

# Reachability, persistence, and constructive chemical reaction networks (part II): a formalism for species composition in chemical reaction network theory and application to persistence

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**Abstract** Chemical Reaction Network Theory uses mathematics to study systems of reactions and infer their properties from their structure. At the onset is an abstract definition of a chemical reaction network which is very general and is pertinent beyond chemistry, e.g. in modeling interactions of microscopic and macroscopic living species. This allows the theory to provide widely applicable theorems. It also results in that the idea of chemical composition is mostly used implicitly in examples to illustrate theorems, not explicitly to establish new properties. In this paper we propose a formalism for species composition in a way that generalizes the idea of atomic composition—for instance, elementary species will extend the idea of atoms. We envision that this formalism could lead to more theorems on classes of networks that are of interest in biochemistry. Toward that prospect, we prove that if there is no isomerism among elementary species, and if a newly formalized and widely applicable reversibility condition holds, then a reaction network is vacuously persistent: no species will tend to extinction if all species are implicitly present at initial time. This paper is the second in a series of three articles. The first paper studies vacuous persistence and the third one probes a class of enzymatic networks.

**Keywords** Chemical reaction network · Species composition · Constructive network · Vacuous persistence · Reachability

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## 1 Introduction

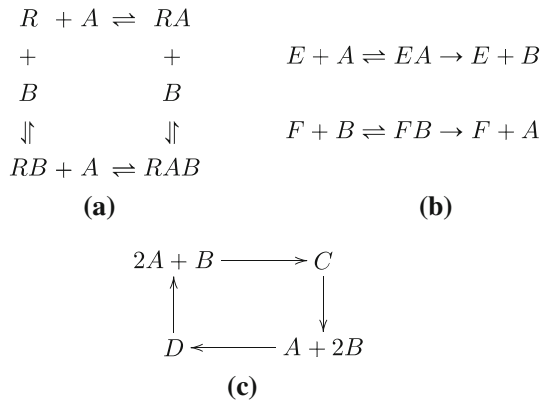
This paper is the second in a series of three articles on the persistence of chemical reaction networks. A reaction network is persistent provided no species tend to extinction if all species are present at initial time. Persistence is inherently interesting and has implications for the global asymptotic stability of positive equilibrium states. In Gnacadja [4], the first article in this series, we introduce and characterize vacuous persistence, a stronger form of persistence in which the initial state is merely required to implicitly have all species. A major motivation for this three-part work was the intuition that persistence should apply to chemical reaction networks in which species are made of building blocks that are conserved and processes are fundamentally reversible. Proving this requires specific and relevant definitions of notions of building blocks, of fundamentally reversible processes, etc. This paper addresses these prerequisites.

We develop a theory of species composition inspired by the idea of atomic composition of molecules—for instance, our concept of elementary species extends that of atoms. In this extension, two elementary species may be distinct and yet have identical composition. We obtain several results. A notable one is Theorem 3.6 on canonical bases for the stoichiometric space and its orthogonal, the conservation space. The basis of the conservation space consists of vectors that are linear combinations of species with nonnegative integer coefficients. This basis describes in a comprehensive and minimal fashion the conservativeness of the network. In the literature, this basis is usually found by visual inspection of networks used to illustrate theorems. That it is a basis of the conservation space is typically a tacit property.

We believe that incorporating the idea of species composition in theoretical investigations could yield more results on classes of networks that model actual biochemical interactions. Instances of such approaches include our work in Gnacadja [3] on the existence, uniqueness and global asymptotic stability of equilibria in networks of reversible binding reactions, and the work of Shinar, Alon and Feinberg [6] on the sensitivity of equilibrium concentrations with respect to total concentrations of elementary species. In this paper, we obtain a sufficient condition for vacuous persistence as follows.

**Theorem 1.1** (Theorem 6.9) *Suppose that a mass-action reaction network is explicitly-reversibly constructive. If there is no isomerism among the elementary species, then the network is vacuously persistent.*

Isomeric species are species that have the same composition. Basically, a network is constructive if species have compositions which are consistent across reactions and can be inferred completely from them, and all required elementary species are actually in the network, possibly with isomerism among them. A network is explicitly-reversibly constructive if in addition, every non-elementary species occurs as the target of a binding reaction and also as the source of a dissociation reaction, and every elementary species occurs in the source of a binding reaction and also in the target of a dissociation reaction. Explicitly-reversibly constructive networks are frequent in pharmacology and biochemistry, e.g. in models of receptor-ligand interactions and enzyme-catalyzed conversions.



**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. (c) This network does not model a biochemical interaction we know of, but it serves as an illustrative example in a number of instances

We have observed that instances of non-persistence and of non-obvious persistence in the literature always involve networks with isomerism among the building blocks. Theorem 1.1 shows that this is not accidental. However, the absence of isomerism among the elementary species is not an absolute requirement for vacuous persistence. Such isomerism occurs among substrates and products in enzymatic networks and yet, they can be vacuously persistent. We show this in Gnacadja [5], the third and final paper in this series of articles.

The remaining content of the paper covers five sections. In Sect. 2, we define and study species compositions, constructive networks and several connected concepts. In Sect. 3, we describe canonical bases for the stoichiometric space and its orthogonal, the conservation space. Section 4 presents results on how to prove that a reaction network is constructive. Section 5 describes the stoichiometry compatibility classes of constructive networks. Finally, in Sect. 6, we discuss topics related to the reachability approach to persistence [4] in the context of construction networks. This culminates with Theorem 6.9 already noted in this introduction as Theorem 1.1.

## 2 Species composition and constructive networks

We propose and develop a formal notion of species composition to account for the idea that species are composed of elementary units or building blocks. As this article is the second in a series of three, we rely on Section 3 of Gnacadja [4], the first article, for general background material on reaction networks. Figure 1 shows examples of reaction networks.

To begin, we set some notations to be used throughout the paper.

**Notation 2.1** For  $m, n \in \mathbb{Z}$ ,  $[m..n] = \{k \in \mathbb{Z} : m \leq k \leq n\}$ . For  $n \in \mathbb{Z}_{\geq 1}$ ,  $0_n$  denotes the  $n$ -tuples whose components all equal 0, and for  $i \in [1..n]$ ,  $e_{n,i}$  denotes the  $n$ -tuple

having 1 in position  $i$  and 0 in the other  $n - 1$  positions. For  $x = (x_1, \dots, x_n) \in \mathbb{R}^n$ , the length of  $x$  is  $|x| = |x_1| + \dots + |x_n| = \|x\|_{\ell^1}$ . For  $x, y \in \mathbb{R}^n$ , we write  $x \leq y$  or  $y \geq x$  (resp.  $x < y$  or  $y > x$ ) to mean that  $x_i \leq y_i$  (resp.  $x_i < y_i$ ) for all  $i \in [1..n]$ . For a finite set  $E$ , we denote  $|E|$  the cardinality of  $E$ ; and when addition makes sense, we write  $\text{sum}(E)$  for the sum of its elements.

A reaction network  $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$  is fixed throughout this section and  $S$  denotes its stoichiometric space.

### Definition 2.2

- A *binding* or *association reaction* is a reaction  $Q' \rightarrow Q''$  such that  $|Q'| \geq 2$  and  $|Q''| = 1$ . ( $Q''$  is a species,  $Q'$  is not.)
- An *unbinding* or *dissociation reaction* is a reaction  $Q' \rightarrow Q''$  such that  $|Q'| = 1$  and  $|Q''| \geq 2$ . ( $Q'$  is a species,  $Q''$  is not.)
- An *isomerization reaction* is a reaction  $Q' \rightarrow Q''$  such that  $|Q'| = |Q''| = 1$ . (Both  $Q'$  and  $Q''$  are species.)
- Two species  $X'$  and  $X''$  are *stoichiometrically isomeric* if  $X' - X'' \in S$ .
- A *bound species* is a species that is the target of a binding reaction or the source of a dissociation reaction (or both).

The notion of stoichiometric isomerism is intended to account for combinations of reactions whose net effect is to transform one species into another, as is the case for instance in enzymatic reactions. Stoichiometric isomerism gives rise to an equivalence relation on the set  $\mathcal{S}$  of species.

For illustration of Definition 2.2, the network of Fig. 1a consists of four reversible binding reactions (four pairs each consisting of a binding reaction and the reverse dissociation reaction). The bound species are  $RA$ ,  $RB$  and  $RAB$  (not because they are denoted with expressions of more than one letter). The network of Fig. 1b consists of two binding reactions and four dissociation reactions. The bound species are  $EA$  and  $FB$ . The species  $A$  and  $B$  are stoichiometrically isomeric because

$$A - B = ((F + A) - FB) + (FB - (F + B)) \in S.$$

The network of Fig. 1c consists of two binding reactions and two dissociation reactions. The bound species are  $C$  and  $D$ . The species  $A$  and  $B$  are stoichiometrically isomeric, and so are the species  $C$  and  $D$ , because

$$\begin{aligned} A - B &= ((2A + B) - D) + (D - (A + 2B)) \in S \text{ and} \\ C - D &= (C - (2A + B)) + ((A + 2B) - D) \in S. \end{aligned}$$

**Definition 2.3** A *species composition map*, or simply a *composition* of  $\mathcal{N}$  is a map  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$ , where  $n$  is a positive integer.

