

Reachability, persistence, and constructive chemical reaction networks (part I): reachability approach to the persistence of chemical reaction networks

Gilles Gnacadja

Received: 13 April 2010 / Accepted: 7 June 2011 / Published online: 3 September 2011
© Springer Science+Business Media, LLC 2011

Abstract For a chemical reaction network, persistence is the property that no species tend to extinction if all species are initially present. We investigate the stronger property of vacuous persistence: the same asymptotic feature with a weaker requirement on initial states, namely that all species be implicitly present. By implicitly present, we mean for instance that if only water is present and the reaction network incorporates the information that water is made of hydrogen and oxygen, then hydrogen and oxygen are implicitly present. Persistence is inherently interesting and has implications for the global asymptotic stability of equilibrium states. Our main tools are the work of A. I. Vol’pert on the nullity and positivity of species concentrations, and the enabling notion of reachability. The main result states that a reaction network is vacuously persistent if and only if the set of all species is the only set of species that both is closed with respect to reachability and causes the implicit presence of all species. This paper is the first in a series of three articles. Two sequel papers introduce additional formalisms and use them to describe two large classes of reaction networks that are used as models in biochemistry and are vacuously persistent.

Keywords Chemical reaction network · Vacuous persistence · Reachability · A. I. Vol’pert

Mathematics Subject Classification (2010) 92C42 · 92C45 · 34D05

This article contains three parts. Part II can be found at doi:[10.1007/s10910-011-9896-2](https://doi.org/10.1007/s10910-011-9896-2) and Part III can be found at doi:[10.1007/s10910-011-9895-3](https://doi.org/10.1007/s10910-011-9895-3).

G. Gnacadja (✉)
Research and Development Information Systems, Amgen, Inc.,
One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA
e-mail: gilles.gnacadja@gmail.com

1 Introduction

A trajectory $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{> 0}^n$ is persistent if it has no ω -limit points on the boundary $\partial\mathbb{R}_{\geq 0}^n = \mathbb{R}_{\geq 0}^n \setminus \mathbb{R}_{> 0}^n$. This means that each of the n trajectory components $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$ does not approach zero as time tends to infinity continuously or discretely. Many dynamical systems, including those that model mass-action reaction networks, are positive: solution trajectories originating in $\mathbb{R}_{> 0}^n$ range in $\mathbb{R}_{> 0}^n$. Such a system is persistent if all solution trajectories originating in $\mathbb{R}_{> 0}^n$ are persistent. A reaction network is said to be persistent if its dynamical system is persistent.

Persistence is inherently interesting because it is concerned with the possibility of species extinction. Furthermore, for certain reaction networks, persistence implies the global asymptotic stability of positive equilibrium states; see e.g. Feinberg [6, Remark 6.1.E] and Siegel and MacLean [16, Theorem 3.2]. Two results of Angeli, De Leenheer and Sontag [4] provide insight into the persistence of conservative reaction networks with reasonable kinetics. Theorem 1 in this reference says that if such a network is persistent, then a fairly broad reversibility condition holds, namely the reaction vectors are positively dependent, i.e. there exists a vanishing linear combination of the reaction vectors in which all coefficients are positive. Theorem 2 in the same reference says that such a network is persistent provided every nonempty siphon contains the support of a nonzero nonnegative conserved vector of species. Shiu and Sturmfels [14, Theorem 3.5] established an equivalent algebraic formulation of this sufficient condition.

One might want to ascertain the non-extinction (i.e. the persistence) of not just the species that are initially present, but also of those that appear after initial time. This would be the case for instance in a biochemical experimental setting in which only building blocks are initially present. We address this concern here by studying vacuous persistence, a stronger form of persistence that covers such circumstances. Vacuous persistence is the property that trajectories are persistent provided all species are implicitly present at the initial state, or in the terminology of this paper, provided the species that are initially present form a stoichiometrically admissible set. In the parlance of Chemical Reaction Network Theory, this (weaker) requirement on the initial state is for it to be stoichiometrically compatible with a positive state. The “vacuous” attribute is to indicate that, in a sense made more specific in the paper, vacuous persistence is persistence together with the absence of opportunities for non-persistence. Our approach is largely based on the concept of reachability and results on the nullity and positivity of trajectory components developed by A. I. Vol’pert [22]. A set of species will be said to be reach-closed if it already contains all the species that can be produced from it. The following theorem is the main result of this paper.

Theorem 1.1 (Theorem 5.5) *Consider a mass-action reaction network for which all concentration trajectories are bounded. The following are equivalent:*

- *The reaction network is vacuously persistent.*
- *Among the subsets of the set \mathcal{S} of all species, only the full set \mathcal{S} is both reach-closed and stoichiometrically admissible.* □

Propositions 3.3 and 3.4 show that the use of siphons in Angeli, De Leenheer and Sontag [4] and of reachability here are somewhat dual. The real value of this

theorem lies in that the approach it offers enables us to establish vacuous persistence for networks in two large classes relevant in biochemistry. These are described in the sequel papers Gnacadja [7, 8].

Following is the organization of the paper. We assemble basic notions of Chemical Reaction Network Theory in Sect. 2; most are from common literature but some are particular to our needs. We discuss reachability in reaction networks in Sect. 3. Section 4 presents the Theorem of A. I. Vol’pert on the positivity and nullity of species concentrations, as well as certain immediate consequences. Finally, we introduce and characterize vacuous persistence in Sect. 5. We prove Vol’pert’s theorem in “Appendix” section. The proof is a specialized form of the much more general work of Vol’pert and should be informative to readers unfamiliar with this interesting piece of mathematics.

2 Reaction networks

We gather certain basic notions of Chemical Reaction Network Theory. Most can be found in the lecture notes of Feinberg [5] and the more recent tutorial of Gunawardena [9].

2.1 Structure of reaction networks

A system of chemical reactions is usually presented as a diagram that shows the interactions of chemical species; see for instance Fig. 1. Following is a rendition of the formal definition that enables mathematical investigations.

Definition 2.1 A *reaction network* is a triple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ where

- \mathcal{S} , the set of *species*, is a nonempty finite set;
- \mathcal{C} , the set of *complexes*, is a nonempty finite subset of the nonnegative orthant $\mathbb{Z}_{\geq 0}\mathcal{S}$ of $\mathbb{Z}\mathcal{S}$; and
- \mathcal{R} , the set of *reactions*, is a relation on \mathcal{C} , i.e. a subset of the Cartesian square $\mathcal{C} \times \mathcal{C}$. \square

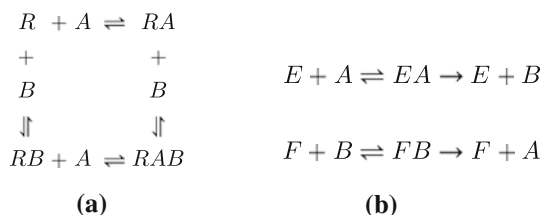


Fig. 1 Examples of chemical reaction networks. (a) The allosteric ternary complex model of pharmacology. The interaction is allosteric, i.e. not orthosteric, because the receptor R has different binding sites for the ligands A and B . (b) Two enzymes E and F catalyzing the interconversion of two substrates A and B . This is a futile cycle because each enzyme reverses the action of the other.

In this definition and throughout the paper, $\mathbb{Z}\mathcal{S}$ denotes the set of formal linear combinations of \mathcal{S} with integer coefficients, equipped naturally with linear operations. (In precise algebraic terms, $\mathbb{Z}\mathcal{S}$ is the free \mathbb{Z} -module over \mathcal{S} , almost a vector space with integer scalars and basis \mathcal{S} .) Similarly, $\mathbb{R}\mathcal{S}$ denotes the real vector space with basis \mathcal{S} . It also denotes the canonically isomorphic vector space of tuples of real entries indexed by \mathcal{S} . The notation $\mathbb{R}_{\geq 0}\mathcal{S}$ (respectively $\mathbb{R}_{> 0}\mathcal{S}$) is for the nonnegative orthant (respectively the positive orthant); it consists of the linear combinations or the tuples in which all coefficients or entries are nonnegative (respectively positive). The space $\mathbb{R}\mathcal{S}$ is equipped with the Euclidean structure with respect to which \mathcal{S} is an orthonormal basis.

