R}_{\geq 0} - \{x_i^*\}. \quad (11)$$

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

$$(x_i - x_i^*) [h_l(x_i) - h_l(x_i^*)] > 0 \quad (12)$$

$$(x_i - x_i^*) [h_l(x_i) - h_l(x_i^*)] < 0. \quad (13)$$

To distinguish between positive and negative feedback signals we assign to each link l a positive sign if (12) holds, and a negative sign if (13) holds, and rewrite (12)-(13) as

$$\text{sign}(\text{link } l)(x_i - x_i^*) [h_l(x_i) - h_l(x_i^*)] > 0 \quad (14)$$

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

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

$$\text{sign}(\text{link } l) \frac{h_l(x_i) - h_l(x_i^*)}{\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)}} \leq \gamma_l. \quad (15)$$

Theorem 1 Consider the system (10), and suppose assumptions A1-A5 hold. If the $M \times M$ dissipativity matrix

$$E_{lk} = \begin{cases} -1/\gamma_l & \text{if } k=l \\ \text{sign}(\text{link } k) & \text{if } \text{source}(l) = \text{sink}(k) \\ 0 & \text{otherwise} \end{cases} \quad (16)$$

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

$$E^T D + D E < 0, \quad (17)$$

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

$$\lim_{x_i \rightarrow \infty} \int_{x_i^*}^{x_i} \frac{h_l(\sigma) - h_l(x_i^*)}{g_i(\sigma)} = \infty, \quad (18)$$

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

$$\lim_{x_i \rightarrow \infty} \int_{x_i^*}^{x_i} \frac{\sigma - x_i^*}{g_i(\sigma)} = \infty, \quad (19)$$

and there exists a class- \mathcal{K}_∞ function² $\omega(\cdot)$ such that

$$(x_i - x_i^*) \left(\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)} \right) \geq |x_i - x_i^*| \omega(|x_i - x_i^*|) \quad \forall x_i \geq 0. \quad (20)$$

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

$$V(x - x^*) = \sum_{l=1}^M d_l V_l(x_{\text{source}(l)} - x_{\text{source}(l)}^*) \quad (21)$$

in which the components are

$$V_l(x_{\text{source}(l)} - x_{\text{source}(l)}^*) = \text{sign}(\text{link } l) \int_{x_{\text{source}(l)}^*}^{x_{\text{source}(l)}} \frac{h_l(\sigma) - h_l(x_{\text{source}(l)}^*)}{g_{\text{source}(l)}(\sigma)} d\sigma \quad (22)$$

² \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}_∞ is the subset of class- \mathcal{K} functions that are unbounded.

and the coefficients $d_l > 0$ are to be determined. The function (21) 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 (14) of the integrand in (22), 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 (22) satisfies the dissipativity property

$$\dot{V}_l \leq y_l \sum_{k=1}^M E_{lk} y_k \quad (23)$$

where

$$y_l := \text{sign}(\text{link } l)[h_l(x_{\text{source}(l)}) - h_l(x_{\text{source}(l)}^*)] \quad (24)$$

$l = 1, \dots, M$, and the coefficients E_{lk} are as in (16). Before we prove this claim, we first note that the diagonal stability property (17) and the estimate (23) together imply that the Lyapunov function (21), with coefficients d_l obtained from the diagonal elements of D , yields a negative definite derivative from which asymptotic stability of x^* follows. If, further, for each node i there exists at least one link $l \in \mathcal{L}_i^-$ such that (18) holds, then the Lyapunov function (21) grows unbounded as $|x| \rightarrow \infty$, thus proving global asymptotic stability.

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 are of the form (10) and are asymptotically stable by A3, asymptotic stability for the equilibrium x^* follows from standard results on cascade interconnections of asymptotically stable systems (see *e.g.* [32, p. 275]). Likewise, when condition (b) holds, (20) and (19) imply an *input-to-state stability* (ISS) property [33] for the driven subsystem of the cascade, and global asymptotic stability follows because the cascade interconnection of an ISS system driven by a globally asymptotically stable system is globally asymptotically stable [33].

