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Global convergence in systems of differential equations arising from chemical reaction networks

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ABSTRACT

It is shown that certain classes of differential equations arising from the modelling of chemical reaction networks have the following property: the state space is foliated by invariant subspaces each of which contains a unique equilibrium which, in turn, attracts all initial conditions on the associated subspace.

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1. Introduction

There are difficult and interesting open questions about allowed asymptotic behaviour in systems of differential equations arising in the modelling of chemical reaction networks (CRNs for short). The main goal in this area is to make claims about the behaviour of these systems which are as far as possible independent of the particular choices of functions or parameters which describe the rates of reaction or “kinetics”. Classical results in this direction [1,2] rely strongly on the choice of “mass action kinetics” leading to particular polynomial differential equations. Mathematically, such results involve proving that solutions of certain parameterised families of polynomial differential equations have certain asymptotic behaviours regardless of the values of the parameters, but provided these have fixed sign. However when the kinetics is constrained only by loose qualitative laws, the family of possible differential equations describing a reaction network becomes much larger, and results become fewer. Here, we provide a general result based on the theory of monotone dynamical systems [3,4], and use it to prove global convergence in certain classes of CRNs where only very mild assumptions are made on the kinetics.

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The key geometrical insight on which the results are built was provided in [5] and generalised in [6]. Stated very briefly, these results show that sometimes the existence of an integral of motion in a strongly order-preserving dynamical system allows the construction of a Liapunov function on each level set, which increases along nontrivial orbits. This in turn has strong implications for the convergence of orbits. While in general it may be an unusual conjunction of affairs to have a first integral, strong monotonicity, and moreover integral and order cone related in a particular way, it actually appears that this situation is not uncommon in CRNs. However identifying when this situation occurs is nontrivial, and explicit construction of families of CRNs satisfying all these conditions becomes important.

The results at several points will be presented in considerably less generality than possible in order to simplify the presentation and highlight the key geometrical points, although where a theoretical result allows greater generality, this may be mentioned.

2. A convergence result

The result presented in this section, and applied in subsequent sections, is essentially derived from Theorem 2.4 in [6], with slight modification and specialisation for our purposes. Note that Theorem 2.4 in [6] stated that all orbits on a level set of the system in question converge to a unique equilibrium, provided the equilibrium exists, while what was actually proved was that all *bounded* orbits converge to the unique equilibrium. As remarked in [7], it remains an open question whether the word “bounded” can be dropped from the statement of the main result as erroneously done in [6]. However for the purposes of this paper all orbits will be bounded and only convergence of bounded orbits is required. Note also that much of the difficulty in the proof of Theorem 2.4 in [6] stemmed from the fact that the integrals of motion considered were in general nonlinear whereas here only the linear case is required.

Standard notions from convex geometry (as in [8–10] for example) will be assumed. Closed, convex and pointed cones in \mathbb{R}^n define partial orders on \mathbb{R}^n . Following [8], cones in \mathbb{R}^n which are closed, convex, pointed and solid will be referred to as *proper*. Standard results in the theory of monotone dynamical systems [3,4] will also be assumed.

Notation. The symbols $<, >, \leq, \geq, \ll, \gg$ will refer to the usual partial ordering of vectors in \mathbb{R}^n derived from the nonnegative orthant $\mathbb{R}_{\geq 0}^n$. So, given $a, b \in \mathbb{R}^n$, $a \leq b$ means $b - a \in \mathbb{R}_{\geq 0}^n$, $a < b$ means $b - a \in \mathbb{R}_{\geq 0}^n \setminus \{0\}$ and $a \ll b$ means $b - a \in \text{int}(\mathbb{R}_{\geq 0}^n)$. When the ordering is defined by some other closed, convex and pointed cone K , the alternative symbols $<, >, \prec, \succ, \ll, \gg$ will be used. So, for example, $a \ll b$ means $b - a \in \text{int } K$, and so forth.

Let Y, K be proper cones in \mathbb{R}^n with $K \supseteq Y$. Define K^* to be the dual cone to K , i.e., $K^* = \{y \in \mathbb{R}^n \mid \langle y, k \rangle \geq 0 \text{ for all } k \in K\}$. Consider a system

$$\dot{x} = F(x) \quad (1)$$

on Y , and assume that (1) defines a local semiflow ϕ on Y .

2.1. Three conditions

We define three conditions on (1) and the associated semiflow which will be referred to as Conditions 1, 2 and 3:

1. ϕ is *monotone* with respect to K , i.e., given $x, y \in Y$ with $x < y$ and any $t > 0$ such that $\phi_t(x)$ and $\phi_t(y)$ are defined, $\phi_t(x) < \phi_t(y)$. Moreover, ϕ is *strongly monotone* in $\text{int } Y$ in the following sense: given $x < y$ with at least one of x or y in $\text{int } Y$, then $\phi_t(x) \ll \phi_t(y)$ for all $t > 0$ such that $\phi_t(x)$ and $\phi_t(y)$ are defined.

2. The system has an *increasing linear first integral*, namely there exists a linear function $H : \mathbb{R}^n \rightarrow \mathbb{R}$ such that (i) $\nabla H \in \text{int}(K^*)$, and (ii) for each $y \in Y$, $\langle \nabla H, F(y) \rangle = 0$. Assume (w.l.o.g.) that $H(0) = 0$.
3. ϕ has no limit points on $\partial Y \setminus \{0\}$.

2.2. Remarks on the conditions

Condition 1. Verifying monotonicity/strong monotonicity of ϕ is generally the most nontrivial step in applications. The natural approach is via examination of the Jacobian matrix of the system as will be spelled out in Section 2.4 below.

Condition 2. For each $h \in \mathbb{R}$ define the level set $S_h = \{y \in Y \mid H(y) = h\}$. The condition $\langle \nabla H, F(y) \rangle = 0$ tells us that H is constant along trajectories, i.e., the sets S_h are invariant. Choosing any set of basis vectors for $(\nabla H)^\perp$ and writing these as the columns of a matrix Γ we can write $F(y) = \Gamma v(y)$ for some function $v : Y \rightarrow \mathbb{R}^{n-1}$. The implication of $\nabla H \in \text{int}(K^*)$ is as follows: given $x, y \in Y$ with $x > y$, by convexity of Y , the line segment between x and y lies in Y , and by integrating ∇H along this line segment we get $H(x) > H(y)$. So H is increasing with respect to the partial order defined by K . This implies in turn that the level sets of H are unordered, and since $H(0) = 0$, $H(y) > 0$ for all $y \in Y \setminus \{0\}$ (so $S_0 = \{0\}$). Since H is linear and Y is a cone, clearly the range of H is $[0, \infty)$, that is, $H : Y \rightarrow [0, \infty)$ is surjective.

Condition 3. Condition 3 is stronger than standard “persistence” assumptions which require only that limit sets of *interior* points in Y may not intersect the boundary. The particular class of examples discussed here can be shown to fulfil Condition 3; however making a weaker persistence assumption leads to similar, slightly rephrased, convergence results to the ones presented here. The choice to make a strong persistence assumption is to reduce technical digressions and allow the main arguments to be more transparent.

2.3. The key theoretical result

The basic theoretical result from which applications to CRNs will follow is:

Theorem 1. Consider System (1) with Conditions 1, 2 and 3 above. For each $h \in [0, \infty)$, S_h contains a unique equilibrium $e(h)$, and $e(h)$ attracts all of S_h .

Proof. Let $E = \{y \in Y \mid F(y) = 0\}$ be the equilibrium set of the system. The main landmarks in the proof are presented below, but the reader may refer to [6] to fill in the details.

