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Lyapunov functions, stationary distributions, and non-equilibrium potential for reaction networks

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Abstract

We consider the relationship between stationary distributions for stochastic models of reaction systems and Lyapunov functions for their deterministic counterparts. Specifically, we derive the well known Lyapunov function of reaction network theory as a scaling limit of the non-equilibrium potential of the stationary distribution of stochastically modeled complex balanced systems. We extend this result to general birth-death models and demonstrate via example that similar scaling limits can yield Lyapunov functions even for models that are not complex or detailed balanced, and may even have multiple equilibria.

1 Introduction

Reaction network models are ubiquitous in the study of various types of population dynamics in biology. For example, they are used in modeling subcellular processes in molecular biology [7, 13, 24, 40], signaling systems [42, 43], metabolism [12], as well as the spread of infectious diseases [1] and interactions between species in an ecosystem [35, 41]. Depending upon the relevant scales of the system, either a deterministic or stochastic model of the dynamics is utilized.

This paper studies the connection between deterministic and stochastic models of reaction systems. In particular, for the class of so-called “complex balanced” models, we make a connection between the stationary distribution of the stochastic model and the classical Lyapunov function used in the study of the corresponding deterministic models. Specifically, we show that in the large volume limit of Kurtz [31, 32], the non-equilibrium potential of the stationary distribution of the scaled stochastic model converges to the standard Lyapunov function of deterministic reaction network theory. Further, we extend this result to birth-death processes.

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In 1972, Horn and Jackson [28] introduced a Lyapunov function for the study of complex balanced systems, and remarked on a formal similarity to Helmholtz free energy functions. Since then the probabilistic interpretation of this Lyapunov function for complex balanced systems has remained obscure. For detailed balanced systems, which form a subclass of complex balanced systems, a probabilistic interpretation for the Lyapunov function is known — see, for example, the work of Peter Whittle [44, Section 5.8] — though these arguments appear to be little known in the mathematical biology community. The key ingredient that enables us to extend the analysis pertaining to detailed balanced systems to complex balanced systems comes from [4], where Anderson, Craciun, and Kurtz showed that the stationary distribution for the class of complex balanced reaction networks can be represented as a product of Poisson random variables; see equation (1) below.

While there are myriad results pertaining to either stochastic or deterministic models, there are relatively few making a connection between the two. Perhaps the best known such connections come from the seminal work of Thomas Kurtz [31, 32, 33], which details the limiting behavior of classically scaled stochastic models on *finite* time intervals, and demonstrates the validity of the usual deterministic ODE models on those intervals. There is even less work on the connection between the deterministic and stochastic models on infinite time horizons, that is, on the long term behavior of the different models, though two exceptions stand out. As alluded to above, Anderson, Craciun, and Kurtz showed that a stochastically modeled complex balanced system — for which the deterministically modeled system has complex balanced equilibrium[1] c — has a stationary distribution of product form,

$$\pi(x) = \frac{1}{Z_\Gamma} \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!}, \; x \in \Gamma \subset \mathbb{Z}^d_{\geq 0}, \tag{1}$$

where Γ is the state space of the stochastic model and $Z_\Gamma > 0$ is a normalizing constant [4]. On the other hand, in [5], Anderson, Enciso, and Johnston provided a large class of networks for which the limiting behaviors of the stochastic and deterministic models are fundamentally different, in that the deterministic model has special "absolutely robust" equilibria whereas the stochastic model necessarily undergoes an extinction event.

In the present paper, we return to the context of complex balanced models studied in [4], and show that the usual Lyapunov function of Chemical Reaction Network Theory (CRNT),

$$\mathscr{V}(x) = \sum_i x_i\big(\ln(x_i) - \ln(c_i) - 1\big) + c_i, \tag{2}$$

can be understood as the limit of the non-equilibrium potential of the distribution (1) in the classical scaling of Kurtz. We extend this result to the class of birth-death models. We then demonstrate through examples that Lyapunov functions for an even wider class of models can be constructed through a similar scaling of stationary distributions. It is not yet clear just

[1]By *equilibrium* we mean a fixed point of a dynamical system. In particular, what is referred to in the biochemistry literature as a "non-equilibrium steady state" is also included in our use of the term equilibrium.

how wide the class of models for which this specific scaling limit provides a Lyapunov function is, and we leave this question open. Similar (non-mathematically rigorous) results have been pointed out in the physics literature though the generality of these results remain unclear [39]. See also [25] for recent mathematical work pertaining to the ergodicity of stochastically modeled reaction systems and [37] for earlier related work pertaining to the irreducibility and recurrence properties of stochastic models.

Before proceeding, we provide a key definition.

Definition 1.

Let $\boldsymbol{\pi}$ be a probability distribution on a countable set Γ such that $\boldsymbol{\pi}(x) > 0$ for all $x \in \Gamma$. The *non-equilibrium potential* of the distribution $\boldsymbol{\pi}$ is the function $\phi_{\pi}: \Gamma \to \mathbb{R}$ defined by

$$\phi_{\pi}(x) = -\ln(\pi(x)).$$

We close the introduction with an illustrative example.

Example 2. Consider the catalytic activation-inactivation network

$$2A \rightleftharpoons A + B, \tag{3}$$

where A and B represent the active and inactive forms of a protein, respectively. The usual *deterministic* mass-action kinetics model for the concentrations (x_A, x_B) of the species A and B is

$$\begin{aligned} \dot{x}_A &= -\kappa_1 x_A^2 + \kappa_2 x_A x_B \\ \dot{x}_B &= \kappa_1 x_A^2 - \kappa_2 x_A x_B, \end{aligned}$$

where $\boldsymbol{\kappa}_1$ and $\boldsymbol{\kappa}_2$ are the corresponding reaction rate constants for the forward and reverse reactions in (3). For a given total concentration $M \overset{\text{def}}{=} x_A(0) + x_B(0) > 0$, these equations have a unique stable equilibrium

$$c_A = \frac{M\kappa_2}{\kappa_1 + \kappa_2},\ c_B = \frac{M\kappa_1}{\kappa_1 + \kappa_2}, \tag{4}$$

which can be shown to be complex balanced.

