Time-dependent product-form Poisson distributions for reaction networks with higher order complexes

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Abstract

It is well known that stochastically modeled reaction networks that are complex balanced admit a stationary distribution that is a product of Poisson distributions. In this paper, we consider the following related question: supposing that the initial distribution of a stochastically modeled reaction network is a product of Poissons, under what conditions will the distribution remain a product of Poissons for all time? By drawing inspiration from Crispin Gardiner's "Poisson representation" for the solution to the chemical master equation, we provide a necessary and sufficient condition for such a product-form distribution to hold for all time. Interestingly, the condition is a dynamical "complex-balancing" for only those complexes that have multiplicity greater than or equal to two (i.e. the higher order complexes that yield non-linear terms to the dynamics). We term this new condition the "dynamical and restricted complex balance" condition (DR for short).

1 Introduction

Reaction networks are commonly utilized in the modeling of biological processes such as gene regulatory networks, signaling networks, viral infections, cellular metabolism, etc., and their dynamics are typically modeled in one of three ways [5, 18]. If the counts of the constituent molecules are low, then the dynamics of the abundances is typically modeled stochastically with a discrete-space, continuous-time Markov chain in $\mathbb{Z}^d_{\geq 0}$, where d is the number of species in the system. If the counts are moderate (perhaps between order 10^2 and order 10^4), then the concentrations of the constituent species may be approximated by some form of continuous diffusion process. If the counts of the constituent species are high, then the evolution of their concentrations is often modeled deterministically via a system of ordinary differential equations.

Analytic treatments of such models are rarely possible, and most existing approaches analyze steady states: fixed points of the concentrations in the deterministic modeling regime and stationary distributions in the stochastic regime. However, most biological processes are not in steady state and experiments typically measure transient dynamics. To identify the underlying interactions, time-dependent solutions of the relevant dynamical equations are needed [16, 20]. For stochastic systems modeled as discrete space, continuous time Markov chains, there are no known explicit formulas for the time dependent distribution of the process, except in the case of monomolecular systems [15]. Because of this, either stochastic simulations or approximation methods are typically employed in the stochastic setting [17, 19, 21]. However, these approaches are computationally expensive and/or give rise to uncontrolled estimation errors [18]. To the

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best of our knowledge, the results presented in this article are the first that provide the exact time dependent distribution for a general class of reaction networks with higher order complexes.

In the series of papers [9, 13, 14], Feinberg, Horn, and Jackson introduced the notion of network deficiency and proved that if the reaction network (i) is weakly reversibility and (ii) has a deficiency of zero, then the resulting deterministically modeled system endowed with mass action kinetics is "complex balanced," regardless of the choice of rate parameters. See [3, 4, 5] for terminology. In [3], Anderson, Craciun, and Kurtz proved a corresponding result for the associated jump Markov models. In particular, they showed that any stochastic model whose deterministic counterpart is complex balanced (which, by the works cited above, includes all models whose network is weakly reversible and has a deficiency of zero) admits a stationary distribution that is a product of Poissons. The specific distribution is

$$\pi(x) = \prod_{i=1}^{d} e^{-\tilde{c}_i} \frac{\tilde{c}_i^{x_i}}{x_i!}, \quad x \in \mathbb{Z}^d_{\geq 0}, \tag{1}$$

where $\tilde{c} \in \mathbb{R}^d_{>0}$ is a complex balanced fixed point of the corresponding deterministically modeled system. See also [1], where the processes considered in [3] were shown to be non-explosive, and [2], where the main result from [3] was generalized to a class of models with non-mass action kinetics. Finally, the interested reader may also see [7], where a converse to the main theorem in [3] is shown. Specifically, they show that if a system admits the stationary distribution (1), then the associated deterministic model is complex balanced.

In this paper we study a related question. Consider a reaction network endowed with stochastic mass action kinetics and let X_t denote the vector whose ith coordinate gives the count of species i at time t. We ask the following: when is it the case that

$$P(X_0 = x) = \prod_{i=1}^{d} e^{-\tilde{c}_i} \frac{\tilde{c}_i^{x_i}}{x_i!}, \tag{2}$$

where $\tilde{c} \in \mathbb{R}^d_{>0}$, implies there is a function of time $c : [0, \infty) \to \mathbb{R}^d_{>0}$ with $c(0) = \tilde{c}$, for which

$$P(X_t = x) = \prod_{i=1}^{d} e^{-c_i(t)} \frac{c_i(t)^{x_i}}{x_i!}, \quad \text{for all } t \geq 0? \tag{3}$$

That is, when can the model admit a time dependent distribution that is always a product of Poissons? Further, when (3) does hold, what is the function c?

A partial answer to this question has been known for quite some time. In particular, in [11] Gardiner showed that if all complexes of the network are either zeroth or first order (which implies linear dynamics), then (2) implies (3) where c is the solution to the associated deterministic model with initial concentration levels given by $c(0)$. In this paper, we fully characterize which models have this desired property. In particular, we introduce a dynamical and restricted (DR) complex balance condition (see Definition 2.3), and prove in Theorem 3.1 that this is a necessary and sufficient condition for (2) to imply (3), with c being the solution to the associated deterministic model.

The outline of the remainder of the paper is as follows. In Section 2, we formally introduce the relevant mathematical models, giving the formal definition of a reaction network together with both the stochastic and deterministic model. We also introduce our new DR condition. In Section 3, we provide our main results, together with their motivation from the physics literature. In particular, we demonstrate how Gardiner's Poisson Representation (PR), equation (10), implies a mathematical conjecture pertaining to which systems of order two can admit a distribution that is a product of Poissons for all times. We then prove this conjecture while also generalizing to models of order two or higher. In Section 4, we provide a series of examples.

2 Mathematical model

We formally introduce the mathematical models considered in this paper, together with some key terminology.

Definition 2.1. A *reaction network* is a triple of finite sets, usually denoted $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$, satisfying the following:

(i) the *species*, $\mathcal{S} = \{S_1, \ldots, S_d\}$, are the components whose abundances we wish to model dynamically;

(ii) the *complexes*, $\mathcal{C}$, are linear combinations of the species over the nonnegative integers. Specifically, if $y \in \mathcal{C}$, then

$$y = \sum_{i=1}^{d} y_i S_i, \tag{4}$$

with $y_i \in \mathbb{Z}_{\geq 0}$.

(iii) The *reactions*, $\mathcal{R}$, are a binary relation on the complexes. The relation is typically denoted with "$\to$", as in $y \to y'$.

We often enumerate the reactions by k, and for $y_k, y_k' \in \mathcal{C}$ with $y_k \to y_k' \in \mathcal{R}$, we call y_k and y_k' the *source* and *product* complexes, respectively, of that reaction.

We also include the following usual conditions in this definition: every species must appear in at least one complex, every complex must appear as the source or product of at least one reaction, and we do not allow reactions of the type $y \to y \in \mathcal{R}$ (i.e., we do not allow the source and product complex of a given reaction to be the same).

Allowing for a slight abuse of notation, we will let y denote both the linear combination of the species, as in (4), and the vector whose ith component is y_i, i.e. $y = (y_1, y_2, \cdots, y_d)^T \in \mathbb{Z}^d_{\geq 0}$. For example, when $\mathcal{S} = \{S_1, S_2, \ldots, S_d\}$, we correspond $2S_1 + S_2$ with $(2, 1, 0, 0, \ldots, 0)^T \in \mathbb{Z}^d_{\geq 0}$.

For a vector $u \in \mathbb{R}^d$, we let $\|u\|_1 = \sum_{i=1}^d |u_i|$. We will say that a reaction network is of *first order* if $\|y\|_1 \leq 1$ for $\forall y \in \mathcal{C}$, is of *second order* if $\|y\|_1 \leq 2$ for $\forall y \in \mathcal{C}$, etc. For example, the network $4S_1 + S_2 \rightleftarrows 3S_3$ is of 5th order.

