Control of a Noncooperative Positive Nonlinear System by Augmented Positive Linear System Regulation

Guanyun Liu and Amor A. Menezes

Abstract— **Positive systems, which are systems whose states are always non-negative, can have both positive linear and positive nonlinear approximations that are valid dynamical models in a prescribed domain. When a linearization of a nonlinear system in a domain near an operating point is equivalent to another linear system representation, a reference-tracking controller for that linear system should also achieve reference-tracking control of the nonlinear system in that domain. Here, we show that only if a linearized positive nonlinear system (PNS) is a positive system (i.e., the PNS is cooperative) will a reference-tracking controller for an equivalent positive linear system realization achieve similar results on the nonlinear system. For an example noncooperative PNS of human blood coagulation, where a published reference-tracking controller assumed a positive linear plant, we develop feedforward and feedback controllers that augment the prior controller to overcome noncooperativity and similarly control the positive nonlinear model.**

Index Terms— **Compartmental and positive systems, biomolecular systems, healthcare and medical systems.**

I. Introduction

POSITIVE systems are prevalent in economics [1], thermodynamics [2], communication networks [3], and physiology [4], where naturally-occurring non-negative states capture physical quantities such as spending, absolute temperature, information, and biochemical concentration, respectively. Positivity is an innate feature in these systems: given non-negative initial conditions and input signals, the states remain in the positive orthant for all time without additional constraints. Positive linear systems (PLSs) are well studied [5], and controllability and reachability results have long existed [6]–[8] for conditions that are more restrictive [9] than those for classical linear systems. The stability and observability of PLSs have also been described [10]–[13].

Unfortunately, positive nonlinear systems (PNSs) are not as well studied as PLSs, in part because it often suffices to linearize the PNS near an operating point or equilibrium and to then apply established theory. PLS theory has been generalized to the nonlinear case [14]–[16]. However, these results are often applicable only to a class of PNSs known as cooperative PNSs, which are systems whose linearization is also a positive system.

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The class of noncooperative PNSs (NPNSs) — PNSs whose linearization is not a positive system — is an important one. NPNSs arise when linearizing around a non-zero equilibrium. Recent results exist on NPNS controllability [17], observability [18], stability [19], stabilizability [20], and reachability [21]. However, the general NPNS control problem remains open. Models of biochemical networks are frequently NPNSs, and thus techniques to regulate these systems are desired for satisfactory biological control.

Biological system models are innately asymptotically stable due to inherent protein concentration degradation (negative) terms in their dynamics. This fact can be leveraged during reference-tracking control by trading-off positive inputs with natural degradation and accepting some oscillatory behavior during tracking, particularly if there are system delays [22]. But not all NPNS states are reachable. A recent cancer chemotherapy study [23] showed that developing a controller for a linearized NPNS to reach the origin of the state space in finite, or even infinite, time was impossible due to system properties [23], and only control to other equilibria was possible in some cases. Hence, detailed system dynamics knowledge is necessary for control design, which is a tall order for biological systems due to incomplete understanding, multiple state interactions, and stochasticity. The resultant feedback control can switch between different linearizations at various equilibria, and harness or avoid different basins of attraction.

In [22], we designed a reference-tracking controller for a biological PLS with input nonlinearities, and in [24], we updated the model dynamics to be a biological PNS. At the typical equilibrium, a transfer function of the linearized dynamics of [24] has the same transfer function as the plant in [22]. The motivation to develop the nonlinear model in [24] was to use states that were experimentally measurable. Typically, when a linearization of a nonlinear system in a domain near an operating point is equivalent to another linear system representation, a reference-tracking controller for that linear system should also achieve reference-tracking control of the nonlinear system in that domain. We applied the controller from [22] to the dynamics in [24], C1 in Fig. 1. Surprisingly, Fig. 2, where nonlinear model states are in blue, the published controller only manipulated the state that received the input (top row), and two states did not move from their initial conditions (middle two rows); thus, the closed-loop system did not achieve reference-tracking of the output state (bottom row). When we applied the published controller to the linearized dynamics of [24], red trajectories in Fig. 2, we found that an intermediate state (second row) goes negative despite output