We conclude the proof by showing that the claim (23) is indeed true. To this end we compute from (22) and (10) the derivative

$$\dot{V}_l = \text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)] \left(-\frac{f_i(x_i)}{g_i(x_i)} + u_i \right) \quad (25)$$

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

$$u_i := \sum_{k \in \mathcal{L}_i^+} h_k(x_{\text{source}(k)}). \quad (26)$$

Adding and subtracting

$$u_i^* := \sum_{k \in \mathcal{L}_i^+} h_k(x_{\text{source}(k)}^*) = \frac{f_i(x_i^*)}{g_i(x_i^*)} \quad (27)$$

within the bracketed term in (25), we obtain

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

Next, noting 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 (11) and (14), and using (15), we obtain the inequality

$$-\text{sign}(\text{link } l)[h_l(x_i) - h_l(x_i^*)] \left(\frac{f_i(x_i)}{g_i(x_i)} - \frac{f_i(x_i^*)}{g_i(x_i^*)}\right) \leq -\frac{1}{\gamma_l}[h_l(x_i) - h_l(x_i^*)]^2. \quad (29)$$

Substituting (29) in (28), and using the variables y_l defined in (24), we get

$$\dot{V}_l = -\frac{1}{\gamma_l}y_l^2 + y_l(u_i - u_i^*). \quad (30)$$

Finally, noting from (26) and (27) that

$$u_i - u_i^* = \sum_{k \in \mathcal{L}_i^+} \text{sign}(\text{link } k)y_k, \quad (31)$$

we rewrite (30) as

$$\dot{V}_l \leq -\frac{1}{\gamma_l}y_l^2 + y_l \sum_{k \in \mathcal{L}_i^+} \text{sign}(\text{link } k)y_k, \quad (32)$$

which is equivalent to (23) by the definition of the coefficients E_{kl} in (16). \square

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 $\forall x_i \geq 0$,

$$\frac{\partial}{\partial x_i} \left(\frac{f_i(x_i)}{g_i(x_i)}\right) > 0. \quad (33)$$

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

$$\text{sign}(\text{link } l) \frac{\partial h_l(x_i)}{\partial x_i} > 0. \quad (34)$$

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

$$\frac{\left|\frac{\partial h_l(x_i)}{\partial x_i}\right|}{\frac{\partial}{\partial x_i} \left(\frac{f_i(x_i)}{g_i(x_i)}\right)} \leq \gamma_l \quad \forall x_i \geq 0. \quad (35)$$

Although the growth assumption (35) 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 $\mathcal{X}_1 \times \dots \times \mathcal{X}_N$ is forward invariant for (10), a less conservative γ_l may be obtained by evaluating (35) 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.

The dissipativity matrix E in (16) 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, (16) assumes the form (8). 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 (10) 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]:

$$\dot{x}_1 = -\frac{b_1 x_1}{c_1 + x_1} + \frac{d_1(1 - x_1)}{e_1 + (1 - x_1)} \frac{\mu}{1 + kx_3} \quad (36)$$

$$\dot{x}_2 = -\frac{b_2 x_2}{c_2 + x_2} + \frac{d_2(1 - x_2)}{e_2 + (1 - x_2)} x_1 \quad (37)$$

$$\dot{x}_3 = -\frac{b_3 x_3}{c_3 + x_3} + \frac{d_3(1 - x_3)}{e_3 + (1 - x_3)} x_2. \quad (38)$$

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 (36)-(38) is of the form (10) with

$$\begin{aligned} f_i(x_i) &= \frac{b_i x_i}{c_i + x_i}, \quad g_i(x_i) = \frac{d_i(1 - x_i)}{e_i + (1 - x_i)}, \quad i = 1, 2, 3, \\ h_i(x_i) &= x_i, \quad i = 1, 2, \quad h_3(x_3) = \frac{\mu}{1 + kx_3}. \end{aligned} \quad (39)$$

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 (16) is of the form (8) and, as proved in [1], its diagonal stability is equivalent to the secant criterion (7). However, unlike the model (5) of [1] which disallows state products, Theorem 1 above accommodates the functions $g_i(x_i)$, and is applicable to (36)-(38).

