

A Contraction Theory Approach to Singularly Perturbed Systems

Domitilla Del Vecchio and Jean-Jacques Slotine

Department of Mechanical Engineering, MIT

Cambridge, 02139

{ddv, jjs}@mit.edu

Abstract

In this paper, we revisit standard results on singular perturbations and multiple time-scales using convergence analysis tools based on nonlinear contraction theory. Specifically, assuming that the fast and slow subsystems are each partially contracting, we obtain explicit bounds on the convergence rate of the trajectories to the slow manifold and on the asymptotic error between the trajectories of the singularly perturbed system and those of the reduced system. As an application example, we illustrate the design of a biomolecular insulation device.

I. INTRODUCTION

Multiple time-scales have been viewed as a key ingredient of the modular architecture of complex systems ever since [27]. In recent years, this perspective has been strengthened in the context of the flurry of research in systems biology, most notably by [13, 15]. A mathematical treatment has been recently proposed [11, 12], in which the difference of time scales between interconnected components is shown to be responsible for functional modularity. Mathematically, the standard description of dynamical systems with multiple time-scales is based on singular perturbation theory, whose main results were established more than 40 years ago [14, 17, 29]. The standard results on the finite time interval require local exponential stability of the slow manifold to show that trajectories starting sufficiently close to the slow manifold approach an ϵ -neighbor of it, in which ϵ is a small parameter quantifying the time scale separation. Results on the infinite time interval additionally require that the origin of the reduced system is locally exponentially stable. Singular perturbation arguments have been extensively employed in biochemical systems to investigate the validity of the quasi-steady state approximation for enzyme kinetics [4, 26, 30]. More recently, singular perturbation theory has been employed for quantifying impedance-like effects, called retroactivity, in biomolecular networks [6] and for designing

biomolecular insulation devices that attenuate retroactivity to enforce modular composition [11, 12]. In these works, time scale separation is due to differences in the order of magnitude of the reaction rates of the processes considered (Section V).

In this paper, we use comparatively recent convergence analysis tools, based on nonlinear contraction theory and virtual dynamical systems, to revisit some key results on singular perturbations. Nonlinear contraction theory [20, 31], a viewpoint on incremental stability which we briefly review in Section II, has emerged as a powerful tool in applications ranging from Lagrangian mechanics to network control. Historically, ideas closely related to contraction can be traced back to [9] and even to [18] (see also [3, 23], and e.g. [19] for a more exhaustive list of related references). In addition, contraction is preserved through a large variety of systems combinations, which may make it particularly suitable in the context of biological systems [13], subject to evolution and development mechanisms. Here, we assume that the fast and slow subsystems are each partially contracting and leverage robustness results in contraction theory to obtain explicit bounds on the difference between the trajectories of the original system and those of the reduced system. Similarly, we provide explicit bounds on the rate of convergence of the trajectories to the slow manifold. Our bounds hold independently of the value of ϵ and they approach, as ϵ tends to zero, those found in standard singular perturbation results [14].

As an illustration of our result, we derive explicit bounds on retroactivity between two interconnected biomolecular systems [12]. When the time scale of the upstream system is faster than that of its input, the retroactivity at the interconnection with a downstream system is attenuated. Hence, the interconnection is functionally modular, that is, loading effects due to the downstream system only minimally perturb the dynamics of the upstream system. In [12], employing singular perturbation theory, the order of convergence and attenuation were determined as function of ϵ . Here, we provide explicit bounds on both the attenuation and rate of convergence. This result is applied to a one-step reaction model of a phosphorylation system to show how it can be tuned so that the interconnection to any downstream system is functionally modular.

This paper is organized as follows. In Section II, tools from contraction theory are reviewed. In Section III, we give the main result of the paper for systems with two time scales, while in Section IV, we illustrate the extension to multiple time scales. In Section V, we specialize the system structure to those of biomolecular interconnections and then consider a concrete example in Section VI.

II. CONTRACTION THEORY TOOLS

Recall that, given a norm $|\cdot|$ on the state space, and its induced matrix norm $\|\mathbf{A}\|$, for an arbitrary square matrix \mathbf{A} , the associated *matrix measure* μ is defined as (see [5], [22]) $\mu(\mathbf{A}) := \lim_{h \rightarrow 0^+} \frac{1}{h} (\|\mathbf{I} + h\mathbf{A}\| - 1)$. The basic result of nonlinear contraction analysis [20] that we shall use in this paper can be stated as follows.

Theorem 1 (Contraction). *Consider the m -dimensional deterministic system $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, t)$ where \mathbf{f} is a smooth nonlinear function. The system is said to be contracting if any two trajectories, starting from different initial conditions, converge exponentially to each other. A sufficient condition for a system to be contracting is the existence of some matrix measure, μ , such that $\exists \lambda > 0, \forall \mathbf{x}, \forall t \geq 0, \mu\left(\frac{\partial \mathbf{f}(\mathbf{x}, t)}{\partial \mathbf{x}}\right) \leq -\lambda$. The scalar λ defines the contraction rate of the system.*

A proof of this theorem for non-Euclidean norms is shown in [20], Section 3.7(iii) (see also [25]). The standard matrix measures used in this paper are listed in Table I. The condition number of an invertible square matrix \mathbf{A} is defined by $|\mathbf{A}| |\mathbf{A}^{-1}|$, which, for the Euclidean norm, is given by the ratio between the largest and smallest singular values of \mathbf{A} . More generally, contraction may be shown by using matrix measures induced by the weighted vector norm $|\mathbf{x}|_{\Theta, i} = |\Theta \mathbf{x}|_i$, with Θ a constant invertible matrix and $i = 1, 2, \infty$. Such measures, denoted with $\mu_{\Theta, i}$, are linked to the standard measures by: $\mu_{\Theta, i}(\mathbf{A}) = \mu_i(\Theta \mathbf{A} \Theta^{-1})$, $\forall i = 1, 2, \infty$. In this paper, we leave the matrix measure and the corresponding vector norm unspecified as the results hold as stated independently of the norm employed.

TABLE I

STANDARD MATRIX MEASURES FOR A REAL $n \times n$ MATRIX, $\mathbf{A} = [a_{ij}]$. THE i -TH EIGENVALUE OF \mathbf{A} IS DENOTED WITH $\lambda_i(\mathbf{A})$.

vector norm, $ \cdot $	induced matrix norm, $ \mathbf{A} $	induced matrix measure, $\mu(\mathbf{A})$
$ \mathbf{x} _1 = \sum_{j=1}^n x_j $	$ \mathbf{A} _1 = \max_j \sum_i a_{ij} $	$\mu_1(\mathbf{A}) = \max_j (a_{jj} + \sum_{i \neq j} a_{ij})$
$ \mathbf{x} _2 = \left(\sum_{j=1}^n x_j ^2\right)^{\frac{1}{2}}$	$ \mathbf{A} _2 = \sqrt{\max_i \lambda_i(\mathbf{A}^T \mathbf{A})}$	$\mu_2(\mathbf{A}) = \max_i \left(\lambda_i \left\{ \frac{A+A^*}{2} \right\} \right)$
$ \mathbf{x} _\infty = \max_{1 \leq j \leq n} x_j $	$ \mathbf{A} _\infty = \max_i \sum_j a_{ij} $	$\mu_\infty(\mathbf{A}) = \max_i (a_{ii} + \sum_{j \neq i} a_{ij})$

For convenience, we will also say that a *function* $\mathbf{f}(\mathbf{x}, t)$ is contracting if the system $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, t)$ satisfies the sufficient condition of Theorem 1. Similarly, we will then say that the corresponding Jacobian *matrix* $\frac{\partial \mathbf{f}}{\partial \mathbf{x}}(\mathbf{x}, t)$ is contracting. We shall also use the following property of contracting systems [20, 28].

