# A Passivity-Based Approach to Stability of Spatially Distributed Systems With a Cyclic Interconnection Structure

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***Abstract*—A class of distributed systems with a cyclic interconnection structure is considered. These systems arise in several biochemical applications and they can undergo diffusion-driven instability which leads to a formation of spatially heterogeneous patterns. In this paper, a class of cyclic systems in which addition of diffusion does not have a destabilizing effect is identified. For these systems global stability results hold if the "secant" criterion is satisfied. In the linear case, it is shown that the secant condition is necessary and sufficient for the existence of a decoupled quadratic Lyapunov function, which extends a recent diagonal stability result to partial differential equations. For reaction–diffusion equations with nondecreasing coupling nonlinearities global asymptotic stability of the origin is established. All of the derived results remain true for both linear and nonlinear positive diffusion terms. Similar results are shown for compartmental systems.**

***Index Terms*—Biochemical reactions, cyclic interconnections, passivity, secant criterion, spatially distributed systems.**

## I. INTRODUCTION

THE FIRST gene regulation system to be studied in detail was the one responsible for the control of lactose metabolism in *E. Coli*, the *lac* operon studied in the classical work of Jacob and Monod [1], [2]. Jacob and Monod's work led Goodwin [3] and later many others [4]–[15] to the mathematical study of systems made up of cyclically interconnected genes and gene products. In addition to gene regulation networks, cyclic feedback structures have been used as models of certain metabolic pathways [16], of tissue growth regulation [17], of cellular signaling pathways [18], and of neuron models [19].

Generally, cyclic feedback systems (of arbitrary order) were shown by Mallet-Paret and Smith [20], [21] to have behaviors no more complicated that those of second-order systems: for precompact trajectories, $\omega$-limit sets can only consist of equilibria, limit cycles, or heteroclinic or homoclinic connections, just as in the planar Poincaré–Bendixson Theorem. When the net effect around the loop is positive, no (stable) oscillations are possible, because the overall system is monotone [22]. On the other hand, inhibitory or "negative feedback" loops give rise to the possibility of periodic orbits, and it is then of interest to provide conditions for oscillations or lack thereof.

Besides the scientific and mathematical interest of the study of cyclic negative feedback systems, there is an engineering motivation as well, which rises from the field of synthetic biology. Oscillators will be fundamental parts of engineered gene bacterial networks, used to provide timing and periodic signals to other components. A major experimental effort, pioneered by the construction of the "repressilator" by Elowitz and Leibler [23], is now under way to build reliable oscillators with gene products. Indeed, the theory of cyclic feedback systems has been proposed as a way to analyze the repressilator and similar systems [24], [25].

In order to evaluate stability properties of negative feedback cyclic systems, [9] and [15] analyzed the Jacobian linearization at the equilibrium, which is of the form

$$A = \begin{bmatrix} -a_1 & 0 & \cdots & 0 & -b_n \\ b_1 & -a_2 & \ddots & & 0 \\ 0 & b_2 & -a_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -a_n \end{bmatrix} \tag{1}$$

$a_i > 0$, $b_i > 0$, $i = 1, \cdots, n$, and showed that $A$ is Hurwitz if the following sufficient condition holds:

$$\frac{b_1 \cdots b_n}{a_1 \cdots a_n} < \sec(\pi/n)^n. \tag{2}$$

This "secant criterion" is also necessary for stability when the $a_i$'s are identical.

An application of the secant condition in a "systems biology" context was in Kholodenko's [18] (see also [26]) analysis of a simplified model of negative feedback around mitogen activated protein kinase (MAPK) cascades. MAPK cascades constitute a highly conserved eukaryotic pathway, responsible for some of the most fundamental processes of life such as cell proliferation and growth [27]–[29]. Kholodenko used the secant condition to establish conditions for asymptotic stability.

### A. Global Stability Considerations

It appears not to be generally appreciated that (local) stability of the equilibrium in a cyclic negative feedback system does not rule out the possibility of periodic orbits. Indeed, the Poincaré–Bendixson Theorem of Mallet-Paret and Smith [20],

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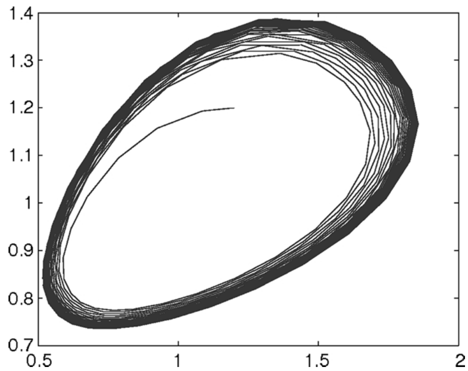


Fig. 1. Trajectory of (3) starting from initial condition $\chi = [1.2\ 1.2\ 1.2]^T$, projected onto the $\chi_1$-$\chi_2$ plane.

[21] allows such periodic orbits to coexist with stable equilibria. As an illustration consider the system

$$\begin{aligned}\dot{\chi}_1 &= -\chi_1 + \varphi(\chi_3)\\ \dot{\chi}_2 &= -\chi_2 + \chi_1\\ \dot{\chi}_3 &= -\chi_3 + \chi_2\end{aligned} \tag{3}$$

where

$$\varphi(\chi_3) = e^{-10(\chi_3-1)} + 0.1\mathrm{sat}\left(25(\chi_3 - 1)\right) \tag{4}$$

and $\mathrm{sat}(\cdot) := \mathrm{sgn}(\cdot)\min\{1, |\cdot|\}$ is a saturation[1] function. The function (4) is decreasing, and its slope has magnitude $b_3 = 7.5$ at the equilibrium $\chi_1 = \chi_2 = \chi_3 = 1$. With $a_1 = a_2 = a_3 = b_1 = b_2 = 1$ and $n = 3$, the secant criterion (2) is satisfied and, thus, the equilibrium is asymptotically stable. However, simulations in Fig. 1 show the existence of a periodic orbit in addition to this stable equilibrium.

To delineate *global* stability properties of cyclic systems with negative feedback, [30] studied (by building on a passivity interpretation of the secant criterion in [31]) the nonlinear model

$$\begin{aligned}\dot{x}_1 &= -f_1(x_1) - g_n(x_n)\\ \dot{x}_2 &= -f_2(x_2) + g_1(x_1)\\ &\vdots\\ \dot{x}_n &= -f_n(x_n) + g_{n-1}(x_{n-1})\end{aligned} \tag{5}$$

and proved global asymptotic stability of the origin[2] under the conditions

$$\sigma f_i(\sigma) > 0,\ \sigma g_i(\sigma) > 0 \qquad \forall \sigma \in \mathbb{R}\setminus\{0\} \tag{C1}$$

$$\frac{g_i(\sigma)}{f_i(\sigma)} \le \gamma_i \qquad \forall \sigma \in \mathbb{R}\setminus\{0\} \tag{C2}$$

$$\gamma_1 \cdots \gamma_n < \sec(\pi/n)^n \tag{C3}$$

$$\lim_{|x_i|\to\infty} \int_0^{x_i} g_i(\sigma)\mathrm{d}\sigma = \infty. \tag{C4}$$

[1]One can easily modify this example to make $\varphi(\cdot)$ smooth while retaining the same stability properties.

[2]In the rest of the paper we assume that an equilibrium exists and is unique (see [30] for conditions that guarantee this) and that this equilibrium has been shifted to the origin with a change of variables.

The conditions (C1)–(C4) encompass the linear system (1), (2) in which $f_i(x_i) = a_i x_i$, $g_i(x_i) = b_i x_i$, and $\gamma_i = b_i/a_i$.

