

Asymptotic amplitudes and Cauchy gains: a small-gain principle and an application to inhibitory biological feedback [☆]

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Received 20 December 2001; received in revised form 7 May 2002; accepted 23 May 2002

Abstract

The notions of asymptotic amplitude for signals, and Cauchy gain for input/output systems, and an associated small-gain principle, are introduced. These concepts allow the consideration of systems with multiple, and possibly feedback-dependent, steady states. A Lyapunov-like characterization allows the computation of gains for state-space systems, and the formulation of sufficient conditions insuring the lack of oscillations and chaotic behaviors in a wide variety of cascades and feedback loops. An application in biology (MAPK signaling) is worked out in detail. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Small-gain principle; Gains; MAPK cascades

1. Introduction

In this note, we introduce the notions of *asymptotic amplitude* for signals and associated *Cauchy gains* for input/output systems. We present a simple small-gain principle for Cauchy gains, and a Lyapunov-like characterization which allows the estimation of gains for state-space systems.

The concepts and results given here should be of general interest in nonlinear stability and control, especially in those cases in which classical small-gain theorems cannot be applied because the location of closed-loop steady-states depends on the precise gain of the feedback law, or because there are multiple such states.

In developing these ideas, we were originally motivated by the problem of guaranteeing the non-existence of oscillations in certain biological inhibitory feedback loops, and specifically in a mathematical model of *mitogen-activated protein kinase (MAPK) cascades*, which represent a “biological module” or subcircuit which is ubiquitous in eukaryotic cell signal transduction processes. (We are greatly indebted to Stas Shvartsman for bringing to our attention this problem and especially Kholodenko’s paper [7], which dealt with the onset of oscillations under high gains.) The general results are illustrated with a numerical computation involving MAPK cascades.

1.1. Cauchy gains

For any metric space M , we write the distance $d_M(a, b)$ between any two elements $a, b \in M$, in the suggestive form “ $|a - b|$ ” even when M has no linear structure (so the “ $-$ ” sign has no meaning, of course), and define the *asymptotic amplitude* of a function

[☆] Supported in part by US Air Force Grant F49620-01-1-0063, National Institutes of Health Grant P20 GM64375, and by funding from Rutgers University to the Institute for Biology at the Interface of the Mathematical and Physical Sciences (BioMaPS Institute).

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$\omega : \mathbb{R}_{\geq 0} \rightarrow M$, where $\mathbb{R}_{\geq 0} = [0, +\infty)$, as follows:

$$\begin{aligned} \|\omega\|_{\text{aa}} &:= \limsup_{s,t \rightarrow \infty} |\omega(t) - \omega(s)| \\ &= \lim_{T \rightarrow \infty} \left(\sup_{t,s \geq T} |\omega(t) - \omega(s)| \right) \in [0, \infty]. \end{aligned}$$

Observe that the condition “ $\|\omega\|_{\text{aa}} = 0$ ” amounts to the Cauchy property for ω : for every $\varepsilon > 0$ there is some $T > 0$ such that $|\omega(t) - \omega(s)| < \varepsilon$ for all $t, s \geq T$. Thus, when M is a complete metric space (for instance, if, as in all our examples, $M \subseteq \mathbb{R}^m$ is any closed subset of a Euclidean space):

$$\|\omega\|_{\text{aa}} = 0 \Leftrightarrow \exists \lim_{t \rightarrow \infty} \omega(t).$$

If $\|\omega\|_{\text{aa}} = 0$, we denote $\omega^\infty := \lim_{t \rightarrow \infty} \omega(t)$.

Let \mathcal{U} and \mathcal{Y} be two complete metric spaces. We define a *behavior with input-value space \mathcal{U} and output-value space \mathcal{Y}* as a relation \mathcal{R} between time-functions with values in \mathcal{U} and \mathcal{Y} , respectively:

$$\mathcal{R} \subseteq [\mathbb{R}_{\geq 0} \rightarrow \mathcal{U}] \times [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Y}]$$

where $[\mathbb{R}_{\geq 0} \rightarrow M]$ is the set of functions $\mathbb{R}_{\geq 0} \rightarrow M$. We call any element $(\omega, \eta) \in \mathcal{R}$ an *input/output pair*, and say that ω is an input signal and η is an output signal of \mathcal{R} .

Typical examples of behaviors, to be discussed in detail later, are those obtained by starting with a system of differential equations with inputs (“forcing functions” or “controls”) ω , and viewing the solutions obtained by solving the system with different initial states, or some components of these solutions, as the outputs η . The formalism that we use, based on abstract relations for the formulation of small-gain results, dates back to Zames’ original paper [21], and the term “behavior” is borrowed from Willems’ work [20].

We use standard terminology for comparison functions: \mathcal{K}_∞ is the class of continuous, strictly increasing, and unbounded functions $\gamma : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$ with $\gamma(0) = 0$.

Definition 1.1. A behavior \mathcal{R} has *Cauchy gain* $\gamma \in \mathcal{K}_\infty$ if

$$\|\eta\|_{\text{aa}} \leq \gamma(\|\omega\|_{\text{aa}})$$

for all $(\omega, \eta) \in \mathcal{R}$.

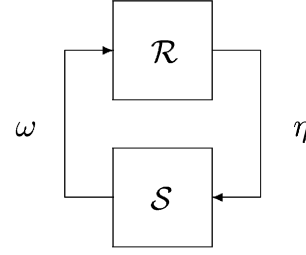


Fig. 1. Feedback interconnection $\mathcal{R} \cap \mathcal{S}^{-1}$.

The existence of a Cauchy gain for \mathcal{R} implies, in particular, the following *converging input converging output* property for \mathcal{R} : if $\omega(t) \rightarrow \bar{u}$ as $t \rightarrow \infty$, for some $\bar{u} \in \mathcal{U}$ (that is, if $\|\omega\|_{\text{aa}} = 0$), and if $(\omega, \eta) \in \mathcal{R}$, then also $\eta(t) \rightarrow \bar{y}$ as $t \rightarrow \infty$, for some $\bar{y} \in \mathcal{Y}$.

The interconnection that results when the output of a system \mathcal{R} is fed back to its input under the action of the system (feedback law) \mathcal{S} is pictorially represented in Fig. 1. The behavioral terminology gives an easy way to define formally the meaning of this interconnection: if \mathcal{R} and \mathcal{S} are behaviors, then the signals that appear when the loop is closed are precisely those pairs (ω, η) such that $(\omega, \eta) \in \mathcal{R}$ and $(\eta, \omega) \in \mathcal{S}$. Put another way, the feedback connection is simply the behavior $\mathcal{R} \cap \mathcal{S}^{-1}$, where, for any behavior \mathcal{S} with input-value space \mathcal{Y} and output-value space \mathcal{U} , we denote by \mathcal{S}^{-1} the inverse behavior, with input-value space \mathcal{U} and output-value space \mathcal{Y} , consisting of all pairs (ω, η) such that $(\eta, \omega) \in \mathcal{S}$.

With this formalism, the basic “small gain principle” is trivial to establish. It states that the interconnection of two systems having Cauchy gains whose composition is a contraction, has the property that the external signals ω and η must always converge to some value as $t \rightarrow \infty$, at least if they are known to have finite asymptotic amplitude:

Lemma 1.2 (Small gain lemma for asymptotic amplitude). *Suppose that \mathcal{R} and \mathcal{S} are two behaviors with Cauchy gains γ_1 and γ_2 , respectively, and that the following condition holds:*

$$\gamma_1(\gamma_2(r)) < r \quad \forall r > 0. \quad (1)$$

Then, for all $(\omega, \eta) \in \mathcal{R} \cap \mathcal{S}^{-1}$ for which $\|\omega\|_{\text{aa}} < \infty$, $\|\omega\|_{\text{aa}} = \|\eta\|_{\text{aa}} = 0$.