Lemma 1. (Robustness) *Assume that the system $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, t)$ is contracting, with an associated metric*

transformation Θ and contraction rate λ , and consider the “perturbed” system $\dot{\mathbf{x}}_p = \mathbf{f}(\mathbf{x}_p, t) + \mathbf{d}(\mathbf{x}_p, t)$ where $\mathbf{d}(\mathbf{x}_p, t)$ is bounded, that is, $\exists d \geq 0, \forall \mathbf{x}_p, \forall t \geq 0, |\mathbf{d}(\mathbf{x}_p, t)| \leq d$. Then, any trajectory of the perturbed system satisfies $|\mathbf{x}_p(t) - \mathbf{x}(t)| \leq \chi e^{-\lambda t} |\mathbf{x}_p(0) - \mathbf{x}(0)| + \frac{d\chi}{\lambda}$, in which χ is an upper bound on the condition number of Θ [20, 21].

Proof: With $R(t) = |\Theta(\mathbf{x}_p(t) - \mathbf{x}(t))|$, one has (see [20]) $\frac{d}{dt}R + \lambda R \leq |\Theta \mathbf{d}(\mathbf{x}_p, t)|$. Similarly, using the 1-norm or the ∞ -norm, and proceeding as in [7] (Chapter 4) one has $\frac{d^+}{dt}R + \lambda R \leq |\Theta \mathbf{d}(\mathbf{x}_p, t)|$ where $\frac{d^+}{dt}$ denotes the right-hand derivative with respect to time. Integrating the above yields the result. ■

This lemma is valid for all norms and matrix measures from Table 1 (employed to compute the contraction rate) as long as they are chosen consistently.

III. BASIC RESULTS

We consider the standard singular perturbation framework [14]

$$\begin{cases} \dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{z}, t) \\ \epsilon \dot{\mathbf{z}} = \mathbf{g}(\mathbf{x}, \mathbf{z}, \epsilon), \epsilon \geq 0 \end{cases} \quad (1)$$

Definition 1. [31] System (1) is said to be *partially contracting in \mathbf{x}* if the virtual system

$$\dot{\mathbf{y}}_x = \mathbf{f}(\mathbf{y}_x, \mathbf{z}(t), t) \quad (2)$$

is contracting for any $\mathbf{z}(t)$ and for all t . Similarly, system (1) is said to be *partially contracting in \mathbf{z}* if the virtual system

$$\epsilon \dot{\mathbf{y}}_z = \mathbf{g}(\mathbf{x}(t), \mathbf{y}_z, \epsilon) \quad (3)$$

is contracting for any $\mathbf{x}(t)$ and for all $\epsilon > 0$.

Theorem 2. *If system (1) is partially contracting in \mathbf{z} , then equation $\mathbf{g}(\mathbf{x}, \mathbf{z}, \epsilon) = \mathbf{0}$ can be equivalently written as $\mathbf{z} = \gamma(\mathbf{x}, \epsilon)$, i.e., there is a unique, global mapping between \mathbf{x}, ϵ and \mathbf{z} .*

Proof: The virtual system $\epsilon \dot{\mathbf{y}}_z = \mathbf{g}(\mathbf{x}_o, \mathbf{y}_z, \epsilon)$ is contracting by hypothesis, for any $\mathbf{x}_o(t)$. If we set \mathbf{x}_o equal to some *constant* vector, this system is also autonomous, and therefore tends to a unique

equilibrium [20]. Thus for any given \mathbf{x}_o , the algebraic equation $\mathbf{g}(\mathbf{x}_o, \mathbf{y}_z, \epsilon) = \mathbf{0}$ has a unique solution, which we can denote $\mathbf{y}_z = \gamma(\mathbf{x}_o, \epsilon)$. ■

Denote $\gamma(\mathbf{x}) := \gamma(\mathbf{x}, 0)$ and assume it is globally differentiable. Differentiating the relation $\mathbf{g}(\mathbf{x}, \gamma(\mathbf{x}), 0) = \mathbf{0}$ with respect to \mathbf{x} then yields the familiar expression

$$\frac{\partial \gamma(\mathbf{x})}{\partial \mathbf{x}} = - \left(\frac{\partial \mathbf{g}}{\partial \mathbf{z}} \right)^{-1} \frac{\partial \mathbf{g}}{\partial \mathbf{x}}(\mathbf{x}, \gamma(\mathbf{x}), 0), \quad (4)$$

which is valid globally, as the matrix $\frac{\partial \mathbf{g}}{\partial \mathbf{z}}$ is uniformly invertible.

Lemma 2. *Assume that system (1) is partially contracting in \mathbf{z} , with an associated metric transformation Θ_z , and let λ_z/ϵ be the contraction rate of (3). Assume further that, given (4), one can write $\exists d \geq 0, \forall \mathbf{x}, \forall \mathbf{z}, \forall t \geq 0, \left| \frac{\partial \gamma(\mathbf{x})}{\partial \mathbf{x}} \mathbf{f}(\mathbf{x}, \mathbf{z}, t) \right| \leq d$ and that $\mathbf{g}(\mathbf{x}, \mathbf{z}, \epsilon)$ is Lipschitz continuous in ϵ with constant K . Then, any trajectory of (1) is such that*

$$|\mathbf{z}(t) - \gamma(\mathbf{x}(t))| \leq \chi_z e^{-(\lambda_z/\epsilon)t} |\mathbf{z}(0) - \gamma(\mathbf{x}(0))| + \frac{(d+K)\chi_z}{\lambda_z} \epsilon \quad \forall t \geq 0, \quad (5)$$

where χ_z is an upper bound on the condition number of Θ_z .

Proof: Note that $\mathbf{y}_z = \mathbf{z}(t)$ is a solution of the contracting virtual system $\epsilon \dot{\mathbf{y}}_z = \mathbf{g}(\mathbf{x}(t), \mathbf{y}_z, \epsilon)$ while $\mathbf{y}_{zd} = \gamma(\mathbf{x}(t))$ is a solution of the ‘‘perturbed’’ contracting virtual system $\epsilon \dot{\mathbf{y}}_{zd} = \mathbf{g}(\mathbf{x}(t), \mathbf{y}_{zd}, \epsilon) + \epsilon \frac{\partial \gamma(\mathbf{x})}{\partial \mathbf{x}} \mathbf{f}(\mathbf{x}(t), \mathbf{z}(t), t) + (\mathbf{g}(\mathbf{x}(t), \mathbf{y}_{zd}, 0) - \mathbf{g}(\mathbf{x}(t), \mathbf{y}_{zd}, \epsilon))$. Let $\mathbf{d}(\mathbf{y}_{zd}, t) := \epsilon \frac{\partial \gamma(\mathbf{x})}{\partial \mathbf{x}} \mathbf{f}(\mathbf{x}(t), \mathbf{z}(t), t) + (\mathbf{g}(\mathbf{x}(t), \mathbf{y}_{zd}, 0) - \mathbf{g}(\mathbf{x}(t), \mathbf{y}_{zd}, \epsilon))$. Then, applying Lemma 1 yields $|\mathbf{y}_z(t) - \mathbf{y}_{zd}(t)| \leq \chi_z e^{-(\lambda_z/\epsilon)t} |\mathbf{y}_z(0) - \mathbf{y}_{zd}(0)| + \frac{\bar{d}\chi_z}{\lambda_z}$, in which \bar{d} is such that $|\mathbf{d}(\mathbf{y}_{zd}, t)| \leq \bar{d}$. By the assumptions of the lemma, in turn, we can take $\bar{d} = \epsilon d + K \epsilon$, which gives the bound (5). ■