Consistently with customary chemical notation, a reaction $R = (Q', Q'')$ is also denoted $Q' \rightarrow Q''$. The complexes $\text{src}(R) := Q'$ and $\text{tgt}(R) := Q''$ are respectively the *source* and the *target* of the reaction R , and we say that Q' *reacts to* Q'' . The vector $\text{tgt}(R) - \text{src}(R) \in \mathbb{Z}\mathcal{S}$ is the *reaction vector* of R . We set

$$\underline{\text{src}}(R) := \text{Supp}(\text{src}(R)) \quad \text{and} \quad \underline{\text{tgt}}(R) := \text{Supp}(\text{tgt}(R)).$$

For illustration, the network of Fig. 1a has six species: R, A, B, RA, RB and RAB ; seven complexes: $R + A, RA, R + B, RB, RB + A, RA + B$ and RAB ; and eight reactions. The network of Fig. 1b has six species: E, F, A, B, EA and FB ; six complexes: $E + A, EA, E + B, F + B, FB$ and $F + A$; and six reactions.

We augment Definition 2.1 with the following customary restrictions:

- (i) Every species is in the support of at least one complex;
- (ii) No complex reacts to itself; and
- (iii) Every complex is the source or the target of at least one reaction.

The *reaction graph* of the reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is the directed graph $(\mathcal{C}, \mathcal{R})$; the complexes are the vertices and the reactions are the directed edges. Given complexes $Q', Q'' \in \mathcal{C}$, we say that Q' *ultimately reacts to* Q'' if there is a path from Q' to Q'' in the reaction graph. The connected components of the associated undirected graph are the *linkage classes* of the network \mathcal{N} . The network is *weakly reversible* if every path in the reaction graph has a reverse path, i.e. if whenever Q' ultimately reacts to Q'' , it also holds that Q'' ultimately reacts to Q' . The network is *reversible* if the reaction graph is reversible.

The network of Fig. 1a is an example of a reversible network. Reversibility and weak reversibility are the two well-established notions of reversibility in Chemical Reaction Network Theory. However they do not reflect certain forms of biochemical reversibility, of which the futile enzymatic cycle of Fig. 1b is an example. In the sequel paper Gnacadja [7], we propose another notion of reversibility which applies to such contexts.

2.2 Stoichiometric compatibility

The *stoichiometric space* of \mathcal{N} is the subspace S of $\mathbb{R}\mathcal{S}$ spanned by the reaction vectors. The *rank* of \mathcal{N} is the dimension of S .

Two elements $v, w \in \mathbb{R}_{\geq 0}\mathcal{S}$ are said to be *stoichiometrically compatible* if $v - w \in S$. This defines an equivalence relation on $\mathbb{R}_{\geq 0}\mathcal{S}$, the equivalence classes of which are the *stoichiometric compatibility classes*. The stoichiometric compatibility class of $u \in \mathbb{R}_{\geq 0}\mathcal{S}$ is

$$P = (u + S) \cap \mathbb{R}_{\geq 0}\mathcal{S}.$$

We have

$$P = P_{>0} \sqcup P_{\neq 0},$$

where

$$P_{>0} = (u + S) \cap \mathbb{R}_{>0}\mathcal{S} \quad \text{and} \quad P_{\neq 0} = (u + S) \cap ((\mathbb{R}_{\geq 0}\mathcal{S}) \setminus (\mathbb{R}_{>0}\mathcal{S})).$$

The sets $P_{>0}$ and $P_{\neq 0}$ consist respectively of the positive and the nonpositive elements of P . They are respectively the interior and the boundary of P , both relative to the affine space $u + S$. We will say that the class P is *degenerate* if its interior $P_{>0}$ is empty ($P_{>0} = \emptyset$), or equivalently if it coincides with its boundary $P_{\neq 0}$ ($P = P_{\neq 0}$).

Definition 2.2 Let $\mathcal{Z} \subseteq \mathcal{S}$. The set \mathcal{Z} is *P-admissible*, where P is a stoichiometric compatibility class, if there exists $u \in P$ such that $\mathcal{Z} = \text{Supp}(u)$. The set \mathcal{Z} is *stoichiometrically admissible* if it is *P-admissible* for some nondegenerate stoichiometric compatibility class P , i.e. if $\mathcal{Z} = \text{Supp}(u)$ for some nonnegative $u \in \mathbb{R}_{\geq 0}\mathcal{S}$ which is stoichiometrically compatible with some positive $v \in \mathbb{R}_{>0}\mathcal{S}$. □

Consider for illustration, the network of Fig. 1b. It has rank three; the three vectors $EA - E - A$, $FB - F - B$, $A - B$ form a basis of its stoichiometric space. Each stoichiometric compatibility class is characterized by a triplet (T_E, T_F, T_{AB}) of non-negative reals, in that the class consists of the 6-tuples $(u_E, u_F, u_A, u_B, u_{EA}, u_{FB})$ of nonnegative reals which satisfy the equations

$$u_E + u_{EA} = T_E, \quad u_F + u_{FB} = T_F, \quad u_A + u_B + u_{EA} + u_{FB} = T_{AB}.$$

The class is nondegenerate if and only if T_E, T_F and T_{AB} are all positive. The set $\{E, FB\}$ is stoichiometrically admissible, while the set $\{A, B\}$ is not. The assertions in this example can be verified by direct calculations. They can also be found by applying results developed in the sequel paper Gnacadja [7].

Definition 2.3 The *conservation space* of \mathcal{N} is S^\perp , the orthogonal of the stoichiometric space S in $\mathbb{R}\mathcal{S}$ (with respect to the Euclidean structure for which \mathcal{S} is an orthonormal basis). □

In Horn and Jackson [10], a reaction network is said to be *conservative* if the conservation space contains a positive vector, i.e. for the network \mathcal{N} here, if $S^\perp \cap \mathbb{R}_{>0}\mathcal{S} \neq \emptyset$. It is also shown that a network is conservative if and only if it has a bounded stoichiometric compatibility class, a condition which is equivalent to all stoichiometric compatibility classes being bounded. The relevance of S^\perp to conservativeness is explained in the next section.

2.3 Kinetics and equilibria of reaction networks

A kinetics on the reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is a family $K = (K_R)_{R \in \mathcal{R}}$ in which for each $R \in \mathcal{R}$, K_R is a continuous function $\mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}$. Associated with a kinetics K is the species formation function $\mathcal{F}(K, -) = (\mathcal{F}_X(K, -))_{X \in \mathcal{S}} : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{S}}$ given for $u = (u_X)_{X \in \mathcal{S}} \in \mathbb{R}^{\mathcal{S}}$ by

$$\mathcal{F}(K, u) = \sum_{R \in \mathcal{R}} K_R(u) (\text{tgt}(R) - \text{src}(R)) ; \quad (2.1)$$

$\mathcal{F}(K, u)$ is the weighted sum of all reaction vectors, with the vector for a reaction $R \in \mathcal{R}$ weighted by $K_R(u)$, which is the rate of the reaction R when the vector of species concentrations is u .