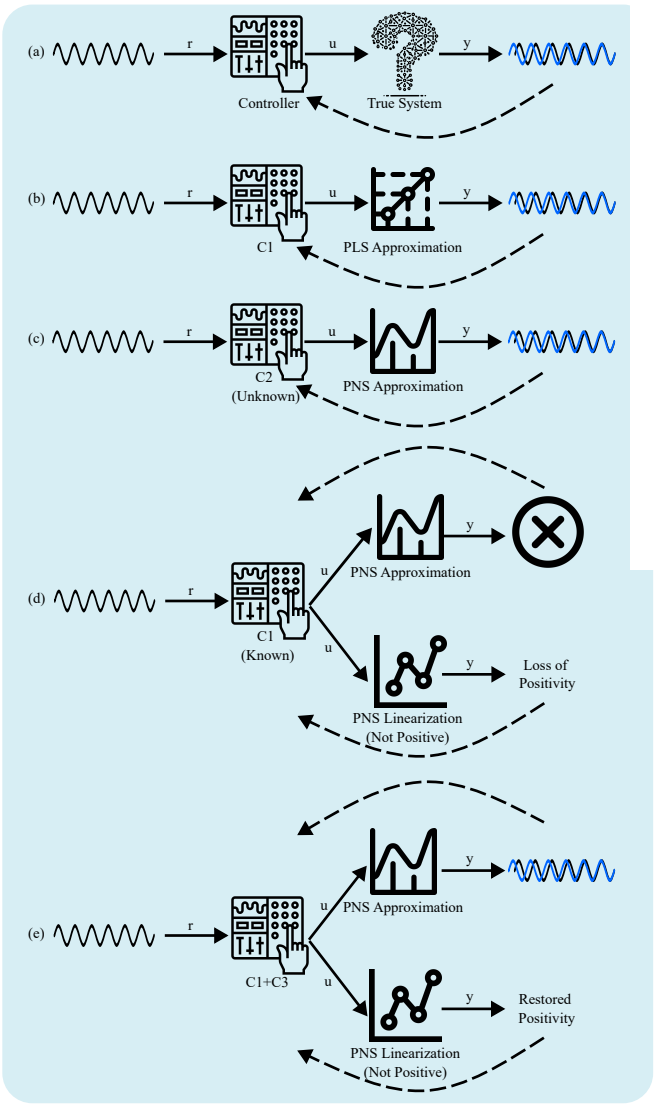

Fig. 1. Paper overview. (a) Our overarching control problem is to design a reference-tracking controller for a highly-complex, poorly characterized, single output, positive system. (b) We assume that there exists a PLS approximation of the unknown system for which a satisfactory reference-tracking controller C1 has already been designed. (c) We also assume that there exists a PNS approximation of the unknown system for which we would like to design a satisfactory reference-tracking controller C2. (d) Even if a linearization of the PNS in part (c) near an operating point yields a linear system that is equivalent to the PLS in part (b), direct application of controller C1 to the PNS as controller C2 cannot always satisfactorily track a reference, and we show here that unsatisfactory results occur when the PNS linearization is not positive. Specifically, unsatisfactory results occur for the class of NPNSs. (e) For this class of systems, we present two forms of controller C3 that overcomes noncooperativity. When C3 is augmented with C1, both controllers together constitute the satisfactory reference-tracking controller C2.

reference-tracking (bottom row). Such negativity cannot occur with the nonlinear model, which turns out to be a NPNS.

This paper recovers the control performance of [22] for the NPNS in [24]. Our intellectual contributions include:

- Insights into positivity loss during the linearization of several biochemical network NPNSs.
- Hybrid phenomenological and mechanistic modeling through non-minimal realizations, so that biological states are meaningful and controller design is simplified.

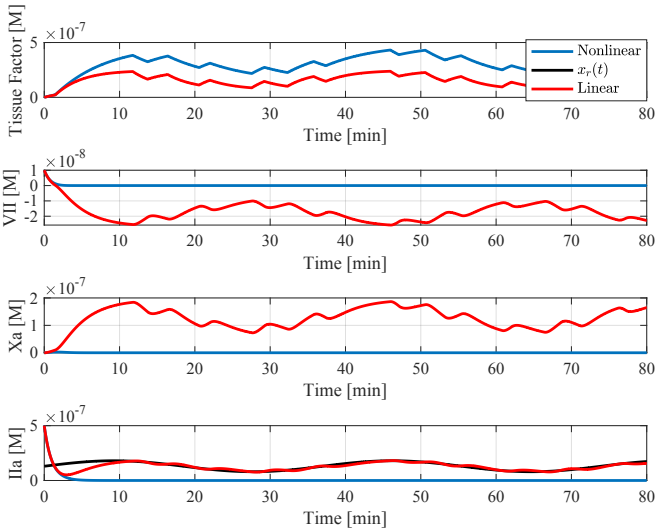

Fig. 2. The reference-tracking controller from [22], C1, applied to a PNS from [24] (blue) is unsuccessful (bottom row). Controller application to the system linearization (red) is successful, but a state is driven negative (second row).

