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A tutorial on monotone systems- with an application to chemical reaction networks

by

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ABSTRACT

Monotone systems are dynamical systems for which the flow preserves a partial order. Some applications will be briefly reviewed in this paper. Much of the appeal of the class of monotone systems stems from the fact that roughly, most solutions converge to the set of equilibria. However, this usually requires a stronger monotonicity property which is not always satisfied or easy to check in applications. Following [20] we show that monotonicity is enough to conclude global attractivity if there is a unique equilibrium and if the state space satisfies a particular condition. The proof given here is self-contained and does not require the use of any of the results from the theory of monotone systems. We will illustrate it on a class of chemical reaction networks with monotone, but otherwise arbitrary, reaction kinetics.

1 Introduction

1.1 What is a monotone system?

The theory of monotone systems has been developed by M.W. Hirsch in a series of papers about two decades ago, see [12, 13, 14, 15, 16] and H.L. Smith's excellent monograph [27] for a review. In general a monotone dynamical system is a continuous semiflow Φ on a metric space X equipped with a compatible partial order $\preceq$, such that the partial order is preserved by the flow:

$$\forall x, y \in X: \quad x \preceq y \Rightarrow \Phi_t(x) \preceq \Phi_t(y), \quad \forall t \in \mathbb{R}_+. \tag{1}$$

Let's consider a system of differential equations:

$$\dot{x} = f(x)$$

with $x \in \mathbb{R}^n$ and f a C^1 vector field which is assumed to be forward complete (although what follows is valid under much weaker conditions, both for the state space and the smoothness of the vector field).

An immediate question that arises is when this system generates a monotone dynamical system with respect to some nontrivial order. This question appears to be very hard to answer. However, when a particular order is given and one asks if the system is monotone with respect to that given order, it is possible to provide testable conditions expressed directly in terms of the vector field f and the graph of the order relation, see [2]. These tests take a particularly simple form in those cases where the partial order is generated by a cone K in $\mathbb{R}^n$. (Recall that a cone K in $\mathbb{R}^n$ is a nonempty, closed set with $K + K \subset K$, $\mathbb{R}_+ K \subset K$ and $K \cap (-K) = \{0\}$). We will review some of these tests next.

Probably the most familiar example is the one where f is *cooperative*, meaning that the Jacobian $\partial f/\partial x$ has nonnegative off-diagonal entries. It is well-known that in this case the flow of system $\dot{x} = f(x)$ is monotone since it preserves the usual componentwise order on $\mathbb{R}^n$, see e.g. Proposition 3.1.1 and Remark 3.1.1 in [27]. More precisely, this order is generated by the orthant cone $\mathbb{R}^n_+$ in $\mathbb{R}^n$:

$$x \preceq y \Leftrightarrow y - x \in \mathbb{R}^n_+.$$

This can be generalized to cases where the partial order is generated by any orthant cone $\mathcal{O}$ of $\mathbb{R}^n$, in which case the order is defined as follows:

$$x \preceq_{\mathcal{O}} y \Leftrightarrow y - x \in \mathcal{O}. \tag{2}$$

For checking monotonicity in this case, a simple graphical test is available, see p. 49 in [27]. It amounts to verifying whether the incidence graph of the system does not contain loops of negative parity (the incidence graph consists of n nodes, each representing a component of the state vector, and signed edges connecting the nodes; an edge from node j to node i is drawn carrying the sign of the partial derivative $\partial f_i/\partial x_j$; of course this requires that the derivative does not change sign and is nonzero in at least one point; the parity of a loop is simply the product of the signs of the edges which make up the loop; self-loops are not taken into account for this test).

If the partial order is generated by an arbitrary cone K in $\mathbb{R}^n$ (simply replace $\mathcal{O}$ by K in (2)), then checking monotonicity is still possible, although the test is not graphical anymore, see [17, 30, 2] for characterizations in terms of dual cones. It is important to note here that all these tests require *a priori* knowledge of the cone which generates the order. In practice however, given a system $\dot{x} = f(x)$, for which one is trying to establish that it is monotone with respect to some nontrivial order, one does not know the partial order in advance.

1.2 A few examples of monotone systems

Monotone systems theory is useful for the analysis of many of the chemostat models studied in [28]. For instance, the variable-yield model can be transformed in a monotone system for which the order is not the usual componentwise order on $\mathbb{R}^n$. In [10], this transformation is also exploited to analyze a similar model with multiple nutrients.

An example which may be of interest to people working in control theory is the Riccati equation defined on the space of real symmetric matrices $\mathcal{S}$:

$$\dot{X} = XAX + BX + XB^T + C$$

where $A, C \in \mathcal{S}$ and B is a real (not necessarily symmetric) matrix. As shown in [30] (where a more general nonautonomous Riccati equation is considered, but where $B = B^T$), the flow generated by this equation preserves the order induced by the cone of symmetric positive semidefinite matrices. We provide a different proof of this fact in an Appendix.

Monotone dynamical systems have been extended to monotone I/O systems in [2] in order to facilitate the study of interconnections of such systems (cascades, feedback). We refer to [4, 3, 5, 6, 8, 9] for further developments and applications of this theory, including examples from molecular biology, ecology and chemical reaction networks. The focus in this paper however, is on monotone dynamical systems without external inputs or outputs.

1.3 What makes monotonicity interesting?

The main reason why monotone systems have been studied so extensively, is probably that much is known about their asymptotic behavior. Roughly speaking, most solutions converge to the set of equilibria. But two issues should be mentioned in this context. First, most of the available convergence results require a stronger monotonicity notion than (1). Typically it is assumed that the semiflow is *strongly order preserving*, see p. 2 in [27], or *(eventually) strongly monotone* -which implies the former-, see p. 3 in the same reference for precise definitions. Checking this condition in practice is often not so easy, or even worse: a system may be monotone, but fails to satisfy one of these stronger notions. Secondly, the proofs of these results are nontrivial and require the use of fundamental results from the theory of monotone systems.

A particular result which seems to be an exception to this, was given in [20], where global asymptotic stability of a cooperative system on $\mathbb{R}^n$ with a unique equilibrium was proved. Following the ideas of that proof we generalize this in an Appendix to monotone continuous semiflows with a unique equilibrium. This result may also be useful for infinite-dimensional systems (such as delay equations). Moreover, the proof given here is completely self-contained.