A reaction network is said to be *weakly reversible* if for any given reaction, $y \to y' \in \mathcal{R}$ say, there are reactions, $y_1 \to y_1', \ldots, y_\ell \to y_\ell' \in \mathcal{R}$ with $y' = y_1$, $y_i' = y_{i+1}$ for each $i \in \{1, \ldots, \ell - 1\}$, and $y_\ell' = y$. That is, a model is weakly reversible if each connected component of the reaction diagram is strongly connected when each complex is written exactly one time.

When working in a theoretical setting, the set of species is often denoted $\{S_1, \ldots, S_d\}$. However, when working with specific examples one often adopts more suggestive notation such as E for an enzyme, P for a protein, etc.

We provide a number of examples to demonstrate the terminology.

Example 2.1. If in our system we have only three species, which we denote by S_1, S_2, and S_3, and the only transition type we allow is the merging of an S_1 and an S_2 molecule to form an S_3 molecule, then we may depict this network by the directed graph

$$S_1 + S_2 \to S_3.$$

For this very simple model our network consists of species $\mathcal{S} = \{S_1, S_2, S_3\}$, complexes $\mathcal{C} = \{S_1 + S_2,\ S_3\}$, and reactions $\mathcal{R} = \{S_1 + S_2 \to S_3\}$. △

Example 2.2. The simplest model for gene transcription and translation assumes the following set of reactions,

$$\begin{aligned} G &\to G + M \quad \textit{(transcription)} \\ M &\to M + P \quad \textit{(translation)} \\ M &\to \emptyset \quad \textit{(degradation)} \\ P &\to \emptyset \quad \textit{(degradation).} \end{aligned}$$

Here, the set of species is $\{G, M, P\}$, representing the gene, mRNA, and Protein, respectively, the set of complexes is $\{G,\ G+M,\ M,\ M+P,\ P,\ \emptyset\}$, and the set of reactions is $\mathcal{R} = \{G \to G+M,\ M \to M+P,\ M \to \emptyset,\ P \to \emptyset\}$. $\triangle$

We now define the two most popular modeling choices for reaction networks: the discrete-space, continuous-time Markov chain model and the deterministic model.

Discrete-space, continuous-time Markov chain model. The usual stochastic model for a reaction network treats the system as a continuous-time Markov chain whose state $X_t \in \mathbb{Z}^d_{\geq 0}$ is a vector whose ith component gives the abundance of species S_i at time $t \geq 0$, and with each reaction modeled as a possible transition of the chain. For the kth reaction, we let $y_k \in \mathbb{Z}^d_{\geq 0}$ and $y'_k \in \mathbb{Z}^d_{\geq 0}$ be the vectors whose ith components gives the multiplicity of species i in the source and product complexes, respectively, and let $\lambda_k : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}_{\geq 0}$ give the *transition intensity*, or rate, at which the reaction occurs. The transition intensities are often referred to as the *propensities*. Specifically, if the kth reaction occurs at time t, then the old state, X_{t-}, is updated by addition of the *reaction vector* $\zeta_k = y'_k - y_k$ and

$$X_t = X_{t-} + \zeta_k.$$

For example, for the reaction $S_1 + S_2 \to S_3$, we have

$$y_k = \begin{bmatrix} 1 \\ 1 \\ 0 \end{bmatrix}, \quad y'_k = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}, \quad \text{and} \quad \zeta_k = \begin{bmatrix} -1 \\ -1 \\ 1 \end{bmatrix}.$$

We now assume that X_t is a continuous-time Markov chain on $\mathbb{Z}^d_{\geq 0}$ with transition rates

$$q(x, x') = \sum_{k:\zeta_k = x'-x} \lambda_k(x),$$

where the sum is over all reactions with reaction vector equal to $x' - x$. The reason for the sum is that different reactions can gave the same reaction vector. For example, the reactions $S_1 \to S_2$ and $2S_1 \to S_1 + S_2$ have the same reaction vector. The most common form for the intensity functions λ_k is given by *stochastic mass action kinetics*, in which case

$$\lambda_k(x) = \kappa_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - y_{ki})!} 1_{\{x_i \geq y_{ki}\}}, \quad x \in \mathbb{Z}^d_{\geq 0}, \tag{5}$$

where y_k is the source complex and $\kappa_k \in \mathbb{R}_{\geq 0}$ is the rate constant.

Other ways to characterize the stochastic model. The model described above is a continuous-time Markov chain in $\mathbb{Z}^d_{\geq 0}$ with infinitesimal generator

$$(\mathcal{A}f)(x) = \sum_k \lambda_k(x)(f(x + \zeta_k) - f(x)), \tag{6}$$

where $f : \mathbb{Z}^d \to \mathbb{R}$ [5, 8]. Kolmogorov's forward equation, termed the *chemical master equation* in much of the biology and chemistry literature, for this class of models is [4, 6, 12]

$$\frac{d}{dt} P_\mu(x, t) = \sum_k \lambda_k(x - \zeta_k) P_\mu(x - \zeta_k, t) 1_{\{x - \zeta_k \in \mathbb{Z}^d_{\geq 0}\}} - \sum_k \lambda_k(x) P_\mu(x, t), \tag{7}$$

where $P_\mu(x, t)$ represents the probability that $X_t = x \in \mathbb{Z}^d_{\geq 0}$, given an initial distribution of μ. Note that there is one such equation (7) for each state in the system (so there are often an infinite number of equations). So long as the process is non-explosive, the different characterizations for the relevant processes are equivalent [4, 5, 8].

Deterministic model. The usual deterministic model with mass action kinetics is the solution to the following ordinary differential equation in $\mathbb{R}^d_{\geq 0}$

$$\frac{d}{dt}c(t) = \sum_k \kappa_k c(t)^{y_k}(y'_k - y_k), \tag{8}$$

where for two vectors $u, v \in \mathbb{R}^d_{\geq 0}$ we define $u^v \equiv \prod_i u_i^{v_i}$ and adopt the convention that $0^0 = 1$.

Definition 2.2. An equilibrium value $c \in \mathbb{R}^d_{\geq 0}$ is said to be *complex balanced* if for each complex $z \in \mathcal{C}$,

$$\sum_{k:y_k=z} \kappa_k c^z = \sum_{k:y'_k=z} \kappa_k c^{y_k},$$

where the sum on the left (respectively, right) is over those reactions with source (respectively, product) complex z.

Here we will introduce a new definition, which is closely related to that of a complex balanced equilibrium. Below and throughout, we denote the 1-norm of a vector u by $\|u\|_1 = \sum_i |u_i|$.

Definition 2.3. We say that a solution $c(t)$ to the deterministic dynamics in (8) satisfies the *dynamical and restricted* (DR, for short) *complex balance condition* if the following holds: for all complexes $z \in \mathcal{C}$ with $\|z\|_1 \geq 2$ and all $t \geq 0$,

$$\sum_{k:y_k=z} \kappa_k c(t)^z = \sum_{k:y'_k=z} \kappa_k c(t)^{y_k}, \tag{9}$$

where the sum on the left (respectively, right) is over those reactions with source (respectively, product) complex z.

Thus, the DR conditions is the same as the complex balanced condition except it allows for time dependence (i.e., is dynamical) and is restricted to those complexes that have non-linear intensity functions. Note that the DR condition holds trivially in the case that $\|z\|_1 \leq 1$ for all $z \in \mathcal{C}$.