We now turn to a *stochastic* model for the network depicted in (3), that tracks the molecular counts for species A and B. Letting V be a scaling parameter, which can be thought of as Avogadro's number multiplied by volume, see section 2.3.1, the standard stochastic mass-action kinetics model can be described in several different ways. For example, the Kolmogorov forward equations governing the probability distribution of the process are

$$\begin{aligned}\frac{d}{dt}p_\mu(x_A,x_B,t) &= \frac{\kappa_1}{V}(x_A+1)x_A p_\mu(x_A+1,x_B-1,t)\\ &+\frac{\kappa_2}{V}(x_A-1)(x_B+1)p_\mu(x_A-1,x_B+1,t)\\ &-\left[\frac{\kappa_1}{V}x_A(x_A-1)+\frac{\kappa_2}{V}x_Ax_B\right]p_\mu(x_A,x_B,t),\end{aligned} \tag{5}$$

where $x_A, x_B \in \mathbb{Z}_{\geq 0}$ are the molecular counts of A and B, respectively, and $p_\mu(x_A, x_B, t)$ denotes the probability that the system is in state (x_A, x_B) at time t given an initial distribution of μ. Note that there is one such differential equation for each state, (x_A, x_B), in the state space. In the biological context the forward equation is typically referred to as the *chemical master equation*.

Assume that the initial distribution for the stochastic model has support on the set $\Gamma^V \overset{\text{def}}{=} \left\{(x_A,x_B)\in\mathbb{Z}^2_{\geq 0} \mid x_A \geq 1, x_A+x_B=VM\right\}$, where $M>0$ is fixed and V is selected so that VM is an integer. Hence, the total number of molecules is taken to scale in V. The stationary distribution can then be found by setting the left hand side of the forward equation (5) to zero and solving the resulting system of equations (one equation for each $(x_A, x_B) \in \Gamma^V$). Finding such a solution is typically a challenging, or even impossible task. However, results in [4] imply that for this particular system the stationary distribution is (almost) a binomial distribution and is of the form (1),

$$\pi^V(x_A,x_B) = \frac{1}{Z^V}\binom{VM}{x_A}\left(\frac{\kappa_2}{\kappa_1+\kappa_2}\right)^{x_A}\left(\frac{\kappa_1}{\kappa_1+\kappa_2}\right)^{x_B},\ (x_A,x_B)\in\Gamma^V, \tag{6}$$

where Z^V is the normalizing constant

$$Z^V \overset{\text{def}}{=} 1-\left(\frac{\kappa_1}{\kappa_1+\kappa_2}\right)^{VM}$$

The distribution is not binomial since the state $(x_A, x_B) = (0, VM)$ cannot be realized in the system.

In order to make a connection between the stochastic and deterministic models, we convert the stochastic model to concentrations by dividing by V. That is, for $x \in \mathbb{Z}$ we let $\tilde{x}^V \overset{\text{def}}{=} V^{-1}x$. Letting $\tilde{\pi}^V(\tilde{x}^V)$ denote the stationary distribution of the scaled process, we find that

$$\tilde{\pi}^V(\tilde{x}^V) = \frac{1}{Z^V}\binom{VM}{V\tilde{x}_A^V}\left(\frac{\kappa_2}{\kappa_1+\kappa_2}\right)^{V\tilde{x}_A^V}\left(\frac{\kappa_1}{\kappa_1+\kappa_2}\right)^{V\tilde{x}_B^V},$$

where $\tilde{x}^V \in \frac{1}{V}\Gamma^V$. We now consider the non-equilibrium potential of $\tilde{\pi}^V$ scaled by V

$$-\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) = \frac{1}{V}\ln\left(Z^V\right) - \frac{1}{V}\ln((VM)!) + \frac{1}{V}\ln\left(\left(V\tilde{x}_A^V\right)!\right) + \frac{1}{V}\ln\left(\left(V\tilde{x}_B^V\right)!\right) - \tilde{x}_A^V\ln\left(\frac{\kappa_2}{\kappa_1+\kappa_2}\right) - \tilde{x}_B^V\ln\left(\frac{\kappa_1}{\kappa_1+\kappa_2}\right).$$

Stirling's formula says that

$$\ln(n!) = n\ln(n) - n + O(\ln(n)) \text{ for } n > 0. \tag{7}$$

Assuming that $\lim_{V\to\infty}\tilde{x}^V = \tilde{x} \in \mathbb{R}^2_{>0}$, and after some calculations, equation (7) yields

$$\lim_{V\to\infty} -\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) = \tilde{x}_A\left(\ln\tilde{x}_A - \ln\left(\frac{\kappa_2}{\kappa_1+\kappa_2}\right)\right) + \tilde{x}_B\left(\ln\left(\tilde{x}_B\right) - \ln\left(\frac{\kappa_1}{\kappa_1+\kappa_2}\right)\right) - M\ln(M) \stackrel{\text{def}}{=} \mathscr{V}(\tilde{x}).$$