The most common kinetics is the mass-action kinetics. It is given by a family $k = (k_R)_{R \in \mathcal{R}} \in \mathbb{R}_{>0}^{\mathcal{R}}$ of reaction rate constants and

$$K_R(u) = k_R u^{\text{src}(R)} = k_R \prod_{X \in \mathcal{S}} u_X^{(\text{src}(R), X)} ;$$

we write $\mathcal{F}(K, -) = \mathcal{F}(k, -)$. For example, the mass-action species formation function of the network of Fig. 1b is given as follows.

$$\begin{aligned} \mathcal{F}_E(k, u) &= -k_{E+A \rightarrow EA} u_E u_A + (k_{EA \rightarrow E+A} + k_{EA \rightarrow E+B}) u_{EA} \\ \mathcal{F}_F(k, u) &= -k_{F+B \rightarrow FB} u_F u_B + (k_{FB \rightarrow F+B} + k_{FB \rightarrow F+A}) u_{FB} \\ \mathcal{F}_A(k, u) &= -k_{E+A \rightarrow EA} u_E u_A + k_{EA \rightarrow E+A} u_{EA} + k_{FB \rightarrow F+A} u_{FB} \\ \mathcal{F}_B(k, u) &= -k_{F+B \rightarrow FB} u_F u_B + k_{EA \rightarrow E+B} u_{EA} + k_{FB \rightarrow F+B} u_{FB} \\ \mathcal{F}_{EA}(k, u) &= -(k_{EA \rightarrow E+A} + k_{EA \rightarrow E+B}) u_{EA} + k_{E+A \rightarrow EA} u_E u_A \\ \mathcal{F}_{FB}(k, u) &= -(k_{FB \rightarrow F+A} + k_{FB \rightarrow F+B}) u_{FB} + k_{F+B \rightarrow FB} u_F u_B \end{aligned}$$

To say that the network \mathcal{N} is governed by the kinetics K is to say the function $c = (c_X)_{X \in \mathcal{S}} : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}^{\mathcal{S}}$ of time representing the concentration of the species obeys the dynamical system

$$\dot{c}(t) = \mathcal{F}(K, c(t)) . \quad (2.2)$$

The function $\mathcal{F}(K, -)$ ranges into the stoichiometric space S , so the solutions of Eq. (2.2) are confined to affine subspaces of $\mathbb{R}^{\mathcal{S}}$ parallel to S . Equivalently, if c is a solution and $v \in S^\perp$, then the function $t \mapsto \langle v, c(t) \rangle$ is conserved (i.e. constant) on $\mathbb{R}_{\geq 0}$. This explains why we call S^\perp the conservation space in Definition 2.3. Under certain conditions on the kinetics K , which are satisfied if K is a mass-action kinetics, every solution that originates at a nonnegative state remains nonnegative, and hence is in fact confined to a stoichiometric compatibility class.

Consider the function $\hat{\mathcal{F}}(K, -) = \left(\hat{\mathcal{F}}_Q(K, -) \right)_{Q \in \mathcal{C}} : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{C}}$ given for $Q \in \mathcal{C}$ and $u \in \mathbb{R}^{\mathcal{S}}$ by

$$\hat{\mathcal{F}}_Q(K, u) = \left(\sum_{R \in \mathcal{R}, \text{tgt}(R)=Q} K_R(u) \right) - \left(\sum_{R \in \mathcal{R}, \text{src}(R)=Q} K_R(u) \right).$$

Then we have $\mathcal{F}(K, u) = \sum_{Q \in \mathcal{C}} \hat{\mathcal{F}}_Q(K, u) Q$. An *equilibrium state* of the network

\mathcal{N} for the kinetics K is any $u \in \mathbb{R}^{\mathcal{S}}$ such that $\mathcal{F}(K, u) = 0$. An equilibrium state $u \in \mathbb{R}^{\mathcal{S}}$ that satisfies the stronger condition $\hat{\mathcal{F}}(K, u) = 0$ is a *complex-balanced state*. The network is said to be *complex-balancing* if it admits a positive complex-balanced state. It is known that a mass-action complex-balancing network must be weakly reversible.

A trajectory originating at an equilibrium state stays at that state. A major concern in Chemical Reaction Network Theory is to understand the local and global asymptotic stability of equilibrium states based on structural information, i.e. with no or limited information on kinetics parameters. The persistence properties which we study in this paper can be helpful in addressing such problems.

2.4 Pertinent elements of polyhedral geometry

The reader familiar with convex geometry will notice that a stoichiometric compatibility class is a (convex, possibly unbounded) polyhedron. A solid triangle and a solid tetrahedron are examples of polyhedra (of dimension two and three respectively). The notion of face in polyhedral geometry generalizes the notions of faces, edges and vertices as ordinarily known for three-dimensional polyhedra. Rockafellar [13] is a classical reference on convexity, but what is needed for stoichiometric compatibility classes is well covered in Anderson and Shiu [2, Section 2.3]. Here we add the notion of support of a face of a stoichiometric compatibility class. The empty set is always a face in polyhedral geometry. In this paper however, the empty set as a face is not of interest and a face will always be nonempty.

Let $P = (u + S) \cap \mathbb{R}_{\geq 0}^{\mathcal{S}}$ be a stoichiometric compatibility class and let A be a face of P . We herein call *intrinsic interior* of A , and denote $\text{int}(A)$, the relative interior of A in the sense of polyhedral geometry. If A is a vertex, then $\text{int}(A) = A$. In particular, if $0 \in P$, then 0 is a vertex of P and $\text{int}(\{0\}) = \{0\}$; we set $\text{Supp}(\{0\}) = \emptyset$. Now suppose $A \neq \{0\}$. Then there is an (unique, nonempty) inclusion-minimal set $\mathcal{Z} \subseteq \mathcal{S}$ of species such that $A = (u + S) \cap \mathbb{R}_{\geq 0}^{\mathcal{Z}}$. We have $\text{int}(A) = (u + S) \cap \mathbb{R}_{> 0}^{\mathcal{Z}}$ and we define the *support of the face* A to be $\text{Supp}(A) = \mathcal{Z}$. So, whether or not A consists only of the vertex 0 , the intrinsic interior $\text{int}(A)$ consists of the points of P whose support is $\text{Supp}(A)$. The class P is the disjoint union of the intrinsic interiors of its faces, and the P -admissible sets (Definition 2.2) are precisely the subsets of \mathcal{S} that occur as supports of faces of P . We remark for the particular case $A = P$ that the intrinsic interior $\text{int}(P)$ and the interior $P_{> 0}$ relative to $u + S$ coincide only if P is nondegenerate.

Consider for illustration a reaction network with three species, rank two, and bounded stoichiometric compatibility classes; e.g. the network with species X_1, X_2, X_3 and reactions $2X_1 \rightleftharpoons X_2, X_1 + X_2 \rightleftharpoons X_3$. Then a nondegenerate stoichiometric compatibility class is a solid triangle, and its faces are the class itself, its three edges and its three vertices. Such examples are easy to visualize. However they do not illustrate the pertinence of considering faces, which is that in general, an arbitrary set of species need not occur as the support of a face of a nondegenerate stoichiometric compatibility class, i.e. need not be stoichiometrically admissible (Definition 2.2). We already noted that nonempty sets that are not stoichiometrically admissible exist for the network of Fig. 1b. This is also the case for the network of Fig. 1a.

3 Reachability in reaction networks

In this section we discuss reachability as it pertains to reaction networks. Reachability is an important topic in the vast mathematical field of systems theory. Sontag [17] has a widely applicable definition of a system in Chap. 2 and an extensive discussion of reachability in Chap. 3. Basically, reachability is concerned with the feasibility of achieving a state of interest from another in a system through (finitely many or a finite-time continuum of) transitions. By default, the state of a reaction network is the vector of species concentrations. But to see our discussion of reachability in the larger context of systems theory, the relevant notion of state is the set of species that are present, i.e. the support of the concentrations vector. Petri nets are then the relevant class of systems. There is abundant literature on Petri nets and a standard comprehensive reference is Murata [11].

A reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and a set $\mathcal{Z} \subseteq \mathcal{S}$ of species are fixed throughout this section. We begin by defining the following sets:

$$\begin{aligned} \text{React}(\mathcal{Z}) &:= \{R \in \mathcal{R} : \underline{\text{src}}(R) \subseteq \mathcal{Z}\}; \\ \text{Prod}(\mathcal{Z}) &:= \left[\bigcup_{R \in \text{React}(\mathcal{Z})} \underline{\text{tgt}}(R) \right] \setminus \mathcal{Z}. \end{aligned}$$

The set $\text{React}(\mathcal{Z})$ consists of the reactions that would occur if only species from \mathcal{Z} were present. The set $\text{Prod}(\mathcal{Z})$ consists of the species that such reactions would produce and which are not already in \mathcal{Z} . Next we define the sets $\text{Reach}_r(\mathcal{Z})$ for $r \in \mathbb{Z}_{\geq 0}$ by induction as follows:

$$\begin{aligned} \text{Reach}_0(\mathcal{Z}) &:= \mathcal{Z}; \\ \text{Reach}_r(\mathcal{Z}) &:= \text{Prod} \left[\bigcup_{\rho=0}^{r-1} \text{Reach}_\rho(\mathcal{Z}) \right], \quad \text{for } r \in \mathbb{Z}_{\geq 1}. \end{aligned}$$

The sets $\text{Reach}_r(\mathcal{Z})$ are obtained recursively by collecting the species we do not already have and can produce from those we already have, starting with \mathcal{Z} . They are pairwise disjoint. Also, if $\text{Reach}_{r_0}(\mathcal{Z}) = \emptyset$, then $\text{Reach}_r(\mathcal{Z}) = \emptyset$ for all $r \geq r_0$.

And because \mathcal{S} is finite, there does exist $r_0 \geq 0$ such that $\text{Reach}_{r_0}(\mathcal{Z}) = \emptyset$. We pose:

$$\begin{aligned} \text{Reach}(\mathcal{Z}) &:= \bigsqcup_{r=0}^{\infty} \text{Reach}_r(\mathcal{Z}); \\ \text{NonReach}(\mathcal{Z}) &:= \mathcal{S} \setminus \text{Reach}(\mathcal{Z}). \end{aligned}$$

Definition 3.1

- The species in $\text{Reach}(\mathcal{Z})$ and in $\text{NonReach}(\mathcal{Z})$ are said to be *reachable* from \mathcal{Z} and *non-reachable* from \mathcal{Z} respectively.
- The species in $\text{Reach}_r(\mathcal{Z})$ are said to have *reachability index* r with respect to \mathcal{Z} .
- The set $\text{Reach}(\mathcal{Z})$ is the *reach-closure* of the set \mathcal{Z} .
- The set \mathcal{Z} is said to be *reach-closed* if $\text{Reach}(\mathcal{Z}) = \mathcal{Z}$. □

The reach-closure $\text{Reach}(\mathcal{Z})$ consists of the species that are reachable from \mathcal{Z} , i.e. the species in \mathcal{Z} and the species that can be produced directly or indirectly with \mathcal{Z} . The set $\text{NonReach}(\mathcal{Z})$ consists of the species that are not in \mathcal{Z} and can not be produced with \mathcal{Z} , whether directly or indirectly. Note that the full set \mathcal{S} and the empty set are always reach-closed. Table 1 illustrates reachability for the futile enzymatic cycle of Fig. 1b.

Another notion from Petri net theory, that of siphon, is the subject of growing use in reaction network theory; see for example Angeli, De Leenheer and Sontag [4], Anderson [1], Shiu and Sturfels [14], and Anderson and Shiu [2]. We define siphons in Definition 3.2 and examples can be found in the literature just cited. Propositions 3.3 and 3.4 show that there is a certain duality relationship between siphons and reach-closures. The reachability perspective has been used advantageously in Siegel and Chen [15] and Siegel and MacLean [16].

Definition 3.2 A set $\mathcal{W} \subseteq \mathcal{S}$ of species is a *siphon* provided $(R \in \mathcal{R} \text{ and } \mathcal{W} \cap \text{tgt}(R) \neq \emptyset) \Rightarrow (\mathcal{W} \cap \text{src}(R) \neq \emptyset)$. □

This definition says that the set \mathcal{W} is a siphon if whenever a reaction has elements of \mathcal{W} among the species it produces, it also has elements of \mathcal{W} among the species it consumes. The full set \mathcal{S} and the empty set are siphons. Siphons are sometimes

Table 1 Selected reachability concepts for the network of Fig. 1b

\mathcal{Z}	$\{EA, F\}$	$\{E, A\}$	$\{A, B\}$
$\text{Reach}_0(\mathcal{Z})$	$\{EA, F\}$	$\{E, A\}$	$\{A, B\}$
$\text{Reach}_1(\mathcal{Z})$	$\{E, A, B\}$	$\{EA\}$	\emptyset
$\text{Reach}_2(\mathcal{Z})$	$\{FB\}$	$\{B\}$	\emptyset
$\text{Reach}_3(\mathcal{Z})$	\emptyset	\emptyset	\emptyset
$\text{Reach}(\mathcal{Z})$	$\{E, F, A, B, EA, FB\}$	$\{E, A, B, EA\}$	$\{A, B\}$
$\text{NonReach}(\mathcal{Z})$	\emptyset	$\{F, FB\}$	$\{E, F, EA, FB\}$

The set $\{A, B\}$ is reach-closed. The set $\{EA, F\}$ has full reach closure. The set $\{E, A\}$ lies between these two limit cases

required to be nonempty by definition. Here, when we need a siphon to be nonempty, we explicitly say so.

Proposition 3.3 *The complement $\text{NonReach}(\mathcal{Z})$ of the reach-closure of \mathcal{Z} is a siphon.*

Proof For any reaction $R \in \mathcal{R}$, we have:

$$\begin{aligned} \text{NonReach}(\mathcal{Z}) \cap \underline{\text{src}}(R) = \emptyset &\Leftrightarrow \underline{\text{src}}(R) \subseteq \text{Reach}(\mathcal{Z}) \\ &\Rightarrow \underline{\text{tgt}}(R) \subseteq \text{Reach}(\mathcal{Z}) \\ &\Leftrightarrow \text{NonReach}(\mathcal{Z}) \cap \underline{\text{tgt}}(R) = \emptyset . \end{aligned}$$

□

Proposition 3.4 *The set \mathcal{Z} is reach-closed if and only if its complement $\mathcal{S} \setminus \mathcal{Z}$ is a siphon.*

Proof

$$\begin{aligned} &(\mathcal{S} \setminus \mathcal{Z} \text{ is a siphon}) \\ &\Leftrightarrow \left((R \in \mathcal{R} \text{ and } (\mathcal{S} \setminus \mathcal{Z}) \cap \underline{\text{src}}(R) = \emptyset) \Rightarrow ((\mathcal{S} \setminus \mathcal{Z}) \cap \underline{\text{tgt}}(R) = \emptyset) \right) \\ &\Leftrightarrow \left((R \in \mathcal{R} \text{ and } \underline{\text{src}}(R) \subseteq \mathcal{Z}) \Rightarrow (\underline{\text{tgt}}(R) \subseteq \mathcal{Z}) \right) \\ &\Leftrightarrow \bigcup_{R \in \text{React}(\mathcal{Z})} \underline{\text{tgt}}(R) \subseteq \mathcal{Z} \\ &\Leftrightarrow \text{Prod}(\mathcal{Z}) = \emptyset \\ &\Leftrightarrow \text{Reach}(\mathcal{Z}) = \mathcal{Z} . \end{aligned}$$

□

Propositions 3.3 and 3.4 immediately imply the following result, which is already intuitively clear.

Proposition 3.5 *The reach-closure $\text{Reach}(\mathcal{Z})$ of \mathcal{Z} is reach-closed; $\text{Reach}(\text{Reach}(\mathcal{Z})) = \text{Reach}(\mathcal{Z})$.*

□

Moreover, $\text{Reach}(\mathcal{Z})$ is the inclusion-minimal subset of \mathcal{S} that contains \mathcal{Z} and is reach-closed. In particular, if $\mathcal{Z}' \subseteq \text{Reach}(\mathcal{Z})$, then $\text{Reach}(\mathcal{Z}') \subseteq \text{Reach}(\mathcal{Z})$. This expresses a transitivity feature of reachability: For $X \in \mathcal{S}$ and $\mathcal{Z}' \subseteq \mathcal{S}$, if X is reachable from \mathcal{Z}' , and if all elements of \mathcal{Z}' are reachable from \mathcal{Z} , then X is reachable from \mathcal{Z} .

