

30 1 Introduction

31 A trajectory $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}^n$ is persistent if it has no ω -limit points on the
32 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 com-
33 ponents $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0}$ does not approach zero as time tends to infinity contin-
34 uously or discretely. Many dynamical systems, including those that model
35 mass-action reaction networks, are positive: solution trajectories originating
36 in $\mathbb{R}_{\geq 0}^n$ range in $\mathbb{R}_{\geq 0}^n$. Such a system is persistent if all solution trajectories
37 originating in $\mathbb{R}_{> 0}^n$ are persistent. A reaction network is said to be persistent
38 if its dynamical system is persistent.

39

40 Persistence is inherently interesting because it is concerned with the possi-
41 bility of species extinction. Furthermore, for certain reaction networks,
42 persistence implies the global asymptotic stability of positive equilibrium
43 states; see e.g. Feinberg [6, Remark 6.1.E] and Siegel and MacLean [16,
44 Theorem 3.2]. Two results of Angeli, De Leenheer and Sontag [4] provide
45 insight into the persistence of conservative reaction networks with reasonable
46 kinetics. Theorem 1 in this reference says that if such a network is persis-
47 tent, then a fairly broad reversibility condition holds, namely the reaction
48 vectors are positively dependent, i.e. there exists a vanishing linear combi-
49 nation of the reaction vectors in which all coefficients are positive. Theorem
50 2 in the same reference says that such a network is persistent provided every
51 nonempty siphon contains the support of a nonzero nonnegative conserved
52 vector of species. Shiu and Sturmfels [14, Theorem 3.5] established an equi-
53 valent algebraic formulation of this sufficient condition.

54

55 One might want to ascertain the non-extinction (i.e. the persistence) of not
56 just the species that are initially present, but also of those that appear after
57 initial time. This would be the case for instance in a biochemical experimen-
58 tal setting in which only building blocks are initially present. We address
59 this concern here by studying vacuous persistence, a stronger form of persis-
60 tence that covers such circumstances. Vacuous persistence is the property
61 that trajectories are persistent provided all species are implicitly present at
62 the initial state, or in the terminology of this paper, provided the species
63 that are initially present form a stoichiometrically admissible set. In the
64 parlance of Chemical Reaction Network Theory, this (weaker) requirement
65 on the initial state is for it to be stoichiometrically compatible with a posi-
66 tive state. The “vacuous” attribute is to indicate that, in a sense made more
67 specific in the paper, vacuous persistence is persistence together with the
68 absence of opportunities for non-persistence. Our approach is largely based

69 on the concept of reachability and results on the nullity and positivity of
70 trajectory components developed by A. I. Vol’pert [22]. A set of species will
71 be said to be reach-closed if it already contains all the species that can be
72 produced from it. The following theorem is the main result of this paper.

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

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

79 Propositions 3.3 and 3.4 show that the use of siphons in Angeli, De Leenheer
80 and Sontag [4] and of reachability here are somewhat dual. The real value
81 of this theorem lies in that the approach it offers enables us to establish va-
82 cuous persistence for networks in two large classes relevant in biochemistry.
83 These are described in the sequel papers Gnacadja [7] and [8].

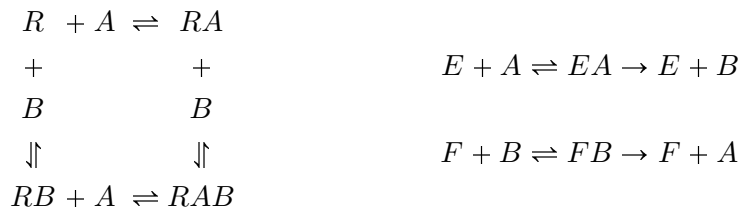
84
85 Following is the organization of the paper. We assemble basic notions of
86 Chemical Reaction Network Theory in Section 2; most are from common
87 literature but some are particular to our needs. We discuss reachability
88 in reaction networks in Section 3. Section 4 presents the Theorem of A.
89 I. Vol’pert on the positivity and nullity of species concentrations, as well
90 as certain immediate consequences. Finally, we introduce and characterize
91 vacuous persistence in Section 5. We prove Vol’pert’s theorem in Appendix
92 Section 7. The proof is a specialized form of the much more general work of
93 Vol’pert and should be informative to readers unfamiliar with this interesting
94 piece of mathematics.

95 2 Reaction Networks

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

99 2.1 Structure of Reaction Networks

100 A system of chemical reactions is usually presented as a diagram that shows
101 the interactions of chemical species; see for instance Figure 2.1. Following is
102 a rendition of the formal definition that enables mathematical investigations.



(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.

Figure 2.1: Examples of chemical reaction networks.

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

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

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

120
 121 Consistently with customary chemical notation, a reaction $R = (Q', Q'')$ is
 122 also denoted $Q' \rightarrow Q''$. The complexes $\text{src}(R) := Q'$ and $\text{tgt}(R) := Q''$ are
 123 respectively the *source* and the *target* of the reaction R , and we say that Q'
 124 *reacts to* Q'' . The vector $\text{tgt}(R) - \text{src}(R) \in \mathbb{Z}\mathcal{S}$ is the *reaction vector* of R .
 125 We set

$$126 \quad \underline{\text{src}}(R) := \text{Supp}(\text{src}(R)) \quad \text{and} \quad \underline{\text{tgt}}(R) := \text{Supp}(\text{tgt}(R)).$$

127 For illustration, the network of Figure 2.1(a) has six species: R , A , B , RA ,
 128 RB and RAB ; seven complexes: $R + A$, RA , $R + B$, RB , $RB + A$, $RA + B$
 129 and RAB ; and eight reactions. The network of Figure 2.1(b) has six species:
 130 E , F , A , B , EA and FB ; six complexes: $E + A$, EA , $E + B$, $F + B$, FB
 131 and $F + A$; and six reactions.