As an illustration, we will show that every solution of a particular kind of chemical reaction networks, converges to an equilibrium.

2 A chemical reaction network

Consider the following reaction network:

$$C_1 \rightleftharpoons \cdots \rightleftharpoons C_{i-1} \rightleftharpoons C_i \rightleftharpoons C_{i+1} \rightleftharpoons \cdots \rightleftharpoons C_{n+1},$$

where each complex C_i is given by a weighted sum of distinct chemicals as follows:

$$C_i = \sum_{k=1}^{n_i} a_i^k X_i^k$$

for positive integers a_i^k.

Some special cases of this network have been studied in [5] (where all complexes consist of precisely one chemical and all chemicals in the network are distinct) and [21] (where $C_1 = X_1 + X_2$ consists of 2 chemicals, all subsequent complexes consist of precisely one chemical, all chemicals in the network are distinct and mass action kinetics is assumed)

Throughout this paper we assume that at least one complex is nontrivial. Equivalently, there is at least one $n_i > 1$. We also assume that each chemical is part of precisely one complex, or $X_i^k \neq X_j^l$ for all k, l whenever $i \neq j$. The concentration vector associated to complex C_i is denoted by $x_i = (x_i^1, ..., x_i^{n_i})^T$ and its associated stoichiometric vector by $a_i = (a_i^1, ..., a_i^{n_i})^T$. We will also use the full concentration vector $x = (x_1^T, ..., x_{n+1}^T)^T$ with $x \in \mathbb{R}_+^N$ where N is the sum of all n_i.

All reaction rates are assumed to be C^1 monotone functions of the concentrations of the reagentia, zero when one of the reagentia is missing, and positive when all of the reagentia are present. The forward reaction rate of the reaction $C_i \rightleftharpoons C_{i+1}$ is denoted by R_i and the backward reaction rate by R_{-i}. Formally, for all $i = 1, ..., n$ it is assumed throughout the rest of this paper that:

$$R_i : \mathbb{R}_+^{n_i} \to \mathbb{R}_+, \;\; R_i(x_i) = 0 \;\; \forall x_i \in \partial\mathbb{R}_+^{n_i}, \;\; R_i(x_i) > 0 \text{ and}$$

$$\partial^T R_i/\partial x_i(x_i) \in \text{int}(\mathbb{R}_+^{n_i}) \;\; \forall x_i \in \text{int}(\mathbb{R}_+^{n_i})$$

and similarly for the backward reaction rates R_{-i}. (But notice that R_{-i} is defined for $x_{i+1} \in \mathbb{R}_+^{n_{i+1}}$.)

The familiar example of *mass action kinetics*, where reaction rates are given by $R_i(x_i) = \kappa_i \prod_{k=1}^{n_i} (x_i^k)^{a_i^k}$ for some $\kappa_i > 0$, satisfies these requirements.

We define the reaction rate vector by:

$$R(x) = (R_1(x_1), R_{-1}(x_2), ..., R_n(x_n), R_{-n}(x_{n+1}))^T$$

and the stoichiometric matrix of the network by:

$$S = \begin{pmatrix} -a_1 & +a_1 & 0 & 0 & \dots & 0 \\ +a_2 & -a_2 & -a_2 & +a_2 & \dots & 0 \\ \vdots & & & \ddots & & \dots \\ 0 & \dots & +a_n & -a_n & -a_n & +a_n \\ 0 & \dots & 0 & 0 & a_{n+1} & -a_{n+1} \end{pmatrix}.$$

Then the differential equations for the concentrations are:

$$\dot{x} = SR(x). \tag{3}$$

A standard argument shows that system (3) is positive, i.e. that the nonnegative orthant $\mathbb{R}^N_+$ is forward invariant. Notice that this system is not monotone with respect to any order generated by an orthant of $\mathbb{R}^N$. This is seen by inspection of the incidence graph associated to system (3), which contains a loop of negative parity. Indeed, consider a loop formed by two nodes corresponding to chemicals in the same complex and a third node corresponding to an arbitrary chemical in a neighboring complex (this is a complex which can be reached from the first complex by a single reaction step). Clearly, such a loop has negative parity. Our main result will be the following:

Theorem 1. *Every solution of system* (3) *converges to an equilibrium point.*

In our subsequent analysis we will assume that there is at least one complex with nonzero initial concentrations for all its constituent chemicals:

$$\exists i : \;\; x_i^k(0) > 0, \;\; \forall k = 1, ..., n_i. \tag{4}$$

For if (4) would not hold, none of the reactions would take place. Note that such initial conditions correspond to equilibria for which theorem 1 holds trivially, so assumption (4) entails no loss of generality.

Associated to each complex C_i with $n_i > 1$, there are $n_i - 1$ independent linear first integrals. Indeed,

$$\frac{d}{dt}\left(\frac{x_i^k}{a_i^k} - \frac{x_i^1}{a_i^1}\right) = 0, \;\; \forall k = 2, ..., n_i \tag{5}$$

along solutions of (3) and thus we have that:

$$x_i^k(t) = \beta_i^k x_i^1(t) + \alpha_i^k, \;\; \forall k = 2, ..., n_i \tag{6}$$

for some $\alpha_i^k \in \mathbb{R}$ (which depends on initial conditions) and $\beta_i^k = a_i^k / a_i^1 > 0$. In fact, we claim that without loss of generality, we may assume that:

$$\alpha_i^k \geq 0, \;\; \forall k = 2, ..., n_i.$$

To see this, notice that after a possible relabeling of the chemicals within each complex, there holds that:

$$\frac{x_i^k(0)}{a_i^k} \geq \frac{x_i^1(0)}{a_i^1}, \;\; \forall k = 2, ..., n_i$$

from which our claim follows immediately.

By (6) it suffices to consider the dynamics of the concentrations of the *first* chemical -x_i^1- of every complex C_i. For every i, define:

$$y_i := x_i^1,\ \ r_i(y_i) := R_i(y_i, \beta_i^2 y_i + \alpha_i^2, ..., \beta_i^{n_i} y_i + \alpha_i^{n_i}),$$
$$r_{-i}(y_{i+1}) := R_{-i}(y_{i+1}, \beta_{i+1}^2 y_{i+1} + \alpha_{i+1}^2, ...).$$

Notice that each r_i is a C^1 function with the following properties:

$$r_i : \mathbb{R}_+ \to \mathbb{R}_+,\ \ r_i(0) = 0,\ \ r_i(y_i) > 0 \text{ and } r_i'(y_i) > 0\ \ \forall y_i > 0$$

and similarly for each r_{-i}.

