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On balance relations for irreversible chemical reaction networks

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Abstract

We investigate a class of irreversible networks whose chemical species can be partitioned into two disjoint sets \mathcal{S}_1 and \mathcal{S}_2 , resulting in a weakly reversible subnetwork \mathcal{G}_2 involving only the species \mathcal{S}_2 , and a *semi-weakly-reversible network* \mathcal{G}_1 ; the latter reduces to a weakly reversible network on formally eliminating the chemical species \mathcal{S}_2 . We introduce a generalized flux balance condition that can be understood as the natural analogue of the complex balance condition for weakly reversible networks, and which serves as a tool for investigating how irreversible networks differ from reversible ones. We also make a connection between the generalized balance condition and the theory of multiscale networks by taking \mathcal{S}_1 to consist of high copy number species ($O(N)$), where N is the system size, and \mathcal{S}_2 to consist of low copy number species ($O(1)$). We show how the generalized balance condition of the full stochastic model is related to a moment balance condition of the corresponding piecewise deterministic Markov process (PDMP) obtained in the thermodynamic limit $N \rightarrow \infty$.

Keywords: chemical reaction networks, detailed balance, irreversibility, multiscale analysis, piecewise deterministic Markov processes, deficiency zero

(Some figures may appear in colour only in the online journal)

1. Introduction

It is well known that much of the interesting dynamical behavior observed in biological systems can be understood by analyzing the underlying chemical components [1]. Chemical reaction network theory provides a unified mathematical approach to studying these chemical processes. By relating the dynamical behavior of a system of chemical interactions to the topology of the reaction network, chemical reaction network theory has been able to identify

general network motifs in various biochemical systems [2–4]. Within chemical reaction network theory, there are usually two types of models one studies: a deterministic model known as the reaction rate equations, and a stochastic model that is often formulated in terms of a chemical master equation [5]. The relationship between the two models is well understood over finite time intervals; it is given by a law of large numbers in terms of the system-size N [6]. However, because the limits $N \rightarrow \infty$ and $t \rightarrow \infty$ do not necessarily commute, understanding the relationship in steady-state has proven to be a more difficult task, and remains an active area of research [7–10]. This task is further complicated when one considers multi-scale systems, which have time-scales that are not dependent on the system-size.

One of the most notable results in chemical reaction network theory is the *deficiency zero theorem* [2], which gives general conditions under which the reaction rate equations have a nontrivial stable equilibrium. More recently, this result has been extended to the chemical master equation, where it has been shown that, under the same conditions, the stochastic model has a product form stationary density [11, 12]. The networks to which these theorems apply are known as *complex balanced* [13], and can be thought of as a generalization of the class of detailed balance networks. In addition to making the computation of the stationary density tractable for a wide class of models, these results link the steady-states of the deterministic model to the stationary behavior of the stochastic model in a concrete way, thereby making progress towards a more complete understanding of how the two models are related. The deficiency zero theorem is also interesting from the perspective of non-equilibrium thermodynamics. For example, it as recently has been shown that for a complex balanced chemical reaction network one can sharpen the second law of thermodynamics [10, 14].

Results concerning complex balanced systems require the underlying network to be *weakly reversible* and *deficiency zero*. These are topological conditions: the former means that every reaction is contained in a closed cycle, while the latter means that all cycles can be realized in the reaction graph [14]. There are many physically relevant networks that violate these conditions, while still behaving similarly to complex balanced networks over long periods of time. For such networks, one can usually obtain a complex balanced network by performing an averaging procedure, but it is not clear what is lost by doing so [15]. In this paper we investigate a class of non-complex balanced networks \mathcal{G} whose chemical species can be partitioned into two disjoint sets \mathcal{S}_1 and \mathcal{S}_2 , resulting in a complex balanced subnetwork \mathcal{G}_2 involving only the species \mathcal{S}_2 , and a *semi-weakly-reversible network* \mathcal{G}_1 ; the latter reduces to a weakly reversible network on formally eliminating the chemical species \mathcal{S}_2 . We introduce a generalized flux balance condition that can be understood as the natural analogue of the complex balance condition for weakly reversible networks, and which serves as a tool for investigating non-equilibrium steady-states in non-complex balanced networks. Our analysis reveals that, in contrast to complex-balanced networks, the structure of probability fluxes in non-complex balanced networks is sensitive to stochasticity. In particular, the equilibria of a deterministic mean-field model of a network can satisfy a balance relation which is violated by the stochastic model. On the other hand, we show that the balance relation is preserved in a partial mean-field limit.

The paper is organized as follows. In section 2 we introduce the background notation and terminology related to reversible chemical reaction networks. In section 3 we formulate our theory of non-complex balanced networks and introduce the generalized flux balance condition. In section 4, we consider various examples of catalytic reaction networks, illustrating how the generalized balance condition can be used, and when it breaks down. Finally, in section 5 we make a connection between the generalized balance condition and the theory of multiscale networks by taking \mathcal{S}_1 to consist of high copy number species ($O(N)$), where N

is the system size, and \mathcal{S}_2 to consist of low copy number species ($O(1)$). We show how the generalized balance condition of the full stochastic model is related to a moment balance condition of the corresponding piecewise deterministic Markov process (PDMP) obtained in the thermodynamic limit $N \rightarrow \infty$.

2. Reversible chemical reaction networks

We begin by giving a general definition of a chemical reaction network for a well-mixed system of p interacting species.

Definition 2.1 (Chemical reaction network [2]). A *chemical reaction network (CRN)* is a triple $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ where

- \mathcal{S} is a finite set of *species* labeled $i = 1, 2, \dots, p$, whose interactions we seek to describe. Species are often denoted by capital letters (e.g. A, B, C, \dots).
- \mathcal{C} is a set of multi-sets of elements in \mathcal{S} called *complexes*. Each complex can be identified with a vector in the *species space* $k \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}|}$. We will adopt the usual abuse of notation and refer to both the multi-set (which lives in *complex space*) and the vector by the same symbol.
- \mathcal{R} is a set of single step *reactions*. That is, for each $\mathcal{R}_j \in \mathcal{R}$

$$\mathcal{R}_j = \{k_j^{\text{in}} \rightarrow k_j^{\text{out}}\}, \quad k_j^{\text{in}}, k_j^{\text{out}} \in \mathcal{C}.$$

We once again abuse notation and refer to $j \in \mathcal{R}$ as both the reaction itself and the index. The species indexed by the nonzero entries of k_j^{in} are referred to as *reactants*, while the species indexed by the nonzero entries of k_j^{out} are *products*.

We refer to $\|k_j^{\text{in}}\|_1 = \sum_{i=1}^p k_{j,i}^{\text{in}}$ as the *order of the j th reaction* and $\max_j \|k_j^{\text{in}}\|_1$ as the *order of \mathcal{G}* . The vector $K_j := k_j^{\text{out}} - k_j^{\text{in}}$ will be referred to as the *reaction direction* or *stoichiometric vector* for the j th reaction.

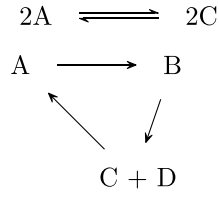
Corresponding to each reaction network \mathcal{G} is a unique, directed graph constructed as follows. The nodes of the graph are given by the set of distinct complexes $z \in \mathcal{C}$. A directed edge is then placed from a complex z to a complex z' if and only if $z \rightarrow z' \in \mathcal{R}$. Each connected component of the graph is called a *linkage class* of the graph, with the number of linkage classes denoted by l . A network is said to be *reversible* if for every forward reaction $k \rightarrow k' \in \mathcal{R}$ there is a corresponding backward reaction $k' \rightarrow k \in \mathcal{R}$. A network is said to be *weakly reversible* if for any reaction $k \rightarrow k' \in \mathcal{R}$, there is a sequence of directed reactions starting with k' as a reactant complex and ending with k as a product complex. If a network is not weakly reversible, we will say that it is *irreversible*. Another important notion is the span of the stoichiometric vectors $K_j = k_j^{\text{out}} - k_j^{\text{in}}$, that is,

$$\mathcal{S} = \text{span}_{j=1, \dots, R} \{K_j\} \subset \mathbb{R}^p.$$

In general, \mathcal{S} will be a subset of \mathbb{R}^p so that $s \equiv \dim[\mathcal{S}] \leq p$.

It should be noted that the terms reversible and irreversible are often used to refer to a dynamical notion of reversibility, namely the time-reversibility of a Markov process. To avoid confusion, we will refer to a time-reversible steady-state of a Markov process as an equilibrium steady-state.

As an illustration, consider the following set of chemical reactions:



There are $p = 4$ chemical species (A, B, C, D), $m = 5$ complexes ($A, B, C + D, 2A, 2C$), and $R = 5$ reactions. There are two disconnected graphs so the number of linkages $l = 2$. The top graph is reversible, whereas the second is weakly reversible. For this example,

$$\mathcal{S} = \text{span} \left\{ \begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \\ -1 \\ -1 \end{bmatrix}, \begin{bmatrix} -2 \\ 0 \\ 2 \\ 0 \end{bmatrix}, \begin{bmatrix} 2 \\ 0 \\ -2 \\ 0 \end{bmatrix} \right\} \tag{2.1}$$

$$= \text{span} \left\{ \begin{bmatrix} -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} 0 \\ -1 \\ 1 \\ 1 \end{bmatrix}, \begin{bmatrix} -2 \\ 0 \\ 2 \\ 0 \end{bmatrix} \right\}, \tag{2.2}$$

so that $s = 3$.