Proof. Since $(\omega, \eta) \in \mathcal{R}$, $\|\eta\|_{\text{aa}} \leq \gamma_1(\|\omega\|_{\text{aa}})$; and since also $(\eta, \omega) \in \mathcal{S}$, $\|\omega\|_{\text{aa}} \leq \gamma_2(\|\eta\|_{\text{aa}})$. If $\|\eta\|_{\text{aa}} \neq 0$, then $\|\eta\|_{\text{aa}} \leq \gamma_1(\gamma_2(\|\eta\|_{\text{aa}})) < \|\eta\|_{\text{aa}}$, a contradiction. Finally, $\|\omega\|_{\text{aa}} \leq \gamma_2(\|\eta\|_{\text{aa}}) = \gamma_2(0) = 0$ gives that also $\|\omega\|_{\text{aa}} = 0$. \square

Remark 1.3. Note that the condition “ $\|\omega\|_{\text{aa}} < \infty$ ” is equivalent to ultimate boundedness, i.e. there are a bounded set $C \subseteq \mathcal{U}$ and some $T \geq 0$ such that $\omega(t) \in C$ for all $t \geq T$. (Writing $|u| := |u - 0|$ for some fixed element $0 \in \mathcal{U}$: if there are some $c, T > 0$ so that $|w(t)| \leq c$ for all $t \geq T$ then $\|\omega\|_{\text{aa}} \leq 2c$; conversely, if $\sup_{t,s \geq T} |\omega(t) - \omega(s)| \leq c$ for some T then $|w(t)| \leq c + |\omega(T)|$ for all $t \geq T$.) In applications to feedback loops involving differential equations, all signals are continuous, and for them, ultimate boundedness is equivalent to just boundedness.

The limiting values of the signals ω and η , whose existence is asserted by Lemma 1.2, need not be unique; for instance bistable systems give rise to nonuniqueness. In order to present a condition which guarantees uniqueness, we introduce a new concept.

Definition 1.4. A behavior \mathcal{R} has *incremental limit gain* $\kappa \in \mathcal{K}_\infty$ if the following property holds:

$$\limsup_{t \rightarrow \infty} |\eta_1(t) - \eta_2(t)| \leq \kappa(|\omega_1^\infty - \omega_2^\infty|),$$

whenever $(\omega_i, \eta_i) \in \mathcal{R}$ are any two pairs with the properties $\|\omega_1\|_{\text{aa}} = \|\omega_2\|_{\text{aa}} = 0$.

In words, this definition says that, if we are given two input/output pairs for which the inputs converge, and if the limits of the two inputs are close to each other, then the outputs become asymptotically close to each other. If \mathcal{R} has an incremental limit gain κ , and if in addition \mathcal{R} also admits a Cauchy gain, then both η_1^∞ and η_2^∞ exist whenever $\|\omega_1\|_{\text{aa}} = \|\omega_2\|_{\text{aa}} = 0$ (converging-input converging-output), and thus the “limsup” in Definition 1.4 is a limit, and the estimate becomes

$$|\eta_1^\infty - \eta_2^\infty| \leq \kappa(|\omega_1^\infty - \omega_2^\infty|). \quad (2)$$

With this concept, we have another obvious observation:

Lemma 1.5 (Small gain lemma for asymptotic amplitude, with uniqueness). *Suppose that \mathcal{R} and \mathcal{S}*

are two behaviors with Cauchy gains γ_1 and γ_2 respectively, and incremental limit gains κ_1 and κ_2 , respectively, and that the following condition holds:

$$\kappa_1(\kappa_2(r)) < r \quad \forall r > 0 \quad (3)$$

in addition to (1). Then, there exist two elements $\bar{u} \in \mathcal{U}$ and $\bar{y} \in \mathcal{Y}$ such that, for every input/output pair $(\omega, \eta) \in \mathcal{R} \cap \mathcal{S}^{-1}$ for which $\|\omega\|_{\text{aa}} < \infty$, $\omega^\infty = \bar{u}$ and $\eta^\infty = \bar{y}$.

Proof. If $\mathcal{R} \cap \mathcal{S}^{-1} = \emptyset$, there is nothing to prove. Otherwise, pick an arbitrary $(\omega_1, \eta_1) \in \mathcal{R} \cap \mathcal{S}^{-1}$ for which $\|\omega_1\|_{\text{aa}} < \infty$. From Lemma 1.2, there exist $\bar{u} := \omega_1^\infty$ and $\bar{y} := \eta_1^\infty$. Pick now any other $(\omega_2, \eta_2) \in \mathcal{R} \cap \mathcal{S}^{-1}$ for which $\|\omega_2\|_{\text{aa}} < \infty$; again by the lemma, ω_2^∞ and η_2^∞ exist. By the incremental limit gain property, in the form (2), both $|\bar{y} - \eta_2^\infty| \leq \kappa_1(|\bar{u} - \omega_2^\infty|)$ and $|\bar{u} - \omega_2^\infty| \leq \kappa_2(|\bar{y} - \eta_2^\infty|)$. From

$$|\bar{y} - \eta_2^\infty| \leq \kappa_1(\kappa_2(|\bar{y} - \eta_2^\infty|))$$

we conclude that $\eta_2^\infty = \bar{y}$, and so also $\omega_2^\infty = \bar{u}$. \square

Once the appropriate definitions have been given, the two lemmas are quite obvious. The harder step is, often, to verify when the lemmas apply. In order to carry out such an application, one needs to find sufficient and easy to check conditions which guarantee the existence of Cauchy and incremental limit gains, for the systems whose feedback interconnection is being studied.

We will mainly study behaviors \mathcal{R} which can be built up from cascades of simpler behaviors \mathcal{R}_i , each of which is either defined by a system of differential equations, by a pure delay, or by a memoryless nonlinearity. The composition \mathcal{R} will represent the input/output pairs of a large set of delay-differential equations. The Cauchy and incremental limit gains of the behaviors \mathcal{R}_i can be composed, so as to provide the gains of the complete system \mathcal{R} . Section 2 describes these general ideas. Section 3 shows how to estimate gains based on contractions of omega-limit sets of signals, and these types of estimates are used in order to justify the Lyapunov-like methods described in Section 4 for state-space systems. Finally, Section 5 specializes the results to a class of inhibitory feedback loops, and in particular for the motivating MAPK example.

This work is related to other work on “non-linear gain” small-gain theorems such as [6,9,5], which in turn was motivated by classical small-gain theorems as in [1,11,12,21]. Future developments will include generalizations to estimates which quantify overshoot, in the ISS (cf. [16]) sense.

2. Simple behaviors and cascades

The delay- τ operator \mathcal{D}_τ on \mathcal{U} , where $\tau \geq 0$, is the behavior, with $\mathcal{Y} = \mathcal{U}$, defined by: $(\omega, \eta) \in \mathcal{D}_\tau$ if and only if $\eta(t) = \omega(t - \tau)$ for all $t \geq \tau$. (The value of the output for $t < \tau$ is arbitrary; in an abstract dynamical systems sense, it forms part of the specification of initial conditions.) It is clear that \mathcal{D}_τ has Cauchy gain I and incremental limit gain I , where I is the identity function, $I(r) = r$.

Given any map $\psi: \mathcal{U} \rightarrow \mathcal{Y}$, the *memoryless behavior associated to ψ* , which we denote by \mathcal{M}_ψ , is the behavior consisting of all pairs of functions (ω, η) such that $\eta(t) = \psi(\omega(t))$ for all t . Suppose that ψ is a Lipschitz map: for some $\lambda \geq 0$, $|\psi(u_1) - \psi(u_2)| \leq \lambda|u_1 - u_2|$ for all $u_1, u_2 \in \mathcal{U}$. Then \mathcal{M}_ψ has Cauchy gain λI and incremental limit gain λI , where $\lambda I(r) = \lambda r$.

Suppose that $\mathcal{R} \subseteq [\mathbb{R}_{\geq 0} \rightarrow \mathcal{U}] \times [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Y}]$ and $\mathcal{S} \subseteq [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Y}] \times [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Z}]$ are two behaviors, with Cauchy gains γ_1 and γ_2 , respectively, and consider the cascade combination shown pictorially in Fig. 2 and defined formally as

$$\begin{aligned} \mathcal{S} \circ \mathcal{R} &:= \{(\omega, \zeta) \mid (\exists \eta \in [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Y}]) \\ &\text{s.t. } (\omega, \eta) \in \mathcal{R} \ \& \ (\eta, \zeta) \in \mathcal{S}\}. \end{aligned}$$

Then, clearly, $\mathcal{S} \circ \mathcal{R}$ has Cauchy gain $\gamma_2 \circ \gamma_1$. Suppose now that also \mathcal{R} and \mathcal{S} have incremental limit gains κ_1 and κ_2 , respectively. Let $(\omega_i, \eta_i) \in \mathcal{R}$ and $(\eta_i, \zeta_i) \in \mathcal{S}$, $\|\omega_i\|_{\text{aa}} = 0$, for $i = 1, 2$. We have that η_1^∞ and η_2^∞ exist, and (2) holds with $\kappa = \kappa_1$. Similarly, since \mathcal{S} has a Cauchy gain, ζ_1^∞ and ζ_2^∞ exist, and $|\zeta_1^\infty - \zeta_2^\infty| \leq \kappa_2(|\eta_1^\infty - \eta_2^\infty|)$. Therefore

$$|\zeta_1^\infty - \zeta_2^\infty| \leq \kappa_2(\kappa_1(|\omega_1^\infty - \omega_2^\infty|))$$

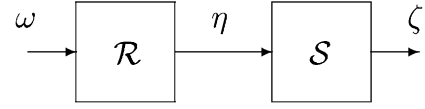


Fig. 2. Cascade $\mathcal{S} \circ \mathcal{R}$.

and hence $\mathcal{S} \circ \mathcal{R}$ has incremental limit gain $\kappa_2 \circ \kappa_1$ (Fig. 2).