1. Any two equilibria e_1, e_2 must satisfy $e_1 \gg e_2$ or $e_1 \ll e_2$. It follows from Conditions 2 and 3 that $E \cap \partial Y = \{0\}$. Consequently given two distinct equilibria \bar{e}_1, \bar{e}_2 at least one of these must lie in $\text{int} Y$. As a result, if \bar{e}_1, \bar{e}_2 satisfy $\bar{e}_1 < \bar{e}_2$, then by strong monotonicity in $\text{int} Y$, $\bar{e}_1 \ll \bar{e}_2$. Now suppose there are equilibria \bar{e}_1, \bar{e}_2 which are unordered by $<$. By repeating the geometrical arguments as in the proof of Lemma 5.11 of [6] we obtain the existence of an equilibrium \tilde{e} such that $\tilde{e} < \bar{e}_1$ (say) but not $\tilde{e} \ll \bar{e}_1$, contradicting the fact that $\tilde{e} < \bar{e}_1$ implies $\tilde{e} \ll \bar{e}_1$.
2. Each S_h is a compact, convex set: by linearity of H , S_h is the intersection of a hyperplane with Y and so convex, while boundedness follows from the condition that $\nabla H \in \text{int}(K^*)$ (see Lemma 3.9 in [6]). Thus each level set contains an equilibrium. Uniqueness of the equilibrium follows from the fact that S_h is unordered, whereas from 1, two equilibria e_1 and e_2 must satisfy $e_1 \gg e_2$ or $e_1 \ll e_2$.
3. The map $e : [0, \infty) \rightarrow E$ which associates to each h the unique equilibrium $e(h)$ on S_h is an order-preserving homeomorphism. That e is an order-preserving bijection with continuous inverse (namely $H|_E$) is immediate from parts 1 and 2, and linearity of H . That e is continuous follows essentially from the fact that E is closed (see Lemma 5.12 in [6]).

4. There is a continuous scalar function $L : Y \rightarrow [0, \infty)$, increasing along nontrivial orbits in $\text{int } Y$, and which attains a global maximum on S_h at $e(h)$. The proofs of these facts follow the related results in [6, Lemmas 5.13 to 5.18]. The value of $L(y)$ is the value of H at the unique point $Q(y)$ where $y - \partial K$ intersects E . Lemmas 5.13 to 5.17 in [6] carry over to the present case immediately. We claim that L is increasing along orbits of those $y \notin E$ for which $L(y) > 0$. Indeed, consider any such y . By the definition of $Q(y)$, $Q(y) < y$. Since $L(y) = H(Q(y)) > 0$, we have $Q(y) \neq 0$, so, by Condition 3, $Q(y) \in \text{int } Y$. Strong monotonicity in $\text{int } Y$ implies that for any $t > 0$, $\phi_t(Q(y)) = Q(y) \ll \phi_t(y)$. Consider any $e \in E$. If $e \leq Q(y)$ then $e \ll \phi_t(y)$, i.e., $e \neq Q(\phi_t(y))$. So $Q(\phi_t(y)) > Q(y)$, and thus $L(\phi_t(y)) > L(y)$, which proves the claim. It remains to notice that $L(y) > 0$ for any $y \in \text{int } Y$, since otherwise $y \in \partial K$, which contradicts $\text{int } Y \subseteq \text{int } K$. We remark that L is well defined at points on ∂Y , but may not be (strictly) increasing if $L(y) = 0$ (this is possible if $y \in \partial Y \cap \partial K$) as the line segment $[0, y]$ lies in ∂Y where we do not necessarily have strong monotonicity.
5. If $h = 0$ it is trivial that $e(h)$ attracts all of $S(h)$ as $S_h = e(h) = \{0\}$. So assume $h \neq 0$. Since S_h is compact, each $x \in S_h$ has a nonempty ω -limit set, $\omega(x)$. The Liapunov function in $\text{int } Y$, strictly increasing along nontrivial trajectories and achieving a maximum at $e(h)$, guarantees that $\omega(x)$ does not intersect $\text{int } Y \setminus \{e(h)\}$. So $\omega(x) \subseteq \partial Y \cup \{e(h)\}$. But by assumption $\omega(x)$ does not intersect $\partial Y \setminus \{0\}$ and $0 \notin S_h$, so $\omega(x) = \{e(h)\}$. \square

Remark. For $h \neq 0$ the equilibrium $e(h)$ defined in the above proof clearly lies in $\text{int } Y$ and so in the relative interior of S_h .

2.4. Jacobian conditions for monotonicity and strong monotonicity

In general, the greatest difficulty in applying Theorem 1 is verifying monotonicity of a local semiflow in Y and strong monotonicity in $\text{int } Y$ in the sense described in Condition 1. For this reason it is useful to have conditions which can more easily be checked for a system.

Terminology. Let J be a square matrix. Given a closed, convex and pointed cone $K \subseteq \mathbb{R}^n$, we will say that J is K -positive if $y \in K$ implies $Jy \in K$. A K -positive matrix J is K -irreducible if the only faces F of K for which $J(F) \subseteq F$ are $\{0\}$ and K . J is K -quasipositive if given any $y \in K$, there exists $\alpha \in \mathbb{R}$ such that $Jy + \alpha y \in K$. Suppose that there exists $\alpha \in \mathbb{R}$ such that $J + \alpha I$ is K -positive and K -irreducible, then we say that J is strictly K -quasipositive.

The following is a slight adaptation of results in [4] for our purposes.

Lemma 2. Consider a proper cone $K \subseteq \mathbb{R}^n$, some open set $U \subseteq \mathbb{R}^n$, and a C^1 vector field $f : U \rightarrow \mathbb{R}^n$ with Jacobian matrix Df . Let $X \subseteq U$ be some convex domain, positively invariant under the local flow ϕ_U defined by f , and let ϕ be the induced local semiflow on X . Assume that Df is K -quasipositive in X . Consider some $x_0, x_1 \in X$ with $x_0 < x_1$. Then $\phi_t(x_0) < \phi_t(x_1)$ for each $t > 0$ such that $\phi_t(x_0), \phi_t(x_1)$ exist. If there exists y_0 on the line segment joining x_0 to x_1 such that $Df(y_0)$ is strictly K -quasipositive, then $\phi_t(x_0) \ll \phi_t(x_1)$ for each $t > 0$ such that $\phi_t(x_0), \phi_t(x_1)$ exist.

Proof. By basic results on monotone dynamical systems (see Section 3.1 in [4]), K -quasipositivity implies monotonicity: given $x_0, x_1 \in X$ with $x_0 < x_1$, $\phi_t(x_0) < \phi_t(x_1)$ for each $t > 0$ such that $\phi_t(x_0), \phi_t(x_1)$ exist. Note that if $Df(y_0)$ is strictly K -quasipositive, then for each $x \in \partial K \setminus \{0\}$, there exists $v \in K^*$ such that $v(x) = 0$ and $v(Df(y_0)x) > 0$ (see Proposition 3.10 of [4]). The final statement now follows from Lemma 3.7 in [4]. \square

Remark. Since we are discussing the Jacobian matrix it reduces technicalities to assume that the vector field is defined on some open set containing the positively invariant set X in which we are interested.

3. Some background material

From now on we fix the state space of interest as $\mathbb{R}_{\geq 0}^m$, the nonnegative orthant in \mathbb{R}^m and focus on systems with a linear first integral. Let Γ be an $m \times n$ matrix, and $v : U \rightarrow \mathbb{R}^n$ be a C^1 function where U is some open neighbourhood of $\mathbb{R}_{\geq 0}^m$. We consider the system

$$\dot{x} = \Gamma v(x) \quad (2)$$

defining a local flow $\tilde{\phi}$ on U . We assume that $\mathbb{R}_{\geq 0}^m$ is (positively) invariant under $\tilde{\phi}$ and so get a local semiflow ϕ on $\mathbb{R}_{\geq 0}^m$.