For $u \in \mathbb{R}_{\geq 0}\mathcal{S}$, we set

$$\begin{aligned} \text{Reach}(u) &:= \text{Reach}(\text{Supp}(u)) , \\ \text{NonReach}(u) &:= \text{NonReach}(\text{Supp}(u)) . \end{aligned}$$

4 The theorem of A. I. Vol’pert on the positivity and nullity of species concentrations

Vol’pert [22] has studied the question of when the solutions of certain dynamical systems have components that remain zero while the other components become and remain positive. The theory is developed for differential equations on graphs, of which mass-action kinetics dynamical systems are instances. The work is revisited in Vasil’ev, Vol’pert and Khudyaev [20] (with an erratum in [21]). The more recent book of Vol’pert and Hudjaev [23] covers the topic in Chap. 12. In this section, we present this work in a form specialized to chemical reaction networks and with a view toward showing in Sect. 5 how it contributes to results on persistence.

Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. Suppose \mathcal{N} is governed by mass-action kinetics and let $k = (k_R)_{R \in \mathcal{R}}$ be the family of reaction rate constants. We set $\mathcal{F} = \mathcal{F}(k, -)$ for the species formation function. Associated with the dynamical system $\dot{c}(t) = \mathcal{F}(c(t))$ is the evolution semigroup $C : \mathbb{R}_{\geq 0}\mathcal{S} \times \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}\mathcal{S}$. Thus, C is continuous; for every $u \in \mathbb{R}_{\geq 0}\mathcal{S}$, the map $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}\mathcal{S}, t \mapsto C(u, t)$ is the concentration trajectory originating at u ; and for all $u \in \mathbb{R}_{\geq 0}\mathcal{S}$ and $t, t' \in \mathbb{R}_{\geq 0}$, we have $C(u, t + t') = C(C(u, t), t')$.

Theorem 4.1 (A. I. Vol’pert) *Let $c = (c_X)_{X \in \mathcal{S}} : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}^{\mathcal{S}}$ be a concentration trajectory with $c(0) \in \mathbb{R}_{\geq 0}\mathcal{S}$. Let $X \in \mathcal{S}$ be a species.*

- *If $X \in \text{NonReach}(c(0))$, then $c_X(t) = 0$ for all $t \geq 0$; and*
- *If $X \in \text{Reach}(c(0))$, then $c_X(t) > 0$ for all $t > 0$.*

Hence, we have $\text{Supp}(c(t)) = \text{Reach}(c(0))$ for all $t > 0$.

The work of Vol’pert provides additional information on trajectories. In particular, it says that if a species X is reachable from $\text{Supp}(c(0))$ with reachability index r , then the following holds for the derivatives at $t = 0$ of order up to r of the trajectory component c_X .

$$c_X^{(\rho)}(0) = 0 \text{ for } \rho = 0, \dots, r - 1 \text{ and } c_X^{(r)}(0) > 0.$$

$$c_X(t) = \frac{1}{r!} c_X^{(r)}(0) t^r + O(t^{r+1}) \text{ as } t \rightarrow 0, t > 0.$$

Thus, if two species X' and X'' have reachability index r' and r'' with $r' < r''$, then there exists $t_0 > 0$ such that $0 < c_{X''}(t) < c_{X'}(t)$ if $0 < t < t_0$. This says that the higher the reachability index, the slower a species starts to appear.

We present a proof of Theorem 4.1 in “Appendix” section. We focus here on its implications. A stoichiometric compatibility class P is fixed for the rest of this section.

Recalling the notion of admissibility from Definition 2.2, the following result is a straightforward observation from Theorem 4.1.

Proposition 4.2 *If a set $\mathcal{L} \subseteq \mathcal{S}$ of species is P -admissible (resp. stoichiometrically admissible), then so is its reach-closure $\text{Reach}(\mathcal{L})$. □*

The converse of Proposition 4.2 is not true: there may be sets that are not P -admissible and are reach-closed. For example, for the network of Fig. 1b, the set $\{A, B\}$ is not stoichiometrically admissible (see Sect. 2.2) but is reach-closed (see Table 1).

We define

$$\Phi(P) := \{u \in P : \text{Supp}(u) \text{ is reach-closed}\}. \quad (4.1)$$

The set \mathcal{S} is reach-closed and is the support of positive vectors, so

$$P_{>0} \subseteq \Phi(P) \subseteq P. \quad (4.2)$$

The combination of Theorem 4.1 and Proposition 3.5 readily gives:

Proposition 4.3 *For any concentration trajectory $c : \mathbb{R}_{\geq 0} \rightarrow P$, we have $c(t) \in \Phi(P)$ for all $t > 0$; only the initial point $c(0)$ may (but need not) be in the subset $P \setminus \Phi(P)$ of the boundary $P_{\neq 0}$. \square*

Vol’pert’s Theorem also leads to certain properties of the faces of stoichiometric compatibility classes.

Proposition 4.4 *Let A be a face of P . The following are equivalent:*

- (i) *The intrinsic interior $\text{int}(A)$ of A contains a trajectory.*
- (ii) *The support $\text{Supp}(A)$ of A is reach-closed.*
- (iii) *The intrinsic interior $\text{int}(A)$ of A is forward-invariant.*
- (iv) *The face A is forward-invariant.*

If these conditions are satisfied and if A is bounded, then A contains an equilibrium state.

Refer to the discussion on polyhedral geometry in Sect. 2.4 for the notions of face and of intrinsic interior and support of a face. The implication (i) \Rightarrow (iv) can be obtained by using an unpublished result of Sontag [19] in the more general context of dynamical systems on manifolds with boundary.

Proof If a trajectory c ranges in $\text{int}(A)$, then all the points along c have $\text{Supp}(A)$ as their support. So we get the implication (i) \Rightarrow (ii) from Proposition 4.3. We have (ii) \Rightarrow (iii) by Theorem 4.1. The implication (iii) \Rightarrow (i) is trivial. We have (iii) \Rightarrow (iv) by the continuity of the evolution semi-group C and because A is the topological closure of $\text{int}(A)$. We have (iv) \Rightarrow (iii) because Theorem 4.1 shows that the support along a trajectory cannot get inclusion-smaller. Now suppose that A is forward-invariant and bounded. Then A is convex, compact and forward-invariant. As a result, A contains an equilibrium state. \square

Recall that a point $z \in \mathbb{R}_{\geq 0}\mathcal{S}$ is an equilibrium state if $\mathcal{F}(z) = 0$. This is equivalent to the condition that $C(z, t) = z$ for all $t \in \mathbb{R}_{\geq 0}$. We denote $\Omega(P)$ the set of equilibrium states in P . A point $z \in \mathbb{R}_{\geq 0}\mathcal{S}$ is an ω -limit point of a point $u \in \mathbb{R}_{\geq 0}\mathcal{S}$ provided there exists a sequence $(t_n)_{n \geq 0}$ in $\mathbb{R}_{\geq 0}$ such that $\lim_{n \rightarrow \infty} t_n = \infty$ and

$\lim_{n \rightarrow \infty} C(u, t_n) = z$. We denote $\omega(u)$ the set of ω -limit points of u . And for $U \subseteq \mathbb{R}_{\geq 0} \mathcal{S}$, we set $\omega(U) = \bigcup_{u \in U} \omega(u)$. Note that, while $\omega(u)$ is the ω -limit set of the point u , $\omega(U)$ is a (possibly proper) subset of the ω -limit set of the set U . Evidently, every equilibrium point is an ω -limit point (of itself):

$$\Omega(P) \subseteq \omega(P) \subseteq P.$$

It is possible to have $\Omega(P) = \omega(P)$. Sontag [18, Theorem 1] has proved that this holds when the network is weakly reversible and the number of complexes exceeds the rank by precisely one. Also, this is trivially the case if the class P contains a point which is a global attractor.

Proposition 4.5

- We have $\Omega(P) \subseteq \Phi(P)$; the support of any equilibrium state in P is reach-closed.
- If all trajectories in P are bounded, then $\omega(P) \subseteq \Phi(P)$; the support of any ω -limit point of any point of P is reach-closed.