- Feedforward and feedback controllers that overcome noncooperativity (Theorem 1) when controlling NPNSs.

The remainder of this paper is as follows. Section II details biochemical NPNSs and their control challenges. Section III develops control laws to address these challenges. Section IV assesses controller performance on the example biochemical NPNS of [24]. Section V presents concluding remarks.

II. Noncooperative Positive Nonlinear Systems

A. Notation and Preliminaries

Let $\mathbb{R}$ denote the set of real numbers; let $\mathbb{R}^n$ and $\mathbb{R}^{n\times m}$ denote the n-dimensional and $n\times m$-dimensional real spaces, respectively; and let $\mathbb{R}^n_+$ denote the n-dimensional real space of vectors with non-negative components. For state $x\in\mathbb{R}^n$, input $u\in\mathbb{R}^m$, and output $y\in\mathbb{R}^p$, we have that

$$\begin{aligned}\dot{x}(t) &= Ax(t)+Bu(t),\\ y(t) &= Cx(t),\end{aligned} \tag{1}$$

is a continuous linear time-invariant system, where time $t\in\mathbb{R}_+$, we are given that $x(0)=x_0$ is an initial condition, the plant is $A\in\mathbb{R}^{n\times n}$, and matrices B and C have appropriate dimensions: $B\in\mathbb{R}^{n\times m}$, $C\in\mathbb{R}^{p\times n}$. More generally,

$$\begin{aligned}\dot{x}(t) &= f(x(t),u(t)),\\ y(t) &= h(x(t)),\end{aligned} \tag{2}$$

is a continuous nonlinear system, where $f:\mathbb{R}^n\times\mathbb{R}^m\to\mathbb{R}^n$ and $h:\mathbb{R}^n\to\mathbb{R}^p$ are continuously differentiable. Suppose that (2) has an equilibrium $e=(x_e,u_e)$ where $\dot{x}(t)=0$. Then the linearization of (2) at e in the form of (1) has plant A as the Jacobian matrix of f with respect to the states, $A=\frac{\partial(f(x,u))}{\partial x}|_e$, B as the Jacobian matrix of f with respect to the input, $B=\frac{\partial(f(x,u))}{\partial u}|_e$, and C as the Jacobian matrix of h with respect to the states, $C=\frac{\partial(h(x))}{\partial x}|_e$.

Systems (1) and (2) are **positive** if, for any initial condition $x_0\in\mathbb{R}^n_+$, the state vector $x(t)\in\mathbb{R}^n_+,\forall t\geq t_0$. The necessary and sufficient condition of positivity for system (1) is that A

is a Metzler matrix, $\{A \in \mathbb{R}^{n\times n} : a_{ij} \geq 0, \forall (i,j), i \neq j\}$ with $Bu \in \mathbb{R}^n_+, \forall t \geq t_0$. For system (2), the positivity condition requires that, for any state $x(t) \in \mathbb{R}^n_+$, if a component $x_i = 0$, then $f_i(x,u) \geq 0$ [23], [25]. This condition ensures that if a state variable x_i reaches 0, then it will either remain at 0 or increase, thereby preserving non-negativity.

A continuously differentiable vector field $f : \mathbb{R}^n \to \mathbb{R}^n$ is **cooperative** if its Jacobian matrix, $\frac{\partial f}{\partial x}(a), \forall a \in \mathbb{R}^n_+ \backslash \{0\}$, is a Metzler matrix [26]. Thus, linearizing a NPNS does not yield a PLS, since the linearized plant is not a Metzler matrix.

