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Monotone chemical reaction networks

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We analyze certain chemical reaction networks and show that every solution converges to some steady state. The reaction kinetics are assumed to be monotone but otherwise arbitrary. When diffusion effects are taken into account, the conclusions remain unchanged. The main tools used in our analysis come from the theory of monotone dynamical systems. We review some of the features of this theory and provide a self-contained proof of a particular attractivity result which is used in proving our main result.

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1. Introduction

The theoretical study of the dynamical behavior of chemical reactions has been a fruitful and very active area of research throughout the past few decades. One particular reason for this continued attention may be that a unified theory, encompassing reaction networks of arbitrary topology as well as reactions with arbitrary kinetics is presently not available. But if one is willing to put restrictions on either the network topology or on the kinetics, then fairly general results can be obtained. For example, the seminal work on what today is known as the Feinberg–Horn–Jackson theory [11,19] – and [7,29] for recent results – restricts the reaction rates to mass action kinetics, but considers quite general topologies. The assumption of mass action kinetics enables the construction of

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Lyapunov functions, which allow one to conclude convergence of the solutions. On the other hand, one can restrict the network topology, but relax the assumption on the kinetics. One such relaxation is to assume that they are monotone functions (of the concentrations of the reagentia of the reactions). For instance, in [21], the following network was studied:

$$A_1 + A_2 \rightleftharpoons B_1 \rightleftharpoons B_2 \rightleftharpoons \cdots B_n$$

in which only the first reversible reaction step is bimolecular and the remaining steps are monomolecular. The purpose of that paper was to point out that the solutions of this network satisfy certain monotonicity properties, in a sense which we will explain below. A related idea can be found in [30], where it was pointed out how certain reaction networks may be transformed into so-called cooperative systems (also discussed below).

The purpose of this paper is to show how global convergence results can be obtained for a particular network topology – which includes and generalizes the one above – in the case of monotone but otherwise arbitrary reaction kinetics. Moreover, our results remain valid if diffusion effects are taken into consideration, thereby generalizing results from [23], which apply to the reversible reaction $A_1 + A_2 \rightleftharpoons B$.

To appreciate why monotonicity can play a role in the context of chemical reactions, we will review the concept of a monotone system next and highlight some of its features. The theory of monotone systems has been developed by Hirsch in a series of papers about two decades ago (see [12–16]) and 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:

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

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. Although in general an answer is not known, tests for checking monotonicity are available in 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 positive 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 $\mathbb{R}^n$ 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 [17,31]).

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. Second, 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 appendix B 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.

Other examples of applications of monotone systems theory can be found in the literature on chemostat models [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.

Monotone dynamical systems have recently been extended to monotone input–output systems in [2] in order to facilitate the study of interconnections of such systems (cascades, feedback). We refer to [3–6,8,9] for further developments and applications of this theory, including examples from molecular biology, ecology, and chemical reaction networks.

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 two 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 $x_i = (x_i^1, \cdots, x_i^{n_i})^T$ and its associated stoichiometric vector by $a_i = (a_i^1, \ldots, a_i^{n_i})^T$. We will also use the full concentration vector $x = (x_1^T, \ldots, x_{n+1}^T)^T$ 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 $i = 1, \ldots, n$ it is assumed throughout the rest of this paper that:

$$R_i : \mathbb{R}_+^{n_i} \to \mathbb{R}_+, \qquad R_i(x_i) = 0 \quad \forall x_i \in \partial\mathbb{R}_+^{n_i}, \quad R_i(x_i) > 0 \text{ and,}$$
$$\partial^T R_i / \partial x_i(x_i) \in \operatorname{int}(\mathbb{R}_+^{n_i}), \quad \forall x_i \in \operatorname{int}(\mathbb{R}_+^{n_i})$$

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 $R_i(x_i) = k_i \Pi_{k=1}^{n_i} (x_i^k)^{a_i^k}$ for some $k_i > 0$, satisfies these requirements.

We define the reaction rate vector by:

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

and the stoichiometric matrix of the network by:

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

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:

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

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,

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

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

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

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

$$\alpha_i^k \geqslant 0, \quad \forall k = 2, \ldots, n_i.$$

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

$$\frac{x_i^k(0)}{a_i^k} \geqslant \frac{x_i^1(0)}{a_i^1}, \quad \forall k = 2, \ldots, n_i$$

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:

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

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

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

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

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

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:

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

The inverse transformation is:

$$y_1 = a_1^1 z_1,$$
$$y_j = a_j^1 (z_j - z_{j-1}), \quad j = 2, \ldots, n.$$

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

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

with compact and convex state space:

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

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 $k \in \{1, \ldots, n-1\}$. 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:

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

where all $a_{ij} > 0$.

