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Remarks on the 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 and problem formulation

It has long been observed in metabolic and gene regulation networks that negative feedback inhibitions can potentially cause instabilities and limit cycles (see *e.g.* [1], [2], and the references therein). A special case of particular interest is a *cyclic* network in which the end product of a sequence of reactions inhibits the rate of the first reaction [3]. To evaluate local stability properties of such networks [4] and [5] 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 it is Hurwitz if the following "secant criterion" holds:

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

Following a *passivity* interpretation of this criterion recently given in [6], the authors of [7] studied the nonlinear model

$$\begin{array}{rcl} \dot{x}_1 &=& -f_1(x_1) \,-\, g_n(x_n) \\ \dot{x}_2 &=& -f_2(x_2) \,+\, g_1(x_1) \\ &\vdots& \\ \dot{x}_n &=& -f_n(x_n) \,+\, g_{n-1}(x_{n-1}) \end{array} \tag{3}$$

and proved global asymptotic stability of the origin[1] under the conditions

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

$$\frac{g_i(\sigma)}{f_i(\sigma)} \,\leq\, \gamma_i, \quad \forall\, \sigma \,\in\, \mathbb{R} \setminus \{0\}, \tag{C2}$$

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

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

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 [7] 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

$$A^T D \,+\, DA \,<\, 0. \tag{4}$$

Using this diagonal stability property [7] constructs a Lyapunov function for (3) 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 $V = x^T D x$.

In this paper we extend the linear and nonlinear results of [4], [5], [7] to spatially distributed models that consist of a cyclic interconnection of n reaction-diffusion equations

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

where ψ_i denotes the state of the ith subsystem which depends on spatial coordinate ξ 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 Ω in $\mathbb{R}^r$, $r = 1$, 2 or 3, with a smooth boundary $\partial\Omega$ and outward unit

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[1] Throughout the paper we assume that an equilibrium exists and is unique (see [7] for conditions that guarantee this) and that this equilibrium has been shifted to the origin with a change of variables.

normal ν. 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 ψ_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 [8], [9]

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

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 $\psi := \left[\begin{array}{ccc} \psi_1 & \cdots & \psi_n \end{array}\right]^T$.

The study of stability properties for distributed system (RD) is important in many biological applications. Our first result, presented in Section II, 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 [7] to partial differential equations. The next result of the paper, presented in Section III, studies the nonlinear reaction-diffusion equation (RD) and proves global asymptotic stability of $\psi = 0$ under assumptions that mimic the conditions (C1)-(C3) of [7], 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 [10] to preserve stability in the presence of linear diffusion terms. Finally, Section IV 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.

II. Cyclic interconnection of linear reaction-diffusion equations

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

$$\begin{array}{c} f_i(\psi_i) := a_i\psi_i,\ g_i(\psi_i) := b_i\psi_i, \\ h_i(\psi_i) := c_i,\ i = 1, \ldots, n, \end{array} \qquad (5)$$

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 (5) are given by

$$\psi_t = \mathcal{A}\psi := C\Delta\psi + A_0\psi, \qquad \text{(LRD)}$$

where $\Delta\psi$ denotes the vector Laplacian, that is $\Delta\psi := \left[\begin{array}{ccc} \Delta\psi_1 & \cdots & \Delta\psi_n \end{array}\right]^T$, $C := \mathrm{diag}\{\left[\begin{array}{ccc} c_1 & \cdots & c_n \end{array}\right]\} > 0$, and

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

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 [9]) that the operator $\partial_{\xi\xi}$ with Neumann boundary conditions is self-adjoint with the following set of eigenfunctions $\{\varphi_k\}$ and corresponding eigenvalues $\{\nu_k\}$:

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

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 nth order equations:

$$\dot{x}_k = A_k x_k, \quad k = 0, 1, \ldots, \qquad (6)$$

with $x_k(t) := \left[\begin{array}{ccc} x_{1,k}(t) & \cdots & x_{n,k}(t) \end{array}\right]^T$,

$$A_k := \left[\begin{array}{ccccc} -\alpha_{1,k} & 0 & \cdots & 0 & -b_n \\ b_1 & -\alpha_{2,k} & \ddots & & 0 \\ 0 & b_2 & -\alpha_{3,k} & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & b_{n-1} & -\alpha_{n,k} \end{array}\right],$$

and $\alpha_{i,k} := a_i - c_i\nu_k = a_i + c_i(k\pi)^2 > 0$. Based on [4], [5] we conclude that each A_k is Hurwitz if (2) holds. Therefore, each subsystem in (6) is exponentially stable and there exist $P_k = P_k^T > 0$ such that