Dynamical systems arising from chemical reaction networks typically take the form (2). In this context, the matrix Γ is termed the *stoichiometric matrix* of the system, and the intersection of any coset of $\text{Im } \Gamma$ with $\mathbb{R}_{\geq 0}^m$ is called a *stoichiometry class*. Clearly stoichiometry classes are positively invariant under ϕ . The function v describes the rates of reaction. A variety of common forms for v exist in the experimental and modelling literature, all of which satisfy the weak assumptions we present later (Section 5.1).

3.1. Qualitative classes and sets of matrices

A real matrix M determines the following three sets of matrices:

1. The qualitative class $\mathcal{Q}(M)$ [11] of all matrices with the same sign pattern as M . Explicitly, $N \in \mathcal{Q}(M)$ if N has the same dimensions as M and satisfies $\text{sign}(N_{ij}) = \text{sign}(M_{ij})$, i.e., $M_{ij} > 0 \Rightarrow N_{ij} > 0$, $M_{ij} < 0 \Rightarrow N_{ij} < 0$ and $M_{ij} = 0 \Rightarrow N_{ij} = 0$.
2. The set $\mathcal{Q}_0(M) \equiv \text{cl}(\mathcal{Q}(M))$, the closure of $\mathcal{Q}(M)$. $\mathcal{Q}_0(M)$ consists of all matrices N such that $M_{ij} > 0 \Rightarrow N_{ij} \geq 0$, $M_{ij} < 0 \Rightarrow N_{ij} \leq 0$ and $M_{ij} = 0 \Rightarrow N_{ij} = 0$.
3. The set $\mathcal{Q}_1(M)$ consisting of all matrices N such that $M_{ij} > 0 \Rightarrow N_{ij} \geq 0$, $M_{ij} < 0 \Rightarrow N_{ij} \leq 0$.

The following fact will often be applied without comment: if $c \in \mathcal{Q}_0(b)$ and $b \in \mathcal{Q}_1(a)$, then $c \in \mathcal{Q}_1(a)$. The next lemma can easily be checked directly.

Lemma 3. Let $a, b \in \mathbb{R}^n$, and let D be an $n \times n$ diagonal matrix with positive diagonal entries. Suppose Da, Db are $(-1, 0, 1)$ -vectors. Then $a + b \in \mathcal{Q}_1(a) \cap \mathcal{Q}_1(b)$.

3.2. Associating digraphs with CRNs

A DSR graph [12] is a signed, labelled, bipartite, multidigraph, examination of which can lead to a number of conclusions about the behaviour of a system of differential equations. In this paper we will be interested only in whether a given digraph is strongly connected, namely whether there is a (directed) path from each vertex in the digraph to each other vertex. So, following [13], we present a closely related but simplified construction. Given an $m \times n$ matrix A and an $n \times m$ matrix B , we construct a bipartite digraph $G_{A,B}$ on $m+n$ vertices as follows: associate a set of m vertices u_1, \dots, u_m with the rows of A ; associate another n vertices v_1, \dots, v_n with the columns of A ; add the arc $u_i v_j$ iff $A_{ij} \neq 0$; add the arc $v_j u_i$ iff $B_{ji} \neq 0$.

Such a digraph $G(x)$ can be associated with System (2) at each point in $x \in \mathbb{R}_{\geq 0}^m$ as follows: define $V(x) \equiv [\partial v_i(x)/\partial x_j]$, and let $G(x) \equiv G_{\Gamma, V(x)}$.

Remark. It is in general possible to factorise a given function in different ways, say $F(x) = \Gamma v(x) = \tilde{\Gamma} \tilde{v}(x)$. These different factorisations result in different digraphs. Thus the digraph associated with System (2) is not strictly associated with the vector field itself, but with a particular factorisation – see [12] for more discussion of this. In the case of CRNs, there is a natural factorisation, where Γ is the stoichiometric matrix.

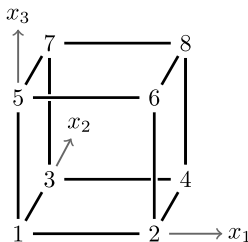


Fig. 1. The 3-cube in \mathbb{R}^3 with vertex n corresponding to column n of B . B_{kn} is the $(4-k)$ th entry in the binary representation of $n-1$. Observe that if $i-1 < 2^{k-1} \bmod 2^k$, then $B_{i+2^{k-1}} - B_i = e_k$ corresponding to the geometrical fact that each basis vector is associated with 4 parallel edges of the cube defined by B . For example $B_{3+2^2} - B_3 = B_7 - B_3 = (0, 1, 1)^T - (0, 1, 0)^T = (0, 0, 1)^T = e_3$.

3.3. The n -cube

Given a matrix M , M_k will refer to the k th column of M , and M^k to the k th row of M .

Fix $n \geq 2$ and define the $n \times 2^n$ matrix B as the $(0, 1)$ -matrix whose j th column read vertically upwards as a binary string gives the number $j-1$ (so $\sum_{i=1}^n 2^{i-1} B_{ij} = j-1$). For example, if $n=3$:

$$B = \begin{pmatrix} 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 \end{pmatrix}.$$

Note that the columns of B are just the vertices of the n -dimensional hypercube, and two vertices are adjacent if they differ in exactly one coordinate. The choice of ordering is important: given $i < j$, B_i and B_j are adjacent iff (i) there exists $k \geq 0$ such that $j = i + 2^k$ and (ii) $i-1 < 2^k \bmod 2^{k+1}$. The following is immediate:

Lemma 4. Given $i \in \{1, \dots, 2^n\}$ and $k \in \{1, \dots, n\}$, if $i-1 \geq 2^{k-1} \bmod 2^k$, then $B_i - B_{i-2^{k-1}} = e_k$ and otherwise $B_{i+2^{k-1}} - B_i = e_k$.

The geometrical meaning of Lemma 4 is illustrated for $n=3$ in Fig. 1.

3.4. Cubic cones

We now construct a class of cones which we refer to as “cubic cones”. First we show that no binary vector is in the convex hull of other, different, binary vectors. Geometrically this is obvious: these binary vectors are precisely the vertices of the n -cube.

Lemma 5. Let B be any $(0, 1)$ -matrix without repeated columns and let p be a nonnegative vector with $\sum_i p_i = 1$. If $Bp = q$ and q is a $(0, 1)$ -vector then $p = e_j$ for some j .

Proof. We look for solutions to $q \equiv Bp$ with q a binary vector and $\sum_i p_i = 1$. For each i , let S_i^0 be the set of indices such that $k \in S_i^0 \Leftrightarrow B_{ik} = 0$. Similarly define S_i^1 via $k \in S_i^1 \Leftrightarrow B_{ik} = 1$. Then:

1. If $q_i = \sum_k B_{ik} p_k = 1$, then $\sum_{k \in S_i^0} p_k = 1$, so $\sum_{k \in S_i^1} p_k = 0$, so $p_k = 0$ for each $k \in S_i^1$.
2. If $q_i = \sum_k B_{ik} p_k = 0$, then $\sum_{k \in S_i^1} p_k = 0$, so $p_k = 0$ for each $k \in S_i^1$.

