A Singular Singular Perturbation Problem Arising from a Class of Biomolecular Feedback Controllers

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***Abstract*— A long-standing challenge in synthetic biology is to engineer biomolecular systems that can perform robustly in highly uncertain cellular environments. Recently, there has been increasing interest to design biomolecular feedback controllers to address this challenge. Molecular sequestration is one of the proposed feedback mechanisms. For this type of design, when all reactions within the controller are sufficiently fast, the process output can reach a set-point regardless of parametric uncertainties and constant disturbances. However, as we demonstrate in this paper, the way in which molecular sequestration affects the fast controller dynamics leads to a singular singularly perturbed (SSP) system. In an SSP system, the boundary layer Jacobian is singular and thus standard singular perturbation approaches cannot be applied, posing difficulties to analytically determine the performance of sequestration-based controllers. In this paper, we consider a class of linear systems that capture the key structure of sequestration-based controllers. We show that, under certain technical conditions, these SSP systems can still be approximated by reduced-order systems that are dependent on the small parameter. This result allows us to analytically evaluate the tracking performance of the linearized model of a sequestration-based controller.**

I. INTRODUCTION

Synthetic biology is an emerging research area at the intersection of biology and engineering aimed at creating useful biomolecular systems for biotechnology applications, from health, to environment, to energy [1]. However, biomolecular systems constructed nowadays often lack robustness, predictability, and precision when operating in highly variable and uncertain cellular environments [2]. Several feedback controllers realizable through biomolecular reactions have been proposed recently to address these problems [2]. Molecular sequestration, in which two species bind together and annihilate, is one of the proposed feedback mechanisms. The production rates of the two species, which we call controller species, each reflect the concentrations of the reference input and process output [3], [4], [5], [6], [7] (see an example in Section II). When such a controller is implemented in living cells, it can achieve set-point regulation if the production and annihilation rates of the controller species are much larger than the rate of cell growth, which typically dictates the dynamics of the process to be regulated [5], [6], [7]. We call the resultant controllers fast sequestration-based feedbacks (FSFs). While numerical studies and experiments have demonstrated the effectiveness of FSFs to perform set-point regulation and reference tracking (e.g., [4], [8]), analytical approaches to determine conditions for these objectives are still largely missing [5], [7].

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The fact that controller reactions in an FSF are much faster than the reactions in the process to be regulated can be exploited to determine the properties of FSFs. While two-time-scale systems are often studied by singular perturbation (SP) [9], we find that standard SP is inapplicable to FSF systems. In particular, if one regards the concentrations of the two controller species as fast variables, the Jacobian of the boundary layer (BL) is singular everywhere in the state space. In SP literatures, such a system is called a singular singularly perturbed (SSP) system [10], [11], [12], [13]. While existing results have provided conditions to reduce the dimensionality of SSP systems, we find that the FSFs we consider do not satisfy these conditions.

In this paper, we perform model reduction for a class of linear SSP systems arising from linearized FSF models as a first step to analyze the dynamics of FSFs and more general SSP problems emerging from them. Our analysis reveals that such an SSP system cannot be approximated by an ϵ-independent reduced model, where ϵ is the small parameter quantifying the timescale separation. However, under appropriate technical conditions, we prove that its trajectory can be effectively approximated by that of an ϵ-parameterized reduced system. In particular, if the process to be regulated is passive, then the reduced system can be regarded as a high-gain ($1/\epsilon$) feedback interconnection of two passive systems (Section IV). Because of this feedback structure, we demonstrate in Section V that even when exact parameter values in an FSF are poorly known, arbitrarily small reference tracking error can still be achieved by increasing the controller reaction rates.

II. MOTIVATING APPLICATION

In Fig. 1, we show an FSF system, where two controller species c_1 and c_2 regulate the concentration of a single protein p. Production rate of c_1 is proportional to a reference $u(t)$, which often reflects the concentration of a molecular stimulus, and c_1 activates the production of protein p. Species c_2 is a "sensor", whose production rate is proportional to the concentration of the output (p). Meanwhile, all species (i.e., $\mathrm{c}_1, \mathrm{c}_2, \mathrm{p}$) are diluted at rate constant δ due to cell growth. These processes follow the chemical reactions:

$$\varnothing \xrightarrow{\mathrm{u(t)}/\epsilon} \mathrm{c}_1, \qquad \mathrm{p} \xrightarrow{\alpha/\epsilon} \mathrm{p} + \mathrm{c}_2, \qquad \mathrm{c}_1 + \mathrm{c}_2 \xrightarrow{\theta/\epsilon} \varnothing, \tag{1a}$$

$$\mathrm{c}_1 \xrightarrow{\beta} \mathrm{c}_1 + \mathrm{p}, \quad \mathrm{c}_1, \mathrm{c}_2, \mathrm{p} \xrightarrow{\delta} \varnothing. \tag{1b}$$

All rate constants are positive, and the small parameter $0 < \epsilon \ll 1$ models the fact that the rates of production and annihilation of c_1 and c_2 in (1a) are much larger than the reaction rates in (1b). In fact, it is shown in [5] that if $u(t)$ is a constant and ϵ is small enough, then the equilibrium output $\bar{p}$ satisfies: $\bar{p} = u/\alpha + \mathcal{O}(\epsilon)$, making FSFs ideal for synthetic biology applications where protein concentration needs to be robustly and tightly regulated at a constant level (e.g., [6]), regardless of, for example, uncertainty in protein production rate β. A mass-action kinetic model of (1) takes the following ordinary differential equation form:

$$\begin{aligned} \epsilon\dot{c}_1 &= u(t) - \epsilon\delta c_1 - \theta c_1 c_2, \\ \epsilon\dot{c}_2 &= \alpha p - \epsilon\delta c_2 - \theta c_1 c_2, \\ \dot{p} &= \beta c_1 - \delta p. \end{aligned} \tag{2}$$