132

133 We augment Definition 2.1 with the following customary restrictions:

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

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

146

147 The network of Figure 2.1(a) is an example of a reversible network. Re-
 148 versibility and weak reversibility are the two well-established notions of re-
 149 versibility in Chemical Reaction Network Theory. However they do not
 150 reflect certain forms of biochemical reversibility, of which the futile enzy-
 151 matic cycle of Figure 2.1(b) is an example. In the sequel paper Gnacadja
 152 [7], we propose another notion of reversibility which applies to such contexts.

153 2.2 Stoichiometric Compatibility

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

156

157 Two elements $v, w \in \mathbb{R}_{\geq 0}^{\mathcal{S}}$ are said to be *stoichiometrically compatible* if
 158 $v - w \in S$. This defines an equivalence relation on $\mathbb{R}_{\geq 0}^{\mathcal{S}}$, the equivalence
 159 classes of which are the *stoichiometric compatibility classes*. The stochio-
 160 metric compatibility class of $u \in \mathbb{R}_{\geq 0}^{\mathcal{S}}$ is

$$161 \quad P = (u + S) \cap \mathbb{R}_{\geq 0}^{\mathcal{S}}.$$

162 We have

$$163 \quad P = P_{>0} \sqcup P_{\neq 0},$$

164 where

$$165 \quad P_{>0} = (u + S) \cap \mathbb{R}_{>0}\mathcal{S} \quad \text{and} \quad P_{\neq 0} = (u + S) \cap ((\mathbb{R}_{\geq 0}\mathcal{S}) \setminus (\mathbb{R}_{>0}\mathcal{S})).$$

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

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

177 Consider for illustration, the network of Figure 2.1(b). It has rank three;
 178 the three vectors $EA - E - A$, $FB - F - B$, $A - B$ form a basis of its stoi-
 179 chio-metric space. Each stoichiometric compatibility class is characterized
 180 by a triplet (T_E, T_F, T_{AB}) of nonnegative reals, in that the class consists
 181 of the 6-tuples $(u_E, u_F, u_A, u_B, u_{EA}, u_{FB})$ of nonnegative reals which satisfy
 182 the equations

$$183 \quad u_E + u_{EA} = T_E, \quad u_F + u_{FB} = T_F, \quad u_A + u_B + u_{EA} + u_{FB} = T_{AB}.$$

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

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

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

198 **2.3 Kinetics and Equilibria of Reaction Networks**

199 A kinetics on the reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is a family $K = (K_R)_{R \in \mathcal{R}}$
 200 in which for each $R \in \mathcal{R}$, K_R is a continuous function $\mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}$. Associated
 201 with a kinetics K is the species formation function
 202 $\mathcal{F}(K, -) = (\mathcal{F}_X(K, -))_{X \in \mathcal{S}} : \mathbb{R}^{\mathcal{S}} \rightarrow \mathbb{R}^{\mathcal{S}}$ given for $u = (u_X)_{X \in \mathcal{S}} \in \mathbb{R}^{\mathcal{S}}$ by

$$203 \quad \mathcal{F}(K, u) = \sum_{R \in \mathcal{R}} K_R(u) (\text{tgt}(R) - \text{src}(R)) ; \quad (2.1)$$

204 $\mathcal{F}(K, u)$ is the weighted sum of all reaction vectors, with the vector for a re-
 205 action $R \in \mathcal{R}$ weighted by $K_R(u)$, which is the rate of the reaction R when
 206 the vector of species concentrations is u .

207

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

$$210 \quad K_R(u) = k_R u^{\text{src}(R)} = k_R \prod_{X \in \mathcal{S}} u_X^{\langle \text{src}(R), X \rangle} ;$$

211 we write $\mathcal{F}(K, -) = \mathcal{F}(k, -)$. For example, the mass-action species formation
 212 function of the network of Figure 2.1(b) is given as follows.

$$\begin{aligned} 213 \quad \mathcal{F}_E(k, u) &= -k_{E+A \rightarrow EA} u_E u_A + (k_{EA \rightarrow E+A} + k_{EA \rightarrow E+B}) u_{EA} \\ 214 \quad \mathcal{F}_F(k, u) &= -k_{F+B \rightarrow FB} u_F u_B + (k_{FB \rightarrow F+B} + k_{FB \rightarrow F+A}) u_{FB} \\ 215 \quad \mathcal{F}_A(k, u) &= -k_{E+A \rightarrow EA} u_E u_A + k_{EA \rightarrow E+A} u_{EA} + k_{FB \rightarrow F+A} u_{FB} \\ 216 \quad \mathcal{F}_B(k, u) &= -k_{F+B \rightarrow FB} u_F u_B + k_{EA \rightarrow E+B} u_{EA} + k_{FB \rightarrow F+B} u_{FB} \\ 217 \quad \mathcal{F}_{EA}(k, u) &= -(k_{EA \rightarrow E+A} + k_{EA \rightarrow E+B}) u_{EA} + k_{E+A \rightarrow EA} u_E u_A \\ 218 \quad \mathcal{F}_{FB}(k, u) &= -(k_{FB \rightarrow F+A} + k_{FB \rightarrow F+B}) u_{FB} + k_{F+B \rightarrow FB} u_F u_B \end{aligned}$$