Recalling that $\tilde{x}_B = M - \tilde{x}_A$, we may rewrite $\mathscr{V}$ in the following useful way

$$\mathscr{V}(\tilde{x}) = \tilde{x}_A\left(\ln\tilde{x}_A - \ln\left(\frac{M\kappa_2}{\kappa_1+\kappa_2}\right) - 1\right) - \frac{M\kappa_2}{\kappa_1+\kappa_2} + \tilde{x}_B\left(\ln\tilde{x}_B - \ln\left(\frac{M\kappa_1}{\kappa_1+\kappa_2}\right) - 1\right) - \frac{M\kappa_1}{\kappa_1+\kappa_2}.$$

Remarkably, this $\mathscr{V}(\tilde{x})$ is exactly the function we would obtain if we were to write the standard Lyapunov function of CRNT, given in (2), for this model. □

The first goal of this paper is to show that the equality between the *scaling limit* calculated for the stochastic model above, and the Lyapunov function for the corresponding deterministic model is not an accident, but in fact holds for all complex balanced systems. We will also demonstrate that the correspondence holds for a wider class of models.

The remainder of this article is organized as follows. In Section 2, we briefly review some relevant terminology and results. In Section 3, we derive the general Lyapunov function of Chemical Reaction Network Theory for complex balanced systems as a scaling limit of the non-equilibrium potential of the corresponding scaled stochastic model. In Section 4, we discuss other, non-complex balanced, models for which the same scaling limit gives a Lyapunov function for the deterministic model. In particular, we characterize this function when the corresponding stochastic system is equivalent to a stochastic birth-death process.

2 Reaction systems and previous results

2.1 Reaction networks

We consider a system consisting of d species, $\{S_1, \ldots, S_d\}$, undergoing transitions due to a finite number, m, of reactions. For the kth reaction, we denote by $\nu_k, \nu'_k \in \mathbb{Z}^d_{\geq 0}$ the vectors representing the number of molecules of each species consumed and created in one instance of the reaction, respectively. For example, for the reaction $S_1 + S_2 \rightarrow S_3$, we have $\nu_k = (1, 1, 0)^T$ and $\nu'_k = (0, 0, 1)^T$, if there are $d = 3$ species in the system. Each ν_k and ν'_k is termed a *complex* of the system. The reaction is denoted by $\nu_k \rightarrow \nu'_k$, where ν_k is termed the *source complex* and ν'_k is the *product complex*. A complex may appear as both a source complex and a product complex in the system.

Definition 3.—Let $\mathcal{S} = \{S_1, \ldots, S_d\}$, $\mathcal{C} = \cup_{k=1}^{m} \{\nu_k, \nu'_k\}$, and $\mathcal{R} = \{\nu_1 \rightarrow \nu'_1, \ldots, \nu_m \rightarrow \nu'_m\}$ denote the sets of species, complexes, and reactions, respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is a *reaction network*.

Definition 4.—The linear subspace $S = \text{span}\{\nu'_1 - \nu_1, \ldots, \nu'_m - \nu_m\}$ is called the *stoichiometric subspace* of the network. For $c \in \mathbb{R}^d_{\geq 0}$ we say $c + S = \{x \in \mathbb{R}^d \mid x = c + s \text{ for some } s \in S\}$ is a *stoichiometric compatibility class*, $(c + S) \cap \mathbb{R}^d_{\geq 0}$ is a *non-negative stoichiometric compatibility class*, and $(c + S) \cap \mathbb{R}^d_{> 0}$ is a *positive stoichiometric compatibility class*.

2.2 Dynamical system models

2.2.1 Stochastic models—

The most common stochastic model for a reaction network $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ treats the system as a continuous time Markov chain whose state X is a vector giving the number of molecules of each species present with each reaction modeled as a possible transition for the chain. The model for the kth reaction is determined by the source and product complexes of the reaction, and a function λ_k of the state that gives the *transition intensity*, or rate, at which the reaction occurs. In the biological and chemical literature, transition intensities are referred to as *propensities*.

Specifically, if the kth reaction occurs at time t the state is updated by addition of the *reaction vector* $\zeta_k \stackrel{\text{def}}{=} \nu'_k - \nu_k$ and

$$X(t) = X(t-) + \zeta_k .$$

The most common choice for intensity functions is to assume the system satisfies the stochastic version of *mass-action kinetics*, which states that the rate functions take the form

$$\lambda_k(x) = \kappa_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - \nu_{ki})!} 1_{\{x_i \geq \nu_{ki}\}}, \tag{8}$$

for some constant $\kappa_k > 0$, termed the rate constant, and where $\nu_k = (\nu_{k1}, \ldots, \nu_{kd})^T$. Under the assumption of mass-action kinetics and a non-negative initial condition, it follows that the dynamics of the system is confined to a particular non-negative stoichiometric compatibility class given by the initial value $X(0)$, namely $X(t) \in (X(0) + S) \cap \mathbb{R}^d_{\geq 0}$.

The number of times that the kth reaction occurs by time t can be represented by the counting process

$$R_k(t) = Y_k\left(\int_0^t \lambda_k(X(s))ds\right),$$

where the $\{Y_k, k \in \{1, \ldots, m\}\}$ are independent unit-rate Poisson processes (see [6, 7, 34], or [15, Chapter 6]). The state of the system then satisfies the equation $X(t) = X(0) + \sum_k R_k(t)\zeta_k$, or

$$X(t) = X(0) + \sum_k Y_k\left(\int_0^t \lambda_k(X(s))ds\right)\zeta_k, \tag{9}$$

where the sum is over the reaction channels. Kolmogorov's forward equation for this model is

$$\frac{d}{dt}P_\mu(x,t) = \sum_k \lambda_k(x - \zeta_k)P_\mu(x - \zeta_k, t) - \sum_k \lambda_k(x)P_\mu(x,t), \tag{10}$$

where $P_\mu(x, t)$ represents the probability that $X(t) = x \in \mathbb{Z}^d_{\geq 0}$ given an initial distribution of μ and $\lambda_k(x-\zeta_k) = 0$ if $x - \zeta_k \notin \mathbb{Z}^d_{\geq 0}$. So long as the process is non-explosive, the two representations for the processes, the stochastic equation (9) and the Markov process with forward equation (10), are equivalent [6, 15].