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

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

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

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 $\{x_k(0)\}_{k \in \mathbb{N}_0} \in l_2^n$ [9, Lemma 5.1.2]. Let s_m denote the mth partial sum, i.e.

$$s_m := \sum_{k=0}^{m} x_k^T(0) P_k x_k(0). \tag{7}$$

For $l < m$ we have

$$\begin{aligned} |s_m - s_l| &= \sum_{k=l+1}^{m} x_k^T(0) P_k x_k(0) \\ &\leq \sum_{k=l+1}^{m} \|P_k\| \|x_k(0)\|^2. \end{aligned} \tag{8}$$

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

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

and use perturbation analysis to express P_k as

$$\begin{aligned} P_k &= \frac{1}{k^2} \left(V_0 + \frac{1}{k^2} V_1 + \frac{1}{k^4} V_2 + \ldots \right) \\ &= \frac{1}{k^2} \sum_{j=0}^{\infty} \frac{1}{k^{2j}} V_j, \end{aligned}$$

where

$$\begin{array}{rcl} F_0 V_0 + V_0 F_0 &=& -I \\ F_0 V_j + V_j F_0 &=& -(A_0^T V_{j-1} + V_{j-1} A_0), \end{array} \tag{9}$$

with $j \in \mathbb{N}$. Solution to (9) is determined by

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

which can be used to obtain

$$\begin{array}{rcl} \|V_0\| &=& 1/(2\pi^2 c_{\min}) \\ \|V_j\| &\leq& \|V_0\| \left(2 \|A_0\| \|V_0\| \right)^j, \quad j \in \mathbb{N} \\ \|P_k\| &\leq& \dfrac{\|V_0\|}{k^2} \sum_{j=0}^{\infty} \left(2 \|A_0\| \|V_0\| / k^2 \right)^j. \end{array}$$

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 $\|P_k\|$:

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

and inequality in (8) simplifies to

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

Hence, for each $\{x_k(0)\}_{k \in \mathbb{N}_0} \in l_2^n$ partial sum (7) represents a Cauchy sequence which guarantees convergence of $\sum_{k=0}^\infty x_k^T(0) P_k x_k(0)$ and consequently

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

Since $\mathcal{D}(\mathcal{A})$ is dense in $L_2^n(0,1)$, by an argument as in [8, p. 51] this inequality can be extended to all $\psi(0) \in L_2^n(0,1)$ which implies exponential stability of $T(t)$ [9, Lemma 5.1.2].

Theorem 1: The C_o-semigroup $T(t)$ generated by operator (LRD)-(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 [7] to PDEs with r spatial coordinates:

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

$$V(\psi) := \langle \psi, D\psi \rangle = \sum_{i=1}^{n} d_i \langle \psi_i, \psi_i \rangle, \quad d_i > 0, \tag{10}$$

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

$$\psi_t = \bar{A}\psi := C\Delta\psi + \bar{A}_0 \psi, \tag{11}$$

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

$$\bar{A}_0 := \begin{bmatrix} -1 & 0 & \cdots & 0 & -\gamma_1 \\ \gamma_2 & -1 & \ddots & & 0 \\ 0 & \gamma_3 & -1 & \ddots & \vdots \\ \vdots & \ddots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & \gamma_n & -1 \end{bmatrix}. \tag{12}$$

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 (10) that establishes exponential stability of (11). The derivative of (10) along the solutions of (11) is given by

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

where we have used Green's integral identity [11] with ψ satisfying the Neumann boundary conditions on $\partial\Omega$, and the fact that C and D commute. The exponential stability of (11) 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 [4].

Sufficiency: Suppose that (C3) holds. Following [7] we define:

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

and differentiate (10) along the solutions of (11) to obtain

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

If (C3) holds then $Q = Q^T$ is a positive definite matrix [7]

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

and hence

$$\frac{\mathrm{d}V(\psi)}{\mathrm{d}t} \leq -\lambda_{\min}(Q)\|\psi\|^2,$$

where $\lambda_{\min}(Q) > 0$ denotes the smallest eigenvalue of Q. Upon integration, we get

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

which yields

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

Since $\mathcal{D}(\bar{\mathcal{A}})$ is dense in $L_2^n(\Omega)$, the last inequality can be extended to all $\psi(0) \in L_2^n(\Omega)$ [8], [9]. 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

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

which proves the exponential stability of $\bar{T}(t)$ [9, 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

$$\begin{aligned} V(\psi) &= \langle \psi, D\psi\rangle, \\ D &:= \Gamma^{-2}\,\mathrm{diag}\{[\ 1/a_1\ \ \cdots\ \ 1/a_n\ ]\}.\end{aligned}$$

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).

