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Certifying spatially uniform behavior in reaction–diffusion PDE and compartmental ODE systems ☆

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ABSTRACT

We present a condition that guarantees spatial uniformity for the asymptotic behavior of the solutions of a reaction–diffusion PDE with Neumann boundary conditions. This condition makes use of the Jacobian matrix of the reaction terms and the second Neumann eigenvalue of the Laplacian operator on the given spatial domain, and eliminates the global Lipschitz assumptions commonly used in mathematical biology literature. We then derive numerical procedures that employ linear matrix inequalities to certify this condition, and illustrate these procedures on models of several biochemical reaction networks. Finally, we present an analog of this PDE result for the synchronization of a network of identical ODE models coupled by diffusion terms. From a systems biology perspective, the main contribution of the paper is to blend analytical and numerical tools from nonlinear systems and control theory to derive a relaxed and verifiable condition for spatial uniformity of biological processes.

1. Introduction

Spatially distributed models are essential for understanding dynamical phenomena that are central to the development of multicellular organisms. Within the cell, gradients of protein activities organize signaling around cellular structures and provide positional cues for important processes, such as division (Kholodenko, 2006). In a field of cells, concentration gradients of morphogens lead to different gene expression patterns, allowing distinct cell types to emerge in early development. One of the theories for spatial organization and pattern formation is based on diffusion-driven instability (Segel & Jackson, 1972; Turing, 1952), which has been a subject of intense study as surveyed in Murray (1989), Cross and Hohenberg (1993) and Othmer, Painter, Umulis, and Xue (2009). This phenomenon occurs when one of the higher spatial modes in the reaction–diffusion partial differential equation (PDE) is destabilized by diffusion, thus causing nonuniformities to grow.

Understanding when the solutions of a reaction–diffusion PDE exhibit asymptotically uniform behavior is an important problem because certification of uniformity rules out diffusion-driven instabilities. In addition, sufficient conditions for uniformity, when negated, serve as necessary conditions for such instabilities and help identify reaction network topologies that have the ability to generate spatial patterns. Indeed, designing circuits for pattern formation is one of the current research topics in synthetic biology, with applications envisioned in tissue engineering, biomaterial fabrication and biosensing (Basu, Gerchman, Collins, Arnold, & Weiss, 2005). The standard approach to proving spatial uniformity in the literature is to establish exponential decay of initial nonuniformities by using global Lipschitz bounds on the vector field representing reaction terms (Ashkenazi & Othmer, 1978; Conway, Hoff, & Smoller, 1978; Jones & Sleeman, 1983; Othmer, 1977).

In the first part of this paper, we study the reaction–diffusion PDE:

$$\frac{\partial x}{\partial t} = f(x) + D\nabla^2 x, \tag{1}$$

subject to Neumann boundary conditions and other technical assumptions detailed in Section 2, and give a condition for uniform behavior of the solutions that does not rely on a global Lipschitz assumption on $f(x)$. Instead, our main result (Theorem 1) requires that a Lyapunov inequality be satisfied by the matrix $J(x) - \lambda_2 D$, where

$$J(x) := \frac{\partial f(x)}{\partial x} \tag{2}$$

is the Jacobian and λ_2 is the second Neumann eigenvalue of the operator $L = -\nabla^2$ on the given spatial domain. Even when the global Lipschitz condition of Ashkenazi and Othmer (1978), Conway et al.

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(1978), Jones and Sleeman (1983) and Othmer (1977) holds, our result can achieve orders of magnitude improvements over the estimates obtained from this Lipschitz bound (see Example 1 for a comparison).

In the second part of the paper (Section 3), we parameterize $J(x)$ with constant matrices and develop procedures to verify the Lyapunov inequality employed in Theorem 1. The first procedure, described in Theorem 2, incorporates $J(x)$ within convex and conic hulls of constant matrices and derives a *linear matrix inequality* (LMI) (Boyd, El Ghaoui, Feron, & Balakrishnan, 1994) for the vertices. The second procedure, presented in Theorem 3, studies a special convex set and reduces the dimension of the LMI in Theorem 2. For reaction networks that exhibit special structures, the LMI in Theorem 3 is also amenable to analytical feasibility tests. One such test is illustrated in Example 1 on a variant (Thron, 1991) of Goodwin's model (Goodwin, 1965) for oscillations in enzyme synthesis. In Example 2, we study a model by Goldbeter (1995) for circadian rhythms and investigate the feasibility of the LMI numerically. These examples are representative of other common reaction network structures and are employed here to illustrate the main results of the paper, rather than to solve specific problems associated with the biological phenomena they represent. Two other examples are presented in Section 4 to demonstrate the applicability of the results to bistable systems (Example 3) and to investigate which structural properties of the reactions cause the conditions of Theorem 1 to fail in a network that exhibits spatial patterns (Example 4).

In a recent study (Jovanović, Arcak, & Sontag, 2008), we gave conditions for the stability of the spatially uniform fixed point for reaction–diffusion systems where the reaction terms exhibit a cyclic structure. In the present paper we do not restrict ourselves to cyclic reactions and, more importantly, we do not require that the attractor be a fixed point. Indeed, the reactions in Examples 1 and 2 exhibit limit cycles and Theorem 1 guarantees spatial uniformity of the oscillations rather than stability of a fixed point.

In the third part of the paper (Section 5), we derive an analog of Theorem 1 for a compartmental ODE model where the compartments represent a finite number of well-mixed spatial domains coupled via diffusion terms (Hale, 1997). Our main result (Theorem 4) in this part employs the same condition as Theorem 1, where λ_2 now represents the second smallest eigenvalue of the Laplacian matrix for the graph describing the coupling of the subsystems. The proof of this result exploits properties of the Laplacian matrix that are analogous to those of the Laplacian operator employed in Theorem 1.