Theorem 3. *Assume, in addition to the hypotheses of the previous Lemma, that system (1) is partially contracting in \mathbf{x} , with an associated metric transformation Θ_x , and let λ_x be the contraction rate of (2). Assume furthermore that $\mathbf{f}(\mathbf{x}, \mathbf{z}, t)$ is Lipschitz continuous in \mathbf{z} , with Lipschitz constant α and that $\gamma(\mathbf{x})$ is Lipschitz continuous with Lipschitz constant α_γ . Let \mathbf{x}_γ be a solution of the reduced system*

$$\dot{\mathbf{x}}_\gamma = \mathbf{f}(\mathbf{x}_\gamma, \gamma(\mathbf{x}_\gamma), t). \quad (6)$$

Then, any trajectory of (1) satisfies

$$|\mathbf{x}(t) - \mathbf{x}_\gamma(t)| \leq \chi_x |\mathbf{x}(0) - \mathbf{x}_\gamma(0)| e^{-\lambda_x t} + \epsilon (C_1 (e^{-\lambda_x t} - e^{-(\lambda_z/\epsilon)t}) + C_2 (1 - e^{-\lambda_x t})), \quad \forall t \geq 0, \quad (7)$$

and

$$|\mathbf{z}(t) - \gamma(\mathbf{x}_\gamma(t))| \leq \chi_z e^{-(\lambda_z/\epsilon)t} |\mathbf{z}(0) - \gamma(\mathbf{x}(0))| + \frac{(d+K)\chi_z}{\lambda_z} \epsilon + \alpha_\gamma \chi_x |\mathbf{x}(0) - \mathbf{x}_\gamma(0)| e^{-\lambda_x t} + \alpha_\gamma \epsilon (C_1 (e^{-\lambda_x t} - e^{-(\lambda_z/\epsilon)t}) + C_2 (1 - e^{-\lambda_x t})), \quad \forall t \geq 0, \quad (8)$$

in which $C_1 = \frac{\chi_x \alpha \chi_z |\mathbf{z}(0) - \gamma(\mathbf{x}(0))|}{(\lambda_z - \epsilon \lambda_x)}$, $C_2 = \frac{\chi_x \alpha \chi_z (d+K)}{\lambda_z \lambda_x}$, and χ_x is an upper bound on the condition number of Θ_x .

Proof: Write $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{z}, t) = \mathbf{f}(\mathbf{x}, \gamma(\mathbf{x}), t) + (\mathbf{f}(\mathbf{x}, \mathbf{z}, t) - \mathbf{f}(\mathbf{x}, \gamma(\mathbf{x}), t))$ and let $\Delta_2(t) := \mathbf{f}(\mathbf{x}, \mathbf{z}, t) - \mathbf{f}(\mathbf{x}, \gamma(\mathbf{x}), t)$. Since \mathbf{f} is Lipschitz continuous in \mathbf{z} , we have that $|\Delta_2(t)| \leq \alpha |\mathbf{z} - \gamma(\mathbf{x})|$, in which, by Lemma 2 we have that $|\mathbf{z} - \gamma(\mathbf{x})| \leq \chi_z |\mathbf{z}(0) - \gamma(\mathbf{x}(0))| e^{-(\lambda_z/\epsilon)t} + \frac{(d+K)\chi_z}{\lambda_z} \epsilon$, $\forall t \geq 0$. Letting $R = |\Theta_x(\mathbf{x} - \mathbf{x}_\gamma)|$, we have that (see proof of Lemma 1) $\frac{d^+}{dt} R + \lambda_x R \leq |\Theta_x \Delta_2(t)|$. Integrating this and considering the bound on $\Delta_2(t)$ leads to inequality (7). Finally, since $|\mathbf{z}(t) - \gamma(\mathbf{x}_\gamma(t))| \leq |\mathbf{z}(t) - \gamma(\mathbf{x}(t))| + |\gamma(\mathbf{x}(t)) - \gamma(\mathbf{x}_\gamma(t))|$ and $\gamma(\mathbf{x})$ is Lipschitz continuous with Lipschitz constant α_γ , inequality (8) follows from Lemma 2 and inequality (7). ■

Remark. In singular perturbation theory, we have that $\mathbf{x}(0) = \mathbf{x}_\gamma(0)$ and that $\epsilon \ll 1$. Under these conditions, Theorem 3 implies that for any given $t_b > 0$, there is an $\epsilon^* > 0$ such that for all $\epsilon \leq \epsilon^*$ we have that $|\mathbf{z}(t) - \gamma(\mathbf{x}_\gamma(t))| = O(\epsilon)$ for all $t \geq t_b$ and that $|\mathbf{x}(t) - \mathbf{x}_\gamma(t)| = O(\epsilon)$ for all $t \geq 0$. The advantage of the approach through contraction theory is that ϵ does not need to be small and the bounds are quantified in terms of known parameters. The conditions required by the contraction approach are, however, stronger than the local exponential stability requirements in singular perturbation theory.

IV. MULTIPLE TIME SCALES

In this section, we apply Theorem 3 to systems with three different time scales:

$$\begin{cases} \dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}, \mathbf{z}, \mathbf{w}, t) \\ \epsilon_1 \dot{\mathbf{z}} &= \mathbf{g}(\mathbf{x}, \mathbf{z}, \mathbf{w}, \epsilon_1), \quad \epsilon_1 \geq 0 \\ \epsilon_2 \dot{\mathbf{w}} &= \mathbf{h}(\mathbf{x}, \mathbf{z}, \mathbf{w}, \epsilon_2), \quad \epsilon_2 \geq 0 \end{cases} \quad (9)$$

Let $\nu_1 := \epsilon_1$, $\nu_2 := \epsilon_2/\epsilon_1$, $\mathbf{q} := (\mathbf{z}, \mathbf{w})$, $\mathbf{H}(\mathbf{x}, \mathbf{q}, \nu_1, \nu_1\nu_2) := (\mathbf{g}(\mathbf{x}, \mathbf{q}, \nu_1), \frac{1}{\nu_2}\mathbf{h}(\mathbf{x}, \mathbf{q}, \nu_1\nu_2))$, and re-write system (9) as

$$\begin{cases} \dot{\mathbf{x}} &= \mathbf{f}(\mathbf{x}, \mathbf{q}, t) \\ \nu_1 \dot{\mathbf{q}} &= \mathbf{H}(\mathbf{x}, \mathbf{q}, \nu_1, \nu_1\nu_2). \end{cases} \quad (10)$$

Assumption 1. System (10) is partially contracting in \mathbf{q} with metric transformation Θ_q . Furthermore, there is $\lambda^* > 0$ such that the contraction rate is given by λ_q/ν_1 in which

$$\lambda_q = \lambda^* \min\left(1, \frac{1}{\nu_2}\right). \quad (11)$$

Proposition 1. Consider system (10) and assume that $J_H := \begin{pmatrix} \frac{\partial \mathbf{g}}{\partial \mathbf{q}} \\ \frac{\partial \mathbf{h}}{\partial \mathbf{q}} \end{pmatrix}$ is such that there is $\lambda > 0$ such that $\mu_\infty(J_H) \leq -\lambda$ for all \mathbf{x} and for all $\nu_1, \nu_2 > 0$. Then, Assumption 1 is satisfied with $\lambda^* = \lambda$ and $\Theta_q = \mathbb{I}$.