Denoting $y = (y_1, ..., y_{n+1})^T$, $r(y) = (r_1(y_1), r_{-1}(y_2), ..., r_n(y_n), r_{-n}(y_{n+1}))^T$ and setting:

$$\tilde{S} = \begin{pmatrix} -a_1^1 & +a_1^1 & 0 & 0 & \dots & 0 \\ +a_2^1 & -a_2^1 & -a_2^1 & +a_2^1 & \dots & 0 \\ \vdots & & & \ddots & & \dots \\ 0 & \dots & +a_n^1 & -a_n^1 & -a_n^1 & +a_n^1 \\ 0 & \dots & 0 & 0 & a_{n+1}^1 & -a_{n+1}^1 \end{pmatrix}$$

we arrive at the following system:

$$\dot{y} = \tilde{S} r(y) \tag{7}$$

where $y \in \mathbb{R}_+^{n+1} \setminus \{0\}$, (note that 0 is excluded because of (4)).

Since $y_1(t)/a_1^1 + y_2(t)/a_2^1 + \cdots + y_{n+1}/a_{n+1}^1(t) = C$ along solutions for some constant $C > 0$ we can reduce the dimension by 1 by dropping the equation for y_{n+1} and then introduce n new variables:

$$z_j = \sum_{i=1}^{j} \frac{y_i}{a_i^1},\ \ j = 1, ..., n.$$

The inverse transformation is:

$$\begin{aligned} y_1 &= a_1^1 z_1 \\ y_j &= a_j^1 (z_j - z_{j-1}),\ \ j = 2, ..., n. \end{aligned}$$

Using these new coordinates, the equations for the reduced system are:

$$\begin{aligned} \dot{z}_1 &= -r_1(a_1^1 z_1) + r_{-1}(a_2^1(z_2 - z_1)) \\ &\vdots \\ \dot{z}_k &= -r_k(a_k^1(z_k - z_{k-1})) + r_{-k}(a_{k+1}^1(z_{k+1} - z_k)),\ \ k = 1, ..., n-1 \\ &\vdots \\ \dot{z}_n &= -r_n(a_n^1(z_n - z_{n-1})) + r_{-n}(a_{n+1}^1(C - z_n)) \end{aligned} \tag{8}$$

with compact and convex state space:

$$\Omega = \{z \in \mathbb{R}^n \,|\, 0 \le z_1 \le z_2 \le \cdots \le z_n \le C\}.$$

Clearly, system (8) is cooperative (and tridiagonal).

Lemma 1. *If $z^* \in \Omega$ is a steady state of system* (8)*, then $z^* \in \text{int}(\Omega)$. Moreover, z^* is hyperbolic and locally asymptotically stable.*

Proof. Suppose that $z^* \in \partial\Omega$ is a steady state of system (8). Then either $z_1^* = 0$ or $z_n^* = C$ or $z_k^* = z_{k+1}^*$ for some $k \in \{1, ..., n-1\}$. Using that all functions r_i and r_{-i} can only be zero at zero, each of these cases will lead to a contradiction with the fact that $C > 0$. This establishes the first part of the lemma.

For the second part, notice that the Jacobian at a steady state has the following structure:

$$J = \begin{pmatrix} -a_{11} - a_{12} & +a_{12} & 0 & \dots & 0 \\ +a_{21} & -a_{21} - a_{23} & +a_{23} & \dots & 0 \\ \vdots & \ddots & \ddots & \ddots & \vdots \\ 0 & \dots & +a_{(n-1)(n-2)} & -a_{(n-1)(n-2)} - a_{(n-1)n} & +a_{(n-1)n} \\ 0 & \dots & 0 & +a_{n(n-1)} & -a_{n(n-1)} - a_{nn} \end{pmatrix}$$

where all $a_{ij} > 0$.

We will prove that J is diagonally dominant and hence Hurwitz.

Recall that an $n \times n$ matrix B is called diagonally dominant if there are n numbers $d_i > 0$ such that:

$$b_{ii}d_i + \sum_{j \neq i} |b_{ij}| d_j < 0, \quad \forall i = 1, ..., n.$$

For a cooperative matrix such as J, the absolute values can be dropped in the above definition. Therefore, we must find a vector d with positive entries, such that the vector Jd is a vector with negative entries. Notice that $J\mathbf{1}$ -where $\mathbf{1}$ is a vector for which all entries are 1- is a vector with negative first and last entries ($-a_{11}$, respectively $-a_{nn}$) and all other entries are 0. This suggest that to find d we could try to look for a suitable perturbation of the vector $\mathbf{1}$.

Define recursively $n-1$ parameters ϵ_j as follows:

$$\begin{aligned} 0 < \ \ \epsilon_1 \ &< \frac{a_{11}}{a_{11} + a_{12}} \\ 0 < \ \ \epsilon_j \ &< \epsilon_{j-1} \frac{a_{j(j-1)}}{a_{j(j-1)} + a_{j(j+1)}}, \quad j = 2, ..., n-1. \end{aligned}$$

Clearly $\epsilon_j < 1$ for all $j = 1, ..., n-1$. Next define the vector d as follows:

$$d_i = 1 - \epsilon_i, \quad i = 1, ..., n-1 \text{ and } d_n = 1.$$

Then it can be checked that Jd is a vector with negative entries, showing that J is diagonally dominant and hence a Hurwitz matrix. This concludes the proof. ☐

Lemma 2. *System* (8) *has a unique, globally asymptotically stable steady state in Ω.*