At a first glance, system (2) appears to have two timescales, with c_1 and c_2 being the fast variables and p being the slow variable. Following the standard SP procedure [9], we write (2) in the fast timescale $\tau = t/\epsilon$:

$$\begin{aligned} \mathrm{d}c_1/\mathrm{d}\tau &= u(t) - \epsilon\delta c_1 - \theta c_1 c_2, \\ \mathrm{d}c_2/\mathrm{d}\tau &= \alpha p - \epsilon\delta c_2 - \theta c_1 c_2, \\ \mathrm{d}p/\mathrm{d}\tau &= \epsilon\beta c_1 - \epsilon\delta p, \end{aligned} \tag{3}$$

and then set $\epsilon = 0$ to "freeze" the slow variable p to obtain the BL dynamics of (2):

$$\mathrm{d}c_1/\mathrm{d}\tau = u - \theta c_1 c_2, \quad \mathrm{d}c_2/\mathrm{d}\tau = \alpha p - \theta c_1 c_2. \tag{4}$$

Since the Jacobian of (4) is singular in the entire BL state space, system (2) is SSP. This property arises from the annihilation reaction, $c_1 + c_2 \to \varnothing$, which affects both fast variables (c_1 and c_2) in an identical fashion ($-\theta c_1 c_2/\epsilon$). SSP problems have been studied in [10], [11], [12], [13]. For these results to be applicable to (2), it is necessary for the Jacobian matrix of the fast timescale system (3) evaluated at $\epsilon = 0$:

$$\begin{bmatrix} -\theta c_2 & -\theta c_1 & 0 \\ -\theta c_2 & -\theta c_1 & \alpha \\ 0 & 0 & 0 \end{bmatrix} \tag{5}$$

to have a zero eigenvalue with same algebraic and geometric multiplicities. Assuming that this condition is satisfied, system (2) can be transformed into standard SP form under additional technical conditions [10], [11], [12], [13]. However, the zero eigenvalue of (5) has algebraic multiplicity 2 and geometric multiplicity 1 for any positive c_1, c_2 and parameters α and θ. In fact, applying the test in [14] to (2), we can prove that there does not exist any ϵ-independent transformation to take (2) to standard SP form.

Given that the BL Jacobian is singular everywhere in the state space, linearizing (2) about any steady state leads to a similar SSP problem. In addition, the multiplicities of the zero eigenvalue of the Jacobian (5) is independent of where it is evaluated in the state space, and consequently, the difficulties applying existing SSP results to nonlinear FSFs carry over to linearized FSFs. In fact, with reference to Fig.1B, when we numerically evaluate the poles of a linearized FSF (see Section V), we find that it has a fast mode (that behaves like $e^{-t/\epsilon}$) and a high frequency damped oscillatory mode (that behaves like $e^{-t}\sin(t/\sqrt{\epsilon})$). One would therefore expect the reduced system of a linearized FSF to contain the parameter ϵ to capture this high frequency damped oscillatory mode, which persists for ϵ small. This observation further reinforces our conclusion that existing SP and SSP tools are inapplicable to the FSFs, because existing tools always lead to an ϵ-independent reduced system.

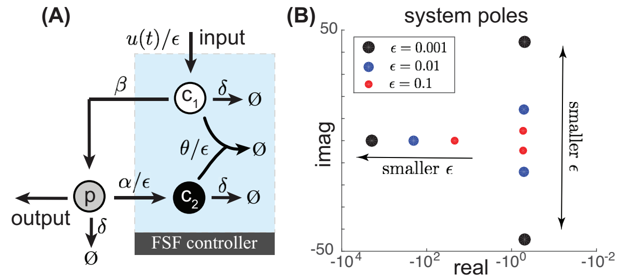

Fig. 1. An example fast sequestration-based feedback (FSF) system. (A) Interactions among molecular species. (B) Poles of a linearized FSF as ϵ changes. The linearized model is (24) with $\alpha = \beta = \theta = \delta = \bar{u} = 1$.

III. PROBLEM FORMULATION

In this section, we describe the linear SSP problem we consider and introduce a transformation to classify the system state variables into three categories. We then construct a candidate reduced system by setting state variables in one of the categories to quasi-steady state.

A. Singular Singularly Perturbed Systems

We consider an ϵ-parameterized linear SP system subject to a scalar time-varying input $u(t)$. We use bold face $\mathbf{u}$ for the derivatives of $u(t)$ (i.e., $\mathbf{u} = [u, \dot{u}, \ddot{u}, \cdots, u^{(n)}]$) and write $\mathbf{u} \in \mathcal{L}_\infty$ to indicate that $u(t)$ has bounded, ϵ-independent derivatives. We write the system as:

$$\begin{aligned} \dot{\xi}_1 &= A_{11}^\epsilon \xi_1 + A_{12}^\epsilon \xi_2 + F_1^\epsilon u(t), \\ \epsilon\dot{\xi}_2 &= A_{21}^\epsilon \xi_1 + A_{22}^\epsilon \xi_2 + F_2^\epsilon u(t), \end{aligned} \tag{6}$$

in which $(\xi_1, \xi_2) \in \mathbb{R}^{q+p}$. We use A_{ij}^ϵ to denote that the ϵ-dependent matrix $A_{ij}(\epsilon)$ is a finite power series of ϵ such that $A_{ij}^\epsilon := \sum_{k=0}^m A_{ij}^k \epsilon^k$ for some non-negative integer m. In the fast timescale, (6) can be equally represented by

$$\begin{aligned} \mathrm{d}\xi_1/\mathrm{d}\tau &= \epsilon A_{11}^\epsilon \xi_1 + \epsilon A_{12}^\epsilon \xi_2 + \epsilon F_1^\epsilon u(t), \\ \mathrm{d}\xi_2/\mathrm{d}\tau &= A_{21}^\epsilon \xi_1 + A_{22}^\epsilon \xi_2 + F_2^\epsilon u(t). \end{aligned} \tag{7}$$

By setting $\epsilon = 0$, we "freeze" the slow ξ_1 dynamics to obtain the BL dynamics:

$$\mathrm{d}\xi_2/\mathrm{d}\tau = A_{21}^0 \xi_1 + A_{22}^0 \xi_2 + F_2^0 u(t). \tag{8}$$

We study the SSP problem in which A_{22}^0 is singular. More specifically, motivated by the properties of (5) in the FSF, we make the following assumption on the system matrix of (7) evaluated at $\epsilon = 0$: $A^0 := \begin{bmatrix} 0 & 0 \\ A_{21}^0 & A_{22}^0 \end{bmatrix}$.