2.1. Tighter estimates: relative gains

Tighter estimates of gains for the cascade $\mathcal{S} \circ \mathcal{R}$ can make use of the following observation. Suppose that the possible output signals of \mathcal{R} all tend, as $t \rightarrow \infty$, to values in a restricted subset Y of \mathcal{Y} . Then the relevant gains γ_2, κ_2 should be the gains of \mathcal{S} when restricted to those signals of the form $(\eta, \zeta) \in \mathcal{S}$ such that $\eta \in [\mathbb{R}_{\geq 0} \rightarrow Y]$. These gains may well be smaller than the original ones, so that smaller overall gains result for the cascade. Let us make this precise.

For any subset $U_0 \subseteq \mathcal{U}$, we write “ $\omega \rightarrow U_0$ ” if $\omega(t)$ converges to U_0 as $t \rightarrow \infty$, that is, for every $\varepsilon > 0$ there is some $T \geq 0$ such that

$$\omega(t) \in B_\varepsilon(U_0) = \{u \in \mathcal{U} \mid (\exists u' \in U_0) |u - u'| \leq \varepsilon\}$$

for every $t \geq T$.

Let $U_0 \subseteq \mathcal{U}$ and let $\mathcal{R} \subseteq [\mathbb{R}_{\geq 0} \rightarrow \mathcal{U}] \times [\mathbb{R}_{\geq 0} \rightarrow \mathcal{Y}]$. We will say that \mathcal{R} has a *Cauchy gain* γ on U_0 if $\|\eta\|_{\text{aa}} \leq \gamma(\|\omega\|_{\text{aa}})$ holds for each input/output pair $(\omega, \eta) \in \mathcal{R}$ for which $\omega \rightarrow U_0$. Similarly, we say that \mathcal{R} has *incremental limit gain* κ on U_0 if $\limsup_{t \rightarrow \infty} |\eta_1(t) - \eta_2(t)| \leq \kappa(|\omega_1^\infty - \omega_2^\infty|)$ holds whenever $(\omega_i, \eta_i) \in \mathcal{R}$ are any two pairs such that ω_1^∞ and ω_2^∞ both exist and belong to U_0 . In the special case $U_0 = \mathcal{U}$, one recovers the definitions of Cauchy and incremental limit gains.

Suppose now that there are two sets $U_0 \subseteq \mathcal{U}$ and $Y_0 \subseteq \mathcal{Y}$ such that:

- \mathcal{R} has Cauchy gain γ_1 on U_0 .
- \mathcal{S} has Cauchy gain γ_2 on Y_0 .
- Whenever $(\omega, \eta) \in \mathcal{R}$ is so that $\omega \rightarrow U_0$, necessarily $\eta \rightarrow Y_0$.

Then, clearly, $\mathcal{S} \circ \mathcal{R}$ has Cauchy gain $\gamma_2 \circ \gamma_1$ on U_0 . An analogous conclusion holds for incremental limit gain on U_0 .

3. A sufficient condition

Recall that, for any metric space \mathcal{U} and function $\omega: \mathbb{R}_{\geq 0} \rightarrow \mathcal{U}$, the omega-limit set $\Omega = \Omega^+[\omega]$ is the set consisting of those points $u \in \mathcal{U}$ for which there exists a convergent sequence $\omega(t_i) \rightarrow u$, for some sequence $\{t_i\} \subseteq \mathbb{R}_{\geq 0}$ such that $t_i \rightarrow \infty$ as $i \rightarrow \infty$. The following properties are elementary (they are usually only shown for trajectories of autonomous systems, but they hold for more arbitrary, not even necessarily continuous, functions): (1) the set Ω is closed; (2) if $\omega \rightarrow U$ and U is closed, then $\Omega \subseteq U$, and so Ω is compact if U is; (3) provided ω is precompact, that is to say, if there is some compact subset $U \subseteq \mathcal{U}$ such that $\omega(t) \in U$ for all $t \geq 0$, then Ω is compact, and $\omega \rightarrow \Omega$ (proof of this last statement: if there is some $\varepsilon > 0$ and some sequence $t_i \rightarrow \infty$ such that $\omega(t_i) \in U \setminus B_\varepsilon(\Omega)$ for all i , then one can pick a subsequence of $\{t_i\}$ such that $\omega(t_{i_j}) \rightarrow u$ for some u , and thus $u \in U \setminus B_{\varepsilon/2}(\Omega)$, a contradiction since $u \in \Omega$ by definition of Ω); (4) if ω is precompact and is a continuous function of t , then Ω is connected (proof: otherwise, there are two nonempty compact subsets with $\Omega = \Omega_1 \cup \Omega_2$ and, for some $\varepsilon > 0$, $\text{dist}(\Omega_1, \Omega_2) > 3\varepsilon$, and by (3) some $T > 0$ such that $\omega(t) \in B = B_\varepsilon(\Omega)$ for all $t \geq T$; from $\Omega_1 \subseteq \Omega$ we know that there is some $t_1 > T$ such that $\omega(t_1) \in B_1 = B_\varepsilon(\Omega_1)$ and from $\Omega_2 \subseteq \Omega$ that there is a $t_2 > t_1$ such that $\omega(t_2) \in B_2 = B_\varepsilon(\Omega_2)$, so, noticing that $B = B_1 \cup B_2$ and that $B_1 \cap B_2 = \emptyset$ by choice of ε , and writing $\mathcal{I} := \{\omega(t), t \in [t_1, t_2]\}$, we have that this connected set can be written as a disjoint union $\mathcal{I} = (\mathcal{I} \cap B_1) \cup (\mathcal{I} \cap B_2)$ of nonempty closed sets, a contradiction).

In general, we denote by $|U|$ the *diameter* $\sup\{|u - v| \mid u, v \in U\}$ of a closed subset U of a metric space \mathcal{U} . For each $\omega: \mathbb{R}_{\geq 0} \rightarrow \mathcal{U}$, it holds that $|\Omega^+[\omega]| \leq \|\omega\|_{\text{aa}}$, and, if ω is precompact,

$$\|\omega\|_{\text{aa}} = |\Omega^+[\omega]|. \quad (4)$$

Indeed, pick any $\varepsilon > 0$ and two elements $u, v \in \Omega$ such that $|u - v| \geq |\Omega| - \varepsilon$; then there are two sequences $\omega(t_i) \rightarrow u$ and $\omega(s_i) \rightarrow v$, so $\|\omega\|_{\text{aa}} = \limsup_{s, t \rightarrow \infty} |\omega(t) - \omega(s)| \geq |u - v| \geq |\Omega| - \varepsilon$. As this is true for every $\varepsilon > 0$, we have $\|\omega\|_{\text{aa}} \geq |\Omega|$. Conversely, if $|\omega(t_i) - \omega(s_i)| \geq \|\omega\|_{\text{aa}} - \varepsilon$ for some two sequences $t_i \rightarrow \infty$ and $s_i \rightarrow \infty$, we may extract first a subsequence of $\{t_i\}$ such that $\omega(t_{i_j})$ is con-

vergent (precompactness is used here), and then a subsequence of $\{s_{i_j}\}$, so that, without loss of generality we may suppose that $\omega(t_i) \rightarrow u$ and $\omega(s_i) \rightarrow v$ for some $u, v \in \Omega$, and thus $|\Omega| \geq |u - v| \geq \|\omega\|_{\text{aa}} - \varepsilon$, so letting $\varepsilon \rightarrow 0$ gives the other inequality.

We say that a mapping Γ assigning subsets of one set to subsets of another is monotonic if $U_1 \subseteq U_2 \Rightarrow \Gamma(U_1) \subseteq \Gamma(U_2)$.