Proof. Since Ω is a compact, convex, forward invariant set for system (8), it has at least one steady state. By the previous lemma, all steady states belong to $\text{int}(\Omega)$. Then the Brouwer degree of the vector field F of system (8) with respect to $\text{int}(\Omega)$ and value 0, is well defined and denoted by $d(F, \text{int}(\Omega), 0)$. Moreover, we claim that:

$$d(F, \text{int}(\Omega), 0) = (-1)^n.$$

To see this, pick an arbitrary point $\bar{x} \in \text{int}(\Omega)$ and consider the following vector field on Ω:

$$G(x) = \bar{x} - x.$$

Obviously,

$$d(G, \text{int}(\Omega), 0) = (-1)^n.$$

We will show that F and G are homotopic, and then our claim follows since the Brouwer degree is a homotopy invariant. Define:

$$H(x,t) = tF(x) + (1-t)G(x)$$

Then H is continuous on $\Omega \times [0,1]$, $H(x,0) = G(x)$ and $H(x,1) = F(x)$. We are left with proving that $H(x,t) \neq 0$ for all $x \in \partial\Omega$ and all $t \in (0,1)$. Suppose that this is not the case, then there is a $\tilde{x} \in \partial\Omega$ and $\tilde{t} \in (0,1)$ such that:

$$F(\tilde{x}) = -\frac{1-\tilde{t}}{\tilde{t}} G(\tilde{x})$$

This implies that F points outwards in $\tilde{x}$ (since $G(\tilde{x})$ clearly points inwards). But this contradicts the fact that Ω is forward invariant and establishes our claim.

By the previous lemma, we know that the Jacobian at each steady state of (8) is nonsingular and hence the number of steady states is finite. By definition of the Brouwer degree for C^1 mappings:

$$d(F, \text{int}(\Omega), 0) = \sum_i \text{sign}\det J(x_i^*)$$

where $J(x_i^*)$ is the Jacobian at a steady state of system (8) and the summation runs over all steady states.

Now by the previous lemma every steady state x_i^* is hyperbolic and locally asymptotically stable, so there holds that:

$$\text{sign}\det J(x_i^*) = (-1)^n$$

and hence there can only be one steady state.

Global asymptotic stability follows from lemma 5 which is proved in an Appendix. To see that this result can be applied, note first that since Ω is compact and forward invariant, system (8) generates a continuous semiflow. Condition 4. is clear by compactness of Ω. Condition 2. follows from the fact that system (8) is cooperative in Ω and therefore generates a monotone semiflow with the order given by the usual componentwise order on $\mathbb{R}^n$[1]. Condition 3. has just been proved and condition 1. is satisfied as well. (Proof: for any compact $K \subset \Omega$, for all $i = 1, ..., n$, let $p_i^* \in K$ be some point in K with maximal i-component. Note that p_i^* exists in K since the projection on the i-th component is continuous and K is compact. Now, Ω is a lattice, i.e. $\sup(a,b) \in \Omega$ whenever $a, b \in \Omega$. Therefore $p := \sup_i(p_i^*) \in \Omega$ and it is easy to see that $\sup(K) = p$. The proof that $\inf(K) \in \Omega$ is similar.) □

[1]Here we have used that Ω is convex, hence p-convex. The conclusion then follows from Proposition 3.1.1 and Remark 3.1.1 in [27].

Remark 1. We could also have proved global asymptotic stability using results of Smillie [26] or even of Mierczynski [22]. But these require verification of stronger monotonicity properties of the flow, which has been avoided here. For a proof using Smillie's results for the case where each complex consists of only one chemical, see [5].

Proof of Theorem 1 This follows from the reduction and transformation of system (3) to system (8), combined with lemma 2.

3 Adding Diffusion

Ordinary differential equation models such as considered in (3) implicitly assume that reactions proceed in a well-mixed environment. While this is a reasonable assumption when diffusion is fast compared to the time scales of reactions, it is of interest as well to incorporate explicitly the effect of diffusion. This leads to *reaction-diffusion* (also known as semilinear parabolic) partial differential equations.

In this section, we show how to extend our results to the case when diffusion is included in the model. Our results intersect, for the special example of the reaction $X_1 + X_2 \rightleftharpoons X_3$, and assuming mass action kinetics, with those given in [23]. That paper dealt with the extension of the Feinberg-Horn-Jackson (FHJ) theory of chemical reactions (see e.g. [11, 19, 29, 7]) from ODE's to reaction-diffusion problems. (See also [24] for the statement of convergence results for reaction-diffusion FHJ systems, but with incomplete proofs.) The techniques in [24, 23] are based upon Lyapunov functions, and are thus different from our approach, which allows treating a different class of reactions and we do not need to restrict ourselves to mass action kinetics. On the other hand, there is an abundance of examples of chemical systems which are of FHJ type but are not monotone, and thus cannot be treated with our techniques.

Our goal in this section is to show how the analogous convergence results for the PDE model follow as easy corollaries from those for ODE's. (An alternative would be to prove all results *ab initio* in the framework of monotone reaction diffusion systems, but the reduction to ODE's is far simpler.) In general, we consider initial/Neumann-boundary "no-flux" PDE problems for functions $x(q,t)$ of space and time, where dot indicates derivative with respect to time, x_ν indicates normal derivative, f is a monotone vector field, and L is a diffusion partial differential operator:

$$\begin{aligned} \dot{x} &= Lx + f(q,x) && t > 0\,, q \in Q \\ x_\nu &= 0 && t > 0\,, q \in \partial Q \\ x(q,0) &= x_0 && q \in \bar{Q}\,. \end{aligned} \tag{9}$$

The key observation that we wish to make is that (under appropriate technical assumptions) every solution of (9) converges to a unique homogeneous equilibrium: $x(q,t) \to c$ as $t \to \infty$, provided that every solution of the associated ODE $\dot{x} = f(x)$ converges to c. Thus, the results proved earlier extend to the diffusion case. (Monotonicity of f is essential – compare to diffusive instability phenomena such as arise in activator-inhibitor mechanisms for pattern formation.) Let us first develop some background, blending results on monotone reaction-diffusion systems from [27], Chapter 7 with some technical facts from [1].