A crucial ingredient in the global asymptotic stability proof of [30] is the observation that the secant criterion (2) is necessary and sufficient for *diagonal stability* of (1), that is for the existence of a diagonal matrix $D > 0$ such that

$$A^T D + DA < 0. \tag{6}$$

Using this diagonal stability property, [30] constructs a Lyapunov function for (5) which consists of a weighted sum of decoupled functions of the form $V_i(x_i) = \int_0^{x_i} g_i(\sigma)\mathrm{d}\sigma$. In the linear case this construction coincides with the quadratic Lyapunov function $V = x^T Dx$.

### *B. Spatial Localization*

Ordinary differential equation models such as described above implicitly assume that reactions proceed in a "well-mixed" environment. However, in cells, certain processes are localized to membranes (activation of pathways by receptors), to the nucleus (transcription factor binding to DNA, production of mRNA), to the cytoplasm (much of signaling), or to one of the specialized organelles in eukaryotes. The exchange of chemical species between these spatial domains has been found to be responsible for dynamical behavior, such as emergence of oscillations, in fundamental cell signaling pathways, see for instance [32]. These exchanges often happen by random movement (diffusion), although transport mechanisms and gated channels are sometimes involved as well.

When each of a finite set of spatial domains is reasonably "well mixed," so that the concentrations of relevant chemicals in each domain are appropriately described by ordinary differential equations (ODEs), a compartmental model may be used. In a compartmental model, several copies of an ODE system are interconnected by "pipes" that tend to balance species concentrations among connected compartments. The overall system is still described by a system of ODEs, but new dynamical properties may emerge from this interconnection. For example, two copies of an oscillating system may synchronize, or two multistable systems may converge to the same steady state.

On the other hand, if a well-mixed assumption in each of a finite number of compartments is not reasonable, a more appropriate mathematical formalism is that of reaction–diffusion partial differential equations (PDEs) [33]–[37]: instead of a dynamics $\dot{x} = f(x)$, one considers equations of the general form

$$\frac{\partial x}{\partial t} = D\Delta x + f(x), \qquad \frac{\partial x}{\partial \nu} = 0 \tag{7}$$

where now the vector $x = x(\xi, t)$ depends on both time $t$ and space variables $\xi$ belonging to some domain $\Omega$, $\Delta x$ is the Laplacian of the vector $x$ with respect to the space variables, $D$ is a matrix of positive diffusion constants, and $\partial x/\partial \nu$ denotes the directional derivative in the direction of the normal to the boundary $\partial\Omega$ of the domain $\Omega$, representing a no-flux or Neumann boundary condition. (Technical details are given later, including generalizations to more general elliptic operators that model space-dependent diffusions.)

Diffusion plays a role in generating new behaviors for the PDE as compared to the original ODE $\dot{x} = f(x)$. In fact, one of the main areas of research in mathematical biology concerns the phenomenon of diffusive instability, which constitutes the basis of Turing's mechanism for pattern formation [38]–[41], and which amounts to the emergence of stable non-homogeneous in space solutions of a reaction–diffusion PDE. The Turing phenomenon has a simple analog, and is easiest to understand intuitively, for an ODE consisting of two identical compartments [41], [42]. Also in the context of cell signaling, and in particular for the MAPK pathway mentioned earlier, reaction–diffusion PDE models play an important role [43].

If diffusion coefficients are very large, diffusion effects may be ignored in modeling. As an illustration, the stability of uniform steady states is unchanged provided that the diffusion coefficient $D$ is sufficiently large compared to the "steepness" of the reaction term $f$, measured for instance by an upper bound $a$ on its Lipschitz constant or equivalently the maximum of its Jacobians at all points (for chemical reaction networks, this is interpreted as the inverse of the kinetic relaxation time, for steady states). Introducing an energy function using the integral of $|\partial x / \partial \xi|^2$, and then integrating by parts and using Poincaré's inequality, one obtains an exponential decrease of this energy, controlled by the difference of $a$ and $D$ ([44], Chapter 11). For instance, Othmer [45] provides a condition $D\mu > a$ in terms of the smallest nonzero eigenvalue of the Neumann Laplacian $\{\Delta x + \mu x = 0, \xi \in \Omega; \partial x/\partial \nu = 0, \xi \in \partial\Omega\}$ to guarantee exponential convergence to zero of spatial nonuniformities, and estimates that his condition is met for intervals $\Omega = [0, L]$ of length $L \approx 10\ \mu\text{m}$, with diffusion of at least about $4 \times 10^{-8}\ \text{cm}^2/\text{sec}$ and $a \approx 10^{-1}$ sec.

On the other hand, if diffusion is not dominant, it is necessary to explicitly incorporate spatial inhomogeneity, whether through compartmental or PDE models. The goal of this paper is to extend the linear and nonlinear secant condition to such compartmental and PDE models, using a passivity-based approach. To illustrate why spatial behavior may lead to interesting new phenomena even for cyclic negative feedback systems, we take a two-compartment version of the system shown in (3)

$$
\begin{aligned}
\dot{\chi}_1 &= -\chi_1 + \varphi(\chi_3) + D(\eta_1 - \chi_1)\\
\dot{\chi}_2 &= -\chi_2 + \chi_1 + D(\eta_2 - \chi_2)\\
\dot{\chi}_3 &= -\chi_3 + \chi_2 + D(\eta_3 - \chi_3)\\
\dot{\eta}_1 &= -\eta_1 + \varphi(\eta_3) + D(\chi_1 - \eta_1)\\
\dot{\eta}_2 &= -\eta_2 + \eta_1 + D(\chi_2 - \eta_2)\\
\dot{\eta}_3 &= -\eta_3 + \eta_2 + D(\chi_3 - \eta_3)
\end{aligned}
\tag{8}
$$

and pick $D = 10^{-4}$. We simulated this system with initial condition $[1.4945\ 1.3844\ 1.0877\ 1\ 1\ 1]^T$, so that the first-compartment $\chi_i(0)$ coordinates start approximately on the limit cycle, and the second-compartment $\eta_i(0)$ coordinates start at the equilibrium. The resulting simulation shows that a new oscillation appears, in which both components oscillate, out of phase (no synchronization), with roughly equal period but very different amplitudes. Fig. 2 shows the solution coordinates $\chi_1$ and $\eta_1$ plotted on a window after a transient behavior. This oscillation is an emergent behavior of the compartmental system, and is different from the limit cycle in the original three-dimensional system. (One may analyze the existence and stability of these orbits using an ISS-like small-gain theorem.)

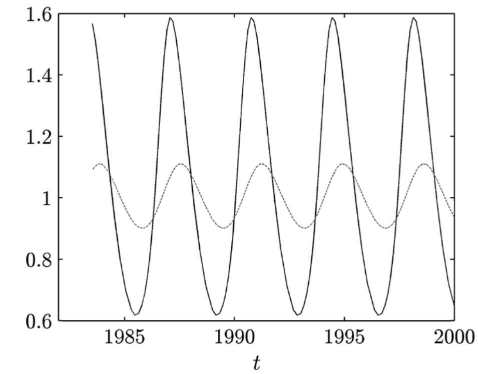


Fig. 2. New oscillations in two-compartment system: $\chi_1$ (solid) and $\eta_1$ (dashed) shown.

Our goal is to show that—in contrast to this example—if the secant condition *does* apply to a negative cyclic feedback system, then no non-homogeneous limit behavior can arise, in compartmental or in PDE models, no matter what is the magnitude of the diffusion effect.

