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Feedback stabilization of positive nonlinear systems with applications to biological systems

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Abstract— **Various feedback stabilizers based on Sontag's "universal" formula for stabilizing control laws are presented, incorporating restrictions inspired by models from systems biology. The main contribution is an extension of Sontag's "universal" formula for positive nonlinear control systems. More specifically, an auxiliary function is introduced in the feedback interconnection, such that invariance of the positive orthant is retained for the system in closed loop with the "universal" stabilizer. We further state a "universal" event-based stabilizer with bounded controls for positive systems. Two examples inspired by systems biology are presented for illustration and demonstration of the effectiveness of the proposed stabilizers. One example considers the problem of regulating the cortisol level, where the methodology is shown to provide clinically realistic control inputs, suitable for treatment in real life.**

I. INTRODUCTION

Control Lyapunov functions (CLFs) serve as an important tool for stabilization of nonlinear control systems, as they reveal controllability properties of the system. For the class of nonlinear control systems which are affine with respect to the control input, a major result is stated in [1], where the existence of a smooth CLF is shown to be equivalent to the existence of a continuous feedback stabilizer. While obtaining CLFs is difficult, in general, they are worth considering, as they reveal more than the existence of feedback stabilizers. Indeed, given a CLF, one can obtain a continuous, even smooth, "universal" formula for the feedback stabilizer [2]. The feedback law is explicitly given by an algebraic expression involving Lie derivatives of the CLF.

Stemming from the "universal" controller in [2], various extensions have been proposed in the literature. We single out the feedback stabilizer in [3], which provides a bounded control input, given an appropriate CLF. In [4], the concept is generalized to the case for which controls are constrained to be bounded or positive. Finally, in [5], the original "universal" feedback law from [2] is utilized for the construction of a so-called self-triggered event-based controller.

More recently, an approach for constructing CLFs by partitioning the state space was introduced in [6], where a continuous and piecewise afffine (CPA) CLF is computed together with a switching control strategy via a mixed integer linear program. Alternatively, a recursive procedure for computing rational CLFs together with polynomial feedback stabilizers was proposed in [7].

Although the mentioned control strategies provide stabilizing feedback laws for nonlinear systems, practical aspects are not considered, in general, such as satisfying state constraints and the need for piecewise constant inputs. Guaranteeing safe closed-loop trajectories and coping with real-time implementation requirements are relevant objectives towards bridging the gap with real-life applications.

In this paper, we consider the feedback stabilization problem for positive nonlinear control systems, for which the states are constrained to be positive. Given an original positive autonomous system, its controlled counterpart is not guaranteed to be positive for a given feedback stabilizer, see e.g. Figure 1 in Section IV, possibly leading to inadmissible trajectories. While the real closed-loop system can never become nonpositive, its closed-loop model can become physiologically infeasible, potentially leading to unpredicted behaviour when applying the designed controller to the real system, such as performance loss or instability. The feedback stabilization problem of a class of positive linear systems was considered in [8]. Therein, necessary and sufficient conditions for the existence of a stabilizing positiveness-preserving affine state feedback were derived.

The design proposed in this paper provides an explicit expression for the feedback stabilizer and incorporates input constraints, originating from [2], [3], based on a single CLF. Via an auxiliary function in the feedback interconnection, the proposed feedback stabilizers render positiveness of the system invariant under the stabilization procedure. Considering the implementation of the proposed control law in real-life applications, the result is extended via self-triggered event-based stabilizers introduced in [5]. By means of an additional event function, the event-based stabilizer with bounded controls preserves positiveness.

It is worth to point out that state and input constraints can also be resolved using model predictive control (MPC). However, for the associated nonlinear (continuous-time) MPC problem, explicit knowledge of a local stabilizing feedback law and CLF pair is in general required for guaranteeing closed-loop stability [9, Section 5]. In this respect, the explicit feedback stabilizers provided in this paper may serve as a useful tool for designing stabilizing ingredients for nonlinear continuous-time MPC for positive systems.

The remainder of this paper is organized as follows: in Section II, we state some preliminaries and the problem formulation. Section III contains the results for the stabilization of positive nonlinear systems. In Section IV, two examples from systems biology are presented, to show the effectiveness and potential of the results for real-life applications. Conclusions are summarized in Section V.

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II. Preliminaries and problem formulation

A. Notation and definitions

The sets of non-negative and positive integers and non-negative and positive reals are denoted by $\mathbb{N}$, $\mathbb{N}_{>0}$, $\mathbb{R}_{\geq 0}$ and $\mathbb{R}_{>0}$, respectively. Given $a \in \mathbb{N}$, $b \in \mathbb{N}$ such that $a < b$, we denote $\mathbb{N}_{[a:b]} := \{a, a+1, \ldots, b-1, b\}$. A set $\mathcal{S} \subseteq \mathbb{R}^n$ is called ξ-proper if it contains $\xi \in \mathbb{R}^n$ in its interior. A function $z : \mathcal{S} \to \mathbb{R}$, with ξ-proper set $S \subseteq \mathbb{R}^n$, is called positive definite w.r.t. $\xi \in \mathbb{R}^n$ if $z(\xi) = 0$ and $z(x) > 0$ for all $x \in \mathcal{S} \setminus \{\xi\}$. For an $x \in \mathbb{R}^n$, let $\|x\|_2$, or simply $\|x\|$, denote the 2-norm of x. A function $z : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ is called radially unbounded if $\|x\| \to \infty$ implies $z(x) \to \infty$.