Assumption 1: The zero eigenvalue of A^0 has algebraic multiplicity $\mu = q + 1$ and geometric multiplicity $\lambda = q$. All other eigenvalues of A^0 have negative real parts.

Remark 1: In a standard SP problem, A_{22}^0 is Hurwitz. As a result, the zero eigenvalue of A^0 must have multiplicities $\mu = \lambda = q$, which is consistent with the dimension of the slow variable ξ_1. When A_{22}^0 has a zero eigenvalue, we are faced with an SSP problem. For a subclass of SSP problems, where the multiplicities of the zero eigenvalue satisfy $\mu = \lambda$, existing results can be applied for model reduction [10], [11], [12], [13]. However, the type of singularity in Assumption 1, where $\mu = q + 1 \neq q = \lambda$, cannot benefit from these previous results.

B. Transformation to Normal SSP Form

In this section, we utilize a transform of (6) to classify the state variables in an SSP problem into three categories. The following Lemma describes the transformed system, which we say is in *normal SSP form.*

Lemma 1: There exists a non-singular real matrix P, independent of ϵ, such that with $z = P\xi$, system (6) can be transformed into the following normal SSP form:

$$\dot{z}_1 = E_{11}^\epsilon z_1 + E_{12}^\epsilon z_2 + E_{13}^\epsilon z_3 + B_1^\epsilon u(t), \tag{9a}$$

$$\epsilon \dot{z}_2 = R^\epsilon z_1 + \epsilon E_{22}^\epsilon z_2 + \epsilon E_{23}^\epsilon z_3 + B_2^\epsilon u(t), \tag{9b}$$

$$\epsilon \dot{z}_3 = \epsilon E_{31}^\epsilon z_1 + \epsilon E_{32}^\epsilon z_2 + S^\epsilon z_3 + B_3^\epsilon u(t). \tag{9c}$$

where $z_1 = \xi_1 \in \mathbb{R}^q$, z_2 is a scalar, $z_3 \in \mathbb{R}^{p-1}$. The matrix $R^0 \in \mathbb{R}^{1\times q}$ is nonzero, and $S^0 \in \mathbb{R}^{(p-1)\times(p-1)}$ is Hurwitz.

Proof: We derive this result using the fast timescale system (7), which can be re-written as

$$\frac{\mathrm{d}}{\mathrm{d}\tau}\begin{bmatrix}\xi_1\\ \xi_2\end{bmatrix} = (\underbrace{\begin{bmatrix}0 & 0\\ A_{21}^0 & A_{22}^0\end{bmatrix}}_{A^0} + \epsilon \underbrace{\begin{bmatrix}A_{11}^\epsilon & A_{12}^\epsilon\\ \tilde{A}_{21}^\epsilon & \tilde{A}_{22}^\epsilon\end{bmatrix}}_{A^\epsilon})\begin{bmatrix}\xi_1\\ \xi_2\end{bmatrix} + \begin{bmatrix}\epsilon F_1^\epsilon\\ F_2^\epsilon\end{bmatrix} u,$$

where $\tilde{A}_{ij}^\epsilon := \sum_{k=1} A_{ij}^k \epsilon^{k-1} = \mathcal{O}(1)$. By Assumption 1, A_{22}^0 must have a non-repeated zero eigenvalue. Therefore, there exists a unique invertible matrix $V \in \mathbb{R}^{p\times p}$ to take A_{22}^0 to real Jordan form: $V^{-1}A_{22}^0 V = \begin{bmatrix}0 & 0\\ 0 & S^0\end{bmatrix}$, where the $(p-1)\times(p-1)$ matrix S^0 is Hurwitz. Let $V^{-1} = \begin{bmatrix}W_{11} & W_{12}\\ W_{21} & W_{22}\end{bmatrix}$, where W_{11} is a scalar and W_{22} is a $(p-1)\times(p-1)$ matrix, and let $[(R^0)^T, (M^0)^T]^T := V^{-1}A_{21}^0$, where $R^0 \in \mathbb{R}^{1\times q}$ and $M^0 \in \mathbb{R}^{(p-1)\times q}$, the ϵ-independent transformation $z = P\xi$ is carried out by $P := \begin{bmatrix}I & 0 & 0\\ 0 & W_{11} & W_{12}\\ M^0 & S^0 W_{21} & S^0 W_{22}\end{bmatrix}$. The resultant z dynamics can be written as

$$\frac{\mathrm{d}}{\mathrm{d}\tau} z = \left(\begin{bmatrix}0 & 0 & 0\\ R^0 & 0 & 0\\ 0 & 0 & S^0\end{bmatrix} + \epsilon E^\epsilon\right) z + \begin{bmatrix}\epsilon B_1^\epsilon\\ B_2^\epsilon\\ B_3^\epsilon\end{bmatrix} u, \tag{10}$$

where $E^\epsilon := PA^\epsilon P^{-1}$, and $B^\epsilon := PF^\epsilon$ are all $\mathcal{O}(1)$. Note that since the upper-left $q\times q$ block of P is identity, we have $z_1 = \xi_1 \in \mathbb{R}^q$ and $B_1^\epsilon = F_1^\epsilon$. By denoting $R^\epsilon := R^0 + \epsilon E_{21}^\epsilon$ and $S^\epsilon := S^0 + \epsilon E_{33}^\epsilon$, system (10) is equivalent to (9) in slow timescale. Matrix R^0 must not be 0, for if otherwise, one would have $PA^0P^{-1} = \mathrm{diag}\{0, S^0\}$, whose zero eigenvalue has multiplicities $\mu = \lambda = q+1$, violating Assumption 1. ■

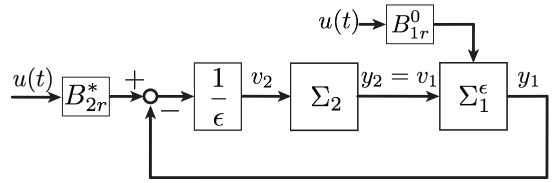

Fig. 2. The candidate reduced system can be decomposed as two subsystems interconnected through high-gain negative feedback.