Since p is not the zero vector, there exists j such that $p_j \neq 0$. Then for each i such that $q_i = 1$, $j \notin S_i^0$, i.e., $j \in S_i^1$, i.e., $B_{ij} = 1$; similarly for each i such that $q_i = 0$, $j \notin S_i^1$, i.e., $j \in S_i^0$, i.e., $B_{ij} = 0$. We have

$q_i = B_{ij}$, i.e., q is just the j th column of B . If there exists $l \neq j$ such that $p_l \neq 0$, then we get $q_i = B_{il}$. Since B has no repeated columns this is impossible, so $p_l = 0$ for $l \neq j$. Since $\sum_i p_i = 1$, $p = e_j$. \square

The construction in the next lemma is crucial to what is to follow:

Lemma 6. Let $m > n$ and consider an $m \times n$ matrix Γ of rank n . Let $c \in \mathbb{R}^m$ be some vector not in $\text{Im } \Gamma$. Define $\mathbf{1}$ to be the vector in \mathbb{R}^{2^n} each of whose entries is 1 and define $\Lambda \equiv c\mathbf{1}^T + \Gamma B$. With Λ defined in this way,

- (i) $K \equiv \{\Lambda z \mid z \geq 0\}$ is a closed, convex and pointed cone in \mathbb{R}^m ;
- (ii) The set of those $r \in \ker \Gamma^T$ for which $r^T c > 0$ is nonempty and is contained in $\text{int}(K^*)$;
- (iii) The nonnegative multiples of the 2^n columns of Λ are precisely the closed one-dimensional faces of K .

Proof. That K is a closed, convex cone is immediate from the definition. Since $c \notin \text{Im } \Gamma$, there exists $r \in \ker \Gamma^T$ such that $r^T c > 0$. For any $p > 0$ and any such r , $r^T \Lambda p = r^T c \mathbf{1}^T p = r^T c \sum p_i > 0$. So $r \in \text{int}(K^*)$. Since $\text{int}(K^*)$ is nonempty, K is pointed.

The third statement fails to be true only if some column of Λ can be written as a nonnegative combination of other columns of Λ . Suppose $\Lambda e_k = \Lambda p$ where $0 \leq p$. Then

$$(c\mathbf{1}^T + \Gamma B)e_k = (c\mathbf{1}^T + \Gamma B)p$$

i.e.,

$$c\left(1 - \sum p_i\right) = \Gamma B(p - e_k).$$

Left-multiplying both sides by r^T gives $r^T c(1 - \sum p_i) = 0$, so $\sum p_i = 1$ and $\Gamma B(p - e_k) = 0$. Since Γ has rank n , $\ker \Gamma = \{0\}$, and so $B(p - e_k) = 0$. By Lemma 5, $p = e_k$. So each column of Λ is an extremal vector of K . \square

Geometrical interpretation. Since Γ defines a linear map from \mathbb{R}^n to \mathbb{R}^m with trivial kernel and B has rank n , the columns of ΓB are the extremal points on an n -dimensional parallelotope in \mathbb{R}^m . Adding on the constant vector c simply translates these points, so the columns of Λ also define an n -parallelotope in \mathbb{R}^m . Ensuring that the constant vector c does not lie in $\text{Im } \Gamma$ means that the cone $K(\Lambda) \equiv \{\Lambda z \mid z \geq 0\}$ is pointed, and the convex hull of columns of Λ , $\text{conv}(\Lambda)$, is a cross-section of this cone. As $\text{conv}(\Lambda)$ is simply the n -cube after an affine mapping we call these cones *cubic cones* and the associated partial orders *cubic orders*.

Obviously, the incidence structure of $\text{conv}(\Lambda)$ is precisely that of the cube, $\text{conv}(B)$, namely the convex hull of any 2^k vectors $A_{r_1}, \dots, A_{r_{2^k}}$ is a k -dimensional face of $\text{conv}(\Lambda)$ if and only if the convex hull of the corresponding vectors $B_{r_1}, \dots, B_{r_{2^k}}$ is a k -dimensional face of the n -cube.

Each vector Γ_k is associated with 2^{n-1} edges of $\text{conv}(\Lambda)$ corresponding to 2^{n-1} parallel edges of $\text{conv}(B)$. More precisely, by Lemma 4, if $i - 1 \geq 2^{k-1} \bmod 2^k$ then

$$\Lambda_i - \Lambda_{i-2^{k-1}} = c + \Gamma B_i - (c + \Gamma B_{i-2^{k-1}}) = \Gamma(B_i - B_{i-2^{k-1}}) = \Gamma_k$$

while if $i - 1 < 2^{k-1} \bmod 2^k$ then

$$\Lambda_{i+2^{k-1}} - \Lambda_i = c + \Gamma B_i - (c + \Gamma B_{i+2^{k-1}}) = \Gamma(B_{i+2^{k-1}} - B_i) = \Gamma_k.$$

So for any $k \in \{1, \dots, n\}$ and any $i \in \{1, \dots, 2^n\}$ we define

$$j(i, k) \equiv \begin{cases} i - 2^{k-1} & (\text{if } i - 1 \geq 2^{k-1} \bmod 2^k), \\ i + 2^{k-1} & (\text{otherwise}) \end{cases}$$

and can always write for any i, k

$$\Gamma_k = \text{sign}(j(i, k) - i)(\Lambda_{j(i, k)} - \Lambda_i).$$

4. Systems preserving cubic orders

We proceed to construct a class of systems to which Theorem 1 can be applied. We do this by prescribing *a priori* the geometric nature of the order to be preserved and then constructing systems which preserve such orders. Via the next two theorems we provide a set of easily checkable conditions which ensure that System (2) has the behaviour described in Theorem 1. Later we will provide examples of CRNs which fulfil these conditions.

Theorem 7. Consider System (2) with Γ now an $(n+1) \times n$ matrix of rank n . Assume:

1. For some $c \neq 0$, $\Lambda \equiv c\mathbf{1}^T + \Gamma B$ satisfies:
 - (a) There exists a nonnegative right-inverse to Λ , i.e., a nonnegative matrix P such that $\Lambda P = I$.
 - (b) There exists a diagonal matrix D with positive diagonal entries such that $D\Lambda$ is a $(-1, 0, 1)$ -matrix.
2. For each $x \in \mathbb{R}_{\geq 0}^{n+1}$, $V(x) \equiv [\partial v_i(x)/\partial x_j] \in \mathcal{Q}_0(-\Gamma^T)$.
3. For each $x \in \text{int}(\mathbb{R}_{\geq 0}^{n+1})$, the digraph $G_{\Gamma, V(x)}$, is strongly connected.

Define

$$K = K(\Lambda) \equiv \{\Lambda z \mid z \geq 0\}.$$

Then:

1. $\mathbb{R}_{\geq 0}^{n+1} \subseteq K$.
2. $c \notin \text{Im } \Gamma$. $\text{int}(K^*)$ is nonempty and K is pointed.
3. Each column of Λ is an extremal vector of K .
4. For each $x \in \mathbb{R}_{\geq 0}^{n+1}$, $\Gamma V(x)$ is K -quasipositive, while for each $x \in \text{int}(\mathbb{R}_{\geq 0}^{n+1})$, $\Gamma V(x)$ is strictly K -quasipositive.

Before proving Theorem 7 we show how when it is combined with Theorem 1 we get a global convergence result.

Theorem 8. Consider System (2) with the assumptions in Theorem 7. Assume further that $\partial \mathbb{R}_{\geq 0}^{n+1} \setminus \{0\}$ contains no limit points of the local semiflow ϕ . Then there exists a linear function $H : \mathbb{R}_{\geq 0}^{n+1} \rightarrow \mathbb{R}$ whose level sets

$$S_h = \{y \in \mathbb{R}_{\geq 0}^{n+1} \mid H(y) = h\},$$

are invariant under ϕ . Moreover if for some h , S_h is nonempty, it contains a unique equilibrium $e(h)$ which attracts all of S_h .