Consider the nonlinear continuous-time, time-invariant, system with control input

$$\dot{x} = \bar{f}(x,u), \quad x(0) =: x_0 \tag{1}$$

where $x \in \mathbb{R}^n$, $u \in \mathbb{U} \subseteq \mathbb{R}^m$ and $\bar{f} : \mathbb{R}^m \times \mathbb{R}^n \to \mathbb{R}^n$ is smooth, i.e., infinitely differentiable. We are concerned with the class of control systems which are affine with respect to the input, i.e, $\bar{f}(x,u) = f(x) + g(x)u$ such that

$$\dot{x} = f(x) + g(x)u, \tag{2}$$

where $f : \mathbb{R}^n \to \mathbb{R}^n$ and $g : \mathbb{R}^n \to \mathbb{R}^n \times \mathbb{R}^m$ are smooth. Furthermore, the autonomous system, i.e. for $u = 0$, has a, possibly unstable, equilibrium $x^\star \in \mathbb{R}^n_{\geq 0}$ such that $f(x^\star) = 0$, and is positive, i.e., the positive orthant $\mathbb{R}^n_{\geq 0}$ is an invariant set for (2). The solution of (2) is denoted by $x(t, x_0, u(t))$, or simply $x(t)$.

Definition 2.1: A function $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ is said to be a control Lyapunov function (CLF) for (2) if it is positive definite w.r.t. $x^\star$, radially unbounded and satisfies the decrease condition

$$\inf_{u \in \mathbb{U}} \nabla W^\top(x) f(x) + \nabla W^\top(x) g(x) u < 0, \ \forall x \in \mathbb{R}^n \setminus \{x^\star\}. \tag{3}$$

Given a control law $u = k(x)$, $k : \mathbb{R}^n \to \mathbb{R}^m$, let the closed-loop system be described by

$$\dot{x} = f(x) + g(x)k(x). \tag{4}$$

Definition 2.2: A set $\mathcal{S} \subseteq \mathbb{R}^n$ is called (positively) invariant for (4) if $x(t, x_0, k(x(t))) \in \mathcal{S}$ for all $t \in \mathbb{R}_{\geq 0}$, when $x_0 \in \mathcal{S}$.

When a CLF for system (2) is known, explicit formulas for a feedback stabilizer that render the closed-loop system asymptotically stable exist, see e.g. [2] and [3]. We will highlight the original "universal" controller [2] in the next subsection.

B. Stabilization via "universal" controllers

The controller that serves as a base for the results in the following section is the so-called "universal" controller, introduced by Sontag in [2]. This controller is a smooth (on $\mathbb{R}^n \setminus \{x^\star\}$) feedback stabilizer that exists whenever a smooth CLF $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ exists for system (2) with $u \in \mathbb{U} = \mathbb{R}^m$ [2, Theorem 1]. The feedback $k : \mathbb{R}^n \to \mathbb{R}^m$, is given by an expression involving Lie derivatives of the CLF W:

$$k(x) := \begin{cases} -\frac{a(x) + \sqrt{a^2(x) + \|b(x)\|^4}}{\|b(x)\|^2} b^\top(x), & \text{if } \|b(x)\| > 0, \\ 0, & \text{if } \|b(x)\| = 0, \end{cases}$$

with $a(x) := \nabla W^\top(x) f(x)$ and $b(x) := \nabla W^\top(x) g(x)$. From [2, Theorem 1] we have that k is continuous at $x^\star$ whenever a small control property for the CLF W is satisfied.

C. Problem formulation

Explicit expressions for feedback stabilizers exist [2], [3] and can be implemented in a sample-and-hold fashion via event-based stabilization [5], [10]. Nevertheless, for positive systems, or more specifically biological systems, one should render positiveness of the system invariant under the closed-loop stabilization, in order to attain a physiologically sensible controller. That is, we require a stabilizing controller such that the positive orthant remains positively invariant for the closed-loop system, as stated in the following problem:

Problem 2.1: Design a control law $u = k(x)$ for system (2) such that the equilibrium $x^\star \in \mathbb{R}^n_{\geq 0}$ of the closed-loop system

$$\dot{x} = f(x) + g(x)k(x) \tag{5}$$

is asymptotically stable and the closed-loop system remains positive, i.e., the positive orthant is an invariant set for (5).