To reduce conservatism in the estimates for the γ_i 's in Theorem 1 we 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

$$\theta_i(x_i) := \frac{f_i(x_i)}{g_i(x_i)}, \quad (40)$$

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

$$x_{i,min} := \theta_i^{-1}(x_{i-1,min}) \quad x_{i,max} := \theta_i^{-1}(x_{i-1,max}) \quad (41)$$

$i = 2, 3$. With the following coefficients from [34]:

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

we obtained γ_i 's numerically by maximizing the left-hand side of (35) 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 [34] 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 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, 35]. As an example of this situation we consider the network in Figure 2 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

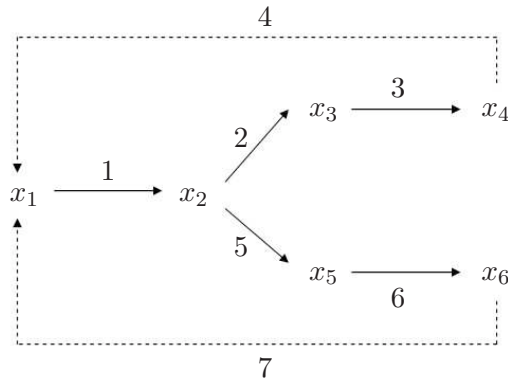


Figure 2: Feedback inhibition in a branched network. The dashed links 4 and 7 indicate negative (inhibitory) feedback signals. The dissipativity matrix obtained from (16) for this network is (43).

enzymes each of which is selectively sensitive to x_4 or x_6 , we represent this network as in (10):

$$\begin{aligned}
\dot{x}_1 &= -f_1(x_1) + h_4(x_4) + h_7(x_6) \\
\dot{x}_2 &= -f_2(x_2) + h_1(x_1) \\
\dot{x}_3 &= -f_3(x_3) + h_2(x_2) \\
\dot{x}_4 &= -f_4(x_4) + h_3(x_3) \\
\dot{x}_5 &= -f_5(x_5) + h_5(x_2) \\
\dot{x}_6 &= -f_6(x_6) + h_6(x_5),
\end{aligned} \tag{42}$$

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 γ_l 's exist as in (35). An application of Theorem 1 then proves global asymptotic stability of the equilibrium if the dissipativity matrix

$$E = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -\frac{1}{\gamma_4} & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -\frac{1}{\gamma_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_7} \end{bmatrix} \tag{43}$$

is diagonally stable. Note that the 4×4 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

$$\gamma_1\gamma_2\gamma_3\gamma_4 < \sec(\pi/4)^4 = 4 \quad \text{and} \quad \gamma_1\gamma_5\gamma_6\gamma_7 < 4, \tag{44}$$

respectively. Because principal submatrices of a diagonally stable matrix are also diagonally stable, we conclude that (44) is a necessary condition for the diagonal stability of (43). In fact, we prove the following necessary and sufficient condition:

Lemma 2 *The matrix E in (43) is diagonally stable iff*

$$\gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7 < \sec(\pi/4)^4 = 4. \tag{45}$$

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

$$D = \text{diag} \left(1, \frac{\gamma_3\gamma_4}{2}, \frac{\gamma_4}{\gamma_2}, \frac{2}{\gamma_2\gamma_3}, \frac{\gamma_6\gamma_7}{2}, \frac{\gamma_7}{\gamma_5}, \frac{2}{\gamma_5\gamma_6} \right) \tag{46}$$

and the matrix

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

We will prove that condition (45) implies that $M \leq 0$. Diagonal stability of E follows from this claim in view of the following argument: Given any γ_i 's satisfying the constraint (45), 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 Δ is some positive diagonal matrix. Now let \tilde{D} be defined for \tilde{E} as in (46) with γ_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 (45) 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_ε , we consider the principal minors $\mu_i(\varepsilon)$, $i = 1, \dots, 7$ of M_ε , and ask that they all have sign $(-1)^i$ for small $\varepsilon > 0$. Each μ_i is a polynomial of degree ≤ 7 on ε . The determinant of M_ε can be expanded as follows:

$$\mu_7(\varepsilon) = \frac{8\gamma_4\gamma_7(\gamma_5 + 2\gamma_6 + \gamma_7)(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3\gamma_5^3\gamma_6} \Delta \varepsilon^2 + O(\varepsilon^3), \quad (47)$$

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_ε is negative definite for all small enough $\varepsilon > 0$ if and only if $\Delta < 0$. In particular, condition (45) implies that $M \leq 0$, as claimed.

