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Boundedness of solutions in feedback systems with antithetic controllers☆

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ABSTRACT

Antithetic feedback controllers have become a key experimental and theoretical tool in synthetic biology. Introduced by Khammash and collaborators about 10 years ago, they are employed in order to achieve the practical regulation of protein expression, including tracking and robust disturbance rejection. In closed-loop, there are unique equilibria which, depending on parameter values, can be unstable. It had been shown, however, that this instability is not arbitrary: any bounded trajectory that stays away from the equilibrium must converge to a periodic orbit. This motivated a long-standing open question: is every trajectory bounded? In other words, even if the equilibrium is unstable, can nonlinear effects prevent unbounded excursions in the state space? This paper provides an affirmative answer, establishing the boundedness of all solutions. Previous attempts to prove this fact using Lyapunov functions had no success. Instead, this paper takes a completely different approach, specific to antithetic configurations, in which the key idea is to think of the controller as providing a "persistently negative feedback" which acts far away from the equilibrium in such a way so as to keep trajectories from diverging. This new approach, although tailored to the antithetic controller, might be useful in other applications as well.

1. Introduction

This paper studies the following nonlinear dynamical system, which represents the closed-loop interconnection of an *antithetic integral controller* (described by the variables $z_1 \in \mathbb{R}_+$ and $z_2 \in \mathbb{R}_+$) with a general positive linear system (described by the state $x \in \mathbb{R}^n_+$ and output $y \in \mathbb{R}_+$):

$$\begin{aligned} \dot{z}_1 &= \alpha_1 - \alpha_2 z_1 z_2 \\ \dot{z}_2 &= \alpha_3 y - \alpha_4 z_1 z_2 \end{aligned} \quad \text{and} \quad \begin{aligned} \dot{x} &= Ax + bz_1, \\ y &= c^\top x. \end{aligned} \tag{1}$$

See Fig. 1. We assume that the constants α_i, for $i = 1, \ldots, 4$, are all positive, the matrix $A \in \mathbb{R}^{n\times n}$ is Hurwitz and Metzler, $b, c \in \mathbb{R}^n_+$, and the DC gain $G := -c^\top A^{-1} b > 0$ is positive. Our main result will show that every solution of this system is bounded.

Since its original formulation in [1], the antithetic controller has attracted sustained attention in both theoretical and experimental systems biology. It is well known from linear systems theory, as well as from several classes of nonlinear systems, that integral feedback, or more generally the presence of an "internal model" of admissible exogenous signals, is essential for robust regulation. This principle also plays a central role in biological processes at both the cellular and organismal levels [2]. Motivated by these considerations, there has been considerable recent effort devoted to implementing integral feedback mechanisms in synthetic biology (see [3] and the references therein). A particularly influential approach, and the focus of this work, is based on sequestration or annihilation reactions between two molecular species (z_1 and z_2 in system (1)). This framework, introduced under the name antithetic control in [1], implements integral action through simple biochemical interactions. Furthermore, it was shown in [4] that such controllers achieve robust perfect adaptation while exhibiting, in a precise sense, minimal structural complexity.

Several research groups have reported experimental realizations of this architecture. An *in vivo* implementation described in [4] uses the σ^W–RsiW regulatory pair in *Bacillus subtilis* as the antithetic species. The implementation described in [5] constructed and analyzed an *in vitro* synthetic biomolecular integral controller that regulates the protein production rate of an output gene via sequestration between *E. coli* σ_{28} and its corresponding anti-factor. Also closely related is a proposed "quasi-integral feedback" mechanism to achieve adaptation under varying ribosome demand, based on sRNA regulation [6].

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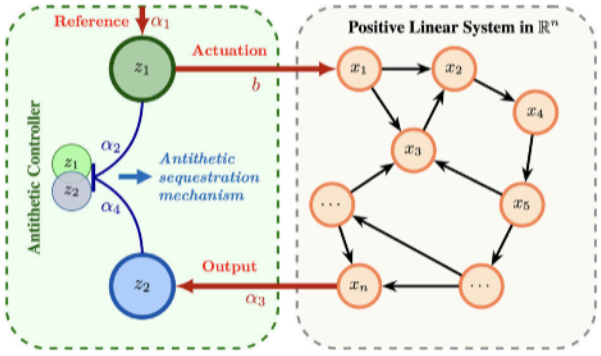


Fig. 1. Closed-loop system (1). The antithetic controller (z_1, z_2) on the left is interconnected with the positive linear plant on the right, where $A \in \mathbb{R}^{n\times n}$ is Hurwitz and Metzler, $b = [b_1, \dots, b_n]^\top, c = [c_1, \dots, c_n]^\top \in \mathbb{R}^n_+$, and the DC gain $G := -c^\top A^{-1} b > 0$. The signal α_1 denotes the constant production rate of z_1. The red arrows indicate the main interconnection signals: z_1 drives the plant input with gain b, and the plant output $y = c^\top x$ feeds back to z_2 with gain α_3. The vertical bar with rate (α_2, α_4) represents the sequestration reaction between z_1 and z_2, implementing integral action. Solid arrows inside the plant denote positive interactions between state variables. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

It is easy to show that the closed-loop system (1) admits a unique equilibrium (z_1^*, z_2^*, x^*, y^*) in the nonnegative orthant, given by

$$z_1^* = \frac{\alpha_1\alpha_4}{\alpha_2\alpha_3 G}, \qquad z_2^* = \frac{\alpha_3 G}{\alpha_4}, \qquad x^* = -A^{-1} b\, z_1^*, \qquad y^* = \frac{\alpha_1\alpha_4}{\alpha_2\alpha_3},$$

for all positive $\alpha_1, \dots, \alpha_4$ and any admissible A, b, c (i.e., A Hurwitz and Metzler, $b, c \in \mathbb{R}^n_+$, and $G > 0$).

There has been substantial work on the global dynamics of such systems, particularly in the special case, described in detail in the Supplemental Materials of Briat et al. [1], in which the linear subsystem is a cascade of two one-dimensional systems. (The problem is already interesting even in the simplest case of static feedback [7].) A key insight is that these systems (for arbitrary cascades of one-dimensional systems, and even for a larger class of tridiagonal-Jacobian systems) can be analyzed using the theory of strongly 2-cooperative systems; see [8–10] which in turn relates closely to contractions in the Birkhoff/Hilbert's projective metric on positive cones, since 2-cooperative systems may be viewed as cooperative systems on an exterior power; see [11]. This theory implies that every bounded trajectory satisfies a strong Poincaré–Bendixson property, in the sense of Weiss and Margaliot [12]. Consequently, every bounded trajectory whose omega-limit set does not contain the equilibrium must approach a periodic orbit. Such orbits do indeed occur: for appropriate choices of parameters and system matrices, the system can exhibit sustained oscillations, as illustrated by the four-dimensional example in Section 4. However, the question of whether *all* trajectories are bounded, for arbitrary initial conditions, was left open. The present work resolves this issue by proving boundedness in full generality.

The key feature of the system is that the damping term $\alpha_2 z_1 z_2$ in $\dot{z}_1 = \alpha_1 - \alpha_2 z_1 z_2$ is not directly available as a feedback signal, but is generated through the x-system being controlled (the "plant") driven by z_1 itself. The central idea is that sufficiently large excursions of z_1 cannot persist indefinitely: if z_1 remains above a threshold $L > L_0$ for a sufficiently large time $T \geq T_0$, the plant output y builds up sufficiently to drive z_2 large enough so that the product $z_1 z_2$ exceeds α_1/α_2, forcing $\dot{z}_1(T_0) < 0$. Further analysis then shows this domination persists for all $t \in [T_0, T]$, from which global boundedness of all states follows. This *input-to-output persistency* exists generically for the x-subsystem and is what allows the proof of boundedness of the integral controller output.

Notice in particular that the proof strategy does not rely on Lyapunov functions, instead working directly with differential inequalities and comparison principles, tracing lower bounds through the plant dynamics via the step-response function $g(t)$. The boundedness mechanism admits a natural interpretation in which forward propagation through the plant is eventually counteracted by the delayed negative feedback through z_2, offering clear insight into how the feedback delay influences the overall system behavior.

Understanding boundedness and stability properties of nonlinear feedback systems is a fundamental problem in control theory. In many applications, the feedback mechanism that regulates a system does not act instantaneously, but is mediated through intermediate dynamics that introduce delays and attenuation. As a result, classical Lyapunov-based approaches may be difficult to apply directly, especially when the feedback enters the system in a nonlinear or multiplicative form. We believe that the techniques introduced here may be helpful in the analysis of many such systems.

The organization of this paper is as follows. In Section 2, we prove the main boundedness result, with a couple of routine technical lemmas deferred to an appendix. In Section 3, we specialize to the motivating four-dimensional case, with the purpose of giving more explicit estimates of the compact region that contains any given trajectory, and provide two numerical examples in Section 4. Finally, in Section 5, we include some additional discussion, including possible extensions of the current result for the interconnection of monotone nonlinear systems and the antithetic control structure.

2. Main boundedness results

We denote the set of real numbers, real vectors of dimension n, and real matrices of dimension $n \times m$ by $\mathbb{R}$, $\mathbb{R}^n$, and $\mathbb{R}^{n\times m}$. The orders $>, <, \geq$, and $\leq$ are interpreted element-wise when applied to vectors and matrices. We also define $\mathbb{R}^{n\times m}_+ := \{A \in \mathbb{R}^{n\times m} \mid A \geq 0\}$; the sets $\mathbb{R}^n_+$ and $\mathbb{R}_+ := [0, \infty)$ are defined similarly. A matrix is called *Metzler* if its off-diagonal entries are nonnegative, and Hurwitz if its eigenvalues have strictly negative real parts.

The main contribution of this paper is the following result, which establishes boundedness of all solutions of (1).

Theorem 1. *Every solution of system (1) starting from an initial condition in $C := \mathbb{R}^2_+ \times \mathbb{R}^n_+$ exists for all $t \geq 0$ and is bounded.*

We prove this theorem in steps. First, we remark forward completeness of the interconnected system (1) in Lemma 2. Then, Theorem 2 establishes the key decrease property: there exist thresholds $L_0, T_0 > 0$ such that whenever $z_1(t) \geq L > L_0$ for a duration $T \geq T_0$, the plant output y builds up enough to drive z_2 large, forcing $z_1 z_2 > \alpha_1/\alpha_2$ and hence $\dot{z}_1 < 0$. Next, this local decrease property is promoted to global boundedness of z_1 in Theorem 3. Finally, boundedness of x and y follows from the Hurwitz stability of A with bounded input z_1 (Lemma 4), and boundedness of z_2 follows from a Lyapunov-like argument via the auxiliary function $W(t) := z_2(t) + \nu^\top x(t)$ (Lemma 5).

2.1. Proof of Theorem 1

We first establish forward invariance of $C = \mathbb{R}^2_+ \times \mathbb{R}^n_+$. Since the vector field defining (1) is polynomial, hence smooth and locally Lipschitz, solutions exist uniquely on a maximal interval $[0, t_{\max})$ for any initial condition in C.

Lemma 1. *Let $w(0) := [z_1(0); z_2(0); x(0)]$ be any point in the nonnegative orthant $C = \mathbb{R}^2_+ \times \mathbb{R}^n_+$. Then the solution $w(t) := [z_1(t); z_2(t); x(t)]$ of (1) initialized at $w(0)$ satisfies $w(t) \in C$ for all $t \in [0, t_{\max})$.*

Proof. This is a standard consequence of the Bony–Brezis invariance theorem applied to the nonnegative orthant. For completeness, a detailed proof is provided in . □

Next, we show that solutions of (1) are globally defined.