III. Stabilization of positive systems

A. A "universal" stabilizer for positive systems

In the following we provide a construction for a control input, based on a candidate CLF, which globally asymptotically stabilizes the equilibrium $x^\star$ and preserves positiveness of the system, by utilizing an adapted version of the feedback presented in [2]. To ensure invariance of the positive orthant, an auxiliary function is introduced in the feedback to guarantee necessary conditions at the boundaries of the positive orthant. More specifically, we consider system (2) with input $u = vp(x_i)$, where $p : \mathbb{R} \to \mathbb{R}$ is any smooth function such that $p(0) = 0$. Smoothness of $p : \mathbb{R} \to \mathbb{R}$ is not necessary for stabilization, but it will render the feedback stabilizer in Theorem 3.1 and Corollary 3.2 smooth, see [2, Theorem 1] and [3], respectively. For the remainder of this section we consider the case when $u \in \mathbb{R}$ is scalar, i.e. $m = 1$, unless otherwise stated.

Theorem 3.1: Consider system (2) with input $u = vp(x_i) \in \mathbb{U} = \mathbb{R}$, where $p : \mathbb{R} \to \mathbb{R}$, $p(0) = 0$, is a smooth function, such that

$$\dot{x} = f(x) + \tilde{g}(x)v, \tag{6}$$

where $\tilde{g}(x) := g(x)p(x_i)$. Assume that $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$, $W(x^\star) = 0$, is a CLF for (6), with the input applied at the i-th entry, i.e. $g_j(x) = 0$ for all $j \in \mathbb{N}_{[1:n]} \setminus \{i\}$. Then, the feedback $v = k(x)$, with

$$k(x) := \begin{cases} -\frac{a(x) + \sqrt{a^2(x) + b^4(x)}}{b(x)}, & \text{if } |b(x)| > 0, \\ 0, & \text{if } |b(x)| = 0, \end{cases}$$

where $a(x) := \nabla W^\top(x) f(x)$, $b(x) := \nabla W^\top(x)\tilde{g}(x)$, globally asymptotically stabilizes $x^\star$ and the closed-loop system

$$\dot{x} = f(x) + \tilde{g}(x)k(x)$$

remains positive, i.e., the positive orthant remains positively invariant.

Proof: First, we prove that the closed-loop system is globally asymptotically stable. We need that

$$\nabla W^\top(x)(f(x) + g(x)p(x_i)v) < 0, \quad \forall x \in \mathbb{R}^n \setminus \{x^\star\},$$

with $v = k(x)$. Indeed, we have

$$\begin{aligned}
&\nabla W^\top(x)(f(x) + g(x)p(x_i)k(x)) \\
&= a(x) - \frac{a(x) + \sqrt{a^2(x) + b^4(x)}}{b(x)} b(x) \\
&= -\sqrt{a^2(x) + b^4(x)} < 0 \quad \forall x \in \mathbb{R}^n \setminus \{x^\star\}.
\end{aligned}$$

Next, we show that the closed-loop system remains positive. We need that

$$\dot{x}_j \geq 0, \quad \forall x \in \mathcal{S}_j := \{x \in \mathbb{R}^n_{\geq 0} \,|\, x_j = 0\},$$

for all $j \in \mathbb{N}_{[1:n]}$. For all $j \in \mathbb{N}_{[1:n]} \setminus \{i\}$, we have

$$\dot{x}_j = f_j(x) \geq 0, \quad \forall x \in \mathcal{S}_j,$$

by the definition of $g(x)$ and since the original system is positive. For the case $j = i \in \mathbb{N}_{[1:n]}$, we have $u = k(x)p(x_i) = 0$ for all $x \in \mathcal{S}_i$ since $b(x) = 0$ for all $x \in \mathcal{S}_i$. But then

$$\dot{x}_i = f_i(x) \geq 0 \quad \forall x \in \mathcal{S}_i,$$

which completes the proof. ∎

An immediate generalization of Theorem 3.1 to the multi-input case with no restriction on $g(x)$ is the following result.

Corollary 3.1: Consider system (2) with $u = vp(x) \in \mathbb{U} = \mathbb{R}^m$, $m \in \mathbb{N}_{>0}$, with $p : \mathbb{R}^n \to \mathbb{R}$, $p(x) = 0$ for all $x \in \partial\mathcal{P}$, where

$$\partial\mathcal{P} := \bigcup_{i \in \mathbb{N}_{[1:n]}} \left\{x \in \mathbb{R}^n_{\geq 0} \,|\, x_i = 0\right\}.$$

Assume that $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ is a CLF for

$$\dot{x} = f(x) + \tilde{g}(x)v, \tag{7}$$

where $\tilde{g}(x) := g(x)p(x)$. Then the feedback $v = k(x)$, k defined as in Section II-B, with $a(x) = \nabla W^\top(x) f(x)$, $b(x) = \nabla W^\top(x)\tilde{g}(x)$, globally asymptotically stabilizes $x^\star$ and the closed-loop system

$$\dot{x} = f(x) + \tilde{g}(x)k(x)$$

remains positive.

A question that arises at this point is: given a CLF W for (2), is W also a CLF for the transformed system (7)? The following proposition provides an answer to this question.