We will prove that J is diagonally dominant and hence Hurwitz, as we show in appendix A.

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

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

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 $\in_j$ as follows:

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

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

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

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 $\text{d}(F; \text{int}(\Omega); 0)$. Moreover, we claim that:

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

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,

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

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:

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

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:

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

and hence there can only be one steady state.

Global asymptotic stability follows from lemma 5, which is proved in appendix B. 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 $i = 1, \ldots, n$, 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 ith 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. Alternatively, we could have proved this claim using lemma 4.) □

Remark 1. We could also have proved global asymptotic stability using results of [26] or even of [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]).

[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].

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 FHJ theory of chemical reactions (see, e.g. [7,11,19,29]) 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 [23,24] 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:

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

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

$$x_0 \colon \bar{Q} \to X,$$

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

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

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

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

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 $\dfrac{\partial x_i}{\partial q_j}$ 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:

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

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 appendix B): 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. p. 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

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

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):

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

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

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

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:

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

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 $\frac{1}{|Q|}\int_Q Z_{ik}(q,0)\mathrm{d}q$ of its initial values, where $|Q|$ is the measure of Q. (Sketch of proof: there is a sequence of eigenvalues and respective eigenvectors $\lambda_i, \phi_i, i =$

$1, 2, \ldots$, of the self-adjoint Neumann Laplacian: solutions of $L\phi + \lambda\phi = 0, \phi_v = 0$. 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.

Appendix A: diagonally dominant matrices are Hurwitz

This result is well-known (see for instance [25]). We provide a short proof here, based on Gershgorin's theorem.

We will first prove a special case and then show that the general case can always be reduced to this special case.

If a matrix A is diagonally dominant with respect to $d_i = 1$ for all $i = 1, \ldots, n$, i.e.:

$$a_{ii} + \sum_{j \neq i} |a_{ij}| < 0, \quad \forall i = 1, \ldots, n$$

then it follows from Gershgorin's theorem that A is Hurwitz.

If a matrix A is diagonally dominant with respect to a set of positive numbers d_i which are not all equal to 1, then we claim that the matrix A is similar to a matrix A^* which is diagonally dominant with respect to $d_i = 1$ for all $i = 1, \ldots, n$. The result then follows straightforwardly.

To prove the claim, define the matrix T as the diagonal matrix with diagonal entries:

$$t_{ii} = 1/di, \quad \forall i = 1, \ldots, n.$$

Then a simple calculation shows that the matrix $A^* = TAT^{-1}$ is such that $a_{ij}^* = a_{ij} d_j / d_i$ for all $i, j = 1, \ldots, n$. But this in turn implies that:

$$a_{ii}^* + \sum_{j \neq i} |a_{ij}^*| = \left(d_i a_{ii} + \sum_{j \neq i} |a_{ij}| d_j \right) \Big/ d_i, \quad \forall i = 1, \ldots, n.$$

These n quantities are of course all negative, concluding the proof of our claim.

Appendix B: 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 $\lim_{t\to\infty} d(\Phi_t(x), \omega(x)) = 0$ (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:

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

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

Choose $t \geqslant 0$ 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 $0 \leqslant t_1 \leqslant t_2$ (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 $t_{l(k)} \geqslant t_k$ 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 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 $t \geqslant 0$:

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

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

Remark 2. In this remark, we will give a test for verification of the first condition, in those cases where the state space X is a subset of some finite-dimensional space.

Suppose that Y is a finite-dimensional normed vector space and that the state space X is a subset of Y. The partial order $\preceq$ on Y – and hence on X – is assumed to be generated by a cone $K \subset Y$. Recall that a cone K is called *normal* if there is some $k > 0$ such that whenever $x, y \in Y$ satisfy $0 \preceq x \preceq y$, then $|x| \leqslant k|y|$. It is easy to see that if K is normal, then every order interval in Y is a bounded set.

The following lemma shows that a cone K in a *finite-dimensional* space Y, is always normal.

Lemma 3. Let Y be a finite-dimensional vector space with cone K, inducing a partial order $\preceq$ on Y. Then K is normal.