B. Examples of Biomolecular NPNSs

Dynamical system representations of biomolecular networks modeled using chemical kinetics are frequently NPNSs. Biologically, their state variables are non-negative concentrations, but mathematically, given nonnegative initial conditions, their nonlinear dynamics satisfy the positivity condition. However, the constant production terms or non-origin equilibria in the dynamics prevent the linearized plant matrix A from being a Metzler matrix. In addition to the previous cancer chemotherapy example [23], two more examples are in Table I. The first is the genetic toggle switch in *Escherichia coli* [27], a foundational synthetic biology result, which has: two states x_1 and x_2; parameters α_1, α_2, β, and γ; and three non-origin equilibria, any one of which can be denoted as (x_{1e}, x_{2e}). The second example is the human regulation of cortisol via the hypothalamic pituitary adrenal (HPA) axis in response to a stress input [28]. This model's zero-input dynamics have: states x_1, x_2, x_3, and x_4; parameters k_{i1}, k_{cd}, k_{i2}, k_{ad}, k, k_{cr}, and k_{rd}; and one to three non-origin equilibria depending on the parameter values, any one of which can be denoted as (x_{1e}, x_{2e}, x_{3e}, x_{4e}). In both examples, the linearized plant matrix A is not a Metzler matrix due to off-diagonal negative terms (red signs in Table I).

C. Biomolecular Problem Motivation

A fourth NPNS that motivates this paper is a model of the coagulation cascade, a network of biochemical reactions triggered by the release of tissue factor (TF) to produce thrombin, a protein that drives clotting. Developing controllers for the coagulation cascade is crucial to treat severe bleeding after trauma, which is a leading cause of death among individuals aged 1 to 44 in the United States [29]. Proteins that are involved in the coagulation cascade are known as coagulation factors, and effective treatment for trauma patients requires the transfusion of specific coagulation factors [30]. Because current treatment protocols rely on the administration of units of uncharacterized fresh frozen plasma (FFP), where the precise concentrations of each coagulation factor in a unit are unknown, severely injured patients that require massive transfusions still have 30% mortality [31]. To personalize treatment, newly-developed controllers must recommend the concentration of one or more coagulation factors to administer to a patient according to their condition [22], [24].

TABLE I

SAMPLE BIOMOLECULAR NPNSS

Model Description	Nonlinear Model	Signs of Jacobian at Equilibrium
Genetic toggle switch in *E. coli*	$\dot{x}_1 = \frac{\alpha_1}{1+x_2^\beta} - x_1$ $\dot{x}_2 = \frac{\alpha_2}{1+x_1^\gamma} - x_2$	$\begin{bmatrix} - & - \\ - & - \end{bmatrix}$
Cortisol level within the HPA axis	$\dot{x}_1 = \frac{k_{i1}}{k_{i1}+x_4} - k_{cd}x_1,$ $\dot{x}_2 = \frac{k_{i2}x_1}{k_{i2}+x_3x_4} - k_{ad}x_2,$ $\dot{x}_3 = \frac{(x_3x_4)^2}{k+(x_3x_4)^2} + k_{cr} - k_{rd}x_3,$ $\dot{x}_4 = x_2 - x_4$	$\begin{bmatrix} - & 0 & 0 & - \\ + & - & - & - \\ 0 & 0 & - & + \\ 0 & + & 0 & - \end{bmatrix}$

This fourth NPNS is a phenomenological model that uses experimental data to fit a mathematical function to describe the underlying biological process [24], [30], [32]:

$$\frac{Y(s)}{U(s)} = \frac{K_n}{s^3 + K_2 s^2 + K_1 s + K_0} e^{-K_d s}, \tag{3}$$

a third-order transfer function, where $U(s)$ is the input TF concentration time-history in the frequency domain, $Y(s)$ is the output time-history of thrombin concentration in the frequency domain, and K_d, K_n, K_2, K_1, and K_0 are parameters. A three-dimensional state-space model for (3) is (4) [22]:

$$\begin{bmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{bmatrix} = \begin{bmatrix} -d_1 & 1 & 0 \\ 0 & -d_2 & 1 \\ 0 & 0 & -d_3 \end{bmatrix} \begin{bmatrix} x_1 \\ x_2 \\ x_3 \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix} g(u(t-\tau)), \tag{4}$$

where $g(u) : \mathbb{R}_+ \to \mathbb{R}_+$ is a non-negative saturation of u:

$$g(u) = \frac{\beta}{2} + \frac{\beta}{2} \tanh\Big(\frac{k_s}{2}(u(t) - \eta)\Big), \tag{5}$$

having β, k_s, and η as positive constants, and $\eta \geq \beta$. A full-state feedback controller (6), denoted as C1 in Fig. 1, tracks desired trajectories of thrombin:

$$u(t) = \left(\operatorname{sgn}\Big(\frac{\operatorname{sgn}(e_1(t)) + 1}{2}\Big)\right)\big(k(e_n(t) - e_n(t_0)) + \nu(t)\big), \tag{6}$$

where $\operatorname{sgn}(x)$ is the signum function, $e_1(t)$ and $e_n(t)$ are error signals [22], $e_n(t_0) \in \mathbb{R}$ is an initial error signal, $k \in \mathbb{R}_+$ is a designed positive constant, and $\nu(t)$ is the solution to an ordinary differential equation [22].