Proposition 3.1: Let $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$ be a CLF for (2) with $\mathbb{U} = \mathbb{R}^m$, $m \in \mathbb{N}_{>0}$, and let $\mathcal{Z}_0 := \{x \in \mathbb{R}^n \setminus \partial\mathcal{P} \,|\, p(x) = 0\} = \emptyset$. Then W is a CLF for (7) if and only if $\nabla W^\top(x) f(x) < 0$ for all $x \in \mathcal{Z}_1 := \partial\mathcal{P} \setminus \{x^\star\}$.

Proof: ($\Leftarrow$) Assume $\nabla W^\top(x) f(x) < 0$ for all $x \in \mathcal{Z}_1$, $\mathcal{Z}_0 = \emptyset$ and W is a CLF for (2), i.e., for all $x \in \mathbb{R}^n \setminus \{x^\star\}$ there is a $u \in \mathbb{R}^m$ so that

$$\nabla W^\top(x) f(x) + \nabla W^\top(x) g(x) u < 0.$$

Then for all $x \in \mathcal{Z}_2 := \mathbb{R}^n \setminus (\partial\mathcal{P} \cup \{x^\star\})$ there is a $v \in \mathbb{U}$ so that

$$\nabla W^\top(x) f(x) + \nabla W^\top(x)\tilde{g}(x) v < 0. \tag{8}$$

Indeed, take $v = \frac{u}{p(x)}$, which exists since $\mathcal{Z}_0 = \emptyset$, then $\nabla W^\top(x)\tilde{g}(x)v = \nabla W^\top(x) g(x) u$, so that (8) holds for all $x \in \mathcal{Z}_2$. Moreover, for all $x \in \mathcal{Z}_1 = \partial\mathcal{P} \setminus \{x^\star\}$, there is a $v \in \mathbb{U}$ so that (8) is true, since for all $x \in \mathcal{Z}_1$

$$\nabla W^\top(x) f(x) + \nabla W^\top(x)\tilde{g}(x) v = \nabla W^\top(x) f(x) < 0.$$

Finally, $\mathcal{Z}_1 \cup \mathcal{Z}_2 = \mathbb{R}^n \setminus \{x^\star\}$, which yields the assertion.

($\Rightarrow$) Assume W is a CLF for (7). Then for all $x \in \mathbb{R}^n \setminus \{x^\star\}$ there is a $v \in \mathbb{U}$ so that (8) holds. Specifically, for all $x \in \mathcal{Z}_1$, there is a $v \in \mathbb{U}$ so that

$$0 > \nabla W^\top(x) f(x) + \nabla W^\top(x)\tilde{g}(x) v = \nabla W^\top(x) f(x)$$

and hence $\nabla W^\top(x) f(x) < 0$ for all $x \in \mathcal{Z}_1$. ∎

Note that the latter result holds *mutatis mutandis* for the transformed system (6), which is a special case of (7).

B. A bounded stabilizer for positive systems

Control inputs are constrained to be bounded in amplitude, in general. We state a slightly adapted version of the universal formula for stabilization with bounded controls from [3], for positive systems. The proposed feedback ensures that the input remains in the open unit ball centered at the origin $\mathbb{B} := \{\mu \in \mathbb{R}^m \,|\, \|\mu\|_2 < 1\}$, while ensuring stability and retaining positiveness of the closed-loop system.

Corollary 3.2: Consider system (2) with input $u = vp(x_i) \in \mathbb{U} = \mathbb{B}$, where $p : \mathbb{R} \to [-1, 1]$, $p(0) = 0$, is a smooth function, such that

$$\dot{x} = f(x) + \tilde{g}(x)v, \tag{9}$$

where $\tilde{g}(x) := p(x_i)g(x)$. Assume that $W : \mathbb{R}^n \to \mathbb{R}_{\geq 0}$, $W(x^\star) = 0$, is a CLF for (9), with the input applied at the i-th entry, i.e. $g_j(x) = 0$ for all $j \in \mathbb{N}_{[1:n]} \setminus \{i\}$. Then, the feedback $v = k_b(x)$, with

$$k_b(x) = \begin{cases} -\frac{a(x) + \sqrt{a^2(x) + b^4(x)}}{b(x)(1 + \sqrt{1 + b^2(x)})}, & \text{if } |b(x)| > 0, \\ 0, & \text{if } |b(x)| = 0, \end{cases}$$

where $a(x) := \nabla W^\top(x) f(x)$, $b(x) := \nabla W^\top(x)\tilde{g}(x)$, globally asymptotically stabilizes $x^\star$, the closed-loop system

$$\dot{x} = f(x) + \tilde{g}(x)k_b(x)$$

remains positive and the input $u = k_b(x)p(x_i) \in \mathbb{B}$.