2.1. Chemical master equation (CME)

Let $X_i(t)$ be the number of molecules of species $i \in \mathcal{S}$ and set $X(t) = (X_i(t))_{i \in \mathcal{S}}$. Suppose the j th reaction occurs at a rate $N\alpha_j(X(t)/N)$. Here N is a dimensionless quantity representing the system size. For example, in gene networks N is typically taken to be the characteristic number of proteins. In other applications it may represent some volume scale factor. Between reactions, $X(t)$ is constant, and hence the time until the next reaction, Δt , is exponentially distributed with rate parameter equal to the sum of the rates. That is,

$$\mathbb{P}(\Delta t > t' | X(t) = x) = \exp \left\{ -t' N \sum_{j \in \mathcal{R}} \alpha_j(X(t)/N) \right\}. \tag{2.3}$$

Appropriate choices for the propensities $N\alpha_j$ can be derived from physical principles. For chemical systems, these are usually taken to be of the form [5]

$$\alpha_j(x/N) := \kappa_j \prod_{i \in \mathcal{S}} \frac{1}{N^{k_{ji}^{\text{in}}}} \frac{x_i!}{(x_i - k_{ji}^{\text{in}})!}, \tag{2.4}$$

where κ_j is a positive constant, and we will assume rates of this form throughout the remainder of the paper.

The process $X(t)$ obtained by repeatedly updating the state according to the reaction direction at exponentially distributed jump times is characterized by the generator [16],

$$Af(x) = \sum_{j \in \mathcal{R}} N\alpha_j(x/N)(f(x + K_j) - f(x)).$$

Using the generator one can write down the *forward Kolmogorov equation* or *chemical master equation* (CME), which describes the evolution of the probability density

$$p(x, t) := \mathbb{P}(X(t) = x | X(0) = x_0). \tag{2.5}$$

The CME is given in terms of the hermitian adjoint of A , denoted A^* :

$$\frac{d}{dt} p(x, t) = A^* p(x, t) = \sum_{j \in \mathcal{R}} \alpha_j([x - K_j]/N) p(x - K_j, t) - \alpha_j(x/N) p(x, t). \tag{2.6}$$

For the remainder of this paper we assume that the process $X(t)$ is irreducible, although the results are easily generalized to the reducible case [5]. Recall that an irreducible Markov chain is one for which any state can be reached from any other. We will say that \mathcal{G} is irreducible when $X(t)$ is.

In practice, the fully stochastic description is often intractable from both the computational and analytical perspectives [5]. This has motivated the development of reduced models by deriving limit theorems in terms of the scaling factor N [17]. In the classical setting, every species in \mathcal{S} is taken to scale with N and so a law of large numbers for the process yields a deterministic system of ODEs. In particular, introducing the concentrations $X_i^N(t) = X_i(t)/N$ and setting $z_i(t) = \lim_{N \rightarrow \infty} X_i^N(t)$, one obtains (provided the limit is interpreted in the appropriate sense) the *reaction rate equations* [2]

$$\frac{dz}{dt} = \sum_{j \in \mathcal{R}} \bar{\alpha}_j(z(t)) K_j \quad \bar{\alpha}_j(z(t)) := \kappa_j \prod_{i \in \mathcal{S}} z_i(t)^{k_{ji}^{\text{in}}}. \tag{2.7}$$

Note that $\bar{\alpha}_j$ is simply the leading order term in the Taylor expansion of (2.4) in N^{-1} , and that for first-order reactions these are identical. It turns out that the classical scaling is over simplified for the vast majority of biologically interesting models. In particular, many systems in biology operate in the *multiscale setting*, where abundances vary over many orders of magnitude between species [18, 19]. This has motivated more sophisticated treatments that allow for only some fraction of the species abundances to scale with N [20] (see section 5).

2.2. Reversibility and deficiency zero theorem

One of the most important results in chemical reaction network theory relates weak reversibility to the equilibria of the deterministic model. In order to state this result, we require the following notion of the deficiency of a CRN: The *deficiency* of a chemical reaction network $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ is the quantity

$$\delta = |\mathcal{C}| - l - s,$$

where l is the number of linkage classes and $s = \dim \mathcal{S}$. Deficiency plays a fundamental role in the study of chemical reaction networks, for a detailed discussion see [11]. Note that the above reaction network has a zero deficiency $\delta = 0$, since $m = 5, l = 2, s = 3$. We now state the deficiency zero theorem.

Theorem 2.1 (Deterministic deficiency zero theorem [5]). *Let $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible deficiency zero CRN. Then \mathcal{G} modeled deterministically according to (2.7) has a unique equilibrium $\zeta \in \mathbb{R}_{>0}^{|\mathcal{S}|}$ satisfying the complex balance relation*

$$\sum_{\{j: k_j^{\text{in}} = k_0\}} \alpha_j(\zeta) = \sum_{\{j: k_j^{\text{out}} = k_0\}} \alpha_j(\zeta) \tag{2.8}$$

for each $k_0 \in \mathcal{C}$.

If $\{j : k_j^{\text{in}} = k_0\}$ and $\{j : k_j^{\text{out}} = k_0\}$ each contain only a single reaction (for example, if \mathcal{G} is given by $A \rightleftharpoons B$), we obtain the *deterministic detailed balance* (DDB) relation (also known as *chemical detailed balance* [9])

$$\alpha_j(\zeta) = \alpha_{j^{-1}}(\zeta) \text{ for each } j \in \mathcal{R}, \quad (2.9)$$

with j^{-1} being the reversal of j . However, many networks admit detailed balanced equilibria even when the aforementioned sets are not singletons. While theorem 2.1 and its generalization require only conditions on the network structure, conditions under which the stronger relation (2.9) holds are given in terms of the specific choice of rate constants [3].

Recently there has been a considerable amount of work on the development of stochastic analogs to theorem 2.1. For example, see [11–13]. We state a result which is essentially a stochastic version of the deficiency zero theorem.

Theorem 2.2 (Stochastic deficiency zero theorem [13, theorem 5.1]). *Let $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible deficiency zero CRN with system size N . Then on each irreducible state space Γ_N there exists a stationary density π_N of the CME satisfying the stochastic complex balance (SCB) relation*

$$\sum_{\{j: k_j^{\text{in}}=k_0\}} \alpha_j([x - K_j]/N) \pi_N(x - K_j) = \sum_{\{j: k_j^{\text{out}}=k_0\}} \alpha_j(x/N) \pi_N(x) \quad (2.10)$$

for each $x \in \Gamma_N$ and $k_0 \in \mathcal{C}$. Moreover, π_N is given by the multivariate Poissonian stationary distribution

$$\pi_N(x) = C_N \prod_{i \in \mathcal{S}} \frac{(N\zeta_i)^{x_i}}{x_i!} e^{-N\zeta_i}, \quad (2.11)$$

where ζ satisfies (2.8) and C_N is a normalization constant.

Note that the detailed balance equation (2.10) is a particular form of the steady-state master equation for the invariant distribution π_N , $A\pi_N = 0$, which holds for time-reversible Markov chains. It states that the probability flux into each complex k_0 is equal to the outgoing probability flux. This is precisely the stochastic analogue of (2.8). In the remainder of this paper, we refer to a network \mathcal{G} that satisfies the hypothesis of theorems 2.1 and 2.2 as *complex balanced*. That is, \mathcal{G} is complex balanced if it is weakly-reversible and deficiency zero.

2.3. Equilibrium stationary distributions and detailed balance

One might wonder whether the existence of a *stochastic detailed balanced* (SDB) stationary density

$$\alpha_j(x - K_j) \pi_N(x - K_j) = \alpha_{j^{-1}}(x) \pi_N(x) \quad (2.12)$$

can be deduced from (2.9). In general it is not true that (2.9) implies (2.12), while it is always true that stochastic detailed balance implies deterministic detailed balance [21]. The following theorem says that they are equivalent for many networks of interest.

Theorem 2.3 (Relationship between SDB and DDB [21]). *Let \mathcal{G} be a reversible CRN and suppose*

$$|\{j \in \mathcal{R} : K_j = K\}| \leq 1$$

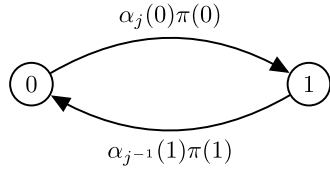


Figure 1. A schematic illustration of stochastic detailed balance for two states $0, 1 \in \Gamma$. The stochastic model is reversible and satisfies detailed balance provided $\alpha_{j-1}(1)\pi(1) = \alpha_j(0)\pi(0)$.

for each $K \in \mathbb{Z}^{|\mathcal{S}|}$. Then the deterministic rate model of \mathcal{G} satisfies deterministic detailed balance if and only if the CME satisfies stochastic detailed balance.