The set Q represents space, and is a bounded, open, connected subset of an Euclidean space $\mathbb{R}^M$ with smooth (class C^4) boundary ∂Q. The vector field f is of class $\mathcal{C}^2$. The notation x_ν indicates directional derivative with respect to the outer unit normal $\nu = \nu(q)$ to ∂Q at the point q. We pick a nonempty closed subset X of $\mathbb{R}^n$ to restrict the allowed values of concentrations, such as for example the nonnegative orthant or the compact and convex state space Ω used in Lemma 1, and assume that X is forward-invariant with respect to the ODE $\dot{x} = f(x)$ (two additional assumptions on X are made below). The initial condition is a function

$$x_0 : \bar{Q} \to X$$

which is twice continuously differentiable and satisfies the boundary requirement $(x_0)_\nu = 0$. By a "solution" of (9) we mean a function

$$x = (x_1, \ldots, x_n)' : \bar{Q} \times [0, T] \to X$$

(prime indicates transpose) such that (9) holds and:

$$\frac{\partial x_i}{\partial t}, \frac{\partial x_i}{\partial q_j}, \frac{\partial^2 x_i}{\partial q_j \partial q_k} \text{ are Hölder continuous on } Q \times (0, T] \text{ for all } i, j, k$$

and

$$\frac{\partial x_i}{\partial q_j}, x_i \text{ are continuous on } \bar{Q} \times (0, T] \text{ for all } i, j\,.$$

These assumptions are as in [1]; in [27] it is only required that $\frac{\partial x_i}{\partial q_j}$ be continuous on $\bar{Q} \times (0, T]$ (also, Hölder continuity is relaxed to just continuity) but less regularity is imposed on initial conditions.

The differential operator L has the following form:

$$Lx = (L_1 x_1, \ldots, L_n x_n)'$$

where for every i,

$$L_i = \sum_{j,k=1}^{n} a^i_{jk}(q) D_j D_k + \sum_{k=1}^{n} a^i_k(q) D_k$$

with each $a^i_{kj} = a^i_{jk} \in \mathcal{C}^2(\bar{Q})$, and L is uniformly elliptic:

$$\exists\, \mu > 0 \text{ such that } \xi' A_i(q) \xi \geq \mu \,|\xi|^2 \;\forall\, \xi \in \mathbb{R}^n$$

where $A_i(q) = (a^i_{jk}(q))$. The main example for us will be the case in which there is independent diffusion of each species: $a^i_{jj} \equiv d_i > 0$, and $a_k \equiv 0$, $a_{jk} \equiv 0$ for all $j \neq k$, i.e. $Lx_i = d_i \Delta x_i$, where Δ is the Laplacian.

Two additional conditions must be imposed on the set of allowed state vectors X. We already asked that it be invariant under the dynamics $\dot{x} = f(x)$. A second requirement is that it should also be invariant under diffusion, in the sense that solving the linear problem $\dot{x} = Lx$ with an initial condition having $x_0(q, 0) \in X$ for all $q \in Q$ should result in a solution with $x(q, t) \in X$ for all $t > 0$ and all $q \in Q$. For this purpose we will assume from now on *either* that Q is an arbitrary open convex set but all operators L_i are the same (for example, there is independent diffusion of each species and $d_i = d_j$ for all i, j), *or* that the L_i's are arbitrary but that Q equals a "rectangle" (a, b), with $b - a \in \mathbb{R}^n_+$ (possibly with $a = -\infty$ or $b = +\infty$).

Assume from now on that an order has been specified on $\mathbb{R}^n$. A last requirement is a lattice requirement on the set X (see also the Appendix): for any compact subset $S \subseteq X$, both $\inf(S)$ and $\sup(S)$ are defined and belong to X. We say that a vector field is *quasi-monotone* (with respect to the given order on $X \subseteq \mathbb{R}^n$) if the flow of $\dot{x} = f(x)$ is monotone. Given two functions x, y with values in X, we write $x \preceq y$ if $x(q,t) \preceq y(q,t)$ for all (q,t) in their common domain. The following is a version of Theorem 3.4 in [27]. We have specialized it to PDE's (in the textbook, it is given in more generality, for partial differential inequalities), and we have stated it for arbitrary orders (the statement in the book is given only for cooperative systems, but, cf. page 142, the same proof is valid for arbitrary orders).

Theorem 2. *If f is quasi-monotone, and y, z are solutions defined on $[0, T)$ such that $y(\cdot, 0) \preceq x_0 \preceq z(\cdot, 0)$ on $\bar{Q}$, then there is a unique solution x of (9), defined at least on the interval $[0, T)$, and $y \preceq x \preceq z$ on $\bar{Q} \times [0, T)$.*

We are now ready to state our conclusions. The first remark is as follows.

Theorem 3. *Suppose that f is quasi-monotone, and that there exists $\xi \in X$ so that every solution of $\dot{x} = f(x)$, $x_0 \in X$, converges to ξ as $t \to \infty$. Then, for each initial condition x_0, there is a unique solution $x(q,t)$ of (9), defined for all $t > 0$, and $x(q,t) \to \xi$ as $t \to \infty$, uniformly on $q \in Q$.*

To prove this statement, we first pick y as a function $\bar{Q} \to X$ which is constantly equal to the minimum value of x_0, and z as a function $\bar{Q} \to X$ which is constantly equal to the maximum of x_0. Furthermore, we observe that the solution $y(t)$ of $\dot{x} = f(x)$, $x(0) = y$ (which is defined for all t and converges to ξ as $t \to \infty$) can be also seen as a solution of (9), simply letting $y(q,t) \equiv y(t)$. Similarly with z, and we are in the situation of Theorem 2. Applying this Theorem on increasing finite intervals $[0, T)$, we obtain existence and uniqueness of $x(q,t)$ on $[0, \infty)$. Furthermore, we have that $y(q,t) \preceq x(q,t) \preceq z(q,t)$, and both $y(q,t) \to \xi$ and $z(q,t) \to \xi$ (uniformly on q), which gives the conclusion.

Unfortunately, as elegant as Theorem 3 is, it is not sufficient by itself when treating the original system (3), because there are many equilibria for this system. We need to make an additional assumption, namely that all diffusion rates coincide.