C. Candidate Reduced System

At a high level, the transformation to normal SSP form separates out three sets of state variables. (A) The dynamics of $z_3 \in \mathbb{R}^{p-1}$ becomes faster as ϵ decreases, we therefore call z_3 the *fast variable*. According to (9c), the $\mathcal{O}(1)$ z_3 dynamics are decoupled from that of z_1 and z_2. Roughly speaking, this decoupling guarantees that fast convergence of z_3 to its quasi-steady state is minimally affected by the slow dynamics, which may contain a high frequency damped oscillatory mode, as we have seen in Fig. 1B. (B) The $\mathcal{O}(1)$ dynamics of $z_1 \in \mathbb{R}^q$ are unaffected by ϵ, we therefore call z_1 the *slow variable*. (C) As ϵ decreases, z_1 has a larger effect on the scalar z_2 dynamics (through R^ϵ/ϵ). Yet, it does not make z_2 dynamics faster. We call z_2 the *pseudo-fast variable*.

Based on this reasoning, we investigate whether we can obtain a reduced model of (9) by setting z_3 to quasi-steady state. In particular, by setting $\epsilon = 0$ in (9c), we have

$$0 = S^0\bar{z}_3 + B_3^0 u(t) \quad \Rightarrow \quad \bar{z}_3 = -(S^0)^{-1}B_3^0 u(t), \tag{11}$$

We construct a candidate *reduced system* whose states x_i are intended to approximate z_i in the *full system* in equation (9). The reduced system is obtained by 1) substituting $\bar{z}_3$ in (11) into the z_1 and z_2 dynamics in (9), and 2) setting all $\mathcal{O}(\epsilon)$ terms in z_1 and z_2 dynamics to 0. This procedure results in the following candidate reduced system:

$$\begin{bmatrix}\dot{x}_1\\ \dot{x}_2\end{bmatrix} = \begin{bmatrix}E_{11}^0 & E_{12}^0\\ R^*/\epsilon & E_{22}^0\end{bmatrix}\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \begin{bmatrix}B_{1r}^0\\ B_{2r}^*/\epsilon\end{bmatrix} u(t), \tag{12a}$$

$$x_3 = \bar{z}_3 = -(S^0)^{-1}B_3^0 u(t), \tag{12b}$$

where,

$$\begin{aligned} R^* &= R^0 + \epsilon R^1, \quad B_{1r}^0 = B_1^0 - E_{13}^0(S^0)^{-1}B_3^0\\ B_{2r}^* &= B_2^0 + \epsilon B_2^1 - \epsilon E_{23}^0(S^0)^{-1}B_3^0. \end{aligned} \tag{13}$$

As shown in Fig. 2, the candidate reduced system (12a) can be decomposed into the feedback interconnection of two subsystems. Specifically, the two subsystems are:

$$\begin{aligned} \Sigma_1^\epsilon &:= \begin{cases}\dot{x}_1 = E_{11}^0 x_1 + E_{12}^0 v_1 + B_{1r}^0 u,\\ y_1 = -R^* x_1 = -(R^0 + \epsilon R^1)x_1,\end{cases}\\ \Sigma_2 &:= \begin{cases}\dot{x}_2 = E_{22}^0 x_2 + v_2,\\ y_2 = x_2.\end{cases} \end{aligned} \tag{14}$$

where $x_1 \in \mathbb{R}^q$ and y_1, x_2, y_2 are scalars. The two subsystems are interconnected according to the rule $v_1 = y_2$ and $v_2 = (B_{2r}^* u - y_1)/\epsilon$. We place the following assumptions on subsystems Σ_2 and Σ_1^0.

Assumption 2: (i) The scalar $E_{22}^0 < 0$. (ii) The pair (E_{11}^0, E_{12}^0) is controllable, and the pair (E_{11}^0, R^0) is observable. (iii) The transfer function from v_1 to y_1 in Σ_1^0:

$$H_1^0(s) := -R^0(sI - E_{11}^0)^{-1}E_{12}^0 \tag{15}$$

is strictly proper, strictly positive real (SPR) and does not contain a zero at E_{22}^0.
According to Assumption 2, the transfer function of Σ_2, $H_2(s) = 1/(s + E_{22}^0)$, is also SPR. Hence, the candidate reduced system can be regarded as a high-gain $(1/\epsilon)$ feedback interconnection of two SPR subsystems Σ_1^ϵ and Σ_2 (Fig. 2).

IV. CLOSENESS OF TRAJECTORIES

In this section, we analyze the error dynamics between the full system (9) and the candidate reduced system (12) to demonstrate that their trajectories are close to each other.

A. Error Dynamics

We define the error between the full system and the candidate reduced system as $e_i := z_i - x_i$. The resultant error dynamics consist of feedback interconnection of a *slow error system* (e_1, e_2) and a *fast error system* (e_3):

$$\begin{bmatrix}\dot e_1\\ \dot e_2\end{bmatrix} = A_s(\epsilon)\begin{bmatrix}e_1\\ e_2\end{bmatrix} + B_{se}^\epsilon e_3 + \epsilon B_{sx}^\epsilon\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \epsilon B_{su}^\epsilon u, \tag{16}$$

$$\epsilon\dot e_3 = A_f^\epsilon e_3 + \epsilon B_{fe}^\epsilon\begin{bmatrix}e_1\\ e_2\end{bmatrix} + \epsilon B_{fx}^\epsilon\begin{bmatrix}x_1\\ x_2\end{bmatrix} + \epsilon B_{fu}^\epsilon\begin{bmatrix}u\\ \dot u\end{bmatrix}. \tag{17}$$