Lemma 3.1. *Suppose given a behavior \mathcal{R} , a compact subset $U_0 \subseteq \mathcal{U}$, a function $\gamma \in \mathcal{K}_\infty$, and a mapping Γ from compact subsets of U_0 to subsets of \mathcal{U} , such that the following properties hold:*

- (a) *For each $(\omega, \eta) \in \mathcal{R}$ for which $\Omega^+[\omega] \subseteq U_0$, the output η is precompact.*
- (b) *For each compact subset $U \subseteq U_0$, and each $(\omega, \eta) \in \mathcal{R}$ for which $\Omega^+[\omega] \subseteq U$, it holds that $\Omega^+[\eta] \subseteq \Gamma(U)$.*
- (c) *For each compact subset $U \subseteq U_0$, it holds that $|\Gamma(U)| \leq \gamma(|U|)$.*

Then \mathcal{R} has Cauchy gain γ on U_0 and incremental limit gain γ on U_0 . Moreover, for each compact subset $U \subseteq U_0$, and each $(\omega, \eta) \in \mathcal{R}$ for which $\omega \rightarrow U$, $\eta \rightarrow \Gamma(\Omega^+[\omega])$. If Γ is monotonic, then also $\eta \rightarrow \Gamma(U)$.

Proof. Pick any $(\omega, \eta) \in \mathcal{R}$ and any compact $U \subseteq U_0$, and suppose that $\omega \rightarrow U$. By (1) and (2) in the previous discussion, the set $\Omega^+[\omega]$ is a compact subset of U . By (a), η is precompact. Therefore $\|\eta\|_{\text{aa}} = |\Omega^+[\eta]|$, and also $\eta \rightarrow \Omega^+[\eta]$. By (b), applied to $\Omega^+[\omega]$ itself, we know that $\Omega^+[\eta] \subseteq \Gamma(\Omega^+[\omega])$, which gives the conclusion $\eta \rightarrow \Gamma(\Omega^+[\omega])$. If Γ is monotonic, then $\Omega^+[\omega] \subseteq U$ implies that $\Gamma(\Omega^+[\omega]) \subseteq \Gamma(U)$, so $\eta \rightarrow \Gamma(U)$. In addition, $|\Omega^+[\eta]| \leq |\Gamma(\Omega^+[\omega])|$ together with (c) give the following inequality:

$$\begin{aligned} \|\eta\|_{\text{aa}} &= |\Omega^+[\eta]| \leq |\Gamma(\Omega^+[\omega])| \\ &\leq \gamma(|\Omega^+[\omega]|) \leq \gamma(\|\omega\|_{\text{aa}}). \end{aligned} \quad (5)$$

When applied in the special case $U = U_0$, this establishes the Cauchy gain conclusion.

Suppose now that $(\omega_i, \eta_i) \in \mathcal{R}$ are any two pairs such that ω_1^∞ and ω_2^∞ both exist and belong to U_0 . In particular, $\omega_1 \rightarrow U_0$ and $\omega_2 \rightarrow U_0$. So both η_1^∞ and η_2^∞ exist, by the Cauchy gain conclusion. Note that $\Omega^+[\omega_i] = \{\omega_i^\infty\}$ and $\Omega^+[\eta_i] = \{\eta_i^\infty\}$ for $i = 1, 2$. We introduce the two-element set $U = \{\omega_1^\infty, \omega_2^\infty\} \subseteq U_0$; note that $|U| = |\omega_1^\infty - \omega_2^\infty|$. From $\Omega^+[\omega_i] \subseteq U$ and

(b), we have that $\Omega^+[\eta_i] \subseteq \Gamma(U)$, that is, $\eta_i^\infty \in \Gamma(U)$, for $i = 1, 2$. Therefore

$$|\eta_1^\infty - \eta_2^\infty| \leq |\Gamma(U)| \leq \gamma(|U|) = \gamma(|\omega_1^\infty - \omega_2^\infty|),$$

which proves the incremental limit property. \square

Remark 3.2. The Cauchy gain (but not the incremental limit gain) results in Lemma 3.1 can be tightened provided that one knows that η is continuous, as is the case when considering behaviors defined by differential equation systems, and even further provided that ω is continuous, as is the case when dealing with feedback configurations $\mathcal{R} \cap \mathcal{S}^{-1}$, in the latter case assuming that \mathcal{U} is locally compact (which is automatically satisfied in all finite dimensional applications of the results). To be precise, let us denote by $|U|_c$ the maximal diameter of the connected components of a set U , that is, the supremum of the quantities $|u - v|$ taken over all pairs u, v which lie in any given connected component of U . In general, for any continuous and precompact ω , and any subset $U \subseteq \mathcal{U}$ such that $\Omega^+[\omega] \subseteq U$, it holds that $\|\omega\|_{aa} \leq |U|_c$, because $\Omega^+[\omega]$ is connected and thus lies entirely in a single connected component of U . Then:

- if η is continuous for every $(\omega, \eta) \in \mathcal{R}$ then assumption (c) can be weakened to “ $|\Gamma(U)|_c \leq \gamma(|U|)$ for every compact subset $U \subseteq U_0$ ”;
- if in addition ω is continuous for every $(\omega, \eta) \in \mathcal{R}$ and \mathcal{U} is locally compact then assumption (c) can be weakened to “ $|\Gamma(U)|_c \leq \gamma(|U|)$ for every compact and connected subset $U \subseteq U_0$ ”.

Indeed, in the proof of Lemma 3.1 observe that if η is precompact and continuous then $\Omega^+[\eta]$ is connected, so $\Omega^+[\eta] \subseteq \Gamma(\Omega^+[\omega])$ implies that $\|\eta\|_{aa} \leq |\Gamma(\Omega^+[\omega])|_c$, and this is all that is needed in (5). If also \mathcal{U} is locally compact and ω is continuous, then $\omega \rightarrow U$ (compact) implies that ω is precompact, which together with continuity says that $\Omega^+[\omega]$ is connected, and therefore in order to prove (5), (c) only needs to be applied with the connected set $U = \Omega^+[\omega]$.

4. Systems of differential equations

A particular class of behaviors, in fact the main objects of interest in this note, are obtained as follows.

We consider systems of differential equations with inputs and outputs ([15]):

$$\dot{x} = f(x, u), \quad y = h(x) \quad (6)$$

for which states $x(t)$ evolve in a subset \mathcal{X} of a Euclidean space \mathbb{R}^n , inputs take values $u(t)$ in a complete metric space \mathcal{U} and outputs take values $y(t)$ in a complete metric space \mathcal{Y} . (Typically in applications, \mathcal{U} and \mathcal{Y} are any two closed subsets of Euclidean spaces.) Technically, we assume that $f: \mathcal{X}_0 \times \mathcal{U} \rightarrow \mathbb{R}^n$ is defined on an open subset $\mathcal{X}_0 \subseteq \mathbb{R}^n$ which contains \mathcal{X} , is continuous, and is locally Lipschitz in x uniformly on compact subsets of $\mathcal{X}_0 \times \mathcal{U}$; the map $h: \mathcal{X} \rightarrow \mathcal{Y}$ is assumed to be continuous. Furthermore, \mathcal{X} is an invariant and forward complete subset, in the sense that, for each Lebesgue-measurable precompact input $\omega: \mathbb{R}_{\geq 0} \rightarrow \mathcal{U}$, and each initial state $x_0 \in \mathcal{X}$, the unique solution $\xi(t) = \varphi(t, x_0, \omega)$ of the initial value problem $\dot{\xi}(t) = f(\xi(t), \omega(t))$, $\xi(0) = x_0$, is defined and satisfies $\xi(t) \in \mathcal{X}$ for all $t \geq 0$. (The function ξ is Lipschitz, and hence differentiable almost everywhere; if ω is continuous, then ξ is continuously differentiable.) To any given system (6) one associates a behavior \mathcal{R} , with input-value space \mathcal{U} and output-value space \mathcal{Y} , defined by $(\omega, \eta) \in \mathcal{R}$ if and only if ω is precompact and Lebesgue-measurable, and there exists some $x_0 \in \mathcal{X}$ such that $\eta(t) = h(\varphi(t, x_0, \omega))$ for all $t \in \mathbb{R}_{\geq 0}$. We call \mathcal{R} the behavior of (6).

Remark 4.1. A minor technicality concerns the fact that Lebesgue-measurable functions are, strictly speaking, not functions but equivalence classes of functions, so one should interpret the “limsup” in the definition of asymptotic amplitude in an “almost everywhere” manner; similarly, we interpret “precompact” as meaning that there is some ω in the given equivalence class whose values all remain in a compact set. From now on, we leave this technicality implicit; in applications to stability of feedback loops involving systems of differential equations, all the functions considered are continuous—even differentiable—so the issue does not even arise.

We will obtain sufficient conditions for the existence of the two types of gains, expressed in terms of Lyapunov-type functions.