For stationary densities satisfying stochastic detailed balance, the product form density (2.11) can often be computed without knowledge of the equilibria ζ by directly solving the stochastic detailed balance relation. Physically speaking, the relation (2.12) says that in steady state the probability flux out of a state $x \in \Gamma$ is equal to the probability flux into x , see figure 1.

Detailed balance and the resulting product form stationary density play a fundamental role in the development of the thermodynamic theory of chemical reaction networks [22]. In particular, detailed balanced stationary densities correspond to *equilibrium steady-states*. In an equilibrium steady-state, the entropy production rate vanishes and the probability of finding the system in a given state is characterized by its internal energy [23]. Classical thermodynamics provides a complete theory of systems in equilibrium; however, since biological systems necessarily exist far from equilibrium, there is an increasing interest in developing an analogous theory for non-equilibrium systems [24].

3. Semi-reversibility, orthogonal decomposability, and generalized balance relations

Calculating the stationary solution of the chemical master equation (if it exists) is non-trivial for even the simplest non-complex balanced networks. In this section, we introduce a form of so-called *semi-reversibility* that applies to a wide class of irreversible networks, particularly those involving catalytic reactions. We then use this to develop a set of generalized balance relations for semi-reversible networks.

Suppose that the species of a non-complex balanced reaction network $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ are decomposed into two disjoint sets \mathcal{S}_1 and \mathcal{S}_2 . Any complex $k \in \mathcal{C}$ can then be written as $k = (u, v)$ with $k_i = u_i$ for $i = 1, \dots, |\mathcal{S}_1|$ and $k_i = v_i$ for $i = 1, \dots, |\mathcal{S}_2|$. Furthermore, suppose that under this decomposition the following properties hold:

- (i) The reactions can be decomposed into two sets \mathcal{R}_1 and \mathcal{R}_2 together with the complexes \mathcal{C}_1 and \mathcal{C}_2 , such that $\mathcal{G}_2 = (\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ forms a complex balanced subnetwork, whereas $\mathcal{G}_1 = (\mathcal{S}, \mathcal{C}_1, \mathcal{R}_1)$ is irreversible and involves a mixture of the species \mathcal{S}_1 and \mathcal{S}_2 . In particular, if $k \in \mathcal{C}_2$ then it can be written as $k = (0, v)$ for some $|\mathcal{S}_2|$ -dimensional vector v , that is, $k_i = 0$ for $i \in \mathcal{S}_1$.
- (ii) The stoichiometric vectors K_j of \mathcal{R}_1 and \mathcal{R}_2 are orthogonal, that is,

$$K_{j,i} = 0 \text{ for } j \in \mathcal{R}_1, \quad i \in \mathcal{S}_2$$

and

$$K_{j,i} = 0, \text{ for } j \in \mathcal{R}_2, \quad i \in \mathcal{S}_1.$$

- (iii) The network \mathcal{G}_1 is *semi-reversible* or *semi-weakly-reversible* as defined below.

Definition 3.1 (Semi-reversibility). The network \mathcal{G}_1 is said to be semi-reversible if it is reversible with respect to the species \mathcal{S}_1 , that is,

$$\{(u_j^{\text{in}}, v_j^{\text{in}}) \rightarrow (u_j^{\text{out}}, v_j^{\text{out}})\} \in \mathcal{R}_1$$

implies there exists

$$\{(u_l^{\text{in}}, v_l^{\text{in}}) \rightarrow (u_l^{\text{out}}, v_l^{\text{out}})\} \in \mathcal{R}_1,$$

such that $u_l^{\text{in}} = u_j^{\text{out}}$ and $u_l^{\text{out}} = u_j^{\text{in}}$. In other words, we relax the requirement that the complexes involved in the reverse reaction have the same elements of \mathcal{S}_2 as the forward reaction. Structurally, eliminating the species \mathcal{S}_2 results in a reversible network denoted by $\tilde{\mathcal{G}}_1$. Similarly, \mathcal{G}_1 is said to be semi-weakly-reversible if $\tilde{\mathcal{G}}_1$ is weakly-reversible deficiency zero with respect to the species \mathcal{S}_1 . We will let $\tilde{\mathcal{C}}_1$ denote the complexes of $\tilde{\mathcal{G}}_1$, which correspond to u in the decomposition $k = (u, v) \in \mathcal{C}_1$.

Definition 3.2 (Orthogonal decomposability). Suppose that an irreversible network $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$ can be decomposed into two subnetworks $\mathcal{G}_1 = (\mathcal{S}, \mathcal{C}_1, \mathcal{R}_1)$ and $\mathcal{G}_2 = (\mathcal{S}_2, \mathcal{C}_2, \mathcal{R}_2)$ such that conditions (i)–(iii) hold. The network \mathcal{G} is then said to be *orthogonally decomposable*.

While a network can have multiple orthogonal decompositions, the examples considered in this paper each have unique orthogonal decompositions. Furthermore, the general results discussed in this paper apply to any orthogonal decomposition, so a discussion of uniqueness is not relevant to the present study. With that said, it should be observed that one can obtain a unique orthogonal decomposition by taking \mathcal{G}_2 to be the reversible subnetwork with the maximum number of species over all such subnetworks satisfying (i)–(iii).

We now assume that all species of the orthogonally decomposable network \mathcal{G} scale with the system size N so that in the thermodynamic limit we have the reaction rate equations (2.7). Let $z = (\eta, \zeta)$ be an equilibrium of the rate equations. We can then rewrite the steady-state equations as follows:

$$0 = \sum_{j \in \mathcal{R}} \alpha_j(\eta, \zeta) K_{j,l} = \sum_{j \in \mathcal{R}} \kappa_j \left[\prod_{i \in \mathcal{S}_1} \eta_i^{k_{j,i}^{\text{in}}} \right] \left[\prod_{i \in \mathcal{S}_2} \zeta_i^{k_{j,i}^{\text{in}}} \right] K_{j,l}, \quad l \in \mathcal{S}.$$

Using orthogonality of the stoichiometric vectors (see condition (ii)) and $k_{j,i}^{\text{in}} = 0$ for $j \in \mathcal{R}_2$ and $l \in \mathcal{S}_1$, we have

$$0 = \sum_{j \in \mathcal{R}_1} \kappa_j \left[\prod_{i \in \mathcal{S}_1} \eta_i^{k_{j,i}^{\text{in}}} \right] \left[\prod_{i \in \mathcal{S}_2} \zeta_i^{k_{j,i}^{\text{in}}} \right] K_{j,l}, \quad l \in \mathcal{S}_1, \quad (3.1a)$$

$$0 = \sum_{j \in \mathcal{R}_2} \kappa_j \left[\prod_{i \in \mathcal{S}_2} \zeta_i^{k_{j,i}^{\text{in}}} \right] K_{j,l} \quad l \in \mathcal{S}_2. \quad (3.1b)$$

Since the subnetwork \mathcal{G}_2 is weakly reversible deficiency zero, we can use the theorems of section 2 to establish that equation (3.1b) has a unique solution ζ . Moreover, setting $\tilde{\kappa}_j(\zeta) = \kappa_j \prod_{i \in \mathcal{S}_2} \zeta_i^{k_{j,i}^{\text{in}}}$, equation (3.1a) can be rewritten as

$$0 = \sum_{j \in \mathcal{R}_1} \tilde{\kappa}_j(\zeta) \left[\prod_{i \in \mathcal{S}_1} \eta_i^{k_{j,i}^{\text{in}}} \right] K_{j,l}, \quad l \in \mathcal{S}_1. \quad (3.2)$$

The semi-reversibility condition (iii) then ensures that these equations correspond to the steady-state equations for a weakly reversible, deficiency zero network $\tilde{\mathcal{G}}_1$, which is obtained by eliminating the species \mathcal{S}_2 from \mathcal{G} . It follows from theorem 2.1 that (3.2) has a unique positive solution η . Moreover, this equilibria satisfies the generalized deterministic complex balance relations

$$\sum_{\{j \in \mathcal{R}_1: u_j^{\text{out}} = u_0\}} \alpha_j(\eta, \zeta) = \sum_{\{j \in \mathcal{R}_1: u_j^{\text{in}} = u_0\}} \alpha_j(\eta, \zeta) \quad (3.3)$$

for each $u_0 \in \tilde{\mathcal{E}}_1$. Similarly, if \mathcal{G}_1 is semi-reversible then a detailed balance condition holds.