Proof. The cone K in Theorem 7 is clearly closed and convex. That it is pointed and solid follow from results 1 and 2 of the theorem. So K is a proper cone. Result 4 of Theorem 7 gives that the Jacobian matrix of the system is K -quasipositive everywhere in $\mathbb{R}_{\geq 0}^{n+1}$ and strictly K -quasipositive in $\text{int}(\mathbb{R}_{\geq 0}^{n+1})$. By Lemma 2, K -quasipositivity implies that given $x_0 < x_1$, $\phi_t(x_0) < \phi_t(x_1)$ (for each $t > 0$ such that $\phi_t(x_0), \phi_t(x_1)$ exist); further, strict K -quasipositivity in $\text{int}(\mathbb{R}_{\geq 0}^{n+1})$ implies that if either of x_0 or x_1 lies in $\text{int}(\mathbb{R}_{\geq 0}^{n+1})$ then $\phi_t(x_0) \ll \phi_t(x_1)$. Thus Condition 1 of Theorem 1 is satisfied.

Since by Theorem 7(2), $c \notin \text{Im } \Gamma$, Lemma 6(ii) allows us to choose $r \in \ker \Gamma^T$ such that $r^T c > 0$. Define $H(x) = r^T x$. H is by definition linear, with $H(0) = 0$, and clearly

$$\langle \nabla H, \Gamma v(y) \rangle = r^T \Gamma v(y) = 0$$

so that level sets of H are invariant. Lemma 6(ii) provides further that $\nabla H = r \in \text{int}(K^*)$, so the integral is increasing. Thus Condition 2 is satisfied.

Finally, Condition 3 is assumed. Thus the assumptions of Theorem 1 are fulfilled and so Theorem 1 can be applied. \square

A somewhat more general statement than the following is proved as Theorem 1 in [13].

Lemma 9. *Let $K \subseteq \mathbb{R}^n$ be a closed, convex and pointed cone, A an $n \times m$ matrix, and B' an $m \times n$ matrix. Suppose that $\text{Im } A \not\subseteq \text{span } F$ for any nontrivial face F of K , and that AB is K -quasipositive for each $B \in \mathcal{Q}_0(B')$. Then whenever $G_{A,B}$ is strongly connected, AB is strictly K -quasipositive.*

4.1. Proof of Theorem 7

The lemmas presented so far make the proof now straightforward.

Proof of Theorem 7. 1. $\mathbb{R}_{\geq 0}^{n+1} \subseteq K$. Since $\Lambda P e_i = e_i$ and $P e_i$ is nonnegative, $e_i \in K$ for each i and so by convexity $\mathbb{R}_{\geq 0}^{n+1} \subseteq K$.

2. $c \notin \text{Im } \Gamma$. There exists $r \in \text{int}(K^*)$ and K is pointed. From the previous part, $\mathbb{R}^{n+1} = K - K$. One consequence is that, regarded as a map from \mathbb{R}^{2^n} to \mathbb{R}^{n+1} , Λ is surjective. It follows that $c \notin \text{Im } \Gamma$: otherwise, since all vectors in $\text{Im } \Lambda$ are of the form $\lambda c + \Gamma b$ (for some scalar λ and some vector b), each vector in $\text{Im } \Lambda$ could be written Γd for some vector d ; however Γ only has rank n contradicting the fact that Λ is surjective.

Since $c \notin \text{Im } \Gamma$, by Lemma 6(ii) there exists $r \in \ker \Gamma^T$ for which $r^T c > 0$, and $r \in \text{int}(K^*)$. Thus K is pointed. Note that since $\mathbb{R}_{\geq 0}^{n+1} \subseteq K$, it follows that $\text{int}(K^*) \subseteq \text{int}(\mathbb{R}_{\geq 0}^{n+1})$, so $r \gg 0$.

3. Each column of Λ is an extremal vector of K . This follows from Lemma 6(iii).

4(a). For each $y \in \mathbb{R}_{\geq 0}^{n+1}$, $\Gamma V(y)$ is K -quasipositive. Fix y and let $V = V(y)$. Recall that for $i \in \{1, \dots, 2^n\}$ and $k \in \{1, \dots, n\}$ there exists $j(i, k) \in \{1, \dots, 2^n\}$ such that

$$\Gamma_k = \text{sign}(j(i, k) - i)(\Lambda_{j(i, k)} - \Lambda_i).$$

Define $\alpha_{ik} = |V^k \Lambda_i|$, $\alpha_i = \sum_k \alpha_{ik}$ and $\alpha = \max_i \alpha_i$. We have

$$\Gamma V \Lambda_i = \sum_k \Gamma_k V^k \Lambda_i.$$

If $i > j(i, k)$, then $\Gamma_k = \Lambda_i - \Lambda_{j(i, k)}$, and by Lemma 3 we have $\Gamma_k \in \mathcal{Q}_1(\Lambda_i)$. Since $-V^k \in \mathcal{Q}_0(\Gamma_k^T)$, $-V^k \in \mathcal{Q}_1(\Lambda_i^T)$, so $-V^k \Lambda_i \geq 0$. Similarly, $i < j(i, k)$ implies $V^k \Lambda_i \geq 0$. So, in either case

$$\begin{aligned} \Gamma_k V^k \Lambda_i + \alpha_{ik} \Lambda_i &= \text{sign}(j(i, k) - i)(\Lambda_{j(i, k)} - \Lambda_i) V^k \Lambda_i + \alpha_{ik} \Lambda_i \\ &= (\Lambda_{j(i, k)} - \Lambda_i) \alpha_{ik} + \alpha_{ik} \Lambda_i = \alpha_{ik} \Lambda_{j(i, k)}. \end{aligned}$$

So

$$\Gamma V \Lambda_i + \alpha_i \Lambda_i = \sum_k (\Gamma_k V^k \Lambda_i + \alpha_{ik} \Lambda_i) = \sum_k \alpha_{ik} \Lambda_{j(i, k)} \in K \quad (3)$$

since $\alpha_{ik} \geq 0$ for each i . Given any $x = \sum_i t_i \Lambda_i \in K$ ($t_i \geq 0$ for each i):

$$\begin{aligned} \Gamma V x + \alpha x &= \sum_i t_i (\alpha \Lambda_i + \Gamma V \Lambda_i) \\ &= \sum_i t_i ((\alpha - \alpha_i) \Lambda_i + \Gamma V \Lambda_i + \alpha_i \Lambda_i). \end{aligned} \quad (4)$$

Since $\alpha - \alpha_i \geq 0$ for each i and $\Gamma V \Lambda_i + \alpha_i \Lambda_i \in K$, $\Gamma V x + \alpha x \in K$.

4(b). For each $y \in \text{int}(\mathbb{R}_{\geq 0}^n)$, $\Gamma V(y)$ is strictly K -quasipositive. By 4(a) we already know that ΓV is K -quasipositive for all V in $\mathcal{Q}_0(-\Gamma^T)$. By assumption, for each $y \in \text{int}(\mathbb{R}_{\geq 0}^{n+1})$, the digraph $G_{\Gamma, V(y)}$, is strongly connected. In order to apply Lemma 9 we need to confirm that $\text{Im } \Gamma \not\subseteq \text{span } F$ for any nontrivial face F of K .