Lemma 2.1. *Consider a reaction network endowed with deterministic mass action kinetics. Let $c(t)$ be the solution to the system (8). If for $\tilde{c} = c(0) \in \mathbb{R}^d_{>0}$ we have that $c(t)$ satisfies the DR condition of Definition 2.3, then, for this particular choice of initial condition, the right-hand side of (8) is linear and $c(t) \in \mathbb{R}^d_{>0}$ for all $t \geq 0$.*

Proof. Denote $\overline{\mathcal{C}} = \{y_k : \|y_k\|_1 \geq 2\}$. We may rewrite the deterministic equation (8) in the following manner,

$$\begin{aligned}
\frac{d}{dt}c(t) &= \sum_k \kappa_k c(t)^{y_k}(y'_k - y_k) = \sum_{k:y_k \in \overline{\mathcal{C}}} \kappa_k c(t)^{y_k}(y'_k - y_k) + \sum_{k:y_k \notin \overline{\mathcal{C}}} \kappa_k c(t)^{y_k}(y'_k - y_k) \\
&= \sum_{z \in \overline{\mathcal{C}}} z \left(\sum_{k:y'_k=z} \kappa_k c(t)^{y_k} - \sum_{k:y_k=z} \kappa_k c(t)^{y_k} \right) + \sum_{k:y_k \notin \overline{\mathcal{C}}} \kappa_k c(t)^{y_k}(y'_k - y_k) \\
&= \sum_{k:y_k \notin \overline{\mathcal{C}}} \kappa_k c(t)^{y_k}(y'_k - y_k).
\end{aligned}$$

Where the third equality uses the *DR condition* of Definition 2.3. Notice that if $y_k \notin \overline{\mathcal{C}}$, we have $\|y_k\|_1 \leq 1$, which guarantees that each of the remaining terms of the form $c(t)^{y_k}$ are linear.

We must now show that $c(t) \in \mathbb{R}^d_{>0}$ for all $t \geq 0$ if $c(0) \in \mathbb{R}^d_{>0}$. This follows by observing that for each i, the differential equation governing the dynamics of $c_i(t)$ is of the form

$$\frac{d}{dt}c_i(t) = \sum_{j \neq i} \beta_j c_j(t) - \overline{\beta}_i c_i(t),$$

where $\beta_j, \overline{\beta}_i \in \mathbb{R}_{\geq 0}$, and comparing with the solution to the ODE $\frac{d}{dt}x(t) = -\overline{\beta}_i x(t)$. □

Remark 2.1. The previous lemma gives us one feasible approach to check whether the DR condition holds for a given model. Specifically if the DR condition holds, then by Lemma 2.1 the system governing the dynamics of $c(t)$ is linear and can therefore be solved explicitly. We can then check whether the solution so found satisfies the DR condition (9). We will utilize this idea in Section 4 on a number of examples.

3 Motivation and results

3.1 Motivation from the physics literature

In the physics literature, there is an alternative representation for the solution to the chemical master equation (7) and is given by Gardiner's *Poisson representation* (PR) [11]. One form of the PR (the "positive PR" [10]) can be derived by first making the following ansatz for $P_\mu(x,t)$ from (7):

$$P_\mu(x,t) = \int_{\mathbb{C}^d} \prod_{i=1}^{d} \mathcal{P}(x_i;u_i)\pi_\nu(u,t)du, \quad u=(u_1,\dots,u_d), \tag{10}$$

where $\mathcal{P}(x_i;u_i) = (e^{-u_i}u_i^{x_i})/x_i!$ is a Poisson distribution in x_i with mean u_i, and where $\pi_\nu(\cdot,\cdot)$ is a function on $\mathbb{C}^d \times \mathbb{R}_{\geq 0}$ satisfying $\pi_\nu(u,0)=\nu(u)$. Note that the integrals in (10) are taken over the whole complex plane for each u_i. Under certain conditions one can use the ansatz (10), together with the chemical master equation (7), to derive an evolution equation for $\pi_\nu(u,t)$ [11]. Specifically, under the further assumption that for each complex $y \in \mathcal{C}$ we have $\|y\|_1 \leq 2$ (i.e. the system is binary), one can formally derive that $\pi_\nu(u,t)$ fulfills the Fokker-Planck equation [11]

$$\frac{\partial}{\partial t}\pi_\nu(u,t) = -\sum_{i=1}^{d}\frac{\partial}{\partial u_i}\left[A_i(u)\pi_\nu(u,t)\right] + \frac{1}{2}\sum_{i,j=1}^{d}\frac{\partial}{\partial u_i}\frac{\partial}{\partial u_j}\left[B_{ij}(u)\pi_\nu(u,t)\right], \tag{11}$$

with drift vector $A(u)$ and diffusion matrix $B(u)$ given by

$$A_i(u) = \sum_k \kappa_k u^{y_k}\zeta_{ki}, \tag{12}$$

$$B_{ij}(u) = \sum_k \kappa_k u^{y_k}(y'_{ki}y'_{kj} - y_{ki}y_{kj} - \delta_{i,j}\zeta_{ki}), \tag{13}$$

where $\delta_{i,j}$ denotes the Kronecker delta, and where the initial condition is $\pi_\nu(u,0)=\nu(u)$.

Now suppose that $B(u)\equiv 0$ and that the initial condition satisfies $\nu(u)=\delta(u-u^0)$, i.e. is the Dirac delta function, for some constant $u^0 \in \mathbb{Z}^d_{\geq 0}$. Note that, from (10), having $\nu(u)=\delta(u-u_0)$ corresponds to a product of Poissons for an initial distribution of the process X_t, i.e. $P_\mu(x,0) = \mu(x) = \prod_{i=1}^d \mathcal{P}(x_i;u_i^0)$. Now note that because $B(u)\equiv 0$ the equation for π_ν in (11) reduces to a Liouville equation and π_ν remains a delta distribution for all times centered around the deterministic process $u(t)$, which fulfills the ordinary differential equation (8). This means that X_t has a distribution given by a product of Poissons for all times: $P_\mu(x,t) = \prod_{i=1}^d \mathcal{P}(x_i;u_i(t))$.

Collecting thoughts, we have shown that the PR representation in the physics literature implies the following conjecture.

Conjecture 1. *Suppose that the following three conditions hold:*

(i) the reaction network is binary, i.e. $\|y\|_1 \leq 2$ for each complex,

(ii) the initial distribution of the stochastically modeled reaction network is a product of Poissons,

(iii) $B(u(t))=0$, where $u(t)$ solves (8) and B is as in (13).

Then the distribution of the process X_t is a product of Poissons for all time.

Note that we trivially have $B(u) = 0$ for all u if the model is unimodal (i.e. if $\|y\|_1 \leq 1$ for each $y \in \mathcal{C}$). We will show that Conjecture 1 is correct. Moreover, we will show that the first condition stated (that the network is binary) is not needed, and then fully characterize those networks that can admit a distribution that is a product of Poissons for all time.

3.2 Main results

Our main result, Theorem 3.1, shows that a stochastically modeled reaction network has a product form distribution for all time if and only if the initial distribution is a product of Poissons and the DR condition from Definition 2.3 holds for the associated deterministic model.

Theorem 3.1. *Consider a stochastically modeled reaction network with intensity functions given by stochastic mass action kinetics (5). Suppose that X_0 has a distribution that is a product of Poissons, i.e. there is a $\tilde{c} \in \mathbb{R}^d_{>0}$ for which*

$$\mu(x) = \prod_{i=1}^{d} e^{-\tilde{c}_i} \frac{\tilde{c}_i^{x_i}}{x_i!}, \tag{14}$$

where $\mu(x) = P_\mu(X_0 = x)$. Then the following three statements are equivalent:

(i) the solution to the ODE (8) with $c(0) = \tilde{c}$ satisfies the DR condition of Definition 2.3;

(ii) the solution to the chemical master equation $P_\mu(x,t)$ satisfies

$$P_\mu(x,t) = \prod_{i=1}^{d} e^{-c_i(t)} \frac{c_i(t)^{x_i}}{x_i!} \text{ for } x \in \mathbb{Z}^d_{\geq 0} \text{ and all } t \geq 0, \tag{15}$$

for some deterministic process $c(t)$ with $c(0) = \tilde{c}$;

(iii) the solution to the chemical master equation $P_\mu(x,t)$ satisfies

$$P_\mu(x,t) = \prod_{i=1}^{d} e^{-c_i(t)} \frac{c_i(t)^{x_i}}{x_i!} \text{ for } x \in \mathbb{Z}^d_{\geq 0} \text{ and all } t \geq 0, \tag{16}$$

for $c(t)$ satisfying (8) with $c(0) = \tilde{c}$.