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

$$223 \quad \dot{c}(t) = \mathcal{F}(K, c(t)) . \quad (2.2)$$

224 The function $\mathcal{F}(K, -)$ ranges into the stoichiometric space S , so the solu-
 225 tions of equation (2.2) are confined to affine subspaces of $\mathbb{R}^{\mathcal{S}}$ parallel to S .
 226 Equivalently, if c is a solution and $v \in S^\perp$, then the function $t \mapsto \langle v, c(t) \rangle$ is
 227 conserved (i.e. constant) on $\mathbb{R}_{\geq 0}$. This explains why we call S^\perp the con-
 228 servation space in Definition 2.3. Under certain conditions on the kinetics

229 K , which are satisfied if K is a mass-action kinetics, every solution that
 230 originates at a nonnegative state remains nonnegative, and hence is in fact
 231 confined to a stoichiometric compatibility class.

232
 233 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 $Q \in \mathcal{C}$
 234 and $u \in \mathbb{R}^{\mathcal{S}}$ by

$$235 \quad \hat{\mathcal{F}}_Q(K, u) = \left(\sum_{R \in \mathcal{R}, \text{tgt}(R)=Q} K_R(u) \right) - \left(\sum_{R \in \mathcal{R}, \text{src}(R)=Q} K_R(u) \right).$$

236 Then we have $\mathcal{F}(K, u) = \sum_{Q \in \mathcal{C}} \hat{\mathcal{F}}_Q(K, u) Q$. An *equilibrium state* of the net-
 237 work \mathcal{N} for the kinetics K is any $u \in \mathbb{R}^{\mathcal{S}}$ such that $\mathcal{F}(K, u) = 0$. An equi-
 238 librium state $u \in \mathbb{R}^{\mathcal{S}}$ that satisfies the stronger condition $\hat{\mathcal{F}}(K, u) = 0$ is a
 239 *complex-balanced state*. The network is said to be *complex-balancing* if it
 240 admits a positive complex-balanced state. It is known that a mass-action
 241 complex-balancing network must be weakly reversible.

242

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

249 2.4 Pertinent Elements of Polyhedral Geometry

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

261

262 Let $P = (u + S) \cap \mathbb{R}_{\geq 0}\mathcal{S}$ be a stoichiometric compatibility class and let A
 263 be a face of P . We herein call *intrinsic interior* of A , and denote $\text{int}(A)$,
 264 the relative interior of A in the sense of polyhedral geometry. If A is a ver-
 265 tex, then $\text{int}(A) = A$. In particular, if $0 \in P$, then 0 is a vertex of P and
 266 $\text{int}(\{0\}) = \{0\}$; we set $\text{Supp}(\{0\}) = \emptyset$. Now suppose $A \neq \{0\}$. Then there
 267 is an (unique, nonempty) inclusion-minimal set $\mathcal{Z} \subseteq \mathcal{S}$ of species such that
 268 $A = (u + S) \cap \mathbb{R}_{\geq 0}\mathcal{Z}$. We have $\text{int}(A) = (u + S) \cap \mathbb{R}_{> 0}\mathcal{Z}$ and we define the
 269 *support of the face A* to be $\text{Supp}(A) = \mathcal{Z}$. So, whether or not A consists
 270 only of the vertex 0 , the intrinsic interior $\text{int}(A)$ consists of the points of P
 271 whose support is $\text{Supp}(A)$. The class P is the disjoint union of the intrinsic
 272 interiors of its faces, and the P -admissible sets (Definition 2.2) are precisely
 273 the subsets of \mathcal{S} that occur as supports of faces of P . We remark for the
 274 particular case $A = P$ that the intrinsic interior $\text{int}(P)$ and the interior $P_{> 0}$
 275 relative to $u + S$ coincide only if P is nondegenerate.

276

277 Consider for illustration a reaction network with three species, rank two, and
 278 bounded stoichiometric compatibility classes; e.g. the network with species
 279 X_1, X_2, X_3 and reactions $2X_1 \rightleftharpoons X_2, X_1 + X_2 \rightleftharpoons X_3$. Then a nondegenerate
 280 stoichiometric compatibility class is a solid triangle, and its faces are the
 281 class itself, its three edges and its three vertices. Such examples are easy
 282 to visualize. However they do not illustrate the pertinence of considering
 283 faces, which is that in general, an arbitrary set of species need not occur as
 284 the support of a face of a nondegenerate stoichiometric compatibility class,
 285 i.e. need not be stoichiometrically admissible (Definition 2.2). We already
 286 noted that nonempty sets that are not stoichiometrically admissible exist
 287 for the network of Figure 2.1(b). This is also the case for the network of
 288 Figure 2.1(a).