## II. Problem Formulation

In this paper, we extend the linear and nonlinear results of [9], [15], [30] to spatially distributed models that consist of a cyclic interconnection of $n$ reaction–diffusion equations

$$
\begin{aligned}
\psi_{1t} &= \nabla \cdot (h_1(\psi_1)\nabla\psi_1) - f_1(\psi_1) - g_n(\psi_n)\\
\psi_{2t} &= \nabla \cdot (h_2(\psi_2)\nabla\psi_2) - f_2(\psi_2) + g_1(\psi_1)\\
&\ \ \vdots\\
\psi_{nt} &= \nabla \cdot (h_n(\psi_n)\nabla\psi_n) - f_n(\psi_n) + g_{n-1}(\psi_{n-1})
\end{aligned}
\tag{RD}
$$

where $\psi_i$ denotes the state of the $i$th subsystem which depends on spatial coordinate $\xi$ and time $t$, $\psi_i(\xi, t)$, and $f_i$, $g_i$, $h_i$ denote static nonlinear functions of their arguments. We consider a situation in which the spatial coordinate $\xi := (\xi_1, \ldots, \xi_r)$ belongs to a bounded domain $\Omega$ in $\mathbb{R}^r$, $r = 1$, 2 or 3, with a smooth boundary $\partial\Omega$ and outward unit normal $\nu$. The state of each subsystem satisfies the Neumann boundary conditions, $\partial\psi_i/\partial\nu := \psi_{i\nu} = 0$ on $\partial\Omega$, $\nabla\psi_i$ is the gradient of $\psi_i$, $\nabla \cdot v$ is the divergence of a vector $v$, and the domain of the $r$-dimensional Laplacian $\Delta := \nabla \cdot \nabla$ is given by [46], [47]

$$
\mathcal{D}(\Delta) := \{\psi_i \in H_2(\Omega),\ \psi_{i\nu} = 0 \text{ on } \partial\Omega\}. \tag{DM}
$$

Here, $H_2(\Omega)$ denotes a Sobolev space of square integrable functions with square integrable second distributional derivatives. The standard $L_2^n(\Omega)$ inner product is given by

$$
\langle \psi, \phi \rangle := \int_{\Omega} \psi^T(\xi)\phi(\xi)\mathrm{d}\xi
$$

where $\mathrm{d}\xi := \mathrm{d}\xi_1 \cdots \mathrm{d}\xi_r$ and $\psi := [\psi_1\ \cdots\ \psi_n]^T$.

As explained in the introduction, the study of stability properties for distributed system (RD) is important in many biological applications. Our first result, presented in Section III, studies the linearization of (RD) and shows that the secant condition (2) is sufficient for the exponential stability despite the presence of diffusion terms. It further shows that the secant condition is necessary and sufficient for the existence of a decoupled Lyapunov function, thus extending the diagonal stability result of [30] to partial differential equations. The next result of the paper, presented in Section IV, studies the nonlinear reaction–diffusion equation (RD) and proves global asymptotic stability of $\psi = 0$ under assumptions that mimic the conditions (C1)–(C3) of [30], and under the additional assumptions that the functions $g_i(\cdot)$ and $h_i(\cdot)$, $i = 1, \cdots, n$, be nondecreasing and positive, respectively. This additional assumption on the $g$-functions ensures convexity of the Lyapunov function which is a crucial property for our stability proof. Indeed, a similar convexity assumption has been employed in [48] to preserve stability in the presence of linear diffusion terms. Finally, Section V studies a compartmental ordinary differential equation model instead of the partial differential equation (RD), and proves global asymptotic stability using the same nondecreasing assumption for $g_i$'s.

## III. Cyclic Interconnection of Linear Reaction–Diffusion Equations

We start our analysis by considering an interconnection of spatially distributed systems (RD) with

$$\begin{aligned} f_i(\psi_i) &:= a_i\psi_i, \; g_i(\psi_i) := b_i\psi_i \\ h_i(\psi_i) &:= c_i, \qquad i = 1, \ldots, n \end{aligned} \tag{9}$$

where each $a_i$, $b_i$, and $c_i$ represents a positive parameter. In this case, system (RD) simplifies to a cascade connection of linear reaction–diffusion equations where the output of the last subsystem is brought to the input of the first subsystem through a negative unity feedback. Abstractly, the dynamics of system (RD), (DM) with $f_i(\cdot)$, $g_i(\cdot)$, and $h_i(\cdot)$ satisfying (9) are given by

$$\psi_t = \mathcal{A}\psi := C\Delta\psi + A_0\psi \tag{LRD}$$

where $\Delta\psi$ denotes the vector Laplacian, that is $\Delta\psi := [\Delta\psi_1 \; \cdots \; \Delta\psi_n]^T$, $C := \operatorname{diag}\{[c_1 \; \cdots \; c_n]\} > 0$, and

$$A_0 := \begin{bmatrix} -a_1 & 0 & \cdots & 0 & -b_n \\ b_1 & -a_2 & \ddots & & 0 \\ 0 & b_2 & -a_3 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -a_n \end{bmatrix}$$
$$a_i > 0, \; b_i > 0, \; i = 1, \ldots, n.$$

### A. *Exponential Stability and the Secant Criterion in One Spatial Dimension*

In this section, we focus on systems with one spatial dimension $\xi \in \Omega := (0,1)$. We show that operator $\mathcal{A}$ with (DM) generates an exponentially stable strongly continuous ($C_o$) semigroup $T(t)$ on $L_2^n(0,1)$ if the *secant criterion* (2) is satisfied. We note that the exponential stability of $T(t)$ in Theorem 1 can be also established using a Lyapunov based approach that we develop for systems with two or three spatial coordinates. However, the proof of Theorem 1 is of independent interest because of the explicit construction of the $C_o$-semigroup and block-diagonalization of operator (LRD), (DM) (which is well suited for a modal interpretation of stability results in one spatial coordinate).

It is well known (see, for example [47]) that the operator $\partial_{\xi\xi}$ with Neumann boundary conditions is self-adjoint with the following set of eigenfunctions $\{\varphi_k\}$ and corresponding eigenvalues $\{\nu_k\}$:

$$\begin{aligned} \varphi_0(\xi) &= 1, \qquad \varphi_l(\xi) = \sqrt{2}\cos l\pi\xi, \qquad l \in \mathbb{N} \\ \nu_0 &= 0, \qquad \nu_l = -(l\pi)^2, \qquad l \in \mathbb{N}. \end{aligned}$$

Since the eigenfunctions $\{\varphi_k\}$ represent an orthonormal basis of $L_2(0,1)$ each $\psi_i(\xi,t)$ can be represented as

$$\psi_i(\xi,t) = \sum_{k=0}^{\infty} x_{i,k}(t)\varphi_k(\xi)$$

where $x_{i,k}(t)$ denote the spectral coefficients given by

$$x_{i,k}(t) = \langle\varphi_k, \psi_i\rangle := \int_0^1 \varphi_k(\xi)\psi_i(\xi,t)\mathrm{d}\xi.$$