Remark 3.1. Note that if a reaction network is weakly reversible and if the rate constants are chosen so that the equilibrium concentration is complex balanced, then the stationary distribution for the model is given by (1), where $\tilde{c}$ is the complex balanced equilibrium [3]. Hence, if we choose $c(0) = \tilde{c}$ (the complex balanced equilibrium) we have that $c(t) = \tilde{c}$ for all $t \geq 0$ and that (16) also holds for all time (with $c(t) = \tilde{c}$). These time-independent solutions are not of interest to us, and we call such solutions *trivial solutions* throughout.

Before proving Theorem 3.1, we note that the next logical question would be: when will the DR condition hold? The following lemma answers this question for binary networks: the DR condition holds if and only if $B(u(t)) = 0$ where $u(t)$ solves the ODE (8).

Lemma 3.1. *Consider a binary reaction network, i.e. $\|y\|_1 \leq 2$ for all $y \in \mathcal{C}$. Then the DR condition from Definition 2.3 holds for the associated deterministic model (8) if and only if $B(u(t)) = 0$ with $u(t)$ satisfying (8).*

Note that taken together, Theorem 3.1 and Lemma 3.1 show that Conjecture 1 stated in the previous section holds.

Proof of Lemma 3.1. First note that if $\|z\|_1 \leq 1$ for all $z \in \mathcal{C}$, then both conditions hold. We may therefore consider the case where $\|z\|_1 \leq 2$ for each $z \in \mathcal{C}$ and $\|z\|_1 = 2$ for at least one complex $z \in \mathcal{C}$.

First, let us rewrite the expression in the parentheses of $B(u)$ in (13) as

$$y'_{ki}y'_{kj} - y_{ki}y_{kj} - \delta_{ij}\zeta_{ki} = f_{ij}(y'_k) - f_{ij}(y_k) \quad \text{where} \quad f_{ij}(y_k) = y_{ki}y_{kj} - \delta_{ij}y_{ki}.$$

It is straightforward to show that for given indices i and j, the expression $f_{ij}(y_k)$ is non-zero if and only if $y_k = e_i + e_j$, where e_i denotes the vector with the i^{th} entry equal to 1 and zero otherwise. This means we can rewrite $B_{ij}(u)$ as

$$\begin{aligned} B_{ij}(u(t)) &= \sum_k \kappa_k u(t)^{y_k}(f_{ij}(y'_k) - f_{ij}(y_k)) \\ &= \sum_{k:y'_k = e_i+e_j} \kappa_k u(t)^{y_k} f_{ij}(e_i+e_j) - \sum_{k:y_k=e_i+e_j} \kappa_k u(t)^{y_k} f_{ij}(e_i+e_j) \\ &= f_{ij}(e_i+e_j)\left(\sum_{k:y'_k=e_i+e_j} \kappa_k u(t)^{y_k} - \sum_{k:y_k=e_i+e_j} \kappa_k u(t)^{y_k}\right). \end{aligned} \tag{17}$$

where the first sum is over those reactions with product complex $e_i + e_j$ and the second sum is over those reactions with source complex $e_i + e_j$. Since each $f_{ij}(e_i + e_j) > 0$, we see that $B(u(t)) = 0$ if and only if the term in parentheses in (17) is zero for each choice of i and j. The equivalence of the two conditions then follows. □

The following proposition will be of use.

Proposition 3.1. *Consider a stochastically modeled reaction network with intensity functions given by stochastic mass action kinetics (5). Suppose there is a deterministic function $c(t)$, defined for $t \geq 0$, for which $P_\mu(x,t)$, the solution to the Kolmogorov forward equation (7), satisfies (15). Then, $E[X(t)] = c(t)$ is the solution to the deterministic equation (8) with $\tilde{c} = c(0)$.*

Proof. The infinitesimal generator of the continous-time markov chain model is the operator $\mathcal{A}$ given by (6). Since the distribution of $X(t)$ is given by (15), we know that $\mathbb{E}[X_i(t)] = c_i(t)$. Moreover,

$$\begin{aligned} \mathbb{E}[\lambda_k(X(s))] &= \kappa_k \mathbb{E}\left[\frac{X(s)!}{(X(s)-y_k)!}\right] \\ &= \kappa_k \mathbb{E}\left[\prod_{i=1}^d \frac{X_i(s)!}{(X_i(s)-y_{ki})!}\right] = \kappa_k \sum_{x\in\mathbb{Z}^d_{\geq 0}} \prod_{i=1}^d \frac{x_i!}{(x_i-y_{ki})!} \prod_{i=1}^d e^{-c_i(s)}\frac{c_i(s)^{x_i}}{x_i!} \\ &= \kappa_k \sum_{x\in\mathbb{Z}^d_{\geq 0}} \prod_{i=1}^d e^{-c_i(s)}\frac{c_i(s)^{x_i}}{(x_i-y_{ki})!} = \kappa_k c(s)^{y_k} \sum_{x\in\mathbb{Z}^d_{\geq 0}} \prod_{i=1}^d e^{-c_i(s)}\frac{c_i(s)^{x_i-y_{ki}}}{(x_i-y_{ki})!} = \kappa_k c(s)^{y_k}, \end{aligned} \tag{18}$$

where the final equality holds since we are summing a probability mass function over all of $\mathbb{Z}^d_{\geq 0}$. For $m > 0$, applying Dynkin's formula with the function $f_m(x) = x_i \wedge m \equiv \min\{x_i, m\}$ yields

$$\begin{aligned} \mathbb{E}[X_i(t)\wedge m] &= \mathbb{E}[X(0)\wedge m] + \mathbb{E}\left[\int_0^t \mathcal{A}f_m(X(s))ds\right] \\ &= \mathbb{E}[X_i(0)\wedge m] + \int_0^t \mathbb{E}\left[\sum_{k=1}^K \lambda_k(X(s))((X_i(s)+\zeta_{ki})\wedge m - X_i(s)\wedge m)\right] ds. \end{aligned}$$

Noting that $\sup_{x\in\mathbb{Z}^d_{\geq 0}} |(x_i+\zeta_{ki})\wedge m - x_i \wedge m| \leq \max_\ell \|\zeta_\ell\|_\infty$ for all i, we may let $m \to \infty$ and apply the Dominated convergence theorem to conclude

$$\mathbb{E}[X(t)] = \mathbb{E}[X(0)] + \int_0^t \mathbb{E}\left[\sum_{k=1}^K \lambda_k(X(s))\zeta_k\right] ds. \tag{19}$$

Combining (19) with (18), together with the fact that $c(t) = E[X(t)]$, yields

$$c(t) = \tilde{c} + \int_0^t \sum_{k=1}^{K} \kappa_k c(s)^{y_k} \zeta_k ds.$$

Differentiating both sides shows that $c(t)$ is the solution to (8). □

We now turn to the proof of Theorem 3.1. We begin by stating two technical lemmas whose proofs are relegated to Appendix A.

Lemma 3.2. *Suppose $P_\mu(x,t)$ is given by (15) with $c(t) \in \mathbb{R}^d_{>0}$ for all $t \geq 0$. Then $P_\mu(x,t)$ is the solution to the Kolmogorov forward equation (7) if and only if $c(t)$ satisfies the deterministic equation (8) and*

$$\sum_k \kappa_k c(t)^{y_k} \left[g_{x,c(t)}(y_k') - g_{x,c(t)}(y_k) \right] = 0 \tag{20}$$

where for each $x \in \mathbb{Z}^d_{\geq 0}$ and $c \in \mathbb{R}^d_{>0}$,

$$g_{x,c}(y_k) = \sum_{j=1}^{d} \left(\frac{x_j}{c_j} - 1 \right) y_{kj} - \frac{x!}{(x-y_k)!} c^{-y_k} + 1. \tag{21}$$

Moreover, if $\|y_k\|_1 \leq 1$, then $g_{x,c}(y_k) = 0$.