289 3 Reachability in Reaction Networks

290 In this section we discuss reachability as it pertains to reaction networks.
 291 Reachability is an important topic in the vast mathematical field of systems
 292 theory. Sontag [17] has a widely applicable definition of a system in Chap-
 293 ter 2 and an extensive discussion of reachability in Chapter 3. Basically,
 294 reachability is concerned with the feasibility of achieving a state of interest
 295 from another in a system through (finitely many or a finite-time continuum
 296 of) transitions. By default, the state of a reaction network is the vector of
 297 species concentrations. But to see our discussion of reachability in the larger
 298 context of systems theory, the relevant notion of state is the set of species
 299 that are present, i.e. the support of the concentrations vector. Petri nets

300 are then the relevant class of systems. There is abundant literature on Petri
 301 nets and a standard comprehensive reference is Murata [11].

302
 303 A reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ and a set $\mathcal{Z} \subseteq \mathcal{S}$ of species are fixed
 304 throughout this section. We begin by defining the following sets:

$$305 \quad \text{React}(\mathcal{Z}) := \{R \in \mathcal{R} : \text{src}(R) \subseteq \mathcal{Z}\};$$

$$306 \quad \text{Prod}(\mathcal{Z}) := \left[\bigcup_{R \in \text{React}(\mathcal{Z})} \text{tgt}(R) \right] \setminus \mathcal{Z}.$$

307
 308 The set $\text{React}(\mathcal{Z})$ consists of the reactions that would occur if only species
 309 from \mathcal{Z} were present. The set $\text{Prod}(\mathcal{Z})$ consists of the species that such
 310 reactions would produce and which are not already in \mathcal{Z} . Next we define
 311 the sets $\text{Reach}_r(\mathcal{Z})$ for $r \in \mathbb{Z}_{\geq 0}$ by induction as follows:

$$312 \quad \text{Reach}_0(\mathcal{Z}) := \mathcal{Z};$$

$$313 \quad \text{Reach}_r(\mathcal{Z}) := \text{Prod} \left(\bigcup_{\rho=0}^{r-1} \text{Reach}_\rho(\mathcal{Z}) \right), \text{ for } r \in \mathbb{Z}_{\geq 1}.$$

314
 315 The sets $\text{Reach}_r(\mathcal{Z})$ are obtained recursively by collecting the species we
 316 do not already have and can produce from those we already have, start-
 317 ing with \mathcal{Z} . They are pairwise disjoint. Also, if $\text{Reach}_{r_0}(\mathcal{Z}) = \emptyset$, then
 318 $\text{Reach}_r(\mathcal{Z}) = \emptyset$ for all $r \geq r_0$. And because \mathcal{S} is finite, there does exist
 319 $r_0 \geq 0$ such that $\text{Reach}_{r_0}(\mathcal{Z}) = \emptyset$. We pose:

$$320 \quad \text{Reach}(\mathcal{Z}) := \bigsqcup_{r=0}^{\infty} \text{Reach}_r(\mathcal{Z});$$

$$321 \quad \text{NonReach}(\mathcal{Z}) := \mathcal{S} \setminus \text{Reach}(\mathcal{Z}).$$

323 Definition 3.1.

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

330 The reach-closure $\text{Reach}(\mathcal{Z})$ consists of the species that are reachable from
 331 \mathcal{Z} , i.e. the species in \mathcal{Z} and the species that can be produced directly or
 332 indirectly with \mathcal{Z} . The set $\text{NonReach}(\mathcal{Z})$ consists of the species that are
 333 not in \mathcal{Z} and can not be produced with \mathcal{Z} , whether directly or indirectly.
 334 Note that the full set \mathcal{S} and the empty set are always reach-closed. Table
 335 3.1 illustrates reachability for the futile enzymatic cycle of Figure 2.1(b).

336

\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	$\{F, FB\}$	$\{E, F, EA, FB\}$

Table 3.1: Selected reachability concepts for the network of Figure 2.1(b). 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.

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

345 **Definition 3.2.** A set $\mathcal{W} \subseteq \mathcal{S}$ of species is a *siphon* provided
 346 $(R \in \mathcal{R} \text{ and } \mathcal{W} \cap \text{tgt}(R) \neq \emptyset) \Rightarrow (\mathcal{W} \cap \text{src}(R) \neq \emptyset)$. \square

347 This definition says that the set \mathcal{W} is a siphon if whenever a reaction R
 348 has elements of \mathcal{W} among the species it produces, it also has elements of
 349 \mathcal{W} among the species it consumes. The full set \mathcal{S} and the empty set are
 350 siphons. Siphons are sometimes required to be nonempty by definition.
 351 Here, when we need a siphon to be nonempty, we explicitly say so.

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

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

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

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

Proof.

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

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

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

370 Moreover, $\text{Reach}(\mathcal{Z})$ is the inclusion-minimal subset of \mathcal{S} that contains \mathcal{Z}
 371 and is reach-closed. In particular, if $\mathcal{Z}' \subseteq \text{Reach}(\mathcal{Z})$, then
 372 $\text{Reach}(\mathcal{Z}') \subseteq \text{Reach}(\mathcal{Z})$. This expresses a transitivity feature of reachabi-
 373 lity: For $X \in \mathcal{S}$ and $\mathcal{Z}' \subseteq \mathcal{S}$, if X is reachable from \mathcal{Z}' , and if all elements
 374 of \mathcal{Z}' are reachable from \mathcal{Z} , then X is reachable from \mathcal{Z} .