A composition map  $\mathcal{E} = (\mathcal{E}_1, \dots, \mathcal{E}_n) : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  for the network  $\mathcal{N}$  is fixed for the rest of this section. The idea of a composition map will become more precise as we develop it, but the basic intuition is that the composition  $\mathcal{E}(X)$  of a species  $X$  indicates how many instances of the species of reference are present in  $X$ . There could be species of reference that are not in the network  $\mathcal{N}$ .

**Definition 2.4**

- A species  $X \in \mathcal{S}$  is  $\mathcal{E}$ -elementary if  $|\mathcal{E}(X)| = 1$ ,  
i.e. if  $\mathcal{E}(X) \in \{e_{n,1}, \dots, e_{n,n}\}$ .
- A species  $X \in \mathcal{S}$  is  $\mathcal{E}$ -composite if  $|\mathcal{E}(X)| \geq 2$ ,  
i.e. if  $\mathcal{E}(X) \in \mathbb{Z}_{>0}^n \setminus \{0_n, e_{n,1}, \dots, e_{n,n}\}$ .
- Two species  $X', X'' \in \mathcal{S}$  are  $\mathcal{E}$ -isomeric if  $\mathcal{E}(X') = \mathcal{E}(X'')$ .

$\mathcal{E}$ -isomerism gives rise to an equivalence relation on the set  $\mathcal{S}$  of species.

Let  $\tilde{\mathcal{E}} = (\tilde{\mathcal{E}}_1, \dots, \tilde{\mathcal{E}}_n) : \mathbb{R}\mathcal{S} \rightarrow \mathbb{R}^n$  be the unique  $\mathbb{R}$ -linear extension of  $\mathcal{E}$ . The map  $\tilde{\mathcal{E}}$  gives rise to a sensible notion of composition of complexes, which leads to a concept of conservation of composition.

**Definition 2.5**

- A reaction  $Q' \rightarrow Q''$  is  $\mathcal{E}$ -conservative if  $\tilde{\mathcal{E}}(Q') = \tilde{\mathcal{E}}(Q'')$ .
- The network  $\mathcal{N}$  is  $\mathcal{E}$ -conservative, or equivalently the composition  $\mathcal{E}$  is conserved in the network  $\mathcal{N}$ , if all reactions are  $\mathcal{E}$ -conservative.

Figure 2 shows examples of conserved compositions for the networks of Fig. 1. These compositions are suggested by visual inspection of the networks. The developments in this paper provide systematic means of ascertaining the conservativeness features that are the reason why one usually needs such compositions.

We record a few obvious results.

**Proposition 2.6** (The network  $\mathcal{N}$  is  $\mathcal{E}$ -conservative)  $\Leftrightarrow (\text{Ker } \tilde{\mathcal{E}} \supseteq S)$ .

**Proposition 2.7** If the network  $\mathcal{N}$  is  $\mathcal{E}$ -conservative, then stoichiometric isomerism implies  $\mathcal{E}$ -isomerism; i.e. if two species are stoichiometrically isomeric, then they are  $\mathcal{E}$ -isomeric.

**Lemma 2.8** For a nonzero nonsingleton complex  $Q \in \mathcal{C}$ , and for a species  $X \in \text{Supp}(Q)$ , we have  $\mathcal{E}(X) \leq \tilde{\mathcal{E}}(Q)$  and  $\mathcal{E}(X) \neq \tilde{\mathcal{E}}(Q)$ .

$X$	$\mathcal{E}(X)$	$X$	$\mathcal{E}(X)$	$X$	$\mathcal{E}(X)$
$R$	$(1, 0, 0)$	$E$	$(1, 0, 0)$	$A$	$1$
$A$	$(0, 1, 0)$	$F$	$(0, 1, 0)$	$B$	$1$
$B$	$(0, 0, 1)$	$A$	$(0, 0, 1)$	$C$	$3$
$RA$	$(1, 1, 0)$	$B$	$(0, 0, 1)$	$D$	$3$
$RB$	$(1, 0, 1)$	$EA$	$(1, 0, 1)$		
$RAB$	$(1, 1, 1)$	$FB$	$(0, 1, 1)$		
<b>(a)</b>		<b>(b)</b>		<b>(c)</b>	

**Fig. 2** Examples of conserved compositions  $\mathcal{E}$  for the networks of Fig. 1. (a)  $\mathcal{E}$  for network of Fig. 1a (b)  $\mathcal{E}$  for network of Fig. 1b (c)  $\mathcal{E}$  for network of Fig. 1c. The upper and lower parts of the tables show the  $\mathcal{E}$ -elementary and the  $\mathcal{E}$ -composite species respectively. In the network of Fig. 1b, the species  $A$  and  $B$  form the only non-singleton  $\mathcal{E}$ -isomerism class. In the network of Fig. 1c, the sets  $\{A, B\}$  and  $\{C, D\}$  are the  $\mathcal{E}$ -isomerism classes. These three compositions are core compositions (Definition 2.10) of their respective networks and the three networks are explicitly-reversibly constructive (Definitions 2.13 and 2.14)

**Proposition 2.9** *Suppose the network  $\mathcal{N}$  is  $\mathcal{E}$ -conservative. Then every bound species is  $\mathcal{E}$ -composite.*

The canonical example of a composition is of course the atomic composition of molecules. In this case,  $n$  could be the number of entries in the Periodic Table of the Elements and positions in composition  $n$ -tuples could represent atomic numbers. However, this example is cumbersome and impractical, especially if the species under consideration are macromolecules. For the network of Fig. 1a for instance, and as illustrated on Fig. 2a, we have an intuition that species  $RAB$  is composed of species  $R$ ,  $A$  and  $B$ , which are elementary within the network, even though they may not be atoms. We formalize this observation with the notion of core composition.

**Definition 2.10** The composition  $\mathcal{E}$  is a *core composition* for  $\mathcal{N}$  provided

- $e_{n,1}, \dots, e_{n,n} \in \mathcal{E}(\mathcal{S})$  and
- $\text{Ker } \tilde{\mathcal{E}} = S$ .

One can verify, either by direct calculations or by applying Theorems 4.2 and 4.3, that the three compositions of Fig. 2 are core compositions. This terminology is intended to express that a core composition  $\mathcal{E}$  is complete, in that all  $n$   $\mathcal{E}$ -elementary compositions do occur in the network, and is minimal, in that  $\mathcal{E}$ -conservativeness does not impose constraints beyond those that stoichiometry already imposes. The following two theorems articulate these in a formal algebraic way. Theorem 2.11 says that any core composition is ‘at the core’ of any conserved composition. Theorem 2.12 essentially says that there can only be one core composition.

**Theorem 2.11** *Any core composition of  $\mathcal{N}$  is universal among all conserved compositions of  $\mathcal{N}$ . For elaboration, suppose that  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  is a core composition of  $\mathcal{N}$ , and let  $\mathcal{F} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^N \setminus \{0_N\}$  be a conserved composition of  $\mathcal{N}$ . Then there exists a unique  $\mathbb{Z}$ -linear map  $\Phi : \mathbb{Z}^n \rightarrow \mathbb{Z}^N$  that makes the following diagram commute, and  $\Phi$  maps  $\mathbb{Z}_{\geq 0}^n$  into  $\mathbb{Z}_{\geq 0}^N$ .*

$$\begin{array}{ccc} \mathcal{S} & \xrightarrow{\mathcal{F}} & \mathbb{Z}^N \\ \mathcal{E} \downarrow & \nearrow \Phi & \\ \mathbb{Z}^n & & \end{array}$$

*Proof* Let  $\tilde{\mathcal{F}} : \mathbb{R}\mathcal{S} \rightarrow \mathbb{R}^N$  be the linear extension of  $\mathcal{F}$ . The map  $\tilde{\mathcal{E}} : \mathbb{R}\mathcal{S} \rightarrow \mathbb{R}^n$  is surjective and  $\text{Ker } \tilde{\mathcal{F}} \supseteq S = \text{Ker } \tilde{\mathcal{E}}$ . Therefore, there exists a unique  $\mathbb{R}$ -linear map  $\tilde{\Phi} : \mathbb{R}^n \rightarrow \mathbb{R}^N$  such that  $\tilde{\mathcal{F}} = \tilde{\Phi} \circ \tilde{\mathcal{E}}$ . Then, by restriction to  $\mathcal{S}$ , we have  $\mathcal{F} = \tilde{\Phi} \circ \mathcal{E}$ . As a result,  $\tilde{\Phi}$  maps  $e_{n,1}, \dots, e_{n,n}$  into  $\mathbb{Z}_{\geq 0}^N$ . Therefore,  $\tilde{\Phi}$  is the extension of a  $\mathbb{Z}$ -linear map  $\Phi : \mathbb{Z}^n \rightarrow \mathbb{Z}^N$  which maps  $e_{n,1}, \dots, e_{n,n}$  into  $\mathbb{Z}_{\geq 0}^N$ . The map  $\Phi$  satisfies  $\mathcal{F} = \Phi \circ \mathcal{E}$ . The uniqueness of  $\tilde{\Phi}$  implies the uniqueness of  $\Phi$ .  $\square$

**Theorem 2.12** *If a reaction network has a core composition, then all core compositions are equivalent up to indexing permutations in composition tuples. For elaboration, suppose  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  and  $\mathcal{E}' : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^{n'} \setminus \{0_{n'}\}$  are core compositions*

of the network  $\mathcal{N}$ . Then  $n = n'$  and the  $\mathbb{Z}$ -linear map  $\Phi$  such that  $\mathcal{E}' = \Phi \circ \mathcal{E}$  is an automorphism of  $\mathbb{Z}^n$  that permutes the canonical basis vectors  $e_{n,1}, \dots, e_{n,n}$ .

