
Passivity-based stability of interconnection structures

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Dedicated to M. Vidyasagar on the occasion of his 60th birthday

Abstract

In the 1970s, Vidyasagar developed an approach to the study of stability of interconnected systems. This paper revisits this approach and shows how it allows one to interpret, and considerably extend, a classical condition used in mathematical biology.

1 Introduction

In Chapter 7 of his influential book *Input-Output Analysis of Large Scale Interconnected Systems* [1], Vidyasagar describes an approach to studying the stability of networks made up of passive subsystems. This approach, which was pioneered in earlier work of Sundareshan and Vidyasagar [2] and Moylan and Hill [3], relies upon verifying the diagonal stability of an associated *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.

As shown in the authors' work [4, 5], diagonal stability, combined with an excess of passivity property on components (the “secant gain” in the terminology in [6]) can be used to rederive, and extend considerably, the classical “secant condition” [7, 8] for the stability of cyclic feedback systems, well-known in mathematical biology. Cyclic feedback structures have classically been used to model autoregulatory feedback loops in gene networks [9, 10, 7, 11, 8], as

well as metabolic pathways [12, 13] and cell signaling [14] In this expository paper, we provide a streamlined version of the key lemma on stability of interconnections due to Vidyasagar and Moylan and Hill, and then show how its hypotheses may be verified for network structures of great interest in biology.

2 The key Lemma

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 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 a family of 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 [6]) such that

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

We then consider the interconnection where

$$u_i(t) = v_i(t) + A_i y(t), \quad (2)$$

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

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

Lemma 1. Suppose that E is diagonally stable, that is, 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 $u, v, y \in (L_e^2)^M$ such that (1) and (2) 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:

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

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

The required passivity properties can be checked through dissipation inequalities involving appropriate Lyapunov-like storage functions, as explained in [4, 5] for several classes of systems which arise in biological applications. Although the conclusion provides a purely input/output stability property, state-space global asymptotic stability results may be obtained as corollaries, by combining I/O stability with appropriate detectability and controllability conditions on subsystems, as discussed in [6]. The verifiable state-space conditions given in these papers 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.

3 Recovering the Classical Secant Condition

The classical ‘‘secant condition’’ applies to systems that are obtained as negative feedback cycles. For such systems,

$$E = E_{cyclic} = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & \cdots & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & \ddots & & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & 1 & -\frac{1}{\gamma_n} \end{bmatrix} \quad (3)$$

and it is shown in [4] that this matrix is diagonally stable if and only if the following condition is satisfied:

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n. \quad (4)$$

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 $n = 3$ (and infinite for $n = 1, 2$). The secant criterion is also necessary for stability of E when the γ_i 's are identical.

A classical result [7, 8] in mathematical biology is that for linear systems (as well as for certain restricted classes of nonlinear feedback systems [7]) is that a matrix of the form:

$$A = \begin{bmatrix} -a_1 & 0 & \cdots & 0 & -b_n \\ b_1 & -a_2 & \ddots & & 0 \\ 0 & b_2 & -a_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -a_n \end{bmatrix} \quad (5)$$

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

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

The matrix A can be interpreted as the closed-loop matrix for a cyclic interconnection of the linear systems with transfer functions $b_i/(s + a_i)$, which are passive with $\gamma_i = \frac{b_i}{a_i}$. Thus, this result is an immediate consequence of Lemma 1 (expressed in state space terms).

4 Branched Structures

It is of interest to ask for characterizations of diagonal stability for the matrices E corresponding to other interconnection structures. In this section, we review recent results from [5] that analyze certain branched structures.