System (4) is a PLS where state x_1 is TF concentration; state x_2 is the concentration of protein complex prothrombinase; state x_3 is the generated thrombin concentration; and τ is an unknown input delay. However, this model is limited by x_2 in practice because no experimental measurement exists for protein complexes. Consequently, an alternate nonlinear realization of (3) was proposed [22] that uses states of single protein concentrations:

$$\begin{aligned} \dot{x}_1 &= -k_{d1}x_1 - \beta x_1 x_2 + g(u(t-\tau)), \\ \dot{x}_2 &= k_{p2} - k_{d2}x_2 - \beta x_1 x_2, \\ \dot{x}_3 &= \gamma x_1 x_2 - k_{d3}x_3, \\ \dot{x}_4 &= k_{n4}x_3 - k_{d4}x_4. \end{aligned} \tag{7}$$

In (7), states x_1 and x_4 are TF and thrombin concentrations, respectively, and states x_2 and x_3 are the concentrations of factor VII and factor Xa, respectively. The parameters $k_{di} \in \mathbb{R}_+$ for $i \in \{1,2,3,4\}$ are the degradation rates of each protein; $k_{p2} \in \mathbb{R}_+$ is the production rate of factor VII; $\beta \in \mathbb{R}_+$ is the sequestration rate of TF and factor VII to form the TF-VII complex; $\gamma \in \mathbb{R}_+$ is the activation rate of factor X; $k_{n4} \in \mathbb{R}_+$ is the rate of thrombin generation; and $u(t-\tau)$ is the control input u with an unknown delay τ. Given non-negative initial

conditions and control input, all states remain in the positive orthant over time, making (7) a PNS.

The linearized plant of (7) at equilibrium $[0, x_{20}, 0, 0]$ is

$$A_l = \begin{bmatrix} -k_{d1} - \beta x_{20} & 0 & 0 & 0 \\ -\beta x_{20} & -k_{d2} & 0 & 0 \\ \gamma x_{20} & 0 & -k_{d3} & 0 \\ 0 & 0 & k_{n4} & -k_{d4} \end{bmatrix}. \quad (8)$$

Since β and x_{20} are positive constants, the off-diagonal term $-\beta x_{20} < 0$, meaning A_l is not Metzler, and thus linearizing (7) does not lead to a PLS. Fig. 2 shows that applying C1 to (8) ensures that output thrombin concentration tracks the desired trajectory, but state x_2 becomes negative. Additionally, C1 fails to control (7), Fig. 2; instead of going negative, state x_2 converges to 0. Thus, x_3 and x_4 also go to zero. Biologically, this is plausible because factor VII is essential for producing factor Xa, which, in turn, generates thrombin. If factor VII were depleted, the entire coagulation cascade would halt. Thus, an additional controller, C3, has to be developed to prevent factor VII from depletion.

III. Controller Design

The control goal is to design controller C3, Fig. 1 (e), to overcome noncooperativity. C3 will enable the positive nonlinear and linear systems to behave similarly, and will augment C1. Therefore, another input u_2 actuated by C3 must restore the positivity of the linearization (8) and ensure that the behaviors of the PNS (7) and its linearization are aligned. We rename u in the first state equation of (7) as u_1, and we choose to add u_2 to the second state equation of (7) to obtain a multi-input, single-output NPNS, which linearizes at the equilibrium to

$$\dot{x} = A_l x + B_l u, \quad (9)$$

where $B_l \triangleq \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{bmatrix}^T$ and $u \triangleq [g(u_1(t-\tau), u_2]^T$. The superscript T is the transpose operator.

A. Feedforward Controller to Overcome Noncooperativity

We make two standard biological control assumptions that are always true in practice:

Assumption 1: All clotting proteins that are not included in our model are present in sufficient concentrations.

Assumption 2: Sequestration, modeled as a negative product of two states, dominates other decay processes.

Assumption 1 ensures that (coagulation) factors external to our focus have no bearing on (clotting) outcome. Assumption 2 harnesses the observation that biochemical kinetic parameters like β and γ are large, and so in (7), states x_1, x_2, and x_3 quickly reach steady state due to the product $x_1 x_2$ in their dynamical equations.