Theorem 4. *Suppose that f is as in Theorem 1, and that, for some $d > 0$, $L_i x_i = d\Delta x_i$ for each coordinate of the state. Then all solutions of (9) converge to (homogeneous) steady states.*

To prove this, we use the same change of coordinates as earlier. Applied to the

PDE, this results in equations of the form

$$\begin{aligned}
\dot{z}_1 &= -r_1(a_1^1 z_1) + r_{-1}(a_2^1(z_2 - z_1)) + d\Delta z_1 \\
&\vdots \\
\dot{z}_k &= -r_k(a_k^1(z_k - z_{k-1})) + r_{-k}(a_{k+1}^1(z_{k+1} - z_k)) + d\Delta z_k, \quad k = 1, ..., n-1 \\
&\vdots \\
\dot{z}_n &= -r_n(a_n^1(z_n - z_{n-1})) + r_{-n}(a_{n+1}^1(C - z_n)) + d\Delta z_n.
\end{aligned}$$

Combining Lemma 2 with Theorem 3, we know that every solution of this system converges to a (unique) homogeneous steady state. Thus, the variables $y_i = x_i^1$ also converge to such steady states. We now prove that the remaining variables do, too.

Recall that there were, for the ODE (no diffusion) $n_i - 1$ independent linear first integrals, as shown in (5):

$$\dot{Z}_{ik} \;=\; 0 \quad \forall\, i \;\; \forall k = 2, ..., n_i\,,$$

where $Z_{ik} = x_i^k/a_i^k - x_i^1/a_i^1$. From there we obtained expressions as in (6):

$$x_i^k(t) \;=\; \beta_i^k x_i^1(t) + \alpha_i^k \quad \forall\, i \;\; \forall k = 2, ..., n_i$$

for some $\alpha_i^k \in \mathbb{R}$ (which depend on initial conditions) and $\beta_i^k > 0$. Thus, when the x_i^1 converge, the same could be concluded for each other variable x_i^k. When adding diffusion, this argument does not work. Equation (5) becomes, instead:

$$\dot{Z}_{ik} \;=\; LZ_{ik} \quad \forall\, i \;\; \forall k = 2, ..., n_i$$

with $LZ = d\Delta Z$, subject to the Neumann condition $(Z_{ik})_\nu = 0$ at boundary points. Every solution of this PDE converges to a constant, namely the average $\frac{1}{|Q|}\int_Q Z_{ik}(q,0)\,dq$ of its initial values, where $|Q|$ is the measure of Q. (Sketch of proof: there is a sequence of eigenvalues and respective eigenvectors λ_i, ϕ_i, $i = 1, 2, \ldots,$ of the self-adjoint Neumann Laplacian: solutions of $L\phi + \lambda\phi = 0$, $\phi_\nu = 0$. These satisfy $\lambda_1 = 0$, $\phi_1 = 1$, and $\lambda_i > 0$ for all $i > 1$, and the ϕ_i form an orthogonal basis of L^2. Now take any continuous and bounded initial condition x_0, viewed as an element of L^2, and expand it in terms of this basis: $x(q,0) = \sum_{i=1}^\infty b_i\phi_i(q)$; then $x(q,t) = \sum_{i=1}^\infty b_i e^{-\lambda_i t}\phi_i(q)$ is the solution of $\dot{Z} = LZ$ with this initial condition, and it converges, in L^2, to the first Fourier term b_1, which is the required average.) In summary, both $x_i^k/a_i^k - x_i^1/a_i^1$ and x_i^1 converge to a constant, so every variable x_i^k does, too.

4 Appendix: A global attractivity result for monotone flows with unique equilibria.

Consider a metric space X with metric d and suppose that a partial order $\preceq$ has been defined on X. It will be assumed that the partial order and the metric topology on X are compatible in the following sense: if $x_n \to x$ and $y_n \to y$ are converging sequences in X with $x_n \preceq y_n$, then $x \preceq y$. We occasionally abuse notation by writing

$x \preceq A$ for some $x \in X$ and $A \subset X$, to denote that $x \preceq y$ for all $y \in A$. We will use the familiar order-theoretic notions $\sup(A)$ and $\inf(A)$ to denote the least upper bound and greatest lower bound of a set $A \subset X$ -provided they exist in X. For two points $p, q \in X$ with $p \preceq q$, we define the *order interval* $[p, q] := \{x \in X \,|\, p \preceq x \preceq q\}$. A set $A \subset X$ is called *order convex* if $[p, q] \subset A$ for every pair $p, q \in A$ with $p \preceq q$.

We will discuss the dynamics generated by a continuous semiflow Φ on X. Recall that this is a continuous map $\Phi : \mathbb{R}_+ \times X \to X$ with $\Phi_t(x) := \Phi(t, x)$ such that $\Phi_0 = Id$ and $\Phi_t \circ \Phi_s = \Phi_{t+s}$ for $t, s \in \mathbb{R}_+$.

The following conditions on X and Φ are introduced:

1. For every compact subset C of X, there holds that $\inf(C), \sup(C) \in X$.
2. Φ is monotone with respect to $\preceq$, i.e. (1) holds.
3. Φ has a unique equilibrium point a in X.
4. For every $x \in X$, the orbit $O(x) := \{\Phi_t(x) \,|\, t \in \mathbb{R}_+\}$ has compact closure in X.

The last condition 4. implies in particular that the ω limit set of x, denoted by $\omega(x)$, is nonempty, compact, invariant (meaning that $\Phi_t(\omega(x)) = \omega(x)$ for all $t \in \mathbb{R}_+$) and $\lim_{t\to\infty} d\left(\Phi_t(x), \omega(x)\right) = 0$ (where the usual distance from a point $x \in X$ to a set $A \subset X$ is given by $d(x, A) = \inf_{y\in A} d(x, y)$). Under conditions $1 - 4$ we have the following result:

Theorem 5. *The equilibrium point a is globally attractive for Φ.*

Proof. Pick $x \in X$ and consider $\omega(x)$. Then we can define:

$$m = \inf(\omega(x)) \text{ and } M = \sup(\omega(x)).$$

We claim that:

$$\Phi_t(m) \preceq m, \;\; \forall t \in \mathbb{R}_+. \tag{10}$$

To see this, we will prove that for all $t \geq 0$, $\Phi_t(m) \preceq \omega(x)$, from which (10) will follow since m is the greatest lower bound of $\omega(x)$.

Choose $t \geq 0$ and select an arbitrary $p \in \omega(x)$. We need to show that $\Phi_t(m) \preceq p$. By invariance of $\omega(x)$ there is some $q \in \omega(x)$ such that $\Phi_t(q) = p$. Now $m \preceq q$ since $q \in \omega(x)$ and thus monotonicity implies that $\Phi_t(m) \preceq \Phi_t(q) = p$, thus proving (10).