Proof: Let $J := \frac{\partial H}{\partial \mathbf{q}} = [J_{ij}]$ be the Jacobian of H and re-write it as $J = \begin{pmatrix} J^a \\ \frac{1}{\nu_2} J^b \end{pmatrix}$ with $J^a = [J_{ij}^a] = \frac{\partial \mathbf{g}}{\partial \mathbf{q}}$ and $J^b = [J_{ij}^b] = \frac{\partial \mathbf{h}}{\partial \mathbf{q}}$. By the assumption of the Lemma, we have that $\max_i (J_{ii}^a + \sum_{j \neq i} |J_{ij}^a|) \leq -\lambda$ and $\max_i (J_{ii}^b + \sum_{j \neq i} |J_{ij}^b|) \leq -\lambda$. Hence, we have that $\mu_\infty(J) = \max_i (J_{ii}^a + \sum_{j \neq i} |J_{ij}^a|) = \max\left(\max_i (J_{ii}^a + \sum_{j \neq i} |J_{ij}^a|), \frac{1}{\nu_2} \max_i (J_{ii}^b + \sum_{j \neq i} |J_{ij}^b|)\right) \leq \max\left(-\lambda, -\frac{\lambda}{\nu_2}\right)$. It thus follows that $\mu_\infty(J) \leq -\lambda \min\left(1, \frac{1}{\nu_2}\right)$, which implies that system (10) is partially contracting in \mathbf{q} with metric μ_∞ , metric transformation $\Theta_q = \mathbb{I}$, and contraction rate λ_q/ν_1 in which $\lambda_q = \lambda \min(1, 1/\nu_2)$. ■

Assumption 2. The equation $\mathbf{H}(\mathbf{x}, \mathbf{q}, 0, 0) = 0$ has a unique global differentiable solution $\mathbf{q} = \gamma_q(\mathbf{x}) = (\gamma_z(\mathbf{x}), \gamma_w(\mathbf{x}))$.

Lemma 3. Assume that one can write $\exists d \geq 0, \forall \mathbf{x}, \forall \mathbf{z}, \forall \mathbf{w}, \forall t \geq 0, \left| \frac{\partial \gamma_q(\mathbf{x})}{\partial \mathbf{x}} \mathbf{f}(\mathbf{x}, \mathbf{z}, \mathbf{w}, t) \right| \leq d$ and that $\mathbf{H}(\mathbf{x}, \mathbf{q}, \nu_1, \nu_1 \nu_2)$ is Lipschitz continuous with respect to ν_1 with constant K . Then, any trajectory of (9) is such that for all $t \geq 0$

$$|(\mathbf{z}(t), \mathbf{w}(t)) - (\gamma_z(\mathbf{x}(t)), \gamma_w(\mathbf{x}(t)))| \leq \chi_q e^{-(\lambda_q/\epsilon_1)t} |(\mathbf{z}(0), \mathbf{w}(0)) - (\gamma_z(\mathbf{x}(0)), \gamma_w(\mathbf{x}(0)))| + \frac{(d+K)\chi_q}{\lambda_q} \epsilon_1, \quad (12)$$

where χ_q is an upper bound on the condition number of Θ_q and $\lambda_q = \lambda^* \min(1, 1/\nu_2)$.

Proof: Apply Lemma 2 to system (10). This system is partially contracting in \mathbf{q} by the assumptions of the Lemma with contraction rate λ_q/ν_1 and λ_q satisfying equation (11). ■

Theorem 4. Assume, in addition to the hypotheses of Lemma 3, that system (10) is partially contracting in \mathbf{x} , with an associated metric transformation Θ_x , and let λ_x be the contraction rate. Assume furthermore that $\mathbf{f}(\mathbf{x}, \mathbf{z}, \mathbf{w}, t)$ is Lipschitz continuous in (\mathbf{z}, \mathbf{w}) , with Lipschitz constant α and

that $\gamma_q(\mathbf{x})$ is Lipschitz continuous with constant α_γ . Let \mathbf{x}_γ be the solution of the reduced system given by $\dot{\mathbf{x}}_\gamma = \mathbf{f}(\mathbf{x}_\gamma, \gamma_z(\mathbf{x}_\gamma), \gamma_w(\mathbf{x}_\gamma), t)$, with $\mathbf{x}_\gamma(0) = \mathbf{x}(0)$. Then, any trajectory of (9) satisfies $|\mathbf{x}(t) - \mathbf{x}_\gamma(t)| \leq \epsilon_1 (C_1(e^{-\lambda_x t} - e^{-(\lambda_q/\epsilon_1)t}) + C_2(1 - e^{-\lambda_x t})) \forall t \geq 0$, and

$$\begin{aligned} |(\mathbf{z}(t), \mathbf{w}(t)) - (\gamma_z(\mathbf{x}_\gamma(t)), \gamma_w(\mathbf{x}_\gamma(t)))| &\leq \chi_q e^{-(\lambda_q/\epsilon_1)t} |(\mathbf{z}(0), \mathbf{w}(0)) - (\gamma_z(\mathbf{x}(0)), \gamma_w(\mathbf{x}(0)))| \\ &\quad + \frac{(d+K)\chi_q}{\lambda_q} \epsilon_1 + \alpha_\gamma \epsilon_1 (C_1(e^{-\lambda_x t} - e^{-(\lambda_q/\epsilon_1)t}) + C_2(1 - e^{-\lambda_x t})), \end{aligned}$$

in which $C_1 = \frac{\chi_x \alpha \chi_q |(\mathbf{z}(0), \mathbf{w}(0)) - (\gamma_z(\mathbf{x}(0)), \gamma_w(\mathbf{x}(0)))|}{(\lambda_q - \epsilon_1 \lambda_x)}$, $C_2 = \frac{\chi_x \alpha \chi_q (d+K)}{\lambda_q \lambda_x}$, and χ_x is an upper bound on the condition number of Θ_x . Furthermore, as $\epsilon_1, \epsilon_2 \rightarrow 0$ the trajectories of system (9) are such that $|\mathbf{x}(t) - \mathbf{x}_\gamma(t)| = O(\epsilon_1) + O(\epsilon_2)$ and for all $t_b > 0$ there are $\epsilon_1^* > 0, \epsilon_2^* > 0$ such that $\epsilon_1 \leq \epsilon_1^*$ and $\epsilon_2 \leq \epsilon_2^*$ imply $|(\mathbf{z}(t), \mathbf{w}(t)) - (\gamma_z(\mathbf{x}_\gamma(t)), \gamma_w(\mathbf{x}_\gamma(t)))| = O(\epsilon_1) + O(\epsilon_2), \forall t \geq t_b$.

Proof: Apply Theorem 3 to system (10). By equation (11), when $\nu_2 > 1$ and $\epsilon_1, \epsilon_2 \rightarrow 0$ we have that $C_1, C_2 = O(\epsilon_2/\epsilon_1)$, while when $\nu_2 \leq 1$ we have that $C_1, C_2 = O(1)$ as $\epsilon_1, \epsilon_2 \rightarrow 0$. This leads to the desired result. \blacksquare

V. ATTAINING MODULARITY IN BIOMOLECULAR SYSTEMS THROUGH TIME SCALE SEPARATION

Here, we illustrate how the tools developed in the previous sections can be applied to obtain explicit bounds on retroactivity attenuation as studied in earlier work [11, 12]. Let $\mathbf{u} \in D_u \subset \mathbb{R}_+^q$, $\mathbf{y} \in D_y \subset \mathbb{R}_+^n$, and $\mathbf{v} \in D_v \subset \mathbb{R}_+^p$ be vectors whose components denote concentrations of chemical species, such as proteins, enzymes, DNA sites, etc. We consider the following model for an isolated biomolecular system (similar to that of metabolic networks [16]):

$$\begin{cases} \dot{\mathbf{u}}_{\text{is}} &= \mathbf{h}(\mathbf{u}_{\text{is}}, t) + G_1 \mathbf{A} \mathbf{r}(\mathbf{y}_{\text{is}}, \mathbf{u}_{\text{is}}) \\ \dot{\mathbf{y}}_{\text{is}} &= G_1 \mathbf{B} \mathbf{r}(\mathbf{y}_{\text{is}}, \mathbf{u}_{\text{is}}) + G_1 \mathbf{l}(\mathbf{y}_{\text{is}}, \mathbf{u}_{\text{is}}), \end{cases} \quad (13)$$