Lemma 2. *The closed-loop system (1) is forward complete, that is for any initial condition $z_1(0), z_2(0) \geq 0$ and $x(0) \geq 0$, the solution exists and is unique for all $t \geq 0$.*

Proof. Consider the maximal interval $[0, t_{\max})$. We will next show that for any finite $t_{\max}$, the solution of (1) initialized in the positive orthant C will remain inside a compact set, which will satisfy the standard continuation theorem and contradict maximality of $t_{\max}$.

Let $z_1(t), z_2(t), x(t)$ be the solution of the initial value problem defined by (1) and initialized at arbitrary $z_1(0), z_2(0), x(0) \geq 0$. Notice that $\dot{z}_1 \leq \alpha_1$ and thus integrating for $t \in [0, t_{\max})$ results in $z_1(t) \leq z_1(0) + \alpha_1 t_{\max} =: z_{1,\max}$. From there write

$$\begin{aligned}\|x(t)\| &= \|e^{At}x(0) + \int_0^t e^{As} b z_1(t-s)\,ds\| \\ &\leq \max_{t\in[0,t_{\max}]} \|e^{At}\| \left(\|x(0)\| + t_{\max}\|b\| z_{1,\max}\right) =: x_{\max}.\end{aligned}$$

Next, notice that $\|y(t)\| = \|c^\top x(t)\| \leq \|c\|\|x(t)\| \leq \|c\| x_{\max} =: y_{\max}$, and finally that $\dot{z}_2 = \alpha_3 y - \alpha_4 z_1 z_2 \leq \alpha_3 y_{\max}$ implying that $z_2(t) \leq z_2(0) + \alpha_3 t_{\max} y_{\max} =: z_{2,\max}$.

We can, then, define the compact set $M = \{[z_1; z_2; x] \in C \mid z_1 \leq z_{1,\max},\ z_2 \leq z_{2,\max},\ \|x\| \leq x_{\max}\}$ which contains the solution $[z_1(t); z_2(t); x(t)]$ for all $t \in [0, t_{\max})$. Hence the maximal solution is bounded on $[0, t_{\max})$, and since the vector field is locally Lipschitz, the standard continuation theorem implies that the solution can be extended beyond $t_{\max}$. Therefore $t_{\max} = \infty$; see, for instance, Proposition C.3.6 in [13]. □

The result above establishes existence of solutions for all time, however those solutions may still be unbounded. We will next focus on showing boundedness of solutions for (1), and the key point that allows us to do that is the characterization of the following property:

Theorem 2. *For the closed loop system in (1), there exist constants $L_0 > 0$ and $T_0 > 0$ such that for every $L > L_0$ and $T \geq T_0$, if a solution satisfies $z_1(0) = L$ and $z_1(t) \geq L$ for all $t \in [0, T]$, then $\dot{z}_1(T) < 0$.*

Proof. The proof proceeds as follows. We first show that if $z_1(t)$ is "large" for a sufficiently long time, then the output $y(t)$ will also become and remain proportionally large. We then show, by a similar argument, that if $y(t)$ is "large" for a sufficiently long time, then $z_2(t)$ will also become proportionally large. Finally, we establish that the product $z_1(t)z_2(t)$ becomes and remains above the threshold α_1/α_2 as long as z_1 stays above the prescribed level, ensuring that $\dot{z}_1 < 0$. The main steps of this argument are illustrated in Fig. 2.

These arguments naturally lead to the thresholds L_0 and T_0, which specify how large z_1 must be and for how long. We first introduce explicit expressions for these thresholds and then prove that they provide the desired guarantees.

Let

$$g(t) := c^\top \int_0^t e^{As} b\,ds = c^\top A^{-1}(e^{At} - I)b.$$

Since A is Metzler, $e^{At} \geq 0$ (element-wise) for all $t \geq 0$ (see, for example [14]). This implies $g(t)$ is nondecreasing since $\dot{g}(t) = c^\top e^{At} b \geq 0$. Moreover, since A is also Hurwitz, the following limit is well defined and finite

$$\lim_{t\to\infty} g(t) = c^\top \int_0^\infty e^{As} b\,ds = -c^\top A^{-1} b = G > 0.$$

Since $g(0) = 0$, $g(t) \to G$ and $g(t)$ is continuous, there exists a smallest time $\Delta > 0$ such that $g(t) \geq G/2$ for all $t \geq \Delta$. We define a function $\tau : \mathbb{R}_+ \to \mathbb{R}_+$, where for each $\ell \in \mathbb{R}_+$, $\tau(\ell)$ is the unique positive solution of

$$\tau(\ell) = \Delta + \frac{\ln(2)}{\alpha_4(\ell + \alpha_1 \tau(\ell))}, \tag{2}$$

which is guaranteed to exist and be unique by Proposition 1 in Appendix A. We also point out here that $\tau(\ell)$ is continuous on $\mathbb{R}_+$, strictly decreasing in ℓ and differentiable on $(0, \infty)$ (with the corresponding right derivative at $\ell = 0$, see Proposition 1(ii)); in particular $\tau'(\ell) < 0$ for every $\ell > 0$. Next, we define L_0 as the unique positive solution ℓ of

$$\frac{\alpha_3 G \ell^2}{4\alpha_4(\ell + \alpha_1 \tau(\ell))} = \frac{\alpha_1}{\alpha_2}, \tag{3}$$

whose existence and uniqueness follow from Proposition 3 in Appendix A. With this definition of L_0, we finally define $T_0 := \tau(L_0)$.

Under the assumption that $z_1(t) \geq L > L_0$ for all $t \in [0, T]$ with $T \geq T_0$, we compute

$$\begin{aligned}y(t) &= c^\top x(t) \\ &= c^\top e^{At} x(0) + \int_0^t c^\top e^{As} b\, z_1(t-s)\,ds \\ &\geq g(t) L,\end{aligned}$$

where we used that $z_1(t-s) \geq L$ and that $c^\top e^{At} x(0) \geq 0$, which follows from $e^{At} \geq 0$, $x(0) \geq 0$, and $b, c \in \mathbb{R}^n_+$. Since $T \geq T_0 = \tau(L_0) > \tau(L) > \Delta$ by Proposition 1(iii), the interval $[\Delta, T]$ is nonempty, and thus

$$y(t) \geq g(t)L \geq \frac{GL}{2} =: \rho_y(L) \qquad \text{for all } t \in [\Delta, T]. \tag{4}$$

We now lower bound z_2 for $t \leq T_0$ by first establishing an upper bound for $z_1(t)$. Define

$$U(\ell, t) := \ell + \alpha_1 t.$$

Since $\dot{z}_1 = \alpha_1 - \alpha_2 z_1 z_2 \leq \alpha_1$ and $z_1(0) = L$, integration gives

$$z_1(t) \leq L + \alpha_1 T_0 = U(L, T_0) \qquad \text{for all } t \in [0, T_0].$$

Using $y(t) \geq \rho_y(L)$ for $t \geq \Delta$ and $z_1(t) \leq U(L, T_0)$ for $t \leq T_0$, we obtain

$$\dot{z}_2 = \alpha_3 y - \alpha_4 z_1 z_2 \geq \alpha_3 \rho_y(L) - \alpha_4 U(L, T_0) z_2 \qquad \text{for all } t \in [\Delta, T_0].$$

By the comparison principle (Gronwall's Lemma), we have $z_2(t) \geq v(t)$ where v solves $\dot{v} = \alpha_3 \rho_y(L) - \alpha_4 U(L, T_0) v$, $v(\Delta) = z_2(\Delta) \geq 0$, with explicit solution

$$v(t) = \frac{\alpha_3 GL}{2\alpha_4 U(L, T_0)}\left[1 - e^{-\alpha_4 U(L,T_0)(t-\Delta)}\right] + z_2(\Delta)\, e^{-\alpha_4 U(L,T_0)(t-\Delta)}.$$

Since $z_2(\Delta) \geq 0$, dropping the initial condition term yields

$$z_2(t) \geq \frac{\alpha_3 GL}{2\alpha_4 U(L, T_0)}\left[1 - e^{-\alpha_4 U(L,T_0)(t-\Delta)}\right] \qquad \text{for all } t \in [\Delta, T_0]. \tag{5}$$

Define

$$\delta(\ell, t) := \frac{\ln 2}{\alpha_4 U(\ell, t)}.$$

Since $U(\ell, t)$ is strictly increasing in t, $\delta(\ell, t)$ is strictly decreasing in t. On the other hand, since $\tau(\ell)$ is strictly decreasing by Proposition 1(ii), $L > L_0$ implies

$$T_0 = \tau(L_0) > \tau(L) = \Delta + \delta(L, \tau(L)) > \Delta + \delta(L, T_0),$$

where the last inequality follows from the strict decrease of $\delta(L, t)$ in t. Hence, the interval $[\Delta + \delta(L, T_0), T_0]$ is nonempty. Evaluating (5) at time $\Delta + \delta(L, T_0)$, the exponential term equals $1/2$ by definition of δ, giving

$$z_2(t) \geq v(t) \geq \frac{\alpha_3 GL}{4\alpha_4(L + \alpha_1 T_0)} =: \rho_z(L, T_0), \qquad \text{for all } t \in [\Delta + \delta(L, T_0), T_0]. \tag{6}$$

Under the assumption that $z_1(t) \geq L$ on $[0, T]$, we have therefore established that, for all $t \in [\Delta + \delta(L, T_0), T_0]$, $z_1(t) \geq L$, $y(t) \geq \rho_y(L)$, and $z_2(t) \geq \rho_z(L, T_0)$. In particular, from (6) and $z_1(T_0) \geq L$, we obtain

$$z_1(T_0) z_2(T_0) \geq L\rho_z(L, T_0) = \frac{\alpha_3 GL^2}{4\alpha_4(L + \alpha_1 T_0)}.$$

By the choice of L_0 and since the map $\ell \mapsto \ell \rho_z(\ell, T_0)$ is strictly increasing on $[0, \infty)$, it follows that for every $L > L_0$,

$$L\rho_z(L, T_0) > L_0 \rho_z(L_0, T_0) = \frac{\alpha_1}{\alpha_2},$$

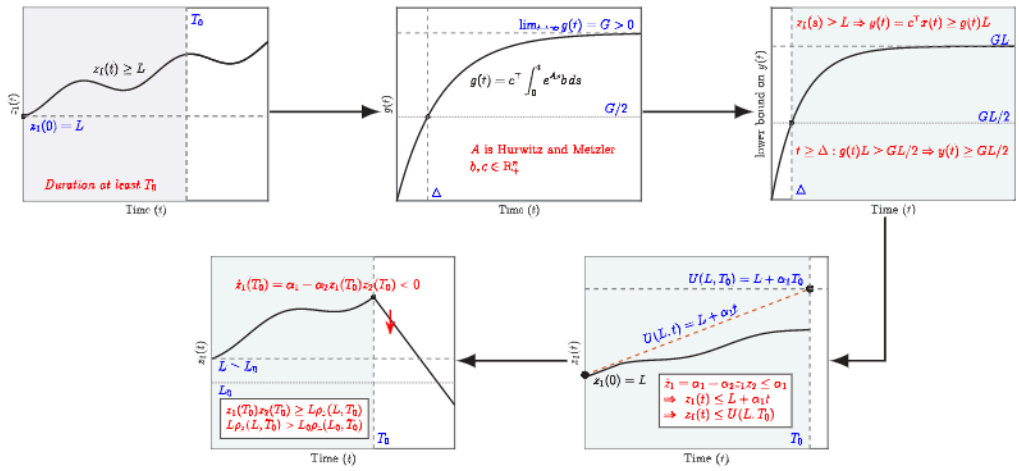


Fig. 2. Graphical illustration of the key decrease property in Theorem 2. If z_1 remains sufficiently large for a sufficiently long time, then the plant output y also becomes proportionally large. This, in turn, causes z_2 to become sufficiently large. Consequently, the product $z_1 z_2$ becomes and remains above α_1/α_2 as long as z_1 stays above the prescribed level, ensuring that $\dot{z}_1 < 0$.

