PRODUCT-FORM STATIONARY DISTRIBUTIONS FOR DEFICIENCY ZERO CHEMICAL REACTION NETWORKS

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We consider both deterministically and stochastically modeled chemical reaction systems and prove that a product-form stationary distribution exists for each closed, irreducible subset of the state space of a stochastically modeled system (with quite general kinetics) if the corresponding deterministically modeled system (with mass-action kinetics) admits a complex balanced equilibrium. Feinberg’s deficiency zero theorem then implies that such a distribution exists so long as the corresponding network is weakly reversible and has a deficiency of zero. We also demonstrate that the main parameter of the stationary distribution is always a complex balanced equilibrium value for the corresponding mass-action, deterministically modeled system, regardless of the kinetics assumed for the stochastically modeled system.

1. Introduction. There are two commonly used models for chemical reaction systems: discrete stochastic models in which the state of the system is a vector giving the number of each molecular species, and continuous deterministic models in which the state of the system is a vector giving the concentration of each molecular species. Discrete stochastic models are typically used when the number of molecules of each chemical species is low and the randomness inherent in the making and breaking of chemical bonds is important. Conversely, deterministic models are used when there are large numbers of molecules for each species and the behavior of the concentration of each species is well approximated by a coupled set of ordinary differential equations.

Typically, the goal in the study of discrete stochastic systems is to either understand the evolution of the distribution of the state of the system or to find the long term stationary distribution of the system, which is the stochastic analog of an equilibrium point. The Kolmogorov forward equation (chemical master equation in the chemistry literature) describes the evolution of the distribution and so work has been done in trying to analyze or solve the forward equation for certain classes of systems ([18]). However, it is typically an extremely difficult task to solve or even numerically compute the solution to the forward equation for all
but the simplest of systems. Therefore, simulation methods have been developed that will generate sample paths so as to approximate the distribution of the state via Monte Carlo methods. These simulation methods include algorithms that generate statistically exact ([1, 20, 21, 19]) and approximate ([3, 22, 7]) sample paths. On the other hand, the continuous deterministic models, and in particular mass-action systems with complex balancing states, have been analyzed extensively in the mathematical chemistry literature, starting with the works of Horn, Jackson, and Feinberg [24, 25, 26, 13], and continuing with Feinberg’s deficiency theory in [14, 15, 16, 17]. Such models have a wide range of applications in the physical sciences, and now they are beginning to play an important role in systems biology [11, 23, 31]. Recent mathematical analysis of continuous deterministic models has focused on their potential to admit multiple equilibria [9, 10] and on dynamical properties such as persistence and global stability [31, 5, 2, 4].

One of the major theorems pertaining to deterministic models of chemical systems is the deficiency zero theorem of Feinberg ([15, 14]). The deficiency zero theorem states that if the network of a system satisfies certain easily checked properties, then within each compatibility class (linear set in which a solution is bound) there is precisely one equilibrium with strictly positive components, and that equilibrium is locally asymptotically stable ([15, 14]). The surprising aspect of the deficiency zero theorem is that the assumptions of the theorem are completely related to the network of the system whereas the conclusions of the theorem are related to the dynamical properties of the system. We will show in this paper that if the conditions of the deficiency zero theorem hold on the network of a stochastically modeled chemical system with quite general kinetics, then there exists a product-form stationary distribution for each closed, irreducible subset of the state space. In fact, we will show a stronger result: that a product-form stationary distribution exists so long as there exists a complex balanced equilibrium for the associated deterministically modeled system. However, the equilibrium values guaranteed to exist by the deficiency zero theorem are complex balanced and so the conditions of that theorem are sufficient to guarantee the existence of the product-form distribution. Finally, the main parameter of the stationary distribution will be shown to be a complex balanced equilibrium value of the deterministically modeled system.

Product-form stationary distributions play a central role in the theory of queueing networks where the product-form property holds for a large, naturally occurring class of models called Jackson networks (see, for example, [27], Chapter 3, and [8], Chapter 2) and a much larger class of quasi-reversible networks ([27], Chapter 3, [8], Chapter 4, [30], Chapter 8). Kelly, [27], Section 8.5, recognizes the possible existence of product-form stationary distributions for a subclass of chemical reaction models and gives a condition for that existence. That condition is essentially the complex balance condition described below, and our main result asserts that for
any chemical reaction model the conditions of the deficiency zero theorem ensure that this condition holds.

The outline of the paper is as follows. In Section 2 we formally introduce chemical reaction networks. In Section 3 we develop both the stochastic and deterministic models of chemical reaction systems. Also in Section 3 we state the deficiency zero theorem for deterministic systems and present two theorems that are used in its proof and that will be of use to us. In Section 4 we present the first of our main results: that every closed, irreducible subset of the state space of a stochastically modeled system with mass-action kinetics has a product-form stationary distribution if the chemical network is weakly reversible and has a deficiency of zero. In Section 5 we present some examples of the use of this result. In Section 6 we extend our main result to systems with more general kinetics.

2. Chemical reaction networks. Consider a system with $m$ chemical species, $\{S_1, \ldots, S_m\}$, undergoing a series of chemical reactions. For the $k$th reaction, denote by $\nu_k, \nu'_k \in \mathbb{Z}^m_{\geq 0}$ the vectors representing the number of molecules of each species consumed and created in one instance of that reaction, respectively. We note that if $\nu_k = \vec{0}$ then the $k$th reaction represents an input to the system, and if $\nu'_k = \vec{0}$ then it represents an output. Using a slight abuse of notation, we associate each such $\nu_k$ (and $\nu'_k$) with a linear combination of the species in which the coefficient of $S_i$ is $\nu_{ik}$, the $i$th element of $\nu_k$. For example, if $\nu_k = [1, 2, 3]^T$ for a system consisting of three species, we associate with $\nu_k$ the linear combination $S_1 + 2S_2 + 3S_3$. For $\nu_k = \vec{0}$, we simply associate $\nu_k$ with $\emptyset$. Under this association, each $\nu_k$ (and $\nu'_k$) is termed a complex of the system. We denote any reaction by the notation $\nu_k \rightarrow \nu'_k$, where $\nu_k$ is the source, or reactant, complex and $\nu'_k$ is the product complex. We note that each complex may appear as both a source complex and a product complex in the system. The set of all complexes will be denoted by $\{\nu_k\} = \cup_k \{\nu_k\} \cup \{\nu'_k\}$.