in which $\mathbf{h}(\mathbf{u}, t) \in \mathbb{R}^q$ is a reaction rate vector modeling the dynamics of species \mathbf{u} , $\mathbf{r}(\mathbf{y}, \mathbf{u}) \in \mathbb{R}^r$ is a reaction rate vector modeling the interaction of species in the vector \mathbf{u} with species in the vector \mathbf{y} , $\mathbf{l}(\mathbf{y}, \mathbf{u}) \in \mathbb{R}^n$ is a reaction rate vector driving the dynamics of \mathbf{y} , $\mathbf{A} \in \mathbb{R}^{r \times q}$, $\mathbf{B} \in \mathbb{R}^{r \times n}$, and G_1 is a positive constant. Consider next the interconnection of this system with a downstream system whose

vector of species is \mathbf{v} :

$$\begin{cases} \dot{\mathbf{u}} = & \mathbf{h}(\mathbf{u}, t) + G_1 \mathbf{A} \mathbf{r}(\mathbf{y}, \mathbf{u}) \\ \dot{\mathbf{y}} = & G_1 \mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{u}) + G_1 \mathbf{l}(\mathbf{y}, \mathbf{u}) + G_2 \mathbf{C} \mathbf{s}(\mathbf{y}, \mathbf{v}) \\ \dot{\mathbf{v}} = & G_2 \mathbf{D} \mathbf{s}(\mathbf{y}, \mathbf{v}), \end{cases} \quad (14)$$

in which $\mathbf{s}(\mathbf{y}, \mathbf{v}) \in \mathbb{R}^s$ is a reaction rate vector modeling the interaction between the \mathbf{y} -subsystem and the \mathbf{v} -subsystem. Here, $G_2 = \beta G_1$ with $\beta > 0$. We assume that $\mathbf{u}(0) = \mathbf{u}_{\text{is}}(0)$ and $\mathbf{y}(0) = \mathbf{y}_{\text{is}}(0)$.

System (14) is a general model for a biomolecular system. Interconnections always occur through reactions, whose rates (\mathbf{r} and \mathbf{s} , in this case) appear in both the upstream and the downstream systems with different coefficients. Constant G_1 models the timescale of the system. We are interested in those cases in which the system evolves on a faster timescale than that of its input, that is, $G_1 \gg 1$. This situation is encountered, for example, when the \mathbf{y} dynamics model protein modification processes (such as phosphorylation, allosteric modification, dimerization, etc.), while the dynamics of \mathbf{u} model slower processes such as protein production and decay or signaling from outside the cell (here modeled by $\mathbf{h}(\mathbf{u}, t)$) [2, 10, 24]. Constant G_2 models the timescale of the interconnection mechanism of the \mathbf{y} -subsystems with the \mathbf{v} -subsystem. For example, when this downstream system models gene expression, \mathbf{s} models the binding and unbinding process of transcription factors to DNA binding sites. This reaction is faster than production and decay of proteins and therefore we also have that $G_2 \gg 1$ [2, 8].

Definition 2. (*Functionally Modular Interconnection*) We say that the interconnection of system (14) is functionally modular provided there are constants $G^*, K_0, K_1, \lambda > 0$ (not depending on G_1 and G_2) such that for all $G_1 > G^*$ we have that $|\mathbf{y}(t) - \mathbf{y}_{\text{is}}(t)| \leq K_0 e^{-\lambda G_1 t} + \frac{K_1}{G_1}$.

Note that system (14) can be viewed as a perturbed version of system (13). Hence, one could, in principle, apply the robustness result given in Lemma 1. Assuming that the isolated system is contracting with contraction rate λG_1 , one would obtain that the trajectories of the perturbed system exponentially converge with rate λG_1 to a neighbor of the isolated system trajectory of amplitude $a G_2 / G_1$ for a suitable $a > 0$. This would not show that the interconnection is functionally modular because this neighbor cannot be made arbitrarily small by increasing G_1 given that $G_2 = \beta G_1$. We show in what follows that even if G_2 is as large as G_1 , the structure of the interconnection and the application of the results of the previous section lead to showing that the interconnection is functionally modular. Assume that system (14) has the two following properties (see [12]).

P1 There is an invertible matrix $\mathbf{T} \in \mathbb{R}^{q \times q}$ and a matrix $\mathbf{M} \in \mathbb{R}^{n \times q}$ such that $\mathbf{T} \mathbf{A} + \mathbf{M} \mathbf{B} = 0$, $\mathbf{M} \mathbf{l}(\mathbf{y}, \mathbf{u}) = 0$ for all (\mathbf{y}, \mathbf{u}) , and $\mathbf{M} \mathbf{C} = 0$;

P2 $\ker(\mathbf{D}) \subseteq \ker(\mathbf{C})$.

Using the change of variables $\mathbf{x} = \mathbf{T} \mathbf{u} + \mathbf{M} \mathbf{y}$, using Property P1, and letting $\epsilon = 1/G_1$, we obtain

$$\begin{cases} \dot{\mathbf{x}}_{is} &= \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x}_{is} - \mathbf{M} \mathbf{y}_{is}), t) \\ \epsilon \dot{\mathbf{y}}_{is} &= \mathbf{B} \mathbf{r}(\mathbf{y}_{is}, \mathbf{T}^{-1}(\mathbf{x}_{is} - \mathbf{M} \mathbf{y}_{is})) + \mathbf{l}(\mathbf{y}_{is}, \mathbf{T}^{-1}(\mathbf{x}_{is} - \mathbf{M} \mathbf{y}_{is})), \end{cases}$$

and

$$\begin{cases} \dot{\mathbf{x}} &= \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t) \\ \epsilon \dot{\mathbf{y}} &= \mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \mathbf{l}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \beta \mathbf{C} \mathbf{s}(\mathbf{y}, \mathbf{v}) \\ \epsilon \dot{\mathbf{v}} &= \beta \mathbf{D} \mathbf{s}(\mathbf{x}, \mathbf{v}). \end{cases}$$

Lemma 4. Assume that system (15) is partially contracting in \mathbf{y}_{is} , with an associated metric transformation $\Theta_{\mathbf{y}}$, and let λ_y/ϵ be the contraction rate. Let $\mathbf{y} = \gamma_{\mathbf{y}}(\mathbf{x})$ be the globally unique and differentiable solution of $\mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \mathbf{l}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) = 0$. Assume that $\exists d \geq 0, \forall \mathbf{y}, \forall \mathbf{x}, \forall t \geq 0, \left| \frac{\partial \gamma_{\mathbf{y}}(\mathbf{x})}{\partial \mathbf{x}} \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t) \right| \leq d$. Further, assume that system (15) is partially contracting in \mathbf{x}_{is} , with an associated metric transformation $\Theta_{\mathbf{x}}$, and let λ_x be the contraction rate. Let $\mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t)$ be Lipschitz continuous in \mathbf{y} , with Lipschitz constant α and let $\gamma_{\mathbf{y}}(\mathbf{x})$ be Lipschitz continuous with constant α_{γ} . Let \mathbf{x}_{γ} be the solution of the reduced system

$$\dot{\mathbf{x}}_{\gamma} = \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x}_{\gamma} - \mathbf{M} \gamma_{\mathbf{y}}(\mathbf{x}_{\gamma})), t), \quad \mathbf{x}_{\gamma}(0) = \mathbf{x}(0). \quad (15)$$

Then, $|\mathbf{y}_{is}(t) - \gamma_{\mathbf{y}}(\mathbf{x}_{\gamma}(t))| \leq \chi_y e^{-(\lambda_y/\epsilon)t} |\mathbf{y}_{is}(0) - \gamma_{\mathbf{y}}(\mathbf{x}(0))| + \frac{d \chi_y \epsilon}{\lambda_y} + \alpha_{\gamma} \epsilon (C_1 (e^{-\lambda_x t} - e^{-(\lambda_y/\epsilon)t}) + C_2 (1 - e^{-\lambda_x t}))$, in which $C_1 = \frac{\chi_x \alpha \chi_y |\mathbf{y}_{is}(0) - \gamma_{\mathbf{y}}(\mathbf{x}_{is}(0))|}{(\lambda_y - \epsilon \lambda_x)}$, $C_2 = \frac{\chi_y \alpha \chi_x d}{\lambda_y \lambda_x}$, with χ_y and χ_x upper bounds on the condition numbers of $\Theta_{\mathbf{y}}$ and $\Theta_{\mathbf{x}}$, respectively.