Using Assumptions 1 and 2, a feedforward C3 aims to keep state x_2 in the vicinity of x_{20}, meaning at steady state (ss), $x_{2_{ss}} = x_{20}$, $x_{4_{ss}} = x_r$, $\dot{x}_{1_{ss}} = \dot{x}_{2_{ss}} = \dot{x}_{3_{ss}} = \dot{x}_{4_{ss}} = 0$. Substituting these into (9) and solving for u_2, we obtain the feedforward control $u_{2_{ff}}$:

$$u_{2_{ff}}(t) = k_{d2} x_{20} + \frac{\beta k_{d3} k_{d4}}{\gamma k_{n4}} x_r(t). \quad (10)$$

This feedforward control law mitigates, but does not fully eliminate, noncooperativity. As we will show later in Fig. 5, $x_2(t)$ may take negative values without finely-tuned C1 gains.

B. Feedback Controller to Overcome Noncooperativity

We make an assumption to define an error signal as $e(t) \triangleq x_{20} - x_2(t)$, which we can feedback for control in Theorem 1.

Assumption 3: State $x_2(t)$ can be instantly measured.

Theorem 1: Using Assumptions 1 and 3, a feedback C3 $u_{2_{fb}}$ to overcome noncooperativity of (9) is

$$u_{2_{fb}}(t) = \Big(\text{sgn}\big(\text{sgn}(e) + 1\big)\Big) \beta x_{20} \int_{t0}^{t} g(u_1(\sigma - \tau)) d\sigma, \quad (11)$$

guaranteeing the positivity of state $x_2(t)$ for all $t \geq t_0$. That is, whenever $x_2 = 0$, (11) guarantees that $\dot{x}_2 \geq 0, \forall t \geq t_0$.

Proof: We prove this claim directly. Recall that the positivity condition for a nonlinear system is that, for any state $x(t) \in \mathbb{R}^n_+$, $\dot{x}_i \geq 0$ whenever $x_i = 0$. First, for system (9), $\dot{x}_1 = -k_{d1} x_1 - \beta x_1 x_{20} + g(u_1(t-\tau))$. Given that $\forall t \geq t_0, g(u_1(t-\tau)) \in \mathbb{R}_+$, when $x_1 = 0$, $\dot{x}_1 = 0 - 0 + g(u_1(t-\tau)) \geq 0$. This implies that x_1 satisfies the positivity condition. Hence, if the initial condition $x_{10} \geq 0$, then $x_1 \geq 0, \forall t \geq t_0$.

Next, since k_{d1}, β, and x_{20} are nonnegative real numbers and $x_1 \in \mathbb{R}_+, \forall t \geq t_0$, we have $-k_{d1} x_1 \leq 0$ and $-\beta x_1 x_{20} \leq 0$. Thus, $\dot{x}_1 \leq g(u_1(t-\tau))$. Integrating both sides gives $x_1 - x_{10} \leq \int_{t_0}^{t} g(u_1(t-\tau)) d\sigma$. As $x_{10} = 0$, we have

$$x_1 \leq \int_{t_0}^{t} g(u_1(t-\tau)) d\sigma. \quad (12)$$

In system (9), $\dot{x}_2 = -k_{d2} x_2 - \beta x_1 x_{20} + u_2$. The positivity condition requires that, when $x_2 = 0$, $\dot{x}_2 \geq 0 \implies \dot{x}_2 = 0 - \beta x_1 x_{20} + u_2 \geq 0$, or after rearranging,

$$u_2 \geq \beta x_1 x_{20}. \quad (13)$$

This means that if u_2 satisfies (13), then $x_2 \in \mathbb{R}_+, \forall t \geq t_0$, provided that $x_{20} > 0$. Let u_2 take the form of (11). When $x_2 = 0 \implies e = x_{20} > 0$, so $\text{sgn}(\text{sgn}(e) + 1)) = 1$. Thus,

$$u_2 = u_{2_{fb}} = \beta x_{20} \int_{t_0}^{t} g(u_1(t-\tau)) d\sigma. \quad (14)$$

Substituting the inequality (12) into (14), $u_2 = u_{2_{fb}} = \beta x_{20} \int_{t_0}^{t} g(u_1(t-\tau)) \geq \beta x_1 x_{20}$. Thus, inequality (13) is satisfied. Therefore, (11) guarantees the positivity of state x_2. ■