where the last equality holds by definition of L_0 in (3). Therefore $z_1(T_0)z_2(T_0) > \alpha_1/\alpha_2$ and hence

$$\dot{z}_1(T_0) = \alpha_1 - \alpha_2 z_1(T_0)z_2(T_0) < 0.$$

However, as T increases beyond T_0, the bound $\rho_z(L, T)$ in (6) decreases in T, so this estimate does not directly extend beyond T_0. To overcome this, we introduce the product

$$p(t) := z_1(t)z_2(t),$$

and point out that $z_1(T_0)z_2(T_0) > \alpha_1/\alpha_2$ from the results above. By Lemma 6, once the threshold $\theta = \alpha_1/\alpha_2$ is exceeded at time T_0, it cannot be crossed again from above. Consequently, $p(t) > \theta$ for all $t \in [T_0, T]$. Therefore,

$$\dot{z}_1(t) = \alpha_1 - \alpha_2 p(t) < \alpha_1 - \alpha_2\theta = 0, \qquad \text{for all } t \in [T_0, T].$$

In particular, $\dot{z}_1(T) < 0$, completing the proof. □

The following two results leverage the results in Theorem 2 to prove boundedness of $z_1(t)$.

Lemma 3. *Let L_0 and T_0 be defined as in Theorem 2. For every $L > L_0$, if a solution satisfies $z_1(0) = L$, then $z_1(t) \leq L + \alpha_1 T_0$ for all $t \geq 0$.*

Proof. We prove the claim by contradiction. Suppose that there exists $t^* > 0$ such that $z_1(t^*) > L + \alpha_1 T_0$. Define

$$t_1 := \min\{t \in (0, t^*) : z_1(t) = L + \alpha_1 T_0\},$$

which exists by the intermediate value theorem since $z_1(0) = L < L + \alpha_1 T_0$ and $z_1(t^*) > L + \alpha_1 T_0$. By definition, $z_1(t_1) = L + \alpha_1 T_0$ and $z_1(t) < L + \alpha_1 T_0$ for all $t \in [0, t_1)$, which implies by Lemma 7 that

$$\dot{z}_1(t_1) \geq 0.$$

Next, define $t_2 := \max\{t \in [0, t_1] : z_1(t) = L\}$. Note that the set is nonempty since $z_1(0) = L$, and that $t_2 < t_1$ because $z_1(t_1) = L + \alpha_1 T_0 > L$. By definition, $z_1(t_2) = L$ and $z_1(t) > L$ for all $t \in (t_2, t_1]$. Since $\dot{z}_1 \leq \alpha_1$, integration on $[t_2, t_1]$ gives

$$L + \alpha_1 T_0 = z_1(t_1) \leq z_1(t_2) + \alpha_1(t_1 - t_2) = L + \alpha_1(t_1 - t_2),$$

hence $t_1 - t_2 \geq T_0$. Since (1) is time-invariant, applying Theorem 2 on the shifted interval $[t_2, t_1]$ with duration $T = t_1 - t_2 \geq T_0$ gives

$$\dot{z}_1(t_1) < 0,$$

contradicting $\dot{z}_1(t_1) \geq 0$. Therefore no such t^* exists, and $z_1(t) \leq L + \alpha_1 T_0$ for all $t \geq 0$. □

Theorem 3. *Let L_0 and T_0 be as in Theorem 2. Every solution of (1) satisfies*

$$z_1(t) \leq \max\{z_1(0),\ L_0\} + \alpha_1 T_0 =: M_{z_1} \qquad \text{for all } t \geq 0.$$

In particular, z_1 is bounded on $[0, \infty)$.

Proof. We consider two cases.

1. **Case 1:** $z_1(0) > L_0$. Set $L := z_1(0) > L_0$. Lemma 3 applies directly and gives

   $$z_1(t) \leq z_1(0) + \alpha_1 T_0 \qquad \text{for all } t \geq 0.$$

2. **Case 2:** $z_1(0) \leq L_0$. Fix any $\varepsilon > 0$ and set $L := L_0 + \varepsilon > L_0$. We claim that $z_1(t) \leq L + \alpha_1 T_0$ for all $t \geq 0$. Suppose for contradiction that there exists $t_1 > 0$ such that $z_1(t_1) > L + \alpha_1 T_0$. Since $z_1(0) \leq L_0 < L$ and $z_1(t_1) > L$, the intermediate value theorem gives that there is a well-defined $t_0 := \max\{t \in [0, t_1] : z_1(t) = L\}$.
   Note that $z_1(t_0) = L$ and $z_1(t) > L$ for all $t \in (t_0, t_1]$. Applying Lemma 3 starting at time t_0 onward with level $L = L_0 + \varepsilon$ gives

   $$z_1(t) \leq L + \alpha_1 T_0 \qquad \text{for all } t \geq t_0,$$

   which contradicts $z_1(t_1) > L + \alpha_1 T_0$. Since the bound $z_1(t) \leq L_0 + \varepsilon + \alpha_1 T_0$ holds for every $\varepsilon > 0$, letting $\varepsilon \to 0^+$ gives $z_1(t) \leq L_0 + \alpha_1 T_0$ for all $t \geq 0$.

Combining both cases yields $z_1(t) \leq \max\{z_1(0), L_0\} + \alpha_1 T_0 =: M_{z_1}$ for all $t \geq 0$. □

From boundedness of $z_1(t)$, boundedness of $x(t)$ and $y(t)$ follows immediately: since A is Hurwitz, the linear subsystem $\dot{x} = Ax + bz_1$ is bounded-input bounded-state stable (BIBS), and a bounded input z_1 therefore produces a bounded state x and output $y = c^\top x$. This is a routine textbook result (see, e.g., Proposition 7.3.3 in [13]), but it is useful to write explicitly the bounds, so we provide details next. Fig. 3 illustrates how the bound on z_1 leads to boundedness of the remaining closed-loop states.

Lemma 4. *Let $z_1(t) \leq M_{z_1}$ for all $t \geq 0$. Then there exist constants $M_x, M_y > 0$ such that $\|x(t)\| \leq M_x$ and $y(t) \leq M_y$ for all $t \geq 0$. In particular, x and y are bounded on $[0, \infty)$.*

Proof. The explicit solution of $\dot{x} = Ax + bz_1$ is given by

$$x(t) = \mathrm{e}^{At}x(0) + \int_0^t \mathrm{e}^{A(t-s)}\, bz_1(s)\, \mathrm{d}s.$$

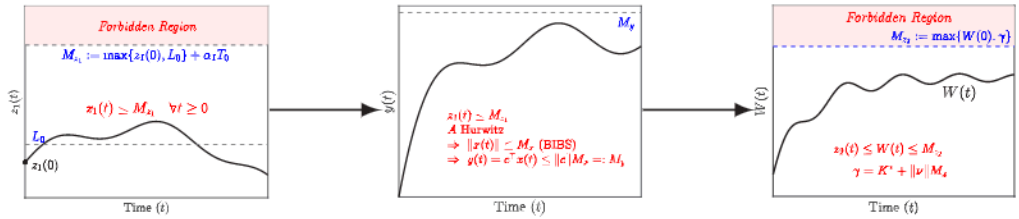


Fig. 3. Graphical illustration of the global boundedness argument. Starting from the key decrease property, Lemmas 3 and 3 establish a uniform bound M_{z_1} on z_1. Since A is Hurwitz, Lemma 4 shows that boundedness of z_1 implies boundedness of the plant state x and output y. Finally, Lemma 5 uses the auxiliary function $W = z_2 + v^\top x$ to establish $z_2(t) \le W(t) \le M_{z_2}$ for all $t \ge 0$. Together, these results complete the proof of Theorem 1.

Since A is Hurwitz, there exist constants $m \ge 1$ and $\lambda > 0$ such that $\|e^{At}\| \le m e^{-\lambda t}$ for all $t \ge 0$. Using the bound $z_1(s) \le M_{z_1}$, we obtain

$$\begin{aligned}\|x(t)\| &\le \|e^{At}\|\|x(0)\| + \int_0^t \|e^{A(t-s)}\|\|b\|\, z_1(s)\,ds \\ &\le m e^{-\lambda t}\|x(0)\| + m M_{z_1}\|b\| \int_0^t e^{-\lambda(t-s)}\,ds \\ &= m e^{-\lambda t}\|x(0)\| + \frac{m M_{z_1}\|b\|}{\lambda}\left(1 - e^{-\lambda t}\right) \\ &\le m\|x(0)\| + \frac{m M_{z_1}\|b\|}{\lambda} =: M_x \qquad \text{for all } t \ge 0,\end{aligned}$$

Hence x is bounded on $[0, \infty)$. Since $y(t) = c^\top x(t)$ and $c \ge 0$, it follows immediately that

$$y(t) \le \|c\| M_x =: M_y \qquad \text{for all } t \ge 0,$$

so y is bounded on $[0, \infty)$. □

Remark 1. The Metzler property of A also allows a componentwise bound. Indeed, define $x_{\text{eq}} := -A^{-1} b M_{z_1}$ and $v := -A^{-1}\mathbf{1}$. Since A is Hurwitz and Metzler, $x_{\text{eq}} \ge 0$ and $v > 0$. Choose $\gamma \ge 0$ sufficiently large so that $\bar{x} := x_{\text{eq}} + \gamma v \ge x(0)$. Then $A\bar{x} + b M_{z_1} = -\gamma \mathbf{1} \le 0$. By positivity and the comparison principle,

$$0 \le x(t) \le \bar{x}, \qquad 0 \le y(t) \le c^\top \bar{x}, \qquad t \ge 0.$$

From boundedness of $x(t)$ and $y(t)$ in Lemma 4, boundedness of $z_2(t)$ follows via a Lyapunov-like argument using the auxiliary function $W(t) := z_2(t) + v^\top x(t)$.