Given a subset $U \subseteq \mathcal{U}$, we will say that a function

$$V : \mathcal{X} \rightarrow \mathbb{R}_{\geq 0}$$

is a U -decrease function provided that the following properties hold:

- V is proper, that is, $\{x \in \mathcal{X} \mid a \leq V(x) \leq b\}$ is a compact subset of \mathcal{X} , for each $a \leq b$ in $\mathbb{R}_{\geq 0}$;
- V is continuous;
- for each $x \in \mathcal{X}$ which does not belong to $Z_V := \{x \mid V(x) = 0\}$, it holds that V is continuously differentiable in a neighborhood of x and

$$\nabla V(x) \cdot f(x, u) < 0 \quad (7)$$

for all $u \in U$.

(We understand continuous differentiability in the following sense: there is a neighborhood of x in \mathcal{X}_0 such that V extends to this neighborhood as a \mathcal{C}^1 function.)

Lemma 4.2. *Suppose that V is a U -decrease function, for some compact subset $U \subseteq \mathcal{U}$. Pick any Lebesgue-measurable precompact $\omega : \mathbb{R}_{\geq 0} \rightarrow \mathcal{U}$ and any solution ξ of the system $\dot{\xi} = f(\xi, \omega)$. Suppose that either:*

- (1) *there is some $T_0 \geq 0$ such that $\omega(t) \in U$ for all $t \geq T_0$, or*
- (2) *$\omega \rightarrow U$ and ξ is precompact.*

Then $\xi \rightarrow Z_V$.

Proof. Given any ω and ξ , we will first let $a > 0$ be arbitrary and prove that the set $V_a := \{x \mid V(x) \leq a\}$ has the property that, for some $T^* \geq 0$,

$$\xi(t) \in V_a \quad \forall t \geq T^*. \quad (8)$$

If the assumption is that $\omega \rightarrow U$ as $t \rightarrow \infty$ and that ξ is precompact, that is to say, there is some compact subset C_0 of \mathcal{X} such that $\xi(t) \in C_0$ for all $t \geq 0$, then we introduce $b := \max\{V(x), x \in C_0\}$ and the set $C := V^{-1}([a, b])$. Note that $\xi(t) \in C$ whenever $V(\xi(t)) \geq a$, by the choice of b . Since, by properness of V , C is a compact subset of $\mathcal{X} \setminus Z_V$, by Property (7) there is some $\alpha > 0$ and some neighborhood \tilde{U} of U in \mathcal{U} so that $\nabla V(x) \cdot f(x, u) \leq -\alpha$ for all $x \in C$ and all $u \in \tilde{U}$. Since $\omega \rightarrow U$, there must be some T_0

such that $\omega(t) \in \tilde{U}$ for all $t \geq T_0$. Thus,

$$\nabla V(x) \cdot f(x, \omega(t)) \leq -\alpha < 0 \quad \forall x \in C \quad \forall t \geq T_0. \quad (9)$$

If, instead, the assumption is that there is some $T_0 \geq 0$ such that $\omega(t) \in U$ for all $t \geq T_0$, we pick T_0 to be any such number, and let $C := \{x \mid V(x) \geq a\}$. So once more we have that $\nabla V(x) \cdot f(x, \omega(t)) < 0$ for all $x \in C$ and all $t \geq T_0$.

Claim. *Let*

$$T_1 := \inf\{t \geq T_0 \mid V(\xi(t)) \leq a\}$$

(if $V(\xi(t)) > a$ for all $t \geq T_0$, we define $T_1 = +\infty$). Then $V(\xi(t)) \leq V(\xi(T_0))$ for all $t \in [T_0, T_1)$ and $V(\xi(t)) \leq a$ for all $t \geq T_1$.

Proof. Suppose that $\xi(t) \in C$ for all t in some interval (τ_1, τ_2) with $\tau_1 \geq T_0$. Then $dV(\xi(t))/dt = \nabla V(\xi(t)) \cdot f(\xi(t), \omega(t)) < 0$ for almost every $t \in (\tau_1, \tau_2)$. Therefore, $V(\xi(t))$ is decreasing on this interval, and we have that $V(\xi(t)) \leq V(\xi(\tau_1))$ for all $t \in (\tau_1, \tau_2)$. In particular, for each $t \in (T_0, T_1)$, by minimality of T_1 we know that $V(\xi(t)) > a$ and so $\xi(t) \in C$. This proves the first part of the claim: $V(\xi(t)) \leq V(\xi(T_0))$ for all $t \in [T_0, T_1)$. If $T_1 = \infty$, there is nothing more to prove. So assume that $T_1 < \infty$ and there exists some $S > T_1$ such that $V(\xi(S)) > a$. Then there is some $T \in [T_1, S)$ such that $V(\xi(T)) = a$. We pick $T' \in [T_1, S)$ to be maximal with this property. It follows that $V(\xi(t)) > a$ for all $t \in (T', S]$. Applying the above argument with $\tau_1 = T'$ and $\tau_2 = S$, we have that $V(\xi(S)) \leq a = V(\xi(T'))$, a contradiction. So the claim holds.

We conclude that $V(\xi(t)) \leq \max\{a, V(\xi(0))\}$ for all $t \geq T_0$. Therefore the trajectory ξ is precompact, and the first case in the lemma is included in the second case, so we can assume that (9) holds. We claim that this means that $T_1 < \infty$, so that (8) holds with $T^* = T_1$. Indeed, if this were not true, then $\xi(t) \in C$ for all $t \geq T_0$, so $dV(\xi(t))/dt \leq -\alpha$ for almost all t , which gives $V(\xi(t)) \leq V(\xi(0)) - \alpha t$ for all $t \geq T_0$, which is impossible since V is nonnegative.

To conclude that $\xi \rightarrow Z_V$, since ξ is precompact we need only show that its omega-limit set $\Omega^+[\xi]$ is contained in Z_V . To see this, we pick any $z \in \Omega^+[\xi]$ and a sequence $\xi(t_i) \rightarrow z$. So $V(\xi(t_i)) \rightarrow V(z)$. If $z \notin Z_V$, let $a := V(z)/2 \neq 0$. Then Property (8) gives

that $V(\xi(t_i)) \leq a$ for all i large enough, which says that $\limsup_i V(\xi(t_i)) \leq a$, contradicting $V(\xi(t_i)) \rightarrow 2a$. Thus $z \in Z_V$. \square

Theorem 1. *Suppose given a behavior \mathcal{R} of a system (6), and for each compact subset $U \subseteq \mathcal{U}$, a U -decrease function V_U . Then:*

- (1) *For each compact subset $U \subseteq \mathcal{U}$ and for every $(\omega, \eta) \in \mathcal{R}$ satisfying $\omega \rightarrow U$, holds that $\eta \rightarrow h(Z_{V_U})$.*
- (2) *If there is a compact subset $U_0 \subseteq \mathcal{U}$ and there is some $\gamma \in \mathcal{K}_\infty$ such that*

$$|h(Z_{V_U})| \leq \gamma(|U|) \quad (10)$$

for every compact $U \subseteq U_0$, then \mathcal{R} has Cauchy gain γ on U_0 and incremental limit gain γ on U_0 .

- (3) *If there is some $\gamma \in \mathcal{K}_\infty$ such that (10) holds for every compact subset $U \subseteq \mathcal{U}$, then \mathcal{R} has Cauchy gain γ and incremental limit gain γ .*

Proof. We will first show that, for every triple (ω, ξ, η) with ω precompact and Lebesgue-measurable, such that $\dot{\xi}(t) = f(\xi(t), \omega(t))$ and $\eta(t) = h(\xi(t))$, the following properties hold:

- (i) ξ and η are precompact;
- (ii) for each compact $U \subseteq \mathcal{U}$, if $\omega \rightarrow U$ then $\xi \rightarrow Z_{V_U}$ and $\eta \rightarrow h(Z_{V_U})$.

(This will prove, in particular, the first assertion of the theorem.) Since ω is precompact, there exists some compact set, let us call it U' , such that $\omega(t) \in U'$ for all t . The first case in Lemma 4.2, applied to U' and $V' = V_U$ with $T_0 = 0$, gives that $\xi(t) \rightarrow Z_{V'}$, so, being continuous as a function of t , ξ is precompact. Next we apply once more Lemma 4.2, using now the second case with any given compact U and the U -decrease function $V = V_U$, to conclude that $\xi \rightarrow Z_V$. Since the set Z_V is compact and the mapping h is continuous, it follows that also $\eta(t) = h(\xi(t)) \rightarrow h(Z_V)$ as $t \rightarrow \infty$, and η is precompact as well.