The assertions in Proposition 4.5 have already been established through other means. The property that equilibrium states have reach-closed support is an earlier result of Feinberg [6, Proposition 5.3.1]. The fact that the ω -limit points of any $u \in P$ have reach-closed supports is proved by Angeli, De Leenheer and Sontag [4, Proposition 5.4], and also by Anderson [1, Theorem 2.5] for $u \in P_{>0}$. The first of the two assertions in Lemma 2.8 of this latter reference is the containment relationship $P_{\neq 0} \cap \Omega(P) \subseteq P_{\neq 0} \cap \Phi(P)$ for weakly reversible deficiency-zero networks.

Proof Let $z \in P$ and $t > 0$. By Proposition 4.3, we have $C(z, t) \in \Phi(P)$. If $z \in \Omega(P)$, then $C(z, t) = z$, and so $z \in \Phi(P)$. The inclusion $\Omega(P) \subseteq \Phi(P)$ is thus proved. For the inclusion $\omega(P) \subseteq \Phi(P)$, the key idea is that when trajectories in P are bounded, the ω -limit set $\omega(u)$ of any $u \in P$ is backward-invariant (in addition to being forward-invariant unconditionally). The details are as follows. Suppose that trajectories in P are bounded and let $u \in P$ and $z \in \omega(u)$. Let $t_0 > 0$. There exists a sequence $(t_n)_{n \geq 0}$ in $\mathbb{R}_{\geq 0}$ such that $t_n \geq t_0$ for all $n \geq 0$, $\lim_{n \rightarrow \infty} t_n = \infty$, and $\lim_{n \rightarrow \infty} C(u, t_n) = z$. We have in P the sequence $(C(u, t_n - t_0))_{n \geq 0}$. This sequence is bounded and P is a closed set, so there exists a sequence $(n_k)_{k \geq 0}$ in $\mathbb{Z}_{\geq 0}$ such that $\lim_{k \rightarrow \infty} n_k = \infty$ and $z^0 = \lim_{k \rightarrow \infty} C(u, t_{n_k} - t_0)$ exists in P . We then have

$$C(z^0, t_0) = \lim_{k \rightarrow \infty} C(C(u, t_{n_k} - t_0), t_0) = \lim_{k \rightarrow \infty} C(u, t_{n_k}) = z.$$

Then, by Proposition 4.3, $\text{Supp}(z)$ is reach-closed.

The condition that all trajectories in P be bounded is of course satisfied if the class P is bounded. The condition is also satisfied if the network is complex-balanced and the class P is nondegenerate. Siegel and MacLean [16, Lemma 3.5] have derived this from the fact that the canonical Lyapunov function decreases along trajectories.

5 Vacuous persistence

We now study persistence using the work of Vol’pert and its consequences discussed in Sect. 4. Some of the results we obtain have equivalent formulations in various references which we indicate in each case. For these, our contribution is to show how they derive from Vol’pert’s Theorem. The main result in this section is Theorem 5.5. It provides a necessary and sufficient condition for vacuous persistence, essentially the complete absence of boundary ω -limit points where the boundary is not all there is. A mass-action reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is fixed for this section.

Definition 5.1 The reaction network is *persistent* (resp. *vacuously persistent*) if we have $\omega(P_{>0}) \subseteq P_{>0}$ (resp. $\omega(P) \subseteq P_{>0}$) for every nondegenerate stoichiometric compatibility class P . \square

Persistence is studied in other areas of mathematics; see for example the discussion in Angeli, De Leenheer and Sontag [4, Section 1.2]. In a persistent reaction network, if all species are present at initial time, then no species approach extinction as time tends to infinity continuously or discretely. In a vacuously persistent reaction network, this asymptotic property holds even if not all species are present at initial time, as long as the stoichiometric compatibility class, by being nondegenerate, allows for the presence of all species. Ordinary persistence can occur with ‘opportunities for non-persistence’, whereby we mean boundary points that are ω -limit points, but only for trajectories confined to the boundary. The qualifier ‘vacuous’ is to indicate the absence of such opportunities. Vacuous persistence is relevant to biochemical experimental settings in which some species may not be initially present.

Persistence is not only important in and of itself, it also affects global asymptotic stability. For instance, it results from Siegel and MacLean [16, Theorem 3.2] that if a mass-action reaction network is persistent and complex-balancing, then each nondegenerate class P contains a unique equilibrium state which is complex-balanced and is an attractor of $P_{>0}$. Extending this fact, we note that with vacuous persistence instead, the equilibrium state is an attractor of P . Efforts to understand the persistence of complex-balanced networks with global asymptotic stability as the motivation include Siegel and Chen [15], Siegel and MacLean [16], Anderson [1], and Anderson and Shiu [2]. The work of Angeli, De Leenheer and Sontag [4] is on persistence as an inherently important property and on approaches to study it through Petri nets. The earlier work of Feinberg [6, Sections 5 and 6] discusses persistence and many of the related ideas in a direct fashion. In particular, Remark 6.1.E in this reference consolidates the topic and includes the conjecture that weakly reversible networks are persistent.

It is easy to see that vacuous persistence is equivalent to persistence together with the non-existence of trajectories entirely contained in the boundary of nondegenerate stoichiometric compatibility classes. Condition (iii) in Proposition 5.2 provides an even simpler characterization.

Proposition 5.2 (Sontag [19]) *Suppose that stoichiometric compatibility classes are bounded. Then the following are equivalent:*

- (i) *The reaction network is vacuously persistent.*

- (ii) *The reaction network is persistent and there are no trajectories on the boundary of nondegenerate stoichiometric compatibility classes.*
- (iii) *The reaction network is persistent and there are no equilibrium points on the boundary of nondegenerate stoichiometric compatibility classes.*

Proof We already noted the equivalence of conditions (i) and (ii). We trivially have (ii)⇒(iii). We obtain (iii)⇒(ii) by contraposition with Proposition 4.4. □

We now proceed through the steps leading to the main theorem of this section. Let P be a stoichiometric compatibility class.

Lemma 5.3 *The set $P_{\neq 0} \cap \Phi(P)$ of boundary points with reach-closed support is forward-invariant and $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{\neq 0}$.*

Proof Let $u \in P_{\neq 0} \cap \Phi(P)$ and $t \geq 0$. The support of u is reach-closed, so $\text{Supp}(C(u, t)) = \text{Supp}(u)$ by Vol’pert’s Theorem 4.1. Therefore, we have $C(u, t) \in P_{\neq 0} \cap \Phi(P)$. Hence, $P_{\neq 0} \cap \Phi(P)$ is forward-invariant. It then follows that $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{\neq 0}$ because the boundary $P_{\neq 0}$ is a closed set. □

Theorem 5.4 *Suppose that all the trajectories in the stoichiometric compatibility class P are bounded. Then the following conditions are equivalent:*

- (i) $\omega(P) \subseteq P_{>0}$; in P , all ω -limit points are positive.
- (ii) $\Phi(P) = P_{>0}$; in P , only the positive points have reach-closed support.
- (iii) Only the entire set \mathcal{S} of species is both reach-closed and P -admissible.
- (iv) We have $\text{Reach}(\mathcal{Z}) = \mathcal{S}$ for every P -admissible set $\mathcal{Z} \subseteq \mathcal{S}$.

The second of the two assertions in Anderson [1, Lemma 2.8] is the implication $(\Omega(P) \subseteq P_{>0}) \Rightarrow$ (iii) for weakly reversible deficiency-zero networks.

Proof Condition (iii) is just another formulation of condition (ii).

Proof that (i)⇒(ii). Assume $\omega(P) \subseteq P_{>0}$. Then in particular $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{>0}$. But by Lemma 5.3, $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{\neq 0}$. Therefore, $\omega(P_{\neq 0} \cap \Phi(P)) = \emptyset$. Trajectories in P have ω -limit points because they are bounded. So necessarily, $P_{\neq 0} \cap \Phi(P) = \emptyset$, i.e. $\Phi(P) \subseteq P_{>0}$. We noted in Eq. (4.2) that $P_{>0} \subseteq \Phi(P)$. So $\Phi(P) = P_{>0}$.