*Proof* Let  $\Phi : \mathbb{Z}^n \rightarrow \mathbb{Z}^{n'}$  (resp.  $\Phi' : \mathbb{Z}^{n'} \rightarrow \mathbb{Z}^n$ ) be the  $\mathbb{Z}$ -linear map such that  $\mathcal{E}' = \Phi \circ \mathcal{E}$  (resp.  $\mathcal{E} = \Phi' \circ \mathcal{E}'$ ). Then we have  $\mathcal{E} = \varphi \circ \mathcal{E}'$  (resp.  $\mathcal{E}' = \varphi' \circ \mathcal{E}$ ) both if  $\varphi = \Phi' \circ \Phi$  and  $\varphi = \text{Id}_{\mathbb{Z}^n}$  (resp.  $\varphi' = \Phi \circ \Phi'$  and  $\varphi' = \text{Id}_{\mathbb{Z}^{n'}}$ ). Therefore  $\Phi' \circ \Phi = \text{Id}_{\mathbb{Z}^n}$  and  $\Phi \circ \Phi' = \text{Id}_{\mathbb{Z}^{n'}}$ . It follows that  $n = n'$  and  $\Phi$  is a  $\mathbb{Z}$ -linear automorphism of  $\mathbb{Z}^n$  with inverse  $\Phi^{-1} = \Phi'$ . Because  $\Phi$  maps  $\mathbb{Z}_{\geq 0}^n$  into itself, we have  $|\Phi(x)| \geq |x|$  for all  $x \in \mathbb{Z}_{\geq 0}^n$ . Likewise, we have  $|\Phi^{-1}(x)| \geq |x|$  for all  $x \in \mathbb{Z}_{\geq 0}^n$ , whence  $|x| \geq |\Phi(x)|$  for all  $x \in \mathbb{Z}_{\geq 0}^n$ . So  $|\Phi(x)| = |x|$  for all  $x \in \mathbb{Z}_{\geq 0}^n$ , and it follows that  $\Phi(\{e_{n,1}, \dots, e_{n,n}\}) = \{e_{n,1}, \dots, e_{n,n}\}$ .  $\square$

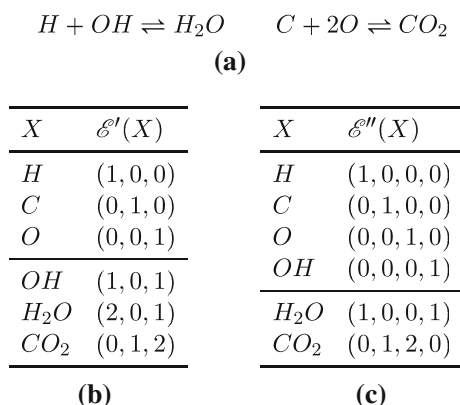
As a result of Theorem 2.12, if  $\mathcal{E}$  is a core composition of  $\mathcal{N}$ , then the notions of  $\mathcal{E}$ -elementary,  $\mathcal{E}$ -composite, and  $\mathcal{E}$ -isomeric species are independent of the choice of  $\mathcal{E}$  among core compositions, and we simply use the terminology of *elementary*, *composite*, and *isomeric* species. Also, stoichiometric isomerism and  $\mathcal{E}$ -isomerism coincide and we simply call isomerism classes the equivalence classes with respect to the two relations.

**Definition 2.13** A reaction network is *constructive* if it admits a core composition.

This terminology is from Shinar, Alon and Feinberg [6, Definition 8.1]. The two usages are consistent because of Theorem 3.6. The notions of elements and compounds in this prior work correspond to our elementary and composite species respectively. We note however that if an element as defined in this prior work is one of many isomers, then the isomers other than the element are compounds.

**Definition 2.14** Consider a reaction network.

- A species  $Y$  is *explicitly constructible* (resp. *explicitly destructible*) if there are isomerization reactions  $Y_0 \rightarrow \dots \rightarrow Y_\ell$  (resp.  $Y_\ell \rightarrow \dots \rightarrow Y_0$ ), where  $\ell \in \mathbb{Z}_{\geq 0}$ , such that  $Y_0$  is the target of a binding reaction (resp. the source of a dissociation reaction) and  $Y_\ell = Y$ .
- A species  $X$  is *explicitly constructive* (resp. *explicitly destructive*) if there is a binding reaction  $Q \rightarrow Y$  (resp. a dissociation reaction  $Y \rightarrow Q$ ) such that  $X \in \text{Supp}(Q)$ .
- The reaction network is *explicitly constructive* provided
  - The network is constructive;
  - Each composite species is explicitly constructible or explicitly destructible or both; and
  - Each elementary species is explicitly constructive or explicitly destructive or both.
- The reaction network is *explicitly-reversibly constructive* provided
  - The network is constructive;
  - Each composite species is both explicitly constructible and explicitly destructible; and
  - Each elementary species is both explicitly constructive and explicitly destructive.



**Fig. 3** (a) A hypothetical network with species in usual chemistry notation. (b)  $\mathcal{E}'$ , a near-core non-core composition for the network shown in (a). (c)  $\mathcal{E}''$ , a core composition for the network shown in (a). The upper and lower parts of the tables show the elementary and the composite species relative to each composition. The composition  $\mathcal{E}'(OH) = (1, 0, 1)$  is suggested by known information not represented in the network. Within the scope of the network, the species  $OH$  is elementary as shown by the core composition  $\mathcal{E}''$ . This reveals that the network may not have all the reactions that were intended.

The pre-complete networks of reversible binding reactions we introduced in Gnacadja [3] are explicitly-reversibly constructive; the network of Fig. 1a is of that class. More generally, if a reaction network consisting of binding and dissociation reactions is constructive and weakly reversible, then it is explicitly-reversibly constructive; the networks of Fig. 1a, c are of that class. The futile enzymatic cycle of Fig. 1b is an example of an explicitly-reversibly constructive network that is not weakly reversible. More generally, futile binary enzymatic networks (see Gnacadja [5]) are explicitly-reversibly constructive networks that are usually not weakly reversible.

### 3 Canonical bases

A reaction network  $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$  with stoichiometric space  $S$  is fixed for this section. The results presented here show that in the presence of a core composition, one has explicit, fairly canonical information about the stoichiometric space  $S$  and the conservation space  $S^\perp$ . Most of these properties do not require that the composition conservativeness of the network be minimal, whence the following definition.

**Definition 3.1** A composition  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  is a *near-core composition* of the network  $\mathcal{N}$  if

- $e_{n,1}, \dots, e_{n,n} \in \mathcal{E}(\mathcal{S})$ , i.e. all  $\mathcal{E}$ -elementary compositions occur, and
- $\text{Ker} \tilde{\mathcal{E}} \supseteq S$ , i.e.  $\mathcal{N}$  is  $\mathcal{E}$ -conservative.

Figure 3 shows an example of a near-core non-core composition.

A near-core composition  $\mathcal{E} = (e_1, \dots, e_n) : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  for the network  $\mathcal{N}$  is fixed for the rest of this section. We set the following notations.