Next, we pick any compact $U_0 \subseteq \mathcal{U}$ as in the second assertion, so that for every compact subset $U \subseteq U_0$ we have that $|h(Z_{V_U})| \leq \gamma(|U|)$, and let $\Gamma(U) := h(Z_{V_U})$. We will apply Lemma 3.1. Property (c) in that lemma holds by definition of Γ . Also, (a) holds, by (i). To prove that (b) is true, suppose that $\Omega^+[\omega] \subseteq U \subseteq U_0$. Since ω is precompact, $\omega \rightarrow \Omega^+[\omega]$, so also $\omega \rightarrow U$. By (ii), we know that $\eta \rightarrow h(Z_{V_U})$, and so $\Omega^+[\eta] \subseteq$

$h(Z_{V_U}) = \Gamma(U)$, as desired. The lemma then says that \mathcal{R} has Cauchy gain γ on U_0 and also has incremental limit gain γ on U_0 .

Finally, given an arbitrary pair $(\omega, \eta) \in \mathcal{R}$, we pick some compact U_0 such that $\omega(t) \in U_0$; then the just-shown Cauchy property on U_0 gives that $\|\eta\|_{\text{aa}} \leq \gamma(\|\omega\|_{\text{aa}})$, and similarly for the incremental gain. \square

5. A class of examples

As an illustration of gain computations and small-gain stability arguments, we consider systems which consist of cascades of several subsystems, each of which can be individually described by some ordinary differential equation $\dot{x}_i = f(x_i, u_i)$ with input u_i . The input $u_1 = u$ to the first of the systems in the cascade is an external one, while the intermediate inputs u_i , $i > 1$, between two stages depend on the state of the preceding stage. In a biological application, $x_i(t)$ might represent the amount present, at any given time t , of the activated form E_i^* of an enzyme E_i whose production rate is, in turn, dependent upon the amount present of the activated form E_{i-1}^* of the enzyme E_{i-1} . We allow transport delays in between stages. This leads to systems given by sets of delay-differential equations as follows:

$$\dot{x}_1(t) = f_1(x_1(t), u(t)),$$

$$\dot{x}_2(t) = f_2(x_2(t), x_1(t - \tau_1)),$$

$$\vdots$$

$$\dot{x}_n(t) = f_n(x_n(t), x_{n-1}(t - \tau_{n-1})),$$

where $\tau_1, \dots, \tau_{n-1} \geq 0$ are the delays among the stages of the process (the particular case in which there are no delays is included in this formalism by setting all $\tau_i = 0$). See Fig. 3, where $x_i^\tau(t) := x_i(t - \tau)$ and we use \mathcal{R}_i to denote the behavior associated to the system $\dot{x} = f_i(x, u)$ with output $y = x$. One often asks about such systems, see e.g. [3,10,17,18], whether adding a feedback loop from the last stage to the first, as shown in Fig. 4, might introduce instabilities, such as oscillations or even chaotic behavior. Specifically, one may have, for instance, that the action of u on the first subsystem is inhibited by the final product x_n . Assuming that all the variables x_i as well as the external input u are scalar, and take only nonnegative values (as is

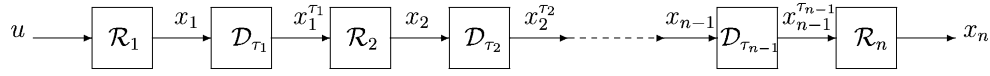


Fig. 3. Cascade of \mathcal{R}_i 's and delays.

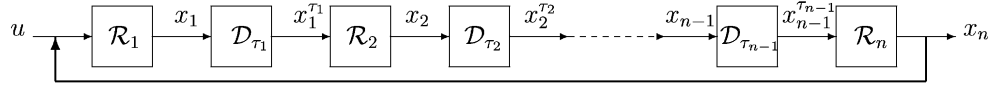


Fig. 4. Cascade of \mathcal{R}_i 's and delays, with feedback to first stage.

for instance the case when variables represent chemical concentrations), a typical model for inhibition is obtained when the first equation becomes

$$\dot{x}_1(t) = f \left(x_1(t), \frac{u(t)}{1 + kx_n(t - \tau_n)} \right)$$

(other expressions for inhibition are also possible, of course), where the “gain” $k \geq 0$ serves to parametrize the feedback strength. Note that we are also allowing for an additional delay in the feedback. Suppose that we are interested in analyzing the case in which $u(t)$ equals a constant value μ , so that the effective input being fed to the first subsystem is $\omega(t) = \psi(x_n^{\tau_n}(t)) = \psi(x_n(t - \tau_n))$, where ψ is the following function:

$$\psi(x) = \frac{\mu}{1 + kx} \tag{11}$$

(for some particular values of μ and k). The closed-loop system may be viewed as the feedback interconnection $\mathcal{R} \cap \mathcal{M}_\psi^{-1}$ of the memoryless behavior \mathcal{M}_ψ with the behavior of the forward composite system with output $x_n^{\tau_n}$, that is, the composition

$$\mathcal{R} = \mathcal{D}_{\tau_n} \circ \mathcal{R}_n \circ \mathcal{D}_{\tau_{n-1}} \circ \dots \circ \mathcal{D}_{\tau_1} \circ \mathcal{R}_1.$$

Suppose that each \mathcal{R}_i has Cauchy gain γ_i and also incremental limit gain γ_i . Then \mathcal{R} has gain $\gamma = \gamma_n \circ \dots \circ \gamma_1$ of both types. Since ψ has Lipschitz constant $k\mu$, \mathcal{M}_ψ has both gains $k\mu I$. Therefore, provided that the small gain condition

$$\gamma(k\mu r) < r \quad \forall r > 0 \tag{12}$$

holds, one concludes from Lemma 1.5 that there is some value \bar{u} such that, for every solution of the closed-loop system, $\omega \rightarrow \bar{u}$. This means, in turn, because each \mathcal{R}_i has a Cauchy gain, that every state variable x_i converges to a unique equilibrium (independently of initial conditions).

The problem, therefore, is to estimate gains γ_i for the systems \mathcal{R}_i . We briefly discuss one situation, itself of great interest, in which estimates can be obtained.

We suppose given intervals $\mathcal{X}_i = [a_i, b_i] \subseteq \mathbb{R}_{\geq 0}$, and sets $\mathcal{U}_i \subseteq \mathbb{R}_{\geq 0}$, $i = 1, \dots, n$, with $\mathcal{U}_i = \mathbb{R}_{\geq 0}$ for $i > 1$, such that any solution of $\dot{x} = f_i(x, u)$ with initial conditions in \mathcal{X}_i and input with values in \mathcal{U}_i remains in \mathcal{X}_i . In a typical biological application, one may have $\mathcal{X}_i = [0, x_i^{\max}]$, where x_i^{\max} is the maximum possible amount of a substance, such as the activated form of an enzyme, that may be synthesized. Also, suppose given, for each i , a strictly increasing and onto function

$$g_i : [a_i, b_i] \rightarrow \mathbb{R}_{\geq 0}$$

with the following properties:

- (1) the restriction of $g_i^{-1} : \mathbb{R}_{\geq 0} \rightarrow [a_i, b_i]$ to \mathcal{U}_i is Lipschitz, with Lipschitz constant λ_i ;
- (2) $x < g_i^{-1}(u) \Rightarrow f_i(x, u) > 0$, and $x > g_i^{-1}(u) \Rightarrow f_i(x, u) < 0$, for every $u \in \mathcal{U}_i$ and $x \in \mathcal{X}_i$.

Then, \mathcal{R} admits both Cauchy and incremental limit gain $\gamma(r) = \lambda_1 \dots \lambda_n r$, and (12) becomes

$$k\mu < \frac{1}{\lambda_1 \dots \lambda_n}. \tag{13}$$

This is proved as follows. Fixing any $i = 1, \dots, n$, we drop subscripts and write $\mathcal{X} = \mathcal{X}_i$, $\mathcal{U} = \mathcal{U}_i$, $g = g_i$, $\lambda = \lambda_i$. For each compact subset $U \subseteq \mathcal{U}$, we let $c := \min U$ and $d := \max U$, so that $U \subseteq [c, d]$ and $|U| = d - c$, and define $V_U : \mathcal{X} \rightarrow \mathbb{R}_{\geq 0}$ to be the distance from any x to the set

$$g^{-1}([c, d]) = [g^{-1}(c), g^{-1}(d)]$$

(recall that g^{-1} is an increasing function). So $Z_{V_U} = [g^{-1}(c), g^{-1}(d)]$, and $V_U(x) = g^{-1}(c) - x$ if $g(x) < c$, $V_U(x) = x - g^{-1}(d)$ if $g(x) > d$. Note that Z_{V_U} has diameter $|Z_{V_U}| \leq \lambda|d - c| = \lambda|U|$.