Lemma 5. *Let $z_1(t) \le M_{z_1}$, $\|x(t)\| \le M_x$, and $y(t) \le M_y$ for all $t \ge 0$. Then there exists a constant $M_{z_2} > 0$ such that $z_2(t) \le M_{z_2}$ for all $t \ge 0$. In particular, z_2 is bounded on $[0, \infty)$.*

Proof. Since A is Hurwitz and Metzler, $-A$ is a nonsingular M-matrix, and hence $-A^{-1} \ge 0$ elementwise. Since $c \ge 0$ and $\alpha_3 > 0$, it follows that $v^\top = -\alpha_3 c^\top A^{-1} = \alpha_3 c^\top(-A^{-1}) \ge 0$. Thus $v \ge 0$. Define the auxiliary function

$$W(t) := z_2(t) + v^\top x(t), \qquad v^\top := -\alpha_3 c^\top A^{-1} \ge 0,$$

where $v \in \mathbb{R}^n$ is well defined since A is invertible. Differentiating and substituting the dynamics (1),

$$\begin{aligned}\dot{W} &= \dot{z}_2 + v^\top \dot{x} \\ &= \left(\alpha_3 y - \alpha_4 z_1 z_2\right) + v^\top\left(Ax + b z_1\right) \\ &= \alpha_3 c^\top x - \alpha_4 z_1 z_2 + (v^\top A)x + (v^\top b)\, z_1.\end{aligned}$$

By the choice of $v^\top = -\alpha_3 c^\top A^{-1}$, the x-terms cancel: $v^\top A = -\alpha_3 c^\top$. Moreover, $v^\top b = -\alpha_3 c^\top A^{-1} b = \alpha_3 G$, where $G := -c^\top A^{-1} b > 0$ is the DC gain. Therefore

$$\dot{W} = \alpha_3 G\, z_1 - \alpha_4 z_1 z_2 = \alpha_4 z_1\left(K^* - z_2\right), \tag{8}$$

where $K^* := \alpha_3 G/\alpha_4 = z_2^*$ is the equilibrium value of z_2.

Since $v \ge 0$ and $x(t) \ge 0$, we have $v^\top x(t) \ge 0$, and therefore

$$z_2(t) = W(t) - v^\top x(t) \le W(t).$$

Thus, it suffices to show that W is bounded, hence yielding boundedness of z_2. Set $\gamma := K^* + \|v\| M_x$. We claim that

$$W(t) \le \max\{W(0), \gamma\} \qquad \text{for all } t \ge 0.$$

We consider two cases.

1. **Case 1:** $W(0) < \gamma$. Suppose for contradiction that $W(t_1) > \gamma$ for some $t_1 > 0$. Define

   $$t_0 := \sup\{t \in [0, t_1] : W(t) \le \gamma\}.$$

   Since $W(0) < \gamma$ and $W(t_1) > \gamma$, we have $t_0 \in [0, t_1)$. By continuity, $W(t_0) = \gamma$, and by definition of t_0, $W(t) > \gamma$ for all $t \in (t_0, t_1]$. By Lemma 4, $\|x(t)\| \le M_x$ for all $t \ge 0$. Notice that, by the Cauchy–Schwarz inequality,

   $$v^\top x(t) \le \|v\|\,\|x(t)\| \le \|v\| M_x \qquad \text{for all } t \ge 0.$$

   Hence, for all $t \in [t_0, t_1]$,

   $$z_2(t) = W(t) - v^\top x(t) \ge W(t) - \|v\| M_x \ge \gamma - \|v\| M_x = K^*.$$

   Thus

   $$\dot{W}(t) = \alpha_4 z_1(t)(K^* - z_2(t)) \le 0 \qquad \text{for all } t \in [t_0, t_1].$$

   Therefore W is nonincreasing on $[t_0, t_1]$, and so

   $$W(t_1) \le W(t_0) = \gamma,$$

   contradicting $W(t_1) > \gamma$. Hence $W(t) \le \gamma$ for all $t \ge 0$.
2. **Case 2:** $W(0) \ge \gamma$. Suppose for contradiction that $W(t_1) > W(0)$ for some $t_1 > 0$. Since $W(t_1) > W(0) \ge \gamma$, the set

   $$\Omega := \{t \in [0, t_1] \mid W(t) > \gamma\}$$

   is nonempty. Let I be the connected component of Ω containing t_1. Then there exists $t_0 \in [0, t_1)$ such that

   $$I = (t_0, t_1] \qquad \text{or} \qquad I = [t_0, t_1],$$

   with $W(t) > \gamma$ for all $t \in I$. Moreover, either $W(t_0) = \gamma$ or $t_0 = 0$. For all $t \in I$, we have

   $$z_2(t) = W(t) - v^\top x(t) \ge W(t) - \|v\| M_x > K^*.$$

   Therefore, using (8),

   $$\dot{W}(t) = \alpha_4 z_1(t)\left(K^* - z_2(t)\right) \le 0 \qquad \text{for all } t \in I.$$

   Hence W is nonincreasing on I.
   If $t_0 = 0$, then, if necessary taking the limit from the right endpoint of the component,

   $$W(t_1) \le W(0),$$

   contradicting the choice of t_1. If $t_0 > 0$, then $W(t_0) = \gamma \le W(0)$, and again taking the right limit if $I = (t_0, t_1]$,

   $$W(t_1) \le W(t_0) = \gamma \le W(0),$$

   contradicting $W(t_1) > W(0)$. Therefore $W(t) \le W(0)$ for all $t \ge 0$ in this case.

Combining both cases, $W(t) \le \max\{W(0), \gamma\}$ for all $t \ge 0$. Consequently, since $v \ge 0$ and $x(t) \ge 0$,

$$z_2(t) \le W(t) - v^\top x(t) \le W(t) \le \max\{W(0), \gamma\} =: M_{z_2} \qquad \text{for all } t \ge 0.$$

Thus z_2 is bounded on $[0, \infty)$. □

We can now conclude the proof of Theorem 1. Lemma 2 gives existence for all $t \ge 0$. Theorem 3 gives boundedness of z_1. Lemma 4 then gives boundedness of x and y, and Lemma 5 gives boundedness of z_2. Hence the full solution (z_1, z_2, x) is bounded on $[0, \infty)$.

3. Explicit boundedness analysis in $\mathbb{R}^4$

As a concrete and biologically motivated instance of (1), originally studied in [1], we consider the four-dimensional system obtained by taking $n = 2$, where the antithetic controller states (z_1, z_2) regulate the two-dimensional linear cascade (x_1, x_2):

$$\begin{aligned} \dot z_1 &= \alpha_1 - \alpha_2 z_1 z_2 \\ \dot z_2 &= \alpha_3 x_2 - \alpha_4 z_1 z_2 \end{aligned} \qquad \text{and} \qquad \begin{aligned} \dot x_1 &= \beta_1 z_1 - \beta_2 x_1 \\ \dot x_2 &= \beta_3 x_1 - \beta_4 x_2, \end{aligned} \tag{9}$$

with $\alpha_i, \beta_i > 0$ for $i = 1, \dots, 4$ and $z_1(0), z_2(0), x_1(0), x_2(0) \ge 0$. Since this system has been widely studied in the literature, we treat it explicitly here. Moreover, the explicit cascade structure $z_1 \to x_1 \to x_2 \to z_2$ allows us to derive bounds stage by stage, rather than through the step-response estimate $y \ge GL/2$ used in the general case, yielding fully explicit bounds $\overline{M}_{z_1}, \overline{M}_{x_1}, \overline{M}_{x_2}, \overline{M}_{z_2}$ in terms of α_i and β_i for $i = 1, \dots, 4$.

The correspondence of (9) with (1) is given by

$$A = \begin{bmatrix} -\beta_2 & 0 \\ \beta_3 & -\beta_4 \end{bmatrix}, \qquad b = \begin{bmatrix} \beta_1 \\ 0 \end{bmatrix}, \qquad c = \begin{bmatrix} 0 \\ 1 \end{bmatrix},$$

so that $x = [x_1, x_2]^\top$, $y = x_2$, and the DC gain is $G = -c^\top A^{-1} b = \beta_1\beta_3/(\beta_2\beta_4) > 0$.

Since (9) is a special case of (1), the main theorem of the general case applies directly:

Corollary 1. *Every solution of system (9) starting from an initial state in $C := \mathbb{R}^4_+$ is bounded.*

The remainder of this section makes the boundedness result explicit in terms of α_i and β_i for $i = 1, \dots, 4$. Corollary 4 gives an explicit bound $\overline{M}_{z_1}$ for z_1, and Corollaries 5–6 give explicit bounds $\overline{M}_{x_1}, \overline{M}_{x_2}, \overline{M}_{z_2}$ for x_1, x_2, z_2 respectively.

3.1. Proof of Corollary 1

We already know, from the general results, that $C := \mathbb{R}^4_+$ is forward invariant. Similarly, forward completeness follows directly from Lemma 2, since (9) is a special case of (1).

Now we proceed to the key property of the proof.

Corollary 2. *Consider system (9). There exist constants $L_0 > 0$ and $T_0 > 0$ such that for every $L > L_0$ and $T \ge T_0$, if a solution satisfies $z_1(0) = L$ and $z_1(t) \ge L$ for all $t \in [0, T]$, then $\dot z_1(T) < 0$.*

Proof. The proof follows the same structure as Theorem 2, but exploits the explicit cascade structure of (9): lower bounds on x_1, x_2, and z_2 are derived stage by stage rather than via the step-response $g(t)$. We then use L_0 to show $z_1(T_0)z_2(T_0) > \alpha_1/\alpha_2$ for every $L > L_0$, forcing $\dot z_1(T_0) < 0$, and verify this domination persists on $[T_0, T]$ while $z_1(t) \ge L$ for all $t \in [0, T]$.

Define $\Delta_1 := \ln 2/\beta_2$, $\Delta_2 := \ln 2/\beta_4$, and $\delta(\ell, t) := \ln 2/(\alpha_4 U(\ell, t))$ for $\ell \ge 0$, $t \ge 0$, where $U(\ell, t) := \ell + \alpha_1 t$. For each $\ell \ge 0$, define $\tau(\ell)$ as the unique positive solution of

$$\tau(\ell) = \Delta_1 + \Delta_2 + \delta(\ell, \tau(\ell)),$$

which is guaranteed to exist by Proposition 1, taking $\Delta := \Delta_1 + \Delta_2$ in that proposition. Then, fix L_0 as the unique positive solution of

$$\frac{\alpha_3 G \ell^2}{8\alpha_4(\ell + \alpha_1 \tau(\ell))} = \frac{\alpha_1}{\alpha_2},$$

whose existence and uniqueness follow from Proposition 3, where $G = \beta_1\beta_3/(\beta_2\beta_4) > 0$ is the DC gain. Once L_0 is fixed, we set $T_0 := \tau(L_0)$, which is a fixed positive constant. Since $\tau(\ell)$ is strictly decreasing (Proposition 1(ii)), for every $L > L_0$ we have $\tau(L) < \tau(L_0) = T_0$, so that $T \ge T_0 > \tau(L)$ whenever $T \ge T_0$. We will next show that the corollary holds for these choices of L_0 and T_0.

Let $L > L_0$, $T \ge T_0$ and suppose

$$z_1(t) \ge L, \qquad \text{for all } t \in [0, T]. \tag{10}$$

We derive lower bounds for $x_1(t)$, $x_2(t)$, and $z_2(t)$, each holding after a finite delay within $[0, T_0] \subset [0, T]$.