Lemma 3.3. *Let $\{z_1, z_2, ..., z_m\} \subset \mathcal{C}$ be the collection of complexes that are at least binary (i.e. $\|z_i\|_1 \geq 2$). Fix a value $c \in \mathbb{R}^d_{>0}$. For each $i \in \{1, \ldots, m\}$ let $f_i : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}$ be defined as*

$$f_i(x) = g_{x,c}(z_i).$$

Then $\{f_i\}_{i=1}^m$ are linear independent.

We now prove Theorem 3.1.

Proof of Theorem 3.1. First note that the implication *(iii)* $\implies$ *(ii)* is trivial. We will now show that *(ii)* $\implies$ *(i)* and that *(i)* $\implies$ *(iii)*.

Proof that *(ii)* $\implies$ *(i)*.

By proposition 3.1, $E[X(t)] = c(t)$ solves the deterministic equation (8) with $\tilde{c} = c(0) \in \mathbb{R}^d_{>0}$. Therefore, we just need to show that $c(t)$ will satisfy the DR condition of Definition 2.3 . Since there is always a positive probability that no reaction takes place by time $t > 0$, we know that $E[X_i(t)] = c_i(t) > 0$. Hence, because $P_\mu(x,t)$ defined in (15) is the solution to the chemical master equation (7), Lemma 3.2 allows us to conclude that (20) holds with $g_{x,c}(y)$ defined as in (21). Since $g_{x,c(t)}(z) = 0$ if $\|z\|_1 \leq 1$, we can rewrite (20) as a summation over complexes which are at least binary:

$$\sum_{z:\|z\|_1 \geq 2} g_{x,c(t)}(z) \left[\sum_{k:y_k'=z} \kappa_k c(t)^{y_k} - \sum_{k:y_k=z} \kappa_k c(t)^{y_k} \right] = 0.$$

Because the above holds for all $x \in \mathbb{Z}^d_{\geq 0}$, Lemma 3.3 allows us to conclude that each term in brackets is identically equal to zero:

$$\sum_{k:y_k'=z} \kappa_k c(t)^{y_k} = \sum_{k:y_k=z} \kappa_k c(t)^{y_k},$$

which is exactly the the DR condition of Definition 2.3.

Proof that *(i)* $\implies$ *(iii)*.

Suppose that for $c(t)$ satisfying the ODE (8) we have

$$\sum_{k:y_k'=z} \kappa_k c(t)^{y_k} = \sum_{k:y_k=z} \kappa_k c(t)^{y_k},$$

for those z with $\|z\|_1 \geq 2$. Then for any $x \in \mathbb{Z}^d_{\geq 0}$ we may multiply the above by the functions $g_{x,c(t)}(z)$ defined in (21) and conclude

$$g_{x,c(t)}(z) \sum_{k:y_k'=z} \kappa_k c(t)^{y_k} = g_{x,c(t)}(z) \sum_{k:y_k=z} \kappa_k c(t)^{y_k}.$$

Note that the previous step is valid since $c(t) \in \mathbb{R}^d_{>0}$ by Lemma 2.1. We now sum over all complexes z (not just those with $\|z\|_1 \geq 2$), while noting that $g_{x,c(t)}(z) = 0$ if $\|z\|_1 \leq 1$, to see

$$\begin{aligned} 0 &= \sum_z g_{x,c(t)}(z) \left(\sum_{k:y_k'=z} \kappa_k c(t)^{y_k} - \sum_{k:y_k=z} \kappa_k c(t)^{y_k} \right) \\ &= \sum_{k=1}^K \kappa_k c(t)^{y_k} \left(g_{x,c(t)}(y_k') - g_{x,c(t)}(y_k) \right). \end{aligned}$$

which, by Lemma 3.2, implies $P_\mu(x,t)$ in (15) is the solution to the chemical master equation. Uniqueness of the solution to the chemical master equation follows from Lemma 1.23 in [6]. □

4 Examples

Theorem 3.1 gives a necessary and sufficient condition (the DR condition of Definition 2.3) for when a system will admit a distribution that is a product of Poissons for all time. Here we provide two examples, Example 4.1 and 4.2, satisfying that condition, and hence admit a time dependent distribution that is a product of Poissons. However, these examples will also make it clear that satisfying the DR condition is difficult in that the parameters of the model must be chosen precisely.

It is well known that for every weakly reversible model, there exists a choice of rate constants for which the model is complex balanced. In Examples 4.3 and 4.4, we demonstrate that in the time-dependent case there exist networks for which *no choice of rate constants* will yield a model that satisfies the DR condition (except in the trivial case–see Remark 3.1–when the initial condition is equal to a complex balanced equilibrium).

Example 4.1. Consider the reaction network with the following network diagram,

$$2X \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} 2Y, \quad \emptyset \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} X, \quad \emptyset \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} Y,$$

where the rate constants are placed next to their respective reaction arrow. Notice that $2X$ and $2Y$ are the only complexes that need to be considered in Definition 2.3. The DR condition for both complexes simplifies to the same equation

$$\kappa_1 x(t)^2 = \kappa_2 y(t)^2 \tag{22}$$

where $x(t), y(t)$ is the solution to the associated deterministic model (8). For the DR condition to be satisfied, we utilize (22) in the deterministic model to get

$$\begin{aligned} \frac{dx}{dt} &= -2\kappa_1 x^2 + 2\kappa_2 y^2 + \kappa_3 - \kappa_4 x = \kappa_3 - \kappa_4 x, & x(0) = x_0 \\ \frac{dy}{dt} &= \quad 2\kappa_1 x^2 - 2\kappa_2 y^2 + \kappa_5 - \kappa_6 y = \kappa_5 - \kappa_6 y, & y(0) = y_0. \end{aligned} \tag{23}$$

Notice that the system of linear equations (23) has become decoupled, and we can solve them exactly:

$$\begin{aligned} x(t) &= \left(x_0 - \frac{\kappa_3}{\kappa_4}\right) e^{-\kappa_4 t} + \frac{\kappa_3}{\kappa_4} \\ y(t) &= \left(y_0 - \frac{\kappa_5}{\kappa_6}\right) e^{-\kappa_6 t} + \frac{\kappa_5}{\kappa_6}. \end{aligned} \tag{24}$$

There are two cases to consider.

1. Suppose $x(0) = \frac{\kappa_3}{\kappa_4}$. Then $x(t) = \frac{\kappa_3}{\kappa_4}$ for all time $t \geq 0$. By (22), we must then have

   $$y(t) = \sqrt{\frac{\kappa_1}{\kappa_2}} x(t) = \frac{\kappa_3}{\kappa_4} \sqrt{\frac{\kappa_1}{\kappa_2}}.$$

   By (24), this only holds true if

   $$y_0 = \frac{\kappa_5}{\kappa_6} = \frac{\kappa_3}{\kappa_4} \sqrt{\frac{\kappa_1}{\kappa_2}}$$

   Notice that in this case, both $x(t)$ and $y(t)$ start at complex balanced equilibrium and stay constant for all time $t \geq 0$. Hence, this case is trivial as noted in Remark 3.1. A similar result holds if we had assumed $y_0 = \kappa_5/\kappa_6$.