The matrices in the slow error system (16) are defined as

$$A_s(\epsilon) := \begin{bmatrix}E_{11}^\epsilon & E_{12}^\epsilon\\ R^\epsilon/\epsilon & E_{22}^\epsilon\end{bmatrix}, \qquad B_{se}^\epsilon := \begin{bmatrix}E_{13}^\epsilon\\ E_{23}^\epsilon\end{bmatrix},$$

$$B_{sx}^\epsilon := \begin{bmatrix}H_{11}^\epsilon & H_{12}^\epsilon\\ H_{21}^\epsilon & H_{22}^\epsilon\end{bmatrix}, \qquad B_{su}^\epsilon := \begin{bmatrix}H_{1u}^\epsilon\\ H_{2u}^\epsilon\end{bmatrix},$$

where $H_q^\epsilon := \sum_{k=1} E_{ij}^k \epsilon^{k-1}$ $(q \in \{11, 12, 22\})$, $H_{21}^\epsilon := \sum_{k=2} R^k\epsilon^{k-2}$, $H_{1u}^\epsilon := \sum_{k=1}[B_1^k - E_{13}^k(S^0)^{-1}B_3^0]\epsilon^{k-1}$, and $H_{2u}^\epsilon := \sum_{k=2} B_2^k\epsilon^{k-2} - \sum_{k=1} E_{23}^k(S^0)^{-1}B_3^0\epsilon^{k-1}$ are all $\mathcal{O}(1)$. Note that we write $A_s(\epsilon)$ instead of A_s^ϵ because it is not a power series of ϵ. In the fast error system (17), $A_f^\epsilon := S^\epsilon, B_{fe}^\epsilon = B_{fx}^\epsilon := [E_{31}^\epsilon, E_{32}^\epsilon]$, and $B_{fu}^\epsilon := [\sum_{k=1}[B_3^k + S^k(S^0)^{-1}B_3^0]\epsilon^{k-1}, (S^0)^{-1}B_3^0]$ are all $\mathcal{O}(1)$.

To determine the magnitude of the approximation errors, we treat the error dynamics as a feedback interconnection of the slow error system (16) and the fast error system (17). Our subsequent analysis is aimed to obtain their respective input-to-state stability (ISS) properties (see Claim 1-2) and then apply an ISS small-gain theorem to provide an upper bound for the approximation errors (Theorem 1).

B. ISS Property of the Slow Error System

Here, we first analyze the ISS property of the slow error system. We use $|\cdot|_Q$ to stand for the vector 2-norm weighted by matrix $Q > 0$. Thus, $|x|_Q^2 = x^TQ^2x$. Accordingly, for a matrix A, $|A|_Q$ is the matrix induced 2-norm weighted by Q: $|A|_Q^2 := \bar\lambda(A^TQ^2A)$, where $\bar\lambda(\cdot)$ stands for the largest eigenvalue. For a square matrix A, we use $\mu_Q(A)$ to represent the matrix measure associated with the Q-weighted 2-norm. In particular, $\mu_Q(A)$ is the largest eigenvalue of the symmetric part of QAQ^{-1}. For a signal $v(t)$, $\|v\|_{a,Q}$ is the asymptotic signal $\mathcal{L}_\infty$ norm weighted by Q: $\|v\|_{a,Q} := \limsup_{t\to\infty}|v(t)|_Q$. For all norms, when the weight matrix Q is identity, we omit the subscript Q for simplicity. The following lemma connects a system matrix measure to its ISS property.

Lemma 2: (Theorem 1 in [15].) Consider an LTI system $\dot x = Ax + Bu(t)$ with input $u(t)$, and suppose that for a real matrix $Q > 0$, there exists $c > 0$ such that $\mu_Q(A) \le -c$. Then for any $u(t) \in \mathcal{L}_\infty$, the system trajectory satisfies:

$$\limsup_{t\to\infty}|x(t)|_Q = \|x\|_{a,Q} \le |B|_Q\|u\|_a/c. \tag{18}$$

To study the ISS property of the slow error system, we use the following result on the matrix measure of $A_s(\epsilon)$.

Lemma 3: Under Assumption 2, there exists a real matrix $Q_1 > 0$ and a positive constant α, both independent of ϵ, such that the matrix measure of $A_s(\epsilon)$ weighted by

$$Q = Q(\epsilon) = \begin{bmatrix}Q_1 & 0\\ 0 & \sqrt\epsilon\end{bmatrix} \tag{19}$$

satisfies $\mu_Q[A_s(\epsilon)] \le -\alpha$ for ϵ sufficiently small.

Proof: We split $A_s(\epsilon)$ into two parts and write it as:

$$A_s(\epsilon) = A_s^0(\epsilon) + D^\epsilon := \begin{bmatrix}E_{11}^0 & E_{12}^0\\ R^0/\epsilon & E_{22}^0\end{bmatrix} + \begin{bmatrix}\epsilon D_{11}^\epsilon & \epsilon D_{12}^\epsilon\\ D_{21}^\epsilon & \epsilon D_{22}^\epsilon\end{bmatrix}.$$

We first show that there exists an ϵ-independent α^* such that $\mu_Q[A_s^0(\epsilon)] \le -\alpha^*$, and then show that $\mu_Q[A_s(\epsilon)] = \mu_Q[A_s^0(\epsilon) + D^\epsilon] \le -\alpha^* + \mathcal{O}(\sqrt\epsilon)$. Due to (ii)-(iii) in Assumption 2 and the KYP lemma, there exists a real matrix $P > 0$ and a positive constant $\bar\alpha$ (both ϵ-independent) such that $PE_{11}^0 + (E_{11}^0)^TP \le -2\bar\alpha P$, and $PE_{12}^0 = -(R^0)^T$. For any real matrices X and $Y > 0$, we write $\Pi(X, Y) := YXY^{-1} + Y^{-1}X^TY$, so $\Pi(X, Y)$ is linear in X and $\mu_Y(X) = \bar\lambda[\Pi(X, Y)/2]$. Take $Q_1 = \sqrt P > 0$, we have

$$\Pi(A_s^0, Q) = \begin{bmatrix}\Pi(E_{11}^0, Q_1) & Q_1^{-1}[PE_{12}^0 + (R^0)^T]/\sqrt\epsilon\\ \star & 2E_{22}^0\end{bmatrix}$$
$$= \begin{bmatrix}Q_1^{-1}[PE_{11}^0 + (E_{11}^0)^TP]Q_1^{-1} & 0\\ 0 & 2E_{22}^0\end{bmatrix} \le \begin{bmatrix}-2\bar\alpha I & 0\\ 0 & 2E_{22}^0\end{bmatrix},$$

from which we have $\bar\lambda[\Pi(A_s^0, Q)/2] \le -\alpha^* := -\min(\bar\alpha, -E_{22}^0) < 0$. On the other hand, we have

$$\Pi(D^\epsilon, Q) = \sqrt\epsilon\begin{bmatrix}\sqrt\epsilon\Pi(D_{11}^\epsilon, Q_1) & Q_1D_{12} + (Q_1^{-1})^TD_{21}^T\\ \star & 2\sqrt\epsilon D_{22}\end{bmatrix}$$