1. **Estimate of $x_1(t)$.** On $[0, T]$, using $\dot x_1 = \beta_1 z_1 - \beta_2 x_1$ together with (10), we obtain

   $$\dot x_1 \ge \beta_1 L - \beta_2 x_1.$$

   Define $\dot w_1(t) = \beta_1 L - \beta_2 w_1(t)$ with $w_1(0) = x_1(0)$. By the comparison principle, this leads to $x_1(t) \ge w_1(t)$ for all $t \in [0, T]$. Hence

   $$x_1(t) \ge \frac{\beta_1 L}{\beta_2}\left[1 - e^{-\beta_2 t}\right] + x_1(0)e^{-\beta_2 t} \ge \frac{\beta_1 L}{\beta_2}\left[1 - e^{-\beta_2 t}\right].$$

   Since $1 - e^{-\beta_2 t}$ is increasing in t. By defining $\Delta_1 := (\ln 2)/\beta_2$, this yields

   $$x_1(t) \ge \frac{\beta_1 L}{\beta_2}\left[1 - e^{-\beta_2 t}\right] \ge \frac{\beta_1 L}{\beta_2}\left[1 - e^{-\beta_2 \Delta_1}\right] = \frac{\beta_1 L}{2\beta_2} =: \bar\rho_1(L) \qquad \text{for all } t \in [\Delta_1, T]. \tag{11}$$

2. **Estimate of $x_2(t)$.** On the interval $[\Delta_1, T]$, using $\dot x_2 = \beta_3 x_1 - \beta_4 x_2$ and (11) results in

   $$\dot x_2 \ge \beta_3 \bar\rho_1(L) - \beta_4 x_2.$$

   Define $\dot w_2(t) = \beta_3 \bar\rho_1(L) - \beta_4 w_2(t)$ with $w_2(\Delta_1) = x_2(\Delta_1)$. By the comparison principle, we have $x_2(t) \ge w_2(t)$ for all $t \in [\Delta_1, T]$. Hence

   $$x_2(t) \ge \frac{\beta_3}{\beta_4}\bar\rho_1(L)\left[1 - e^{-\beta_4(t-\Delta_1)}\right] + x_2(\Delta_1)e^{-\beta_4(t-\Delta_1)} \ge \frac{\beta_3}{\beta_4}\bar\rho_1(L)\left[1 - e^{-\beta_4(t-\Delta_1)}\right].$$

   Since $t - \Delta_1 \ge 0$, thus $1 - e^{-\beta_4(t-\Delta_1)}$ is increasing in t. Defining $\Delta_2 := (\ln 2)/\beta_4$, this results in

   $$\begin{aligned} x_2(t) &\ge \frac{\beta_3}{\beta_4}\bar\rho_1(L)\left[1 - e^{-\beta_4(t-\Delta_1)}\right] \ge \frac{\beta_3}{\beta_4}\bar\rho_1(L)\left[1 - e^{-\beta_4 \Delta_2}\right] \\ &= \frac{\beta_3}{2\beta_4}\bar\rho_1(L) =: \bar\rho_2(L) \qquad \text{for all } t \in [\Delta_1 + \Delta_2, T]. \end{aligned} \tag{12}$$

3. **Upper bound for z_1.** Before lower bounding z_2, we must first derive an upper bound for z_1 in the interval. From the equation $\dot z_1 = \alpha_1 - \alpha_2 z_1 z_2$ and the nonnegativity $z_1, z_2 \ge 0$, we obtain $\dot z_1(t) = \alpha_1 - \alpha_2 z_1 z_2 \le \alpha_1$ for all $t \ge 0$. Integrating on any interval $[0, t]$ yields

   $$z_1(t) \le z_1(0) + \alpha_1 t.$$

   Using the assumption $z_1(t) \ge L$ for all $t \in [0, T_0]$ and $z_1(0) = L$, then for every $t \in [0, T_0]$,

   $$z_1(t) \le L + \alpha_1 t \le L + \alpha_1 T_0 = U(L, T_0). \tag{13}$$

   Thus, on any time interval of length T_0 on which z_1 remains above L, it is also bounded from above by $U(L, T_0)$.

4. **Estimate of $z_2(t)$.** On the interval $[\Delta_1 + \Delta_2, T_0]$, using $\dot z_2 = \alpha_3 x_2 - \alpha_4 z_1 z_2$, (12), and (13) yield

   $$\dot z_2(t) \ge \alpha_3 \bar\rho_2(L) - \alpha_4 U(L, T_0)\, z_2(t).$$

Define $\dot{v}(t) = \alpha_3\bar{\rho}_2(L) - \alpha_4 U(L,T_0)v(t)$ with $v(\Delta_1+\Delta_2) = z_2(\Delta_1+\Delta_2)$. By the comparison principle we have $z_2(t) \geq v(t)$ for all $t \in [\Delta_1+\Delta_2, T_0]$. Hence, with $\bar{U} := U(L,T_0)$,

$$z_2(t) \geq \frac{\alpha_3}{\alpha_4\bar{U}}\bar{\rho}_2(L)\left[1 - e^{-\alpha_4\bar{U}(t-(\Delta_1+\Delta_2))}\right] + z_2(\Delta_1+\Delta_2)\,e^{-\alpha_4\bar{U}(t-(\Delta_1+\Delta_2))}$$
$$\geq \frac{\alpha_3}{\alpha_4\bar{U}}\bar{\rho}_2(L)\left[1 - e^{-\alpha_4\bar{U}(t-(\Delta_1+\Delta_2))}\right].$$

Since $t-(\Delta_1+\Delta_2) \geq 0$, thus $1-e^{-\alpha_4\bar{U}(t-(\Delta_1+\Delta_2))}$ is increasing in t. Using $\delta(L,T_0) = (\ln 2)/(\alpha_4 U(L,T_0))$,

$$z_2(t) \geq \frac{\alpha_3}{2\alpha_4 U(L,T_0)}\bar{\rho}_2(L)$$
$$= \frac{\alpha_3 GL}{8\alpha_4(L+\alpha_1 T_0)} =: \bar{\rho}_z(L,T_0) \qquad \text{for all } t \in [\Delta_1+\Delta_2+\delta(L,T_0), T_0]. \tag{14}$$

Note that the bounds on x_1 and x_2 persist while $z_1(t) \geq L$, and hence are valid on $[\Delta_1, T]$ and $[\Delta_1+\Delta_2, T]$ respectively. For z_2, however, the damping coefficient $\alpha_4 z_1$ depends on z_1 itself, so we need the upper bound $z_1(t) \leq U(L,T_0)$, which is only available on $[0,T_0]$. This is why the estimate for z_2 is restricted to $[0,T_0]$.

Unlike the general case, where $y \geq GL/2$ follows from $g(t) \geq G/2$, here the bounds on x_1, x_2, and z_2 are derived explicitly stage by stage through the cascade $z_1 \to x_1 \to x_2 \to z_2$. From (10) and (14), $z_1(T_0)z_2(T_0) \geq L\bar{\rho}_z(L,T_0)$. By the choice of L_0 and since $\ell \mapsto \ell\bar{\rho}_z(\ell,T_0)$ is strictly increasing in ℓ, for every $L > L_0$,

$$L\bar{\rho}_z(L,T_0) > L_0\bar{\rho}_z(L_0,T_0) = \frac{\alpha_1}{\alpha_2},$$

where the last equality holds by definition of L_0. Thus $z_1(T_0)z_2(T_0) > \alpha_1/\alpha_2$ and $\dot{z}_1(T_0) = \alpha_1 - \alpha_2 z_1(T_0)z_2(T_0) < 0$.

However, as T increases beyond T_0, the bound $\bar{\rho}_z(L,T)$ decreases in T, so this estimate does not directly extend beyond T_0. As in the proof of Theorem 2, introduce the product $p(t) := z_1(t)z_2(t)$ and $\theta := \alpha_1/\alpha_2$. We claim that $p(t) > \theta$ for all $t \in [T_0, T]$. Indeed, the proof is identical to that of Lemma 6, with ρ_z replaced by $\bar{\rho}_z$ and $L^* := 2\alpha_4\theta/(\alpha_3 G)$ replaced by $L_* := 4\alpha_4\theta/(\alpha_3 G)$.[1] Therefore,

$$\dot{z}_1(t) = \alpha_1 - \alpha_2 p(t) < \alpha_1 - \alpha_2\theta = 0, \qquad \text{for all } t \in [T_0, T].$$

In particular, $\dot{z}_1(T) < 0$, completing the proof. □

With Corollary 2 established, the global boundedness of z_1 follows by exactly the same argument as in the general case (Lemmas 3 and 3).

Corollary 3. *Let L_0 and T_0 be defined as in Corollary 2. For every $L > L_0$, if a solution satisfies $z_1(0) = L$, then $z_1(t) \leq L + \alpha_1 T_0$ for all $t \geq 0$.*

Corollary 4. *Let L_0 and T_0 be defined as in Corollary 2. Every solution of (9) satisfies*

$$z_1(t) \leq \max\{z_1(0),\, L_0\} + \alpha_1 T_0 =: \overline{M}_{z_1} \qquad \text{for all } t \geq 0.$$

In particular, z_1 is bounded on $[0,\infty)$.

Once z_1 is known to be bounded by $\overline{M}_{z_1}$, boundedness of x_1 and x_2 follows by direct comparison.

Corollary 5. *Let $z_1(t) \leq \overline{M}_{z_1}$ for all $t \geq 0$. There exist constants*

$$\max\left\{x_1(0),\, \frac{\beta_1}{\beta_2}\overline{M}_{z_1}\right\} =: \overline{M}_{x_1} > 0, \qquad \max\left\{x_2(0),\, \frac{\beta_3}{\beta_4}\overline{M}_{x_1}\right\} =: \overline{M}_{x_2} > 0,$$

such that $x_1(t) \leq \overline{M}_{x_1}$ and $x_2(t) \leq \overline{M}_{x_2}$ for all $t \geq 0$. In particular, x_1 and x_2 are bounded on $[0,\infty)$.

Once x_1 and x_2 are known to be bounded, boundedness of z_2 follows by the same Lyapunov-like argument as in the proof of Lemma 5. The auxiliary function $W(t) := z_2(t) + v^\top x(t)$ takes the explicit form $W(t) := z_2(t) + cx_1(t) + dx_2(t)$, where $c := \beta_3\alpha_3/(\beta_2\beta_4)$ and $d := \alpha_3/\beta_4$ are the explicit values of $v^\top = -\alpha_3 c^\top A^{-1}$ for this system, and $K_* := \alpha_3 G/\alpha_4$ coincides with K^* in Lemma 5, now with $G = \beta_1\beta_3/(\beta_2\beta_4)$ explicit.

Corollary 6. *Let $z_1(t) \leq \overline{M}_{z_1}$, $x_1(t) \leq \overline{M}_{x_1}$, and $x_2(t) \leq \overline{M}_{x_2}$ for all $t \geq 0$. There exists a constant $\overline{M}_{z_2} > 0$ such that $z_2(t) \leq \overline{M}_{z_2}$ for all $t \geq 0$. In particular, z_2 is bounded on $[0,\infty)$.*

4. Numerical example

4.1. Positive linear system in $\mathbb{R}^n$

We first illustrate the boundedness result for the general system (1) with $n = 12$. The system parameters are $\alpha_1 = 1$, $\alpha_2 = 30$, $\alpha_3 = 1$, and $\alpha_4 = 30$. The matrix A is constructed as a Hurwitz Metzler matrix by choosing a nonnegative off-diagonal matrix $R \in \mathbb{R}^{12\times 12}$ with randomly generated nonnegative entries and zero diagonal, and setting

$$A = R - \mathrm{diag}\Big(1 + \sum_j R_{ij}\Big),$$

so that A is Metzler and strictly diagonally dominant with negative diagonal entries, hence Hurwitz. The vectors $b, c \in \mathbb{R}^{12}_+$ are chosen with random positive entries. The resulting theoretical constants are

$$\Delta_x \approx 0.6587, \quad G \approx 2.0684, \quad L_0 \approx 2.3237, \quad T_0 \approx 0.6664.$$

To illustrate the dependence on the initial condition, we simulate ten trajectories with $z_2(0) = 0$, $x(0) = 0$, and $z_1(0)$ uniformly distributed in the interval $[0, L_0)$. Since $z_1(0) \leq L_0$ for all simulations, the theoretical bounds are identical across all trajectories and are given by

$$M_{z_1} \approx 2.9901, \qquad M_x \approx 7.4848, \qquad M_{z_2} \approx 13.2746.$$

Fig. 4 shows the simulated trajectories together with the corresponding theoretical bounds. Although the trajectories originate from different initial conditions, they all remain below the same bounds, illustrating the uniform nature of the estimates within the region $z_1(0) \leq L_0$. The bound M_{z_1} is relatively tight, while M_x and M_{z_2} are more conservative, as expected from the use of norm estimates and comparison arguments in the proof.