Finally, we prove the necessity of (45) for the diagonal stability of E in (43). 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 (45) 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 (45) 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 (10), 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 orientation to each link and define the $n \times m$ incidence matrix S as

$$s_{jk} := \begin{cases} +1 & \text{if node } j \text{ is the sink of link } k \\ -1 & \text{if node } j \text{ is the source of link } k \\ 0 & \text{otherwise.} \end{cases} \quad (48)$$

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

We first prove a general stability result (Theorem 3 below) for a class of compartmental models interconnected as described by the incidence matrix S . We then apply this result in Corollary 4 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

$$\mu_{k,i}(x_{\text{sink}(k),i} - x_{\text{source}(k),i}) \quad (49)$$

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

$$\sigma \mu_{k,i}(\sigma) \leq 0, \quad \forall \sigma \in \mathbb{R}. \quad (50)$$

Then, the coupled dynamics of the compartments become:

$$\dot{X}_j = F_j(X_j) + (S_{j,\cdot} \otimes I_N) \mu((S^T \otimes I_N)X) \quad j = 1, \dots, n \quad (51)$$

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,

$$X := [X_1^T \dots X_n^T]^T \quad (52)$$

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

$$\mu(z) := [\mu_{1,1}(z_1) \cdots \mu_{1,N}(z_N) \cdots \cdots \mu_{m,1}(z_{(m-1)N+1}) \cdots \mu_{m,N}(z_{mN})]^T \quad (53)$$

We now prove stability of the coupled system (51) 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 3 Consider the system (51) where the function $\mu(\cdot)$ is as in (53) and (50). If there exists a Lyapunov function $V : \mathbb{R}^N \rightarrow \mathbb{R}$ of the form

$$V(x) = V_1(x_1) + \cdots + V_N(x_N) \quad (54)$$

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

$$\nabla V(x) F_j(x) \leq -\alpha(|x|) \quad j = 1, \dots, n \quad (55)$$

for some class- \mathcal{K} function $\alpha(\cdot)$, then the origin $X = 0$ of (51) is asymptotically stable. If, further, $V(\cdot)$ is radially unbounded, then $X = 0$ is globally asymptotically stable.

Proof: We employ the composite Lyapunov function

$$\mathcal{V}(X) = \sum_{j=1}^n V(X_j), \quad (56)$$

and obtain from (51) and (55):

$$\dot{\mathcal{V}}(X) \leq -\sum_{j=1}^n \alpha(|X_j|) + [\nabla V(X_1) \cdots \nabla V(X_n)](S \otimes I_N) \mu((S^T \otimes I_N)X). \quad (57)$$

We next rewrite the second term in the right-hand side of (57) as

$$\left((S^T \otimes I_N) \begin{bmatrix} \nabla V^T(X_1) \\ \vdots \\ \nabla V^T(X_n) \end{bmatrix} \right)^T \mu((S^T \otimes I_N)X), \quad (58)$$

and note from (48) that (58) equals

$$\sum_{k=1}^m [\nabla V^T(X_{\text{sink}(k)}) - \nabla V^T(X_{\text{source}(k)})] \begin{bmatrix} \mu_{k,1} \\ \vdots \\ \mu_{k,N} \end{bmatrix} \quad (59)$$

where $\mu_{k,i}$, $i = 1, \dots, N$, denotes the diffusion function (49), and the argument is dropped for

brevity. Next, using (54), we rewrite (59) as

$$\sum_{k=1}^m \sum_{i=1}^N [\nabla V_i(x_{\text{sink}(k),i}) - \nabla V_i(x_{\text{source}(k),i})] \mu_{k,i}. \quad (60)$$