375

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

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

380 **4 The Theorem of A. I. Vol’pert on the Positivity and Nullity of**
 381 **Species Concentrations**

382 A. I. Vol’pert [22] has studied the question of when the solutions of certain
 383 dynamical systems have components that remain zero while the other com-
 384 ponents become and remain positive. The theory is developed for differential
 385 equations on graphs, of which mass-action kinetics dynamical systems are
 386 instances. The work is revisited in Vasil’ev, Vol’pert and Khudyaev [20]
 387 (with an erratum in [21]). The more recent book of Vol’pert and Hudjaev
 388 [23] covers the topic in Chapter 12. In this section, we present this work
 389 in a form specialized to chemical reaction networks and with a view toward
 390 showing in Section 5 how it contributes to results on persistence.

391 Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. Suppose \mathcal{N} is governed by
 392 mass-action kinetics and let $k = (k_R)_{R \in \mathcal{R}}$ be the family of reaction rate
 393 constants. We set $F = F(k, -)$ for the species formation function. ASSO-
 394 CIATED WITH THE DYNAMICAL SYSTEM $\dot{c}(t) = F(c(t))$ IS THE EVOLUTION SEMIGROUP
 395 $C : \mathbb{R}_{\geq 0} \mathcal{S} \times \mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0} \mathcal{S}$. Thus, C is continuous; for every $u \in \mathbb{R}_{\geq 0} \mathcal{S}$, the
 396 MAP $\mathbb{R}_{\geq 0} \rightarrow \mathbb{R}_{\geq 0} \mathcal{S}$, $t \mapsto C(u, t)$ IS THE CONCENTRATION TRAJECTORY ORIGINATING AT
 397 u ; AND FOR ALL $u \in \mathbb{R}_{\geq 0} \mathcal{S}$ AND $t, t' \in \mathbb{R}_{\geq 0}$, WE HAVE $C(u, t + t') = C(C(u, t), t')$.

399 **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 con-*
 400 *centration trajectory with $c(0) \in \mathbb{R}_{\geq 0} \mathcal{S}$. Let $X \in \mathcal{S}$ be a species.*

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

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

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

$$408 \quad c_X^{(\rho)}(0) = 0 \text{ for } \rho = 0, \dots, r-1 \quad \text{and} \quad c_X^{(r)}(0) > 0.$$

$$409 \quad c_X(t) = \frac{1}{r!} c_X^{(r)}(0) t^r + O(t^{r+1}) \text{ as } t \rightarrow 0, t > 0.$$

410 Thus, if two species X' and X'' have reachability index r' and r'' with
 411 $r' < r''$, then there exists $t_0 > 0$ such that $0 < c_{X''}(t) < c_{X'}(t)$ if $0 < t < t_0$.
 412 This says that the higher the reachability index, the slower a species starts

413 to appear.

414

415 We present a proof of Theorem 4.1 in Appendix Section 7. We focus here
416 on its implications. A stoichiometric compatibility class P is fixed for the
417 rest of this section.

418

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

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

423 The converse of Proposition 4.2 is not true: there may be sets that are not
424 P -admissible and are reach-closed. For example, for the network of Figure
425 2.1(b), we saw that the set $\{A, B\}$ is not stoichiometrically admissible (Sec-
426 tion 2.2) but is reach-closed (Table 3.1).

427

428 We define

$$429 \quad \Phi(P) := \{u \in P : \text{Supp}(u) \text{ is reach-closed}\}. \quad (4.1)$$

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

$$431 \quad P_{>0} \subseteq \Phi(P) \subseteq P. \quad (4.2)$$

432 The combination of Theorem 4.1 and Proposition 3.5 readily gives:

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

436 Vol'pert's Theorem also leads to certain properties of the faces of stoichio-
437 metric compatibility classes.

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

439 (i) *The intrinsic interior $\text{int}(A)$ of A contains a trajectory.*

440 (ii) *The support $\text{Supp}(A)$ of A is reach-closed.*

441 (iii) *The intrinsic interior $\text{int}(A)$ of A is forward-invariant.*

442 (iv) *The face A is forward-invariant.*

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

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

449 *Proof.* If a trajectory c ranges in $\text{int}(A)$, then all the points along c have
 450 $\text{Supp}(A)$ as their support. So we get the implication (i) \Rightarrow (ii) from Propo-
 451 sition 4.3. We have (ii) \Rightarrow (iii) by Theorem 4.1. The implication (iii) \Rightarrow (i)
 452 is trivial. We have (iii) \Rightarrow (iv) by the continuity of the evolution semi-group
 453 C and because A is the topological closure of $\text{int}(A)$. We have (iv) \Rightarrow (iii)
 454 because Theorem 4.1 shows that the support along a trajectory cannot get
 455 inclusion-smaller. Now suppose that A is forward-invariant and bounded.
 456 Then A is convex, compact and forward-invariant. As a result, A contains
 457 an equilibrium state. \square