It is of interest to characterize the long-term behavior of the process. Let $\Gamma \subset \mathbb{Z}^d_{\geq 0}$ be a closed component of the state space; that is, Γ is closed under the transitions of the Markov chain. A probability distribution $\pi(x)$, $x \in \Gamma$, is a stationary distribution for the chain on Γ if

$$\sum_k \pi(x - \zeta_k)\lambda_k(x - \zeta_k) = \pi(x)\sum_k \lambda_k(x) \tag{11}$$

for all $x \in \Gamma$. (If $x - \zeta_k \notin \Gamma$ then $\pi(x - \zeta_k)$ is put to zero.) If in addition Γ is irreducible, that is, any state in Γ can be reached from any other state in Γ (for example, Γ^V in Example 2 is an irreducible component) and π exists, then π is unique [30].

Solving equation (11) is in general a difficult task, even when we assume each λ_k is determined by mass-action kinetics. However, if in addition there exists a complex balanced equilibrium for the associated deterministic model, then equation (11) can be solved explicitly, see Theorem 6 below.

2.2.2 Deterministic models and complex balanced equilibria—For two vectors $u, v \in \mathbb{R}^d_{\geq 0}$ we define $u^v \overset{\text{def}}{=} \prod_i u_i^{v_i}$ and adopt the convention that $0^0 = 1$.

Under an appropriate scaling limit (see Section 2.3.1) the continuous time Markov chain model described in the previous section becomes

$$x(t) = x(0) + \sum_k \left(\int_0^t f_k(x(s))ds \right) (\nu'_k - \nu_k), \tag{12}$$

where

$$f_k(x) = \kappa_k x_1^{\nu_{k1}} x_2^{\nu_{k2}} \cdots x_d^{\nu_{kd}} = \kappa_k x^{\nu_k}, \tag{13}$$

and $\kappa_k > 0$ is a constant. We say that the deterministic system (12) has *deterministic mass-action kinetics* if the rate functions f_k have the form (13). The system (12) is equivalent to the system of *ordinary differential equations* (ODEs) with a given initial condition $x_0 = x(0)$,

$$\dot{x} = \sum_k \kappa_k x^{\nu_k} (\nu'_k - \nu_k). \tag{14}$$

The trajectory with initial condition x_0 is confined to the non-negative stoichiometric compatibility class $(x_0 + S) \cap \mathbb{R}^d_{\geq 0}$.

Some mass-action systems have complex balanced equilibria [27, 28],[2] which have been shown to play an important role in many biological mechanisms [9, 20, 29, 42]. An equilibrium point $c \in \mathbb{R}^d_{\geq 0}$ is said to be complex balanced if and only if for each complex $z \in \mathscr{C}$ we have

$$\sum_{\{k:\nu'_k = z\}} \kappa_k c^{\nu_k} = \sum_{\{k:\nu_k = z\}} \kappa_k c^{\nu_k}, \tag{15}$$

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. For such an equilibrium the total inflows and the total outflows balance out at each complex [16, 23].

[2]For example, it is known that all weakly reversible networks with a deficiency of zero give rise to systems that have complex balanced equilibria [16, 17].

In [28] it is shown that if there exists a complex balanced equilibrium $c \in \mathbb{R}^d_{>0}$ for a given model then

1. There is one, and only one, positive equilibrium point in each positive stoichiometric compatibility class.
2. Each such equilibrium point is complex balanced.
3. Each such complex balanced equilibrium point is locally asymptotically stable relative to its stoichiometric compatibility class.

Whether or not each complex balanced equilibrium is globally asymptotically stable relative to its positive stoichiometric compatibility class is the content of the Global Attractor Conjecture, which has received considerable attention [2, 3, 8, 11, 21, 36]. The local asymptotic stability is concluded by an application of the Lyapunov function (2).

2.2.3 Lyapunov functions

Definition 5.: Let $E \subset \mathbb{R}^d_{\geq 0}$ be an open subset of $\mathbb{R}^d_{\geq 0}$ and let $f : \mathbb{R}^d_{\geq 0} \to \mathbb{R}$. A function $\mathscr{V} : E \to \mathbb{R}$ is called a (strict) *Lyapunov function* for the system $\dot{x} = f(x)$ at $x_0 \in E$ if x_0 is an equilibrium point for f, that is, $f(x_0) = 0$, and

1. $\mathscr{V}(x) > 0$ for all $x \neq x_0$, $x \in E$ and $V(x_0) = 0$
2. $\nabla \mathscr{V}(x) \cdot f(x) \leq 0$, for all $x \in E$, with equality if and only if $x = x_0$, where $\nabla \mathscr{V}$ denotes the gradient of $\mathscr{V}$.

If these two conditions are fulfilled then the equilibrium point x_0 is *asymptotically stable* [38]. If the inequality in (2) is not strict for $x_0 \neq x$ then x_0 is *stable* and not necessarily asymptotically stable. If the inequality is reversed, $\dot{\mathscr{V}}(x) > 0, x \neq x_0$, then the equilibrium point is *unstable* [38].

We will see that in many cases the large volume limit of the non-equilibrium potential of a stochastically modeled system is a Lyapunov function defined on the interior of the nonnegative stoichiometric subspace.