Thus, a spectral decomposition of operator $\partial_{\xi\xi}$ in (LRD) yields the following infinite-dimensional system on $l_2^n$ of decoupled $n$th order equations:

$$\dot{x}_k = A_k x_k, \qquad k = 0, 1, \ldots \tag{10}$$

with $x_k(t) := [x_{1,k}(t) \; \cdots \; x_{n,k}(t)]^T$

$$A_k := \begin{bmatrix} -\alpha_{1,k} & 0 & \cdots & 0 & -b_n \\ b_1 & -\alpha_{2,k} & \ddots & & 0 \\ 0 & b_2 & -\alpha_{3,k} & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -\alpha_{n,k} \end{bmatrix}$$

and $\alpha_{i,k} := a_i - c_i\nu_k = a_i + c_i(k\pi)^2 > 0$. Based on [9], [15] we conclude that each $A_k$ is Hurwitz if (2) holds. Therefore, each subsystem in (10) is exponentially stable and there exist $P_k = P_k^T > 0$ such that

$$A_k^T P_k + P_k A_k = -I, \qquad k = 0, 1, \ldots.$$

Now, since $\mathcal{A}$ is the infinitesimal generator of the following $C_o$-semigroup:

$$T(t)\psi(0) := T(t)\psi(\xi,0) = \sum_{k=0}^{\infty} \mathrm{e}^{A_k t}x_k(0)\varphi_k(\xi)$$

we have

$$\begin{aligned}\int_0^\infty \|T(t)\psi(0)\|^2\,\mathrm{d}t &:= \int_0^\infty \langle T(t)\psi(0), T(t)\psi(0)\rangle\,\mathrm{d}t \\ &= \sum_{k=0}^\infty x_k^T(0)\left(\int_0^\infty \mathrm{e}^{A_k^T t}\mathrm{e}^{A_k t}\mathrm{d}t\right)x_k(0) \\ &= \sum_{k=0}^\infty x_k^T(0)P_k x_k(0).\end{aligned}$$

We will show the exponential stability of the $C_o$-semigroup $T(t)$ on $L_2^n(0,1)$ by establishing convergence of the infinite sum $\sum_{k=0}^\infty x_k^T(0)P_k x_k(0)$ for each $\{x_k(0)\}_{k\in\mathbb{N}_0} \in l_2^n$ [47, Lemma 5.1.2]. Let $s_m$ denote the $m$th partial sum, i.e.

$$s_m := \sum_{k=0}^m x_k^T(0)P_k x_k(0). \tag{11}$$

For $l < m$ we have

$$\begin{aligned}|s_m - s_l| &= \sum_{k=l+1}^m x_k^T(0)P_k x_k(0) \\ &\le \sum_{k=l+1}^m \|P_k\|\,\|x_k(0)\|^2.\end{aligned} \tag{12}$$

Now, we represent $A_k$, for $k \neq 0$, as

$$\begin{aligned}A_k &= k^2\left(F_0 + (1/k^2)A_0\right) \\ F_0 &:= -\pi^2 \mathrm{diag}\{[c_1 \quad \cdots \quad c_n]\} < 0\end{aligned}$$

and use perturbation analysis to express $P_k$ as

$$P_k = \frac{1}{k^2}\sum_{j=0}^\infty \frac{1}{k^{2j}}V_j$$

where

$$\begin{aligned}F_0V_0 + V_0F_0 &= -I \\ F_0V_j + V_jF_0 &= -\left(A_0^T V_{j-1} + V_{j-1}A_0\right)\end{aligned} \tag{13}$$

with $j \in \mathbb{N}$. Solution to (13) is determined by

$$\begin{aligned}V_0 &= -(1/2)F_0^{-1} \\ V_j &= \int_0^\infty \mathrm{e}^{F_0 t}\left(A_0^T V_{j-1} + V_{j-1}A_0\right)\mathrm{e}^{F_0 t}\mathrm{d}t\end{aligned}$$

which can be used to obtain

$$\begin{aligned}\|V_0\| &= 1/(2\pi^2 c_{\min}) \\ \|V_j\| &\le \|V_0\|\left(2\|A_0\|\|V_0\|\right)^j, \qquad j \in \mathbb{N} \\ \|P_k\| &\le \frac{\|V_0\|}{k^2}\sum_{j=0}^\infty \left(2\|A_0\|\|V_0\|/k^2\right)^j.\end{aligned}$$

Clearly, for $k^2 > 2\|A_0\|\|V_0\|$ the geometric series in the last inequality converges. This immediately gives the following upper bound for $\|P_k\|$:

$$\|P_k\| \le \frac{\|V_0\|}{k^2 - 2\|A_0\|\|V_0\|}$$

and inequality in (12) simplifies to

$$|s_m - s_l| \le \frac{\|V_0\|}{(l+1)^2 - 2\|A_0\|\|V_0\|}\sum_{k=l+1}^m \|x_k(0)\|^2.$$

Hence, for each $\{x_k(0)\}_{k\in\mathbb{N}_0} \in l_2^n$ partial sum (11) represents a Cauchy sequence which guarantees convergence of $\sum_{k=0}^\infty x_k^T(0)P_k x_k(0)$ and consequently

$$\int_0^\infty \|T(t)\psi(0)\|^2\,\mathrm{d}t < \infty \qquad \forall \psi(0) \in \mathcal{D}(\mathcal{A}).$$

Since $\mathcal{D}(\mathcal{A})$ is dense in $L_2^n(0,1)$, by an argument as in [46, p. 51] this inequality can be extended to all $\psi(0) \in L_2^n(0,1)$ which implies exponential stability of $T(t)$ [47, Lemma 5.1.2].

*Theorem 1:* The $C_o$-semigroup $T(t)$ generated by operator (LDR)-(Dm) on $L_2^n(0,1)$ is exponentially stable if the secant criterion (2) is satisfied.

### *B. The Existence of a Decoupled Quadratic Lyapunov Function*

The following theorem extends the diagonal stability result of [30] to PDEs with $r$ spatial coordinates:

*Theorem 2:* For system (LRD), (DM) there exist a decoupled quadratic Lyapunov function

$$V(\psi) := \langle \psi, D\psi\rangle = \sum_{i=1}^n d_i\langle \psi_i, \psi_i\rangle, \qquad d_i > 0 \tag{14}$$

that establishes exponential stability on $L_2^n(\Omega)$ if and only if (2) holds.

*Proof:* We prove the theorem for a system given by

$$\psi_t = \bar{\mathcal{A}}\psi := C\Delta\psi + \bar{A}_0\psi \tag{15}$$

where $C := \mathrm{diag}\{[c_1 \; \cdots \; c_n]\} > 0$, and

$$\bar{A}_0 := \begin{bmatrix} -1 & 0 & \cdots & 0 & -\gamma_1 \\ \gamma_2 & -1 & \ddots & & 0 \\ 0 & \gamma_3 & -1 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & \gamma_n & -1 \end{bmatrix}. \tag{16}$$

This is because all operators of the form (LRD) can be obtained by acting on $\bar{A}_0$ from the left with a diagonal matrix which does not change the existence of a decoupled quadratic Lyapunov function. We will prove that the secant criterion (C3) is both necessary and sufficient for the existence of a decoupled quadratic Lyapunov function.

*Necessity:* Suppose that there exist a Lyapunov function of the form (14) that establishes exponential stability of (15). The derivative of (14) along the solutions of (15) is given by

$$\begin{aligned}\frac{\mathrm{d}V(\psi)}{\mathrm{d}t} &= \langle \psi_t, D\psi\rangle + \langle \psi, D\psi_t\rangle \\ &= \langle C\Delta\psi + \bar{A}_0\psi, D\psi\rangle + \langle \psi, DC\Delta\psi + D\bar{A}_0\psi\rangle \\ &= -2\sum_{i=1}^{n} c_i d_i \langle \nabla\psi_i, \nabla\psi_i\rangle + \left\langle \psi, \left(\bar{A}_0^T D + D\bar{A}_0\right)\psi\right\rangle \\ &\le \left\langle \psi, \left(\bar{A}_0^T D + D\bar{A}_0\right)\psi\right\rangle\end{aligned}$$

where we have used Green's integral identity [49] with $\psi$ satisfying the Neumann boundary conditions on $\partial\Omega$, and the fact that $C$ and $D$ commute. The exponential stability of (15) and the above expression for $\mathrm{d}V(\psi)/\mathrm{d}t$ imply that $\bar{A}_0$ is Hurwitz. But (C3) is a necessary condition for a matrix $\bar{A}_0$ with equal diagonal entries to be Hurwitz [9].