4.2. Positive linear system in $\mathbb{R}^2$

As an example, consider the positive linear system in $\mathbb{R}^2$ given by (9), with parameters $\alpha_i, \beta_i > 0$ for $i = 1, \ldots, 4$. We choose the parameter values as in [1], with $\alpha_2 = \alpha_4 = 30$, $\beta_1 = 10$, and $\alpha_1 = \alpha_3 = \beta_2 = \beta_3 = \beta_4 = 1$. The resulting system is

$$\begin{aligned} \dot{z}_1 &= 1 - 30z_1z_2, \\ \dot{z}_2 &= x_2 - 30z_1z_2, \end{aligned} \qquad \text{and} \qquad \begin{aligned} \dot{x}_1 &= 10z_1 - x_1, \\ \dot{x}_2 &= x_1 - x_2. \end{aligned} \tag{15}$$

This system admits oscillatory solutions: see Fig. 5(d) for a periodic orbit and Fig. 5(b) for a solution approaching this periodic orbit when initialized at $z_1(0) = z_2(0) = x_1(0) = x_2(0) = 0$. We compare the theoretical bounds with the simulated trajectories.

The computed threshold and waiting time are $L_0 = 1.5293$ and $T_0 = 1.3942$, which yield

$$\overline{M}_{z_1} = L_0 + \alpha_1 T_0 \approx 2.9235$$
$$\overline{M}_{x_1} = 10\,\overline{M}_{z_1} \approx 29.2351$$
$$\overline{M}_{x_2} = \overline{M}_{x_1} \approx 29.2351.$$

[1] The factor-of-two difference between L^* and L_* reflects the difference in the lower bound on y: in the general case, $y \geq GL/2$ follows from the step-response estimate $g(t) \geq G/2$, while here the explicit cascade gives $x_2 \geq \bar{\rho}_2(L) = GL/4$, which carries an additional factor of $1/2$ through the two cascade stages. The remainder of the argument is unchanged: one shows $L_*\bar{\rho}_z(L_*, \tau(L_*)) < \theta$, which implies $L_0 > L_*$, and hence $\alpha_3\bar{\rho}_2(L_0) - \alpha_4\theta > 0$, giving $\dot{p}(t_0) > 0$ and contradicting $\dot{p}(t_0) \leq 0$.

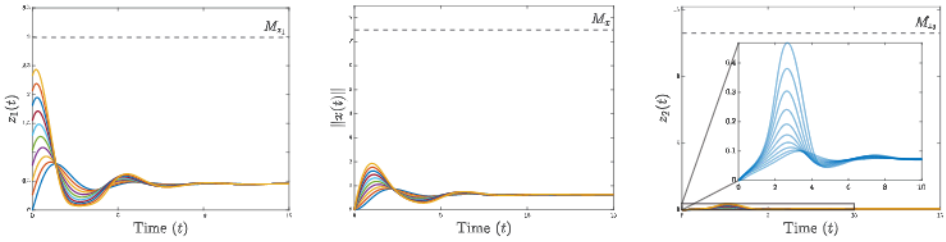


Fig. 4. Numerical simulation for the general positive linear system with $n = 12$. (a) Evolution of z_1 for ten initial conditions satisfying $0 \le z_1(0) \le L_0$, together with the common theoretical bound M_{z_1}. (b) Evolution of $\|x(t)\|$ for the same initial conditions, together with the common bound M_x. (c) Evolution of z_2 for the same initial conditions, together with the common bound M_{z_2}.

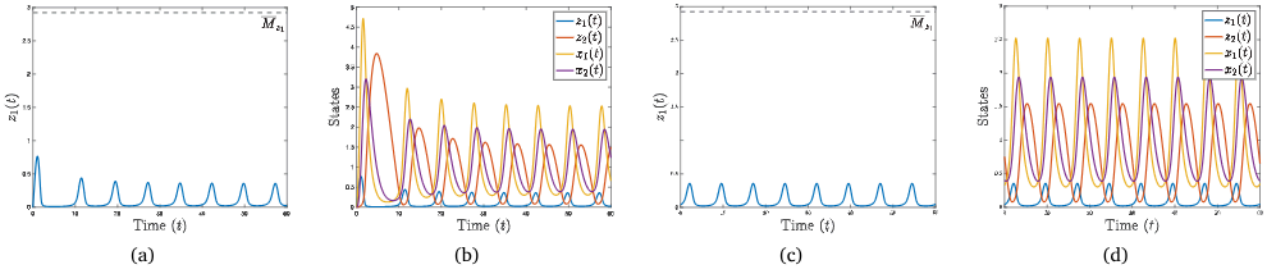


Fig. 5. (a) Evolution of z_1 together with the theoretical bound $\overline{M}_{z_1}$ for the initial condition $[z_1(0), z_2(0), x_1(0), x_2(0)]^\top = [0, 0, 0, 0]^\top$. (b) Evolution of all states for the same initial condition. (c) Evolution of z_1 together with the theoretical bound $\overline{M}_{z_1}$ for the initial condition $[z_1(0), z_2(0), x_1(0), x_2(0)]^\top = [0.043,\ 0.756,\ 0.332,\ 0.407]^\top$. (d) Evolution of all states for the same initial condition.

Finally, since $K_* = \alpha_3 G/\alpha_4 = 1/3$, $c = 1$, and $d = 1$, we obtain

$$\overline{M}_{z_2} = K_* + c\overline{M}_{x_1} + d\overline{M}_{x_2} \approx 58.8036.$$

Below are simulations from two different initial conditions,

$$[z_1(0),\ z_2(0),\ x_1(0),\ x_2(0)]^\top = [0, 0, 0, 0]^\top$$
$$[z_1(0),\ z_2(0),\ x_1(0),\ x_2(0)]^\top = [0.043,\ 0.756,\ 0.332,\ 0.407]^\top.$$

We report only the bound $\overline{M}_{z_1}$ explicitly in Fig. 5(a) and (c), since the bounds $\overline{M}_{x_1}$, $\overline{M}_{x_2}$, and $\overline{M}_{z_2}$ follow directly from $\overline{M}_{z_1}$ through the cascade comparison arguments. In particular, $\overline{M}_{x_1}$ and $\overline{M}_{x_2}$ scale proportionally with $\overline{M}_{z_1}$, while $\overline{M}_{z_2}$ accumulates contributions from the upstream states, making it the most conservative bound. This explains why the theoretical bounds are considerably larger than the observed trajectories.

5. Discussion

5.1. Boundedness mechanism and biological interpretation

In this paper, we studied boundedness of a class of nonlinear feedback systems motivated by antithetic control. Our main result establishes that all nonnegative trajectories remain bounded, even without assuming stability of the closed-loop equilibrium.

The key idea behind the boundedness proof was to view the dynamics of z_1 as a system subject to negative feedback whose effective gain is determined by z_2. The crucial property is that whenever z_1 remains above a certain threshold L_0 for a sufficiently large time, the resulting growth of z_2 eventually generates a feedback action strong enough to overcome the positive drift of z_1. We may think of this mechanism as a form of *persistently negative feedback*: a persistently large value of z_1 ultimately produces a corrective damping action that drives z_1 downward.

To establish this property, one must relate the behavior of z_1 to that of the intermediate subsystem described by the variables x, with input $u = z_1$ and output y. Intuitively, a persistently large input should produce a persistently large output, which in turn causes z_2 to increase and strengthen the negative feedback acting on z_1. A natural framework for formalizing this idea is provided by the theory of monotone control systems developed in [15]. In particular, if for each constant input u the subsystem admits a globally asymptotically stable equilibrium, yielding an input-state characteristic in the sense of that work, then persistent increases in the input are reflected in corresponding increases in the asymptotic state and output. Such a property can be established under a variety of technical assumptions. For simplicity, we restricted attention here to the case in which the intermediate subsystem is linear and positive, a special case of monotone systems. This restriction is motivated by our main application, where the x-subsystem is a two-dimensional positive linear system.

From a biological perspective, our analysis considers an idealized antithetic feedback system without additional mechanisms that impose bounds on molecular concentrations. In particular, the model does not incorporate saturation of production, limitations imposed by finite cellular resources, or other nonlinear constraints that may prevent concentrations from becoming arbitrarily large. Although such mechanisms may ensure boundedness in biological implementations, they do not resolve the mathematical question of whether boundedness follows from the idealized feedback dynamics themselves. This is precisely the question addressed in this work.

5.2. Extensions and future directions

The connection with monotone control systems suggests that our boundedness argument may extend beyond positive linear plants. In the recent preprint [16], we have considered nonlinear extensions in which the controlled system is allowed to be a positive cooperative nonlinear system. Further directions include studying mass-action, Hill-type, and Michaelis–Menten dynamics, as well as exploring input-to-state stability and passivity-based approaches to boundedness.

Another extension concerns basal or "leaky" production in genetic circuits. Such production leads to an affine positive plant of the form

$$\dot{x} = Ax + bz_1 + d, \qquad y = c^\top x,$$

where A is Hurwitz and Metzler, and $b, c, d \geq 0$. The corresponding basal output is $y_{\text{basal}} = -c^\top A^{-1} d \geq 0$. Although the plant admits a nonnegative equilibrium for every constant nonnegative input, the closed-loop system admits a nonnegative equilibrium only when the controller setpoint $r = (\alpha_1\alpha_4)/(\alpha_2\alpha_3)$ satisfies $r > y_{\text{basal}}$, assuming $-c^\top A^{-1} b > 0$.

When $r < y_{\text{basal}}$, the controller cannot reduce the output below its basal level, and the controller state z_2 necessarily becomes unbounded. The boundary case $r = y_{\text{basal}}$ admits no finite nonnegative closed-loop equilibrium. When $r > y_{\text{basal}}$, a nonnegative equilibrium exists, and establishing global boundedness in this affine setting is one of our immediate directions for future research.

These extensions may help clarify how the boundedness mechanism identified in this work extends to more general biological systems and under what conditions it remains valid.

CRediT authorship contribution statement

Moh Kamalul Wafi: Writing – original draft, Validation, Software, Methodology, Formal analysis, Conceptualization. **Arthur Castello B. de Oliveira:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Eduardo D. Sontag:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors worked closely with several AI assistants to brainstorm ideas, search the literature, develop proofs, check arguments, and write and edit the paper. The authors verified all mathematical statements and proofs and take full responsibility for the content.