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 (50) that the function $\mu_{k,i}$ in (49) 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 (60) is nonpositive and, hence, (57) becomes

$$\dot{\mathcal{V}}(x) \leq - \sum_{j=1}^n \alpha(|X_j|), \quad (61)$$

from which the conclusions of the theorem follow. \square

Theorem 3 is applicable when each compartment is as described in Section 3, $h_l(\cdot)$ satisfies (34), and $g_i(\cdot)$'s, $i = 1, \dots, N$, are nonincreasing functions. This is because the Lyapunov construction (21) in Section 3 consists of a sum of terms as in (54), each of which is convex when the derivative of (22) is nondecreasing:

Corollary 4 Consider the system (51) where the function $\mu(\cdot)$ is as in (53) and (50), and $F_j(x)$, $j = 1, \dots, n$, are identical and represent the right-hand side of (10). If all assumption of Theorem 1 hold and if, in addition, $h_l(\cdot)$ satisfies (34), 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 Comparison of the State-Space and Input/Output Approaches

The earlier paper [2] gave a purely input/output (instead of state-space) version of the secant criterion, phrased in the language of passivity of L^2 operators. We now explain how to extend this I/O approach to the general graphs studied in this paper. The result follows easily by imposing an appropriate diagonal stability condition, combined with a key lemma due to Moylan and Hill [27], and Vidyasagar [28]. Below we give a streamlined version of this lemma, and compare it with the state space approach employed earlier in this paper.

We denote by L_e^2 the extended space of signals (thought of as time functions) $w : [0, \infty) \rightarrow \mathbb{R}$ which have the property that each restriction $w_T = w|_{[0,T]}$ is in $L^2(0, T)$, for every $T > 0$. Given an element $w \in L_e^2$ and any fixed $T > 0$, we write $\|w\|_T$ for the L^2 the norm of this restriction w_T , and given two functions $v, w \in L_e^2$ and any fixed $T > 0$, the inner product of v_T and w_T is denoted by $\langle v, w \rangle_T$. The same notation is used for vector functions.

We view the M subsystems to be interconnected as operators $\Sigma_i : L_e^2 \rightarrow L_e^2 : u_i \mapsto y_i$, and impose the following strict passivity property: there exist constants $\gamma_i > 0$ (“secant gains” in [2]) such that

$$\|y_i\|_T^2 \leq \gamma_i \langle y_i, u_i \rangle_T \text{ for each } i = 1, \dots, M \text{ and each } T > 0. \quad (62)$$

We then consider the interconnection where

$$u_i(t) = v_i(t) + A_i y(t), \quad (63)$$

or just $u = v + Av$, where the v_i 's are external inputs, $y = \text{col}(y_1, \dots, y_M)$, $v = \text{col}(v_1, \dots, v_M)$, and the A_i , $i = 1, \dots, M$ are the rows of an interconnection matrix $A \in \mathbb{R}^{M \times M}$. In other words, the i th subsystem receives as inputs an external input plus an appropriate linear combination of outputs from the remaining systems (including possibly feedback from itself, if the corresponding diagonal entry of A is nonzero). We introduce:

$$E := A - \Gamma$$

where $\Gamma = \text{diag}(\frac{1}{\gamma_1}, \dots, \frac{1}{\gamma_M})$.

Lemma. Suppose that there exists a diagonal positive definite matrix $D \in \mathbb{R}^{M \times M}$ such that

$$DE + E'D < 0.$$

Then, the system obtained from the systems Σ_i using the interconnection matrix A is L^2 stable as a system with input v and output y . More precisely, there is some constant $\rho > 0$ such that, for any $u, v, y \in (L^2_e)^M$ such that (62) and (63) hold, necessarily $\|y\|_T \leq \rho \|v\|_T$ for all $T > 0$ (and therefore also $\|y\| \leq \rho \|v\|$, if $v \in (L^2)^M$).