Consider a nontrivial face F of K . We put the columns $\Lambda_i \in F$ into a matrix Λ_F . Suppose $\text{Im } \Gamma \subseteq \text{Im } \Lambda_F$, i.e., there exists a matrix T such that $\Gamma = \Lambda_F T$. Since Λ_F simply consists of a subset of the columns of Λ , for any i there exists $j(i)$ such that $\Lambda_F e_i = c + \Gamma B_{j(i)}$, and as $\Gamma = \Lambda_F T$, $c = \Lambda_F(e_i - T B_{j(i)})$. Thus $\Lambda = \Lambda_F[(e_i - T B_{j(i)}) \mathbf{1}^T + T B]$. This shows that $\text{Im } \Lambda \subseteq \text{Im } \Lambda_F$, contradicting the fact that F is a nontrivial face of K . Thus $\text{Im } \Gamma \not\subseteq \text{span } F$ for any nontrivial face F of K .

It now follows from Lemma 9 that $\Gamma V(y)$ is strictly K -quasipositive for each $y \in \text{int}(\mathbb{R}_{\geq 0}^n)$. \square

5. Applications to chemical reaction networks

5.1. Assumptions on reaction kinetics: Condition K

We consider chemical reaction networks of the form (2) defined on $\mathbb{R}_{\geq 0}^m$. At various points above we have mentioned weak assumptions on the kinetics of reactions, and here we spell these out. Let x_i refer to the concentration of the i th chemical. Each reaction has a left-hand side and a right-hand side: let $\mathcal{I}_{j,l}$ be the indices of chemicals occurring on the left of reaction j and $\mathcal{I}_{j,r}$ be the indices of the chemicals occurring on the right of reaction j . Define Γ_{ij} to be the difference between the number of molecules of the i th chemical occurring on the right of reaction j and on the left of reaction j . Let v_j represent the rate at which reaction j proceeds to the right. With these definitions we indeed get the dynamical system (2) for the evolution of the concentrations. We assume that reactions are either reversible or irreversible, and for an irreversible reaction we make the arbitrary choice that the substrates occur on the left and products on the right so the reaction always proceeds with nonnegative velocity to the right.

We assume:

(K1) $\Gamma_{ij}(\partial v_j / \partial x_i) \leq 0$, and if $\Gamma_{ij} = 0$ then $\partial v_j / \partial x_i = 0$. In other words $V(x) \equiv [\frac{\partial v_j(x)}{\partial x_j}] \in \mathcal{Q}_0(-\Gamma^T)$.

This condition has been discussed before in [14,15] for example, and is satisfied by all reasonable kinetics provided no chemical occurs on both sides of a reaction.

(K2) If reaction j is irreversible then:

(i) $v_j \geq 0$ with $v_j = 0$ if and only if $x_i = 0$ for some $i \in \mathcal{I}_{j,l}$.

(ii) If $x_i > 0$ for all $i \in \mathcal{I}_{j,l}$, then $\partial v_j / \partial x_i > 0$ for each $i \in \mathcal{I}_{j,l}$.

(K3) If reaction j is reversible then:

(i) If $x_i = 0$ for some $i \in \mathcal{I}_{j,l}$ (resp. for some $i \in \mathcal{I}_{j,r}$) then $v_j \leq 0$ (resp. $v_j \geq 0$).

(ii) If $x_i = 0$ for some $i \in \mathcal{I}_{j,l}$ (resp. for some $i \in \mathcal{I}_{j,r}$), then $v_j < 0$ (resp. $v_j > 0$) if and only if $x_{i'} > 0$ for each $i' \in \mathcal{I}_{j,r}$ (resp. for each $i' \in \mathcal{I}_{j,l}$).

(iii) If $x_i > 0$ for all $i \in \mathcal{I}_{j,l}$ (resp. for all $i \in \mathcal{I}_{j,r}$) then, for each $i \in \mathcal{I}_{j,l}$ (resp. $i \in \mathcal{I}_{j,r}$), $\partial v_j(x) / \partial x_i > 0$ (resp. $\partial v_j(x) / \partial x_i < 0$).

We will refer to these very mild and natural assumptions collectively as *Condition K*. The following simple result will be useful in the sequel:

Lemma 10. *Let a system of the form (2) satisfy Condition K. Then for any $x \in \mathbb{R}_{\geq 0}^m$, any j and any i such that $x_i = 0$ there holds $\Gamma_{ij}v_j(x) \geq 0$. Consequently, for such a system $\mathbb{R}_{\geq 0}^m$ is positively invariant.*

Proof. Suppose the contrary: then there exists a reaction j , some $x \in \mathbb{R}_{\geq 0}^m$ and a chemical i such that $x_i = 0$ and $\Gamma_{ij}v_j(x) < 0$. First of all, if chemical i does not participate in reaction j then $\Gamma_{ij} = 0$, so this cannot be the case. If i occurs on the left side of j and j is irreversible then, by (K2)(i), $v_j(x) = 0$, consequently $\Gamma_{ij}v_j(x) = 0$. If i occurs only on the right of irreversible j then $\Gamma_{ij} > 0$, and, again by (K2)(i), $\Gamma_{ij}v_j(x) \geq 0$. Assume now that reaction j is reversible. Since, by application of (K3)(i), if chemical i occurs on both sides of reaction j then $x_i = 0$ implies $v_j(x) = 0$, this is excluded. Consequently, either (i) chemical i occurs only on the left of reaction j and $v_j(x) > 0$, or (ii) chemical i occurs only on the right of reaction j and $v_j(x) < 0$. These possibilities are ruled out by assumption (K3)(i). \square

Given a reversible system of reactions satisfying Condition K, knowledge of the sign pattern of Γ allows us to determine the sign pattern of $V(x)$ at each $x \in \mathbb{R}_{\geq 0}^m$; this in turn allows construction of the digraph at each x . (When some reactions are irreversible, if we have knowledge of how products affect reaction rates, then again we can determine the zero pattern of $V(x)$ from Γ alone, and hence construct the digraph.) In particular, if all reactions are reversible then in fact for each $x \in \text{int}(\mathbb{R}_{\geq 0}^m)$, $V(x) \in \mathcal{Q}(-\Gamma^T)$, and $G_{\Gamma, V(x)} = G_{\Gamma, \Gamma^T}$.

5.2. Repelling faces of $\mathbb{R}_{\geq 0}^m$

Let $S \subseteq \{1, \dots, m\}$ be a subset of $\{1, \dots, m\}$, and $S^c = \{1, \dots, m\} \setminus S$. Define

$$F_S = \{x \in \mathbb{R}^m \mid x_i > 0, i \in S \text{ and } x_i = 0, i \in S^c\}.$$

Following [16], F_S will be referred to as an *elementary face* of $\mathbb{R}_{\geq 0}^m$. (Elementary faces are the relative interiors of the closed faces of $\mathbb{R}_{\geq 0}^m$.) If S is a proper, nonempty subset of $\{1, \dots, m\}$, then F_S will be termed a *nontrivial elementary face* of $\mathbb{R}_{\geq 0}^m$. Given a vector field on $\mathbb{R}_{\geq 0}^m$ defining a local semiflow on $\mathbb{R}_{\geq 0}^m$, F_S is *repelling* if, at each $x \in F_S$ there exists $i \in S^c$ such that $\dot{x}_i > 0$. The following is almost obvious:

Lemma 11. *Consider a vector field on $\mathbb{R}_{\geq 0}^m$ which defines a local semiflow ϕ on $\mathbb{R}_{\geq 0}^m$, and assume that some elementary face $F \subseteq \partial\mathbb{R}_{\geq 0}^m$ is repelling. Then F contains no ω -limit points of ϕ .*