Recall from section 2 that in the case of weakly reversible networks, there is a strong connection between the existence of an equilibrium of the deterministic reaction rate equations and a stationary distribution π_N of the corresponding CME. In other words, there is a stochastic analog of the deterministic complex balance relation, see theorems 2.1 and 2.2. In the case of an orthogonally decomposable network, the generator of the CME can be written as

$$Af(x) = \sum_{j \in \mathcal{R}_1} N \alpha_j(x/N) (f(x + U_j, y) - f(x)) + \sum_{j \in \mathcal{R}_2} N \alpha_j(x/N) (f(x, y + V_j) - f(x)), \quad (3.4)$$

where $\{x_i, i = 1, \dots, |\mathcal{S}_1|\}$, and $\{y_i, i = 1, \dots, |\mathcal{S}_2|\}$ denote the species counts, and we have set $K_j = (U_j, V_j)$ with $U_j = u_j^{\text{out}} - u_j^{\text{in}}$ and $V_j = v_j^{\text{out}} - v_j^{\text{in}}$. From condition (ii) we see that $U_j = 0$ for $j \in \mathcal{R}_2$ and $V_j = 0$ for $j \in \mathcal{R}_1$. The existence of the generalized deterministic complex balance relation (3.3) for an orthogonally decomposable network then suggests that we define a *generalized stochastic complex balance* relation according to

$$\begin{aligned} & \sum_{\{j \in \mathcal{R}_1: u_j^{\text{out}} = u_0\}} \sum_{\{y: \alpha_j(x - U_j, y) \neq 0\}} \alpha_j(x - U_j, y) \pi_N(x - U_j, y) \\ &= \sum_{\{j \in \mathcal{R}_1: u_j^{\text{in}} = u_0\}} \sum_{\{y: \alpha_j(x, y) \neq 0\}} \alpha_j(x, y) \pi_N(x, y), \end{aligned} \quad (3.5)$$

for each $u_0 \in \tilde{\mathcal{E}}_1$. Note that the inner sum is taken over all y for which the rates are not identically zero. Similarly, if j has a unique semi-reversal $j^{-1} \in \mathcal{R}_1$, we introduce the *generalized stochastic detailed balance* relation

$$\begin{aligned} & \sum_{\{y: \alpha_j(x - U_j, y) \neq 0\}} \alpha_j(x - U_j, y) \pi_N(x - U_j, y) \\ &= \sum_{\{y: \alpha_{j^{-1}}(x, y) \neq 0\}} \alpha_{j^{-1}}(x, y) \pi_N(x, y) \end{aligned} \quad (3.6)$$

for each $j \in \mathcal{R}_1$. Like (2.12) and (2.10), (3.6) and (3.5) impose restrictions on the stationary density of the Markov chain modeling a CRN in terms of probability fluxes. In contrast to the complex balance relation, these relations are valid when the underlying network is irreversible. Through some specific examples, we now show that, unlike weakly reversible networks, the existence of the deterministic balance relation (3.2) for an orthogonally decomposable network does not necessarily ensure that the corresponding stochastic balance relation (3.5) also holds.

4. Examples of orthogonally decomposable chemical reaction networks

4.1. Example 1: calculation of a stationary distribution when generalized detailed balance holds

Consider an irreversible chemical reaction network \mathcal{G} given by the set of reactions



This reaction network (4.1) describes the interactions of a population of species in the set $\{A, B, C, D\}$. The positive constants κ_i indicate the rates at which the reactions occur. In this network, the chemical species A is converted into B in the presence of a catalyst C. Similarly, B is converted into A in the presence of a catalyst D. Finally, D and C are spontaneously converted into each other. In terms of definition 2.1, we have $\mathcal{G} = (\mathcal{S}, \mathcal{C}, \mathcal{R})$, where

$$\begin{aligned} \mathcal{S} &= \{A, B, C, D\} \\ \mathcal{C} &= \{A + C, B + C, A + D, B + D, C, D\}. \end{aligned}$$

If we instead choose to represent complexes as vectors in \mathbb{Z}^4 , then

$$\mathcal{C} = \{(1, 0, 1, 0), (0, 1, 1, 0), (1, 0, 0, 1), (0, 1, 0, 1), (0, 0, 0, 1), (0, 0, 0, 1)\}.$$

The set \mathcal{R} consists of four reactions: the second-order reactions

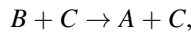
$$\begin{aligned} \{A + C \rightarrow B + C\} &= \{(1, 0, 1, 0) \rightarrow (0, 1, 1, 0)\}, \quad k_1 = (-1, 1, 0, 0) \\ \{B + D \rightarrow A + D\} &= \{(0, 1, 0, 1) \rightarrow (1, 0, 0, 1)\}, \quad k_2 = (1, -1, 0, 0), \end{aligned}$$

and the reversible first-order reactions

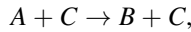
$$\begin{aligned} \{D \rightarrow C\} &= \{(0, 0, 0, 1) \rightarrow (0, 0, 1, 0)\}, \quad k_3 = (0, 0, 1, -1) \\ \{C \rightarrow D\} &= \{(0, 0, 1, 0) \rightarrow (0, 0, 0, 1)\}, \quad k_4 = (0, 0, -1, 1). \end{aligned}$$

Note that (4.1) is deficiency one.

It is clear that the network (4.1) is not reversible in the standard reaction-wise sense. For example, the reaction



corresponding to the reversal of



is not present in \mathcal{G} . \mathcal{G} is also not weakly reversible. However, it is orthogonally decomposable according to definition 3.2, as illustrated schematically in figure 2. First, we set $\mathcal{S}_1 = \{A, B\}$ and $\mathcal{S}_2 = \{C, D\}$ and

$$\mathcal{R}_1 = \{A + C \rightarrow B + C, B + D \rightarrow A + D\}, \quad \mathcal{R}_2 = \{D \rightleftharpoons C\}.$$

It is straightforward to check that conditions (i)–(iii) hold. In particular, \mathcal{G}_2 is reversible and \mathcal{G}_1 is semi-reversible. The latter follows from the fact that $A + C \rightarrow B + C$ has the ‘semi-reverse’ reaction $B + D \rightarrow A + D$. Therefore, \mathcal{G}_1 inherits deterministic detailed balance from the reversible network $\tilde{\mathcal{G}}_1$ consisting of the reactions $A \rightleftharpoons B$. That is,

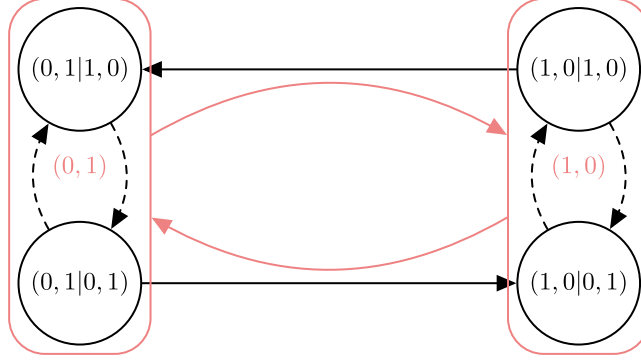


Figure 2. The complex space $\Gamma = \{0, 1\}^4$ of the orthogonally decomposable network (4.1) is shown in black with $k = (k_A, k_B|k_C, k_D)$. The arrows represent edges in the graph of the corresponding transition matrix. In red we see the complexes (k_A, k_B) of the reversible network $A \rightleftharpoons B$ obtained by eliminating C, D along the lines of the definition of semi-reversibility.

$$\tilde{\kappa}_1 z_A = \tilde{\kappa}_2 z_B, \tag{4.2}$$

where $\tilde{\kappa}_1 = \kappa_1 z_C$ and $\tilde{\kappa}_2 = \kappa_2 z_D$. Figure 2 can be simplified further by noting that the components of the complexes satisfy $k_A + k_B = 1$ and $k_C + k_D = 1$. Hence we can represent every complex uniquely by $(k_A, k_C) \in \{0, 1\}^2$. The simplified diagram is shown in figure 3.

We now turn to the stochastic model. Let X_A, X_B, Y_C and Y_D denote the species counts. Noting that the system has two conservation laws, we take the *classical scaling* $X_A + X_B = N$ and $Y_C + Y_D = N$ with $N \gg 1$. (In section 5 we consider a multiscale network where A and B have high copy numbers, whereas C and D have low copy numbers, that is, we take $X_A + X_B = N$ and $Y_C + Y_D = 1$.) Note that due to the conservation laws, the coordinates (x_A, y_C) uniquely specify the state of the system. Under the classical scaling, the four reactions have the following propensities:

$$\begin{aligned} N\alpha_1((x_A, y_C)/N) &= \kappa_1 N x_A y_C, & N\alpha_2((x_A, y_C)/N) &= \kappa_2 N (1 - x_A/N)(1 - y_C/N), \\ N\alpha_3(y_C/N) &= \kappa_3 (N - y_C), & N\alpha_4(y_C/N) &= \kappa_4 N y_C. \end{aligned}$$

We have used the conservation conditions to set $x_B = N - x_A$ and $y_D = N - y_C$. The CME takes the explicit form

$$\begin{aligned} \frac{dp}{dt} &= N\alpha_1([x_A + 1], y_C)/N p(x_A + 1, y_C, t) - N\alpha_1((x_A, y_C)/N) p(x_A, y_C, t) \\ &\quad + N\alpha_2([x_A - 1], y_C)/N p(x_A - 1, y_C, t) - N\alpha_2((x_A, y_C)/N) p(x_A, y_C, t) \\ &\quad + \alpha_3([y_C - 1]/N) p(x_A, y_C - 1, t) + \alpha_4([y_C + 1]/N) p(x_A, y_C + 1, t) \\ &\quad - \alpha_3(y_C/N) p(x_A, y_C, t) - \alpha_4(y_C/N) p(x_A, y_C, t). \end{aligned} \tag{4.3}$$

Rescaling and taking the limit $N \rightarrow \infty$ recovers the rate equations considered above.