Monotonicity implies that $\Phi_t(m)$ is nonincreasing, i.e. $\Phi_{t_2}(m) \preceq \Phi_{t_1}(m)$ if $0 \leq t_1 \leq t_2$. (simply apply Φ_{t_1} to (10) where $t = t_2 - t_1$)

We now claim that $\omega(m) = \{a\}$.[2] We will first show that $p, q \in \omega(m)$ implies that $p = q$. Pick sequences $\Phi_{t_k}(m) \to p$ and $\Phi_{t_l}(m) \to q$ with $t_k, t_l \to \infty$. Since $\Phi_t(m)$ is nonincreasing, it is possible to find for every t_k, some $t_{l(k)} \geq t_k$ such that $\{t_{l(k)}\}$ forms a subsequence of $\{t_l\}$ and $\Phi_{t_{l(k)}}(m) \preceq \Phi_{t_k}(m)$. After taking limits, we

[2]This claim would immediately follow from the Convergence Criterion for monotone systems (Theorem 1.2.1 in [27]), using uniqueness of the equilibrium a. However, here we prefer to give a self-contained yet short proof, without having to resort to any of the results from the theory of monotone systems.

find that $q \preceq p$. A similar argument shows that $p \preceq q$ and therefore $p = q$. So this shows that $\omega(m)$ is a singleton. Invariance of ω limit sets then implies that $\omega(m)$ must consist of an equilibrium. Uniqueness of the equilibrium a then implies that $\omega(m) = \{a\}$, proving the claim.

A similar argument yields that $\Phi_t(M)$ is monotonically increasing and that $\omega(M) = \{a\}$.

Finally, we have that for all $t \geq 0$:

$$\Phi_t(m) \preceq m \preceq \omega(x) \preceq M \preceq \Phi_t(M)$$

and upon taking limits for $t \to \infty$, we obtain that $\omega(x) = a$, which concludes the proof. □

Remark 2. Theorem 5 may also be useful for flows on infinite dimensional spaces. For instance, in delay equations one often considers spaces of continuous functions defined on a compact interval such as $X = C([-r, 0], \mathbb{R}^n)$ or $X = C([-r, 0], \mathbb{R}^n_+)$ with the usual metric induced by the supremum norm and with the usual partial order, defined by $f_1 \preceq f_2$ iff $f_2(t) - f_1(t) \in \mathbb{R}^n_+$ for all $t \in [-r, 0]$. In both cases, the inf and sup of compact sets exist in X, see [18].

Remark 3. Condition 1. appeared in the work of [20] whose ideas we have followed here. More recently, this condition also surfaced in the work of [18]. There, a stronger monotonicity property is imposed on the semiflow, but equilibria need not be unique. The result is that the set of quasiconvergent points (a point is quasiconvergent if its omega limit set is contained in the set of equilibria) contains an open and dense set. The proof relies on a number of fundamental results from the theory of monotone systems.

Remark 4. Although lemma 5 is sufficient for proving our main result on chemical reaction networks (theorem 1), we can generally conclude stability of the equilibrium a as well, provided the space X and the flow Φ satisfy extra conditions.

C Every neighborhood of every point $x \in X$ contains a compact, order convex neighborhood C of x.

Then we obtain the following result:

Lemma 3. *Assume that for every $t \in \mathbb{R}_+$, Φ_t is an open mapping. Then under conditions $1-4$ and* **C**, *the equilibrium point a is globally asymptotically stable for Φ.*

Proof. By lemma 5 it suffices to prove that a is a stable equilibrium. We will repeatedly use the fact that for all $p, q \in X$ with $p \preceq q$, there holds that:

$$\Phi_t([p, q]) \subset [\Phi_t(p), \Phi_t(q)], \ \forall t \in \mathbb{R}_+,$$

which follows from monotonicity of Φ.

Choose an arbitrary neighborhood U of a. Then by condition **C**, there is some compact and order convex neighborhood C of a with $C \subset U$. By condition 1., we can define:

$$i = \inf(C) \text{ and } s = \sup(C)$$

and consider the order interval $[i,s]$. Then obviously, $C \subset [i,s]$, so $[i,s]$ is also a neigborhood of a. Consequently, since for every $t \in \mathbb{R}_+$, Φ_t is an open mapping, $\Phi_t([i,s])$ is also a neighborhood of a.

Now choose $T > 0$ such that:

$$\Phi_t(i), \Phi_t(s) \in C, \;\; \forall t \geq T. \tag{11}$$

Such a T exists by lemma 5.

Now consider the neigborhood $V := \Phi_T([i,s])$ of a. Then for all $t \geq 0$, there holds that:

$$\Phi_t(V) = \Phi_t(\Phi_T([i,s])) \subset \Phi_t([\Phi_T(i), \Phi_T(s)]) \subset [\Phi_{t+T}(i), \Phi_{t+T}(s)] \subset C \subset U$$

where we used the fact from above in proving the first two inclusions, and (11) and **C** (and in particular for the first time that C is order convex), for proving the third inclusion. This concludes the proof. □

5 Appendix: Riccati equations are monotone systems

Here we provide an alternative proof of the fact that the solutions of the real, symmetric Riccati differential equation generate a monotone flow.

Let's start by introducing some terminology. The real, n^2-dimensional vector space of real $n \times n$ matrices is denoted by $\mathcal{R}$. We assume that $\mathcal{R}$ is equipped with an inner product $\langle .,. \rangle$, defined by $\langle X, Y \rangle = \operatorname{tr}\left(XY^T\right)$. This inner product induces a norm (known as the Frobenius norm) and thus a metric on $\mathcal{R}$ in the obvious way. We shall assume that all topological notions are with respect to this metric. Note that the normed vector space $\mathcal{R}$ is isometrically isomorphic to $\mathbb{R}^{n^2}$ (with the usual Euclidean norm). To see this define $T : \mathcal{R} \to \mathbb{R}^{n^2}$ by:

$$T(X) = (x_1 x_2 \ldots x_n)^T,$$

where x_i is the ith row of X. Then it is easily checked that T is an isomorphism and an isometry. Occasionally, it is useful to have this 'equivalence' of both spaces in mind, in particular when considering systems of differential equations or geometric objects (such as subspaces or cones which will be introduced below). The set of real symmetric matrices will be denoted by $\mathcal{S} = \{S \in \mathcal{R} \,|\, S = S^T\}$. Clearly, $\mathcal{S}$ is a linear subspace of $\mathcal{R}$ of dimension $n(n+1)/2$. Let $\mathcal{P}(\mathcal{P}^+) \subset \mathcal{S}$ denote the set of symmetric positive semidefinite (definite) matrices. Then $\mathcal{P}$ is nonempty and closed (with respect to the subspace topology on $\mathcal{S}$), $\mathbb{R}_+\mathcal{P} \subset \mathcal{P}$, $\mathcal{P} + \mathcal{P} \subset \mathcal{P}$ and $\mathcal{P} \cap (-\mathcal{P}) = \emptyset$. Thus, $\mathcal{P}$ is a cone in $\mathcal{R}$ and in $\mathcal{S}$. Note that $\operatorname{int}(\mathcal{P}) = \mathcal{P}^+$ in $\mathcal{S}$ (but obviously $\operatorname{int}(\mathcal{P})$ would be empty in $\mathcal{R}$). We shall also need the concept of the *dual cone*. If $(X, \langle .,. \rangle)$ is a finite-dimensional real inner product space and if $K \subset X$ is a cone, then the dual cone of K is denoted by K^* and defined by:

$$K^* = \{y \in X \,|\, \langle y, k \rangle \geq 0, \; \forall k \in K\}.$$

Next we collect -without proof- some facts about the cone $\mathcal{P} \subset \mathcal{S}$ and its dual cone $\mathcal{P}^*$.

Lemma 4. *$\mathcal{P} = \mathcal{P}^*$.*

Lemma 5. *If $P \in \mathcal{P}$ and $P^* \in \mathcal{P}^*$ are such that $\langle P^*, P\rangle = 0$, then $P^*P = 0 = PP^*$.*

Lemma 6. *Let $P, Q \in \mathcal{P}^+$ and $Q - P \in \mathcal{P}$. Then $P^{-1}, Q^{-1} \in \mathcal{P}^+$ and $P^{-1} - Q^{-1} \in \mathcal{P}$.*

With this background material in place, we are ready to introduce the matrix Riccati differential equation on $\mathcal{R}$:

$$\dot{X} = XAX + B_1X + XB_2^T + C, \tag{12}$$

where $X \in \mathcal{R}$ and A, B_1, B_2 and C are given matrices in $\mathcal{R}$.

Obviously, solutions exist and are unique for every $X_0 \in \mathcal{R}$, since the vectorfield of (12) is locally Lipschitz. We will denote the solution by $X(t, X_0)$ with $t \in \mathcal{I}$, where $\mathcal{I}$ is the (open) maximal interval of existence in $\mathbb{R}$, which contains 0. We will also consider the forward maximal interval of existence which is defined by $\mathcal{I}^+ = \mathcal{I} \cap \mathbb{R}_+$.

On the other hand, this system is not necessarily (forward) complete. (Forward) completeness means that for every solution we have that $\mathcal{I} = \mathbb{R}$ ($\mathcal{I}^+ = \mathbb{R}_+$). For instance, consider the scalar Riccati equation with $A = 1$, $B_1 = B_2 = C = 0$ with initial condition $X(0) = 1$. Then the corresponding solution is $X(t, 1) = 1/(1 - t)$, which is of course only defined for $t \in (-\infty, 1)$.

We will study system (12) under the following additional constraint:

(S) A, $C \in \mathcal{S}$ and $B_1 = B_2$.

An immediate consequence is that if (S) holds, then $\mathcal{S}$ is an invariant set of (12). This follows from the fact that if $X(t)$ is a solution of (12), then $X^T(t)$ is also a solution of (12). Uniqueness of solutions then implies that if $X(0) \in S$, then $X(t) = X^T(t)$ for all t for which the solution exists. This observation justifies the restriction of the dynamics of system (12) to the invariant set $\mathcal{S}$, which will be assumed henceforth.

Our goal is to show that assuming (S), system (12) is monotone on $\mathcal{S}$. The partial order on $\mathcal{S}$ which will be preserved by the solutions is generated by the cone of positive semidefinite matrices $\mathcal{P}$. Thus, for $X_0, Y_0 \in \mathcal{S}$, $X_0 \preceq Y_0$ if and only if $Y_0 - X_0 \in \mathcal{P}$. In view of the above fact that the Riccati equation is not necessarily forward complete, we must slightly relax our original definition of a monotone system (which assumed that the solutions of the system generate a semiflow; in particular this implies that solutions are defined for all $t \in \mathbb{R}_+$). The modification is not at all surprising. We will say that system (12) is monotone on S (with respect to the order generated by $\mathcal{P}$) if:

$$\forall X_0, Y_0 \in \mathcal{S}: \;\; X_0 \preceq Y_0 \Rightarrow X(t, X_0) \preceq X(t, Y_0), \;\; \forall t \in \mathcal{I}_1^+ \cap \mathcal{I}_2^+,$$

where $\mathcal{I}_1^+$ and $\mathcal{I}_2^+$ are the maximal forward intervals of existence of the solutions $X(t, X_0)$ and $X(t, Y_0)$.

Theorem 6. *Let (S) hold. Then system* (12) *is monotone on $\mathcal{S}$.*

Proof. Since $\mathcal{S}$ is convex, (hence in particular p-convex) it suffices by Theorem 1.1 and 1.2 in [17] to verify that:

$$\forall (P, Q) \in \partial\mathcal{P} \times \mathcal{P}^*: \;\; \langle Q, P\rangle = 0 \Rightarrow \langle Q, DF_X(P)\rangle \geq 0,$$

where $DF_X(Y) = XAY + YAX + B_1Y + YB_1^T$, the linearization of system (12) at X.

Now if $(P, Q) \in \partial\mathcal{P} \times \mathcal{P}^*$, satisfy $\langle Q, P\rangle = 0$, then lemma 5 implies that $QP = PQ = 0$. From this we get:

$$\langle Q, DF_X(P)\rangle = \mathrm{tr}\left(Q[XAP + PAX + B_1P + PB_1^T]\right) = 0,$$

which concludes the proof. □

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