Proof: We pick an $\alpha > 0$ such that $DE + E'D < -2\alpha I$, and observe that, for any $T > 0$ and any function $z \in L^2(0, T)$, it holds that

$$\langle Dz, Ez \rangle = \int_0^T z(s)' DEz(s) ds = \int_0^T \frac{1}{2} z'(s) (DE + E'D) z(s) ds \leq -\alpha \int_0^T z'(s) z(s) ds = -\alpha \|z\|^2.$$

Fix an arbitrary $T > 0$, and write $D = \text{diag}(d_1, \dots, d_M)$. Since, for each i , $\langle y_i, u_i - \frac{1}{\gamma_i} y_i \rangle_T \geq 0$, it follows that also $\langle d_i y_i, u_i - \frac{1}{\gamma_i} y_i \rangle_T \geq 0$, or, in vector form:

$$\langle Dy, u - \Gamma y \rangle_T \geq 0.$$

Substituting $u = v + Ay$, we obtain: $\langle Dy, v + Ey \rangle_T \geq 0$, from which, using the Cauchy-Schwartz inequality:

$$\beta \|v\|_T \|y\|_T \geq \langle Dy, v \rangle_T \geq -\langle Dy, Ey \rangle_T \geq \alpha \|y\|_T^2$$

for some $\beta > 0$. So $\|y\|_T \leq \rho \|u\|_T$, with $\rho = \frac{\beta}{\alpha}$, as desired. \square

State-space stability results may be obtained as corollaries, by combining this I/O result with appropriate detectability and controllability conditions, as discussed in [2]. However, the direct Lyapunov approach employed earlier in this paper allowed 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 state-space approach further made it possible to prove robustness of our stability criterion in

the presence of diffusion terms.

7 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 (16) which incorporates information about the passivity properties of the subsystems, the interconnection structure of the network, and the signs of the interconnection terms. Although diagonal stability can be checked numerically with efficient linear matrix inequality (LMI) tools [36], 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 Example 2 we have derived a similar analytical condition for a branched cyclic interconnection structure. Further studies for deriving analytical conditions for practically important interconnection structures 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 [37], and are currently studying more general interconnection structures.

References

- [1] M. Arcak and E. Sontag. Diagonal stability of a class of cyclic systems and its connection with the secant criterion. *Automatica*, 42(9):1531–1537, 2006.
- [2] E.D. Sontag. Passivity gains and the “secant condition” for stability. *Systems Control Lett.*, 55(3):177–183, 2006.
- [3] B.C. Goodwin. Oscillatory behavior in enzymatic control processes. *Adv. Enzyme Reg.*, 3:425–439, 1965.
- [4] J. Tiwari, A. Fraser, and R. Beckmann. Genetic feedback repression. i. single locus models. *J. Theor. Biol.*, 45:311–326, 1974.
- [5] A. Fraser and J. Tiwari. Genetic feedback repression. ii. cyclic genetic systems. *J. Theor. Biol.*, 47:397–412, 1974.
- [6] S.P. Hastings, J. Tyson, and D. Webster. Existence of periodic orbits for negative feedback cellular control systems. *Journal of Differential Equations*, 25(1):39–64, 1977.
- [7] M. Sanglier and G. Nicolis. Sustained oscillations and threshold phenomena in an operon control circuit. *Biophys Chem.*, 4:113–121, 1976.