IV. Controller Application

We show controller efficacy in regulating blood coagulation for a trauma patient with abnormal clotting. The model parameters are: $k_{d1} = 0.1298$, $k_{d2} = 0.0488$, $k_{d3} = 0.2596$, $k_{d4} = 0.2595$, $k_{p2} = 4.8763 \times 10^{-10}$, $k_{n4} = 2.4820$, $\beta = 1.2978 \times 10^7$, $\gamma = 2.4830 \times 10^8$. These parameters are obtained from a severely injured trauma patient. The initial concentrations (M) for all proteins are $x_0 = [0, 10 \times 10^{-9}, 0, 500 \times 10^{-9}]^T$. The simulation goal is to regulate elevated thrombin (factor IIa), as seen in some trauma patients [32], to a normal range, and to track a sinusoid inside the range to showcase robustness: $x_r = \big(130 + 50 \times \sin(0.17t)\big) \times 10^{-9}$ M.

The feedforward and feedback versions of controller C restore the tracking performance of controller C1, Figs. 3 an 4, respectively, confirming C3 efficacy. The blue solid line are the state responses of the NPNS, while the red dashe lines are the state responses of the linearized system. The black solid lines are the desired trajectories.

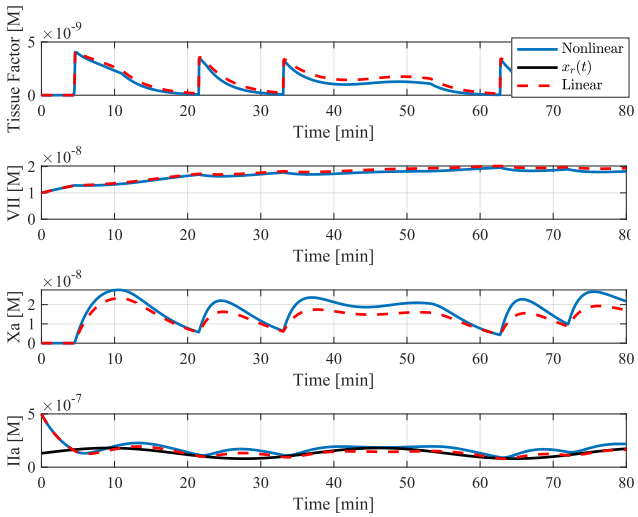

Fig. 3. State responses of systems (7) (blue solid curves) and (9) (red dashed curves) with u_1 (6) augmented by the feedforward C3, $u_{2_{ff}}$.

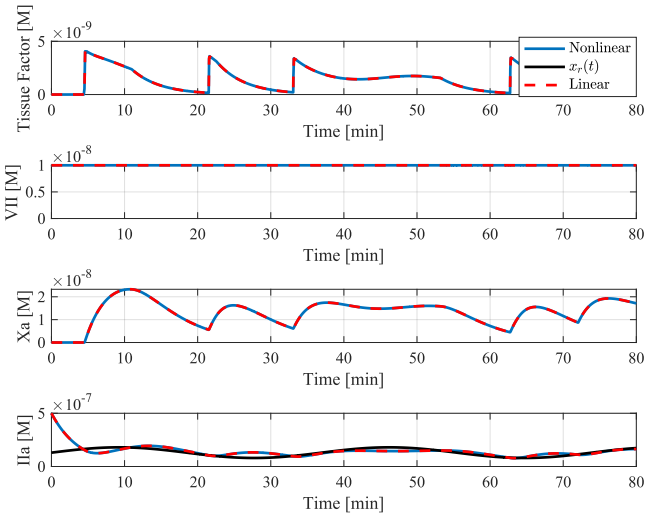

Fig. 4. State responses of systems (7) (blue solid curves) and (9) (red dashed curves) with u_1 (6) augmented by the feedback C3, $u_{2_{fb}}$.

For factor VII, the feedback version of C3 maintains state x_2 near its equilibrium value, x_{20}, enabling the NPNS to behave similar to its linearization. Hence, in Fig. 4, the linearized system responses (red dashed) overlap with those of the nonlinear system (blue solid). In contrast, factor VII in Fig. 3 deviates from x_{20}, resulting in a slightly different behavior between the linearized and NPNS state responses. In fact, if controller C1 gains are not finely tuned, it is possible for state x_2 to go negative, Fig. 5.