Proof: First, we show that $x^\star$ is globally asymptotically stable with $u = k_b(x)p(x_i)$, i.e.

$$\nabla W^\top(x)(f(x) + g(x)p(x_i)v) < 0, \quad \forall x \in \mathbb{R}^n \setminus \{x^\star\},$$

with $v = k_b(x)$. Indeed, we have

$$\begin{aligned}
&\nabla W^\top(x) f(x) + g(x)p(x_i)k_b(x)) \\
&= a(x) + b(x)k_b(x) \\
&= a(x) - \frac{a(x) + \sqrt{a^2(x) + b^4(x)}}{1 + \sqrt{1 + b^2(x)}} \\
&= a(x) + b(x)\alpha(a(x), b(x)),
\end{aligned}$$

with

$$\alpha(a, b) := \begin{cases} -\frac{a+\sqrt{a^2+b^4}}{b(1+\sqrt{1+b^2})}, & \text{if } |b| > 0, \\ 0, & \text{if } |b| = 0. \end{cases}$$

Consider the set $\mathbb{D} := \{(a, b) \in \mathbb{R}^2 \mid a < |b|\}$. Then we have $(a(x), b(x)) \in \mathbb{D}$ for all $x \in \mathbb{R}^n \setminus \{x^\star\}$, since condition (3) with $\mathbb{U} = \mathbb{B}$ is equivalent to $a(x) < |b(x)|$ [3]. But then $\dot{W}(x(t)) < 0$ since $a + b\alpha(a, b) < 0$ for all $(a, b) \in \mathbb{D}$ [3, Lemma 2.3].

Proving positiveness of the closed-loop system is trivial. Indeed, we need that

$$\dot{x}_j \geq 0, \quad \forall x \in \mathcal{S}_j := \{x \in \mathbb{R}^n_{\geq 0} \mid x_j = 0\},$$

for all $j \in \mathbb{N}_{[1:n]}$. For all $j \in \mathbb{N}_{[1:n]} \setminus \{i\}$, we have that

$$\dot{x}_j = f_j(x) \geq 0, \quad \forall x \in \mathcal{S}_j,$$

by the definition of $g(x)$ and since the original system is positive. For $j = i \in \mathbb{N}_{[1:n]}$ we have $\dot{x}_i = f_i(x) \geq 0$ for all $x \in \mathcal{S}_i$, by the definition of $k_b(x)$, since $b(x) = 0$ for all $x \in \mathcal{S}_i$.

Finally, we show that the control $u = k_b(x)p(x_i) \in \mathbb{B}$ for all $x \in \mathbb{R}^n$. We have

$$|k_b(x)| = |\alpha(a(x), b(x))| < 1,$$

since $\alpha(a, b) < 1$ for all $(a, b) \in \mathbb{D}$, [3, Lemma 2.3]. But then $\|u\| = |k_b(x)||p(x_i)| < |p(x_i)| \leq 1$, and therefore $u \in \mathbb{B}$. ■

C. A bounded event-based stabilizer for positive systems

So far, explicit positiveness-preserving (bounded) feedback stabilizers were derived. The possible necessity for piecewise constant inputs in practical applications is in general, however, not met by these feedback stabilizers. In the following result we propose an event-based stabilizer based on Corollary 3.2, which retains positiveness of the system via a dedicated event function. The resulting stabilizer is an adaptation of the bounded event based controller in [10, Theorem II.1] for positive systems, which in turn extends the controller in [5] that does not consider input constraints.

Corollary 3.3: Consider again system (2) with $\mathbb{U} = \mathbb{B}$ and assume that W is a CLF for (9). Then the event-based feedback $u = k_b(\xi)p(\xi_i)$, $p : \mathbb{R} \to [-1, 1]$, $p(0) = 0$, with

$$k_b(\xi) = \begin{cases} -\frac{a(\xi)+\sqrt{a^2(\xi)+b^4(\xi)}}{b(\xi)(1+\sqrt{1+b^2(\xi)})} & \text{if } |b(\xi)| > 0, \\ 0 & \text{if } |b(\xi)| = 0, \end{cases}$$

$$\begin{aligned}
e(x, \xi) &:= -a(x) - b_o(x)k_b(\xi)p(\xi_i) \\
&\quad + \sigma \frac{a(x)\sqrt{1 + b^2(x)} - \sqrt{a^2(x) + b^4(x)}}{1 + \sqrt{1 + b^2(x)}}, \\
e_p(x, \xi) &:= f_i(x) + g_i(x)k(\xi)p(\xi_i) + |e^{-|x_i|} - 1|z,
\end{aligned}$$

where $\sigma \in [0, 1)$, $z \in \mathbb{R}_{>0}$, $a(x) := \nabla W^\top(x)f(x)$, $b(x) := \nabla W^\top(x)g(x)p(x_i)$, $b_o(x) := \nabla W^\top(x)g(x)$ and

$$\xi = \begin{cases} x & \text{if } (e(x, \xi) \leq 0) \vee (e_p(x, \xi) < 0), x \in \mathbb{R}^n \setminus \{x^\star\}, \\ \xi & \text{elsewhere}, \end{cases}$$

with $\xi(0) = x(0)$, globally asymptotically stabilizes $x^\star$, the closed-loop system

$$\dot{x} = f(x) + g(x)p(\xi_i)k_b(\xi)$$

remains positive and the input $u = k_b(\xi)p(\xi_i) \in \mathbb{B}$.