Therefore, we can write $\Pi(A_s(\epsilon), Q) = \Pi(A_s^0, Q) + \mathcal{O}(\sqrt\epsilon)$. The proof is completed by applying eigenvalue perturbation [16] (Sec IV, Thm 3.3) to $\Pi(A_s(\epsilon), Q)$: for ϵ small enough, we have $\mu_Q[A_s(\epsilon)] = \bar\lambda[\Pi(A_s(\epsilon), Q)/2] = \bar\lambda[\Pi(A_s^0, Q)/2] + \mathcal{O}(\sqrt\epsilon) \le -\alpha^* + \mathcal{O}(\sqrt\epsilon) \le -\alpha$ for some ϵ-independent $\alpha > 0$. ■

With Lemma 2-3, and by treating $e_3(t)$, $x_{12}(t) := [x_1^T, x_2]^T$ and $u(t)$ as external inputs to the slow error system (16), we derive its ISS property.

Claim 1: Under Assumption 2, for $e_3(t), x_{12}(t), u(t) \in \mathcal{L}_\infty$, there exists positive constants k_{ie}, k_{ix} and k_{iu} $(i = 1, 2)$, all independent of ϵ, such that for ϵ sufficiently small, the trajectory of (16) satisfies

$$\|e_1\|_a \le k_{1e}\|e_3\|_a + \epsilon k_{1x}\|x_{12}\|_a + \epsilon k_{1u}\|u\|_a, \tag{20a}$$

$$\|e_2\|_a \le \frac{k_{2e}}{\sqrt{\epsilon}}\|e_3\|_a + \sqrt{\epsilon}k_{2x}\|x_{12}\|_a + \sqrt{\epsilon}k_{2u}\|u\|_a. \tag{20b}$$

Proof: Let $e_{12} := [e_1^T, e_2]^T$, by applying the result in Lemma 3 to Lemma 2, we obtain:

$$\|e_{12}\|_{a,Q} \le \frac{|B_{se}^\epsilon|_Q}{\alpha}\|e_3\|_a + \epsilon\frac{|B_{sx}^\epsilon|_Q}{\alpha}\|x_{12}\|_a + \epsilon\frac{|B_{su}^\epsilon|_Q}{\alpha}\|u\|_a.$$

Let $d := \sqrt{\underline{\lambda}(Q_1^2)} > 0$ (ϵ-independent), where $\underline{\lambda}(\cdot)$ stands for the smallest eigenvalue, since $d|e_1(t)| \le |e_{12}(t)|_Q$, we have $d\|e_1\|_a \le \|e_{12}\|_{a,Q}$, and subsequently,

$$\|e_1\|_a \le \frac{|B_{se}^\epsilon|_Q}{\alpha d}\|e_3\|_a + \epsilon\frac{|B_{sx}^\epsilon|_Q}{\alpha d}\|x_{12}\|_a + \epsilon\frac{|B_{su}^\epsilon|_Q}{\alpha d}\|u\|_a.$$

Similarly, since $\sqrt{\epsilon}\|e_2\|_a \le \|e_{12}\|_a$, we have

$$\|e_2\|_a \le \frac{|B_{se}^\epsilon|_Q}{\alpha\sqrt{\epsilon}}\|e_3\|_a + \sqrt{\epsilon}\frac{|B_{sx}^\epsilon|_Q}{\alpha}\|x_{12}\|_a + \sqrt{\epsilon}\frac{|B_{su}^\epsilon|_Q}{\alpha}\|u\|_a.$$

By eigenvalue perturbation [16], there exists an ϵ-independent $\kappa > 0$ such that $|B_{se}^\epsilon|_Q^2 = \bar{\lambda}[(E_{13}^\epsilon)^T Q_1^2 E_{13}^\epsilon + \epsilon(E_{23}^\epsilon)^T E_{23}^\epsilon] \le \bar{\lambda}((E_{13}^0)^T Q_1^2 E_{13}^0) + \kappa\epsilon^2$. Hence, for small enough ϵ, there exists an ϵ-independent $L_{se} > 0$ such that $|B_{se}^\epsilon|_Q \le L_{se}$. Similarly, we can find ϵ-independent L_{sx} and L_{su} such that $|B_{sx}^\epsilon|_Q \le L_{sx}$ and $|B_{su}^\epsilon|_Q \le L_{su}$. Claim 1 is proved by substituting these results into the above inequalities for $\|e_i\|_a$. ∎

C. ISS Property of the Fast Error System

Now we study the ISS property of the fast error system (17), treating $e_{12}(t) := [e_1^T, e_2]^T$, u, $\dot{u}$ and $x_{12}(t)$ as its inputs.

Claim 2: If Assumption 1 is satisfied, then for $e_{12}(t)$, $x_i(t)$, $u(t), \dot{u}(t) \in \mathcal{L}_\infty$, there exists positive constants k_{3e}, k_{3x} and k_{3u}, all independent of ϵ, such that the trajectory of (17) satisfies

$$\|e_3\|_a \le \epsilon k_{3e}\|e_{12}\|_a + \epsilon k_{3x}\|x_{12}\|_a + \epsilon k_{3u}\left\|[u, \dot{u}]\right\|_a, \tag{21}$$

for ϵ sufficiently small.