**Notation 3.2**

- For  $i \in [1..n]$ ,  $\mathcal{X}_i := \mathcal{E}^{-1}(e_{n,i})$  is the  $\mathcal{E}$ -isomerism class of  $\mathcal{E}$ -elementary species with  $\mathcal{E}$ -composition  $e_{n,i}$ , and  $p_i := |\mathcal{X}_i|$  is the number of these species.
  - $I := \mathcal{E}(\mathcal{S}) \setminus \{e_{n,1}, \dots, e_{n,n}\}$  is the set of  $n$ -tuples that occur as  $\mathcal{E}$ -composition of  $\mathcal{E}$ -composite species;  $I \subset \mathbb{Z}_{\geq 0}^n \setminus \{0_n, e_{n,1}, \dots, e_{n,n}\}$ .
  - For  $\alpha \in I$ ,  $\mathcal{Y}_\alpha := \mathcal{E}^{-1}(\alpha)$  is the  $\mathcal{E}$ -isomerism class of  $\mathcal{E}$ -composite species with  $\mathcal{E}$ -composition  $\alpha$ , and  $q_\alpha := |\mathcal{Y}_\alpha|$  is the number of these species.
  - $\mathcal{S}_e$  is the set of  $\mathcal{E}$ -elementary species;  $\mathcal{S}_e = \bigsqcup_{i \in [1..n]} \mathcal{X}_i$ .  
 $\mathcal{S}_c$  is the set of  $\mathcal{E}$ -composite species;  $\mathcal{S}_c = \bigsqcup_{\alpha \in I} \mathcal{Y}_\alpha$ .  
 $\mathcal{S}_e^1$  is the set of  $\mathcal{E}$ -elementary species whose  $\mathcal{E}$ -isomerism classes are singletons;  
 $\mathcal{S}_e^1 = \bigsqcup_{i \in [1..n], |p_i|=1} \mathcal{X}_i$ .
- For  $i \in [1..n]$ ,  $\mathcal{S}_{c,i}$  is the set of composite species whose  $\mathcal{E}$ -composition has a positive term of index  $i$ ;  $\mathcal{S}_{c,i} := \{Y \in \mathcal{S}_c : \mathcal{E}_i(Y) \geq 1\}$ .
- $p := |\mathcal{S}_e| = \sum_{i=1}^n p_i$  is the total number of  $\mathcal{E}$ -elementary species.  
 $q := |\mathcal{S}_c| = \sum_{\alpha \in I} q_\alpha$  is the total number of  $\mathcal{E}$ -composite species.  
 $r := |\mathcal{S}| = p + q$  is the total number of species.  
 $n$  already denotes the number of  $\mathcal{E}$ -isomerism classes of elementary species.  
 $m := |I|$  is the number of  $\mathcal{E}$ -isomerism classes of composite species.

Here is, for illustration, what these notations evaluate to for the futile enzymatic cycle of Fig. 1b with the core composition of Fig. 2b:

$$\begin{aligned} \mathcal{X}_1 &= \{E\}, \mathcal{X}_2 = \{F\}, \mathcal{X}_3 = \{A, B\}, p_1 = 1, p_2 = 1, p_3 = 2, \\ I &= \{(1, 0, 1), (0, 1, 1)\}, \\ \mathcal{Y}_{(1,0,1)} &= \{EA\}, \mathcal{Y}_{(0,1,1)} = \{FB\}, q_{(1,0,1)} = 1, q_{(0,1,1)} = 1, \\ \mathcal{S}_e &= \{E, F, A, B\}, \mathcal{S}_c = \{EA, FB\}, \\ \mathcal{S}_e^1 &= \{E, F\}, \mathcal{S}_{c,1} = \{EA\}, \mathcal{S}_{c,2} = \{FB\}, \mathcal{S}_{c,3} = \{EA, FB\}, \\ p &= 4, q = 2, r = 6, n = 3, m = 2. \end{aligned}$$

By the Rank-Nullity Theorem, we have:

**Theorem 3.3**

$$\text{nullity}(\tilde{\mathcal{E}}) = \dim \text{Ker} \tilde{\mathcal{E}} = r - n = p + q - n = q + \sum_{i=1}^n (p_i - 1).$$

*In particular, if (and only if) there is no  $\mathcal{E}$ -isomerism among the  $\mathcal{E}$ -elementary species (i.e.  $\mathcal{S}_e^1 = \mathcal{S}_e$ ), then the nullity of  $\tilde{\mathcal{E}}$  equals the number of  $\mathcal{E}$ -composite species. Note that if  $\mathcal{E}$  is a core composition, then the nullity of  $\tilde{\mathcal{E}}$  equals the rank of the network.*

Using Theorem 3.3 on the networks of Figs. 1a, b, c and 3a, and their core compositions of Figs. 2a, b, c and 3c, we readily obtain that they have rank 3, 3, 3 and 2

respectively. Thus, this can be helpful in calculating the deficiency, an integer attribute of a reaction network of importance in Chemical Reaction Network Theory. See for instance Feinberg [2] for the definition and some implications of the deficiency. The rank of a network is the one ingredient that is usually the least readily available. The other ingredients, the number of complexes and the number of linkages classes, are usually obtained by visual inspection. Of course, for this remark to be pertinent, we must have convenient ways to find core compositions. Section 4 addresses this matter.

We continue in this section with results on canonical bases. Theorem 3.4 provides a canonical basis for  $\text{Ker}\tilde{\mathcal{E}}$ . Theorem 3.5 provides for the orthogonal  $(\text{Ker}\tilde{\mathcal{E}})^\perp$  of  $\text{Ker}\tilde{\mathcal{E}}$  a canonical basis consisting of vectors that are linear combinations of species with nonnegative integer coefficients. Finally, Theorem 3.6 combines these two results with canonical bases for the stoichiometric and conservation spaces  $S$  and  $S^\perp$  in the case where  $\mathcal{C}$  is a core composition.

We define the linear map  $\rho : \mathbb{R}\mathcal{S} \rightarrow \mathbb{R}\mathcal{S}$  by

$$\rho(Z) = Z - \sum_{i=1}^n \frac{\mathcal{E}_i(Z)}{p_i} \text{sum}(\mathcal{X}_i) \quad \text{for } Z \in \mathcal{S}. \quad (3.1)$$

In particular,

$$\rho(X) = X - \frac{1}{p_i} \text{sum}(\mathcal{X}_i) \quad \text{if } X \in \mathcal{X}_i, \text{ and} \quad (3.2)$$

$$\rho(Y) = Y - \sum_{i=1}^n \frac{\alpha_i}{p_i} \text{sum}(\mathcal{X}_i) \quad \text{if } Y \in \mathcal{Y}_\alpha. \quad (3.3)$$

**Theorem 3.4** For each  $i \in [1..n]$ , let  $\mathcal{B}_i$  be one of the  $p_i$  sets of  $(p_i - 1)$  elements obtained by excising one element from the set  $\{\rho(X) : X \in \mathcal{X}_i\}$ . Then let

$$\mathcal{B} = \{\rho(Y) : Y \in \mathcal{S}_c\} \sqcup \bigsqcup_{i=1}^n \mathcal{B}_i = \{\rho(Y) : Y \in \mathcal{S}_c\} \sqcup \bigsqcup_{\substack{1 \leq i \leq n \\ p_i > 1}} \mathcal{B}_i.$$

The set  $\mathcal{B}$  is a basis of  $\text{Ker}\tilde{\mathcal{E}}$ .

*Proof* We see from Eqs. 3.2 and 3.3 that the vectors  $\rho(Z)$  for  $Z \in \mathcal{S} \setminus \mathcal{S}_c^1$  are pairwise distinct. So the disjoint unions in the expression of  $\mathcal{B}$  are justified and the cardinality of  $\mathcal{B}$  is equal to the dimension of  $\text{Ker}\tilde{\mathcal{E}}$  as provided by Theorem 3.3.

From Eq. 3.1, we get that  $\tilde{\mathcal{E}}(\rho(Z)) = 0_n$  for all  $Z \in \mathcal{S}$ . Hence,  $\mathcal{B} \subset \text{Ker}\tilde{\mathcal{E}}$ .

One can verify that the set  $\{\rho(Y) : Y \in \mathcal{S}_c\}$  is linearly independent, and that so is the set  $\mathcal{B}_i$  for each  $i \in [1..n]$  with  $p_i > 1$ . Furthermore, the sets  $\mathcal{B}_i$  are pairwise orthogonal because  $\mathcal{B}_i \subset \mathbb{R}\mathcal{X}_i$ . So the set  $\bigsqcup_{i=1}^n \mathcal{B}_i$  is linearly independent. Now, intersecting the subspaces spanned by  $\{\rho(Y) : Y \in \mathcal{S}_c\}$  and by  $\bigsqcup_{i=1}^n \mathcal{B}_i$  yields the zero space. So the set  $\mathcal{B}$  is linearly independent.  $\square$

Let the linear map  $\tau : \mathbb{R}^n \rightarrow \mathbb{R}^{\mathcal{S}}$  be defined by  $\tau(e_{n,i}) = T_i$  for  $i \in [1..n]$ , where

$$T_i := \text{sum}(\mathcal{X}_i) + \sum_{\alpha \in I} \alpha_i \text{sum}(\mathcal{Y}_\alpha) = \text{sum}(\mathcal{X}_i) + \sum_{Y \in \mathcal{S}_c} \mathcal{E}_i(Y) Y. \tag{3.4}$$

**Theorem 3.5** *We have  $(\text{Ker} \tilde{\mathcal{E}})^\perp = \text{Im} \tau$  and the set  $\mathcal{B}' = \{T_1, \dots, T_n\}$  is a basis of  $(\text{Ker} \tilde{\mathcal{E}})^\perp$ . In particular,  $\mathcal{B}'$  is a linearly independent subset of the conservation space  $S^\perp$ .*

*Proof* We obtain the adjunction property

$$\langle \tau(x), Q \rangle = \langle x, \tilde{\mathcal{E}}(Q) \rangle, \quad \forall x \in \mathbb{R}^n, \forall Q \in \mathbb{R}^{\mathcal{S}} \tag{3.5}$$

by verifying that each side of the equality equals  $\mathcal{E}_i(Q)$  when  $x \in \{e_{n,1}, \dots, e_{n,n}\}$  and  $Q \in \mathcal{S}_c$  or  $Q \in \mathcal{S}$ . As a result, we have  $(\text{Im} \tau)^\perp = \text{Ker} \tilde{\mathcal{E}}$ . Hence,  $(\text{Ker} \tilde{\mathcal{E}})^\perp = \text{Im} \tau$ , and the set  $\{T_1, \dots, T_n\}$  spans  $(\text{Ker} \tilde{\mathcal{E}})^\perp$ . From Theorem 3.3,  $(\text{Ker} \tilde{\mathcal{E}})^\perp$  has dimension  $n$ , so the set  $\{T_1, \dots, T_n\}$  is a basis of  $(\text{Ker} \tilde{\mathcal{E}})^\perp$ . □

We combine in Theorem 3.6 what Theorems 3.4 and 3.5 say when  $\mathcal{E}$  is a core composition.