*Sufficiency:* Suppose that (C3) holds. Following [30] we define:

$$\begin{aligned} &r := (\gamma_1 \cdots \gamma_n)^{1/n} > 0, \qquad D := \Gamma^{-2} \\ &\Gamma := \mathrm{diag}\left\{1, -\frac{\gamma_2}{r}, \frac{\gamma_2\gamma_3}{r^2}, \ldots, (-1)^{n+1}\frac{\gamma_2\cdots\gamma_n}{r^{n-1}}\right\}\end{aligned}$$

and differentiate (14) along the solutions of (15) to obtain

$$\frac{\mathrm{d}V(\psi)}{\mathrm{d}t} \le \left\langle \psi, \left(\bar{A}_0^T D + D\bar{A}_0\right)\psi\right\rangle =: -\langle \psi, Q\psi\rangle.$$

If (C3) holds then $Q = Q^T$ is a positive definite matrix [30]

$$\begin{aligned} Q &:= -\left(\bar{A}_0^T D + D\bar{A}_0\right) \\ &= -\Gamma^{-1}\left(\Gamma\bar{A}_0^T\Gamma^{-1} + \Gamma^{-1}\bar{A}_0\Gamma\right)\Gamma^{-1} > 0\end{aligned}$$

and hence $\mathrm{d}V(\psi)/\mathrm{d}t \le -\lambda_{\min}(Q)\|\psi\|^2$, where $\lambda_{\min}(Q) > 0$ denotes the smallest eigenvalue of $Q$. Upon integration, we get

$$\begin{aligned} 0 &\le \langle \psi(t), D\psi(t)\rangle \\ &\le \langle \psi(0), D\psi(0)\rangle - \lambda_{\min}(Q)\int_0^t \left\|\bar{T}(t)\psi(0)\right\|^2 \mathrm{d}\tau\end{aligned}$$

which yields

$$\int_0^t \left\|\bar{T}(t)\psi(0)\right\|^2 \mathrm{d}\tau \le \frac{1}{\lambda_{\min}(Q)}\langle \psi(0), D\psi(0)\rangle \qquad \forall t \ge 0 \qquad \forall \psi(0) \in \mathcal{D}(\bar{\mathcal{A}}).$$

Since $\mathcal{D}(\bar{\mathcal{A}})$ is dense in $L_2^n(\Omega)$, the last inequality can be extended to all $\psi(0) \in L_2^n(\Omega)$ [46], [47]. Thus, for every $\psi(0) \in L_2^n(\Omega)$ there is $\mu_\psi := \langle \psi(0), D\psi(0)\rangle/\lambda_{\min}(Q) > 0$ such that

$$\int_0^\infty \left\|\bar{T}(t)\psi(0)\right\|^2 \mathrm{d}\tau \le \mu_\psi$$

which proves the exponential stability of $\bar{T}(t)$ [47, Lemma 5.1.2]. ∎

*Remark 1:* The exponential stability of $T(t)$ in Theorem 1 can be also established using a Lyapunov based approach with

$$V(\psi) = \langle \psi, D\psi\rangle, \qquad D := \Gamma^{-2}\mathrm{diag}\left\{[1/a_1 \quad \cdots \quad 1/a_n]\right\}.$$

However, the proof of Theorem 1 is of independent interest because of the explicit construction of the $C_o$-semigroup and block-diagonalization of operator (LRD), (DM).

## IV. Extension to Nonlinear Reaction–Diffusion Equations

We next show global asymptotic stability of the origin of the nonlinear distributed system (RD), (DM). This result holds in the $L_2^n(\Omega)$ sense under the following assumption:

*Assumption 1:* The functions $f_i(\cdot)$, $g_i(\cdot)$, and $h_i(\cdot)$ in (RD) are continuously differentiable. Moreover, the functions $f_i(\cdot)$ and $g_i(\cdot)$ satisfy (C1)–(C3), the functions $h_i(\cdot)$ are positive, and the functions $g_i(\cdot)$ are nondecreasing, i.e.

$$h_i > 0, \qquad g_{i\sigma} := \partial g_i/\partial\sigma \ge 0 \qquad \forall \sigma \in \mathbb{R}. \tag{C5}$$

A new ingredient in Assumption 1 compared to the properties of $f_i(\cdot)$ and $g_i(\cdot)$ in (5) is a nondecreasing assumption on the functions $g_i(\cdot)$. This additional assumption provides convexity of the Lyapunov function, which is essential for establishing stability in the presence of linear diffusion terms. For nonlinear diffusion terms we also assume that each $h_i(\cdot)$ is a positive function.

*Theorem 3:* Suppose that system (RD), (DM) satisfies Assumption 1. Consider the Lyapunov function candidate

$$V(\psi) = \sum_{i=1}^{n} d_i\gamma_i \int_\Omega \left(\int_0^{\psi_i(\xi)} g_i(\sigma)\mathrm{d}\sigma\right)\mathrm{d}\xi$$

where the $d_i$'s are defined as in Section III, and suppose that there exists some function $\alpha(\cdot)$ of class $\mathcal{K}_\infty$ such that

$$V(\psi) \ge \alpha\left(\|\psi\|\right) \qquad \forall \psi \in L_2^n(\Omega). \tag{C6}$$

Then $\psi = 0$ is a globally asymptotically stable equilibrium point of (RD), (DM), in the $L_2^n(\Omega)$ sense.

*Remark 2 (Well-Posedness):* Standard arguments (see, for example, [36], [50], [51]) can be used to establish that (RD), (DM) has a unique solution on $[0, t_{\max})$. The existence of a unique solution on the time interval $[0, \infty)$ follows from the asymptotic stability of the origin of (RD), (DM).

*Proof:* We represent the $i$th subsystem of (RD), (DM) by:

$$H_i : \begin{cases} \psi_{it} = \nabla\cdot(h_i(\psi_i)\nabla\psi_i) - f_i(\psi_i) + u_i \\ y_i = g_i(\psi_i) \\ \psi_{i\nu} = 0 \text{ on } \partial\Omega. \end{cases}$$

The derivative of

$$V_i(\psi_i) := \gamma_i \int_\Omega \left( \int_0^{\psi_i(\xi)} g_i(\sigma) \mathrm{d}\sigma \right) \mathrm{d}\xi \tag{17}$$

along the solutions of $H_i$ is determined by

$$\begin{aligned} \dot{V}_i &= \gamma_i \langle g_i(\psi_i), \psi_{it} \rangle \\ &= \gamma_i \langle g_i(\psi_i), \nabla \cdot (h_i(\psi_i) \nabla \psi_i) - f_i(\psi_i) + u_i \rangle . \end{aligned}$$

Green's integral identity [49], in combination with the Neumann boundary conditions on $\psi_i$, can be used to obtain

$$\dot{V}_i = -\gamma_i \langle g_{i\psi_i} \nabla \psi_i, h_i \nabla \psi_i \rangle - \gamma_i \langle g_i, f_i \rangle + \gamma_i \langle g_i, u_i \rangle.$$

Now, from (C5) we have $h_i g_{i\sigma} \geq 0$. Using this property and the fact that $-\gamma_i f_i(\sigma) g_i(\sigma) \leq -g_i^2(\sigma)$ (cf. (C1)–(C2)) we arrive at

$$\dot{V}_i \leq -\langle g_i, g_i \rangle + \gamma_i \langle g_i, u_i \rangle = -\langle y_i, y_i \rangle + \gamma_i \langle y_i, u_i \rangle.$$

This upper bound on $\dot{V}_i$ and the following Lyapunov function candidate $V(\psi) := \sum_{i=1}^n d_i V_i(\psi_i)$ yield

$$\begin{aligned} \dot{V} &\leq \langle y, \left( \bar{A}_0^T D + D \bar{A}_0 \right) y \rangle \\ &\leq -\lambda_{\min}(Q) \|y\|^2 = -\lambda_{\min}(Q) \sum_{i=1}^n \|g_i\|^2. \end{aligned} \tag{18}$$

Since the $d_i$'s are defined as in Section III, we have used the fact that $Q = Q^T := -(\bar{A}_0^T D + D \bar{A}_0)$ represents a positive definite matrix (see the proof of Theorem 2).