DEINITION 2.1. Let $\mathcal{S} = \{S_i\}$, $\mathcal{C} = \{\nu_k\}$, and $\mathcal{R} = \{\nu_k \rightarrow \nu'_k\}$ denote the sets of species, complexes, and reactions, respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is called a chemical reaction network.

The structure of chemical reaction networks plays a central role in both the study of stochastically and deterministically modeled systems. As alluded to in the Introduction, it will be conditions on the network of a system that guarantee certain dynamical properties for both models. Therefore, the remainder of this section consists of definitions related to chemical networks that will be used throughout the paper.

DEINITION 2.2. A chemical reaction network, $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, is called weakly
reversible if for any reaction $\nu_k \to \nu'_k$, there is a sequence of directed reactions beginning with $\nu'_k$ as a source complex and ending with $\nu_k$ as a product complex. That is, there exist complexes $\nu_1, \ldots, \nu_r$ such that $\nu'_k \to \nu_1 \to \nu_2, \ldots, \nu_r \to \nu_k \in \mathcal{R}$. A network is called reversible if $\nu'_k \to \nu_k \in \mathcal{R}$ whenever $\nu_k \to \nu'_k \in \mathcal{R}$.

REMARK. The definition of a reversible network given in Definition 2.2 is distinct from the notion of a reversible stochastic process. However, in Section 4.1 we point out a connection between the two concepts for systems that are detailed balanced.

To each reaction network, $\{S, \mathcal{C}, \mathcal{R}\}$, there is a unique, directed graph constructed in the following manner. The nodes of the graph are the complexes, $\mathcal{C}$. A directed edge is then placed from complex $\nu_k$ to complex $\nu'_k$ if and only if $\nu_k \to \nu'_k \in \mathcal{R}$. Each connected component of the resulting graph is termed a linkage class of the graph. We denote the number of linkage classes by $\ell$. It is easy to see that a chemical reaction network is weakly reversible if and only if each of the linkage classes of its graph is itself weakly reversible.

DEFINITION 2.3. $S = \text{span}_{\{\nu_k \to \nu'_k \in \mathcal{R}\}} \{\nu'_k - \nu_k\}$ is the stoichiometric subspace of the network. For $c \in \mathbb{R}^m$ we say $c + S$ and $(c + S) \cap \mathbb{R}^m_{\geq 0}$ are the stoichiometric compatibility classes and positive stoichiometric compatibility classes of the network, respectively. Denote $\dim(S) = s$.

It is simple to show that for both stochastic and deterministic models, the state of the system remains within a single stoichiometric compatibility class for all time. This fact is important because it changes the types of questions that are reasonable to ask about a given system. For example, unless there is only one stoichiometric compatibility class, and so $S = \mathbb{R}^m$, it is not reasonable to ask whether there is a unique fixed point for a given deterministic system. Instead, it is appropriate to ask if within each stoichiometric compatibility class there is a unique fixed point. Analogously, asking for a closed form stationary distribution for a stochastically modeled system that is valid on all of $\mathbb{R}^m$ would be unreasonable. However, asking for a stationary distribution valid on a closed, irreducible subset of the state space, itself contained within a compatibility class, would not be.

The final definition of this section is that of the deficiency of a network ([14]). It is not a difficult exercise to show that the deficiency of a network is always greater than or equal to zero.

DEFINITION 2.4. The deficiency of a chemical reaction network, $\{S, \mathcal{C}, \mathcal{R}\}$, is $\delta = |\mathcal{C}| - \ell - s$, where $|\mathcal{C}|$ is the number of complexes, $\ell$ is the number of linkage classes of the network graph, and $s$ is the dimension of the stoichiometric subspace of the network.
While the deficiency is, by definition, only a property of the network, we will see in Sections 3.2, 4, and 6 that a deficiency of zero has implications for the long-time dynamics of both deterministic and stochastic models of chemical reaction systems.

3. Dynamical models. The notion of a chemical reaction network is the same for both stochastic and deterministic systems and the choice of whether to model the evolution of the state of the system stochastically or deterministically is made based upon the details of the specific chemical or biological problem at hand. Typically if the number of molecules is low, a stochastic model is used, and if the number of molecules is high, a deterministic model is used. For cases between the two extremes a diffusion approximation can be used or, for cases in which the system contains multiple scales, pieces of the reaction network can be modeled stochastically, while others can be modeled deterministically (or, more accurately, absolutely continuously with respect to time). See, for example, [6].

3.1. Stochastic models. The simplest stochastic model for a chemical network \( \{S,C,R\} \) treats the system as a continuous time Markov chain whose state \( X \in \mathbb{Z}_{\geq 0}^m \) is a vector giving the number of molecules of each species present with each reaction modeled as a possible transition for the state. The model for the \( k \)th reaction, \( \nu_k \rightarrow \nu'_k \), is determined by the vector of inputs, \( \nu_k \), specifying the number of molecules of each chemical species that are consumed in the reaction, the vector of outputs, \( \nu'_k \), specifying the number of molecules of each species that are created in the reaction, and a function of the state, \( \lambda_k(X) \), that gives the rate at which the reaction occurs. Specifically, if the \( k \)th reaction occurs at time \( t \), the new state becomes

\[
X(t) = X(t-) + \nu'_k - \nu_k.
\]

Let \( R_k(t) \) denote the number of times that the \( k \)th reaction occurs by time \( t \). Then the state of the system at time \( t \) can be written as

\[
X(t) = X(0) + \sum_k R_k(t) (\nu'_k - \nu_k),
\]

where we have enumerated over the reactions. \( R_k \) is a counting process with intensity \( \lambda_k(X(t)) \) (called the \textit{propensity} in the chemistry literature) and can be written as

\[
R_k(t) = Z_k \left( \int_0^t \lambda_k(X(s)) \, ds \right),
\]

where the \( Z_k \) are independent, unit-rate Poisson processes ([29, 12]). The generator for the Markov chain is the operator, \( A \), defined by

\[
Af(x) = \sum_k \lambda_k(x)(f(x + \nu'_k - \nu_k) - f(x)),
\]
where \( f \) is any function defined on the state space.