**Theorem 3.6** *Suppose that  $\mathcal{E}$  is a core composition of  $\mathcal{N}$ . Then:*

- *The set  $\mathcal{B}$  from Theorem 3.4 is a basis of the stoichiometric space  $S$ .*
- *The set  $\mathcal{B}'$  from Theorem 3.5 is a basis of the conservation space  $S^\perp$ . Each vector in  $\mathcal{B}'$  is a linear combination of species with nonnegative integer coefficients.*

The basis  $\mathcal{B}'$  provides a canonical, comprehensive and minimal description of the conservativeness of the network. Because of Theorem 2.12, the basis  $\mathcal{B}'$  is independent of the choice of a core composition for the (constructive) network  $\mathcal{N}$ . This result and its proof are rigorous statement and justification for the common practice of cataloging conservation laws by visual inspection of reaction networks. Section 4 provides means of finding core compositions, thereby turning Theorem 3.6 into a useful tool for applications. To illustrate this theorem, we use the futile enzymatic cycle of Fig. 1b, its core composition of Fig. 2b, and the related values of the notations of Notation 3.2 listed earlier in this section. We have

$$\begin{aligned} \rho(E) = 0, \quad \rho(F) = 0, \quad \rho(A) = \frac{1}{2}(A - B), \quad \rho(B) = \frac{1}{2}(B - A), \\ \rho(EA) = EA - E - \frac{1}{2}(A + B), \quad \rho(FB) = FB - F - \frac{1}{2}(A + B), \\ T_1 = E + EA, \quad T_2 = F + FB, \quad T_3 = A + B + EA + FB. \end{aligned}$$

Below are one of the two possible bases  $\mathcal{B}$  and the basis  $\mathcal{B}'$ .

$$\mathcal{B} = \left\{ \frac{1}{2}(A - B), EA - E - \frac{1}{2}(A + B), FB - F - \frac{1}{2}(A + B) \right\}$$

$$\mathcal{B}' = \{E + EA, F + FB, A + B + EA + FB\}$$

### 4 Finding core compositions

Let  $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$  be a reaction network and let  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  be a composition of  $\mathcal{N}$ . We devote this section to ways to prove that  $\mathcal{E}$  is a core composition of  $\mathcal{N}$  when it is known that  $\mathcal{E}$  is a near-core composition. We adopted this approach because the common practice of cataloging conservation laws by visual inspection produces near-core compositions. The difficulty lies in the minimality aspect of a core composition, i.e. the fact that  $\text{Ker} \tilde{\mathcal{E}} \subseteq S$ . Because of Theorem 3.4, this containment relationship is equivalent to the property that  $\rho(Z) \in S$  for all  $Z \in \mathcal{S}$ . But proving this from the expressions of Eqs. 3.1, 3.2 and 3.3 may not be obvious. The following result provides other useful expressions for these vectors.

**Lemma 4.1** *Suppose that  $\mathcal{E}$  is a near-core composition of  $\mathcal{N}$  and refer to Notation 3.2.*

- For  $i \in [1..n]$  and  $X \in \mathcal{X}_i$ , we have

$$\rho(X) = \frac{1}{p_i} \sum_{W \in \mathcal{X}_i} (X - W). \tag{4.1}$$

- For  $\alpha \in I$  and  $Y \in \mathcal{Y}_\alpha$ , we have

$$\rho(Y) = \frac{1}{p_1 \cdots p_n} \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} \left( Y - \sum_{i=1}^n \alpha_i W_i \right). \tag{4.2}$$

*Proof* Eq. 4.1 is an obvious reformulation of Eq. 3.2. We prove Eq. 4.2. We have:

$$\begin{aligned} & \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} \left( \sum_{i=1}^n \alpha_i W_i \right) \\ &= \sum_{i=1}^n \left( \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} \alpha_i W_i \right) \\ &= \sum_{i=1}^n \alpha_i \left( \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} W_i \right) \\ &= \sum_{i=1}^n \alpha_i \left( \sum_{(W_1, \dots, W_{i-1}, W_{i+1}, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_{i-1} \times \mathcal{X}_{i+1} \times \dots \times \mathcal{X}_n} \left( \sum_{W_i \in \mathcal{X}_i} W_i \right) \right) \end{aligned}$$

$$\begin{aligned}
 &= \sum_{i=1}^n \alpha_i \left( \sum_{(W_1, \dots, W_{i-1}, W_{i+1}, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_{i-1} \times \mathcal{X}_{i+1} \times \dots \times \mathcal{X}_n} \text{sum}(\mathcal{X}_i) \right) \\
 &= \sum_{i=1}^n \alpha_i p_1 \cdots p_{i-1} p_{i+1} \cdots p_n \text{sum}(\mathcal{X}_i) \\
 &= p_1 \cdots p_n \sum_{i=1}^n \frac{\alpha_i}{p_i} \text{sum}(\mathcal{X}_i) \\
 &= p_1 \cdots p_n (Y - \rho(Y)).
 \end{aligned}$$

It follows that:

$$\begin{aligned}
 p_1 \cdots p_n \rho(Y) &= p_1 \cdots p_n Y - \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} \left( \sum_{i=1}^n \alpha_i W_i \right) \\
 &= \sum_{(W_1, \dots, W_n) \in \mathcal{X}_1 \times \dots \times \mathcal{X}_n} \left( Y - \sum_{i=1}^n \alpha_i W_i \right).
 \end{aligned}$$

□

Following is one of the two main results of this section.

**Theorem 4.2** Refer to Notation 3.2 and suppose that:

- (1)  $\mathcal{E}$  is a near-core composition of  $\mathcal{N}$ ;
- (2) For every  $i \in [1..n]$ , all ( $\mathcal{E}$ -elementary) species of composition  $e_{n,i}$  are stoichiometrically isomeric, i.e.  $(X, W \in \mathcal{X}_i) \Rightarrow (X - W \in S)$ ; and
- (3) For every  $\alpha \in I$  and  $Y \in \mathcal{Y}_\alpha$ , there exist  $W_1 \in \mathcal{X}_1, \dots, W_n \in \mathcal{X}_n$  such that

$$Y - \sum_{i=1}^n \alpha_i W_i \in S.$$

Then  $\mathcal{E}$  is a core composition of  $\mathcal{N}$ .

*Proof* We just need to show that  $\rho(Z) \in S$  for all  $Z \in \mathcal{S}$ .

Condition (2) of the theorem along with Eq. 4.1 of Lemma 4.1 imply that  $\rho(X) \in S$  if  $X \in \mathcal{X}_i$  for some  $i \in [1..n]$ .

Let  $\alpha \in I$  and  $Y \in \mathcal{Y}_\alpha$ . With Condition (3), we have  $W_1^0 \in \mathcal{X}_1, \dots, W_n^0 \in \mathcal{X}_n$  such that  $Y - \sum_{i=1}^n \alpha_i W_i^0 \in S$ . Let  $W_1 \in \mathcal{X}_1, \dots, W_n \in \mathcal{X}_n$ . For every  $i \in [1..n]$ , both  $W_i^0$  and  $W_i$  are in  $\mathcal{X}_i$ , and so  $W_i^0 - W_i \in S$  by Condition (2). Hence,

$$Y - \sum_{i=1}^n \alpha_i W_i = Y - \sum_{i=1}^n \alpha_i W_i^0 + \sum_{i=1}^n \alpha_i (W_i^0 - W_i) \in S.$$

Then, Eq. 4.2 of Lemma 4.1 implies that  $\rho(Y) \in S$ .