2.3 Product form stationary distributions

The following result from [4], utilized in (6), provides a characterization of the stationary distributions of complex balanced systems. See also [18, 26] for related work.

Theorem 6.—*Let* $\{\mathscr{S}, \mathscr{C}, \mathscr{R}\}$ *be a reaction network and let* $\{\kappa_k\}$ *be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with a complex balanced equilibrium* $c \in \mathbb{R}^d_{>0}$. *Then the stochastically modeled system with intensities* (8) *has a stationary distribution on* $\mathbb{Z}^d_{\geq 0}$ *consisting of the product of Poisson distributions,*

$$\pi(x) = \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \ for\ x \in \mathbb{Z}^d_{\geq 0}. \tag{16}$$

If $\mathbb{Z}^d_{\geq 0}$ *is irreducible, then* (16) *is the unique stationary distribution. If* $\mathbb{Z}^d_{\geq 0}$ *is not irreducible, then the stationary distribution,* $\boldsymbol{\pi}_\Gamma$*, of an irreducible component of the state space* $\Gamma \subset \mathbb{Z}^d_{\geq 0}$ *is*

$$\pi_\Gamma(x) = \frac{1}{Z_\Gamma} \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \ for\ x \in \Gamma,$$

and $\boldsymbol{\pi}_\Gamma(x) = 0$ *otherwise, where* Z_Γ *is a positive normalizing constant.*

Each irreducible component of the state space is necessarily contained in a single non-negative stoichiometric compatibility class (Definition 4). The choice of the complex balanced equilibrium point c in the theorem is independent of Γ and the particular stoichiometric compatibility class containing it [4]. Since $\Gamma \subset \mathbb{Z}^d_{\geq 0}$, it follows that

$$Z_\Gamma = \sum_{x \in \Gamma} \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i} \leq \sum_{x \in \mathbb{Z}^d_{\geq 0}} \prod_{i=1}^{d} \frac{c_i^{x_i}}{x_i!} e^{-c_i} = 1. \tag{17}$$

2.3.1 The classical scaling—We may convert from molecular counts to concentrations by scaling the counts by V, where V is the volume of the system times Avogadro's number. Following [4], define $|\nu_k| = \sum_i \nu_{ki}$. Let $\{\boldsymbol{\kappa}_k\}$ be a set of rate constants and define the scaled rate constants, κ_k^V, for the stochastic model in the following way,

$$\kappa_k^V = \frac{\kappa_k}{V^{|\nu_k|-1}} \tag{18}$$

(see [45, Chapter 6]). Let $x \in \mathbb{Z}^d_{\geq 0}$ be an arbitrary state of the system and denote the intensity function for the stochastic model by

$$\lambda_k^V(x) = \frac{V\kappa_k}{V^{|\nu_k|}} \prod_{i=1}^{d} \frac{x_i!}{(x_i - \nu_{ki})!}$$

Note that $\tilde{x} \overset{\text{def}}{=} V^{-1}x$ gives the concentrations in moles per unit volume and that if $\tilde{x} = \Theta(1)$ (that is, if $x = \Theta(V)$), then by standard arguments

$$\lambda_k^V(x) \approx V\kappa_k \prod_{i=1}^{d} \tilde{x}_i^{\nu_{ki}} = V\lambda_k(\tilde{x}),$$

where the final equality determines λ_k, and justifies the definition of deterministic mass-action kinetics in (13).

Denote the stochastic process determining the abundances by $X^V(t)$ (see (9)). Then, normalizing the original process X^V by V and defining $\tilde{X}^V \overset{\text{def}}{=} V^{-1}X^V$ yields

$$\tilde{X}^V(t) \approx \tilde{X}^V(0) + \sum_k \frac{1}{V} Y_k\left(V\int_0^t \lambda_k\left(\tilde{X}^V(s)\right)ds\right)\zeta_k.$$

Since the law of large numbers for the Poisson process implies $V^{-1}Y(Vu) \approx u$, we may conclude that a good approximation to the process $\tilde{X}^V$ is the function $x = x(t)$ defined as the solution to the ODE

$$\dot{x} = \sum_k \kappa_k x^{\nu_k}\left(\nu_k' - \nu_k\right),$$

which is (14). For a precise formulation of the above scaling argument, termed the *classical scaling*, see [7].

The following is an immediate corollary to Theorem 6, and can also be found in [4]. The result rests upon the fact that if c is a complex balanced equilibrium for a given reaction network with rates $\{\kappa_k\}$, then Vc is a complex balanced equilibrium for the reaction network endowed with rates $\left\{\kappa_k^V\right\}$ of (18).

Theorem 7.: *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network and let $\{\kappa_k\}$ be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with a complex balanced equilibrium $c \in \mathbb{R}^d_{>0}$. For some $V > 0$, let $\left\{\kappa_k^V\right\}$ be related to $\{\kappa_k\}$ via* (18)*. Then the stochastically modeled system with intensities* (8) *and rate constants $\left\{\kappa_k^V\right\}$ has a stationary distribution on $\mathbb{Z}^d_{\geq 0}$ consisting of the product of Poisson distributions,*

$$\pi^V(x) = \prod_{i=1}^{d} \frac{(Vc_i)^{x_i}}{x_i!} e^{-Vc_i}, \quad for\ x \in \mathbb{Z}^d_{\geq 0}. \tag{19}$$

If $\mathbb{Z}^d_{\geq 0}$ is irreducible, then (19) *is the unique stationary distribution. If $\mathbb{Z}^d_{\geq 0}$ is not irreducible, then the stationary distribution, π^V_Γ, of an irreducible component of the state space $\Gamma \subset \mathbb{Z}^d_{\geq 0}$ is*

$$\pi_{\Gamma}^{V}(x) = \frac{1}{Z_{\Gamma}^{V}} \prod_{i=1}^{d} \frac{\left(Vc_i\right)^{x_i}}{x_i!} e^{-Vc_i}, \ for\ x \in \Gamma, \tag{20}$$

and $\pi_{\Gamma}^{V}(x) = 0$ *otherwise, where* Z_{Γ}^{V} *is a positive normalizing constant.*