2. Spatially uniform behavior in reaction–diffusion PDEs

Let Ω be a bounded domain in $\mathbb{R}^r$ with smooth boundary $\partial\Omega$, and consider (1) where $x(t,\xi) \in \mathbb{R}^n$, $f(\cdot)$ is a continuously differentiable vector field, and $\nabla^2 x := [\nabla^2 x_1 \cdots \nabla^2 x_n]^T$ is the vector Laplacian with respect to the spatial variable ξ. We take $D \in \mathbb{R}^{n\times n}$ to be an arbitrary real matrix for generality; however, in a typical reaction–diffusion system, D is a diagonal matrix of zero or positive diffusion coefficients d_i for species $i = 1,\ldots,n$. We assume Neumann boundary conditions:

$$\nabla x_i(\xi)\cdot\hat{n}(\xi) = 0 \quad \forall\xi\in\partial\Omega,\ i = 1,\ldots,n \tag{3}$$

where $\hat{n}$ is a vector normal to the boundary $\partial\Omega$. Well-posedness of (1)–(3) is not emphasized in this paper; we refer the reader to Morgan (1989), Smith (1995, Chapter 7.3) and Smoller (1983, Chapter 14) for results on the existence of *classical* solutions to reaction–diffusion PDEs with a diagonal diffusion matrix D.

To establish a condition under which solutions $x(t,\xi)$ exhibit uniform behavior over the spatial domain Ω, we denote by:

$$\pi\{v\} := v - \bar{v} \tag{4}$$

the deviation of a function $v = v(\xi)$ from its average:

$$\bar{v} := \frac{1}{|\Omega|}\int_\Omega v(\xi)\mathrm{d}\xi. \tag{5}$$

In the derivations below, we also use the $L_2(\Omega)$ inner product:

$$\langle u, v\rangle_{L_2(\Omega)} := \int_\Omega u^T(\xi)v(\xi)\mathrm{d}\xi \tag{6}$$

and norm:

$$\|v\|_{L_2(\Omega)} := \sqrt{\langle v, v\rangle_{L_2(\Omega)}}. \tag{7}$$

We let $0 = \lambda_1 \le \lambda_2 \le \cdots \le \lambda_k \le \cdots$ denote the eigenvalues of the operator $L = -\nabla^2$ on Ω with Neumann boundary condition:

$$L\phi_k(\xi) = \lambda_k\phi_k(\xi), \qquad \nabla\phi_k(\xi)\cdot\hat{n}(\xi) = 0 \quad \forall\xi\in\partial\Omega, \tag{8}$$

and make use of the second smallest eigenvalue, λ_2, in our main result:

Theorem 1. *Consider the reaction–diffusion system (1)–(3) and let λ_2 be the second smallest eigenvalue of the operator $L = -\nabla^2$ on Ω with Neumann boundary condition as in (8). If there exists a convex set $\mathcal{X} \subseteq \mathbb{R}^n$, a matrix $P = P^T > 0$, and a constant $\epsilon > 0$ such that*

$$P\left(J(x) - \lambda_2 D\right) + \left(J(x) - \lambda_2 D\right)^T P \le -\epsilon I \quad \forall x\in\mathcal{X} \tag{9}$$

$$PD + D^T P \ge 0, \tag{10}$$

then, for every classical solution $x(t,\xi) : [0,\infty)\times\Omega \to \mathcal{X}$,

$$\|\pi\{x(t,\xi)\}\|_{L_2(\Omega)} \to 0 \tag{11}$$

exponentially as $t\to\infty$, where $\pi\{\cdot\}$ is as defined in (4)–(5). □

The second Neumann eigenvalue λ_2 is a measure of the well-connectedness of the spatial domain. Indeed, of all sets of given volume, λ_2 is maximized by the ball (Henrot, 2006). In situations where λ_2 is not easily calculable for the given domain Ω, Theorem 1 can be applied with a lower bound on λ_2 at the cost of making (9)–(10) more restrictive. A commonly used lower bound on λ_2 was derived for the Laplacian operator by Cheeger (1970), and extended in Chung (1997) to Laplacian matrices of graphs.

Othmer (1977), followed by other papers (Ashkenazi & Othmer, 1978; Conway et al., 1978; Jones & Sleeman, 1983), studied the reaction–diffusion system (1)–(3) with $D = \mathrm{diag}\{d_1,\ldots,d_n\}$, and proved uniform behavior of the solutions under the condition:

$$\sup_{x\in\mathcal{X}}\|J(x)\| < \lambda_2\min_i\{d_i\}. \tag{12}$$

Note that (12) implies (9) with $P = I$, which means that Theorem 1 incorporates Othmer's condition (12) as a special case. Assumption (9) of Theorem 1 is far less restrictive than (12), and is applicable to numerous practically important systems which do not satisfy global Lipschitz bounds. As an illustration, consider the Fitzhugh–Nagumo model of neuron excitation and oscillations (see e.g. Edelstein-Keshet, 2005), augmented here with diffusion terms:

$$\frac{\partial x_1}{\partial t} = c\left(x_1 - \frac{1}{3}x_1^3 + x_2\right) + d_1\nabla^2 x_1 \tag{13}$$

$$\frac{\partial x_2}{\partial t} = \frac{1}{c}\left(-x_1 - bx_2 + a\right) + d_2\nabla^2 x_2, \quad c, b, d_1, d_2 > 0. \tag{14}$$

The Jacobian matrix:

$$J(x) = \begin{bmatrix} c(1-x_1^2) & c \\ -\dfrac{1}{c} & -\dfrac{b}{c}\end{bmatrix} \tag{15}$$