Proof. By the definition of a repelling face, each point on F is a start point of ϕ : given $x \in F$ since there exists i such that $x_i = 0$ and $\dot{x}_i > 0$, there can clearly be no negative continuation of the trajectory through x . But since $\mathbb{R}_{\geq 0}^m$ is locally compact, no ω -limit set of ϕ can contain a start point of ϕ (Theorem 5.6 in [17]) and so F cannot intersect any ω -limit set of ϕ . \square

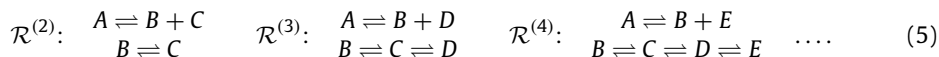
Remark. The following implication of Condition K will be needed below. Given an elementary face F_S , some $y, y' \in F_S$, some $i \in S^c$, and any j such that $\Gamma_{ij} \neq 0$, then $v_j(y) > 0$ (resp. $v_j(y) < 0$, resp. $v_j(y) = 0$) implies $v_j(y') > 0$ (resp. $v_j(y') < 0$, resp. $v_j(y') = 0$).

Lemma 12. *Consider a system of the form (2) defined on $\mathbb{R}_{\geq 0}^m$ and satisfying Condition K. If for some elementary face $F_S \subseteq \mathbb{R}_{\geq 0}^m$ there exists $x \in F_S$ where $f(x)$ is not tangent to F_S (i.e., $f(x) \notin \text{span } F_S$) then F_S is repelling.*

Proof. If $f(x)$ is not tangent to F_S , then there must exist $i \in S^c$ with $\dot{x}_i \neq 0$. As $\dot{x}_i = \sum_j \Gamma_{ij}v_j(x)$ and each of the summands is, by Lemma 10, nonnegative, it follows that $\dot{x}_i > 0$. As a consequence of the remark above, for any $y \in F_S$, $\dot{y}_i = \sum_j \Gamma_{ij}v_j(y) > 0$. Thus F_S is repelling. \square

5.3. A family of globally convergent CRNs

We consider the following class of CRNs with n reactions on $n + 1$ chemicals ($n \geq 2$). We refer to the n th member of this class as $\mathcal{R}^{(n)}$ and its stoichiometric matrix as $\Gamma^{(n)}$. The CRNs are



Fixing n , and choosing a convenient ordering for the reactions the stoichiometric matrix $\Gamma = \Gamma^{(n)}$ is defined by the rules:

1. Column 1

$$j = 1: \begin{cases} \Gamma_{ij} = -1, & i = n, \\ \Gamma_{ij} = 1, & i = n + 1, \\ \Gamma_{ij} = 0, & \text{otherwise.} \end{cases}$$

2. Columns 2, \dots , $n - 1$

$$j = 2, \dots, n - 1: \begin{cases} \Gamma_{ij} = 1, & i = n - j + 1, \\ \Gamma_{ij} = -1, & i = n - j + 2, \\ \Gamma_{ij} = 0, & \text{otherwise.} \end{cases}$$

3. Column n

$$j = n: \begin{cases} \Gamma_{ij} = 1, & i = 1, \\ \Gamma_{ij} = -1, & i = 2, \\ \Gamma_{ij} = -1, & i = n + 1, \\ \Gamma_{ij} = 0, & \text{otherwise.} \end{cases}$$

$\Gamma^{(n)}$ for $n = 2, 3, 4$ are

$$\Gamma^{(2)} = \begin{pmatrix} 0 & 1 \\ -1 & -1 \\ 1 & -1 \end{pmatrix}, \quad \Gamma^{(3)} = \begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & -1 \\ -1 & -1 & 0 \\ 1 & 0 & -1 \end{pmatrix},$$

$$\Gamma^{(4)} = \begin{pmatrix} 0 & 0 & 0 & 1 \\ 0 & 0 & 1 & -1 \\ 0 & 1 & -1 & 0 \\ -1 & -1 & 0 & 0 \\ 1 & 0 & 0 & -1 \end{pmatrix}.$$

Theorem 13. Assuming that all reactions are reversible, and the kinetics fulfils Condition K, the CRN $\mathcal{R}^{(k)}$ ($k \geq 2$) has the following behaviour: each stoichiometry class contains a unique equilibrium to which all trajectories are attracted.

Proof. The result follows from Theorem 8 if all the conditions in Theorem 7 can be shown to be met, and additionally, $\partial \mathbb{R}_{\geq 0}^{n+1} \setminus \{0\}$ contains no limit points of the local semiflow. Note first that for each n , $\Gamma^{(n)}$ is an $(n + 1) \times n$ matrix and it is straightforward that $\ker \Gamma^{(n)}$ is trivial. We fix $n \geq 2$, and for

notational simplicity omit the superscript (n) from all objects. Defining B as before, let Λ be the $(n+1) \times 2^n$ matrix:

$$\Lambda = e_n \mathbf{1}^T + \Gamma B.$$

For example, for $n = 3$,

$$\begin{aligned} \Lambda &= \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix} (1, 1, 1, 1, 1, 1, 1, 1) + \begin{pmatrix} 0 & 0 & 1 \\ 0 & 1 & -1 \\ -1 & -1 & 0 \\ 1 & 0 & -1 \end{pmatrix} \begin{pmatrix} 0 & 1 & 0 & 1 & 0 & 1 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 & 0 & 1 & 1 \\ 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 \end{pmatrix} \\ &= \begin{pmatrix} 0 & 0 & 0 & 0 & 1 & 1 & 1 & 1 \\ 0 & 0 & 1 & 1 & -1 & -1 & 0 & 0 \\ 1 & 0 & 0 & -1 & 1 & 0 & 0 & -1 \\ 0 & 1 & 0 & 1 & -1 & 0 & -1 & 0 \end{pmatrix}. \end{aligned}$$

1. Note that $\{\Lambda_i\}$ are of the form

$$e_n + \sum_{i \in S} \Gamma_i$$

where S can be any subset of $\{1, \dots, n\}$. We have

$$\begin{aligned} e_n &= \Lambda_1, \\ e_{n+1} &= e_n + \Gamma_1 = \Lambda_2, \\ e_{n-k} &= e_n + \sum_{i=2}^{k+1} \Gamma_i = \Lambda_{2^{k+1}}, \quad k = 1, \dots, n-2, \\ e_1 &= e_n + e_{n+1} + \sum_{i=2}^n \Gamma_i = \Lambda_2 + \Lambda_{2^n-1}. \end{aligned}$$

Each of these facts can quickly be proved by induction. Consequently, there exists a nonnegative matrix P such that $\Lambda P = I$. For example, for $n = 3$,

$$P = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Thus Condition 1(a) of Theorem 7 is met.

- It is easy to confirm that the k th entry of any sum of columns of Γ has value $-1, 0$ or 1 for $k \neq n$ and value $-2, -1$ or 0 for $k = n$. Consequently, Λ is a $(-1, 0, 1)$ -matrix. Thus Condition 1(b) of Theorem 7 is met.
- An immediate consequence of Condition K is that for each $x \in \mathbb{R}_{\geq 0}^{n+1}$, $V(x) \equiv [\partial v_i(x)/\partial x_j] \in \mathcal{Q}_0(-\Gamma^T)$. Thus Condition 2 of Theorem 7 is met.