2. Now suppose that neither $x(t)$ and $y(t)$ start at their complex balanced equilibriums. By taking the solution (24), plugging it back into (22), and matching terms, we find that the rate constants need to satisfy the following conditions for the DR condition to hold

   $$\kappa_4 = \kappa_6, \quad \frac{\sqrt{\kappa_1}}{\sqrt{\kappa_2}} = \frac{\kappa_5}{\kappa_3} = \frac{y_0}{x_0}.$$

   For example, taking

   $$x_0 = 1, \quad y_0 = 2, \quad \kappa_1 = 4, \quad \kappa_2 = 1, \quad \kappa_3 = 1, \quad \kappa_4 = \frac{1}{2}, \quad \kappa_5 = 2, \quad \text{and} \quad \kappa_6 = \frac{1}{2},$$

   yields the solution

   $$\begin{aligned} x(t) &= 2 - e^{-t/2} \\ y(t) &= 4 - 2e^{-t/2}, \end{aligned}$$

   which one can readily check satisfies both the deterministic ODEs (23) and the DR condition (22). Hence, by Theorem 3.1 we have that for any $z \in \mathbb{Z}^2_{\geq 0}$ and $t \geq 0$,

   $$P_\mu(z,t) = e^{-(x(t)+y(t))} \frac{x(t)^{z_1}}{z_1!} \frac{y(t)^{z_2}}{z_2!}.$$

A few remarks are in order. First, note that for this example the diffusion matrix B from (13) is

$$B(u) = \begin{pmatrix} -2\kappa_1 u^2 + 2\kappa_2 u_2^2 & 0 \\ 0 & 2\kappa_1 u_1^2 - 2\kappa_2 u_2^2 \end{pmatrix},$$

which also yields the equation (22) when we set $B((x(t), y(t))) = 0$.

Second, this model will admit a complex balanced equilibrium if and only if

$$\frac{\sqrt{\kappa_1}}{\sqrt{\kappa_2}} = \frac{\kappa_4}{\kappa_6} \cdot \frac{\kappa_5}{\kappa_3},$$

which is a *less* restrictive condition on the parameters of the model than we have found for the DR condition to hold. Said differently, there are choices of rate constants (for example when $\kappa_4 \neq \kappa_6$) for which the underlying model is complex balanced, but for which the DR condition does not hold. △

For some choices of rate constants, the previous model admitted a positive complex balanced equilibrium. The next example shows that a time dependent distribution that is a product of Poissons may still exist even if the associated deterministic model admits no positive equilibria for any choice of rate constants.

Example 4.2. Consider the network with reactions

$$X \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} 2Y, \quad X \xrightarrow{\kappa_3} \emptyset, \quad Y \xrightarrow{\kappa_4} \emptyset.$$

The DR condition of Definition 2.3 is

$$\kappa_1 x(t) = \kappa_2 y(t)^2 \tag{25}$$

where $x(t)$ and $y(t)$ are the solutions to the associated deterministic model (8). We search for solutions that satisfy the DR condition by plugging (25) into the deterministic model (8)

$$\begin{aligned} \frac{dx}{dt} &= -\kappa_1 x + \kappa_2 y^2 - \kappa_3 x = -\kappa_3 x & x(0) &= x_0 \\ \frac{dy}{dt} &= \quad 2\kappa_1 x - 2\kappa_2 y^2 - \kappa_4 y = -\kappa_4 y & y(0) &= y_0. \end{aligned} \tag{26}$$

As in the previous example, the system of equations (26) can be solved exactly yielding a solution of

$$x(t) = x_0 e^{-\kappa_3 t} \qquad y(t) = y_0 e^{-\kappa_4 t}.$$

Requiring that (25) holds enforces the following conditions

$$\kappa_3 = 2\kappa_4 \quad \text{and} \quad \frac{\kappa_1}{\kappa_2} = \frac{y_0^2}{x_0}. \tag{27}$$

Hence, any model satisfying the conditions (27) will yield a distribution satisfying (16).

For example, suppose we have

$$\kappa_1 = 9, \quad \kappa_2 = 1, \quad \kappa_3 = 2, \quad \kappa_4 = 1, \quad x_0 = 1, \quad \text{and} \quad y_0 = 3.$$

Then the solution to (8) is

$$x(t) = e^{-2t}, \quad y(t) = 3e^{-t},$$

which can be readily checked to satisfy the DR condition (25). Hence, by Theorem 3.1 we have that for any $z \in \mathbb{Z}^2_{\geq 0}$ and $t \geq 0$,

$$P_\mu(z,t) = e^{-(x(t)+y(t))} \frac{x(t)^{z_1}}{z_1!} \cdot \frac{y(t)^{z_2}}{z_2!}.$$

Note that even though $2X(t) + Y(t)$ is a conserved quantity for the model, the relevant state space is still all of $\mathbb{Z}^2_{\geq 0}$ as our initial distribution is the product of Poissons

$$\mu(z) = e^{-(x_0+y_0)} \frac{x_0^{z_1}}{z_1!} \cdot \frac{y_0^{z_2}}{z_2!},$$

which has support on all of $\mathbb{Z}^2_{\geq 0}$. △

For any weakly reversible model, there exists a choice of rate constants that make the resulting model complex balanced. The next two examples demonstrate that there are weakly reversible networks for which no nontrivial (in the sense of Remark 3.1) solution to the forward equation is a product of Poissons, regardless of the choice of rate constants.

Example 4.3. Consider the network

$$X \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} 2Y, \quad \emptyset \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} X, \quad \emptyset \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} Y,$$

where the rate constants have been placed next to their respective reactions. Note that this model is weakly reversible, and there is therefore a choice of rate constants for which it is complex balanced. For this model, the DR condition of Definition 2.3 is

$$\kappa_1 x(t) = \kappa_2 y(t)^2 \tag{28}$$

where $x(t)$ and $y(t)$ are the solutions to the associated deterministic model (8). To see when the DR conditions is satisfied, we utilize (28) in the deterministic model to get

$$\begin{aligned} \frac{dx}{dt} &= -\kappa_1 x + \kappa_2 y^2 + \kappa_3 - \kappa_4 x = \kappa_3 - \kappa_4 x \qquad x(0) = x_0 \\ \frac{dy}{dt} &= \quad 2\kappa_1 x - 2\kappa_2 y^2 + \kappa_5 - \kappa_6 y = \kappa_5 - \kappa_6 y \qquad y(0) = y_0. \end{aligned} \tag{29}$$

Notice that the system of linear equation (29) is exactly the same as the system (23), and we have

$$\begin{aligned} x(t) &= \left(x_0 - \frac{\kappa_3}{\kappa_4}\right) e^{-\kappa_4 t} + \frac{\kappa_3}{\kappa_4} \\ y(t) &= \left(y_0 - \frac{\kappa_5}{\kappa_6}\right) e^{-\kappa_6 t} + \frac{\kappa_5}{\kappa_6}. \end{aligned} \tag{30}$$

We will now demonstrate that there is not choice of parameters, except in the trivial case, that will satisfy (28). As before, there are two cases that need consideration.

1. Suppose $x(0) = \frac{\kappa_3}{\kappa_4}$. Then $x(t) = \frac{\kappa_3}{\kappa_4}$ for all time $t \geq 0$. By (28), we must then have

   $$y(t) = \sqrt{\frac{\kappa_1}{\kappa_2} x(t)} = \sqrt{\frac{\kappa_1 \kappa_3}{\kappa_2 \kappa_4}}.$$

   By (30), the above only holds true if

   $$y_0 = \frac{\kappa_5}{\kappa_6} = \sqrt{\frac{\kappa_1 \kappa_3}{\kappa_2 \kappa_4}}$$

   Notice that in this case, both $x(t)$ and $y(t)$ start at complex balanced equilibrium and stay constant for all time $t \geq 0$. Hence, this is the trivial case discussed in Remark 3.1. A similar result is found if one assumes first that $y_0 = \frac{\kappa_5}{\kappa_6}$.

2. Suppose now that neither $x(t)$ nor $y(t)$ starts at its equilibrium. We then take the solution (30) and plug it back into (28), yielding

   $$\kappa_1 \left(\left(x_0 - \frac{\kappa_3}{\kappa_4}\right) e^{-\kappa_4 t} + \frac{\kappa_3}{\kappa_4}\right) = \kappa_2 \left(y_0 - \frac{\kappa_5}{\kappa_6}\right)^2 e^{-2\kappa_6 t} + 2\kappa_2 \frac{\kappa_5}{\kappa_6} \left(y_0 - \frac{\kappa_5}{\kappa_6}\right) e^{-\kappa_6 t} + \kappa_2 \frac{\kappa_5^2}{\kappa_6^2}.$$

   The key observation is that in order to balance the three exponential terms, one of them *must* have a coefficient that is zero. However, this would imply that we are back in case 1.