□

Theorem 4.2 is directly applicable if each composite species is explicitly constructible or explicitly destructible from a non-singleton complex in which all species are elementary. This is the case for the networks of Fig. 1b and 1c. Theorem 4.2 does readily show that the compositions of Fig. 2b and 2c are core compositions. But this is not the case for the allosteric ternary complex model of Fig. 1a. To show that the composition of Fig. 2a is a core composition, or in other such cases, one can ascertain Condition (3) of Theorem 4.2 by induction, or one can use the following theorem.

**Theorem 4.3** *Suppose that:*

- (1)  $\mathcal{E}$  is a near-core composition of  $\mathcal{N}$ ;
- (2)  $\mathcal{E}$ -isomerism implies stoichiometric isomerism; and
- (3) Every  $\mathcal{E}$ -composite species is stoichiometrically isomeric to a bound species.

Then  $\mathcal{E}$  is a core composition of  $\mathcal{N}$ .

We state and prove a technical result, which we then use to prove Theorem 4.3. For  $\alpha \in I$ , let  $I_\alpha = \{\beta \in I : \beta \leq \alpha \text{ and } \beta \neq \alpha\}$ .

**Lemma 4.4** *Assume the hypotheses of Theorem 4.3 and refer to Notation 3.2. Let  $Y \in \mathcal{S}_c$  and  $\alpha = \mathcal{E}(Y)$ . There exist  $\sigma_i \in \mathbb{Z}_{\geq 0}$  for  $i \in [1..n]$  and  $\sigma_\beta \in \mathbb{Z}_{\geq 0}$  for  $\beta \in I_\alpha$  such that, for all  $i \in [1..n]$  and  $X_i \in \mathcal{X}_i$ , and all  $\beta \in I_\alpha$  and  $Y_\beta \in \mathcal{Y}_\beta$ , we have*

$$Y - \left( \sum_{i=1}^n \sigma_i X_i + \sum_{\beta \in I_\alpha} \sigma_\beta Y_\beta \right) \in S.$$

We have the conservation relation  $\alpha = (\sigma_1, \dots, \sigma_n) + \sum_{\beta \in I_\alpha} \sigma_\beta \beta$ .

*Proof* Condition (3) of Theorem 4.3 implies the existence of a complex  $Q = \sum_{Z \in \mathcal{C}} Q_Z Z \in \mathcal{C}$  of length  $|Q| \geq 2$  such that  $Y - Q \in S$ . For each  $i \in [1..n]$ , let  $\sigma_i = \sum_{Z \in \mathcal{X}_i} Q_Z$  and  $X_i \in \mathcal{X}_i$ . For each  $\beta \in I$ , let  $\sigma_\beta = \sum_{Z \in \mathcal{Y}_\beta} Q_Z$  and  $Y_\beta \in \mathcal{Y}_\beta$ . One can verify that

$$-Q = - \left( \sum_{i=1}^n \sigma_i X_i + \sum_{\beta \in I} \sigma_\beta Y_\beta \right) + \sum_{i=1}^n \sum_{Z \in \mathcal{X}_i} Q_Z (X_i - Z) + \sum_{\beta \in I} \sum_{Z \in \mathcal{Y}_\beta} Q_Z (Y_\beta - Z).$$

With Condition (2) of Theorem 4.3, we get that  $X_i - Z \in S$  for  $i \in [1..n]$  and  $Z \in \mathcal{X}_i$ , and  $Y_\beta - Z \in S$  for  $\beta \in I$  and  $Z \in \mathcal{Y}_\beta$ . Plus we already have  $Y - Q \in S$ . Therefore

$$Y - \left( \sum_{i=1}^n \sigma_i X_i + \sum_{\beta \in I} \sigma_\beta Y_\beta \right) \in S.$$

And because  $S \subseteq \text{Ker } \tilde{\mathcal{E}}$ , it follows that  $\alpha = (\sigma_1, \dots, \sigma_n) + \sum_{\beta \in I} \sigma_\beta \beta$ .

It remains to show that  $\sigma_\beta = 0$  for  $\beta \in I \setminus I_\alpha$ . Let  $\beta \in I$ . We have  $\sigma_\beta \beta \leq \alpha$ , so if  $\sigma_\beta \geq 1$ , then  $\beta \leq \alpha$ . By contraposition, if  $\beta \notin I_\alpha$  and  $\beta \neq \alpha$ , then  $\sigma_\beta = 0$ . We now need to show that  $\sigma_\alpha = 0$ . We in particular have  $\sigma_\alpha \alpha \leq \alpha$ , so  $\sigma_\alpha \leq 1$ . Suppose  $\sigma_\alpha = 1$ . Then we successively have  $0_n = -\alpha + (\sigma_1, \dots, \sigma_n) + \sum_{\beta \in I} \sigma_\beta \beta = (\sigma_1, \dots, \sigma_n) + \sum_{\beta \in I \setminus \{\alpha\}} \sigma_\beta \beta$ ;  $\sigma_i = 0$  for  $i \in [1..n]$  and  $\sigma_\beta = 0$  for  $\beta \in I \setminus \{\alpha\}$ ; and  $|\mathcal{Q}| = \sum_{Z \in \mathcal{S}} \mathcal{Q}_Z = \sum_{i=1}^n \sigma_i + \sum_{\beta \in I} \sigma_\beta = \sigma_\alpha = 1$ . But  $|\mathcal{Q}| \geq 2$ . So  $\sigma_\alpha = 0$ .  $\square$

*Proof (Theorem 4.3)* Refer to Notation 3.2. Just as for Theorem 4.2, we only need to prove that  $\rho(Z) \in S$  for all  $Z \in \mathcal{S}$ . Condition (2) of Theorem 4.3 along with Eq. 4.1 of Lemma 4.1 imply that  $\rho(X) \in S$  if  $X \in \mathcal{X}_i$  for some  $i \in [1..n]$ . For a species  $Y$  with  $\mathcal{E}(Y) = \alpha \in I$ , we show that

$$\forall X_1 \in \mathcal{X}_1, \dots, \forall X_n \in \mathcal{X}_n, Y - \sum_{i=1}^n \alpha_i X_i \in S. \tag{4.3}$$

This together with Eq. 4.2 of Lemma 4.1 will imply that  $\rho(Y) \in S$ . We proceed by induction on the length  $|\alpha|$  of  $\alpha$  to prove Property (4.3).

If  $|\alpha| = 2$ , then  $I_\alpha = \emptyset$  and Property (4.3) holds by Lemma 4.4.

Let  $\ell \geq 3$  and assume for induction that Property (4.3) holds if  $|\alpha| < \ell$ . Suppose  $|\alpha| = \ell$  and let  $Y \in \mathcal{Y}_\alpha$ . Let  $\sigma_i$  for  $i \in [1..n]$  and  $\sigma_\beta$  for  $\beta \in I_\alpha$  be as in Lemma 4.4. Then let  $X_i \in \mathcal{X}_i$  for  $i \in [1..n]$  and  $Y_\beta \in \mathcal{Y}_\beta$  for  $\beta \in I_\alpha$ . For each  $\beta \in I_\alpha$ , we have

$|\beta| < \ell$ , and so by the induction hypothesis, we have  $Y_\beta - \sum_{i=1}^n \beta_i X_i \in S$ . Then:

$$\begin{aligned} S &\ni Y - \sum_{i=1}^n \sigma_i X_i - \sum_{\beta \in I_\alpha} \sigma_\beta Y_\beta \\ &= Y - \sum_{i=1}^n \sigma_i X_i - \sum_{i=1}^n \sum_{\beta \in I_\alpha} \sigma_\beta \beta_i X_i + \sum_{\beta \in I_\alpha} \sum_{i=1}^n \sigma_\beta \beta_i X_i - \sum_{\beta \in I_\alpha} \sigma_\beta Y_\beta \\ &= Y - \sum_{i=1}^n \left( \sigma_i + \sum_{\beta \in I_\alpha} \sigma_\beta \beta_i \right) X_i - \sum_{\beta \in I_\alpha} \sigma_\beta \left( Y_\beta - \sum_{i=1}^n \beta_i X_i \right) \\ &= Y - \sum_{i=1}^n \alpha_i X_i - \sum_{\beta \in I_\alpha} \sigma_\beta \left( Y_\beta - \sum_{i=1}^n \beta_i X_i \right). \end{aligned}$$

It follows that  $Y - \sum_{i=1}^n \alpha_i X_i \in S$ . Property (4.3) is thus proved.  $\square$

### 5 Stoichiometry compatibility classes of constructive networks

Stoichiometric compatibility classes are canonical invariants in the dynamics of reaction networks. General background material may be found in Section 2 of Gnacadja [4], the first article in this series of three papers. Here we elaborate on the stoichiometric compatibility classes of constructive networks. Let  $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$  be a constructive network, let  $S$  be the stoichiometric space of  $\mathcal{N}$ , and let  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  be a core composition of  $\mathcal{N}$ . Notation 3.2 is in effect.