A commonly chosen form for the intensity functions, \( \lambda_k \), is that of stochastic mass-action, which says that the rate of the \( k \)th reaction should be given by

\[
\lambda_k(x) = \kappa_k \prod_{\ell=1}^{m} \frac{x_{\ell}^!}{\nu_{\ell k}!} = \kappa_k \prod_{\ell=1}^{m} \frac{x_{\ell}!}{(x_{\ell} - \nu_{\ell k})!},
\]

for some constant \( \kappa_k \). Note that the rate (4) is proportional to the number of distinct subsets of the molecules present that can form the inputs for the reaction. Intuitively, this assumption reflects the idea that the system is well-stirred in the sense that all molecules are equally likely to be at any location at any time. For concreteness, we will assume that the intensity functions satisfy (4) throughout most of the paper. In Section 6 we will generalize our results to systems with more general kinetics.

A probability distribution \( \{\pi(x)\} \) is a stationary distribution for the chain if

\[
\sum_x \pi(x) Af(x) = 0
\]

for a sufficiently large class of functions \( f \) or, taking \( f(y) = 1_{x}(y) \) and using equation (3), if

\[
\sum_k \pi(x - \nu_k + \nu_k) \lambda_k(x - \nu_k + \nu_k) = \pi(x) \sum_k \lambda_k(x)
\]

for all \( x \) in some closed, irreducible subset of the state space. If the network is weakly reversible, then the state space of the Markov chain is a union of closed, irreducible communicating classes. Also, each closed, irreducible communicating class is either finite or countable. Therefore, if a stationary distribution with support on a single communicating class exists it is unique and

\[
\lim_{t \to \infty} P(X(t) = x \mid X(0) = y) = \pi(x),
\]

for all \( x, y \) in that communicating class. Thus, the stationary distribution gives the long-term behavior of the system.

Solving equation (5) is in general a formidable task. However, in Section 4 we will do so if the network is weakly reversible, has a deficiency of zero, and if the rate functions \( \lambda_k(x) \) satisfy mass-action kinetics, (4). We will also show that the stationary distribution is of product form. More specifically, we will show that for each communicating class there exists a \( c \in \mathbb{R}_{>0}^m \) and a normalizing \( M \) such that

\[
\pi(x) = M \prod_{i=1}^{m} \pi_i(x_i) = M \prod_{i=1}^{m} \frac{c_i x_i^!}{x_i!}
\]

satisfies equation (5). The \( c_i \) in the definition of \( \pi_i \) will be shown to be the \( i \)th component of an equilibrium value of the analogous deterministic system described in the next section. In Section 6 we will solve (5) for more general kinetics.
3.2. Deterministic models and the deficiency zero theorem. Under an appropriate scaling limit (see, for example, [28]) the continuous time Markov chain (1), (2), (4) becomes

\begin{equation}
    x(t) = x(0) + \sum_k \left( \int_0^t f_k(x(s))ds \right) (\nu'_k - \nu_k) = x(0) + \int_0^t f(x(s))ds,
\end{equation}

where the last equality is a definition and

\begin{equation}
    f_k(x) = \kappa_k x_1^{\nu_{1k}} x_2^{\nu_{2k}} \cdots x_m^{\nu_{mk}}.
\end{equation}

We say that the deterministic system (6) has mass-action kinetics if the rate functions $f_k$ have the form (7). The proof of the following theorem by Feinberg can be found in [14] or [17]. We note that the full statement of the deficiency zero theorem actually says more than what is given below and the interested reader is encouraged to see the original work.

**Theorem 3.1 (The Deficiency Zero Theorem).** Consider a weakly reversible, deficiency zero chemical reaction network \{S, C, R\} with dynamics given by (6), (7). Then for any choice of rate constants $\kappa_k$, within each positive stoichiometric compatibility class there is precisely one equilibrium value, and that equilibrium value is locally asymptotically stable relative to its compatibility class.

The dynamics of the system (6), (7) take place in $\mathbb{R}^m_\geq 0$. However, to prove the deficiency zero theorem it turns out to be more appropriate to work in complex space, denoted $\mathbb{C}$, which we will describe now. For any $U \subseteq C$ let $\omega_U : C \to \{0, 1\}$ denote the indicator function $\omega_U(\nu_k) = 1_{\{\nu_k \in U\}}$. Complex space is defined to be the space with basis \{\$\omega_{\nu_k}$ | $\nu_k \in C\}$, where we have denote \$\omega_{\nu_k}$ by $\omega_{\nu_k}$.

If $u$ is a vector with nonnegative integer components and $w$ is a vector with nonnegative real components, then let $u! = \prod_i u_i !$ and $w^u = \prod_i w_i^{u_i}$, where we interpret $0^0 = 1$. Let $\Psi : \mathbb{R}^m \to \mathbb{C}$ and $A_k : \mathbb{C} \to \mathbb{C}$ be defined by:

\begin{align*}
    \Psi(x) &= \sum_{\nu_k \in C} x^{\nu_k} \omega_{\nu_k}, \\
    A_k(y) &= \sum_{\nu_k \to \nu'_k \in R} \kappa_k y_{\nu_k} (\omega_{\nu'_k} - \omega_{\nu_k}),
\end{align*}

where a choice of rate constants, $\kappa_k$, has been made for the function $A_k$. Let $Y : \mathbb{C} \to \mathbb{R}^m$ be the linear map whose action on the basis elements \{$\omega_{\nu_k}$\} is defined by $Y(\omega_{\nu_k}) = \nu_k$. Then equations (6), (7) can be written as the coupled set of ordinary differential equations

\begin{equation}
    \dot{x}(t) = f(x(t)) = Y(A_k(\Psi(x(t)))).
\end{equation}
Therefore, in order to show that a value \( c \) is an equilibrium of the system, it is sufficient to show that \( A_k(\Psi(c)) = 0 \). The following has been shown in [26] and [14] (see also [23]).