Proof: We first prove that the closed-loop system is GAS; that is $\dot{W}(x(t)) < 0$ for all $t \in \mathbb{R}_{\geq 0}$, $x_0 \in \mathbb{R}^n \setminus \{x^\star\}$. Let $\tau \in \mathbb{R}_{\geq 0}$ denote the time instant, at which an update of the state ξ is performed and let ξ be the corresponding state, i.e., $\xi := \xi(\tau) = x(\tau)$. Define $\bar{W}(t) := W(x(t))$, then

$$\begin{aligned}
\dot{\bar{W}}(\tau) &= \nabla W^\top(\xi)f(\xi) + \nabla W^\top(\xi)g(\xi)p(\xi_i)k_b(\xi) \\
&= a(\xi) + b(\xi)k_b(\xi) \\
&= a(\xi) + b(\xi)\alpha(a(\xi), b(\xi)) < 0,
\end{aligned}$$

since $(a(\xi), b(\xi)) \in \mathbb{D}$, as W is a CLF for $\dot{x} = f(x) + g(x)p(x_i)v$ (see also the proof of Corollary 3.2). With the updated control, the event function is

$$\begin{aligned}
e(\xi, \xi) &= -a(\xi) - b_o(\xi)p(\xi_i)k_b(\xi) \\
&\qquad + \sigma \frac{a(\xi)\sqrt{1 + b^2(\xi)} - \sqrt{a^2(\xi) + b^4(\xi)}}{1 + \sqrt{1 + b^2(\xi)}} \\
&= -a(\xi) - b(\xi)k_b(\xi) \\
&\qquad + \sigma \frac{a(\xi)\sqrt{1 + b^2(\xi)} - \sqrt{a^2(\xi) + b^4(\xi)}}{1 + \sqrt{1 + b^2(\xi)}} \\
&= (\sigma - 1) \underbrace{\frac{a(\xi)\sqrt{1 + b^2(\xi)} - \sqrt{a^2(\xi) + b^4(\xi)}}{1 + \sqrt{1 + b^2(\xi)}}}_{=\dot{\bar{W}}(\tau) < 0} \\
&> 0.
\end{aligned}$$

Between switching instants, we clearly have

$$\begin{aligned}
0 < e(x, \xi) &= -\underbrace{(a(x) + b_o(x)k_b(\xi)p(\xi_i))}_{=\dot{W}(x(t))} \\
&\qquad + \sigma \frac{a(x)\sqrt{1 + b^2(x)} - \sqrt{a^2(x) + b^4(x)}}{1 + \sqrt{1 + b^2(x)}}
\end{aligned}$$

by continuity and the decrease of W along the trajectory is directly revealed.

Next, we show positiveness of the closed-loop system. Suppose that the positive orthant is not invariant. Then there exists an $x \in \mathcal{S}_i$ such that $\dot{x}_i < 0$, i.e., $f_i(x) + g_i(x)k_b(\xi)p(\xi_i) < 0$. But then $e_p(x, \xi) < 0$ such that $\xi = x$, by definition, and thus

$$e_p(x, x) = f_i(x) + g_i(x)k_b(x)p(x_i) = f_i(x) \geq 0.$$

We arrive at a contradiction, thus we can conclude that the system remains positive.

Finally, $u = k_b(\xi)p(\xi_i) \in \mathbb{B}$, since $k_b(x)p(x_i) \in \mathbb{B}$ for all $x \in \mathbb{R}^n$ (see the proof of Corollary 3.2). ■

Remark 3.1: The control input is $u = k_b(\xi)p(\xi_i)$, i.e., we also "sample-and-hold" $p(\xi_i)$, while we assume W to be a CLF for the system $\dot{x} = f(x) + g(x)p(x_i)v$. The key here is that the state x and "memory" state ξ coincide when a switch is performed, so that the event function is positive at the switching time instant and consequently remains positive between switching time instants, by continuity.

Remark 3.2: The idea behind the construction of e_p is that it coincides with the dynamics at the i-th entry for all $x \in \mathcal{S}_i$, i.e., $e_p(x, \xi) = f_i(x) + g_i(x)k(\xi)p(\xi_i)$ for all $x \in \mathcal{S}_i$. If we look at $|e^{-|x_i|} - 1|z$, we see that it goes to z asymptotically and vanishes at $x_i = 0$. This means that if we choose $z \in \mathbb{R}_{>0}$ large enough, the event function e_p can only become negative close to or on $\mathcal{S}_i$.

IV. Numerical examples

A. Example 1: Toggle switch in Escherichia coli

Consider the dimensionless model representing the behavior of a toggle switch in Escherichia coli [11], given by

$$\begin{cases} \dot{x}_1 &= \frac{\alpha_1}{1+x_2^\beta} - x_1, \\ \dot{x}_2 &= \frac{\alpha_2}{1+x_1^\gamma} - x_2, \end{cases} \tag{10}$$

where x_1 and x_2 represent the concentration of repressor 1 and 2, respectively, and the parameters are given by $\alpha_1 = 1.3$, $\alpha_2 = 1$, $\beta = 3$ and $\gamma = 10$. This system has two stable equilibria $E_1 = (0.6668\ 0.9829)^\top$, $E_3 = (1.2996\ 0.0678)^\top$ and one unstable equilibrium $E_2 = (0.8807\ 0.7808)^\top$. Our goal is to stabilize the unstable equilibrium $x^\star := E_2$, located at the separatrix between E_1 and E_3, with the input acting on x_2. That is, let $g(x) = (0\ 1)^\top$ and let $f(x)$ describe the autonomous system (10), such that the open-loop system considered is $\dot{x} = f(x) + g(x)u$.