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 [13, 15]. As an example of this situation we consider the network in Figure 1 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

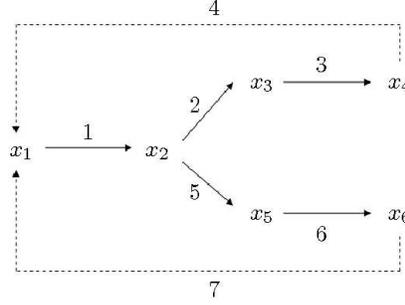


Fig. 1. Feedback inhibition in a branched network. The dashed links 4 and 7 indicate negative (inhibitory) feedback signals. The E matrix for this network is (6).

by two isofunctional enzymes each of which is selectively sensitive to x_4 or x_6 , this example may be seen as an interconnection of several (one-dimensional) subsystems, one for each of the variables, and, under reasonable hypotheses, each of these systems is strictly passive, with appropriate constants γ_i 's, as required in Lemma 1 (see [5] for details). Thus, in order to conclude stability, we must study when the matrix

$$E = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & -\frac{1}{\gamma_4} & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & -\frac{1}{\gamma_5} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_6} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 & -\frac{1}{\gamma_7} \end{bmatrix} \quad (6)$$

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 [4], diagonal stability is equivalent to the secant criteria

$$\gamma_1 \gamma_2 \gamma_3 \gamma_4 < \sec(\pi/4)^4 = 4 \quad \text{and} \quad \gamma_1 \gamma_5 \gamma_6 \gamma_7 < 4, \quad (7)$$

respectively. Because principal submatrices of a diagonally stable matrix are also diagonally stable, we conclude that (7) is a necessary condition for the diagonal stability of (6). In fact, we prove the following necessary and sufficient condition:

Lemma 2. The matrix E in (6) is diagonally stable iff

$$\gamma_1\gamma_2\gamma_3\gamma_4 + \gamma_1\gamma_5\gamma_6\gamma_7 < \sec(\pi/4)^4 = 4. \quad (8)$$

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

$$D = \text{diag} \left(1, \frac{\gamma_3\gamma_4}{2}, \frac{\gamma_4}{\gamma_2}, \frac{2}{\gamma_2\gamma_3}, \frac{\gamma_6\gamma_7}{2}, \frac{\gamma_7}{\gamma_5}, \frac{2}{\gamma_5\gamma_6} \right) \quad (9)$$

and the matrix

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

We will prove that condition (8) 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 (8), 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 (9) 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 (8) 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 and, upon lengthy calculations omitted here, the determinant of M_ε can be expanded as follows:

$$\mu_7(\varepsilon) = \frac{8\gamma_4\gamma_7(\gamma_5 + 2\gamma_6 + \gamma_7)(\gamma_2 + 2\gamma_3 + \gamma_4)}{\gamma_1\gamma_2^3\gamma_3\gamma_5^3\gamma_6} \Delta \varepsilon^2 + O(\varepsilon^3), \quad (10)$$

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 (8) implies that $M \leq 0$, as claimed.

Finally, we prove the necessity of (8) for the diagonal stability of E in (6). 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 (8) 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 (8) is necessary for the diagonal stability of E .

Extension of our results to more general classes of branched structures are being currently developed.

5 A Signaling Network

We study in this section the diagonal stability of the matrices E associated respectively to the three graphs shown in Figure 2). These interconnection

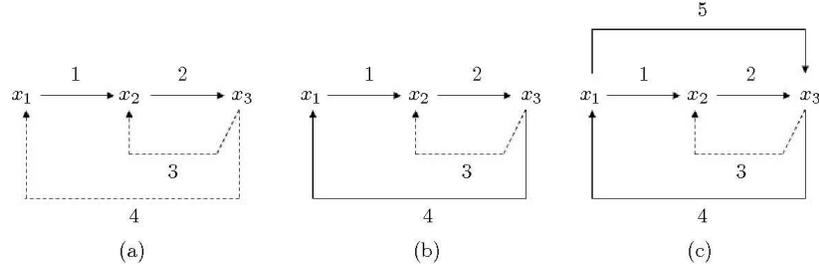


Fig. 2. Three feedback configurations.

graphs are motivated by the paper [16], which dealt with MAPK (mitogen-activated protein kinase) cascades in PC-12 cells. The nodes x_1 , x_2 and x_3 represent the proteins Raf-1, Mek1/2 and Erk1/2, respectively, and dashed lines represent negative feedback signals. The authors of [16] showed that there are topological differences depending on whether the cells are activated with (a) epidermal or (b) neuronal growth factors, leading in particular to a change of sign in the feedback from Erk1/2 to Raf-1. In addition, there is

an increased connectivity from Raf-1 to Erk1/2 when neuronal growth factor activation is observed over a longer period. The paper [16] also relates the differences in dynamic behavior to the change in functionality (proliferation or differentiation) of the network.