**Theorem 3.2.** Let \( \{S, C, \mathcal{R}\} \) be a chemical reaction network with dynamics given by (6), (7) for some choice of rate constants, \( \kappa_k \). Suppose there exists a \( c \in \mathbb{R}_{>0}^m \) for which \( A_k(\Psi(c)) = 0 \), then the following hold:

1. The network is weakly reversible.
2. Every fixed point with strictly positive components, \( x \in \mathbb{R}_{>0}^m \) with \( f(x) = 0 \), satisfies \( A_k(\Psi(x)) = 0 \).
3. If \( Z = \{ x \in \mathbb{R}_{>0}^m \mid f(x) = 0 \} \), then \( \ln Z \doteq \{ y \in \mathbb{R}^m \mid \exists x \in Z \text{ and } y_i = \ln(x_i) \} \) is a coset of \( S^\perp \). That is, there is a \( k \in \mathbb{R}^m \) such that \( \ln Z = \{ w \in \mathbb{R}^m \mid w = k + u \text{ for some } u \in S^\perp \} \).
4. There is one, and only one, fixed point in each positive stoichiometric compatibility class.
5. Each fixed point of a positive stoichiometric compatibility class is locally asymptotically stable relative to its stoichiometric compatibility class.

Thus, the conclusion of the deficiency zero theorem holds so long as there exists at least one \( c \in \mathbb{R}_{>0}^m \) such that \( A_k(\Psi(c)) = 0 \). The condition that the system has a deficiency of zero only plays a role in showing that there does exist such a \( c \). A proof of the following can be found in [14], [15], or [17].

**Theorem 3.3.** Let \( \{S, C, \mathcal{R}\} \) be a chemical reaction network with dynamics given by (6), (7) for some choice of rate constants, \( \kappa_k \). If the network has a deficiency of zero, then there exists a \( c \in \mathbb{R}_{>0}^m \) such that \( A_k(\Psi(c)) = 0 \) if and only if the network is weakly reversible.

A chemical reaction network with mass-action kinetics that admits a \( c \) for which \( A_k(\Psi(c)) = 0 \) is called complex balanced in the literature. We see from Theorem 3.2 that the conclusions of the deficiency zero theorem hold for any complex balanced system. The surprising aspect of the deficiency zero theorem, however, is that it gives simple and checkable sufficient conditions on the network structure alone that guarantee that a system is complex balanced for any choice of rate constants. We will see in the following sections that the main results of this paper have the same property: product-form stationary distributions exist for all stochastic systems that are complex balanced when viewed as deterministic systems, and \( \delta = 0 \) is a sufficient condition to guarantee this for weakly reversible networks.
4. Main result for mass-action systems. We now state and prove our main result for systems with mass-action kinetics.

**Theorem 4.1.** Let \( \{S, C, R\} \) be a chemical reaction network and let \( \kappa_k \) be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with equilibrium \( c \in \mathbb{R}_m^+ \). Then, for any closed, irreducible subset of the state space, \( \Gamma \), the stochastically modeled system with intensities \( 4 \) has a product-form stationary distribution

\[
\pi(x) = M \frac{e^x}{x!} = M \prod_{i=1}^{m} \frac{e^{x_i}}{x_i!},
\]

valid for \( x \in \Gamma \), where \( M \) is a normalizing constant.

**Proof.** For all \( x \in \Gamma \), let

\[
\pi(x) = M \frac{e^x}{x!},
\]

where \( M \) is a normalizing constant and \( c \) satisfies \( A_k(\Psi(c)) = 0 \). To show that \( \pi(x) \) is stationary, we will verify that equation (5) holds for all \( x \in \Gamma \). Plugging (8) and (4) into equation (5) and simplifying yields

\[
\sum_k \kappa KC_{\nu_k}^{\nu_k'} \frac{1}{(x - \nu_k')!} = \sum_k \kappa_k \frac{1}{(x - \nu_k)!},
\]

Equation (9) will be satisfied if for each complex \( z \in C \),

\[
\sum_{\{k: \nu_k' = z\}} \kappa_k e^{\nu_k} \frac{1}{(x - z)!} = \sum_{\{k: \nu_k = z\}} \kappa_k \frac{1}{(x - z)!},
\]

where the sum on the left is over reactions for which \( z \) is the product complex and the sum on the right is over reactions for which \( z \) is the source complex. \( z \) is fixed in the above equation, and so (10) is equivalent to

\[
\sum_{\{k: \nu_k' = z\}} \kappa_k e^{\nu_k} = \sum_{\{k: \nu_k = z\}} \kappa_k e^{\nu_k}.
\]

The condition \( A_k(\Psi(c)) = 0 \) is

\[
\sum_k \kappa_k e^{\nu_k} (\omega_{\nu_k'} - \omega_{\nu_k}) = 0,
\]

which, after rearranging terms, is precisely equation (11).  

\( \square \)
The following theorem gives simple and checkable conditions that guarantee the existence of a product-form stationary distribution of the form (8).

**Theorem 4.2.** Let \( \{S, C, R\} \) be a chemical reaction network that has a deficiency of zero and is weakly reversible. Then, for any choice of rate constants and for any closed, irreducible subset of the state space, \( \Gamma \), the stochastically modeled system with intensities (4) has a product form stationary distribution

\[
\pi(x) = M \frac{e^x}{x!} = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!},
\]

valid for \( x \in \Gamma \), where \( M \) is a normalizing constant and \( c \) is an equilibrium value guaranteed to exist by the deficiency zero theorem.

**Proof.** This is a direct result of Theorems 3.3 and 4.1.

Consider the case where \( \mathbb{Z}_{\geq 0}^m \) is the unique irreducible communication class for a stochastically modeled system that has a product-form stationary measure of the form (8). The following Corollary points out that when in distributional equilibrium the species numbers: (a) are independent and (b) have Poisson distributions. Thus, in this case, both property (a) and property (b) follow from conditions on the communication class and not on properties of the reactions themselves. Previous results required that each reaction \( \nu_k \rightarrow \nu_{k}' \) satisfy \( |\nu_k|, |\nu_{k}'| \in \{0, 1\} \) ([18]). We return to this point in examples 5.2 and 5.3.