For  $b \in \mathbb{R}^n$ , let

$$P(b) := \tilde{\mathcal{E}}^{-1}(b) \cap (\mathbb{R}_{\geq 0}\mathcal{S}) . \tag{5.1}$$

More explicitly,  $P(b)$  consists of the points  $u = (u_Z)_{Z \in \mathcal{S}} \in \mathbb{R}_{\geq 0}\mathcal{S}$  that satisfy:

$$\forall i \in [1..n], \sum_{X \in \mathcal{X}_i} u_X + \sum_{\alpha \in I} \alpha_i \sum_{Y \in \mathcal{Y}_\alpha} u_Y = b_i . \tag{5.2}$$

**Theorem 5.1** *The correspondence  $b \mapsto P(b)$  in which  $b$  ranges over  $\mathbb{R}_{\geq 0}^n$  establishes a bijective parameterization of the stoichiometric compatibility classes of the network  $\mathcal{N}$ .*

*Proof* The stoichiometric compatibility classes are the nonempty traces on  $\mathbb{R}_{\geq 0}\mathcal{S}$  of the affine subspaces of  $\mathbb{R}\mathcal{S}$  parallel to  $S$ . Because  $\mathcal{E}$  is a core composition, the linear map  $\tilde{\mathcal{E}} : \mathbb{R}\mathcal{S} \rightarrow \mathbb{R}^n$  is surjective with kernel  $S$ . As a result, the affine spaces parallel to  $S$  are  $\tilde{\mathcal{E}}^{-1}(b)$  for  $b \in \mathbb{R}^n$ . Therefore, the stoichiometric compatibility classes are the sets  $P(b)$  for  $b \in \mathbb{R}^n$  such that  $P(b) \neq \emptyset$ . One can verify that  $P(b) \neq \emptyset$  if and only if  $b \in \mathbb{R}_{\geq 0}^n$ , and that if  $b, b' \in \mathbb{R}_{\geq 0}^n$  and  $P(b) = P(b')$ , then  $b = b'$ .  $\square$

Let  $b \in \mathbb{R}_{> 0}^n$ . We consider the interior  $P_{> 0}(b) = P(b) \cap \mathbb{R}_{> 0}\mathcal{S}$  and the boundary  $P_{\neq 0}(b) = P(b) \setminus P_{> 0}(b)$  of  $P(b)$ , both relative to the affine space parallel to  $S$  that contains  $P(b)$ . The class  $P(b)$  is nondegenerate, i.e. its interior  $P_{> 0}(b)$  is nonempty, if and only if  $b \in \mathbb{R}_{> 0}^n$ . Consider also the subsets  $P_e(b)$  and  $P_e^1(b)$  of  $P(b)$  consisting of the points  $u = (u_Z)_{Z \in \mathcal{S}} \in P(b)$  that satisfy the following properties.

$$P_e(b) : \begin{cases} \forall i \in [1..n], \sum_{X \in \mathcal{X}_i} u_X = b_i \\ \forall Y \in \mathcal{S}_u, u_Y = 0 . \end{cases}$$

$$P_e^1(b) : \exists X_1 \in \mathcal{X}_1, \dots, \exists X_n \in \mathcal{X}_n : \begin{cases} (u_{X_1}, \dots, u_{X_n}) = b \\ \forall Z \in \mathcal{S} \setminus \{X_1, \dots, X_n\}, u_Z = 0 . \end{cases}$$

One readily sees that  $P_e^1(b) \subseteq P_e(b) = P(b) \cap \mathbb{R}\mathcal{S}_e \subseteq P_{\neq 0}(b)$ , and that  $P_e^1(b)$  is a finite set of cardinality  $|P_e^1(b)| = \prod_{i=1}^n p_i = \prod_{\substack{1 \leq i \leq n \\ p_i > 1}} p_i$ . If there is no



isomerism among the elementary species, i.e. if  $\mathcal{S}_e^1 = \mathcal{S}_e$ , then  $P_e^1(b) = P_e(b) = P(b) \cap \mathbb{R}\mathcal{S}_e = \{b\}$ .

The interpretation of the set  $P(b)$  is that it consists of all concentration vectors such that for each  $i \in [1..n]$ ,  $b_i$  is the total concentration of all the occurrences of the elementary composition  $e_{n,i}$ . The subset  $P_e(b)$  consists of those concentration vectors for which only elementary species are present. Further restricting by allowing only one elementary species in each isomerism class yields  $P_e^1(b)$ . The stoichiometric compatibility class  $P(b)$  is a compact convex polytope. The set  $P_e(b)$  is a face of  $P(b)$ , the maximal one lying in the elementary species subspace  $\mathbb{R}\mathcal{S}_e$ . The points in  $P_e^1(b)$  are the vertices of  $P_e(b)$ , or equivalently the vertices of  $P(b)$  lying in  $\mathbb{R}\mathcal{S}_e$ .

We illustrate this discussion by continuing with the example that closed Section 3, i.e. the futile enzymatic cycle of Fig. 1b. For  $b = (b_1, b_2, b_3) \in \mathbb{R}_{\geq 0}^3$ , we describe the following sets by the condition that  $u = (u_E, u_F, u_A, u_B, u_{EA}, u_{FB}) \in \mathbb{R}_{\geq 0}\mathcal{S}$  must satisfy to be a member.

$$\begin{aligned}
 P(b) & : u_E + u_{EA} = b_1, \quad u_F + u_{FB} = b_2, \quad u_A + u_B + u_{EA} + u_{FB} = b_3 \\
 P_e(b) & : u_E = b_1, \quad u_F = b_2, \quad u_A + u_B = b_3, \quad u_{EA} = 0, \quad u_{FB} = 0 \\
 P_e^1(b) & : (u_E, u_F, u_A, u_B, u_{EA}, u_{FB}) = (b_1, b_2, b_3, 0, 0, 0) \text{ or } (b_1, b_2, 0, b_3, 0, 0)
 \end{aligned}$$

The class  $P(b)$  is nondegenerate if and only if  $b_1, b_2, b_3 > 0$ . If  $b_3 > 0$ , then  $P_e(b)$  is a line segment and  $P_e^1(b)$  consists of its two vertices.

### 6 Persistence in constructive networks

This final section brings together the developments on species composition in this paper and on reachability and persistence in the preceding paper Gnacadja [4] to consider vacuous persistence in constructive networks. Vacuous persistence is the property that no species tend to extinction whenever all species are implicitly present at initial time. We will see that having a core composition map can facilitate efforts to satisfy the necessary and sufficient condition for vacuous persistence from that work. We begin by recalling the result to be applied.

**Theorem 6.1** (Gnacadja [4, Theorem 5.5]) *Consider a mass-action reaction network for which that all trajectories are bounded. Then the following are equivalent:*

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

All necessary explanations are in the paper. These include discussions on stoichiometric admissibility, reachability and siphons. The next few preparatory results are about understanding more about these concepts for constructive networks and lead to the main results of Theorems 6.8 and 6.9. Let  $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$  be a constructive network and let  $\mathcal{E} : \mathcal{S} \rightarrow \mathbb{Z}_{\geq 0}^n \setminus \{0_n\}$  be a core composition of  $\mathcal{N}$ . Notation 3.2 is in effect.

The following result is a consequence of the characterization of stoichiometric compatibility classes of Eq. 5.2.

**Proposition 6.2** Let  $\mathcal{Z} \subseteq \mathcal{S}$ , let  $b \in \mathbb{R}_{\geq 0}^n$ , and let  $i \in [1..n]$ . Suppose that  $\mathcal{Z}$  is  $\mathcal{P}(b)$ -admissible. We have  $\mathcal{Z} \cap (\mathcal{X}_i \sqcup \mathcal{S}_{c,i}) \neq \emptyset$ , i.e. the elementary composition  $e_{n,i}$  occurs in  $\mathcal{Z}$ , either explicitly from an elementary species, or implicitly from a composite species, or both, if and only if  $b_i > 0$ .

The next result is obtained by inductively applying Lemma 2.8.

**Lemma 6.3** Suppose that all composite species are explicitly destructible. Consider a reach-closed set  $\mathcal{Z} \subseteq \mathcal{S}$  and let  $i \in [1..n]$ . If  $\mathcal{Z} \cap \mathcal{S}_{c,i} \neq \emptyset$ , then  $\mathcal{Z} \cap \mathcal{X}_i \neq \emptyset$ ; if the elementary composition  $e_{n,i}$  occurs implicitly (i.e. from a composite species) in  $\mathcal{Z}$ , then it occurs explicitly (i.e. from an elementary species) in  $\mathcal{Z}$ .

The combination of Proposition 6.2 and Lemma 6.3 immediately yields the following result.

**Proposition 6.4** Suppose that all composite species are explicitly destructible. Let a set of species  $\mathcal{Z} \subseteq \mathcal{S}$  be both reach-closed and stoichiometrically admissible. Then  $\mathcal{Z} \cap \mathcal{X}_i \neq \emptyset$  for all  $i \in [1..n]$ ; there is in  $\mathcal{Z}$  a species from each isomerism class of elementary species. In particular, if there is no isomerism among the elementary species, then  $\mathcal{S}_e \subseteq \mathcal{Z}$ ; all elementary species are in  $\mathcal{Z}$ .