Note that Theorem 7 implies that a stationary distribution for the scaled model $\tilde{X}^V$ is

$$\tilde{\pi}^{V}\left(\tilde{x}^{V}\right) = \pi^{V}\left(V\tilde{x}^{V}\right), \text{ for } \tilde{x}^{V} \in \frac{1}{V}\mathbb{Z}^{d}_{\geq 0}. \tag{21}$$

3 Complex balanced systems

We are ready to state and prove our first result. For an increasing series of volumes V_i, $i = 1$, 2, …, we consider converging sequences of points $\tilde{x}^{V_i}$ in $\frac{1}{V_i}\mathbb{Z}^{d}_{\geq 0}$. To ease the notation we omit the index i and write, for example, $\lim_{V\to\infty}\tilde{x}^{V}$ instead of $\lim_{i\to\infty}\tilde{x}^{V_i}$.

Theorem 8.

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ *be a reaction network and let* $\{\kappa_k\}$ *be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced. For* $V > 0$, *let* $\{\kappa_k^V\}$ *be related to* $\{\kappa_k\}$ *via* (18). *Fix a sequence of points* $\tilde{x}^V \in \frac{1}{V}\mathbb{Z}^{d}_{\geq 0}$ *for which* $\lim_{V\to\infty}\tilde{x}^V = \tilde{x} \in \mathbb{R}^{d}_{> 0}$. *Further let c be the unique complex balanced equilibrium within the positive stoichiometric compatibility class of* $\tilde{x}$.

Let $\boldsymbol{\pi}^V$ *be given by* (19) *and let* $\tilde{\pi}^V$ *be as in* (21) *, then*

$$\lim_{V\to\infty}\left[-\frac{1}{V}\ln\left(\tilde{\pi}^{V}\left(\tilde{x}^{V}\right)\right)\right] = \mathcal{V}(\tilde{x}),$$

where $\mathcal{V}$ *satisfies* (2) *. In particular,* $\mathcal{V}$ *is a Lyapunov function (Definition 5).*

Further, suppose $\Gamma^V \subset Z^{d}_{\geq 0}$ *is an irreducible component of the state space for the Markov model with rate constants* $\{\kappa_k^V\}$ *such that* $V \cdot \tilde{x}^V \in \Gamma^V$: Let $\pi_{\Gamma^V}^V$ *be given by* (20). *For* $\tilde{w}^V \in \frac{1}{V}\Gamma^V$, *define* $\tilde{\pi}_{\Gamma^V}^V\left(\tilde{w}^V\right) \overset{\text{def}}{=} \pi_{\Gamma^V}^V\left(V\tilde{w}^V\right)$, *then*

$$\lim_{V\to\infty} V^{-1}\ln\left(Z_{\Gamma^V}^V\right) = 0, \tag{22}$$

and

$$\lim_{V\to\infty}\left[-V^{-1}\ln(\tilde{\pi}^V_{\Gamma^V}(\tilde{x}^V))\right]=\mathscr{V}(\tilde{x}), \tag{23}$$

where $\mathscr{V}$ *satisfies*(2). *In particular,* $\mathscr{V}$ *is a Lyapunov function (Definition 5).*

Proof. We prove the second statement. The proof of the first is the same with the exception that $Z^V_{\Gamma^V}\equiv 1$.

We first consider the limit (22). Begin by supposing that there is a sequence $\tilde{y}^V\in\frac{1}{V}\Gamma^V$ for which $\tilde{y}^V\to c$. In this case,

$$1\geq Z^V_{\Gamma^V}=\sum_{y\in\Gamma^V}\prod_{i=1}^d\frac{(Vc_i)^{y_i}}{y_i!}e^{-Vc_i}\geq\prod_{i=1}^d\frac{(Vc_i)^{V\tilde{y}_i^V}}{(V\tilde{y}_i^V)!}e^{-Vc_i}\geq C\prod_{i=1}^d\frac{1}{\sqrt{V\tilde{y}_i^V}}\left(\frac{c_i}{\tilde{y}_i^V}\right)^{V\tilde{y}_i^V}e^{V(\tilde{y}_i^V-c_i)},$$

where the first inequality follows from (17) and the third from an application of Stirling's formula (C is a constant). Taking the logarithm and dividing by V, it follows that $\lim_{V\to\infty}V^{-1}\ln\left(Z^V_{\Gamma^V}\right)=0$. Thus, the limit (22) will be shown so long as we can prove the existence of the sequence $\tilde{y}^V\in\frac{1}{V}\Gamma^V$ converging to the complex balanced equilibrium c.