Therefore, we may conclude that no nontrivial solution exists and, by Theorem 3.1, there is no choice of parameters which yields a distribution that is a product of Poissons for all time. △

Example 4.4. Consider the network

$$\emptyset \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X + Y, \quad \emptyset \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} X, \quad \emptyset \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} Y, \quad X \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} Y,$$

and assume that $\kappa_1, \kappa_2 > 0$. We will show that this model can not satisfy the DR condition of Definition 2.3 for any choice of rate constants.

First note that for this model the DR condition reduces to

$$\kappa_1 = \kappa_2 x(t) y(t) \qquad \Longleftrightarrow \qquad x(t) = \frac{\kappa_1}{\kappa_2} y(t)^{-1}, \tag{31}$$

where $x(t)$ and $y(t)$ are the solutions to the associated deterministic model (8), and we are assuming that $y(t) > 0$ for all $t \geq 0$. Assuming the DR condition holds, the associated deterministic model is

$$\begin{aligned} \frac{dx}{dt} &= \kappa_3 + \kappa_8 y - (\kappa_4 + \kappa_7)x \qquad & x(0) &= x_0 \\ \frac{dy}{dt} &= \kappa_5 + \kappa_7 x - (\kappa_6 + \kappa_8)y \qquad & y(0) &= y_0. \end{aligned} \tag{32}$$

Instead of solving this system explicitly, which leads to quite a messy solution, we note that (31) implies

$$\frac{dx}{dt} = -\frac{\kappa_1}{\kappa_2} y^{-2} \frac{dy}{dt}.$$

Plugging (32) into the above equation yields

$$\kappa_3 + \kappa_8 y - (\kappa_4 + \kappa_7)x = -\frac{\kappa_1}{\kappa_2} y^{-2} \left(\kappa_5 + \kappa_7 x - (\kappa_6 + \kappa_8)y\right),$$

which, after again using that we must have $x = \frac{\kappa_1}{\kappa_2} y^{-1}$ due to (31), becomes

$$\kappa_3 + \kappa_8 y - (\kappa_4 + \kappa_7)\frac{\kappa_1}{\kappa_2} y^{-1} = -\kappa_5 \frac{\kappa_1}{\kappa_2} y^{-2} - \kappa_7 \frac{\kappa_1^2}{\kappa_2^2} y^{-3} + (\kappa_6 + \kappa_8)\frac{\kappa_1}{\kappa_2} y^{-1}$$

or

$$\kappa_3 y^3 + \kappa_8 y^2 - \left[(\kappa_4 + \kappa_7)\frac{\kappa_1}{\kappa_2} + (\kappa_6 + \kappa_8)\frac{\kappa_1}{\kappa_2}\right] y^2 + \kappa_5 \frac{\kappa_1}{\kappa_2} y + \kappa_7 \frac{\kappa_1^2}{\kappa_2^2} = 0.$$

We have assumed that $y(t)$ is a nontrivial solution of the system, so the equation above implies the associated polynomial has an infinite number of roots. Of course, this can not be as a third degree polynomial has at most 3 roots. Hence, we may conclude that each of the coefficients of the above polynomial must be zero. Combining this fact with the assumption that $\kappa_1, \kappa_2 > 0$ we find

$$\kappa_3 = \kappa_4 = \kappa_5 = \kappa_6 = \kappa_7 = \kappa_8 = 0.$$

Hence, the only possibility is if the entire network is $\emptyset \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} X + Y$. However, then there can not be a nontrivial solution that satisfies the DR condition as $\kappa_1 = \kappa_2 x(t) y(t)$ implies that $x(t), y(t)$ is at equilibrium (thereby yielding a trivial solution). △

The logic at the end of the previous example can be used to characterize all one-dimensional models that satisfy the DR condition.

Proposition 4.1. *Consider a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ with one species, i.e., $\|\mathcal{S}\| = 1$ and suppose that the initial distribution of the associated Markov model satisfies (14). Then the solution to the forward equation (7) is given by (16) for some nontrivial process $c(t)$ if and only if the reaction network is of first order, in which case $\mathcal{C} = \{\emptyset, X\}$.*

Proof. Of course, if the system is first order, then the DR condition automatically holds and Theorem 3.1 implies that the solution to the forward equation (7) is given by (16).

We now show the other direction, and the proof will proceed by contradiction. Thus, suppose that there is a complex of the form $z = kX$ for some $k \geq 2$, and suppose that the solution to the forward equation (7) is given by (16) for some nontrivial process $c(t)$. By Theorem 3.1, we may

assume that the solution to the deterministic model (8) satisfies the DR condition of Definition 2.3 for the complex z. That is,

$$\sum_{k:y_k=z} \kappa_k c(t)^z = \sum_{k:y'_k=z} \kappa_k c(t)^{y_k},$$

where, as usual, the sum on the left is over those reactions with source complex z and the sum on the right is over those with product complex z. Consider the function

$$f(x) = \sum_{k:y_k=z} \kappa_k x^{\|z\|_1} - \sum_{k:y'_k=z} \kappa_k x^{\|y_k\|_1}.$$

Note that f is a polynomial in x. Also, each sum is nonempty and, because $\|y_k\|_1 \neq \|z\|_1$ for each term in the second sum, f is not identically equal to zero. Thus, f has a finite number of roots. However, $f(c(t)) = 0$, and $c(t)$ is nontrivial, implying f has an infinite number of roots, which is a contradiction. Thus, the result is shown. □

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A Proofs of Lemmas 3.2 and 3.3

We restate Lemma 3.2 for the sake of reference.

Lemma 3.2 *Suppose $P_\mu(x,t)$ is given by (15) with $c(t) \in \mathbb{R}^d_{>0}$ for all $t \geq 0$. Then $P_\mu(x,t)$ is the solution to the Kolmogorov forward equation (7) if and only if $c(t)$ satisfies the deterministic equation (8) and*

$$\sum_k \kappa_k c(t)^{y_k} \left[g_{x,c(t)}(y'_k) - g_{x,c(t)}(y_k) \right] = 0 \tag{20}$$

where for each $x \in \mathbb{Z}^d_{\geq 0}$ and $c \in \mathbb{R}^d_{>0}$,

$$g_{x,c}(y_k) = \sum_{j=1}^d \left(\frac{x_j}{c_j} - 1 \right) y_{kj} - \frac{x!}{(x-y_k)!} c^{-y_k} + 1. \tag{21}$$

Moreover, if $\|y_k\|_1 \leq 1$, then $g_{x,c}(y_k) = 0$.

Proof. We will first assume that $P_\mu(x,t)$ is as in (15) and that it is the solution to the Kolmogorov forward equation(7). Our goal is to show that (20) holds.