Proof: By Lemma 1, $A_f^0 = S^0$ is Hurwitz. Hence, there exists ϵ-independent Θ and β_0 such that $\mu_\Theta(A_f^0) \le -\beta_0$. Since B_{fe}^0, B_{fx}^0 and B_{fu}^0 are all ϵ-independent, we can find L_i^0 such that $|B_i^0|_\Theta \le L_i^0$. By the same arguments as in Lemma 3 and Claim 1, since A_f^ϵ and B_i^ϵ are ϵ-regular perturbations of A_f^0 and B_i^0, respectively, for ϵ small enough, we can find positive constants β and L_i such that $|A_f^\epsilon|_\Theta \le -\beta$ and $|B_i^\epsilon|_\Theta \le L_i$. Note that since $\mu_\Theta(A_f^\epsilon/\epsilon) = \mu_\Theta(A_f^\epsilon)/\epsilon$, by Lemma 2, we have,

$$\|e_3\|_{a,\Theta} \le \epsilon\frac{L_{fe}}{\beta}\|e_{12}\|_a + \epsilon\frac{L_{fx}}{\beta}\|x_{12}\|_a + \epsilon\frac{L_{fu}}{\beta}\left\|[u, \dot{u}]\right\|_a.$$

Since $\|e_3\|_a \le \|e_3\|_{a,\Theta}/\sqrt{\underline{\lambda}(\Theta^2)}$, and that Θ is independent of ϵ, we have (21) verified. ∎

D. Error between the Full and the Reduced Systems

In Claim 1 and 2, the error bounds depend on the candidate reduced system states x_{12}. The next claim provides an upper bound on these states.

Claim 3: Assume that $u(t)$ has bounded derivatives (i.e., $\mathbf{u} \in \mathcal{L}_\infty$) and that Assumption 2 is satisfied, then there exists a positive constant $k_r = k_r(\|\mathbf{u}\|_\infty)$, independent of ϵ, such that for ϵ sufficiently small, the trajectory of (12) satisfies $\|x_{12}\|_a \le k_r/\sqrt{\epsilon}$.

Proof: (Sketch.) Theorem 2 in [15] establishes that tracking error of a high-gain ($1/\epsilon$) negative feedback interconnection of two SPR systems is $\mathcal{O}(\sqrt{\epsilon})$. With reference to Fig. 2, in the context of (14), this implies that $v_2 = \mathcal{O}(1/\sqrt{\epsilon})$. Regarding v_2 as an input to the series interconnection of Σ_2 and Σ_1^ϵ, since all matrices representing the two systems are $\mathcal{O}(1)$, all state variables are bounded above by $\mathcal{O}(1/\sqrt{\epsilon})$. ∎

Finally, based on Claim 1-3, we are ready to state our main result, which provides ultimate upper bounds of e_1 and e_3 (i.e., $\|e_1\|_a$ and $\|e_3\|_a$) that decrease asymptotically with ϵ. The proof relies on the ISS small-gain theorem [17], [18].

Theorem 1: Assume that $\mathbf{u} \in \mathcal{L}_\infty$ and that Assumptions 1-2 are satisfied, then there exists positive constants $K_i = K_i(\|\mathbf{u}\|_\infty)$, independent of ϵ, such that for ϵ sufficiently small, the trajectories of the full system (9) and the reduced system (12) satisfy $\|z_i - x_i\|_a \le K_i\sqrt{\epsilon}$ for $i = 1, 3$.

Proof: We treat the error dynamics as a feedback interconnection of the slow and fast error dynamics, with states e_{12} and e_3 and external inputs $x_{12}(t)$, $u(t)$ and $\dot{u}(t)$. By inequalities (20), for ϵ sufficiently small, there exists ϵ-independent constants k_{se}, k_{sx} and k_{su} such that the slow error system states e_{12} are bounded by:

$$\|e_{12}\|_a \le \frac{k_{se}}{\sqrt{\epsilon}}\|e_3\|_a + \sqrt{\epsilon}k_{sx}\|x_{12}\|_a + \sqrt{\epsilon}k_{su}\|u\|_a. \tag{22}$$

Therefore, the input-to-state (IS) gain of the slow error system (16) is $k_{se}/\sqrt{\epsilon}$. From (21), the IS gain of the fast error system (17) is ϵk_{3e}. Therefore, the error system IS loop gain satisfies $\epsilon k_{3e} \cdot k_{se}/\sqrt{\epsilon} = \sqrt{\epsilon}k_{se}k_{3e} < 1$ for ϵ small enough. By the ISS small gain theorem (Thm. 10.6.1 in [17]), the error system is ISS. By substituting (22) into (21), for ϵ small enough, we can find ϵ-independent positive constants κ_x and κ_u such that $\|e_3\|_a \le \epsilon\kappa_x\|x_{12}\|_a + \epsilon\kappa_u\|[u, \dot{u}]\|_a$. Using the bound of $\|x_{12}\|_a$ developed in Claim 3, for ϵ small enough, we can find a $K_3 = K_3(\|\mathbf{u}\|_\infty) > 0$ such that $\|e_3\|_a \le \sqrt{\epsilon}(\kappa_x k_r + \sqrt{\epsilon}\kappa_u\|[u, \dot{u}]\|_a) \le K_3\sqrt{\epsilon}$, and subsequently from (20a), there exists a $K_1 = K_1(\|\mathbf{u}\|_\infty) > 0$ such that $\|e_1\|_a \le K_1\sqrt{\epsilon}$. ∎

V. MOTIVATING APPLICATION REVISITED

Here, we apply Theorem 1 to perform model reduction for the linearized FSF in Section II and then use the reduced model to analyze its tracking performance. Suppose the input can be written as $u(t) = \bar{u} + \tilde{u}(t)$, according to [5], the equilibrium $\bar{\zeta}$ corresponding to the constant input $\bar{u}$ satisfies

$$\bar{\zeta}(\bar{u}, \epsilon) := [\bar{c}_1^\epsilon, \bar{c}_2^\epsilon, \bar{p}^\epsilon]^T = \left[\frac{\delta\bar{u}}{\alpha\beta}, \frac{\alpha\beta}{\theta\delta}, \frac{\bar{u}}{\alpha}\right]^T + \mathcal{O}(\epsilon). \tag{23}$$