For $M>0$, define the set $\left(M+\mathbb{Z}^d_{\geq 0}\right)=\left\{w\in\mathbb{Z}^d: w_i\geq M \text{ for each } i\in\left\{1,\ldots,d\right\}\right\}$. for each $i\in\{1,\ldots,d\}$. From the remark below Lemma 4.1 in [37], there is an $M_0>0$ so that for all V large enough

$$\Gamma^V\cap\left(M_0+\mathbb{Z}^d_{\geq 0}\right)=\left(V\cdot\tilde{x}^V+\operatorname{span}_{\mathbb{Z}}\{\zeta_k\}\right)\cap\left(M_0+\mathbb{Z}^d_{\geq 0}\right). \tag{24}$$

Thus, for V large enough, Γ^V has constant positive density on its stoichiometric compatibility class. Let $V\cdot\tilde{c}^V$ be the unique complex balanced equilibrium in the positive stoichiometric compatibility class of $V\cdot\tilde{x}^V$. It follows that $\tilde{c}^V$ is the unique complex balanced equilibrium in the positive stoichiometric compatibility class of $\tilde{x}^V$, from which we may conclude that $\lim_{V\to\infty}\left(\tilde{c}^V-c\right)=0$ (since $\tilde{x}^V\to\tilde{x}$) [10]. Finally, define $\tilde{y}^V$ via the relation

$$V\cdot\tilde{y}^V=\left[V\tilde{c}^V\right],$$

where $\left[V\tilde{c}^V\right]$ is a minimizer of $f(z)=\left|z-V\tilde{c}^V\right|$ over the set $\Gamma^V\cap\left(M_0+\mathbb{Z}^d_{\geq 0}\right)$. Note that $\tilde{y}^V\in\frac{1}{V}\Gamma^V$. From (24), we see that $\tilde{y}^V-\tilde{c}^V=O\left(V^{-1}\right)$, which, when combined with $\lim_{V\to\infty}\left(\tilde{c}^V-c\right)\to 0$, gives the desired result.

We now turn to (23). We have

$$-V^{-1}\ln(\tilde{\pi}^V_{\Gamma^V}(\tilde{x}^V)) = -V^{-1}\ln\left(\prod_{i=1}^{d} e^{-Vc_i}\frac{(Vc_i)^{V\tilde{x}_i^V}}{(V\tilde{x}_i^V)!}\right) + V^{-1}\ln\left(Z^V_{\Gamma^V}\right)$$

$$= -V^{-1}\sum_{i=1}^{d}\left[-Vc_i + (V\tilde{x}_i^V)\ln(V) + (V\tilde{x}_i^V)\ln(c_i) - \ln((V\tilde{x}_i^V)!)\right] + V^{-1}\ln\left(Z^V_{\Gamma V}\right).$$

Applying Stirling's formula (7) to the final term and performing some algebra yields

$$\begin{aligned}-V^{-1}\ln(\tilde{\pi}^V_{\Gamma^V}(\tilde{x}^V)) = -V^{-1}\sum_{i=1}^{d}\Big\{&-Vc_i + (V\tilde{x}_i^V)\ln(V) + (V\tilde{x}_i^V)\ln(c_i)\\ &-\left[(V\tilde{x}_i^V)\ln(V\tilde{x}_i^V) - (V\tilde{x}_i^V) + O(\ln(V\tilde{x}_i^V))\right]\Big\} + V^{-1}\ln(Z^V_{\Gamma^V})\\ = \sum_{i=1}^{d}&\left[\tilde{x}_i^V\left\{\ln(\tilde{x}_i^V) - \ln(c_i) - 1\right\} + c_i\right] + O(V^{-1}\ln(V\tilde{x}_i^V)) + V^{-1}\ln(Z^V_{\Gamma^V}).\end{aligned}$$

The sum is the usual Lyapunov function $\mathscr{V}$, and the result is shown after letting $V \to \infty$, utilizing (22), and recalling that $\tilde{x}^V \to \tilde{x} \in \mathbb{R}^d_{>0}$. □

The theorem above can be applied to Example 2. The unique equilibrium point given in (4) is easily seen to fulfil the complex balanced condition in (15).

4 Non-complex balanced systems

4.1 Birth-death processes and reaction networks

In this section we will study reaction networks that also are birth-death processes. Many results are known for birth-death processes. In particular, a characterization of the stationary distribution can be accomplished [30].

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with one species only, $\mathcal{S} = \{S\}$, and assume all reaction vectors are either $\zeta_k = (-1)$ or $\zeta_k = (1)$. This implies that the number of molecules of S goes up or down by one each time a reaction occurs. For convenience, we re-index the reactions and the reaction rates in the following way. By assumption, a reaction of the form $nS \to n'S$ will either have $n' = n + 1$ or $n' = n - 1$. In the former case we index the reaction by n and denote the rate constant by κ_n and in the latter case by $-n$ and κ_{-n}, respectively. Note that this stochastically modeled reaction network can be considered as a birth-death process with birth and death rates

$$p_i = \sum_{\{n \mid \zeta_n = (1)\}} \lambda_n^V(i) = \sum_{\{n \geq 0\}} \lambda_n^V(i),$$
$$q_i = \sum_{\{n \mid \zeta_n = (-1)\}} \lambda_n^V(i) = \sum_{\{n < 0\}} \lambda_n^V(i), \tag{25}$$

for $i \geq 0$, respectively.

If the stochastically modeled system has absorbing states (i.e. states for which $p_i = q_i = 0$) we make the following modification to the intensity functions of the system. Let $i_0 \in \mathbb{Z}_{\geq 0}$ be the smallest value such that (i) all birth rates of i_0 are non-zero, that is, $\lambda_n(i_0) > 0$ for $n \geq 0$, and (ii) all death rates of $i_0 + 1$ are non-zero, that is, $\lambda_n(i_0 + 1) > 0$ for $n < 0$. We modify the system by letting $\lambda_n(i_0) = 0$ for $n < 0$. Note that the modified system has a lowest state i_0, which is not absorbing.

As an example of the above modification, consider the system with network

$$3S \xrightarrow{\kappa_{-3}} 2S,\ 4S \xrightarrow{\kappa_4} 5S\,. \tag{26}$$

This model has rates $\lambda_4(x) = \kappa_4 x(x-1)(x-2)(x-3)$ and $\lambda_{-3}(x) = \kappa_{-3} x(x-1)(x-2)$. The modified system would simply take $\lambda_{-3}(4) = 0$.