Given the generalized deterministic detailed balance relation (4.2), is there a corresponding generalized detailed balance condition? It turns out that for the particular network (4.1), the answer is yes, namely,

$$(x_A + 1)\kappa_1 \pi_N(x_A + 1, 1) = (N - x_A)\kappa_2 \pi_N(x_A, 0). \tag{4.4}$$

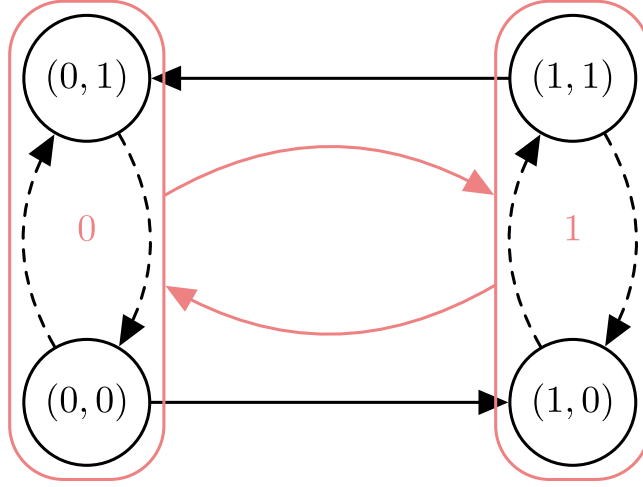


Figure 3. Simplified version of figure 2 for $\Gamma = \{0, 1\} \times \{0, 1\}$ with complexes $k = (k_A, k_C)$.

This relation is automatically satisfied, since the probability flux is balanced across graph cuts, see [25] for details, and is illustrated graphically in figure 4 for $N = 1$. Setting $p = \pi_N$ in equation (4.3) shows that $\pi_N(x, y)$, $y = 0, 1$, satisfy the pair of equations

$$\begin{aligned} 0 &= \kappa_1(x + 1)\pi_N(x + 1, 1) - \kappa_1x\pi_N(x, 1) + \kappa_4\pi_N(x, 0) - \kappa_3\pi_N(x, 1), \\ 0 &= \kappa_2(N - x + 1, 0)\pi_N(x - 1, 0) - \kappa_2(N - x)\pi_N(x, 0) + \kappa_3\pi_N(x, 1) - \kappa_4\pi_N(x, 0). \end{aligned}$$

We can utilize the balance condition (4.4) to decouple these equations. After simplification, the resulting uncoupled system is

$$\begin{aligned} (x + 1) \left(1 + \frac{\kappa_4}{\kappa_2(N - x)} \right) \kappa_1\pi_N(x + 1, 1) &= (\kappa_3 + \kappa_1x)\pi_N(x, 1), \\ (N - x + 1) \left(1 + \frac{\kappa_3}{x\kappa_1} \right) \kappa_2\pi_N(x - 1, 0) &= (\kappa_4 + \kappa_2(N - x))\pi_N(x, 0). \end{aligned}$$

This allows us to write, for example,

$$\begin{aligned} \pi_N(x, 1) &= C_1 \prod_{k=x}^{N-1} \frac{\kappa_1(k + 1) \left(1 + \frac{\kappa_4}{\kappa_2(N - k)} \right)}{(\kappa_3 + \kappa_1k)} \\ &= C_1 \frac{(x + 1)_{N-x} \left(x - N - \frac{\kappa_4}{\kappa_2} \right)_{N-x}}{(x - N)_{N-x} \left(x + \frac{\kappa_3}{\kappa_1} \right)_{N-x}} \end{aligned}$$

for some normalization constant C_1 . Here we are using the Pochhammer symbol,

$$(x)_a = \frac{\Gamma(x + a)}{\Gamma(x)}.$$

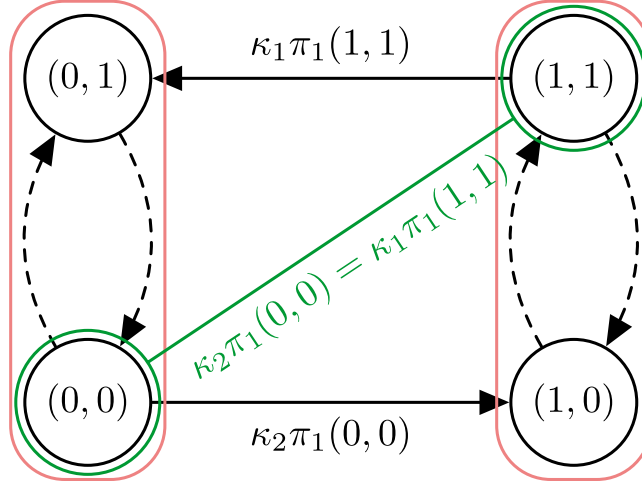


Figure 4. An illustration of the generalized detailed balance condition for the network (4.1) with $N = 1$. Here the states are labeled by (x_A, y_C) . The condition (3.6) holds when $\kappa_1\pi(1, 1) = \kappa_2\pi(1, 1)$.

Similarly,

$$\pi_N(x, 0) = C_2 \frac{(x - N - 1)_{2-x} \left(x + \frac{\kappa_3}{\kappa_1}\right)_{2-x}}{(x)_{2-x} \left(x - N - \frac{\kappa_4}{\kappa_2}\right)_{2-x}}.$$

The constants C_1 and C_2 can be computed by summing over the state space and imposing normalization conditions on the result. However, we omit the expressions, as they are somewhat complicated.

4.2. Example II: breakdown of generalized stochastic detailed balance

To illustrate the more general balance relation (3.5), consider the orthogonally decomposable network \mathcal{G} given by



Again $\mathcal{S}_1 = \{A, B\}$ and $\mathcal{S}_2 = \{C, D\}$ but now

$$\mathcal{R}_1 = \{A + C \rightarrow B + C, B + D \rightarrow A + D\}, \quad \mathcal{R}_2 = \{2D \rightleftharpoons C + D\}.$$

Conditions (i)–(iii) still hold so that we have the generalized detailed balance equation of the form (4.2). However, in this case the corresponding CME does not satisfy generalized stochastic detailed balance. In order to illustrate this, suppose $X_A + X_B = 1$ and $Y_D + Y_C = 2$. If initially $Y(t) = (Y_D(t), Y_C(t)) = (0, 2)$, then after the 4th reaction $Y(t) = (1, 1)$. The third reaction then returns us to the state $Y(t) = (0, 2)$. As a result, this model has a stationary density on the irreducible component

$$\Gamma = \{(1, 0, 2, 0), (1, 0, 1, 1), (0, 1, 2, 0), (0, 1, 1, 1)\}.$$

This is contrast to the previous example where the effect of the third and fourth reactions was to switch between having one D molecule and one C molecule. As a consequence the symmetry of the previous model that led to a generalized stochastic detailed balance reaction is broken.

It is straightforward to establish that the stationary density is given by

$$\begin{aligned} \pi(1, 0, 1, 1) &= C\kappa_1\kappa_3\kappa_4 \\ \pi(1, 0, 0, 2) &= C2\kappa_1\kappa_4(\kappa_2 + \kappa_4) \\ \pi(0, 1, 1, 1) &= C\kappa_2\kappa_3(\kappa_1 + \kappa_2 + \kappa_3 + \kappa_4) \\ \pi(0, 1, 0, 2) &= C\kappa_2\kappa_4(\kappa_2 + \kappa_3 + \kappa_4) \end{aligned}$$

for some normalization constant C . In order to see that complex rather than detailed balance holds, consider the left hand side of (3.5) with $u_0 = ((u_0)_A, (u_0)_B) = (1, 0)$. The only reaction containing u_0 as an outgoing complex is $B + D \xrightarrow{\kappa_2} A + D$. Therefore,

$$\begin{aligned} &\sum_{\{j \in \mathcal{R}_1: u_j^{\text{out}} = u_0\}} \sum_{\{y: \alpha_j(x - U_j, y) \neq 0\}} \alpha_j(x - U_j, y) \pi(x - U_j, y) \\ &= \kappa_1(x_B + 1)2\pi(x - (1, -1), 0, 2) + \kappa_1(x_B + 1)\pi(x - (1, -1), 1, 1). \end{aligned}$$

To make this expression nonzero we set $x = (1, 0)$, which yields

$$\kappa_1 2\pi(0, 1, 0, 2) + \kappa_1 \pi(0, 1, 1, 1) = C2\kappa_1\kappa_2\kappa_4(\kappa_2 + \kappa_3 + \kappa_4).$$

Similarly, taking $x = (1, 0)$ on the right hand side of (3.5),

$$\begin{aligned} &\sum_{\{j \in \mathcal{R}_1: k_j^{\text{in}} = k_0\}} \sum_{\{y: \alpha_j(x, y) \neq 0\}} \alpha_j(x, y) \pi(x, y) \\ &= \alpha_1(1, 0, 1, 1)\pi(1, 0, 1, 1) = C2\kappa_1\kappa_2\kappa_4(\kappa_2 + \kappa_3 + \kappa_4). \end{aligned}$$

The resulting equality shows that equation (3.5) is satisfied. This complex balance relation is illustrated in figure 5, where we have recreated figure 4 for this network.