**Corollary 4.3.** Let \( \{S, C, R\} \) be a chemical reaction network that, when modeled deterministically, has a complex balanced equilibrium, \( c \). Suppose further that, when modeled stochastically with intensities (4), \( \Gamma = \mathbb{Z}_{\geq 0}^m \) is the unique closed, irreducible communication class of the state space. Then, when in distributional equilibrium, the species numbers of the stochastically modeled system are independent and have Poisson distributions with parameters \( c_i \).

**Proof.** By Theorem 4.1 the stationary distribution is given by (8). Summing over the state space we see that for each \( x \in \mathbb{Z}_{\geq 0}^m \)

\[
\pi(x) = e^{-\sum_{i=1}^{m} c_i} \prod_{i=1}^{m} \frac{c_i^{x_i}}{x_i!} = \prod_{i=1}^{m} e^{-c_i} \frac{c_i^{x_i}}{x_i!}.
\]

\( \square \)
4.1. Reversibility and detail balance. A reversible (in the sense of Definition 2.2), deterministically modeled chemical reaction network with equilibrium value \( c \) is said to be detailed balanced if for each pair of reversible reactions, \( \nu_k \leftrightarrow \nu'_k \), we have

\[
\kappa_k c^{\nu_k} = \kappa'_k c^{\nu'_k},
\]

where \( \kappa_k, \kappa'_k \) are the rate constants for the reactions \( \nu_k \to \nu'_k, \nu'_k \to \nu_k \), respectively. It is immediate that any system that is detailed balanced is also complex balanced. The fact that a product-form stationary distribution of the form (8) exists for detailed balanced systems is known. See, for example, [32]. Theorems 4.1 and 4.2 can therefore be viewed as an extension of that result. However, more can be said in the case when the deterministic system is detailed balanced. As mentioned in the remark following Definition 2.2, the term “reversible” has a meaning in the context of stochastic processes that differs from that of Definition 2.2. The following standard definition is taken from [27].

**Definition 4.4.** A stochastic process \( X(t) \) is reversible if \( (X(t_1), \ldots, X(t_n)) \) has the same distribution as \( (X(\tau-t_1), \ldots, X(\tau-t_n)) \) for all \( t_1, \ldots, t_n, \tau \in \mathbb{R} \).

The following is proved in chapter 7 of [32].

**Theorem 4.5.** Let \( \{S, C, R\} \) be a reversible (in the sense of Definition 2.2) chemical reaction network with rate constants \( \kappa_k \). Then the deterministically modeled system has an equilibrium for which it is detailed balanced if and only if the stochastically modeled system with intensities (4) is reversible, in the sense of Definition 4.4, when in its stationary distribution.

4.2. Non-uniqueness of \( c \). For stochastically modeled chemical reaction systems any irreducible subset of the state space, \( \Gamma \), is contained within \( (y+\mathbb{R}^m_{\geq 0}) \cap \mathbb{Z}^m \) for some \( y \in \mathbb{R}^m_{\geq 0} \). Therefore, each \( \Gamma \) is associated with a stoichiometric compatibility class. For weakly reversible systems with a deficiency of zero, Theorems 3.2 and 3.3 guarantee that each such stoichiometric compatibility class has an associated equilibrium value for which \( A_k(\Psi(c)) = 0 \). However, neither Theorem 4.1 nor Theorem 4.2 makes the requirement that the equilibrium value used in the product-form stationary measure \( \pi(\cdot) \) be contained within the stoichiometric compatibility class associated with \( \Gamma \). Therefore we see that one such \( c \) can be used to construct a product-form stationary distribution for every closed, irreducible subset. Conversely, for a given irreducible subset \( \Gamma \) any positive equilibrium value to the system (6), (7) can be used to construct \( \pi(\cdot) \). This fact seems to be contrary to the uniqueness of the stationary distribution, however it can be understood through the third conclusion of Theorem 3.2 as follows.
Let $\Gamma$ be a closed, irreducible subset of the state space with associated positive stoichiometric compatibility class $y + S$, and let $c_1, c_2 \in \mathbb{R}_{>0}^m$ be such that $A_k(\Psi(c_1)) = A_k(\Psi(c_2)) = 0$. For $i \in \{1, 2\}$ and $x \in \Gamma$, let $\pi_i(x) = M_i c_i^x / x!$, where $M_1$ and $M_2$ are normalizing constants. Then for each $x \in \Gamma$

$$\frac{\pi_1(x)}{\pi_2(x)} = \frac{M_1 c_1^x}{x!} \frac{x!}{M_2 c_2^x} = \frac{M_1}{M_2} \frac{c_1^x}{c_2^x}.$$

For any vector $u$, we define $(\ln(u))_i = \ln(u_i)$. Then for $x \in \Gamma \subset y + S$

$$\frac{c_1^x}{c_2^x} = e^{x(\ln c_1 - \ln c_2)} = e^{\Psi(\ln c_1 - \ln c_2)} = \frac{c_1^y}{c_2^y},$$

where the second equality follows from the third conclusion of Theorem 3.2. Therefore,

$$\frac{\pi_1(x)}{\pi_2(x)} = \frac{M_1}{M_2} \frac{c_1^y}{c_2^y}.$$

Finally,

$$1 = \left( \frac{M_1}{M_2} \sum_{x \in \Gamma} \frac{c_1^x}{x!} \right) / \left( \sum_{x \in \Gamma} \frac{c_2^x}{x!} \right)$$

$$= \frac{M_1}{M_2} \left( \frac{c_1^y}{c_2^y} \sum_{x \in \Gamma} \frac{c_2^x}{x!} \right) / \left( \sum_{x \in \Gamma} c_2^x / x! \right)$$

$$= \frac{\pi_1(x)}{\pi_2(x)},$$

where the second equality follows from equation (14) and the third equality follows from equation (15). We therefore see that the stationary measure is independent of the choice of $c_i$, as expected.