458 Recall that a point $z \in \mathbb{R}_{\geq 0}\mathcal{S}$ is an equilibrium state if $F(z) = 0$. This is
 459 equivalent to the condition that $C(z, t) = z$ for all $t \in \mathbb{R}_{\geq 0}$. We denote $\Omega(P)$
 460 the set of equilibrium states in P . A point $z \in \mathbb{R}_{\geq 0}\mathcal{S}$ is an ω -limit point
 461 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
 462 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
 463 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
 464 $\omega(u)$ is the ω -limit set of the point u , $\omega(U)$ is a (possibly proper) subset of
 465 the ω -limit set of the set U . Evidently, every equilibrium point is an ω -limit
 466 point (of itself):

$$467 \quad \Omega(P) \subseteq \omega(P) \subseteq P.$$

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

472 **Proposition 4.5.**

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

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

485 *Proof.* Let $z \in P$ and $t > 0$. By Proposition 4.3, we have $C(z, t) \in \Phi(P)$. If
 486 $z \in \Omega(P)$, then $C(z, t) = z$, and so $z \in \Phi(P)$. The inclusion $\Omega(P) \subseteq \Phi(P)$
 487 is thus proved. For the inclusion $\omega(P) \subseteq \Phi(P)$, the key idea is that when
 488 trajectories in P are bounded, the ω -limit set $\omega(u)$ of any $u \in P$ is backward-
 489 invariant (in addition to being forward-invariant unconditionally). The de-
 490 tails are as follows. Suppose that trajectories in P are bounded and let
 491 $u \in P$ and $z \in \omega(u)$. Let $t_0 > 0$. There exists a sequence $(t_n)_{n \geq 0}$ in $\mathbb{R}_{\geq 0}$
 492 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
 493 in P the sequence $(C(u, t_n - t_0))_{n \geq 0}$. This sequence is bounded and P is a
 494 closed set, so there exists a sequence $(n_k)_{k \geq 0}$ in $\mathbb{Z}_{\geq 0}$ such that $\lim_{k \rightarrow \infty} n_k = \infty$
 495 and $z^0 = \lim_{k \rightarrow \infty} C(u, t_{n_k} - t_0)$ exists in P . We then have

$$496 \quad C(z^0, t_0) = \lim_{k \rightarrow \infty} C(C(u, t_{n_k} - t_0), t_0) = \lim_{k \rightarrow \infty} C(u, t_{n_k}) = z.$$

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

498 The condition that all trajectories in P be bounded is of course satisfied
 499 if the class P is bounded. The condition is also satisfied if the network is
 500 complex-balanced and the class P is nondegenerate. Siegel and MacLean
 501 [16, Lemma 3.5] have derived this from the fact that the canonical Lyapunov
 502 function decreases along trajectories.

503 5 Vacuous Persistence

504 We now study persistence using the work of Vol'pert and its consequences
 505 discussed in Section 4. Some of the results we obtain have equivalent for-
 506 mulations in various references which we indicate in each case. For these,
 507 our contribution is to show how they derive from Vol'pert's Theorem. The
 508 main result in this section is Theorem 5.5. It provides a necessary and suffi-
 509 cient condition for vacuous persistence, essentially the complete absence of

510 boundary ω -limit points where the boundary is not all there is. A mass-
511 action reaction network $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is fixed for this section.

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

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

528
529 Persistence is not only important in and of itself, it also affects global asymp-
530 totic stability. For instance, it results from Siegel and MacLean [16, Theo-
531 rem 3.2] that if a mass-action reaction network is persistent and complex-
532 balancing, then each nondegenerate class P contains a unique equilibrium
533 state which is complex-balanced and is an attractor of $P_{>0}$. Extending this
534 fact, we note that with vacuous persistence instead, the equilibrium state is
535 an attractor of P . Efforts to understand the persistence of complex-balanced
536 networks with global asymptotic stability as the motivation include Siegel
537 and Chen [15], Siegel and MacLean [16], Anderson [1], and Anderson and
538 Shiu [2]. The work of Angeli, De Leenheer and Sontag [4] is on persistence
539 as an inherently important property and on approaches to study it through
540 Petri nets. The earlier work of Feinberg [6, Sections 5 and 6] discusses per-
541 sistence and many of the related ideas in a direct fashion. In particular,
542 Remark 6.1.E in this reference consolidates the topic and includes the con-
543 jecture that weakly reversible networks are persistent.

544
545 It is easy to see that vacuous persistence is equivalent to persistence together
546 with the non-existence of trajectories entirely contained in the boundary of
547 nondegenerate stoichiometric compatibility classes. Condition (iii) in Pro-
548 position 5.2 provides an even simpler characterization.

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

- 551 (i) *The reaction network is vacuously persistent.*
 552 (ii) *The reaction network is persistent and there are no trajectories on the*
 553 *boundary of nondegenerate stoichiometric compatibility classes.*
 554 (iii) *The reaction network is persistent and there are no equilibrium points*
 555 *on the boundary of nondegenerate stoichiometric compatibility classes.*

556 *Proof.* We already noted the equivalence of conditions (i) and (ii). We triv-
 557 ially have (ii) \Rightarrow (iii). We obtain (iii) \Rightarrow (ii) by contraposition with Proposition
 558 4.4. \square

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

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

563 *Proof.* Let $u \in P_{\neq 0} \cap \Phi(P)$ and $t \geq 0$. The support of u is reach-closed, so
 564 $\text{Supp}(C(u, t)) = \text{Supp}(u)$ by Vol’pert’s Theorem 4.1. Therefore, we have
 565 $C(u, t) \in P_{\neq 0} \cap \Phi(P)$. Hence, $P_{\neq 0} \cap \Phi(P)$ is forward-invariant. It then fol-
 566 lows that $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{\neq 0}$ because the boundary $P_{\neq 0}$ is a closed set. \square