4.3. Example III: breakdown of generalized stochastic complex balance

Consider the network



For simplicity we set all the rate constants to 1 and impose the conservation laws

$$X_A + X_B + X_C = 2$$

and

$$Y_D + Y_E = 1.$$

For this model $\mathcal{S}_1 = \{A, B, C\}$ and $\mathcal{S}_2 = \{D, E\}$ with

$$\mathcal{R}_1 = \{A + D \rightarrow B + D, B + D \rightarrow C + D, C + E \rightarrow A + E\}, \quad \mathcal{R}_2 = \{E \rightleftharpoons D\}.$$

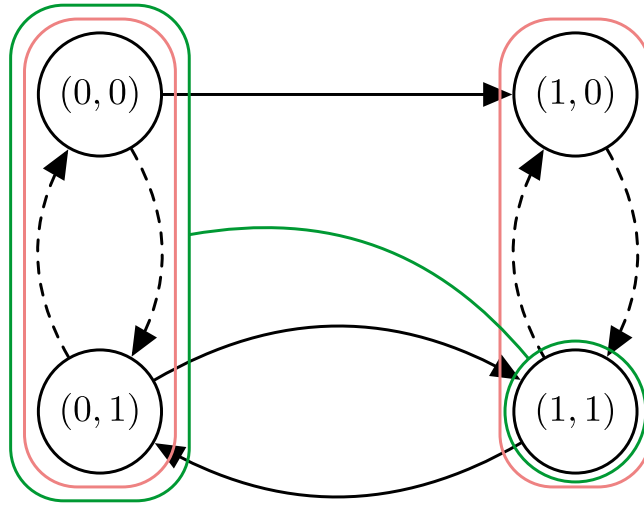
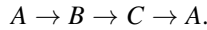


Figure 5. An illustration of the generalized complex balance condition on the reaction network (4.5). Here the states are labeled by (x_A, y_C) . The green overlay illustrates how the condition (3.5) relates $\pi(0, 1)$ to $\pi(1, 0)$ and $\pi(0, 0)$.

It is straightforward to check that conditions (i)–(iii) hold with \mathcal{G}_2 reversible and \mathcal{G}_1 semi-weakly-reversible. The latter follows from the fact that eliminating D and E yields the network $\tilde{\mathcal{G}}_1$ given by the linear cycle



Moreover, the latter clearly satisfies the hypothesis of theorem 2.2, that is, it is weakly reversible and deficiency zero.

The state space of the model is

$$\Gamma = \{(2, 0, 0, 1, 0), (1, 1, 0, 1, 0), (0, 1, 1, 1, 0), (1, 0, 1, 1, 0), (0, 0, 2, 1, 0), (0, 2, 0, 1, 0), (2, 0, 0, 0, 1), (1, 1, 0, 0, 1), (0, 1, 1, 0, 1), (1, 0, 1, 0, 1), (0, 0, 2, 0, 1), (0, 2, 0, 0, 1)\}.$$

Note that using the conservation laws the state of the system is uniquely specified by the tuple (x_A, x_B, x_D) . The complete state space along with the transition arrows is depicted in figure 6. The size of the state-space makes it cumbersome to obtain general relations, but in order to show that this network does not satisfy (3.5) we only need to select one u_0 and x for which the condition is violated. We will take $u_0 = ((u_0)_A, (u_0)_B, (u_0)_C) = (1, 0, 0)$ and $x = (x_A, x_B, x_C) = (1, 1, 0)$. u_0 appears in the outgoing complex in the third reaction, $C + E \xrightarrow{1} A + E$, and in the ingoing complex in the first reaction, $A + D \xrightarrow{1} B + D$. Finally, the relevant reaction direction appearing in (3.5) is $U_3 = (1, 0, -1)$. Combing this information, we find that (3.5) is of the form

$$\sum_y \alpha_3(x - U_3, y)\pi(x - U_1, y) = \sum_y \alpha_1(x, y)\pi(x, y),$$

which simplifies to $\pi(1, 1, 0, 0, 1) = \pi(0, 1, 1, 1, 0)$. On the other hand, computing the stationary density of the corresponding CME amounts to finding the nullspace of a 12×12 matrix, which can easily be done in any modern computer algebra system. One finds that $\pi(1, 1, 0, 0, 1) = 7/96$ while $\pi(0, 1, 1, 1, 0) = 5/48$, implying that equation (3.5) is not satisfied. Hence, this example shows that although the averaged network satisfies the stochastic

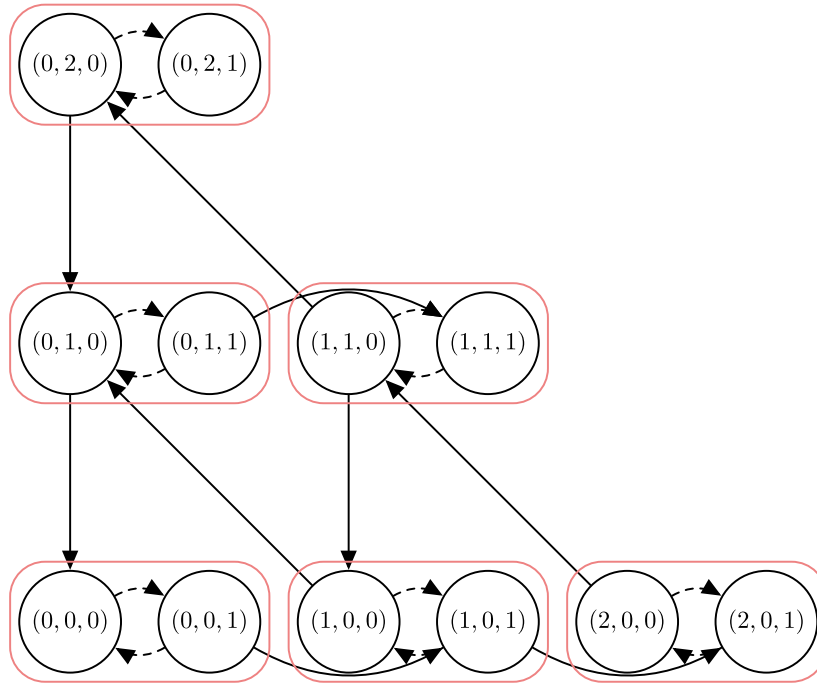


Figure 6. The state space of the network (4.6). We have used the conserved quantities to label the states by (x_A, x_B, y_D) .

complex balance relation (2.10), this does not guarantee that the full network satisfies the generalized relation (3.6).

5. Balance relations for multiscale networks

In our analysis of orthogonally decomposable chemical reaction networks (sections 3 and 4), we assumed that all species scaled with the system size N (classical scaling). However, aside from the derivation of the reaction rate equations, the choice of scaling played no significant role in the analysis. In particular orthogonal decomposability is a structural property of a network that is independent of the choice of scaling. In this section we consider a form of multi-scaling where \mathcal{S}_1 is identified with species having high copy numbers ($O(N)$), whereas \mathcal{S}_2 is identified with low copy number species ($O(1)$). This is often the case in catalytic reaction networks such as those considered in section 4.

Let $(x, y) \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}_1|+|\mathcal{S}_2|}$ denote the state variables of an orthogonally decomposable network \mathcal{G} . The stochastic process associated with \mathcal{G} is generated by (compare with equation (3.4))

$$\begin{aligned}
 Af(x, y) &= A_1f(x, y) + A_2f(x, y) \\
 &= N \sum_{j \in \mathcal{R}_1} \alpha_j(x/N, y) (f(x + U_j, y) - f(x, y)) \\
 &\quad + \sum_{j \in \mathcal{R}_2} \alpha_j(x/N, y) (f(x, y + V_j) - f(x, y)).
 \end{aligned} \tag{5.1}$$

After introducing the rescaled state variable $(X^N(t), Y(t)) = (X(t)/N, Y(t))$ and defining the limiting process $(Z(t), Y(t)) = \lim_{N \rightarrow \infty} (X^N(t), Y(t))$, we obtain the piecewise deterministic Markov process (PDMP) [20]

$$\frac{dZ_i}{dt} = \sum_{j \in \mathcal{R}_1}^p \alpha_j(Z, Y(t)) U_{j,i}, \quad i \in \mathcal{S}_1, \quad (5.2)$$

while the time to the next jump in $Y(t)$ now depends on $Z(t)$. In terms of the notation used earlier, see equation (2.3),

$$\mathbb{P}(\Delta t > t' | (z(t), Y(t)) = (z, y)) = \exp \left\{ - \int_0^{t'} \sum_{j \in \mathcal{R}_2} \alpha_j(z(s), Y(t)) ds \right\}.$$

The generator corresponding to the process $(Z(t), Y(t))$ is

$$\begin{aligned} \bar{A}f(z, y) &= \bar{A}_1 f(z, y) + A_2 f(z, y) \\ &= \sum_{j \in \mathcal{R}_1} \alpha_j(z, y) U_j \cdot \nabla f(z, y) + \sum_{j \in \mathcal{R}_2} \alpha_j(z, y) (f(z, y + V_j) - f(z, y)), \end{aligned} \quad (5.3)$$

and in place of the CME we have a differential Chapman–Kolmogorov (dCK) equation for $\bar{p} = \bar{p}(z, y, t)$:

$$\frac{\partial}{\partial t} \bar{p}(z, y, t) = \bar{A}^* \bar{p}(z, y, t). \quad (5.4)$$

In practice, the problem of obtaining information about the density of the thermodynamic limit is usually much more manageable than attempting to study the full stochastic model. In particular, the PDMP is much less costly to simulate [26].