Furthermore, V_U is a U -decrease function, because V_U is continuous, proper, differentiable outside Z_{V_U} , and satisfies the decrease condition. Indeed, pick any $x \in \mathcal{X} \setminus Z_{V_U}$ and $u \in U$. There are two cases: $x < g^{-1}(c)$ or $x > g^{-1}(d)$. In the first case, $x < g^{-1}(c) \leq g^{-1}(u)$ (since $u \in [c, d]$), so $\nabla V(x) \cdot f(x, u) = (-1) \cdot f(x, u) < 0$, and the second case is similar. Theorem 1 (part 3) then applies, so the corresponding behavior \mathcal{R}_i has both Cauchy and incremental limit gain $\gamma_i(r) = \lambda_i r$, and therefore the cascade (with arbitrary delays) has both gains equal to γ , as claimed.

The requirement that each $g_i^{-1} : \mathcal{U}_i \rightarrow [a_i, b_i]$ must have Lipschitz constant λ_i can be relaxed to:

the restriction of g_i^{-1} to U_i is Lipschitz with Lipschitz constant λ_i (14)

for each $i = 1, \dots, n$, where we define, inductively, the intervals $U_1 := \mathcal{U}_1$ and

$$U_{i+1} := Z_{V_{U_i}} = g_i^{-1}(U_i) \subseteq \mathcal{U}_{i+1}$$

for $i = 1, \dots, n$. For each compact subset $U \subseteq U_i$, we have that $|Z_{V_U}| \leq \lambda_i |U|$, so, by Theorem 1 (part 2, applied n times, with $U_0 = U_i$, $i = 1, \dots, n$) we conclude that each \mathcal{R}_i has Cauchy gain as well as incremental limit gain $\gamma_i(r) = \lambda_i r$ on U_i . In addition, for each $i = 1, \dots, n-1$ and every $(\omega, \eta) \in \mathcal{R}_i$ such that $\omega \rightarrow U_i$, Theorem 1 (part 1) insures that $\eta \rightarrow U_{i+1}$. The pure delays D_{τ_i} have identity gains, and of course satisfy $\omega \rightarrow U_{i+1} \Rightarrow \eta \rightarrow U_{i+1}$. So, arguing (for each consecutive pair of subsystems in the cascade) as in Section 2.1, we conclude that \mathcal{R} admits both Cauchy and incremental limit gain $\gamma(r) = \lambda_1 \dots \lambda_n r$ provided condition (14) holds.

Let us specialize even further. We assume from now on that each function f_i has the following form:

$$f_i(x, u) = -\alpha_i(x) + u\beta_i(x),$$

where the functions α_i and β_i are nonnegative on $\mathcal{X} = [a_i, b_i]$, α_i is strictly increasing and β_i is strictly decreasing, and $\alpha_i(a_i) = \beta_i(b_i) = 0$. Since $f_i(a_i, u) > 0$ and $f_i(b_i, u) < 0$ for all $u \in \mathcal{U}_i$, the interval $\mathcal{X}_i = [a_i, b_i]$ is invariant. For each i , we let

$$g_i(x) := \frac{\alpha_i(x)}{\beta_i(x)}$$

for $x \in [a_i, b_i]$. Then g_i is strictly increasing, because α_i increases and β_i decreases, and it satisfies

$g_i(a_i) = 0$ and $g_i(x) \rightarrow \infty$ as $x \rightarrow b_i^-$, so it is onto $\mathbb{R}_{\geq 0}$. Given any $x \in [a_i, b_i]$ and $u \in \mathcal{U}_i$, if $x < g_i^{-1}(u)$ then $\alpha_i(x)/\beta_i(x) = g_i(x) < u$ implies $f_i(x, u) > 0$ and similarly $x > g_i^{-1}(u) \Rightarrow f_i(x, u) < 0$. If $x = b_i$ then $f_i(x, u) = -\alpha_i(b) < 0$.

In conclusion, the functions $g_i(x) := \alpha_i(x)/\beta_i(x)$ are as required for the above computations, and the gains can be computed in terms of the Lipschitz constants in (14), computed on the sets U_i .

5.1. MAPK cascades

As an application, and in fact the original motivation for this study, we pick the case when every $\mathcal{X}_i = [0, 1]$ (for now, we let \mathcal{U}_1 be arbitrary, but it will be restricted below), and

$$\alpha_i(x) = \frac{b_i x}{c_i + x} \quad \text{and} \quad \beta_i(x) = \frac{d_i(1-x)}{e_i + (1-x)}$$

(for some positive constants b_i, c_i, d_i, e_i). We wish to study the stability of the inhibitory closed-loop system:

$$\dot{x}_1 = -\frac{b_1 x_1}{c_1 + x_1} + \frac{\mu}{1 + kx_3^{\tau_3}} \frac{d_1(1-x_1)}{e_1 + (1-x_1)}, \quad (15)$$

$$\dot{x}_2 = -\frac{b_2 x_2}{c_2 + x_2} + x_1^{\tau_1} \frac{d_2(1-x_2)}{e_2 + (1-x_2)}, \quad (16)$$

$$\dot{x}_3 = -\frac{b_3 x_3}{c_3 + x_3} + x_2^{\tau_2} \frac{d_3(1-x_3)}{e_3 + (1-x_3)}, \quad (17)$$

where the $\tau_i \geq 0$. Such equations arise, for instance, as follows.

Mitogen-activated protein kinase (MAPK) cascades constitute a type of “biological module” or “sub-circuit” which is implicated, in several variants, in a large variety of eukaryotic cell signal transduction processes, cf. [4,8,19]. This highly conserved signaling cascade processes inputs—themselves triggered, in turn, by extracellular stimuli—into output signals responsible for diverse cellular behaviors: proliferation, growth, and differentiation (hence the name), as well as movement, stress responses, and death. The basic mechanism is that of a cascade of three subsystems, each of which consists of one or more reversible enzyme activations.

Subject to conservation laws (stoichiometry relations), each subsystem is usually described in terms of one or two differential equations, see for instance [4,7,13,14]. (The models in these references do not include delays among levels in the cascade, but in our

formalism, arbitrary delays do not affect the results, and they are biologically plausible.) For simplicity, we pick a model with one equation in each level, as in [13,14] and the last section of [7]. In general, one would have all $\mathcal{X}_i = [0, E_i]$, where E_i is the total amount of enzyme present (activated plus nonactivated), but we may take all $\mathcal{X}_i = [0, 1]$ after nondimensionalization, as was done in [13,14]. These references, and especially Kholodenko’s work, emphasized the fact that inhibitory feedback, which seems to be present in naturally occurring cells, could, theoretically, produce oscillations. As oscillations in MAPK cascades do not appear to occur naturally, an interesting mathematical question is to find conditions on gains insuring lack of oscillations. We do this next.

We first show that the functions g_i^{-1} are always Lipschitz, and compute an estimate of the constant. This will prove that stability is preserved under small enough feedback, but the estimates may be too conservative. After that, we describe a numerical approach which allows sometimes quite tight estimates. To obtain the general bounds, we compute, for $x \in [0, 1]$:

$$g'_i(x) = \frac{b_i e_i x^2 + c_i(x-1)^2 + c_i e_i}{d_i (c_i + x)^2 (1-x)^2}$$

and use (taking derivatives to minimize) these lower bounds:

$$e_i x^2 + c_i(x-1)^2 \geq \frac{c_i e_i}{e_i + c_i},$$

$$(c_i + x)(1-x) \leq (1/4)(c_i + 1)^2$$

so as to obtain the following estimate:

$$g'_i(x) \geq \delta_i := 16 \frac{b_i}{d_i} \frac{c_i e_i}{(c_i + 1)^4} \left(1 + \frac{1}{e_i + c_i}\right) > 0.$$

Thus $\lambda_i = 1/\delta_i$ are Lipschitz constants as desired.