III. 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.

$$h_i > 0, \quad g_{i\sigma} := \partial g_i/\partial\sigma \geq 0, \quad \forall\,\sigma \in \mathbb{R}. \qquad \text{(C5)}$$

A new ingredient in Assumption 1 compared to the properties of $f_i(\cdot)$ and $g_i(\cdot)$ in (3) 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 II, and suppose that there exists some function $\alpha(\cdot)$ of class $\mathcal{K}_\infty$ such that

$$V(\psi) \geq \alpha(\|\psi\|), \quad \forall\,\psi \in L_2^n(\Omega). \qquad \text{(C6)}$$

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, [12]–[14]) 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 ith subsystem of (RD)-(DM) by:

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

The derivative of

$$V_i(\psi_i) := \gamma_i \int_\Omega \left(\int_0^{\psi_i(\xi)} g_i(\sigma)\,\mathrm{d}\sigma\right)\mathrm{d}\xi \qquad (13)$$

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 [11], in combination with the Neumann boundary conditions on ψ_i, can be used to obtain

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

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

$$\begin{aligned}\dot{V}_i &\leq -\left\langle g_i, g_i\right\rangle + \gamma_i \left\langle g_i, u_i\right\rangle \\ &= -\left\langle y_i, y_i\right\rangle + \gamma_i \left\langle y_i, u_i\right\rangle .\end{aligned}$$

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

$$\begin{aligned}\dot{V} &\leq \left\langle y, (\bar{A}_0^T D + D\bar{A}_0) y\right\rangle \\ &\leq -\lambda_{\min}(Q)\|y\|^2 \;=\; -\lambda_{\min}(Q)\sum_{i=1}^{n}\|g_i\|^2 .\end{aligned} \tag{14}$$

Since the d_i's are defined as in Section II, 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 [15]. 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 (14) 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 (13), provides the desired estimate. This relaxation allows for inclusion of many relevant nonlinearities arising in biological applications. 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 $\int_\Omega u^T(\xi)\, v(\xi)\,\mathrm{d}\xi$).

IV. 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 [16]. Instead of the lumped model (3) we now consider m compartments, and represent their interconnection structure with a graph in which the vertices $j = 1, \cdots, m$ represent the compartments. The edges labeled $l = 1, \cdots, p$ indicate the presence of diffusion between the compartments they connect. Although the graph is undirected, for notational convenience we assign an orientation to each edge and define the $m \times p$ *incidence matrix* S as

$$s_{jl} := \begin{cases} +1 & \text{if vertex } j \text{ is the sink of edge } l \\ -1 & \text{if vertex } j \text{ is the source of edge } l \\ \;\;0 & \text{otherwise.} \end{cases} \tag{15}$$

The particular choice of the orientation does not change the derivations below.

We let $x_{j,i}$ be the concentration of species i in compartment j, and for each edge $l = 1, \cdots, p$, we denote by

$$\mu_{l,i}(x_{\mathrm{sink}(l),i} - x_{\mathrm{source}(l),i}) \tag{16}$$

the diffusion term for the species i, flowing from compartment $\mathrm{source}(l)$ to $\mathrm{sink}(l)$. The functions $\mu_{l,i}(\cdot)$, $l = 1, \cdots, p$, $i = 1, \cdots, n$, satisfy

$$\sigma\mu_{l,i}(\sigma) \;\leq\; 0, \quad \forall\, \sigma \,\in\, \mathbb{R}. \tag{C7}$$

To incorporate the diffusion terms (16), we denote the right-hand side of (3) for compartment j by $F(X_j)$, where

$$X_j := (x_{j,1}, \cdots, x_{j,n})^T$$

is the state vector of concentrations $x_{j,i}$ in compartment j, and obtain:

$$\dot{X}_j = F(X_j) + (S_{j,\cdot} \otimes I_n)\mu((S^T \otimes I_n)X) \tag{CM}$$

where $S_{j,\cdot}$ is the jth row of the incidence matrix S, I_n is the $n \times n$ identity matrix, "$\otimes$" represents the Kronecker product,

$$X := [X_1^T \cdots X_m^T]^T \tag{17}$$

and $\mu : \mathbb{R}^{np} \to \mathbb{R}^{np}$ is defined as

$$\mu(z) := \tag{18}$$
$$[\mu_{1,1}(z_1)\cdots\mu_{1,n}(z_n) \;\cdots\;\cdots\; \mu_{p,1}(z_{(p-1)n+1})\cdots\mu_{p,n}(z_{np})]^T.$$

In the absence of the diffusion term μ, the dynamics of the compartments in (CM) are decoupled, and coincide with (3) which is shown in [7] 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 $F(\cdot)$ denotes the vector field in (3). 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 $\mu_{l,i}(\cdot)$ is as in (C7) then the origin $X = 0$ is globally asymptotically stable.