Now, since $V(\psi) \geq \alpha(\|\psi\|)$ for each $\psi \in L_2^n(\Omega)$, with $\alpha(\cdot) \in \mathcal{K}_\infty$, for any $\epsilon > 0$ there exist $\delta > 0$ such that $\|\psi(0)\| < \delta$ implies $\|\psi(t)\| < \epsilon$ for all $t \geq 0$. This follows from positive invariance of the set $\Omega_k := \{\psi \in L_2^n(\Omega), V(\psi) < k\}$, $k > 0$, and continuity of Lyapunov function $V$ [34]. Furthermore, $V(\psi)$ is a nonincreasing function of time bounded below by zero and, thus, there exists a limit of $V(\psi(t))$ as time goes to infinity. If this limit is positive then (C1), (C6), and (18) imply the existence of $m > 0$ such that $\sup_{t \geq 0} \dot{V}(\psi(t)) \leq -m$. But then $V(\psi(t)) \leq V(\psi(0)) - mt$ and $V(\psi(t))$ will eventually become negative which contradicts nonnegativity of $V(\psi(t))$, for all $t \geq 0$. Therefore, both $V(\psi(t))$ and $\|\psi(t)\|$ converge asymptotically to zero. From the radial unboundedness of $V(\psi)$ (cf. (C6)) and the above analysis we conclude global asymptotic stability of the origin, in the $L_2^n(\Omega)$ sense. ■

*Remark 3:* The condition (C6) on $V(\psi)$ can be weakened by working on $L_1^n(\Omega)$, in which case Jensen's inequality, applied to (17), provides the desired estimate (see Appendix A). This relaxation allows for inclusion of many relevant nonlinearities arising in biological applications; one such example is provided in Section VI. Using a similar argument to the one presented in Theorem 3, the global asymptotic stability of the origin in the $L_1^n(\Omega)$ sense can be established (with keeping in mind that, in this case, $\langle u, v \rangle$ denotes a *symbol* for $\int_\Omega u^T(\xi) v(\xi) \mathrm{d}\xi$).

## V. Stability Analysis for a Compartmental Model

An alternative to the partial differential equation representation (RD) is a *compartmental model* which divides the reaction into compartments that are individually homogeneous and well-mixed, and represents them with ordinary differential equations. Compartmental models are preferable in situations where reactions are separated by physical barriers such as cell and intracellular membranes which allow limited flow between the compartments [52]. Instead of the lumped model (5) we now consider $m$ compartments where the dynamics of the $j$th compartment, $j = 2, \cdots, m-1$, are given by

$$\begin{aligned} \dot{x}_{j,1} &= \mu_{j-1,1}(x_{j-1,1} - x_{j,1}) - \mu_{j,1}(x_{j,1} - x_{j+1,1}) \\ &\quad - f_1(x_{j,1}) - g_n(x_{j,n}) \\ \dot{x}_{j,2} &= \mu_{j-1,2}(x_{j-1,2} - x_{j,2}) - \mu_{j,2}(x_{j,2} - x_{j+1,2}) \\ &\quad - f_2(x_{j,2}) + g_1(x_{j,1}) \\ &\vdots \\ \dot{x}_{j,n} &= \mu_{j-1,n}(x_{j-1,n} - x_{j,n}) - \mu_{j,n}(x_{j,n} - x_{j+1,n}) \\ &\quad - f_n(x_{j,n}) + g_{n-1}(x_{j,n-1}). \end{aligned} \tag{CM}$$

The functions $\mu_{j,i}(\cdot), i = 1, \cdots, n, j = 1, \cdots, m-1$, represent the diffusion terms between the compartments and possess the property

$$\sigma \mu_{j,i}(\sigma) \geq 0 \qquad \forall \sigma \in \mathbb{R}. \tag{C7}$$

For the first and last compartments $j = 1$ and $j = m$, respectively the first and the second terms in the right-hand side of (CM) must be dropped because $x_{0,i}$ and $x_{m+1,i}$ are not defined.

In the absence of the diffusion terms, the dynamics of the compartments in (CM) are decoupled, and coincide with (5) which is shown in [30] to be globally asymptotically stable under the conditions (C1)–(C4). The following theorem makes an additional assumption that the function $g_i(\cdot)$ be nondecreasing and proves that global asymptotic stability is preserved in the presence of diffusion terms:

*Theorem 4:* Consider the compartmental model (CM), $j = 1, \ldots, m$, where for $j = 1$ and $j = m$, respectively the first and the second terms in the right-hand side of (CM) are to be interpreted as zero. If the functions $f_i(\cdot)$ and $g_i(\cdot)$ satisfy the conditions (C1)–(C4) and if, further, $g_i(\cdot)$ is a nondecreasing function and $\mu_{j,i}(\cdot)$ is as in (C7) then the origin $x_{j,i} = 0$ is globally asymptotically stable.

*Proof:* We first introduce the notation

$$\begin{aligned} x_j &:= [x_{j,1} \quad \cdots \quad x_{j,n}]^T, \qquad j = 1, \cdots, m \\ x &:= \left[ x_1^T \quad \cdots \quad x_m^T \right]^T \\ \mu_j(x_j - x_{j+1}) &:= [\mu_{j,1} \quad \cdots \quad \mu_{j,n}]^T \\ & \qquad j = 1, \cdots, m-1. \end{aligned} \tag{19}$$

In the absence of the diffusion terms in (CM), the reference [30] constructs a Lyapunov function of the form

$$V(x_j) = \sum_{i=1}^n d_i \gamma_i \int_0^{x_{j,i}} g_i(\sigma) \mathrm{d}\sigma \tag{20}$$

where $d_i$, $i = 1, \cdots, n$, are the diagonal entries of a matrix $D$ obtained from (6) with $A$ selected as in (16), and proves that its time derivative satisfies the estimate

$$\dot{V}(x_j) \leq -\epsilon \left\|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\right\|^2 \tag{21}$$

for some $\epsilon > 0$. In the presence of the diffusion terms in (CM), the estimate (21) becomes

$$\begin{aligned}\dot{V}(x_j) \leq & -\epsilon \left\|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\right\|^2 \\ & + \frac{\partial V(x_j)}{\partial x_j}\mu_{j-1}(x_{j-1} - x_j) \\ & - \frac{\partial V(x_j)}{\partial x_j}\mu_j(x_j - x_{j+1}) \\ & j = 2, \cdots, m-1,\end{aligned} \tag{22}$$

while for $j = 1$:

$$\dot{V}(x_1) \leq -\epsilon\left\|(g_1(x_{1,1}), \cdots, g_n(x_{1,n}))\right\|^2 - \frac{\partial V(x_1)}{\partial x_1}\mu_1(x_1 - x_2) \tag{23}$$

and for $j = m$:

$$\begin{aligned}\dot{V}(x_m) \leq -\epsilon \left\|(g_1(x_{m,1}), \cdots, g_n(x_{m,n}))\right\|^2 \\ + \frac{\partial V(x_m)}{\partial x_m}\mu_{m-1}(x_{m-1} - x_m).\end{aligned}$$