Assuming once again one-dimensional systems (this may be generalized to a more realistic model that keeps track of phosphorylation states), one may assume that each system is passive with appropriate constants γ_i (see [5] for details), so we study the associated E matrices, which are, for the feedback configurations (a) and (b) in Figure 2:

$$E_a = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & -1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix} \quad E_b = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} \end{bmatrix} \quad (11)$$

and for configuration (c) is:

$$E_c = \begin{bmatrix} -\frac{1}{\gamma_1} & 0 & 0 & 1 & 0 \\ 1 & -\frac{1}{\gamma_2} & -1 & 0 & 0 \\ 0 & 1 & -\frac{1}{\gamma_3} & 0 & 1 \\ 0 & 1 & 0 & -\frac{1}{\gamma_4} & 1 \\ 0 & 0 & 0 & 1 & -\frac{1}{\gamma_5} \end{bmatrix}. \quad (12)$$

The following lemma derives necessary and sufficient conditions for the diagonal stability of E_a and E_b :

Lemma 3. The matrix E_a in (11) 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 3×3 principal submatrix \tilde{E}_a obtained by deleting the third row and column of E_a exhibits the cyclic form (3) 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 (3) 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 [17, 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

The matrix E_c

It is harder to establish conditions for the diagonal stability of the matrix E_c in (12). As a first observation, note that 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 [17, Theorem 2.3] to the positivity of the principal minors of $-\tilde{E}_c$, which results in the condition:

$$\gamma_1\gamma_2\gamma_4 + \gamma_4\gamma_5 < 1. \quad (13)$$

Because principal submatrices of a diagonally stable matrix are also diagonally stable, (13) 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 3).

We explored numerically the dependence on γ_3 and γ_4 when the remaining parameters are fixed; Figure 3 is an example of the conditions obtained. Specifically, we sketch the exact diagonal stability region in the parameter

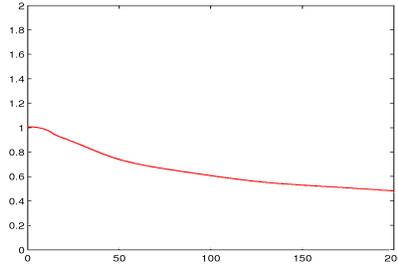


Fig. 3. The region under the curve is the diagonal stability region for (12) in the (γ_3, γ_4) -plane when the other gains are fixed at $\gamma_1 = 1$, $\gamma_2 = \gamma_5 = 0.5$.

plane (γ_3, γ_4) when fixing $\gamma_1 = 1$, $\gamma_2 = \gamma_5 = 0.5$ (so that (13) becomes $\gamma_4 < 1$), plotting the region in which diagonal stability is confirmed numerically by a linear matrix inequality (LMI) solver. Observe that there is a gap between the necessary condition (13) and the exact condition: this feasibility region is 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 γ_3 . The precise characterization of diagonal stability for matrices of the form E_c is still open.

6 Conclusions

The interconnection approach pioneered by Vidyasagar has long had a deep impact in control and systems theory. Supplemented with explicit characterizations of diagonal stability and with procedures for verifying passivity in reaction network models [4, 5], this approach is now throwing new light onto classical results in mathematical biology, and suggesting new directions for further research in that field. A most noteworthy feature of this approach is its “robustness” to uncertainty in dynamics and parameters. Once that the interconnection structure is known, inserting any subsystems that have appropriate passivity properties (quantified by the γ_i ’s) will result in a stable interconnection. In systems molecular biology, often precise estimates of parameters are very hard to come by, as discussed in [18]. Approaches like this one, that only require a relatively small amount of quantitative information, are particularly useful in that context.

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