5. Examples. Our first example points out that the existence of a product-form stationary distribution for the closed, irreducible subsets of the state space does not necessarily imply independence of the species numbers.

Example 5.1. (Non-independence of species numbers) Consider the simple reversible system

$$\begin{align*}
\frac{k_1}{k_2} & \\
S_1 & \rightleftharpoons S_2,
\end{align*}$$

where $k_1$ and $k_2$ are nonzero rate constants. We suppose that $X_1(0) + X_2(0) = N$, and so $X_1(t) + X_2(t) = N$ for all $t$. This system has two complexes, one linkage.
class, and the dimension of the stoichiometric compatibility class is one. Therefore it has a deficiency of zero. Since it is also weakly reversible, our results hold. An equilibrium to the system that satisfies the complex balance equation is

\[ c = \left( \frac{k_2}{k_1 + k_2}, \frac{k_1}{k_1 + k_2} \right), \]

and the product-form stationary distribution for the system is

\[ \pi(x) = M \frac{c_{x_1}^{x_1} c_{x_2}^{x_2}}{x_1! x_2!}, \]

where \( M \) is a normalizing constant. Using that \( X_1(t) + X_2(t) = N \) for all \( t \) yields

\[ \pi_1(x_1) = M \frac{c_{x_1}^{N-x_1}}{x_1!(N-x_1)!} = \frac{M}{x_1!(N-x_1)!} c_1^{x_1} (1 - c_1)^{N-x_1}. \]

After setting \( M = N! \), we see that \( X_1 \) is binomially distributed. Similarly,

\[ \pi_2(x_2) = \binom{N}{x_2} c_2^{x_2} (1 - c_2)^{N-x_2}. \]

Therefore, we trivially have that \( P(X_1 = N) = c_1^N \) and \( P(X_2 = N) = c_2^N \), but \( P(X_1 = N, X_2 = N) = 0 \neq c_1^N c_2^N \), and so \( X_1 \) and \( X_2 \) are not independent.

**Remark.** The conclusion of the previous example, that independence does not follow from the existence of a product-form stationary distribution, extends trivially to any network with a conservation relation among the species.

**Example 5.2.** (First order reaction networks) The results presented below for first order reaction networks are known in both the queueing theory and mathematical chemistry literature. See, for example, [27] and [18]. We present them here to point out how they follow directly from Theorem 4.2.

We say a reaction network is a first order reaction network if \( |\nu_k| \in \{0, 1\} \) for each complex \( \nu_k \in \mathcal{C} \). It is simple to show that first order reaction networks necessarily have a deficiency of zero. Therefore, the results of this paper are applicable to all first order reaction networks that are weakly reversible. Consider such a reaction network with only one linkage class (for if there is more than one linkage class we may consider the different linkage classes as distinct networks). We say that the network is open if there is at least one reaction, \( \nu_k \rightarrow \nu'_k \), for which \( \nu_k = \vec{0} \). Otherwise we say the network is closed. If the network is open we see that \( S = \mathbb{R}^m \), \( \Gamma = \mathbb{Z}_{\geq 0}^m \) and so, by Corollary 4.3, for all \( x \in \Gamma \),

\[ \pi(x) = e^{-\sum_{i=1}^m c_i} \prod_{i=1}^m \frac{c_i^{x_i}}{x_i!}, \]
where \( c \in \mathbb{R}^m_{>0} \) is the equilibrium of the associated (linear) deterministic system. Therefore, when in distributional equilibrium, the species numbers are independent and have Poisson distributions. As pointed out in the remarks preceding Corollary 4.3, neither the independence nor the Poisson distribution resulted from the fact that the system under consideration was a first order system. Instead both facts followed from \( \Gamma \) being all of \( \mathbb{Z}^m_{\geq 0} \).

In the case of a closed first order reaction network, it is easy to see that there is a unique conservation relation \( X_1(t) + \cdots + X_m(t) = N \), for some \( N \). Thus, in distributional equilibrium, \( X(t) \) has a multinomial distribution. That is for any \( x \in \mathbb{Z}^m_{\geq 0} \) satisfying \( x_1 + x_2 + \cdots + x_m = N \)

\[
\pi(x) = \left( \begin{array}{c} N \\ x_1, x_2, \ldots, x_m \end{array} \right) c^x = \frac{N!}{x_1! \cdots x_m!} c_{x_1}^{x_1} \cdots c_{x_m}^{x_m},
\]

where \( c \in \mathbb{R}^m_{>0} \) is the equilibrium of the associated deterministic system and has been chosen so that \( \sum_i c_i = 1 \). As in the case of the open network, we note that the form of the equilibrium distribution does not follow from the fact that the network only has first order reactions. Instead (16) follows from the structure of the closed, irreducible communication classes.

**Example 5.3. (Enzyme kinetics I)** Consider the possible model of enzyme kinetics given by

\[
E + S \rightleftharpoons ES \rightleftharpoons E + P, \quad E \rightleftharpoons \emptyset \rightleftharpoons S,
\]

where \( E \) represents an enzyme, \( S \) represents a substrate, \( ES \) represents an enzyme-substrate complex, \( P \) represents a product, and some choice of rate constants has been made. We note that both \( E \) and \( S \) are being allowed to enter and leave the system.

The network (17) is reversible and has six complexes and two linkage classes. The dimension of the stoichiometric subspace is readily checked to be four, and so the network has a deficiency of zero. Theorem 4.2 applies and so the stochastically modeled system has a product-form stationary distribution of the form (8). Ordering the species as \( X_1 = E, X_2 = S, X_3 = ES, \) and \( X_4 = P \), the reaction vectors for this system include

\[
\left\{ \begin{array}{ccc}
1 & 0 & -1 \\
0 & 1 & -1 \\
0 & 0 & 1 \\
0 & 0 & -1 \\
0 & 0 & 1
\end{array} \right\}.
\]

We therefore see that \( \Gamma = \mathbb{Z}^4_{\geq 0} \) is the unique closed, irreducible communication class of the stochastically modeled system and Corollary 4.3 tells us that in dis-
tributional equilibrium the species values are independent and have Poisson distributions with parameters $c_i$, which are given by the equilibrium value of the corresponding deterministically modeled system.