Proof: Apply Theorem 3 to system (15) with $\mathbf{x} = \mathbf{x}_{is}$, $\mathbf{z} = \mathbf{y}_{is}$, $\mathbf{f}(\mathbf{x}, \mathbf{z}, t) = \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t)$, and $\mathbf{g}(\mathbf{x}, \mathbf{z}, \epsilon) = \mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \mathbf{l}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}))$. \blacksquare

Lemma 5. Let the assumptions of Lemma 4 be satisfied. Let system (15) be partially contracting in $\mathbf{z} = (\mathbf{y}, \mathbf{v})$ with associated metric transformation $\Theta_{\mathbf{z}}$ and let λ_z/ϵ be the contraction rate. Let $\mathbf{z} = \gamma_{\mathbf{z}}(\mathbf{x})$ be the globally unique solution of $\{\mathbf{D} \mathbf{s}(\mathbf{x}, \mathbf{v}) = 0$ and $\mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \mathbf{l}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \beta \mathbf{C} \mathbf{s}(\mathbf{y}, \mathbf{v}) = 0\}$. Assume that $\exists d' \geq 0, \forall \mathbf{z}, \forall \mathbf{x}, \forall t \geq 0, \left| \frac{\partial \gamma_{\mathbf{z}}(\mathbf{x})}{\partial \mathbf{x}} \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t) \right| \leq d'$. Let $\gamma_{\mathbf{z}}(\mathbf{x})$ be Lipschitz continuous with constant α'_{γ} . Let x_{γ} be the solution of the reduced system (15). Then,

$|\mathbf{y}(t) - \gamma_y(\mathbf{x}_\gamma(t))| \leq \chi_z e^{-(\lambda_z/\epsilon)t} |\mathbf{z}(0) - \gamma_z(\mathbf{x}(0))| + \frac{d' \chi_z \epsilon}{\lambda_z} + \alpha'_\gamma \epsilon (C'_1 (e^{-\lambda_x t} - e^{-(\lambda_z/\epsilon)t}) + C'_2 (1 - e^{-\lambda_x t}))$, in which $C'_1 = \frac{\chi_z \alpha \chi_x |\mathbf{z}(0) - \gamma_z(\mathbf{x}(0))|}{(\lambda_z - \epsilon \lambda_x)}$, $C'_2 = \frac{\chi_z \alpha \chi_x d'}{\lambda_z \lambda_x}$, with χ_z and χ_x upper bounds on the condition numbers of Θ_z and Θ_x , respectively.

Proof: Apply Theorem 3 with $\mathbf{f}(\mathbf{x}, \mathbf{z}, t) = \mathbf{T} \mathbf{h}(\mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y}), t)$, $\mathbf{g}(\mathbf{x}, \mathbf{z}, \epsilon) = (\mathbf{B} \mathbf{r}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \mathbf{l}(\mathbf{y}, \mathbf{T}^{-1}(\mathbf{x} - \mathbf{M} \mathbf{y})) + \beta \mathbf{C} \mathbf{s}(\mathbf{y}, \mathbf{v}), \beta \mathbf{D} \mathbf{s}(\mathbf{y}, \mathbf{v}))$ and take into account that $\mathbf{D} \mathbf{s}(\mathbf{y}, \mathbf{v}) = 0$ implies $\mathbf{C} \mathbf{s}(\mathbf{y}, \mathbf{v}) = 0$ by Property P2 so that $\gamma_z(\mathbf{x}) = (\gamma_y(\mathbf{x}), \gamma_v(\mathbf{x}))$ with $\gamma_y(\mathbf{x})$ as in Lemma 4. ■

Theorem 5. *Let the assumptions of Lemma 4 and Lemma 5 hold. Then, the interconnected system (14) satisfies the modular interconnection property with $\lambda = \min\{\lambda_y, \lambda_z\}$, $K_0 = \chi_y |\mathbf{y}_{is}(0) - \gamma_y(\mathbf{x}_{is}(0))| + \chi_z |\mathbf{z}(0) - \gamma_z(\mathbf{x}(0))|$, $K_1 = \frac{d \chi_y}{\lambda_y} + \alpha_\gamma (2\bar{C}_1 + C_2) + \frac{d' \chi_z}{\lambda_z} + \alpha'_\gamma (2\bar{C}'_1 + C'_2)$, $G^* = \frac{2\lambda_x}{\min\{\lambda_y, \lambda_z\}}$, in which $\bar{C}_1 = \frac{\chi_x \alpha \chi_y |\mathbf{y}_{is}(0) - \gamma_y(\mathbf{x}_{is}(0))|}{\lambda_y/2}$ and $\bar{C}'_1 = \frac{\chi_z \alpha \chi_x |\mathbf{z}(0) - \gamma_z(\mathbf{x}(0))|}{\lambda_z/2}$.*

Proof: From Lemma 4, Lemma 5, and the triangular inequality, we have that if $G_1 > G^*$ then $|\mathbf{y}(t) - \mathbf{y}_{is}(t)| \leq \chi_y e^{-\lambda_y G_1 t} |\mathbf{y}_{is}(0) - \gamma_y(\mathbf{x}_{is}(0))| + \frac{d \chi_y}{G_1 \lambda_y} + \frac{\alpha_\gamma}{G_1} (2\bar{C}_1 + C_2) + \chi_z e^{-\lambda_z G_1 t} |\mathbf{z}(0) - \gamma_z(\mathbf{x}(0))| + \frac{d' \chi_z}{\lambda_z G_1} + \frac{\alpha'_\gamma}{G_1} (2\bar{C}'_1 + C'_2)$. ■

VI. EXAMPLE

As an example, we consider a one-step reaction model of a phosphorylation cycle and demonstrate that the interconnection to downstream targets can be rendered functionally modular by suitably adjusting the values of the cycle parameters. For how to apply separation of time scales to show modularity in a two-step reaction model of a phosphorylation cycle, the reader is referred to [12]. Here, using contraction theory, we provide bounds explicitly in terms of the cycle parameters.

Phosphorylation cycles are among the most common intracellular signal transduction mechanisms. They have been observed in virtually every organism, carrying signals that regulate processes such as cell motility, nutrition, interaction with environment and cell death [1]. In this paper, we describe a phosphorylation system extracted from the MAPK cascade [10] similar to the device proposed in [6]. For any species X , we denote by X (italics) its concentration. Let Z be a kinase expressed at (time-varying) rate $k(t)$ and degraded at rate δ . Let its substrate be X and let X^* denote the phosphorylated version of X . Let the total amount of X be constant and denoted by X_T . Let Y be the phosphatase in total amount Y_T . Then, the phosphorylation reactions are given by $Z + X \xrightarrow{k_1} X^* + Z$, $Y + X^* \xrightarrow{k_2} X + Y$,

and the binding reaction with downstream targets p is given by $X^* + p \xrightleftharpoons[k_{\text{off}}]{k_{\text{on}}} C$. We denote the total concentration of downstream targets by p_T . The system also has conservation laws $p_T = C + p$ and $X_T = X^* + X + C$. In this system, we have that $k_1 X_T, k_2 Y_T, k_{\text{off}} \gg \delta, k(t)$. Define $G_1 := k_1 X_T / \delta$ and let $\eta := (k_2 Y_T) / (k_1 X_T)$. Define $G_2 := k_{\text{off}} / \delta$ and let $k_d := k_{\text{off}} / k_{\text{on}}$. Letting also $u := Z, y := X^*, v := C$, and assuming that $p_T / X_T \ll 1$ the isolated system can be written as