Since we are ultimately interested in the effect of inhibitory feedback given by a function $\psi(\xi) = \mu/(1+k\xi)$ as in (11), where ξ is a (possibly delayed) value of x_3 , which ranges over the interval $[0, 1]$, the only inputs u that must be considered are those in $[\mu/(1+k), \mu]$. So, from now, on we suppose that the first input set has the form:

$$\mathcal{U}_1 = [\bar{u}, \infty)$$

for some $\bar{u} > 0$. The appropriate value of \bar{u} will depend upon assumed prior upper bounds on feedback gains k and lower bounds on external inputs μ . We let $U_1 = \mathcal{U}_1$ and introduce $U_{i+1} = g_i^{-1}(U_i)$ for $i = 1, 2, 3$ as

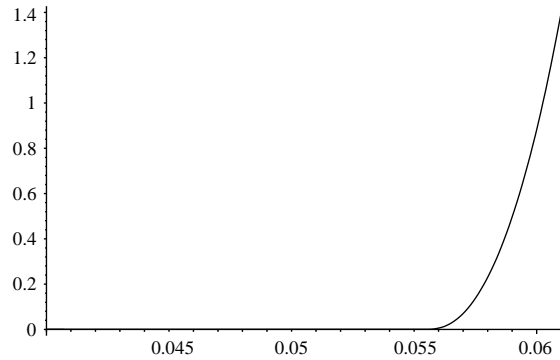


Fig. 5. The function θ .

done earlier, and compute a Lipschitz constant λ_i for the restriction of g_i^{-1} to U_i for each $i=1, 2, 3$ as in (14). Writing $\bar{x}_0 = \bar{u}$ and $\bar{g}_i(x_i) := \bar{x}_{i-1}$ for $i = 1, 2, 3$, we have that $U_2 \subseteq [\bar{x}_1, 1]$, $U_3 \subseteq [\bar{x}_2, 1]$, $U_4 \subseteq [\bar{x}_3, 1]$. When applying the small-gain condition (13), the quantity of interest is the “total gain” $\lambda = \lambda_1 \lambda_2 \lambda_3$ of the cascade. An upper bound on each λ_i can be obtained, for any given \bar{u} , by maximizing the derivative of g_i^{-1} on U_i , or equivalently (and most conveniently, as this involves no functional inversion and each g_i is a simple rational function) as $\lambda_i = \theta_i(\bar{u}_i)^{-1}$, where $\theta_i(\bar{u})$ is the minimum of g'_i on $[\bar{x}_i, 1]$. The functions θ_i depend, of course, on the actual parameters b_i , etc. Defining $\theta(\bar{u}) := \theta_1(\bar{u})\theta_2(\bar{u})\theta_3(\bar{u})$, we conclude that every solution of the delay-differential system (15)–(17) will satisfy $x_i(t) \rightarrow 0$ as $t \rightarrow \infty$ provided that the following condition holds:

$$k < \min \left\{ \frac{\theta(\bar{u})}{\mu}, \frac{\mu}{\bar{u}} - 1 \right\}. \tag{18}$$

The first term represents the small gain condition (13) (since $\bar{u} = 1/\lambda$), while the second insures that $u = \psi(x_3^{\tau_3}) = \mu/(1+kx_3^{\tau_3})^{-1}$ belongs to the input set $\mathcal{U}_1 = [\bar{u}, \infty)$ for all $x_3 \in [0, 1]$. Fig. 5 provides a plot (obtained using the “minimize” function in Maple) of the function θ for a concrete numerical example which takes the coefficients used in [14]:

$$\begin{aligned} b_1 = c_1 = e_1 = b_2 = 0.1, \\ c_2 = e_2 = c_3 = e_3 = 0.01, \quad b_3 = 0.5, \\ d_1 = d_2 = d_3 = 1. \end{aligned} \tag{19}$$

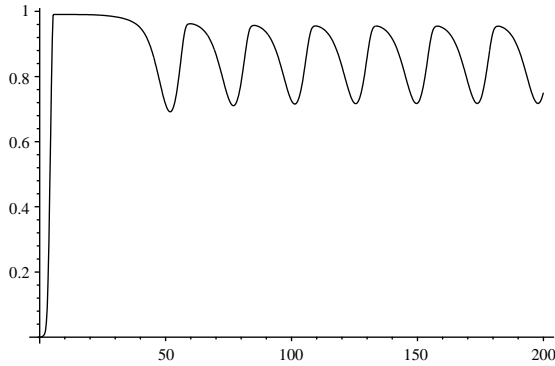


Fig. 6. Oscillations when $k = 5.2$ and $\mu = 0.3$.

There is a sharp transition at around $\bar{u} = 0.055$. In order to obtain λ small, let us say $\lambda < 1$, it is reasonable to pick the value $\bar{u} = 0.061$, for which $\theta(\bar{u}) \approx 1.39933$ and so $\lambda = 1/\theta(\bar{u}) \approx 0.71463$ (picking instead $\bar{u} = 0.06$ would give $\lambda \approx 1.134$). If we now pick $\mu = 0.3$, as in [14], constraints (18) become $k < \min\{4.6644, 3.918\} = 3.918$. In conclusion, *any feedback with gain $k < 3.9$ is guaranteed to preserve stability* (for external input $u(t) \equiv 0.3$, and for any delays).

One may ask how tight is the bound $k < 3.9$. For the system with no delays, numerical experimentation leads to the conclusion that, as the parameter k increases, a Hopf bifurcation occurs at around $k = 5.1$. The coordinate x_3 of the solution with initial conditions $x(0) = 0$, and $\mu = 0.3$, $k = 5.2$ is oscillatory and is plotted in Fig. 6. (Linear instability in this context always leads to existence of periodic solutions, cf. [3,18].) Thus the bound is fairly tight even when there are no delays.

5.2. Local exponential stability

For systems of the special form being considered, linearized stability analysis can be employed in order to determine local exponential stability of the feedback system, appealing to classical small-gain theorems as in [1,11,12,21]. (A computational difficulty when doing this, however, is that feedback laws such as $u = \psi(x)$ change equilibria, and the new equilibria are usually not computable in closed-form.) Given any system of the form $\dot{x} = f(x, u) = -\alpha(x) + u\beta(x)$ as above, and any \bar{u} , we may compute the linearized

system $\dot{z} = az + bv$ at the equilibrium values $x = \bar{x} = g^{-1}(\bar{u})$ and $u = \bar{u}$. This has $a = \partial f/\partial x(\bar{x}, \bar{u})$ and $b = \partial f/\partial u(\bar{x}, \bar{u})$. From $a/b = (-\alpha'(\bar{x}) + \bar{u}\beta'(\bar{x}))/\beta(\bar{x})$ and $\bar{u} = \alpha(\bar{x})/\beta(\bar{x}) = g(\bar{x})$, one obtains

$$\left| \frac{a}{b} \right| = \frac{\alpha'(\bar{x})\beta(\bar{x}) - \alpha(\bar{x})\beta'(\bar{x})}{\beta^2(\bar{x})} = g'(\bar{x}) = \frac{1}{(g^{-1})'(\bar{u})}.$$

On the other hand, the H_∞ gain (induced \mathcal{L}^2 operator norm) of the system $\dot{z} = az + bv$ is $\max\{|b|/|\omega + a|, \omega \in \mathbb{R}\} = |b/a|$. We conclude that $(g^{-1})'(\bar{u})$ equals the H_∞ gain of the linearized system. By induction on the cascade, *the linearized cascade system has an H_∞ gain equal to λ* , so the same inequalities on κ and μ insure local exponential stability. (Linearized analysis cannot by itself guarantee the existence of equilibria for the closed-loop system; only after equilibria are known to exist, this linearized small gain argument can be used.)

The “secant condition” for stability, see [2,7,10,17,18], is often used for linearized stability analysis of inhibitory feedback systems such as the ones considered here. This condition says that a matrix

$$\begin{pmatrix} \alpha_1 & 0 & \cdots & 0 & -\beta_1 \\ \beta_2 & \alpha_2 & \cdots & 0 & -0 \\ \vdots & \vdots & & & \vdots \\ 0 & 0 & \cdots & \beta_n & \alpha_n \end{pmatrix}$$

with all $\alpha_i < 0$ and all $\beta_i > 0$ is Hurwitz provided that:

$$\left| \frac{\beta_1 \cdots \beta_n}{\alpha_1 \cdots \alpha_n} \right| < \left(\sec \frac{\pi}{n} \right)^n.$$

For $n = 3$ as in our example, this means that a closed-loop gain margin of $(\sec \pi/3)^3 = 8$ can be tolerated while preserving stability, for the linearized system (no assertion is made about phase, so no delays are allowed). The condition $k \leq \mu/\bar{u} - 1$, which guarantees that $u = \psi(x_3)$ belongs to the input set $[\bar{u}, \infty)$, must still be satisfied, but the bound (18) may be relaxed to $k < \min\{8\theta(\bar{u})/\mu, \mu/\bar{u} - 1\}$. In order to exploit this condition for the above numerical example, a bit of experimentation leads us to pick $\bar{u} = 0.05763$ (instead of 0.061), so $\lambda = 1/\theta(\bar{u}) \approx 6.32$. Using again $\mu = 0.3$, the condition $k \leq \mu/\bar{u} - 1$ imposes a constraint of approximately $k \leq 4.2$. For any

such k , we have that $k \cdot \mu \cdot \lambda < 7.9632 < 8$, as wanted. In other words, the secant rule allows us to conclude that a feedback gain of $k \leq 4.2$ may be tolerated so as to guarantee linearized stability. This is only a slight improvement over the estimate $k \leq 3.9$ obtained from the nonlinear small-gain result, and it comes at the cost of assuming *no delays* and insuring only *local* stability for the original system.

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