**Example 5.4. (Enzyme kinetics II)** Consider the possible model for enzyme kinetics given by

$$E + S \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} ES \overset{k_2}{\underset{k_{-2}}{\rightleftharpoons}} E + P \quad \emptyset \overset{k_3}{\underset{k_{-3}}{\rightleftharpoons}} E,$$

where the species $E, S, ES,$ and $P$ are as in Example 5.3. We are now allowing only the enzyme $E$ to enter and leave the system. The network is reversible, there are five complexes, two linkage classes, and the dimension of the stoichiometric compatibility class is three. Therefore, Theorem 4.2 implies that the stochastically modeled system has a product-form stationary distribution of the form (8). The only conserved quantity of the system is $S + ES + P$, and so $X_2(t) + X_3(t) + X_4(t) = N$ for some $N > 0$ and all $t$. Therefore, after solving for the normalizing constant, we have that for any $x \in \mathbb{Z}^4_{\geq 0}$ satisfying $x_2 + x_3 + x_4 = N$

$$\pi(x) = e^{-c_1} c_1^{x_1} / x_1! c_2^{x_2} c_3^{x_3} c_4^{x_4} = e^{-c_1} c_1^{x_1} \frac{N!}{x_2! x_3! x_4!} c_2^{x_2} c_3^{x_3} c_4^{x_4},$$

where $c = (k_3 / k_{-3}, c_2, c_3, c_4)$ has been chosen so that $c_2 + c_3 + c_4 = 1$. Thus, when the stochastically modeled system is in distributional equilibrium we have that: (a) $E$ has a Poisson distribution with parameter $k_3 / k_{-3}$, (b) $S, ES,$ and $P$ are multinomially distributed, and (c) $E$ is independent from $S, ES,$ and $P$.

**6. More general kinetics.** In this section we extend our results to systems with more general kinetics than stochastic mass action. The generalizations we make are more or less standard for the types of results presented in this paper (see, for example, [27, 32]). What is surprising, however, is that the conditions of the deficiency zero theorem of Feinberg (which are conditions on mass-action deterministic systems) are also sufficient to guarantee the existence of certain stationary distributions of stochastically modeled systems even when the intensity functions are not given by (4). It is interesting to note that the generalizations made here for the stochastic deficiency zero theorem 4.2 are similar to those made in [31], which generalized Feinberg’s deficiency zero theorem 3.1.

Suppose that the intensity functions of a stochastically modeled systems are given by

$$\lambda_k(x) = \kappa_k \prod_{i=1}^m \prod_{j=0}^{v_{ik}-1} \theta_i(x_i - j) = \kappa_k \prod_{i=1}^m \theta_i(x_i) \theta_i(x_i - 1) \theta_i(x_i - (v_{ik} - 1)),$$
where the $\kappa_k$ are positive constants, $\theta_i : \mathbb{Z}_{\geq 0} \to \mathbb{R}_{\geq 0}$ and $\theta_i(x) = 0$ if $x \leq 0$. As pointed out in [27], the function $\theta_i$ should be thought of as the “rate of association” of the $i$th molecule. Giving just a few interesting choices for $\theta_i$, we first note that if $\theta_i(x_i) = x_i$, then (19) is stochastic mass-action kinetics. However, if

$$\theta_i(x_i) = \frac{v_i x_i}{k_i + x_i},$$

for some positive constants $k_i$ and $v_i$, then the system has a type of stochastic Michaelis-Menten kinetics. Finally, if $|\nu_k| \in \{0, 1\}$ and $\theta_i(x_i) = \min\{n_i, x_i\}$, then the dynamical system models an $M/M/n$ queueing network in which the $i$th species (and in this case complex) represents the queue length of the $i$th queue, which has $n_i$ servers who work on a first come, first serve basis.

The main restriction imposed by (19) is that for any reaction for which the $i$th species appears in the source complex, the rate of that reaction must depend upon $X_i$ via $\theta_i(X_i)$ only. Therefore, if, say, the $i$th species is governed by Michaelis-Menten kinetics (20), then the constants $k_i$ and $v_i$ must be the same for each intensity which depends upon $X_i$. However, systems with intensities given by (19) are quite general in that different kinetics can be incorporated into the same model through the functions $\theta_i$. For example, if in a certain system species $S_1$ is governed by Michaelis-Menten kinetics (20) and species $S_2$ is governed by mass-action kinetics, then the reaction $S_1 + S_2 \to \nu'_k$ would have intensity

$$\lambda_k(x) = \kappa_k \frac{v_1 x_1}{k_1 + x_1} x_2,$$

for some constant $\kappa_k$.

**Theorem 6.1.** Let $\{S, C, R\}$ be a stochastically modeled chemical reaction network with intensity functions (19). Suppose that the associated mass-action deterministic system with rate constants $\kappa_k$ has a complex balanced equilibrium $c \in \mathbb{R}_{\geq 0}^m$. Then for any closed, irreducible communicating equivalence class, $\Gamma$, the stochastic system has a product-form stationary distribution

$$\pi(x) = M \prod_{i=1}^m \frac{c_i^{x_i}}{\prod_{j=1}^{\nu_i} \theta_i(j)}, \quad x \in \Gamma,$$

where $M$ is a normalizing constant, provided that (21) is summable.

**Proof.** As before, the proof consists of plugging (21) and (19) into equation (5) and verifying that $c$ being a complex balanced equilibrium is sufficient. The details are similar to before and so are omitted. \qed
Theorem 6.2. Let \( \{S, C, R\} \) be a stochastically modeled chemical reaction network with intensity functions (19). Suppose that the network of the model is weakly reversible and has a deficiency of zero. Then for any closed, irreducible communicating equivalence class, \( \Gamma \), the stochastic system has a product-form stationary distribution

\[
\pi(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)}, \quad x \in \Gamma,
\]

where \( M \) is a normalizing constant, provided that (22) is summable.