By Proposition 3.1, $c(t)$ satisfies (8). In particular, it is differentiable. Because $P_\mu(x,t)$ is as

in (15), the left-hand side of (7) satisfies

$$\begin{aligned}
\frac{d}{dt}P_\mu(x,t) &= \frac{d}{dt}\left(\prod_{i=1}^{d} e^{-c_i(t)}\frac{c_i(t)^{x_i}}{x_i!}\right) \\
&= \sum_{j=1}^{d}\prod_{i\neq j} e^{-c_i(t)}\frac{c_i(t)^{x_i}}{x_i!}\left(-c_j'(t)e^{-c_j(t)}\frac{c_j(t)^{x_j}}{x_j!} + x_j e^{-c_j(t)}\frac{c_j(t)^{x_j-1}}{x_j!}c_j'(t)\right) \\
&= \prod_{i=1}^{d} e^{-c_i(t)}\frac{c_i(t)^{x_i}}{x_i!}\sum_{j=1}^{d}\left(-c_j'(t) + x_j\frac{c_j'(t)}{c_j(t)}\right) \\
&= e^{-c(t)}\frac{c(t)^x}{x!}\sum_{j=1}^{d} c_j'(t)\left(\frac{x_j}{c_j(t)} - 1\right) \\
&= e^{-c(t)}\frac{c(t)^x}{x!}\sum_{j=1}^{d}\sum_{k=1}^{K}\kappa_k c(t)^{y_k}(y_{kj}' - y_{kj})\left(\frac{x_j}{c_j(t)} - 1\right) \\
&= \left(e^{-c(t)}\frac{c(t)^x}{x!}\right)\sum_{k=1}^{K}\kappa_k c(t)^{y_k}\sum_{j=1}^{d}\left(\frac{x_j}{c_j(t)} - 1\right)(y_{kj}' - y_{kj}).
\end{aligned} \tag{33}$$

The right hand side of (7) is

$$\begin{aligned}
&\sum_{k=1}^{K}\lambda_k(x-\zeta_k)P_\mu(x-\zeta_k,t) - \sum_{k=1}^{K}\lambda_k(x)P_\mu(x,t) \\
&= \sum_{k=1}^{K}\kappa_k\left(\frac{(x-\zeta_k)!}{(x-\zeta_k-y_k)!}e^{-c(t)}\frac{c(t)^{x-\zeta_k}}{(x-\zeta_k)!}\right) - \sum_{k=1}^{K}\kappa_k\left(\frac{x!}{(x-y_k)!}e^{-c(t)}\frac{c(t)^x}{x!}\right) \\
&= \left(e^{-c(t)}\frac{c(t)^x}{x!}\right)\sum_{k=1}^{K}\kappa_k\left(\frac{x!}{(x-\zeta_k-y_k)!}c(t)^{-\zeta_k} - \frac{x!}{(x-y_k)!}\right) \\
&= \left(e^{-c(t)}\frac{c(t)^x}{x!}\right)\sum_{k=1}^{K}\kappa_k c(t)^{y_k}\left(\frac{x!}{(x-y_k')!}c(t)^{-y_k'} - \frac{x!}{(x-y_k)!}c(t)^{-y_k}\right).
\end{aligned} \tag{34}$$

Since $P_\mu(x,t)$ is the solution to (7), we must have that (33) and (34) are equal. That is,

$$\sum_{k=1}^{K}\kappa_k c(t)^{y_k}\left(\sum_{j=1}^{d}\left[\left(\frac{x_j}{c_j(t)} - 1\right)(y_{kj}' - y_{kj}) - \left(\frac{x!}{(x-y_k')!}c(t)^{-y_k'} - \frac{x!}{(x-y_k)!}c(t)^{-y_k}\right)\right]\right) = 0. \tag{35}$$

Define the following function

$$f_{x,c}(y_k) = \sum_{j=1}^{d}\left(\frac{x_j}{c_j} - 1\right)y_{kj} - \frac{x!}{(x-y_k)!}c^{-y_k}$$

and let $g_{x,c}(y_k) = f_{x,c}(y_k) + 1$. Then we can rewrite equation (35) above as

$$\sum_{k=1}^{K}\kappa_k c(t)^{y_k}\left[g_{x,c(t)}(y_k') - g_{x,c(t)}(y_k)\right] = 0,$$

which shows (20) holds.

To show the other direction, suppose $c(t)$ is the solution to the deterministic equation (8) and that (20) is satisfied. We must show that $P_\mu(x,t)$ as in (16) is the solution to the Kolmogorov forward equation (7). However, this follows by reversing the steps above.

All that remains is to demonstrate that if $\|y_k\|_1 \leq 1$, then $g_{x,c}(y_k) = 0$. There are only two cases that need consideration.

Case 1. If $y_k = \vec{0}$, then

$$g_{x,c}(y_k) = \sum_{j=1}^{d} \left(\frac{x_j}{c_j} - 1 \right) y_{kj} - \frac{x!}{(x - y_k)!} c^{-y_k} + 1 = 0 - 1 + 1 = 0.$$

Case 2. If $y_k = e_\ell$, the vector whose ℓ^{th} entry is 1 and all other entries are zero, then

$$g_{x,c}(y_k) = \sum_{j=1}^{d} \left(\frac{x_j}{c_j} - 1 \right) y_{kj} - \frac{x!}{(x - y_k)!} c^{-y_k} + 1 = \frac{x_\ell}{c_\ell} - 1 - \frac{x_\ell}{c_\ell} + 1 = 0.$$

Hence, the proof is complete. □

We restate Lemma 3.3 for the sake of reference.

Lemma 3.3 *Let $\{z_1, z_2, ..., z_m\} \subset \mathcal{C}$ be the collection of complexes that are at least binary (i.e. $\|z_i\|_1 \geq 2$). Fix a value $c \in \mathbb{R}^d_{>0}$. For each $i \in \{1, \ldots, m\}$ let $f_i : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}$ be defined as*

$$f_i(x) = g_{x,c}(z_i),$$

where the functions $g_{x,c}$ are defined in the proof of Lemma 3.2. Then $\{f_i\}_{i=1}^m$ are linear independent.

The main idea of the proof rests on noticing that this collection of functions consists of polynomials of different leading orders. An example will be helpful to illustrate. Let us turn to the binary case with two species, and denote $\mathcal{C} = \{2e_1, 2e_2, e_1 + e_2\}$. Then the relevant functions are

$$\begin{aligned}
f_1(x) &= 2\left(\frac{x_1}{c_1} - 1 \right) - \frac{x_1(x_1 - 1)}{c_1^2} + 1 = -\frac{x_1^2}{c_1^2} + \left(2 + \frac{1}{c_1} \right) \frac{x_1}{c_1} - 1 \\
f_2(x) &= 2\left(\frac{x_2}{c_2} - 1 \right) - \frac{x_2(x_2 - 1)}{c_2^2} + 1 = -\frac{x_2^2}{c_2^2} + \left(2 + \frac{1}{c_2} \right) \frac{x_2}{c_2} - 1 \\
f_3(x) &= \left(\frac{x_1}{c_1} - 1 \right) + \left(\frac{x_2}{c_2} - 1 \right) - \frac{x_1 x_2}{c_1 c_2} + 1 = -\frac{x_1 x_2}{c_1 c_2} + \frac{x_1}{c_1} + \frac{x_2}{c_2} - 1.
\end{aligned}$$

To see why they are linearly independent, let α_i be such that $\alpha_1 f_1(x) + \alpha_2 f_2(x) + \alpha_3 f_3(x) = 0$ for all x. Since the leading powers of the monomials are different, we therefore conclude that we must have $\alpha_1 = \alpha_2 = \alpha_3 = 0$.

Proof of Lemma 3.3. Suppose there exists α_i for $i = 1, 2, ..., m$ such that

$$\alpha_1 f_1(x) + \cdots + \alpha_m f_m(x) = 0,$$

for all $x \in \mathbb{Z}^d_{\geq 0}$.

Let $s = \max_{i=1,2,\ldots,m} \|z_i\|_1$ and denote $\tilde{\mathcal{C}} = \{z_i : \|z_i\|_1 = s\}$. Notice that for any function f_i where $z_i \in \tilde{\mathcal{C}}$, $f_i(x)$ is a polynomial in x and the leading term of the polynomial is $\frac{1}{c^{z_i}} x^{z_i}$. Notice that for $i \neq j$, we have $z_i \neq z_j$ and hence $x^{z_i} \neq x^{z_j}$. We may therefore conclude that $\alpha_i = 0$ for any $z_i \in \tilde{\mathcal{C}}$.

The proof is then concluded by noting that the above procedure can be performed iteratively as you decrease the 1-norm of the complexes. □

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