As a specific example, let us return to the network (4.1). The four reactions propensities of the network under a multiscale scaling are given by

$$\begin{aligned} N\alpha_1(x_A/N, y_C) &= \kappa_1 N x_A y_C, & N\alpha_2(x_A/N, y_C) &= \kappa_2 N (N - x_A) (1 - y_C), \\ \alpha_3(y_C/N) &= \kappa_3 (1 - y_C), & \alpha_4(y_C) &= \kappa_4 y_C \end{aligned}$$

where we now have $y_D = 1 - y_C \in \{0, 1\}$. The corresponding CME becomes

$$\begin{aligned} \frac{dp}{dt} &= N\alpha_1([x_A + 1]/N, y_C) p(x_A + 1, y_C, t) - N\alpha_1(x_A/N, y_C) p(x_A, y_C, t) \\ &\quad + N\alpha_2([x_A - 1]/N, y_C) p(x_A - 1, y_C, t) - N\alpha_2(x_A/N, y_C) p(x_A, y_C, t) \\ &\quad + \alpha_3(1 - y_C) p(x_A, 1 - y_C, t) + \alpha_4(1 - y_C) p(x_A, 1 - y_C, t) \\ &\quad - \alpha_3(y_C) p(x_A, y_C, t) - \alpha_4(y_C) p(x_A, y_C, t). \end{aligned} \quad (5.5)$$

Applying the system-size expansion to the first four terms on the right-hand side in the large- N limit with $z = x_A/N$ now yields the dCK equation

$$\begin{aligned} \frac{\partial \bar{p}(z, y_C, t)}{\partial t} &= - \frac{\partial}{\partial z} [\alpha_2(z, y_C) - \alpha_1(z, y_C)] \bar{p}(z, y_C, t) \\ &\quad + \alpha_3(1 - y_C) \bar{p}(z, 1 - y_C, t) + \alpha_4(1 - y_C) \bar{p}(z, 1 - y_C, t) \\ &\quad - \alpha_3(y_C) \bar{p}(z, y_C, t) - \alpha_4(y_C) \bar{p}(z, y_C, t). \end{aligned} \quad (5.6)$$

This represents the evolution of the probability density for sample paths of the following piecewise deterministic Markov process (PDMP) for $(Z(t), Y_C(t))$ [20]:

$$\frac{dZ}{dt} = \alpha_2(Z, Y_C) - \alpha_1(Z, Y_C), \tag{5.7}$$

with $Y_C \in \{0, 1\}$ given by the two-state Markov process

$$0 \xrightleftharpoons[\kappa_4]{\kappa_3} 1.$$

Since the transition rates κ_3, κ_4 are independent of Z , the PDMP is said to be without any feedback.

We now add one further restriction on the orthogonally decomposable, multiscale network \mathcal{G} , namely, that the complex balanced network $\tilde{\mathcal{G}}_1$ (see definition 3.1) is first-order and conservative. We then have the following theorem, which gives a relationship between the stationary density of the CME and the moments of the PDMP.

Theorem 5.1. *Let $\mathcal{G} = (\mathcal{G}_1, \mathcal{G}_2)$ be an orthogonally decomposable, multiscale network such that $\tilde{\mathcal{G}}_1$ is first-order and conservative. Let π_N denote the stationary density of the CME of \mathcal{G} generated by (5.1), and let $(Z(t), Y(t))$ be the process generated by (5.3). Then*

$$\mathbb{E} \left[\mathbf{1}\{Y(t) = y\} \prod_{i \in \mathcal{S}_1} Z_i^{x_i}(t) \right] = \pi_N(x, y) \tag{5.8}$$

for $\sum_i x_i = N$, with the expectation being taken with respect to the stationary density of the PDMP. The index function $\mathbf{1}\{Y(t) = y\} = 1$ when $Y(y) = y$ and is zero otherwise.

Proof. Consider the time-dependent moment

$$\begin{aligned} \mathcal{M}(x, y, t) &:= \mathbb{E} \left[\mathbf{1}\{Y(t) = y\} \prod_{i \in \mathcal{S}_1} Z_i^{x_i}(t) \right] \\ &= \int_0^1 dz \sum_{y'} \left[\mathbf{1}\{y' = y\} \prod_{i \in \mathcal{S}_1} z_i^{x_i} \right] \bar{p}(z, y', t), \end{aligned} \tag{5.9}$$

where \bar{p} evolves according to equation (5.4). The proof involves showing that $\mathcal{M}(x, y, t)$ evolves according to the same evolution equation as the CME for $p(x, y, t)$. First, differentiating both sides of equation (5.9) with respect to t gives

$$\frac{d}{dt} \mathcal{M}(x, y, t) = \int_0^1 dz \sum_{y'} \left[\mathbf{1}\{y' = y\} \prod_{i \in \mathcal{S}_1} z_i^{x_i} \right] \frac{\partial}{\partial t} \bar{p}(z, y', t).$$

Substituting equation (5.4) then yields

$$\frac{d}{dt} \mathcal{M}(x, y, t) = \int_0^1 dz \sum_{y'} \bar{A} \left[\mathbf{1}\{y' = y\} \prod_{i \in \mathcal{S}_1} z_i^{x_i} \right] \bar{p}(z, y', t). \tag{5.10}$$

For $x \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}_1|}$ define

$$f_{y',x}(z, y) = \mathbf{1}\{y = y'\} \prod_{i \in \mathcal{S}_1} z_i^{x_i},$$

and note the useful identities

$$\begin{aligned}\frac{\partial}{\partial z_i} f_{y',x}(z,y) &= \mathbf{1}\{y = y'\} x_i \prod_{i' \in \mathcal{S}_1} z_{i'}^{x_{i'} - \delta_{i',i}} = x_i f_{y',x_1, \dots, x_i-1, \dots, x_i}(z,y) \\ &= x_i f_{y',x-e_i}(z,y),\end{aligned}$$

where e_i denotes the unit vector with only the i th component non-zero, and

$$\begin{aligned}\alpha_j(z,y) f_{y',x}(z,y) &= \tilde{\kappa}_j(y) \mathbf{1}\{y = y'\} \prod_{i \in \mathcal{S}_1} z_i^{k_j^{\text{in}}} \prod_{i \in \mathcal{S}_1} z_i^{x_i} \\ &= \tilde{\kappa}_j(y) \mathbf{1}\{y = y'\} \prod_{i \in \mathcal{S}_1} z_i^{k_j^{\text{in}} + x_i} = \tilde{\kappa}_j(y) f_{y',x+k_j^{\text{in}}}(z,y),\end{aligned}$$

where $\tilde{\kappa}_j$ is the effective rate constant that depends on y . Applying \bar{A} to $f_{y',x}(z,y)$ yields

$$\begin{aligned}\bar{A} f_{y',x}(z,y) &= \sum_{i \in \mathcal{S}_1} \sum_{j \in \mathcal{R}_1} U_{j,i} \tilde{\kappa}_j(y) x_i f_{y',x-e_i+k_j^{\text{in}}}(z,y) \\ &\quad + \sum_{j \in \mathcal{R}_2} \tilde{\kappa}_j(y - V_j) f_{y',x}(z,y - V_j) - \tilde{\kappa}_j(y) f_{y',x}(z,y).\end{aligned}$$

Substituting the results into equation (5.10) yields the evolution equation

$$\frac{d}{dt} \mathcal{M}(x,y,t) = L_1 \mathcal{M}(x,y,t) + L_2 \mathcal{M}(x,y,t) \quad (5.11)$$

with

$$\begin{aligned}L_1 f(x,y) &:= \sum_{i \in \mathcal{S}_1} \sum_{j \in \mathcal{R}_1} U_{j,i} \tilde{\kappa}_j(y) x_i f(x - e_i + k_j^{\text{in}}, y) \\ L_2 f(x,y) &:= \sum_{j \in \mathcal{R}_2} \tilde{\kappa}_j(y - V_j) f(x, y - V_j) - \tilde{\kappa}_j(y) f(x, y).\end{aligned}$$