$$\begin{cases} \dot{u} = & k(t) - \delta u \\ \dot{y} = & G_1 \delta \left(u \left(1 - \frac{y}{X_T} \right) - \eta y \right), \end{cases}$$

and the interconnection with downstream targets is given by

$$\begin{cases} \dot{u} = & k(t) - \delta u \\ \dot{y} = & G_1 \delta \left(u \left(1 - \frac{y}{X_T} \right) - \eta y \right) - G_2 \left(\frac{\delta}{k_d} y (p_T - v) - \delta v \right) \\ \dot{v} = & G_2 \left(\frac{\delta}{k_d} y (p_T - v) - \delta v \right), \end{cases}$$

which are in the forms of equations (13)-(14) with $r(y, u) = 0$, $h(u, t) = k(t) - \delta u$, $l(y, u) = \delta \left(u \left(1 - \frac{y}{X_T} \right) - \eta y \right)$, $s(y, v) = ((\delta/k_d)y(p_T - v) - \delta v)$. Note that system (16) is already in the form (15) and system (16) is already in the form (15) with $\epsilon = 1/G_1$ and $\beta = G_2/G_1$. Hence, we can take $T = \mathbb{I}$ and $M = 0$. One can easily verify the assumptions of Theorem 5. In particular, the isolated system is partially contracting in $\mathbf{y} = y$ and in $\mathbf{x} = u$ with $\Theta_x = \Theta_y = \mathbb{I}$, $\lambda_x = \delta$, $\lambda_y = \eta\delta$, and $\chi_x = \chi_y = 1$. The function $h(u, t) = k(t) - \delta u$ is Lipschitz continuous and $\gamma_y(u)$ is given by $\gamma_y(u) = \frac{u}{(u/X_T + \eta)}$, which is globally defined, differentiable, and Lipschitz continuous. Assuming that $k(t)$ is bounded, we also have that $\left| \frac{\partial \gamma_y(u)}{\partial u} h(u, t) \right| < d$ with $d = \frac{\max_t |k(t) - \delta u(t)|}{\eta}$. Furthermore, we have that $\alpha = 0$ and $\alpha_\gamma = 1/\eta$. As a consequence, $C_1 = 0$ and $C_2 = 0$.

The connected system is partially contracting in $\mathbf{z} = (y, v)$ with measure μ_2 and $\Theta_z = \mathbb{I}$ or with measure μ_1 and $\Theta_z = \text{diag}(1, \theta)$ for suitable $\theta > 1$. In what follows we show contraction of the system employing measure μ_1 . The Jacobian J is given by $J = \delta \begin{pmatrix} -(u/X_T) - \eta - (\beta/k_d)(p_T - v) & \beta y/k_d + \beta \\ (\beta/k_d)(p_T - v) & -(\beta/k_d)y - \beta \end{pmatrix}$. Denote $a := \delta(u/X_T) + \delta\eta$, $b = \delta(\beta/k_d)(p_T - v)$, and $c = \delta\beta(y/k_d + 1)$. Letting $\Theta_z = \text{diag}(1, \theta)$, we obtain that $\mu_1(\Theta_z J \Theta_z^{-1}) = \max(-a - b + \theta b, (c/\theta) - c)$. In order for such a maximum to be negative, we need that $\theta \in (1, 1 + (a/b))$. Furthermore, we have that $\gamma_z(u) = \left(\frac{u}{(u/X_T + \eta)}, \frac{p_T y}{y + k_d} \right)$ with $y = \frac{u}{u/X_T + \eta}$, which is uniquely defined, differentiable everywhere and globally Lipschitz continuous. Assuming that $k(t)$ is bounded, we also have that $\left| \frac{\partial \gamma_z(u)}{\partial u} h(u, t) \right| \leq d'$ with $d' = \max_t |k(t) - \delta u(t)| \max(1/(\eta), p_T/(k_d \eta))$. In summary, for the connected system, we have $\chi_z = \theta$, $\lambda_z = \max((a_m + b_M) - \theta b_M, c_m(1 - 1/\theta))$,

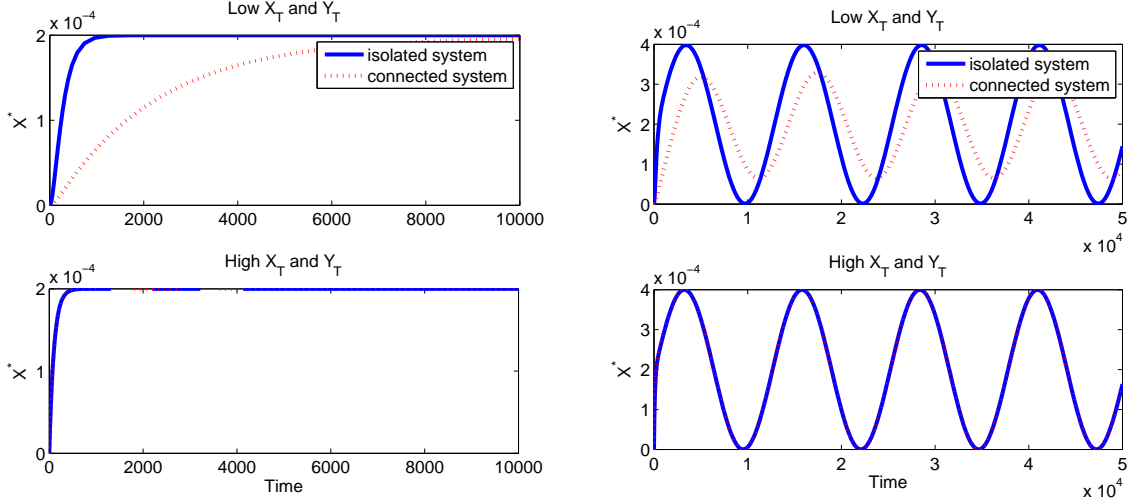


Fig. 1. **Effect of speeding up the time scale of the phosphorylation system by increasing X_T and Y_T .** (Left) Step response for low and high values of X_T and Y_T . (Right). Response to a periodic input for low and high values of X_T and Y_T . In all simulations, we have set $k_1 = 10^{-3}$, $k_2 = 0.01$, $\delta = 0.01$, $k_{on} = 50$, $k_{off} = 100$, $p_T = 20$ for the connected system and $p_T = 0$ for the isolated system, in the upper plots, we have $X_T = 0.2$ and $Y_T = 0.5$, while in the lower plots these values are $X_T = 2 \cdot 10^4$ and $Y_T = 5 \cdot 10^4$. For the step response, we have $k(t) = 5 \cdot 10^{-5}$, while for the periodic response, we have $k(t) = 5 \cdot 10^{-5}(1 + \sin(\omega t))$ with $\omega = 5 \cdot 10^{-4}$.