Consider the quadratic candidate CLF $W(x) = (x - x^\star)^\top P(x - x^\star)$, where

$$P = 10 \begin{pmatrix} 1.1490 & 0.2826 \\ 0.2826 & 0.6311 \end{pmatrix},$$

such that the feedback $u = k_b(x)p(x_2)$ is applied, with $k_b(x)$ as in Corollary 3.2. We select $p : \mathbb{R} \to \mathbb{R}$, $p(\zeta) = e^{-4\zeta} - 1$. Note that $p(0) = 0$, as required. Figure 1 shows the vector field corresponding to the closed-loop system together with some level sets of W and a trajectory initiated in $(4\ 0)^\top$ in red. For comparison we show a trajectory with appliance of the "universal" controller from [2], i.e., the controller in Theorem 3.1 with $p(\zeta) = 1$, in black. It can be seen that the trajectory in black leaves the positive orthant, while the trajectory in red resides in the positive orthant. Figure 2 shows the inputs corresponding to the trajectories initiated in $(4\ 0)^\top$.

Next, the bounded event-based feedback $u = k_b(\xi)p(\xi_2)$ from Corollary 3.3, is applied, which guarantees that the closed-loop system remains positive. We set $z := 1000$ and $\sigma := 0.3$. Figure 1 shows a trajectory for the closed-loop system initiated in $(4\ 0)^\top$ in green. For comparison, the bounded event-based feedback $u = k_b(\xi)$ from [10, Theorem II.1] is applied, which is equivalent to the controller

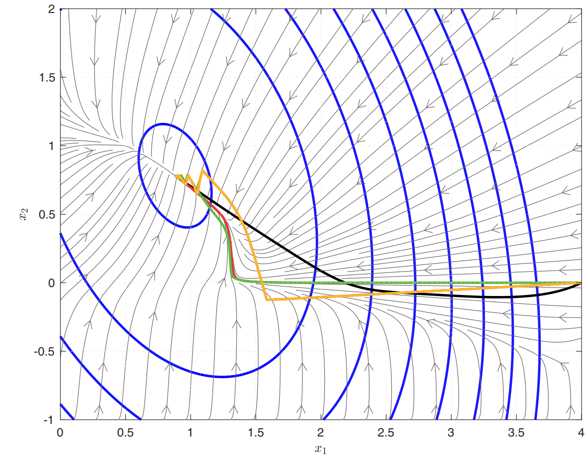

Fig. 1. Some level sets of W-blue and trajectories initiated in $(4\ 0)^\top$ for Example 1 with $u = k_b(\xi)$-yellow, $u = k_b(\xi)p(\xi_2)$-green, $u = k_b(x)p(x_2)$-red and the controller from [2]-black.

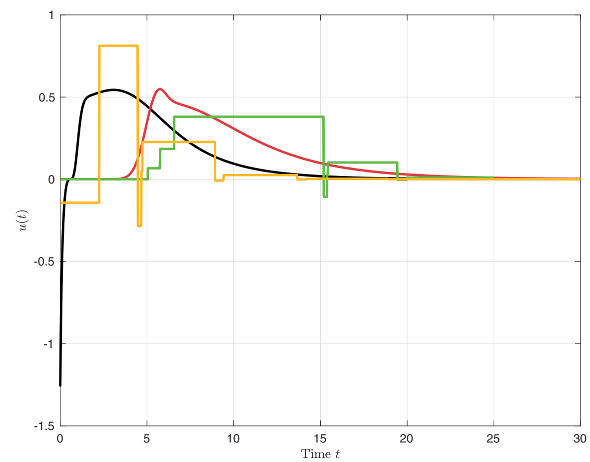

Fig. 2. Inputs $u(t) = k_b(\xi(t))$-yellow, $u(t) = k_b(\xi(t))p(\xi_2(t))$-green, $u(t) = k_b(x(t))p(x_2(t))$-red and the controller from [2]-black.

in Corollary 3.3 with $p(\zeta) = 1$ and $e_p(x, \xi) = c$ for some $c \in \mathbb{R}_{\geq 0}$. Figure 1 shows the resulting trajectory in yellow, which leaves the positive orthant, i.e., the positive orthant is not positively invariant. The corresponding inputs $u(t) = k_b(\xi(t))p(\xi_2(t))$ and $u(t) = k_b(\xi(t))$ are shown in Figure 2, in green and yellow, respectively.