Proof. We will show that

$$M := \sup\{|z| | 0 \preceq z \preceq x, |x| = 1\}$$

is a finite real number. From this, we claim that the conclusion will follow when we choose k in the definition of normality to be equal to M. Indeed, whenever

[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.

$0 \preceq x \preceq y$ with $y \neq 0$ (which can be assumed without loss of generality), it follows that $0 \preceq x/|y| \preceq y/|y|$. But, then $|x/|y|| \leqslant M$ and so letting $k = M$ the claim follows.

Let us now prove that M is finite. Suppose it's not, then there are sequences $\{x_n\}$ and $\{z_n\}$ satisfying $0 \preceq z_n \preceq x_n$ such that $|x_n| = 1$ for all n and $|z_n| \to \infty$. Consider the sequence $\{y_n\}$ where $y_n = z_n/|z_n|$. Obviously, $|y_n| = 1$ for all n and by compactness of the unit sphere in Y (since Y is finite-dimensional), we may pick a converging subsequence y_{n_k} with limit y^*. Clearly, $|y^*| = 1$ and $x_{n_k}/|z_{n_k}| \to 0$. So by compatibility of the partial order and the metric topology, we find that:

$$0 \preceq y^* \preceq 0.$$

But this is equivalent with the statement that $y^* \in K \cap (-K)$ and thus that $y^* = 0$ (since K is a cone). This contradicts $|y^*| = 1$ and concludes the proof. □

Recall that a partially ordered set X is a *lattice* if $\sup(p, q), \inf(p, q) \in X$ for all $p, q \in X$. We say that a set $S \subset X$ is *order bounded* in X if there are $a, b \in X$ such that $S \subset [a, b]$.

Lemma 4. Let Y be a finite-dimensional normed vector space with cone K and let $X \subset Y$ be a lattice. Suppose that every bounded set in X is order bounded in X. If C is a compact subset of X, then $\inf(C), \sup(C) \in X$.

Proof. We will only prove the result that $\sup(C) \in X$. The proof that $\inf(C) \in X$ is similar.

Since C is bounded, it is also order bounded and thus there are $a, b \in X$ such that $C \subset [a, b]$. Compact sets in metric spaces are separable, so we may pick a countable and dense subset $\{c_k\}$ of C. Since X is a lattice, we can construct a sequence $\{x_k\}$ in X as follows:

$$\begin{aligned} x_1 &= c_1, \\ x_k &= \sup(c_k, x_{k-1}), \quad k > 1. \end{aligned}$$

This sequence has the following properties:

1. $\{x_k\}$ is increasing, i.e. $x_k \preceq x_{k+1}$ for all $k \geqslant 1$.
2. $\{x_k\} \subset [a, b]$.

The order interval $[a, b]$ is closed (by compatibility of the metric topology and the partial order) and bounded (because K is normal), hence compact. Thus, we have an increasing sequence $\{x_k\}$ which remains in a compact set $[a, b]$ and thus there is some some $x \in [a, b] \subset X$ such that $x_k \to x$ (we have proved this fact in the proof of theorem 5). Now we claim that:

$$\sup(C) = x.$$

Let us prove this claim in two steps. First we will show that x is an upper bound for C. Second we will show that it is the least upper bound.

Pick $c \in C$. Since $\{c_k\}$ is dense in C, we may extract from $\{c_k\}$ a converging subsequence $\{c_{n_k}\}$ with limit c. We already know that $c_{n_k} \preceq x$ for all n_k, so compatibility implies that $c \preceq x$. Finally, let y be an arbitrary upper bound for C. Then in particular $c_k \preceq y$ for all k and hence $x_k \preceq y$ for all k. Taking limits and using compatibility once more we get that $x \preceq y$, so x is the least upper bound of C. □

For instance, suppose that $Y = \mathbb{R}^n$ and $K = \mathbb{R}^n_+$ and that X is either $\mathbb{R}^n_+$ or $\mathbb{R}^n$. Then clearly, X is a lattice and every bounded set in X is order bounded. Hence, lemma 4 implies that compact subsets of X have infimum and supremum in X.

Remark 3. 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 4. 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 quasi-convergent points (a point is quasi-convergent 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.

Although Theorem 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 5. 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 Theorem 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:

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

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:

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

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:

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

Such a T exists by Theorem 5.

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

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