Proof that (iii)⇒(i). Assume that property (iii) holds. Let $u \in \omega(P)$. Then $\text{Supp}(u)$ is P -admissible, and by Proposition 4.5, is also reach-closed. Therefore, $\text{Supp}(u) = \mathcal{S}$, i.e. $u \in P_{>0}$.

Proof that (iii)⇒(iv). Assume (iii). Suppose that $\mathcal{Z} \subseteq \mathcal{S}$ is P -admissible. Then the set $\text{Reach}(\mathcal{Z})$ is P -admissible and reach-closed by Propositions 4.2 and 3.5 respectively. Therefore, $\text{Reach}(\mathcal{Z}) = \mathcal{S}$.

Proof that (iv)⇒(iii). Assume (iv). Suppose that \mathcal{Z} is both reach-closed and P -admissible. We have $\text{Reach}(\mathcal{Z}) = \mathcal{S}$ because \mathcal{Z} is P -admissible, and $\text{Reach}(\mathcal{Z}) = \mathcal{Z}$ because \mathcal{Z} is reach-closed. So $\mathcal{Z} = \mathcal{S}$. □

We now obtain the final and main result of this paper as an immediate corollary of Theorem 5.4.

Theorem 5.5 *Suppose that all trajectories are bounded. Then the following are equivalent:*

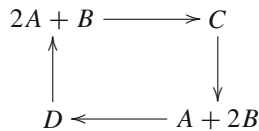
- *The reaction network is vacuously persistent.*
- *Among the subsets of the set \mathcal{S} of all species, only the full set \mathcal{S} is both reach-closed and stoichiometrically admissible.* \square

We note that the recent work of Peter and Dittrich [12] bears a resemblance with ours in terms of the concerns and the methods. In this paper, an ‘organization’ is a set of species that is ‘closed’ and ‘self-maintaining’, and the relation between organizations and ω -limit points is investigated.

We illustrate Theorem 5.5 with two small examples.

First, consider the reaction network with species X_1, X_2, X_3 and reactions $2X_1 \rightleftharpoons X_2, X_1 + X_2 \rightleftharpoons X_3$. (We already used this network in Sect. 2.4.) The eight nonempty subsets of species have full reach closure; it is enough to verify this for the three singleton subsets. So the seven nonempty nonfull subsets of species are not reach-closed. On another hand, the empty set is not stoichiometrically admissible because the nondegenerate stoichiometric compatibility classes, which are solid triangles in three-dimensional space, do not contain the origin. Hence, only the full set is both reach-closed and stoichiometrically admissible. By Theorem 5.5, the network is vacuously persistent.

Second, consider the following reaction network.



Let $\mathcal{L} = \{A\}$. The set \mathcal{L} is reach-closed because no reactions can occur if only A is present. It is also stoichiometrically admissible because, with $u = 8A$ and $v = A + B + C + D$, we have $\text{Supp}(u) = \mathcal{L}$, v has full support, and u and v are stoichiometrically compatible because

$$\begin{aligned}
 u - v &= (C - (2A + B)) + 2((A + 2B) - C) \\
 &\quad + 5(D - (A + 2B)) + 6((2A + B) - D).
 \end{aligned}$$

Hence the set \mathcal{L} is non-full, is reach-closed and is stoichiometrically admissible. By Theorem 5.5, this network is not vacuously persistent. However, it is shown in Angeli, De Leenheer and Sontag [3, Section 10] that it is persistent.

The larger the number of species, the more challenging it can be to directly apply Theorem 5.5 because of the exponentially growing number of subsets. In two sequel papers, we pursue additional mathematical investigations and arrive at two large classes of networks that are vacuously persistent and are actually used as models of biochemical interactions. The networks of Fig. 1a, b are instances of the classes of networks we study in Gnacadja [7,8] respectively.

6 Conclusion

We have provided a structural necessary and sufficient condition for a mass-action reaction network with bounded trajectories to have vacuous persistence, a strict form of persistence which takes into account nondegenerate trajectories that are not considered in ordinary persistence. The fact that there is a necessary and sufficient condition for vacuous persistence based on network structure alone could be viewed as an indication that this is the natural way to think about the persistence of reaction networks. We employed the work of Vol’pert which we hope will gain more awareness in the Chemical Reaction Network Theory community. This paper is the first in a series of three articles on persistence. The two sequel papers develop additional formalisms of independent interest: the second paper on species composition and the third paper on binary enzymatic networks. In each case, the new formalism is used to present a large class of biochemically valid networks that are vacuously persistent.

Acknowledgments This paper benefited from the comments the author received from Eduardo Sontag, Martin Feinberg, Anne Shiu and the anonymous reviewers.

7 Appendix: Proof of A. I. Vol’pert’s Theorem 4.1

This section is devoted to proving Vol’pert’s Theorem 4.1. We begin with a few preparatory steps. First, we note that if a trajectory originates at a nonnegative state, then it remains nonnegative. This is a well-known fact with several proofs in the literature, including the work of Vol’pert. Second, we record the following elementary fact of calculus for convenient subsequent reference.

Lemma 7.1 *Let $I \subseteq \mathbb{R}$ be an interval and let $\alpha : I \rightarrow \mathbb{R}$ and $\beta : I \rightarrow \mathbb{R}$ be continuous functions. Consider the C^1 -function $A : I \times I \rightarrow \mathbb{R}$ given by $A(t_0, t) = \int_{t_0}^t \alpha(\tau) d\tau$. A function $x : I \rightarrow \mathbb{R}$ satisfies $\dot{x}(t) = \alpha(t)x(t) + \beta(t)$ if and only if $x(t) = e^{A(t_0,t)}x(t_0) + \int_{t_0}^t e^{A(\tau,t)}\beta(\tau)d\tau$. □*

The third and final preparation step is to note certain alternate expressions of the species formation function. For any species $X \in \mathcal{S}$ and any reaction $R \in \mathcal{R}$, let $\sigma(R, X) = \langle X, \text{tgt}(R) - \text{src}(R) \rangle$. Then the species formation function \mathcal{F} of Eq. (2.1) is given by

$$\mathcal{F}_X(u) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R u^{\text{src}(R)}. \tag{7.1}$$

Let \mathcal{Z} be a siphon. For any reaction $R \in \mathcal{R}$ such that $\mathcal{Z} \cap (\text{src}(R) \cup \text{tgt}(R)) \neq \emptyset$, we in fact have $\mathcal{Z} \cap \text{src}(R) \neq \emptyset$. Consider then a selected species $\nu(R) \in \mathcal{Z} \cap \text{src}(R)$. Then there is a (unique) monomial function

μ_R on $\mathbb{R}^{\mathcal{S}}$ such that $u^{\text{src}(R)} = \mu_R(u) u_{v(R)}$. It follows that for $X \in \mathcal{L}$, Eq. (7.1) becomes

$$\mathcal{F}_X(u) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R \mu_R(u) u_{v(R)}. \tag{7.2}$$

On another hand, consider for any species $X \in \mathcal{S}$ the polynomial functions g_X and h_X on $\mathbb{R}^{\mathcal{S}}$ given by

$$\begin{aligned} g_X(u) u_X &= \sum_{R \in \mathcal{R}, \sigma(R, X) < 0} |\sigma(R, X)| k_R u^{\text{src}(R)}; \\ h_X(u) &= \sum_{R \in \mathcal{R}, \sigma(R, X) > 0} \sigma(R, X) k_R u^{\text{src}(R)}. \end{aligned}$$

They give rise to another relevant form of Eq. (7.1):

$$\mathcal{F}_X(u) = -g_X(u) u_X + h_X(u). \tag{7.3}$$

We are now ready for the announced proof.