Our augmented control laws are robust in that even when operating points for linearization are far from equilibrium, thrombin tracking is still satisfactory. We use the notion of the gap metric [33], [34] to quantify the difference between

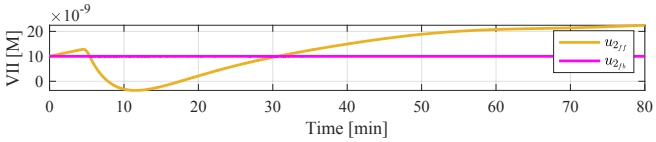

Fig. 5. The feedforward C3, $u_{2_{ff}}$, cannot guarantee factor VII positivity.

the linearized PNS approximation at any operating point and the baseline linear system (3). The gap metric can take values between 0 and 1, with 0 representing systems that are exactly the same and 1 representing systems that are completely different. Linearizing when $x_2 = 0$ leads to a gap metric of 1. Fig. 6 confirms satisfactory tracking in this extreme case.

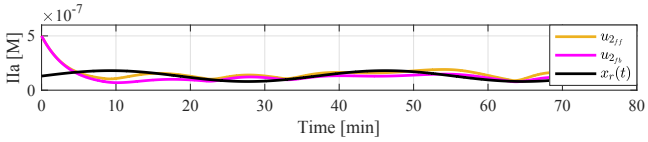

Fig. 6. Output response for a gap metric 1 linearization at $x_2 = 0$.

V. Discussion and Concluding Remarks

We augmented our previous controller C1 for system (7) with an additional controller, C3, to rectify tracking performance. C3 has two forms: feedforward ($u_{2_{ff}}$) and feedback ($u_{2_{fb}}$). Augmenting C1 with either C3 form effectively restores C1 tracking performance, enabling personalized protein concentration manipulation and clotting treatment.

Although our feedforward C3 controller has no guarantees of positivity for the linearized system (Fig. 5), a potential challenge with using feedback control in a clinical setting is our assumption that protein concentrations can be measured instantly, which if untrue may introduce a time delay in the feedback signal. Then again, biological systems are quite slow, so the feedback controller with small measurement delay may not be a problem. In any case, the feedforward C3 controller is easier to apply since it does not depend on state measurements, eliminating any concerns about time delays.

The signum function in $u_{2_{fb}}$ introduces a discontinuity into the system, but this is a typical input for biological systems. In practice, therapies can only be added to a system, not removed. When the concentration of a state exceeds a target level, the only way to reduce concentration is to stop therapy delivery so that natural degradation reduces concentration.

In the proof of Theorem 1, it is initially plausible that C3 can take a simpler form, $u_2 = \beta x_1 x_{20}$, which would perfectly cancel out the problematic term, $-\beta x_1 x_{20}$, in the matrix A_l of (9). However, this is not achievable in practice since state x_1, TF concentration, requires time to measure. Thus, u_2 is based on a delayed measurement, and so $u_2 = \beta x_1(t-\tau_d)x_{20}$, where τ_d is the measurement delay. This prevents perfect cancelation.

We observe that C1 works well for PLSs, regardless of whether the system is a minimal realization or not. However, this is not the case for the nonlinear model unless we keep state x_2 near its equilibrium point, even though its linearization satisfies the full-rank controllability matrix condition — a condition, if met, implies the local controllability of the nonlinear model. A possible explanation

is that the transfer function of the linear system is always third-order for any non-negative state vector $x(t)$, but the transfer function of the linearized nonlinear system is only third-order when $x_2 = x_{20}$. While using a non-minimal realization may seem like an overcomplication, it offers the advantage of hybridizing phenomenological and mechanistic modeling approaches. The internal states of a small phenomenological model may not have physical meaning, but using a non-minimal realization adds a few meaningful states, such as protein concentrations, while preserving a simple underlying transfer function. Developing controllers for such a non-minimal realization opens up the possibility of providing recommended dosages for other critical coagulation factors, such as factor VIII. The trade-off, however, is a NPNS that loses observability at the equilibrium point.

Our central contributions are why a new controller must be appended to our prior controller [22] and what form this new controller should take given realistic dynamics [24], so that an implementation is realizable in practice. This lens gives insight into NPNS control theory. Future work includes generalizing our control strategies and exploring their applicability to other NPNS; comparing the performance of our developed controllers with other control laws such as backstepping; implementing adaptive control and/or neural networks to compensate for the system uncertainties that are typical of biochemical models; and validating our control laws experimentally.

Code Availability

MATLAB code is available at:
https://github.com/SYBORGS-Lab/Control-of-a-NPNS

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