Appendix A. Technical results

Proposition 1. *Let $\Delta > 0$ and $\alpha_1, \alpha_4 > 0$. For each $\ell \in \mathbb{R}_+$, consider the fixed-point equation*

$$\tau(\ell) = \Delta + \frac{\ln(2)}{\alpha_4(\ell + \alpha_1 \tau(\ell))}. \tag{16}$$

Then, $\tau(\ell)$ satisfies:

(i) *the unique positive solution $\tau^* = \tau(\ell)$ exists;*
(ii) *$\tau(\ell)$ is continuous on $[0, \infty)$, differentiable on $(0, \infty)$, and strictly decreasing; moreover, the right derivative at $\ell = 0$ exists and is negative;*
(iii) *$\tau(\ell) > \Delta$ for all $\ell \geq 0$, and $\lim_{\ell \to \infty} \tau(\ell) = \Delta$.*
(iv) *the solution $\tau(\ell; \Delta)$ is strictly increasing in Δ for each fixed $\ell \geq 0$.*

Proof. The uniqueness can be easily verified by noticing that the LHS of the equation above is the line with unit slope, while the RHS is a shifted hyperbola, implying they must cross exactly once for $\ell \geq 0$. More precisely, setting $\psi := \ln(2)/\alpha_4$, the fixed-point equation becomes $\tau(\ell) = \Delta + \psi/(\ell + \alpha_1\tau(\ell))$. Equivalently $(\tau(\ell) - \Delta)(\ell + \alpha_1\tau(\ell)) = \psi$ or $q(\tau(\ell)) := \alpha_1\tau(\ell)^2 + (\ell - \alpha_1\Delta)\tau(\ell) - (\Delta\ell + \psi) = 0$, which has exactly one positive root

$$\tau^* = \frac{\alpha_1\Delta - \ell + \sqrt{(\ell + \alpha_1\Delta)^2 + 4\alpha_1\psi}}{2\alpha_1}. \tag{17}$$

Hence $\tau^* = \tau(\ell)$ is well defined, which proves (i). The fixed-point equation also gives

$$\tau(\ell) - \Delta = \frac{\ln(2)}{\alpha_4(\ell + \alpha_1\tau(\ell))} > 0 \qquad \text{for every } \ell \geq 0.$$

The explicit formula (17) shows that τ is continuous on $[0, \infty)$ and differentiable on $(0, \infty)$. Moreover, the derivative extends continuously to $\ell = 0$, where it equals the right derivative. Differentiating $q(\tau(\ell))$ with respect to ℓ yields

$$2\alpha_1\tau(\ell)\tau'(\ell) + \tau(\ell) + (\ell - \alpha_1\Delta)\tau'(\ell) - \Delta = 0,$$

from which it follows that

$$\tau'(\ell) = \frac{\Delta - \tau(\ell)}{2\alpha_1\tau(\ell) + \ell - \alpha_1\Delta} = -\frac{\ln(2)}{\alpha_4\left(\ell + \alpha_1\tau(\ell)\right)^2 + \alpha_1\ln(2)} < 0.$$

The formula is valid for all $\ell > 0$ and extends continuously to $\ell = 0$, where it gives the right derivative. Since $\tau(\ell) > \Delta$, it follows that $\tau'(\ell) < 0$. Therefore $\tau(\ell)$ is strictly decreasing, proving (ii). Furthermore, using the expansion[2]

$$\sqrt{(\ell + \alpha_1\Delta)^2 + 4\alpha_1\psi} = \ell + \alpha_1\Delta + \frac{2\alpha_1\psi}{\ell + \alpha_1\Delta} + o\Big(\frac{1}{\ell}\Big), \qquad \ell \to \infty,$$

and substituting this into the expression for $\tau(\ell)$ gives, as $\ell \to \infty$, $\lim_{\ell\to\infty} \tau(\ell) = \Delta$. Together with the inequality $\tau(\ell) > \Delta$ proved above, this proves point (iii).

Finally, to prove (iv), view the solution as $\tau = \tau(\ell; \Delta)$ and differentiate the fixed-point equation with respect to Δ. This gives

$$\frac{\partial\tau}{\partial\Delta} = 1 - \frac{\alpha_1\ln(2)}{\alpha_4(\ell + \alpha_1\tau)^2}\frac{\partial\tau}{\partial\Delta} = \frac{1}{1 + \dfrac{\alpha_1\ln(2)}{\alpha_4(\ell + \alpha_1\tau)^2}} > 0.$$

Therefore, for each fixed $\ell \geq 0$, $\tau(\ell; \Delta)$ is strictly increasing in Δ, proving (iv). □

Proposition 2. *Let $\tau(\ell) : \mathbb{R}_+ \to \mathbb{R}_+$ be defined as in (16), $\alpha_3 > 0$ and $G := -c^\top A^{-1} b > 0$. For each $\ell \in \mathbb{R}_+$, define*

$$\rho_z(\ell, \tau(\ell)) := \frac{\alpha_3 G \ell}{4\alpha_4(\ell + \alpha_1\tau(\ell))}.$$

Then $\rho_z : \mathbb{R}_+ \to \mathbb{R}_+$ is strictly increasing with $\lim_{\ell\to\infty} \rho_z(\ell, \tau(\ell)) = \alpha_3 G/(4\alpha_4)$.

Proof. Denote $\alpha := \alpha_3 G/(4\alpha_4) > 0$. From the definition of $\rho_z(\ell, \tau(\ell))$, it suffices to study the function

$$\phi(\ell) := \frac{\ell}{\ell + \alpha_1\tau(\ell)},$$

since $\rho_z(\ell, \tau(\ell)) = \alpha\phi(\ell)$. Differentiating, we obtain

$$\phi'(\ell) = \frac{(\ell + \alpha_1\tau(\ell)) - \ell(1 + \alpha_1\tau'(\ell))}{(\ell + \alpha_1\tau(\ell))^2} = \frac{\alpha_1\left(\tau(\ell) - \ell\tau'(\ell)\right)}{(\ell + \alpha_1\tau(\ell))^2}.$$

By Proposition 1, $\tau(\ell) > 0$ and $\tau'(\ell) < 0$ for all $\ell \geq 0$, hence $\tau(\ell) - \ell\tau'(\ell) > 0$, and therefore $\phi'(\ell) > 0$ for all $\ell \geq 0$. Thus $\phi(\ell)$, and hence

[2] Let $a := \ell + \alpha_1\Delta$. Then $\sqrt{a^2 + 4\alpha_1\psi} = a\sqrt{1 + 4\alpha_1\psi/a^2}$. Since $a \to \infty$ as $\ell \to \infty$, the quantity $x := 4\alpha_1\psi/a^2$ satisfies $x \to 0$. Using the Taylor expansion $\sqrt{1+x} = 1 + x/2 + o(x)$ as $x \to 0$, we obtain $\sqrt{a^2 + 4\alpha_1\psi} = a + 2\alpha_1\psi/a + o(1/a)$. Substituting back $a = \ell + \alpha_1\Delta$ yields the stated expansion.

$\rho_z(\ell, \tau(\ell))$, is strictly increasing on $[0, \infty)$. Moreover, since Proposition 1 gives $\lim_{\ell\to\infty} \tau(\ell) = \Delta < \infty$, it follows that $\lim_{\ell\to\infty} \phi(\ell) = 1$, and hence $\lim_{\ell\to\infty} \rho_z(\ell, \tau(\ell)) = \alpha_3 G/(4\alpha_4)$. □

Proposition 3. *Let $\rho_z(\ell, \tau(\ell))$ be defined as in Proposition 2. Then the map $\ell \mapsto \ell\rho_z(\ell, \tau(\ell))$ is strictly increasing on $[0, \infty)$ and satisfies*

$$\lim_{\ell\to\infty} \ell\rho_z(\ell, \tau(\ell)) = \infty.$$

Consequently, for every $a > 0$, there exists a unique $\ell^* > 0$ such that $\ell^*\rho_z(\ell^*, \tau(\ell^*)) = a$.

Proof. By Proposition 2, $\rho_z(\ell, \tau(\ell)) \geq 0$ for all $\ell \geq 0$ and ρ_z is strictly increasing, so that $\ell \mapsto \ell\rho_z(\ell, \tau(\ell))$ is strictly increasing on $[0, \infty)$. Moreover, Proposition 2 gives $\lim_{\ell\to\infty} \rho_z(\ell, \tau(\ell)) = \alpha_3 G/(4\alpha_4) > 0$, and it follows that $\lim_{\ell\to\infty} \ell\rho_z(\ell, \tau(\ell)) = \infty$. Since $\ell \mapsto \ell\rho_z(\ell, \tau(\ell))$ is continuous, strictly increasing, and satisfies

$$\lim_{\ell\to 0^+} \ell\rho_z(\ell, \tau(\ell)) = 0, \qquad \lim_{\ell\to\infty} \ell\rho_z(\ell, \tau(\ell)) = \infty,$$

the intermediate value theorem implies that for every $a > 0$ there exists a unique $\ell^* > 0$ such that $\ell^*\rho_z(\ell^*, \tau(\ell^*)) = a$. Taking $a = \alpha_1/\alpha_2$ gives the desired threshold L_0. □

Lemma 6. *Let $\theta := \alpha_1/\alpha_2$. Consider the dynamics of $z_1(t)$ and $z_2(t)$ in (1). Suppose that $z_1(t) \geq L > L_0$ for all $t \in [0, T]$ with $T \geq T_0$. Assume, in addition, that $p(T_0) > \theta$. Then $p(t) > \theta$ for all $t \in [T_0, T]$.*

Proof of Lemma 6. Recall that $\theta := \alpha_1/\alpha_2$. We prove that $p(t) > \theta$ for all $t \in [T_0, T]$ by contradiction. Suppose instead that there exists $t \in (T_0, T]$ such that $p(t) \leq \theta$. Since $p(T_0) > \theta$, the intermediate value theorem implies that there exists $\bar{t} \in (T_0, t]$ such that $p(\bar{t}) = \theta$.