567 **Theorem 5.4.** *Suppose that all the trajectories in the stoichiometric com-*
 568 *patibility class P are bounded. Then the following conditions are equivalent:*

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

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

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

576 Proof that (i) \Rightarrow (ii). Assume $\omega(P) \subseteq P_{>0}$. Then in particular
 577 $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{>0}$. But by Lemma 5.3, $\omega(P_{\neq 0} \cap \Phi(P)) \subseteq P_{\neq 0}$. There-
 578 fore, $\omega(P_{\neq 0} \cap \Phi(P)) = \emptyset$. Trajectories in P have ω -limit points because

579 they are bounded. So necessarily, $P_{\neq 0} \cap \Phi(P) = \emptyset$, i.e. $\Phi(P) \subseteq P_{>0}$. We
 580 noted in Equation (4.2) that $P_{>0} \subseteq \Phi(P)$. So $\Phi(P) = P_{>0}$.

581 Proof that (iii) \Rightarrow (i). Assume that property (iii) holds. Let $u \in \omega(P)$. Then
 582 $\text{Supp}(u)$ is P -admissible, and by Proposition 4.5, is also reach-closed. There-
 583 fore, $\text{Supp}(u) = \mathcal{S}$, i.e. $u \in P_{>0}$.

584 Proof that (iii) \Rightarrow (iv). Assume (iii). Suppose that $\mathcal{Z} \subseteq \mathcal{S}$ is P -admissible.
 585 Then the set $\text{Reach}(\mathcal{Z})$ is P -admissible and reach-closed by Propositions
 586 4.2 and 3.5 respectively. Therefore, $\text{Reach}(\mathcal{Z}) = \mathcal{S}$.

587 Proof that (iv) \Rightarrow (iii). Assume (iv). Suppose that \mathcal{Z} is both reach-closed
 588 and P -admissible. We have $\text{Reach}(\mathcal{Z}) = \mathcal{S}$ because \mathcal{Z} is P -admissible, and
 589 $\text{Reach}(\mathcal{Z}) = \mathcal{Z}$ because \mathcal{Z} is reach-closed. So $\mathcal{Z} = \mathcal{S}$. \square

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

592 **Theorem 5.5.** *Suppose that all trajectories are bounded. Then the follow-*
 593 *ing are equivalent:*

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

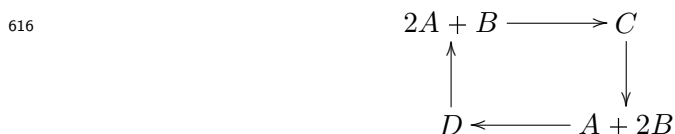
597 We note that the recent work of Peter and Dittrich [12] bears a resemblance
 598 with ours in terms of the concerns and the methods. In this paper, an ‘or-
 599 ganization’ is a set of species that is ‘closed’ and ‘self-maintaining’, and the
 600 relation between organizations and ω -limit points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

601
 602 We illustrate Theorem 5.5 with two small examples.

603
 604 First, consider the reaction network with species X_1, X_2, X_3 and reactions
 605 $2X_1 \rightleftharpoons X_2, X_1 + X_2 \rightleftharpoons X_3$. (We already used this network in Section 2.4.)
 606 The eight nonempty subsets of species have full reach closure; it is enough
 607 to verify this for the three singleton subsets. So the seven nonempty nonfull
 608 subsets of species are not reach-closed. On another hand, the empty set is
 609 not stoichiometrically admissible because the nondegenerate stoichiometric
 610 compatibility classes, which are solid triangles in three-dimensional space,
 611 do not contain the origin. Hence, only the full set is both reach-closed and
 612 stoichiometrically admissible. By Theorem 5.5, the network is vacuously
 613 persistent.

614

615 Second, consider the following reaction network.



617 Let $\mathcal{Z} = \{A\}$. The set \mathcal{Z} is reach-closed because no reactions can occur
 618 if only A is present. It is also stoichiometrically admissible because, with
 619 $u = 8A$ and $v = A + B + C + D$, we have $\text{Supp}(u) = \mathcal{Z}$, v has full support,
 620 and u and v are stoichiometrically compatible because

621

$$\begin{aligned}
 622 \quad u - v &= (C - (2A + B)) + 2((A + 2B) - C) \\
 623 &\quad + 5(D - (A + 2B)) + 6((2A + B) - D). \\
 624
 \end{aligned}$$

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

628
 629 The larger the number of species, the more challenging it can be to directly
 630 apply Theorem 5.5 because of the exponentially growing number of subsets.
 631 In two sequel papers, we pursue additional mathematical investigations and
 632 arrive at two large classes of networks that are vacuously persistent and
 633 are actually used as models of biochemical interactions. The networks of
 634 Figures 2.1(a) and 2.1(b) are instances of the classes of networks we study
 635 in Gnacadja [7] and [8] respectively.