- [8] J. J. Tyson and H. G. Othmer. The dynamics of feedback control circuits in biochemical pathways. In R. Rosen and F. M. Snell, editors, *Progress in Theoretical Biology*, volume 5, pages 1–62. Academic Press, 1978.
- [9] H.T. Banks and J.M. Mahaffy. Global asymptotic stability of certain models for protein synthesis and repression. *Quart. Appl. Math.*, 36:209–221, 1978.
- [10] H.T. Banks and J.M. Mahaffy. Stability of cyclic gene models for systems involving repression. *J. Theor. Biol.*, 74:323–334, 1978.
- [11] J.M. Mahaffy. Cellular control models with linked positive and negative feedback and delays. i. the models. *J Theor Biol.*, 106:89–102, 1984.
- [12] J.M. Mahaffy. Cellular control models with linked positive and negative feedback and delays. ii. linear analysis and local stability. *J Theor Biol.*, 106:103–118, 1984.
- [13] L. Glass and J. S. Pasternack. Prediction of limit cycles in mathematical models of biological control systems. *Bulletin of Mathematical Biology*, pages 27–44, 1978.
- [14] C. D. Thron. The secant condition for instability in biochemical feedback control - Parts I and II. *Bulletin of Mathematical Biology*, 53:383–424, 1991.
- [15] B.N. Kholodenko. Negative feedback and ultrasensitivity can bring about oscillations in the mitogen-activated protein kinase cascades. *Eur. J. Biochem*, 267:1583–1588, 2000.
- [16] S.Y. Shvartsman, M.P. Hagan, A. Yacoub, P. Dent, H.S. Wiley, and D.A. Lauffenburger. Context-dependent signaling in autocrine loops with positive feedback: Modeling and experiments in the egfr system. *Am. J. Physiol. Cell Physiol.*, 282:C545–C559, 2001.
- [17] M. Morales and D. McKay. Biochemical oscillations in controlled systems. *Biophys. J.*, 7:621–625, 1967.
- [18] G.N. Stephanopoulos, A.A. Aristidou, and J. Nielsen. *Metabolic Engineering Principles and Methodologies*. Academic Press, 1998.
- [19] J.C. Willems. Dissipative dynamical systems Part I: General theory; Part II: Linear systems with quadratic supply rates. *Archive for Rational Mechanics and Analysis*, 45:321–393, 1972.
- [20] A. J. van der Schaft. *\mathcal{L}_2 -gain and Passivity Techniques in Nonlinear Control*. Springer-Verlag, New York and Berlin, second edition, 2000.
- [21] R. Sepulchre, M. Janković, and P. Kokotović. *Constructive Nonlinear Control*. Springer-Verlag, New York, 1997.
- [22] P.V. Kokotović and M. Arcak. Constructive nonlinear control: a historical perspective. *Automatica*, 37(5):637–662, 2001.
- [23] A.N. Michel and R.K. Miller. *Qualitative Analysis of Large Scale Dynamical Systems*. Academic Press, New York, 1977.

- [24] D.D. Šiljak. *Large-Scale Systems: Stability and Structure*. North Holland, New York, 1978.
- [25] M. Araki. Application of M-matrices to the stability problems of composite dynamical systems. *Journal of Mathematical Analysis and Applications*, 52:309–321, 1975.
- [26] M. Araki. Input-output stability of composite feedback systems. *IEEE Transactions on Automatic Control*, 21:254–259, 1976.
- [27] P.J. Moylan and D.J. Hill. Stability criteria for large-scale systems. *IEEE Trans. Autom. Control*, 23(2):143–149, 1978.
- [28] M. Vidyasagar. *Input-Output Analysis of Large Scale Interconnected Systems*. Springer-Verlag, Berlin, 1981.
- [29] E. Kaszkurewicz and A. Bhaya. *Matrix Diagonal Stability in Systems and Computation*. Birkhauser, Boston, 2000.
- [30] J. Mallet-Paret and H.L. Smith. The Poincaré-Bendixson theorem for monotone cyclic feedback systems. *J. of Dynamics and Differential Equations.*, 2:367–421, 1990.
- [31] J. Mallet-Paret. The Poincaré-Bendixson theorem for monotone cyclic feedback systems with delay. *J. of Differential Equations*, pages 441–489, 1996.
- [32] W. Hahn. *Stability of Motion*. Springer-Verlag, Berlin, 1967.
- [33] E.D. Sontag. Smooth stabilization implies coprime factorization. *IEEE Transactions on Automatic Control*, 34:435–443, 1989.
- [34] E.D. Sontag. Asymptotic amplitudes and Cauchy gains: a small-gain principle and an application to inhibitory biological feedback. *Systems and Control Letters*, 47:167–179, 2002.
- [35] Y. Chitour, F. Gognard, and G. Bastin. Equilibria and stability analysis of a branched metabolic network with feedback inhibition. *Networks and Heterogeneous Media*, 1:219–239, 2006.
- [36] S. Boyd, L. El Ghaoui, E. Feron, and V. Balakrishnan. *Linear Matrix Inequalities in System and Control Theory*, volume 15 of *SIAM Studies in Applied Mathematics*. SIAM, Philadelphia, PA, 1994.
- [37] M.R. Jovanović, M. Arcak, and E.D. Sontag. Remarks on the stability of spatially distributed systems with a cyclic interconnection structure. To appear in the *Proceedings of the 2007 American Control Conference*, 2007.