Proof: In the absence of the diffusion terms in (CM), the reference [7] constructs a Lyapunov function of the form

$$V(X_j) = \sum_{i=1}^{n} d_i \gamma_i \int_0^{x_{j,i}} g_i(\sigma)\,\mathrm{d}\sigma \qquad (19)$$

where d_i, $i = 1, \cdots, n$, are the diagonal entries of a matrix D obtained from (4) with A selected as in (12), and proves that it satisfies the estimate

$$\nabla V(X_j)F(X_j) \leq -\epsilon \|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\|^2 \qquad (20)$$

for some $\epsilon > 0$. In the presence of the diffusion terms in (CM), the time derivative of $V(X_j)$ satisfies:

$$\begin{aligned}\dot{V}(X_j) \leq & -\epsilon \|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\|^2 \\ & + \nabla V(X_j)(S_{j,\cdot} \otimes I_n)\mu((S^T \otimes I_n)X).\end{aligned} \qquad (21)$$

For the concatenated system (17) we employ the Lyapunov function

$$\mathcal{V}(X) \; = \; \sum_{j=1}^{m} V(X_j), \qquad (22)$$

and obtain from (21):

$$\begin{aligned}\dot{\mathcal{V}}(x) \leq & -\epsilon \sum_{j=1}^{m} \|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\|^2 \\ & + [\nabla V(X_1) \cdots \nabla V(X_m)](S \otimes I_n)\mu((S^T \otimes I_n)X).\end{aligned} \qquad (23)$$

We next rewrite the second term in the right-hand side of (23) as

$$\left((S^T \otimes I_n) \begin{bmatrix} \nabla V^T(X_1) \\ \vdots \\ \nabla V^T(X_m) \end{bmatrix} \right)^T \mu((S^T \otimes I_n)X), \qquad (24)$$

and note from (15) that (24) equals

$$\sum_{l=1}^{p} [\nabla V^T(X_{\mathrm{sink}(l)}) - \nabla V^T(X_{\mathrm{source}(l)})] \begin{bmatrix} \mu_{l,1} \\ \vdots \\ \mu_{l,n} \end{bmatrix} \qquad (25)$$

where $\mu_{l,i}$, $i = 1, \cdots, n$, denotes the diffusion function (16), and the argument is dropped for brevity. Finally, noting from (19) that

$$\nabla V(X_j) \; = \; \left[\, d_1\gamma_1 g_1(x_{j,1}) \cdots d_n \gamma_n g_n(x_{j,n}) \,\right], \qquad (26)$$

and substituting (26) in (25), we obtain:

$$= \sum_{l=1}^{p} \sum_{i=1}^{n} d_i \gamma_i [g_i(x_{\mathrm{sink}(l),i}) - g_i(x_{\mathrm{source}(l),i})]\, \mu_{l,i}. \qquad (27)$$

Because $g_i(\cdot)$ is a nondecreasing function by assumption, we note that $[g_i(x_{\mathrm{sink}(l),i}) - g_i(x_{\mathrm{source}(l),i})]$ possesses the same sign as $(x_{\mathrm{sink}(l),i} - x_{\mathrm{source}(l),i})$. We next recall from the sector property (C7) that the function $\mu_{l,i}$ in (16) possesses the opposite sign of its argument $(x_{\mathrm{sink}(l),i} - x_{\mathrm{source}(l),i})$. This means that each term in the sum (27) is non-positive and, hence, (23) becomes

$$\dot{\mathcal{V}}(x) \leq -\epsilon \sum_{j=1}^{m} \|(g_1(x_{j,1}), \cdots, g_n(x_{j,n}))\|^2. \qquad (28)$$

Because the Lyapunov function $\mathcal{V}(x)$ is proper from property (C4) and because the right-hand side of (28) 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 (13) and (19). A similar convex Lyapunov function assumption has been employed in [10] to preserve asymptotic stability in the presence of diffusion terms. Unlike the local result in [10], however, in this paper we have established *global* asymptotic stability and allowed nonlinear diffusion terms by exploiting the specific structure of the system.

V. 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 [7] 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.

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