Proof. This follows immediately from Theorems 3.3 and 6.1. \( \square \)

Example 6.3. Consider a network, \( \{S, C, R\} \), that is weakly reversible and has a deficiency of zero. Suppose we have modeled the dynamics stochastically with intensity functions given by (19) with each \( \theta_i \) given via (20) for some choice of positive constants \( v_i \) and \( k_i \). That is, we consider a system endowed with stochastic Michaelis-Menten kinetics. Then,

\[
\prod_{j=1}^{x_i} \theta_i(j) = \prod_{j=1}^{x_i} \frac{v_{ij} j}{k_i + j} = v_i^{x_i} / \left( \frac{k_i + x_i}{x_i} \right).
\]

Thus, our candidate for a stationary distribution is

\[
\pi(x) = M \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)} = M \prod_{i=1}^{m} \left( \frac{k_i + x_i}{x_i} \right) \left( \frac{c_i}{v_i} \right)^{x_i}.
\]

Noting that

\[
\left( \frac{k_i + x_i}{x_i} \right) = O(x_i^{k_i}), \quad x_i \to \infty,
\]

we see that \( \pi(x) \) given by (23) is summable if \( c_i < v_i \) for each species \( S_i \) whose possible abundances are unbounded. In this case, (23) is indeed a stationary distribution for the system.

The result of Example 6.3 pertaining to the summability of (23) can be generalized in the following manner.

Theorem 6.4. Suppose that for some \( \Gamma \subset \mathbb{Z}_{\geq 0}^m \), \( \pi : \Gamma \to \mathbb{R} \) satisfies

\[
\pi(x) = \prod_{i=1}^{m} \frac{c_i^{x_i}}{\prod_{j=1}^{x_i} \theta_i(j)},
\]

for some \( c \in \mathbb{R}_{\geq 0}^m \). Then \( \pi(x) \) is summable if for each \( i \) for which \( \sup\{x_i \mid x \in \Gamma\} = \infty \) we have that \( \theta_i \) is monotonically increasing and \( \lim_{j \to \infty} \theta_i(j) > c_i \).
PROOF. The conditions of the theorem immediately imply that there are positive constants $C$ and $\rho$ for which $\pi(x) < Ce^{-\rho|x|}$, for all $x \in \Gamma$, which implies that $\pi(x)$ is summable.

It is tempting to believe that the conditions of theorem 6.4 are in fact necessary. The following simple example shows this not to be the case.

EXAMPLE 6.5. Consider the reaction system with network

\[ \emptyset \rightleftharpoons S_1 + S_2, \]

where the rate of the reaction $\emptyset \to S_1 + S_2$ is $\lambda_1(x) = 1$, and the rate of the reaction $S_1 + S_2 \to \emptyset$ is $\lambda_2(x) = 1 \times \theta_1(x_1)\theta_2(x_2)$, where

\[ \theta_1(x_1) = \frac{3x_1}{1 + x_1}, \quad \theta_2(x_2) = \frac{(1/2)x_2}{1 + x_2}. \]

Assume further that $X_1(0) = X_2(0)$. For the more physically minded readers, we note that this model could describe a reaction system for which there is a chemical complex $C = S_1S_2$ that sporadically breaks into its chemical constituents, which may then re-form. The complex $C$ may be present in such high numbers relative to free $S_1$ and $S_2$ that we choose to model it as fixed, which leads to the above reaction network.

We note that in this case, the reaction rates for the corresponding deterministic system are both equal to one, and so the equilibrium value guaranteed to exist for the deterministically modeled system by the deficiency zero theorem is $c = (1, 1)$. This system does not satisfy the assumptions of theorem 6.4 because both $X_1$ and $X_2$ are unbounded and $\lim_{j \to \infty} \theta_2(j) = 1/2 < 1 = c_2$. However, for any $x \in \Gamma = \{x \in \mathbb{Z}_2^2 : x_1 = x_2\}$,

\[ \pi(x) = \left(1 + x_1\right)^{x_1} \left(1 + x_2\right)^{x_2} \left(\frac{1}{(1/2)}\right)^{x_2} = \left(1 + x_1\right)^2 \left(\frac{2}{3}\right)^{x_1}, \]

which is summable over $\Gamma$.

Finally, let the intensity functions of a stochastically modeled system be given by

\[ \lambda_k(x) = \kappa_k \frac{\theta(x)}{\theta(x - \nu_k)}, \]

where the $\kappa_k$ are positive constants, and $\theta : \mathbb{Z}^m \to \mathbb{R}_{\geq 0}$. Note that if

\[ \theta(x) = \prod_{i=1}^{m} \prod_{j=1}^{x_i} \theta_i(j), \]
for some functions $\theta_i$, then (24) is equivalent to (19). The following two theorems are proved in manners similar to theorems 6.1 and 6.2.

**Theorem 6.6.** Let $\{S, C, R\}$ be a stochastically modeled chemical reaction network with intensity functions (24). Suppose that the associated mass-action deterministic system with rate constants $\kappa_k$ has a complex balanced equilibrium $c \in \mathbb{R}^m_{>0}$. Then for any closed, irreducible communicating equivalence class, $\Gamma$, the stochastic system has stationary distribution

$$
\pi(x) = M \frac{1}{\theta(x)} c^x = M \frac{1}{\theta(x)} \prod_{i=1}^{m} c_i^{x_i}, \quad x \in \Gamma,
$$

where $M$ is a normalizing constant, provided that (25) is summable.

**Theorem 6.7.** Let $\{S, C, R\}$ be a stochastically modeled chemical reaction network with intensity functions (24). Suppose that the network of the model is weakly reversible and has a deficiency of zero. Then for any closed, irreducible communicating equivalence class, $\Gamma$, the stochastic system has stationary distribution

$$
\pi(x) = M \frac{1}{\theta(x)} c^x = M \frac{1}{\theta(x)} \prod_{i=1}^{m} c_i^{x_i}, \quad x \in \Gamma,
$$

where $M$ is a normalizing constant, provided that (26) is summable.

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