with $a_m = \delta\eta$ (the smallest value of a), $b_M = \delta p_T \beta / k_d$ (the largest value of b), and $c_m = \delta\beta$ (the smallest value of c). We can choose for θ the value such that $a_m + b_M - \theta b_M = c_m(1 - 1/\theta)$, which gives $\theta = ((a_m + b_M - c_m) + ((a_m + b_M - c_m)^2 + 4b_M c_m))^{1/2} / (2b_M)$. Furthermore, we have that $\alpha'_\gamma = \max\{1/\eta, p_T/(k_d\eta)\}$ and $\alpha' = 0$. As a consequence, we have that $C'_1 = C'_2 = 0$. For this example, we have that the functionally modular property is satisfied with $\lambda = \min\{\lambda_y, \lambda_z\}$, $K_0 = 0$, and $K_1 = \frac{dX_y}{\lambda_y} + \frac{d'X_z}{\lambda_z} = \max_t |k(t) - \delta u(t)| \left(\frac{1}{\eta\lambda_y} + \frac{\max(1, p_T/k_d)\theta}{\eta\lambda_z} \right)$. These calculations indicate that the bounds can be improved by either decreasing the ratio p_T/k_d or by increasing $k_2 Y_T$ with respect to $k_1 X_T$. This information could not be obtained by the singular perturbation analysis performed in [12]. For the parameter values employed in the simulations of Figure 1 when large amounts of X_T and Y_T are employed, we obtain that $K_1/G_1 = 2 \cdot 10^{-6}$, which is an upper bound on the error between the isolated and connected system trajectories. The numerical simulation of Figure 1 shows an error of about $5 \cdot 10^{-8}$. Between our bound and the measured error, there is a factor of about 40. This is because the two eigenvalues of the Jacobian J there is also a factor of about 40 and that λ_z basically accounts for the slowest eigenvalue of J . By virtue of Theorem 7, the difference between the isolated and connected system behavior can be rendered arbitrarily small by increasing the value of G_1 , which

can be performed by increasing the amounts of total substrate X_T and phosphatase Y_T by comparable amounts. This point is illustrated by numerical simulation in Figure 1. This Figure illustrates that for low values of X_T and Y_T corresponding to $G_1 = 0.02$ and $G_2 = 5 \cdot 10^4$ the difference between the isolated and connected system behaviors is substantial. Increasing X_T and Y_T so that $G_1 = 2 \cdot 10^3$ is comparable to $G_2 = 5 \cdot 10^4$, the difference between the isolated and connected system behaviors is attenuated. The amounts of X_T and Y_T in synthetic circuits in living cells can be easily tuned. Specifically, one can place the genes expressing proteins X and Y under the control of constitutive promoters with desired strength.

VII. CONCLUSIONS

In this paper, we have shown how using contraction theory one can obtain explicit and global convergence bounds for systems with multiple time scales. We have illustrated how to employ these techniques to analyze the problem of functionally modular interconnections in biomolecular systems and provided a concrete example consisting of a phosphorylation system. This problem was considered before in [12], in which under weaker assumptions singular perturbation theory allowed to obtain the order of convergence of trajectories. Here, using contraction theory, we provided explicit bounds, which are in general useful to guide how the parameters should be tuned in the design of biomolecular systems.

REFERENCES

- [1] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, and P. Walter. *Molecular Biology of the Cell*. Garland Science, 2002.
- [2] U. Alon. *An introduction to systems biology. Design principles of biological circuits*. Chapman-Hall, 2007.
- [3] D. Angeli. A Lyapunov approach to incremental stability properties. *IEEE Transactions on Automatic Control*, 47:410–321, 2002.
- [4] J. Borghans, R. de Boer, and L. Segel. Extending the quasi-steady state approximation by changing variables. *Bulletin of Mathematical Biology*, 58(1):43–63, January 1996.
- [5] G. Dahlquist. *Stability and error bounds in the numerical integration of ordinary differential equations*. Transactions of the Royal Institute Technology (Stockholm), 1959.
- [6] D. Del Vecchio, A. J. Ninfa, and E. D. Sontag. Modular cell biology: Retroactivity and insulation. *Molecular Systems Biology*, 4:161, 2008.
- [7] C. M. Desoer and M. Vidyasagar. *Feedback Systems: Input-Output Properties*. Academic Press, 1975.
- [8] Gordon L. Hager and Akhilesh K. Nagaich. Transcription factor dynamics. In Jun Ma, editor, *Gene Expression and Regulation*, chapter 30, pages 493–502. Springer New York, New York, NY, 2006.
- [9] P. Hartman. On stability in the large for systems of ordinary differential equations. *Canadian Journal of Mathematics*, 13:480–492, 1961.

- [10] J. J. Hornberg, B. Binder, F. J. Bruggeman, B. Schoeber, R. Heinrich, and H. V. Westerhoff. Control of MAPK signaling: from complexity to what really matters. *Oncogene*, 24:5533–5542, 2005.
- [11] S. Jayanthi and D. Del Vecchio. Retroactivity attenuation in transcriptional networks: Design and analysis of an insulation device. *Proc. IEEE Conf. Decision and Control*, pages 774–780, 2008.
- [12] S. Jayanthi and D. Del Vecchio. Retroactivity attenuation in biomolecular systems based on timescale separation. *IEEE Trans. Automatic Control*, 56(4):748–761, 2010.
- [13] N. Kashtan and U. Alon. Spontaneous evolution of modularity and network motifs. *Proc. of the Natl. Acad. of Sci.*, 39:13773–13778, 2005.
- [14] H. Khalil. *Nonlinear Systems*. Prentice Hall, 2002.
- [15] M. W. Kirschner and J. C. Gerhart. *The Plausibility of Life: Resolving Darwin’s Dilemma*. Yale University Press, 2005.
- [16] E. Klipp, R. Herwig, A. Kowald, C. Wierling, and H. Lehrach. *Systems Biology in Practice*. Wiley-VCH, 2005.
- [17] P. Kokotovic, H. K. Khalil, and J. O’Reilly. *Singular Perturbation Methods in Control*. SIAM, 1999.
- [18] D. C. Lewis. Metric properties of differential equations. *American Journal of Mathematics*, 71:294–312, 1949.
- [19] W. Lohmiller and J. J. Slotine. Contraction analysis of non-linear distributed systems. *International Journal of Control*, 78:678–688, 2005.
- [20] W. Lohmiller and J. J. E. Slotine. On contraction analysis for non-linear systems. *Automatica*, 34:683–696, 1998.
- [21] W. Lohmiller and J.J.E Slotine. Nonlinear process control using contraction theory. *A.I.Ch.E. Journal*, 2000.
- [22] S. M. Lozinskii. Error estimate for numerical integration of ordinary differential equations. I. *Izv. Vtssh. Uchebn. Zaved Matematika*, 5:222–222, 1959.
- [23] A. Pavlov, A. Pogromvsky, N. van de Wouf, and H. Nijmeijer. Convergent dynamics, a tribute to Boris Pavlovich Demidovich. *Systems and Control Letters*, 52:257–261, 2004.
- [24] J. M. Rohwer, N. D. Meadow, S. Roseman, H. V. Westerhoff, and P. W. Postma. Understanding glucose transport by the bacterial phosphoenolpyruvate: glucose phosphotransferase system on the basis of kinetic measurements in vitro. *The Journal of biological chemistry*, 275(45):34909–34921, November 2000.
- [25] G. Russo, M. di Bernardo, and J. J. Slotine. A graphical approach to prove contraction of nonlinear circuits and systems. *IEEE Transactions on Circuits and Systems II*, 57(11):336–348, 2010.
- [26] L. Segel. On the validity of the steady state assumption of enzyme kinetics. *Bulletin of Mathematical Biology*, 50(6):579–593, November 1988.
- [27] Herbert A. Simon. The architecture of complexity. *Proceedings of the American Philosophical Society*, 6:467–482, 1962.
- [28] J.J. Slotine. Modular stability tools for distributed computation and control. *International Journal of Adaptive Control and Signal Processing*, 17:397–416, 2003.
- [29] A. N. Tikhonov. Systems of differential equations containing small parameters multiplying the derivatives. *Mat. Sborn.*, 31:575–586, 1952.
- [30] A. Tzafiriri and E. R. Edelman. The total quasi-steady-state approximation is valid for reversible enzyme kinetics. *Journal of Theoretical Biology*, 226(3):303–313, February 2004.
- [31] W. Wang and J. J. E. Slotine. On partial contraction analysis for coupled nonlinear oscillators. *Biological Cybernetics*, 92:38–53, 2005.