B. Example 2: Control of the cortisol level within the HPA axis

Consider the model representing the behavior of the hypothalamic-pituitary-adrenal gland (HPA) axis from [12], given by

$$\begin{cases} \dot{x}_1 &= \frac{k_{i1}}{k_{i1}+x_4} - k_{cd}x_1, \\ \dot{x}_2 &= \frac{k_{i2}x_1}{k_{i2}+x_3x_4} - k_{ad}x_2, \\ \dot{x}_3 &= \frac{(x_3x_4)^2}{k+(x_3x_4)^2} + k_{cr} - k_{rd}x_3, \\ \dot{x}_4 &= x_2 - x_4, \end{cases} \tag{11}$$

with the parameters given by $k_{i1} = k_{i2} = 0.1$, $k_{cd} = 1$, $k_{ad} = 10$, $k_{cr} = 0.05$, $k_{rd} = 0.9$ and $k = 0.001$. This system possesses two stable equilibria E_1 and E_2, which

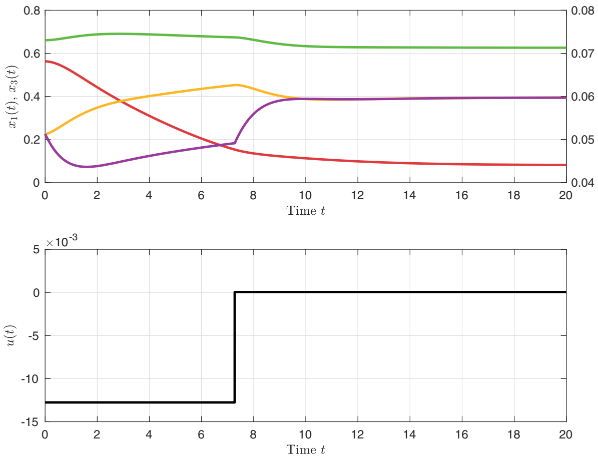

Fig. 3. Input $u(t) = k_b(\xi(t))p(\xi_4(t))$ and states $x_1(t)$-green, $x_2(t)$-yellow, $x_3(t)$-red, $x_4(t)$-violet for the HPA axis.

are unhealthy and healthy, respectively. The unhealthy equilibrium E_1 represents an abnormal low cortisol concentration (x_4) corresponding to hypocortisolism. The goal is to redirect trajectories to the healthy equilibrium $x^\star := E_2$.

We propose to compute a clinically realistic feedback stabilizer, considering both input and state constraints (positiveness), via an input $u \in \mathbb{B}$ such that $\dot{x} = f(x) + g(x)u$, with $g(x) = (0\,0\,0\,1)^\top$, implying that the control input will act on the cortisol state x_4. In [13] it was shown that manipulating the cortisol concentration is a plausible strategy for achieving this goal. Therein an unconstrained model predictive controller was utilized, which turned out to generate non-clinically realistic input values. Thereto, a suboptimal manually constructed control strategy was proposed in the form of an intervention on the cortisol concentration. In [14, Section 6.4.2], the original "universal" controller from [2] was applied via a quadratic CLF. Therein, a different model was used, but it is noted that the same reasoning applies to the well functioning of the HPA axis (11).

We will construct a bounded event-based feedback stabilizer for positive systems via Corollary 3.3. Consider the candidate CLF $W : \mathbb{R}^4 \to \mathbb{R}_{\geq 0}$, $W(x) = (x - x^\star)^\top P(x - x^\star)$, where P satisfies the equality

$$\left(\frac{\partial f(x)}{\partial x}\right)^\top_{x=x^\star} P + P\left(\frac{\partial f(x)}{\partial x}\right)_{x=x^\star} = -Q, \qquad (12)$$

with $Q = 0.08I$ and consider the feedback $u = k_b(\xi)p(\xi_4)$ with $p(\zeta) := e^{-100\zeta} - 1$, $\sigma := 0.9$ and $z := 1000$. Figure 3 shows the simulation results for the closed-loop system with $x(0) = E_1$, i.e., the trajectory is initialized in the unhealthy equilibrium of the autonomous system. The negative supplement of cortisol concentration corresponds to a pharmaceutical removal of circulating cortisol [13]. Note that the control input $u(t) = k_b(\xi(t))p(\xi_4(t))$ closely resembles the clinically realistic treatment in [13], up to scaling, cf. [13, Figure 4]. The manually constructed control strategy from [13] is therefore secured by the bounded event-based feedback stabilizer in Corollary 3.3.

V. Conclusions

For a specific class of positive nonlinear systems, we have proposed various "universal" feedback stabilizers that retain the positive orthant invariant for the resulting closed-loop system. The results were extended for event-based stabilization, aiming at implementation of the feedback stabilizers for real-life applications. By two examples from systems biology, we have shown that the proposed feedback stabilizers render positiveness of the systems invariant under the stabilization procedure, such that the closed-loop system remains biologically admissible, as opposed to the original "universal" feedback stabilizer. Via an application to a benchmark four-state HPA-axis model, we have shown that the bounded event-based stabilizer for positive systems can even deliver clinically realistic treatment strategies, while guaranteeing positiveness and providing a systematic way for the construction of such a feedback, as opposed to manually constructed interventions.

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