636 6 Conclusion

637 We have provided a structural necessary and sufficient condition for a mass-
 638 action reaction network with bounded trajectories to have vacuous persis-
 639 tence, a strict form of persistence which takes into account nondegenerate
 640 trajectories that are not considered in ordinary persistence. The fact that
 641 there is a necessary and sufficient condition for vacuous persistence based
 642 on network structure alone could be viewed as an indication that this is
 643 the natural way to think about the persistence of reaction networks. We
 644 employed the work of Vol'pert which we hope will gain more awareness in
 645 the Chemical Reaction Network Theory community. This paper is the first
 646 in a series of three articles on persistence. The two sequel papers develop
 647 additional formalisms of independent interest: the second paper on species
 648 composition and the third paper on binary enzymatic networks. In each

649 case, the new formalism is used to present a large class of biochemically
650 valid networks that are vacuously persistent.

651 7 Appendix: Proof of A. I. Vol’pert’s Theorem 4.1

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

658 **Lemma 7.1.** *Let $I \subseteq \mathbb{R}$ be an interval and let $\alpha : I \rightarrow \mathbb{R}$ and $\beta : I \rightarrow \mathbb{R}$
659 be continuous functions. Consider the C^1 -function $A : I \times I \rightarrow \mathbb{R}$ given by
660 $A(t_0, t) = \int_{t_0}^t \alpha(\tau) d\tau$. A function $x : I \rightarrow \mathbb{R}$ satisfies $\dot{x}(t) = \alpha(t)x(t) + \beta(t)$
661 if and only if $x(t) = e^{A(t_0, t)}x(t_0) + \int_{t_0}^t e^{A(\tau, t)}\beta(\tau)d\tau$. \square*

662 The third and final preparation step is to note certain alternate expressions
663 of the species formation function. For any species $X \in \mathcal{S}$ and any reaction
664 $R \in \mathcal{R}$, let $\sigma(R, X) = \langle X, \text{tgt}(R) - \text{src}(R) \rangle$. Then the species formation
665 function \mathcal{F} of Equation (2.1) is given by

$$666 \quad \mathcal{F}_X(u) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R u^{\text{src}(R)}. \quad (7.1)$$

667 Let \mathcal{Z} be a siphon. For any reaction $R \in \mathcal{R}$ such that
668 $\mathcal{Z} \cap (\text{src}(R) \cup \text{tgt}(R)) \neq \emptyset$, we in fact have $\mathcal{Z} \cap \text{src}(R) \neq \emptyset$. Consider
669 then a selected species $\nu(R) \in \mathcal{Z} \cap \text{src}(R)$. Then there is a (unique) mono-
670 mial function μ_R on $\mathbb{R}^{\mathcal{S}}$ such that $u^{\text{src}(R)} = \mu_R(u) u_{\nu(R)}$. It follows that for
671 $X \in \mathcal{Z}$, Equation (7.1) becomes

$$672 \quad \mathcal{F}_X(u) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R \mu_R(u) u_{\nu(R)}. \quad (7.2)$$

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

$$675 \quad g_X(u) u_X = \sum_{R \in \mathcal{R}, \sigma(R, X) < 0} |\sigma(R, X)| k_R u^{\text{src}(R)} ;$$

$$676 \quad h_X(u) = \sum_{R \in \mathcal{R}, \sigma(R, X) > 0} \sigma(R, X) k_R u^{\text{src}(R)} .$$

677

678 They give rise to another relevant form of Equation (7.1):

$$679 \quad \mathcal{F}_X(u) = -g_X(u) u_X + h_X(u). \quad (7.3)$$

680 We are now ready for the announced proof.

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

$$684 \quad \dot{v}_X(t) = \sum_{R \in \mathcal{R}, \text{src}(R) \cup \text{tgt}(R) \ni X} \sigma(R, X) k_R \mu_R(c(t)) v_{\nu(R)}(t) \quad (7.4)$$

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

689

690 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 Equa-
691 tion (7.3) and Lemma 7.1, we get

$$692 \quad c_X(t) = e^{-G_{X,c}(0,t)} c_X(0) + \int_0^t e^{-G_{X,c}(\tau,t)} h_X(c(\tau)) d\tau.$$

693 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 $t \geq 0$.
694 Therefore, if $X \in \text{Supp}(c(0))$, then $c_X(t) > 0$ for all $t \geq 0$.

695

696 Let $r \in \mathbb{Z}_{\geq 1}$ and assume for induction that if X has reachability index $< r$,
697 then $c_X(t) > 0$ for all $t > 0$. Suppose that X has reachability index r .
698 Then there exists a reaction $R \in \mathcal{R}$ such that $X \in \text{tgt}(R)$ and all species
699 in $\text{src}(R)$ have reachability index $< r$; in particular, $X \notin \text{src}(R)$. Because
700 $X \notin \text{src}(R)$ and $X \in \text{tgt}(R)$, we have $\sigma(R, X) > 0$. Plus, as noted earlier, we
701 have $c(\tau) \geq 0$ for all $\tau \geq 0$. Therefore, $h_X(c(\tau)) \geq \sigma(R, X) k_R (c(\tau))^{\text{src}(R)}$
702 for all $\tau \geq 0$. Because all species in $\text{src}(R)$ have reachability index $< r$, the
703 induction hypothesis implies that $(c(\tau))^{\text{src}(R)} > 0$ for all $\tau > 0$. Therefore,
704 $h_X(c(\tau)) > 0$ for all $\tau > 0$. As a result, $c_X(t) > 0$ for all $t > 0$. \square

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