Let t_0 denote the first time at which this occurs, i.e., $t_0 := \min\{s \in (T_0, T] : p(s) = \theta\}$. Then $p(t) > \theta$ for all $t \in [T_0, t_0)$ and $p(t_0) = \theta$. Hence, the first-crossing argument in Lemma 7 implies that

$$\dot{p}(t_0) \leq 0.$$

However, notice that since $p(t_0) = \theta$ by definition of t_0, $\dot{z}_1(t_0) = \alpha_1 - \alpha_2\theta = 0$, which implies that

$$\dot{p}(t_0) = z_1(t_0)\dot{z}_2(t_0) = \big[\alpha_3 y(t_0) - \alpha_4\theta\big] z_1(t_0).$$

Since $z_1(t_0) \geq L > 0$, the sign of $\dot{p}(t_0)$ is determined by the term in parentheses. Since $t_0 > T_0 > \Delta$, we have $y(t_0) \geq \rho_y(L)$ from (4), and since $\rho_y(L) = GL/2$ is increasing in L and $L > L_0$,

$$\alpha_3 y(t_0) - \alpha_4\theta \geq \alpha_3\rho_y(L) - \alpha_4\theta > \alpha_3\rho_y(L_0) - \alpha_4\theta.$$

It remains to show that L_0 satisfies $\alpha_3 G L_0/2 > \alpha_4\theta$, or equivalently,

$$L_0 > L^* := 2\alpha_4\theta/(\alpha_3 G).$$

Notice that $L_0\rho_z(L_0, T_0) = \theta$ by definition of L_0 in (3). Since $\ell\rho_z(\ell, \tau(\ell))$ is strictly increasing in ℓ (Proposition 3), it suffices to show that $L^*\rho_z(L^*, \tau(L^*)) < \theta$, which would imply $L_0 > L^*$. Indeed,

$$L^*\rho_z(L^*, \tau(L^*)) = \frac{\alpha_3 G(L^*)^2}{4\alpha_4\big(L^* + \alpha_1\tau(L^*)\big)} < \frac{\alpha_3 G(L^*)^2}{4\alpha_4 L^*} = \frac{\alpha_3 G L^*}{4\alpha_4} = \frac{\theta}{2} < \theta,$$

where we used $\tau(L^*) > 0$ in the first inequality and substituted $L^* = 2\alpha_4\theta/(\alpha_3 G)$ in the last equality. Hence $L_0 > L^*$, so $\alpha_3 G L_0/2 > \alpha_4\theta$, and therefore

$$\dot{p}(t_0) = z_1(t_0)\left[\alpha_3 y(t_0) - \alpha_4\theta\right] > 0,$$

contradicting $\dot{p}(t_0) \leq 0$. □

Lemma 7 (*First Hitting-Time*). *Let $f : [0, \infty) \to \mathbb{R}$ be differentiable, and let $Q \in \mathbb{R}$. Suppose that the set $\{t \geq 0 : f(t) = Q\}$ is nonempty and define $t^* := \min\{t \geq 0 : f(t) = Q\}$.*

1. *If $f(0) < Q$, then $f(t) \leq Q$ for all $t \in [0, t^*]$, and $\dot{f}(t^*) \geq 0$.*
2. *If $f(0) > Q$, then $f(t) \geq Q$ for all $t \in [0, t^*]$, and $\dot{f}(t^*) \leq 0$.*

Proof. We prove the case $f(0) < Q$; the case $f(0) > Q$ is analogous with the inequalities reversed. Since t^* is the first time at which f reaches the level Q and $f(0) < Q$, we have $f(t) < Q$ for all $t \in [0, t^*)$ and $f(t^*) = Q$. Hence $f(t) \leq Q$ for all $t \in [0, t^*]$.

For $h < 0$ sufficiently small, we have $t^* + h < t^*$, and so $f(t^* + h) < Q = f(t^*)$. Therefore, $\frac{1}{h}[f(t^* + h) - f(t^*)] \geq 0$. Passing to the limit as $h \to 0^-$ gives $\dot{f}(t^*) \geq 0$. □

Appendix B. Additional technical proofs

Proof of Lemma 1. To prove invariance of the positive orthant C, we invoke the Bony–Brezis Theorem, which states that a closed set is forward invariant under a vector field $f(\cdot)$ (i.e. solutions of that vector field initialized in the set remain in the set) if and only if $\langle f(w), v\rangle \leq 0$ for every exterior normal vector v at any boundary point w of C. To do that, first formally define for (1)

$$f(w) = f([z_1; z_2; x]) := \begin{bmatrix} \alpha_1 - \alpha_2 z_1 z_2 \\ \alpha_3 c^\top x - \alpha_4 z_1 z_2 \\ Ax + bz_1 \end{bmatrix},$$

and let ∂C denote the boundary of C. Note that

$$\partial C = \{(z_1, z_2, x) \in C : \text{at least one coordinate of } (z_1, z_2, x) \text{ is zero}\},$$

since if all coordinates are strictly positive, then a small neighborhood still lies entirely in C, so the point is in the interior.

Next, at any point $w \in \partial C$ let $I(w) := \{i \in \{1, \dots, n+2\} \mid w_i = 0\}$ and denote $I(w) = I$ if the point w is clear by context. We will prove that the exterior normal cone of C at w is given by $\{v \in \mathbb{R}^{n+2} \mid v = -\sum_{i\in I} \lambda_i e_i,\ \lambda_i \geq 0\}$. For any closed convex set (such as the positive orthant) the exterior normal cone can be defined as $\mathcal{N}_C(w) := \{v \in \mathbb{R}^{n+2} \mid \langle v, \xi - w\rangle \leq 0 \text{ for all } \xi \in C\}$. Pick any $v \in \mathcal{N}_C(w)$ and consider two cases: first, if $i \notin I$, then $w_i > 0$ and thus for sufficiently small $\varepsilon > 0$, $w \pm \varepsilon e_i \in C$. Using the definition of $\mathcal{N}_C(w)$ with $\xi = w + \varepsilon e_i$ gives that $\langle v, \varepsilon e_i\rangle \leq 0$ and thus $v_i \leq 0$. Repeating the same logic for $\xi = w - \varepsilon e_i$ gives $v_i \geq 0$ and thus $v_i = 0$; second, if $i \in I$ then for any sufficiently small $\varepsilon > 0$, $w + \varepsilon e_i \in C$, and again using the definition of the normal cone gives $v_i \leq 0$. This means $v_i = 0$ if $i \notin I$ and $v_i \leq 0$ if $i \in I$, thus $v = -\sum_{i\in I} \lambda_i e_i$, $\lambda_i := -v_i \geq 0$, and thus $\mathcal{N}_C(w) \subseteq \{v \in \mathbb{R}^{n+2} \mid v = -\sum_{i\in I} \lambda_i e_i,\ \lambda_i \geq 0\}$.

To prove the converse pick any $v = -\sum_{i\in I} \lambda_i e_i$, with $\lambda_i \geq 0$. Then for any $\xi \in C$, $\langle v, \xi - w\rangle = -\sum_{i\in I} \lambda_i(\xi_i - w_i) = -\sum_{i\in I} \lambda_i\xi_i \leq 0$, proving that $\mathcal{N}_C(w) \supseteq \{v \in \mathbb{R}^{n+2} \mid v = -\sum_{i\in I} \lambda_i e_i,\ \lambda_i \geq 0\}$ and proving equality.

Finally we prove invariance of the positive orthant under (1). First, notice that any point $w = (z_1, z_2, x)$ satisfying $z_1 = 0$ is such that $\{f(w)\}_1 = \dot{z}_1|_w = \alpha_1 - \alpha_2 z_1 z_2 = \alpha_1 > 0$, and thus $\langle f(w), -e_1\rangle = -\alpha_1 < 0$. Next, notice that since $c \geq 0$ by assumption, at any point $w \in \partial C$, $x \geq 0$ in particular, implying that $c^\top x \geq 0$. Thus, if $z_2 = 0$ at w, then $\langle f(w), -e_2\rangle = -\alpha_3 y + \alpha_4 z_1 z_2 = -\alpha_3 y \leq 0$. Finally, for any $i \in I$ assume w is such that $x_{i-2} = 0$ and compute $\langle f(w), -e_i\rangle = -(\sum_{j=1}^n A_{(i-2),j} x_j + b_{i-2} z_1)$. Since $b \geq 0$ and $z_1 \geq 0$ at w, $b_{i-2} z_1 \geq 0$. Furthermore, since A is Metzler and $x_{i-2} = 0$ then $\sum_{j=1}^n A_{(i-2),j} x_j \geq 0$, implying that $\langle f(w), -e_i\rangle \leq 0$. We, thus, have proven that for all $w \in \partial C$ and all $i \in I = \{i \in \{1, \dots, n+2\} \mid w_i = 0\}$, $\langle f(w), -e_i\rangle \leq 0$. By conic combination, we conclude that for all $v \in \mathcal{N}_C(w)$, $\langle f(w), v\rangle = -\sum_{i\in I} \lambda_i\langle f(w), e_i\rangle \leq 0$, concluding the proof. □

Proof of Corollary 3. The proof is identical to Lemma 3. □

Proof of Corollary 4. The proof is identical to that of Theorem 3, using Corollary 3 in place of Lemma 3. □

Proof of Corollary 5. Since $z_1(t) \leq \overline{M}_{z_1}$ for all $t \geq 0$, this gives $\dot{x}_1 \leq \beta_1\overline{M}_{z_1} - \beta_2 x_1$. Let w_1 solve $\dot{w}_1 = \beta_1\overline{M}_{z_1} - \beta_2 w_1$ with $w_1(0) = x_1(0)$.

Its explicit solution is

$$w_1(t) = \frac{\beta_1 \overline{M}_{z_1}}{\beta_2} + \left[x_1(0) - \frac{\beta_1 \overline{M}_{z_1}}{\beta_2}\right] e^{-\beta_2 t}.$$

By the comparison principle, $x_1(t) \le w_1(t)$ for all $t \ge 0$. Since $w_1(t)$ remains between $w_1(0)$ and its equilibrium $\beta_1 \overline{M}_{z_1}/\beta_2$,

$$x_1(t) \le \max\left\{x_1(0), \frac{\beta_1}{\beta_2}\overline{M}_{z_1}\right\} =: \overline{M}_{x_1} \qquad \text{for all } t \ge 0. \tag{18}$$

Next, using $x_1(t) \le \overline{M}_{x_1}$, the equation for x_2 gives $\dot{x}_2 \le \beta_3 \overline{M}_{x_1} - \beta_4 x_2$. Let w_2 solve $\dot{w}_2 = \beta_3 \overline{M}_{x_1} - \beta_4 w_2$ with $w_2(0) = x_2(0)$. Then

$$w_2(t) = \frac{\beta_3 \overline{M}_{x_1}}{\beta_4} + \left[x_2(0) - \frac{\beta_3 \overline{M}_{x_1}}{\beta_4}\right] e^{-\beta_4 t}.$$

By the comparison principle, $x_2(t) \le w_2(t)$ for all $t \ge 0$. Hence

$$x_2(t) \le \max\left\{x_2(0), \frac{\beta_3}{\beta_4}\overline{M}_{x_1}\right\} =: \overline{M}_{x_2} \qquad \text{for all } t \ge 0. \tag{19}$$

Thus x_1 and x_2 are bounded on $[0, \infty)$. □

Proof of Corollary 6. The proof is identical to that of Lemma 5, with x replaced by $[x_1, x_2]^\top$, $v^\top$ replaced by $[c, d]$, K^* replaced by $K_* := \alpha_3 G/\alpha_4$ with $G = \beta_1\beta_3/(\beta_2\beta_4)$, and γ replaced by $\bar{\gamma} := K_* + c\overline{M}_{x_1} + d\overline{M}_{x_2}$. The key computation is that by the choice of c and d, the x_1- and x_2-terms cancel in $\dot{W}$, giving $\dot{W} = \alpha_4 z_1 (K_* - z_2)$. From this, one shows that W cannot exceed $\bar{\gamma}$: whenever $W(t) > \bar{\gamma}$, we have $z_2(t) > K_*$, which forces $\dot{W}(t) \le 0$, preventing further growth. It then follows that $W(t) \le \max\{W(0), \bar{\gamma}\}$ for all $t \ge 0$. Since $c, d \ge 0$ and $x_1(t), x_2(t) \ge 0$, we have $z_2(t) = W(t) - c x_1(t) - d x_2(t) \le W(t)$. Therefore

$$z_2(t) \le W(t) \le \max\{W(0), \bar{\gamma}\} =: \overline{M}_{z_2} \qquad \text{for all } t \ge 0$$

completing the proof. □

Data availability

No data was used for the research described in the article.

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