Then the Lyapunov function

$$\mathcal{V}(x) = \sum_{j=1}^{m} V(x_j) \tag{24}$$

satisfies

$$\begin{aligned}\dot{\mathcal{V}}(x) \leq & -\epsilon \sum_{j=1}^{m} \left\|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\right\|^2 \\ & - \sum_{j=1}^{m-1}\left(\frac{\partial V(x_j)}{\partial x_j} - \frac{\partial V(x_{j+1})}{\partial x_{j+1}}\right)\mu_j(x_j - x_{j+1}).\end{aligned} \tag{25}$$

Substituting (19) and

$$\frac{\partial V(x_j)}{\partial x_j} = [d_1\gamma_1 g_1(x_{j,1}) \quad \cdots \quad d_n\gamma_n g_n(x_{j,n})] \tag{26}$$

which is obtained from (20), we get

$$\begin{aligned}&\sum_{j=1}^{m-1}\left(\frac{\partial V(x_j)}{\partial x_j} - \frac{\partial V(x_{j+1})}{\partial x_{j+1}}\right)\mu_j(x_j - x_{j+1}) \\ &= \sum_{j=1}^{m-1}\sum_{i=1}^{n} d_i\gamma_i \left[g_i(x_{j,i}) - g_i(x_{j+1,i})\right]\mu_{j,i}(x_{j,i} - x_{j+1,i}).\end{aligned} \tag{27}$$

Because $g_i(\cdot)$ is a nondecreasing function by assumption, we note that $[g_i(x_{j,i}) - g_i(x_{j+1,i})]$ possesses the same sign as $(x_{j,i} - x_{j+1,i})$. We next recall from property (C7) that $\mu_{j,i}(x_{j,i} - x_{j+1,i})$ also possesses the same sign as $(x_{j,i} - x_{j+1,i})$ and, thus,

$$\left[g_i(x_{j,i}) - g_i(x_{j+1,i})\right]\mu_{j,i}(x_{j,i} - x_{j+1,i}) \geq 0 \tag{28}$$

which, according to (27) and (25), implies

$$\dot{\mathcal{V}}(x) \leq -\epsilon \sum_{j=1}^{m} \left\|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\right\|^2. \tag{29}$$

Because the Lyapunov function $\mathcal{V}(x)$ is proper from property (C4) and because the right-hand side of (29) is negative definite from property (C1), we conclude that the origin $x = 0$ is globally asymptotically stable. ■

*Remark 4:* Theorems 3 and 4 both rely on the assumption that $g_i(\cdot)$ is nondecreasing, which translates to the convexity of the Lyapunov functions (17) and (20). A similar convex Lyapunov function assumption has been employed in [48] to preserve asymptotic stability in the presence of diffusion terms. Unlike the local result in [48], however, in this paper we have established *global* asymptotic stability and allowed nonlinear diffusion terms by exploiting the specific structure of the system.

## VI. Example

We illustrate our main results with the analysis of a negative feedback loop around a simple MAPK cascade model. As described in the introduction, MAPK cascades are functional modules, highly conserved throughout evolution and across species, which mediate the transmission of signals generated by receptor activation into diverse biochemical and physiological responses involving cell cycle regulation, gene expression, cellular metabolism, stress responses, and other functions. The control of MAPK and similar kinase cascades by therapeutic intervention is being investigated as a target for drugs, particularly in the areas of cancer and inflammation [53]. Several MAPK cascades have been found in yeast [54] and at least a dozen in mammalian cells [55], and much effort is directed to the understanding of their dynamical behavior [28], [56], [57].

There are many models of MAPK cascades, with varying complexity. The simplest class of models [18], [58], using quasi-steady-state approximations for enzymatic mechanisms and a single phosphorylation site, involves a chain of three subsystems

$$\begin{aligned}\dot{x}_1 &= -\frac{b_1 x_1}{c_1 + x_1} + u\frac{d_1(1 - x_1)}{e_1 + (1 - x_1)} \\ \dot{x}_2 &= -\frac{b_2 x_2}{c_2 + x_2} + x_1\frac{d_2(1 - x_2)}{e_2 + (1 - x_2)} \\ \dot{x}_3 &= -\frac{b_3 x_3}{c_3 + x_3} + x_2\frac{d_3(1 - x_3)}{e_3 + (1 - x_3)}\end{aligned}$$

where $u$ is an input and $x_3$ is seen as an output. The variables $x_i$ denote the "active" forms of each of three proteins, and the terms $1-x_i$ indicate the inactive forms of the respective proteins (after nondimensionalizing and assuming that the total concentration of each of the $\text{proteins} = 1$). For example, the term $x_1 d_2(1-x_2)/(e_2+(1-x_2))$ indicates the rate at which the inactive form of the second protein is being converted to active form. This rate is proportional to the concentration of the active form of the protein $x_1$, which facilitates the conversion. Similarly, active $x_2$ facilitates the activation of the third protein. The first term in each of the right-hand sides models the inactivation of the respective protein, a mechanism that proceeds at a rate that is independent of the activation process. The saturated form of the nonlinearities reflects the assumption that reactions are rate limited by resources such as the amount of enzymes available (an assumption that is not always valid). For this model, Kholodenko proposed in [18] the study of inhibitory feedback from the last to the first element, mathematically represented by a feedback law $u = \mu/(1+kx_3)$. See [18] for a description of the physical mechanism (an inhibitory phosphorylation of "SOS" protein, upstream of the system, by the last protein, p42/p44 MAPK or ERK) that might produce this inhibition.

Linearizing the system about an equilibrium, there results a linear system to which one may apply the secant condition [18]. A linear model also arises when considering *weakly activated pathways*, the behavior of the pathway when there is only a low level of kinase phosphorylation. In this case, one assumes that the inactive forms dominate: $1 - x_i \approx 1$; this is the analysis in [58] and [59]. An intermediate case would be that in which activations are weak but the coefficients $c_i$ are small enough that the negative terms in the above equations cannot be replaced by linear functions; in that case, we are lead to equations as follows, for the closed-loop system:

$$\begin{aligned}\dot{x}_1 &= -\frac{b_1 x_1}{c_1 + x_1} + \frac{\mu}{1 + k x_3}\\ \dot{x}_2 &= -\frac{b_2 x_2}{c_2 + x_2} + d_2 x_1\\ \dot{x}_3 &= -\frac{b_3 x_3}{c_3 + x_3} + d_3 x_2. \end{aligned} \tag{30}$$

Both linearizations, as well as this nonlinear system, can be analyzed using our techniques. For our simulations we pick the nonlinear model, as it is more interesting. Denoting by $\bar{x}$ the equilibrium of (30) and introducing the shifted variable $\tilde{x} = x - \bar{x}$, we represent system (30) as in (5) with

$$\begin{aligned} f_i(\tilde{x}_i) &= \frac{b_i x_i}{c_i + x_i} - \frac{b_i \bar{x}_i}{c_i + \bar{x}_i}, \qquad i = 1,2,3\\ g_i(\tilde{x}_i) &= d_{i+1}\tilde{x}_i, \qquad i = 1,2\\ g_3(\tilde{x}_3) &= \frac{\mu}{1 + k\bar{x}_3} - \frac{\mu}{1 + k x_3}. \end{aligned}$$

We first note that condition (C1) is satisfied because $f_i(\tilde{x}_i)$ and $g_i(\tilde{x}_i)$, $i = 1,2,3$, are strictly increasing functions. Next, we recall from [30, Section 6] that a set of gains $\gamma_i$, $i = 1,2,3$, that do not depend on the specific location of $\bar{x}$ can be obtained by