Proof (Proof of A. I. Vol’pert’s Theorem 4.1) Recall from Proposition 3.3 that $\mathcal{L} := \text{NonReach}(c(0))$ is a siphon. Therefore, thanks to Eq. (7.2), we may consider the system of differential equations

$$\dot{v}_X(t) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R \mu_R(c(t)) v_{v(R)}(t) \tag{7.4}$$

for $v = (v_X)_{X \in \mathcal{S}} : \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}^{\mathcal{S}}$. We impose the initial condition $v(0) = 0$. Then the zero function is a solution. It results from Eq. (7.2) that the function $t \mapsto (c_X(t))_{X \in \mathcal{L}}$ is also a solution. Therefore c_X is identically zero for all $X \in \mathcal{L}$.

Now let X be any species and let $G_{X,c}(t_0, t) = \int_{t_0}^t g_X(c(\tau)) d\tau$. With Eq. (7.3) and

Lemma 7.1, we get

$$c_X(t) = e^{-G_{X,c}(0,t)} c_X(0) + \int_0^t e^{-G_{X,c}(\tau,t)} h_X(c(\tau)) d\tau.$$

We have $c(\tau) \geq 0$ for all $\tau \geq 0$, so $c_X(t) \geq e^{-G_{X,c}(0,t)} c_X(0)$ for all $t \geq 0$. Therefore, if $X \in \text{Supp}(c(0))$, then $c_X(t) > 0$ for all $t \geq 0$.

Let $r \in \mathbb{Z}_{\geq 1}$ and assume for induction that if X has reachability index $< r$, then $c_X(t) > 0$ for all $t > 0$. Suppose that X has reachability index r . Then there exists a reaction $R \in \mathcal{R}$ such that $X \in \text{tgt}(R)$ and all species in $\text{src}(R)$ have reachability index $< r$; in particular, $X \notin \text{src}(R)$. Because $X \notin \text{src}(R)$ and $X \in \text{tgt}(R)$,

we have $\sigma(R, X) > 0$. Plus, as noted earlier, we have $c(\tau) \geq 0$ for all $\tau \geq 0$. Therefore, $h_X(c(\tau)) \geq \sigma(R, X) k_R(c(\tau))^{\text{src}(R)}$ for all $\tau \geq 0$. Because all species in $\text{src}(R)$ have reachability index $< r$, the induction hypothesis implies that $(c(\tau))^{\text{src}(R)} > 0$ for all $\tau > 0$. Therefore, $h_X(c(\tau)) > 0$ for all $\tau > 0$. As a result, $c_X(t) > 0$ for all $t > 0$. \square

References

1. D.F. Anderson, Global asymptotic stability for a class of nonlinear chemical equations. *SIAM J. Appl. Math.* **68**(5), 1464–1476 (2008). doi:[10.1137/070698282](https://doi.org/10.1137/070698282)
2. D.F. Anderson, A. Shiu, The dynamics of weakly reversible population processes near facets. *SIAM J. Appl. Math.* **70**(6), 1840–1858 (2010). doi:[10.1137/090764098](https://doi.org/10.1137/090764098)
3. D. Angeli, P. De Leenheer, E.D. Sontag, A Petri net approach to persistence analysis in chemical reaction networks, in *Biology and Control Theory: Current Challenges*, ed. by I. Queinnec, S. Tarbouriech, G. Garcia, S.-I. Niculescu. Lecture Notes in Control and Information Sciences, vol. 357 (Springer, Berlin, 2007), pp. 181–216. doi:[10.1007/978-3-540-71988-5](https://doi.org/10.1007/978-3-540-71988-5)
4. D. Angeli, P. De Leenheer, E.D. Sontag, A Petri net approach to the study of persistence in chemical reaction networks. *Math. Biosci.* **210**(2), 598–618 (2007). doi:[10.1016/j.mbs.2007.07.003](https://doi.org/10.1016/j.mbs.2007.07.003)
5. M. Feinberg, Lectures on Chemical Reaction Networks (1980), <http://www.che.eng.ohio-state.edu/~Feinberg/LecturesOnReactionNetworks/>.
6. M. Feinberg, Chemical reaction network structure and the stability of complex isothermal reactors—I. The deficiency zero and deficiency one theorems. *Chem. Eng. Sci.* **42**(10), 2229–2268 (1987). doi:[10.1016/0009-2509\(87\)80099-4](https://doi.org/10.1016/0009-2509(87)80099-4)
7. G. Gnacadja, Reachability, persistence, and constructive chemical reaction networks (part II): a formalism for species composition in chemical reaction network theory and application to persistence. *J. Math. Chem.* (2011). doi:[10.1007/s10910-011-9896-2](https://doi.org/10.1007/s10910-011-9896-2)
8. G. Gnacadja, Reachability, persistence, and constructive chemical reaction networks (part III): a mathematical formalism for binary enzymatic networks and application to persistence. *J. Math. Chem.* (2011). doi:[10.1007/s10910-011-9895-3](https://doi.org/10.1007/s10910-011-9895-3)
9. J. Gunawardena, *Chemical Reaction Network Theory for In-Silico Biologists* (2003), <http://www.jeremy-gunawardena.com/papers/crnt.pdf>.
10. F. Horn, R. Jackson, General mass action kinetics. *Arch. Rat. Mech. Anal.* **47**(2), 81–116 (1972). doi:[10.1007/BF00251225](https://doi.org/10.1007/BF00251225)
11. T. Murata, Petri nets: properties, analysis and applications. *Proc. IEEE* **77**(4), 541–580 (1989). doi:[10.1109/5.24143](https://doi.org/10.1109/5.24143)
12. S. Peter, P. Dittrich, On the relation between organizations and limit sets in chemical reaction systems. *Adv. Complex Syst.* **14**(1), 77–96 (2011)
13. R.T. Rockafellar, *Convex Analysis*. Princeton Landmarks in Mathematics and Physics, (Princeton University Press, 1997), ISBN: 9780691015866
14. A. Shiu, B. Sturmfels, Siphons in chemical reaction networks. *Bull. Math. Biol.* **72**(6), 1448–1463 (2010). doi:[10.1007/s11538-010-9502-y](https://doi.org/10.1007/s11538-010-9502-y)
15. D. Siegel, Y.F. Chen, Global stability of deficiency zero chemical networks. *Can. Appl. Math. Q.* **2**(3), 413–434 (1994)
16. D. Siegel, D. MacLean, Global stability of complex balanced mechanisms. *J. Math. Chem.* **27**, 89–110 (2000). doi:[10.1023/A:1019183206064](https://doi.org/10.1023/A:1019183206064)
17. E.D. Sontag, *Mathematical Control Theory: Deterministic Finite Dimensional Systems*, 2nd ed., Textbooks in Applied Mathematics, vol. 6. (Springer, 1998) ISBN:0387984895
18. E.D. Sontag, Structure and stability of certain chemical networks and applications to the kinetic proofreading model of T-cell receptor signal transduction. *IEEE Trans. Autom. Control* **46**(7), 1028–1047 (2001). doi:[10.1109/9.935056](https://doi.org/10.1109/9.935056)
19. E.D. Sontag, Private communication, January 2010
20. V.M. Vasil'ev, A.I. Vol'pert, S.I. Khudyaev, A method of quasi-stationary concentrations for the equations of chemical kinetics. *USSR Comput. Math. Math. Phys.* **13**(3), 187–206 (1973). doi:[10.1016/0041-5553\(73\)90108-0](https://doi.org/10.1016/0041-5553(73)90108-0)

21. V.M. Vasil'ev, A.I. Vol'pert, S.I. Khudyaev, On the paper "The method of quasi-stationary concentrations for the equations of chemical kinetics". USSR Comput. Math. Math. Phys. **14**(1), 268 (1974). doi:[10.1016/0041-5553\(74\)90161-X](https://doi.org/10.1016/0041-5553(74)90161-X)
22. A.I. Vol'pert, Differential equations on graphs. Math. USSR-Sbornik **17**(4), 571–582 (1972). doi:[10.1070/SM1972v017n04ABEH001603](https://doi.org/10.1070/SM1972v017n04ABEH001603)
23. A.I. Vol'pert, S.I. Hudjaev, *Analysis in Classes of Discontinuous Functions and Equations of Mathematical Physics*. Mechanics: Analysis, vol. 8. (Springer, 1985) ISBN:9789024731091.