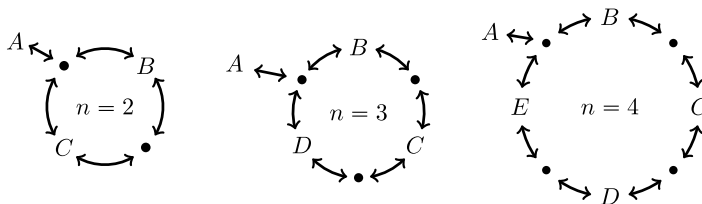


Fig. 2. The digraphs associated with reaction networks in (5) for $n = 2, 3, 4$ under the assumption that $[\frac{\partial v_i(x)}{\partial x_j}] \in \mathcal{Q}(-\Gamma^T)$. Vertices associated with rows of Γ (i.e., with particular chemicals) are labelled, while those associated with columns (i.e., with reactions) are filled circles. Antiparallel edge-pairs are shown as bidirected edges. As the only matter of interest is connectivity of the graphs, edge signs and labels are omitted.

4. Using (K3)(iii), the digraphs $G_{\Gamma, V(x)}$ at any point $x \in \text{int}(\mathbb{R}_{\geq 0}^{n+1})$ can be inferred. These are illustrated for $n = 2, 3, 4$ in Fig. 2. Clearly they are strongly connected, each consisting of a single double-cycle with one offshoot. Thus Condition 3 of Theorem 7 is met.
5. Each nontrivial elementary face of $\mathbb{R}_{\geq 0}^{n+1}$ is repelling. If this is not so for some nontrivial elementary face $F_S \subseteq \mathbb{R}_{\geq 0}^{n+1}$, then by Lemma 12, $\Gamma v(x)$ is tangent to F_S at each $x \in F_S$. This in turn implies for each $x \in F_S$ and each $i \in S^c$, that $\dot{x}_i = 0$. Since, by Lemma 10, $i \in S^c$ implies $\Gamma_{ij} v_j(x) \geq 0$ for each j , $\dot{x}_i = 0$ now implies that $\Gamma_{ij} v_j(x) = 0$ for each j . Thus whenever $\Gamma_{ij} \neq 0$ then $v_j(x) = 0$. Consider some j such that $\Gamma_{ij} \neq 0$. Note that no chemical occurs on more than one side of this reaction system and that all reactions are reversible. Suppose that chemical i appears only on the right of reaction j so that $\Gamma_{ij} > 0$. $v_j(x) = 0$ then implies, via (K3)(ii), that there exists $i' \in \mathcal{I}_{j,l} \cap S^c$, and so $\Gamma_{i'j} < 0$. Suppose, on the other hand that chemical i appears only on the left of reaction j so that $\Gamma_{ij} < 0$. In this case, via (K3)(ii), there exists $i' \in \mathcal{I}_{j,r} \cap S^c$ and so $\Gamma_{i'j} > 0$. Thus, for a system of reversible reactions such as this, with no chemical appearing on more than one side of any reaction, the condition that $\Gamma v(x)$ is tangent to F_S at each $x \in F_S$ has a simple interpretation in terms of Γ : each column of the submatrix Γ^{S^c} of Γ with only rows indexed by S^c must contain either both a positive and a negative entry, or only zeros. That this does not occur in $\Gamma^{(n)}$ for any nonempty $S \subsetneq \{1, \dots, n+1\}$ can be checked. If S includes 1, it must include 2 or $n+1$; if S includes k where $2 \leq k \leq n$, then it must include $k+1$ and $k-1$; if S includes $n+1$, then it must include 1; thus if S is nonempty then $S = \{1, \dots, n+1\}$. In the terminology of [18], the systems have no “siphons”. In physical terms, setting any proper subset of reactant concentrations to zero, there always remains some active reaction producing one of the absent reactants with positive rate. Consequently, by Lemma 11, no nontrivial elementary face of $\mathbb{R}_{\geq 0}^{n+1}$ contains any ω -limit points of the associated semiflow ϕ . As $\partial \mathbb{R}_{\geq 0}^{n+1} \setminus \{0\}$ is precisely the union of these nontrivial elementary faces, it contains no ω -limit points of the semiflow. \square

5.4. Another example

The family of CRNs presented in the previous section are not the only CRNs preserving cubic orders. As another example of a CRN which preserves a cubic order, consider the following:



giving

$$\Gamma = \begin{pmatrix} 0 & 0 & 2 \\ 0 & 1 & -1 \\ -1 & -1 & 0 \\ 1 & -1 & 0 \end{pmatrix}.$$

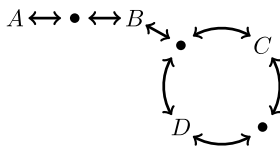


Fig. 3. The digraph $G_{\Gamma,V}$ for the reaction system in (6). Conventions are as in Fig. 2.

$\ker \Gamma = \{0\}$ and the positive vector $(1, 2, 1, 1)^T$ lies in $\ker \Gamma^T$. Defining B in the usual way,

$$\Lambda \equiv e_3 \mathbf{1}^T + \Gamma B = \begin{pmatrix} 0 & 0 & 0 & 0 & 2 & 2 & 2 & 2 \\ 0 & 0 & 1 & 1 & -1 & -1 & 0 & 0 \\ 1 & 0 & 0 & -1 & 1 & 0 & 0 & -1 \\ 0 & 1 & -1 & 0 & 0 & 1 & -1 & 0 \end{pmatrix}.$$

Left-multiplying Λ by the diagonal matrix $\text{diag}\{1/2, 1, 1, 1\}$ gives a $(-1, 0, 1)$ -matrix. The matrix

$$P = \begin{pmatrix} 1/2 & 0 & 1 & 0 \\ 0 & 1 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 1/2 & 0 & 0 & 0 \end{pmatrix}$$

can be confirmed to be a nonnegative right-inverse for Λ . Consequently, assumption 1 in Theorem 7 is satisfied. Assuming that the kinetics fulfils (K3)(iii), the digraph in $\text{int}(\mathbb{R}_{\geq 0}^4)$ is shown in Fig. 3 and is clearly strongly connected.

Thus all the conditions of Theorem 7 are fulfilled. Further, it can easily be checked, using the approach in part 5 of the proof of Theorem 13, that each nontrivial elementary face of $\mathbb{R}_{\geq 0}^{n+1}$ is repelling and so by Lemma 11, $\partial \mathbb{R}_{\geq 0}^{n+1} \setminus \{0\}$ contains no ω -limit points of the associated semiflow ϕ . Thus by Theorem 8 each stoichiometry class contains a unique equilibrium to which all trajectories are attracted. Clearly with the exception of the equilibrium at 0, these globally attracting equilibria lie in $\text{int}(\mathbb{R}_{\geq 0}^{n+1})$.

We remark that in the above examples, the assumption that all reactions are reversible can be relaxed provided that this is done in such a way that the digraph in $\text{int}(\mathbb{R}_{\geq 0}^{n+1})$ remains strongly connected, and such that nontrivial elementary faces of $\mathbb{R}_{\geq 0}^{n+1}$ remain repelling.

6. Concluding remarks

Systems of differential equations arising in chemistry and displaying strong convergence properties have been presented. The examples are only intended to illustrate the applicability of the main theorems (Theorems 7 and 8): characterising fully the set of CRNs for which global convergence can be proved via these theorems remains a task for the future.

In addition, a number of variants on the same theme remain to be explored. While this work has focussed on systems preserving so-called cubic orders, these are by no means the only partial orders which may be preserved by a system of chemical reactions as demonstrated in [19]. Closely related results can be derived where the geometrical construction in this paper is restricted to linear invariant subspaces: this approach throws up further examples of chemical reaction networks with strong global convergence properties. These themes will be explored in forthcoming papers.

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