To prove the relation (5.8) we now simply identify an equivalence between the moment equation (5.11) and the CME

$$\frac{d}{dt} p(x,y,t) = A_1^* p(x,y,t) + A_2^* p(x,y,t),$$

where A_1 and A_2 generate the dynamics induced by \mathcal{R}_1 and \mathcal{R}_2 respectively. Note that the terms involving changes in the low copy variable y are trivially identical to those appearing in the moment flow equations. Turning to the first term, and using the fact that \mathcal{S}_1 is first-order, we have

$$A_1^* f(x,y) = \sum_{j \in \mathcal{R}_1} \tilde{\kappa}_j(y) (x_{i_j^{\text{in}}} + 1) f(x - U_j, y) - \tilde{\kappa}_j(y) x_{i_j^{\text{in}}} f(x,y),$$

with i_j^{in} and i_j^{out} denoting the ingoing and outgoing species of the j th reaction. Since $x_{i_j^{\text{in}}} + 1 = x_{i_j^{\text{out}}}$ and

$$U_{j,i} = \delta_{i,i_j^{\text{out}}} - \delta_{i,i_j^{\text{in}}},$$

it follows that

$$\begin{aligned} A_1^* f(x, y) &= \sum_{j \in \mathcal{R}_1} \tilde{\kappa}_j(y) x_{j^{\text{out}}} f(x - e_{j^{\text{out}}} + k_j^{\text{in}}, y) - \tilde{\kappa}_j(y) x_{j^{\text{in}}} f(x - e_{j^{\text{in}}} + k_j^{\text{in}}, y) \\ &= \sum_{j \in \mathcal{R}_1} \sum_{i=1}^{|\mathcal{S}_1|} U_{j,i} \tilde{\kappa}_j(y) x_i f(x - e_i + k_j^{\text{in}}, y) \\ &= L_1 f(x, y). \end{aligned}$$

Hence, the evolution equation for $\mathcal{M}(x, y, t)$ is formally identical to that of $p(x, y, t)$. Taking the limit $t \rightarrow \infty$ with $p(x, y, t) \rightarrow \pi_N(x, y)$ [27] then establishes equation (5.8). \square

Returning to the network (4.1) and the stochastic detailed balance condition (4.4), theorem 5.1 implies the following:

$$(x+1)\kappa_1 \mathbb{E}[Z_A^{x+1} Z_B^{N-x-1}(t) \mathbf{1}\{Y_C(t) = 1\}] = (N-x)\kappa_2 \mathbb{E}[Z_A^x Z_B^{N-x}(t) \mathbf{1}\{Y_C(t) = 0\}] \quad (5.12)$$

for all $N > 0$, $0 \leq x \leq N$ with the expectation being taken with respect to the invariant density of the PDMP arising from \mathcal{G} . Using the theory developed thus far, we can interpret (5.12) as a flux balance condition on the moments. To see how this relates to the classical deterministic detailed balance condition, take $N = 1$. Then

$$\kappa_1 \mathbb{E}[Z_A(t) \mathbf{1}\{Y_C(t) = 0\}] = \kappa_2 \mathbb{E}[Z_B(t) \mathbf{1}\{Y_C(t) = 1\}],$$

which has a clear resemblance to (2.9), with the expectation of the piecewise deterministic variable playing the role of the deterministic equilibrium ζ .

To establish a more general result, we introduce the *moment detailed balance* condition

$$\begin{aligned} \sum_{\{y: \alpha_j(x-U_j, y) \neq 0\}} \mathbb{E} \left[\prod_{i \in \mathcal{S}_1} \alpha_j(Z(t), Y(t))^{x_i - U_j} \mathbf{1}\{Y(t) = y\} \right] \\ = \sum_{\{y: \alpha_{j^{-1}}(x, y) \neq 0\}} \mathbb{E} \left[\prod_{i \in \mathcal{S}_1} \alpha_{j^{-1}}(Z(t), y)^{x_i} \mathbf{1}\{Y(t) = y\} \right], \end{aligned} \quad (5.13)$$

with j^{-1} denoting the reversal of j in \mathcal{R}_1 (with respect to the orthogonal decomposition). We say that the PDMP satisfies moment detailed balance if (5.13) holds for each j and each $x = (x_1, x_2, \dots, x_{|\mathcal{S}_1|}) \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}_1|}$. Noting that $\alpha_j(x, y)$ is linear in x for a first order chemical reaction network, we have the following corollary of theorem 5.1:

Corollary 5.1. *Let \mathcal{G} be an orthogonally decomposable multiscale network with $\tilde{\mathcal{G}}_1$ a first-order conservative reversible network. Then the CME of the full network \mathcal{G} satisfies generalized stochastic detailed balance if and only if the stationary PDMP obtained in the large- N limit satisfies moment detailed balance for each x such that $\sum_i x_i = N$.*

This result should be interpreted as partial progress towards a generalization of theorem 2.3 in the multi-scale setting.

6. Discussion

We have investigated the stationary behavior of class of *non-complex balanced* stochastic chemical reaction networks based on the notions of semi-reversibility and orthogonal

decomposition. Following recent publications in the area of stochastic chemical reaction network theory [11–13], the focus of our investigation has been the flux balancing structure of the stationary densities for the stochastic model. In particular, we have identified a natural generalization of the well studied stochastic complex balance condition [2], which is essentially a probability flux balance relation, and shown through examples how the flux balance condition can break down. This demonstrates a fundamental difference in the behavior of non-complex balanced networks, even when they appear to have similar topological properties as reversible ones. It further suggests, as a future avenue for study, the identification of the class of irreducible networks for which the flux balance conditions are preserved.

Finally, we have generalized the existing theory by exploring the relationship between the PDMP obtained in the multiscale, large system-size limit and the full stochastic model. We proved that under certain additional constraints, the generalized complex balance relation for the chemical master equation is equivalent to a moment balance condition for the PDMP. This result is similar in spirit to existing results relating the equilibria of the reaction rate equations to the stationary density of the chemical master equation [11, 21].

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References

- [1] Gillespie D T 1977 *J. Phys. Chem.* **81** 2340–61
- [2] Feinberg M 1995 *Arch. Ration. Mech. Anal.* **132** 311–70
- [3] Feinberg M 1989 *Chem. Eng. Sci.* **44** 1819–27
- [4] Gunawardena J 2003 <http://vcp.med.harvard.edu/papers/crnt.pdf>
- [5] Anderson D F and Kurtz T G 2015 *Stochastic Analysis of Biochemical Systems* vol 1 (New York: Springer) (<https://doi.org/10.1007/978-3-319-16895-1>)
- [6] Kurtz T G 1972 *J. Chem. Phys.* **57** 2976
- [7] Anderson D F, Craciun G, Gopalkrishnan M and Wiuf C 2015 *Bull. Math. Biol.* **77** 1744–67
- [8] Agazzi A, Dembo A and Eckmann J P 2017 arXiv:1701.02126
- [9] Ge H and Qian H 2016 *Chem. Phys.* **472** 241–8
- [10] Ge H and Qian H 2016 arXiv:1604.07115
- [11] Anderson D F, Craciun G and Kurtz T G 2010 *Bull. Math. Biol.* **72** 1947–70
- [12] Anderson D F and Cotter S L 2016 *Bull. Math. Biol.* **78** 2390–407
- [13] Cappelletti D and Wiuf C 2016 *SIAM J. Appl. Math.* **76** 411–32
- [14] Polettini M, Wachtel A and Esposito M 2015 *J. Chem. Phys.* **143** 184103
- [15] Cappelletti D and Wiuf C 2016 *Ann. Appl. Probab.* **26** 2915–58
- [16] Ethier S N and Kurtz T G 1986 *Markov Processes: Characterization and Convergence* 1st edn (New York: Wiley) (<https://doi.org/10.1002/9780470316658>)
- [17] Gardiner C W *et al* 1985 *Handbook of Stochastic Methods* vol 4 (Berlin: Springer)
- [18] Duncan A, Erban R and Zygalakis K 2016 *J. Computat. Phys.* **326** 398–419
- [19] Crudu A, Debussche A and Radulescu O 2009 *BMC Syst. Biol.* **3** 1
- [20] Kang H W, Kurtz T G and Drive L 2013 *Ann. Appl. Probab.* **23** 1–49
- [21] Joshi B 2015 *Discrete Continuous Dyn. Syst. Ser. B* **20** 1077–105

- [22] Wang H and Qian H 2007 *J. Math. Phys.* **48** 013303
- [23] Zhang X J, Qian H and Qian M 2012 *Phys. Rep.* **510** 1–86
- [24] England J L 2013 *J. Chem. Phys.* **139** 121923
- [25] Kelly F 2011 *Reversibility and Stochastic Networks* <http://dl.acm.org/citation.cfm?id=2025239>
- [26] Levien E and Bressloff P C 2016 arXiv:1609.02502
- [27] Brémaud P 2013 *Markov Chains: Gibbs Fields, Monte Carlo Simulation, and Queues* vol 31 (New York: Springer) (<https://doi.org/10.1007/978-1-4757-3124-8>)