We linearize (2) about $(\bar{u}, \bar{\zeta})$ to obtain $\epsilon\dot{c}_1 = \tilde{u}(t) - (\theta\bar{c}_2^{\epsilon} + \epsilon\delta)c_1 - \theta\bar{c}_1^{\epsilon}c_2$, $\epsilon\dot{c}_2 = \alpha p - \theta\bar{c}_2^{\epsilon}c_1 - (\theta\bar{c}_1^{\epsilon} + \epsilon\delta)c_2$, and $\dot{p} = \beta c_1 - \delta p$. Following Lemma 1, we find that the ϵ-independent transformation $z_1 = p$, $z_2 = c_1 - c_2$, and $z_3 = \theta\bar{c}_2^0(\bar{c}_1^0 + \bar{c}_2^0)c_1/(\alpha\bar{c}_1^0) + \theta(\bar{c}_1^0 + \bar{c}_2^0)c_2/\alpha - p$ takes the system into normal SSP form:

$$\begin{aligned} \dot{z}_1 &= E_{11}^0 z_1 + E_{12}^0 z_2 + E_{13}^0 z_3, \\ \epsilon\dot{z}_2 &= R^0 z_1 + \epsilon E_{22}^0 z_2 + B_2^0\tilde{u}(t), \\ \epsilon\dot{z}_3 &= \epsilon E_{31}^{\epsilon} z_1 + \epsilon E_{32}^{\epsilon} z_2 + S^{\epsilon} z_3 + B_3^0\tilde{u}(t), \end{aligned} \tag{24}$$

where $R^0 = -\alpha$, $E_{22}^0 = -\delta$, $B_2^0 = 1$, $S^0 = -\theta(\bar{c}_1^0 + \bar{c}_2^0)$, $E_{11}^0 = \frac{\alpha\beta\bar{c}_1^0}{\theta(\bar{c}_1^0+\bar{c}_2^0)^2} - \delta$, $E_{12}^0 = \frac{\beta\bar{c}_1^0}{\bar{c}_1^0+\bar{c}_2^0}$, $B_3^0 = \frac{\theta\bar{c}_2^0(\bar{c}_1^0+\bar{c}_2^0)}{\alpha\bar{c}_1^0}$, and $E_{13}^0 = \frac{\alpha\beta\bar{c}_1^0}{\theta(\bar{c}_1^0+\bar{c}_2^0)^2}$. Using $\bar{\zeta}(\bar{u}, 0)$ computed in (23), we can prove that for any positive rate constants $\alpha, \beta, \theta, \delta$ and input $\bar{u}$, we have $E_{11}^0 < 0$ and $E_{12}^0 > 0$. Hence, independent of exact parameter values, $H_1^0(s) = -R^0(sI - E_{11}^0)^{-1}E_{12}^0 = \alpha E_{12}^0/(s - E_{11}^0)$ is SPR and Assumption 2 can be verified. By (12)-(13), the reduced system of (24) is

$$\begin{aligned} &\dot{x}_1 = E_{11}^0 x_1 + E_{12}^0 x_2 + B_{1r}^0\tilde{u}(t), \\ &\dot{x}_2 = [\tilde{u}(t) - \alpha x_1]/\epsilon - \delta x_2, \quad x_3 = -(S^0)^{-1}B_3\tilde{u}(t), \end{aligned} \tag{25}$$

where $B_{1r}^0 = \beta\bar{c}_2^0/(\bar{c}_1^0 + \bar{c}_2^0)^2$. By Theorem 1, given $\tilde{\mathbf{u}}(t) \in \mathcal{L}_\infty$, we have $\|z_i - x_i\|_a = \mathcal{O}(\sqrt{\epsilon})$ for $i = 1, 3$. In Fig. 3A-B, for a fixed $\epsilon = 0.01$, we demonstrate the closeness of z_i in the full system (24) and x_i in the reduced system (25) when they are subject to the same band-limited white noise input $\tilde{u}(t)$ $(i = 1, 3)$. In Fig. 3C-D, we show that the approximation errors $|e_1|$ and $|e_3|$ decrease with ϵ.

Since $z_1 = p$ is the concentration of the regulated protein, we treat z_1 (x_1) as the output of the full (reduced) system. The reduced system (25) is a high-gain negative feedback interconnection of two SPR systems and tracking performance of such systems has been evaluated in [15]: $\|x_1 - \tilde{u}(t)/\alpha\|_a = \mathcal{O}(\sqrt{\epsilon})$. Therefore, by triangle inequality, tracking performance of the full system must satisfy $\|z_1 - \tilde{u}(t)/\alpha\|_a = \mathcal{O}(\sqrt{\epsilon})$. We thus conclude that independent of the exact rate constants, the linearized FSF in Fig. 1A can track a time-varying input with arbitrarily small error ($\mathcal{O}(\sqrt{\epsilon})$) by increasing all controller reaction rates (decreasing ϵ).

VI. CONCLUSIONS

In this paper, we study a class of linear SSP problems arising from the linearization of FSFs. We have shown that, under certain conditions, such an SSP system can be approximated by an ϵ-dependent reduced-order system, which is a high-gain feedback interconnection of two SPR systems. This result allows us to analytically establish the tracking performance of linearized FSFs. Our future work will focus on reducing the conservativeness of these results in a few directions including, but not limited to, providing an approximation error bound for the pseudo-fast variable (z_2) and computing the error convergence rate. To study the nonlinear FSF model in (2), we also plan to extend our results to nonlinear SSP systems.

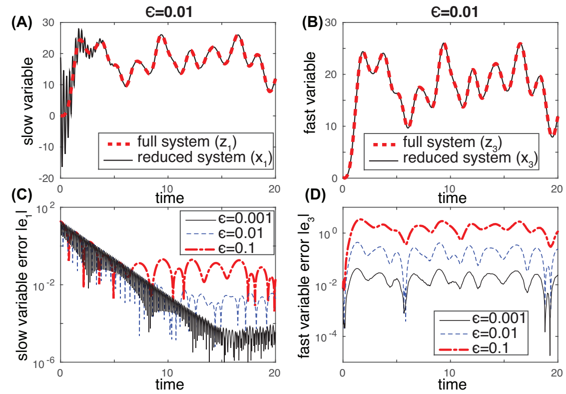

Fig. 3. (A-B): Fast and slow variables in the full and reduced systems with $\epsilon = 0.01$. (C-D) The approximation error of z_1 and z_3 decreases with ϵ. Simulation parameters: $\alpha = \theta = \delta = \bar{u} = 1$.

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