**Lemma 6.5** Consider a siphon  $\mathcal{Z} \subseteq \mathcal{S}$ .

- (i) Suppose that a species  $Y \in \mathcal{Z}$  is explicitly constructible. Then there exists a species  $Z \in \mathcal{Z}$  such that  $\mathcal{E}(Z) \leq \mathcal{E}(Y)$  and  $\mathcal{E}(Z) \neq \mathcal{E}(Y)$ .
- (ii) Suppose that a species  $X \in \mathcal{Z}$  is explicitly destructive. Then there exists a species  $Z \in \mathcal{Z}$  such that  $\mathcal{E}(Z) \geq \mathcal{E}(X)$  and  $\mathcal{E}(Z) \neq \mathcal{E}(X)$ .

*Proof* We prove statement (i). Let  $Y \in \mathcal{S}$  be explicitly constructible. Then let  $Q$  be a complex and  $Y_0, \dots, Y_\ell$  be species such that we have the binding reaction  $Q \rightarrow Y_0$  and the isomerization reactions  $Y_0 \rightarrow \dots \rightarrow Y_\ell$ , and  $Y_\ell = Y$ . By the conservation of composition, we have  $\tilde{\mathcal{E}}(Q) = \mathcal{E}(Y)$ . Then, because  $|Q| \geq 2$ , we have  $\mathcal{E}(Z) \leq \mathcal{E}(Y)$  and  $\mathcal{E}(Z) \neq \mathcal{E}(Y)$  for all  $Z \in \text{Supp}(Q)$  by Lemma 2.8. Now suppose that  $Y \in \mathcal{Z}$ . Because  $\mathcal{Z}$  is a siphon we obtain  $Y_0 \in \mathcal{Z}$  by induction, and therefore  $Z \in \mathcal{Z}$  for some  $Z \in \text{Supp}(Q)$ .

We prove statement (ii). Let  $X \in \mathcal{S}$  be explicitly destructive. Then let  $Z \rightarrow Q$  be a dissociation reaction such that  $X \in \text{Supp}(Q)$ . By the conservation of composition, we have  $\mathcal{E}(Z) = \tilde{\mathcal{E}}(Q)$ . Then, because  $|Q| \geq 2$  and  $X \in \text{Supp}(Q)$ , we have  $\mathcal{E}(Z) \geq \mathcal{E}(X)$  and  $\mathcal{E}(Z) \neq \mathcal{E}(X)$  by Lemma 2.8. Now suppose that  $X \in \mathcal{Z}$ . Because  $\mathcal{Z}$  is a siphon, we have  $Z \in \mathcal{Z}$ .  $\square$

**Proposition 6.6** Consider a siphon  $\mathcal{Z} \subseteq \mathcal{S}$ .

- (i) Suppose that all composite species are explicitly constructible. If  $\mathcal{S}_c \cap \mathcal{Z} \neq \emptyset$ , then  $\mathcal{S}_e \cap \mathcal{Z} \neq \emptyset$ .
- (ii) Suppose that all elementary species are explicitly destructive. If  $\mathcal{S}_e \cap \mathcal{Z} \neq \emptyset$ , then  $\mathcal{S}_c \cap \mathcal{Z} \neq \emptyset$ .

*Proof* Statement (i) of Proposition 6.6 is proved by reasoning by induction with Statement (i) of Lemma 6.5. Statement (ii) of Proposition 6.6 is a direct consequence of Statement (ii) of Lemma 6.5.  $\square$

Since the reach-closed sets are the complements of siphons, we immediately get the following result from Proposition 6.6.

**Theorem 6.7** *Suppose that the reaction network  $\mathcal{N}$  is explicitly-reversibly constructive and let  $\mathcal{Z} \subseteq \mathcal{S}$ . If  $\mathcal{Z}$  is reach-closed, and if  $\mathcal{S}_e \subseteq \mathcal{Z}$  or  $\mathcal{S}_c \subseteq \mathcal{Z}$ , then  $\mathcal{Z} = \mathcal{S}$ .*

The next result is a direct consequence of the combination of Theorems 6.7 and 6.1. It characterizes vacuous persistence in mass-action explicitly-reversibly constructive networks.

**Theorem 6.8** *Suppose that the reaction network  $\mathcal{N}$  is explicitly-reversibly constructive. Then the following are equivalent:*

- *If a subset  $\mathcal{Z} \subseteq \mathcal{S}$  is both reach-closed and stoichiometrically admissible, then  $\mathcal{S}_e \subseteq \mathcal{Z}$  or  $\mathcal{S}_c \subseteq \mathcal{Z}$ .*
- *Only  $\mathcal{S}$  is both reach-closed and stoichiometrically admissible.*
- *If the network is governed by mass-action kinetics, then it is vacuously persistent.*

The particular case highlighted in Proposition 6.4 yields a means of satisfying the first of the three conditions in Theorem 6.8, whence the main result that follows.

**Theorem 6.9** *Suppose that the reaction network  $\mathcal{N}$  is explicitly-reversibly constructive, that there is no isomerism among the elementary species, and that the network is governed by mass-action kinetics. Then the network is vacuously persistent.*

It results from Siegel and MacLean [7, Theorem 3.2] that if a mass-action reaction network is persistent and complex-balancing, then each nondegenerate stoichiometric compatibility class contains a unique equilibrium state which is complex-balanced and is an attractor of the interior of the class. Therefore, if the network  $\mathcal{N}$  satisfies the hypotheses of Theorem 6.9, and if in addition  $\mathcal{N}$  is complex-balancing (in particular if  $\mathcal{N}$  is weakly reversible and has deficiency zero), then for every  $b \in \mathbb{R}_{>0}^n$ , the (unique, positive, complex-balanced) equilibrium state in  $P_{>0}(b)$  is an attractor of  $P(b)$ .

Theorem 6.9 shows that for a mass-action explicitly-reversibly constructive network, the failure of vacuous persistence requires that there be isomerism among the elementary species. (Isomerism among composite species does not affect this feature.) This explains the fact that instances of non-persistence and of non-obvious persistence in the literature always involve networks with isomerism among the building blocks. However, the absence of isomerism among elementary species is not necessary for vacuous persistence. This requirement is simply the easiest way to realize the implications

$$(\mathcal{Z} \cap \mathcal{X}_i \neq \emptyset) \Rightarrow (\mathcal{X}_i \subseteq \mathcal{Z}) ; i = 1, \dots, n . \quad (6.1)$$

By Proposition 6.4, the implying clause in each of the  $n$  Implications (6.1) is true for reach-closed, stoichiometrically admissible subsets  $\mathcal{Z} \subseteq \mathcal{S}$ . If on another hand

all  $n$  implied clauses are true for such sets  $\mathcal{Z}$ , we have  $\mathcal{S}_e \subseteq \mathcal{Z}$  and the first condition of Theorem 6.8 is satisfied. Therefore, that the  $n$  Implications 6.1 are true is a sufficient condition for vacuous persistence. (This is also tautologically necessary because both clauses of each implication are trivially true when  $\mathcal{Z} = \mathcal{S}$ .) Realizing one of these implications amounts to seeking some kind of mutual reachability among isomeric elementary species. For example, isomerism among elementary species can occur with substrates and products in enzymatic networks, and one could consider that a substrate reaches a product modulo a catalyzing enzyme. In Gnacadja [5], the third and final paper in this series of articles, we explore these ideas and arrive at a subclass of biochemically important enzymatic networks that have isomerism among elementary species and are vacuously persistent.

With Theorem 6.9, we obtain that the allosteric ternary complex model of Fig. 1a is vacuously persistent. The theorem is not applicable to the networks of Fig. 1b and 1c because both have isomerism among their elementary species. However, the futile enzymatic cycle of Fig. 1b is in the class of networks that are shown in Gnacadja [5] to be vacuously persistent. On another hand, we saw in Gnacadja [4, Section 5] that the network of Fig. 1c is not vacuously persistent, and also that Angeli, De Leenheer and Sontag [1, Section 10] showed that it is persistent.

## 7 Conclusion

Motivated by the intuition that a reaction network should be persistent if it is constructed from building blocks that cannot be depleted, we developed a formalism for species composition. This yielded the result that if a mass-action reaction network is explicitly-reversibly constructive, then the absence of isomerism among the elementary species implies that it is vacuously persistent. The requirement that there be no isomerism among the elementary species is partially lifted with the work on binary enzymatic networks in the third and last article in this series of three papers. We think that there is more to be discovered by incorporating the species composition formalism in theoretical investigations of reaction networks. For instance, there probably is within mass-action explicitly-reversibly constructive networks a class of oscillation-free networks, and such class should contain a class of networks that are monostationary and globally asymptotically stable. Just like we noticed that instances of non-persistence and of non-obvious persistence in the literature always involve networks with isomerism among the building blocks, we also observe that multistationarity seems to always be illustrated with networks that possess this same property, and cases of oscillations come with even more particular traits.

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