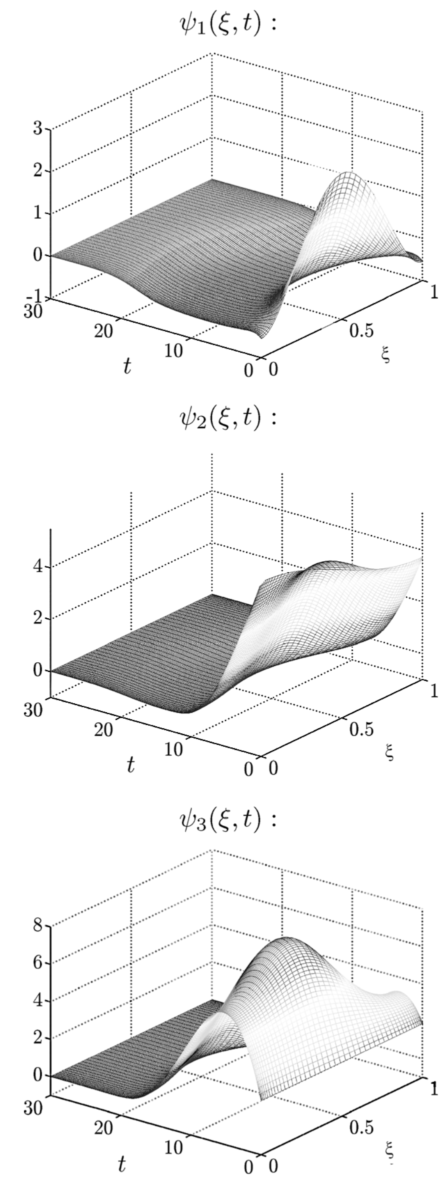


Fig. 3. Plots of $\psi_i(\xi,t) := \phi_i(\xi,t) - \bar{\phi}$, $i = 1,2,3$, for system (EX) with $\phi(\xi,0) = [16\xi^2(1-\xi^2)^2 \;\; 5+\cos\pi\xi \;\; 2]^T$.

evaluating the maximum value of the slope ratio $g_i'/f_i'$ in the interval $x_i \in [0,1]$ in which $x_i$ evolves. Upon trivial calculations, we obtain

$$\begin{aligned}\gamma_i &= \frac{d_{i+1}(c_i+1)^2}{b_i c_i}, \qquad i = 1,2\\ \gamma_3 &= \frac{k\mu}{b_3 c_3}\max\left\{c_3^2, \frac{(c_3+1)^2}{(1+k)^2}\right\}.\end{aligned}$$

We pick the parameters $b_i = c_i = 1$, $i = 1,2,3$, $k = 1$, $d_2 = d_3 = \mu = 0.4$, which satisfy the secant condition (C3). (Although we chose the parameters to be $\mathcal{O}(1)$ as in [58], we do not claim that these are physiologically realistic, nor are the diffusion constants that we pick below. We are merely interested in illustrating the theoretical results.) Adding diffusion terms with coefficients $h_1 = h_2 = h_3 = 0.001$, we obtain the reaction–diffusion equations

$$\begin{aligned}\phi_{1t} &= 0.001\phi_{1\xi\xi} - \frac{\phi_1}{1+\phi_1} + \frac{0.4}{1+\phi_3}\\ \phi_{2t} &= 0.001\phi_{2\xi\xi} - \frac{\phi_2}{1+\phi_2} + 0.4\phi_1\\ \phi_{3t} &= 0.001\phi_{3\xi\xi} - \frac{\phi_3}{1+\phi_3} + 0.4\phi_2\end{aligned} \tag{EX}$$

with the Neumann boundary conditions, $\phi_{i\xi}(0,t) = \phi_{i\xi}(1,t) = 0$. System (EX) can be brought to the form (RD) using the following coordinate transformation: $\psi := \phi - \bar{\phi}$, where $\bar{\phi} = [0.5501\ 0.2821\ 0.1272]^T$ denotes the equilibrium point of (EX). Asymptotic convergence of $\phi(x,t)$ to $\bar{\phi}$ is illustrated in Fig. 3. A spatial discretization of the diffusion operator with Neumann boundary conditions is obtained using a Matlab Differentiation Matrix Suite [60].

## VII. Concluding Remarks

We identify a class of systems with a cyclic interconnection structure in which addition of diffusion does not have a destabilizing effect. For these systems, we demonstrate global stability if the "secant" criterion is satisfied. In the linear case, we show that the secant condition is necessary and sufficient for the existence of a decoupled Lyapunov function, which extends the diagonal stability result [30] to spatially distributed systems. For reaction–diffusion equations with nondecreasing coupling nonlinearities, we establish global asymptotic stability of the origin. Under some fairly mild assumptions, we also allow for nonlinear diffusion terms by exploiting the specific structure of the system.

## Appendix

### A. Relaxation of Condition (C6)

Let us represent $V_i(\psi_i)$ in (17) by

$$V_i(\psi_i) := \gamma_i \int_\Omega p_i\left(\psi_i(\xi)\right) \mathrm{d}\xi, \qquad p_i(s) := \int_0^s g_i(\sigma)\mathrm{d}\sigma$$

and let $\Omega_p$ (respectively, $\Omega_m$) denote the set of points in $\Omega$ where $\psi_i(\xi)$ is positive (respectively, negative), i.e.

$$\Omega_p := \left\{\xi \in \Omega, \psi_i(\xi) > 0\right\}, \qquad \Omega_m := \left\{\xi \in \Omega, \psi_i(\xi) < 0\right\}.$$

Then, $V_i(\psi_i)$ can be rewritten as

$$V_i(\psi_i) := \gamma_i \int_{\Omega_p} p_{ip}\left(|\psi_i(\xi)|\right) \mathrm{d}\xi + \gamma_i \int_{\Omega_m} p_{im}\left(|\psi_i(\xi)|\right) \mathrm{d}\xi$$

where

$$p_{ip}(s) := \int_0^s g_i(\sigma)\mathrm{d}\sigma, \qquad p_{im}(s) := \int_0^{-s} g_i(\sigma)\mathrm{d}\sigma, \qquad s > 0.$$

We observe that the first two derivatives of the functions $p_{ip}$ and $p_{im}$, respectively, satisfy

$$\left\{p'_{ip}(s) = g_i(s) > 0,\ p''_{ip}(s) = g'_i(s) \geq 0\right\}$$
$$\left\{p'_{im}(s) = -g_i(-s) > 0,\ p''_{im}(s) = g'_i(-s) \geq 0\right\}$$

which implies that both these functions are of class $\mathcal{K}_\infty$ and convex. Using convexity, we may apply Jensen's inequality [49] to obtain

$$V_i(\psi_i) \geq \gamma_i\left(|\Omega_p| p_{ip}\left(\|\psi_i\|_1/|\Omega_p|\right) + |\Omega_m| p_{im}\left(\|\psi_i\|_1/|\Omega_m|\right)\right)$$

where $|\Omega_r|$ denotes the measure of set $\Omega_r$, and $\|\psi_i\|_1$ is the $L_1(0,1)$-norm of $\psi_i$. Since $p_{ip}$ and $p_{im}$ are $\mathcal{K}_\infty$-functions we conclude that condition (C6) on $V(\psi)$ always holds if the underlying state-space is $L_1^n(\Omega)$ (that is, there exists some function $\alpha(\cdot)$ of class $\mathcal{K}_\infty$ such that $V(\psi) \geq \alpha(\|\psi\|_1), \forall \psi \in L_1^n(\Omega)$).

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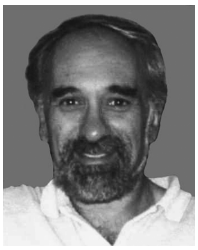

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