Let n_u (u for 'up') be the largest n for which κ_n is a non-zero reaction rate and similarly let n_d (d for 'down') be the largest n for which κ_{-n} is a non-zero rate constant. For the network (26), $n_u = 4$ and $n_d = 3$.

Theorem 9.—*Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a reaction network with one species only. Assume that all reaction vectors are of the form $\zeta_n = (-1)$ or $\zeta_n = (1)$, and assume that there is at least one of each form. Let $\{\kappa_n\}$ be a choice of rate constants and assume, for some $V > 0$, that $\{\kappa_n^V\}$ is related to $\{\kappa_n\}$ via* (18)*. Then a stationary distribution, $\boldsymbol{\pi}^V$, for the modified birth-death process with rates* (25) *and rate constants κ_n^V exists on the irreducible component $\Gamma = \{i \mid i \geq i_0\}$ if and only if either of the following holds,*

1. $n_d > n_u$, *or*
2. $nd = nu$ *and* $\kappa_{-n_d} > \kappa_{n_u}$,

in which case such a $\boldsymbol{\pi}^V$ exists for each choice of $V > 0$.

If either of conditions (1) or (2) holds, and if $\tilde{x}^V \to \tilde{x} \in (0, \infty)$, where each $\tilde{x}^V \in \frac{1}{V}\mathbb{Z}_{\geq 0}$, then

$$\lim_{V \to \infty} -V^{-1} \ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) = g(\tilde{x}) \overset{def}{=} -\int_{\tilde{x}_{\max}}^{\tilde{x}} \ln\left(\frac{\sum_{n \geq 0} \kappa_n u^{\nu_n}}{\sum_{n < 0} \kappa_n u^{\nu_n}}\right) du, \tag{27}$$

where $\tilde{\pi}^V$ *is the stationary distribution for the stochastic model scaled by* $V > 0$ *and state space* $\frac{1}{V}\mathbb{Z}_{\geq 0}$ *(as in* (21)*), and* $\tilde{x}_{\max}$ *is a value of* $\tilde{x} \in [0, \infty)$ *(potentially not unique) that maximizes the integral*

$$\int_0^{\tilde{x}} \ln\left(\frac{\sum_{n \geq 0} \kappa_n u^{\nu_n}}{\sum_{n < 0} \kappa_n u^{\nu_n}}\right) du.$$

Further, the function $g(\tilde{x})$ *of* (27) *fulfills condition (2) in Definition 5; that is,* $g(\tilde{x})$ *decreases along paths of the deterministically modeled system with rate constants* $\{\kappa_n\}$.

Proof. Since all reactions have $\zeta_n = (1)$ or $\zeta_n = (-1)$ it follows that the system is equivalent to a birth-death process with birth and death rates (25). As in the discussion below (25), let i_0 be the smallest value the chain may attain. Potentially after modifying the system as detailed above, we have that $p_i > 0$ for all $i \geq i_0$ and $q_i > 0$ for all $i \geq i_0 + 1$. Hence, $\Gamma = \{i \in \mathbb{Z} \mid i \geq i_0\}$ is irreducible and the stationary distribution, if it exists, is given by (see [30])

$$\pi^V(x) = \frac{1}{Z^V} \prod_{i=i_0+1}^{x} \frac{p_{i-1}}{q_i} = \frac{1}{Z^V} \frac{p_{i_0} \cdots p_{x-1}}{q_{i_0+1} \cdots q_x}, \quad x \geq i_0,$$

where the empty product $\Pi_{i=i_0+1}^{i_0}$ is taken to be equal to 1, and the partition function Z^V satisfies

$$Z^V = \sum_{x=i_0}^{\infty} \prod_{i=i_0+1}^{x} \frac{p_{i-1}}{q_i} \tag{28}$$

Let $\delta = n_d - n_u$. Note that for $\epsilon > 0$ arbitrarily small, there exists an $m > 0$ such that

$$(1+\epsilon)\frac{V^\delta}{i^\delta}\frac{\kappa_{n_u}}{\kappa_{-n_d}} \geq \frac{p_{i-1}}{q_i} \geq (1-\epsilon)\frac{V^\delta}{i^\delta}\frac{\kappa_{n_u}}{\kappa_{-n_d}} \text{ for } i > mV, \tag{29}$$

for all $V > 0$. Hence,

$$Z^V = \Theta\left(\sum_{i=i_0}^{\infty} \frac{V^{\delta i}}{(i!)^\delta}\left(\frac{\kappa_{n_u}}{\kappa_{-n_d}}\right)^i (1+\epsilon)^i\right),$$

which is finite if and only if one of the two conditions (1) and (2) in the theorem is fulfilled, in which case it is finite for all $V > 0$. If $\delta = 0$, one should choose ϵ such that

$(1+\epsilon)\kappa_{n_u}/\kappa_{-n_d} < 1$. Since a stationary distribution exists if and only if Z^V is finite (see [30]), this concludes the first part of the theorem.

We assume now that the stationary distribution exists, that is, that one of the two conditions (1) and (2) are fulfilled, and consider the non-equilibrium potential. Letting $\tilde{x}^V = V^{-1}x$ with $x \geq i_0$, the scaled non-equilibrium potential takes the form

$$\begin{aligned} -V^{-1}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) &= -V^{-1}\ln\left(\pi^V\left(V\tilde{x}^V\right)\right) \\ &= -V^{-1}\left[\sum_{i=i_0+1}^{V\tilde{x}^V}\left(\ln\left(p_{i-1}\right)-\ln\left(q_i\right)\right)\right]+V^{-1}\ln\left(Z^V\right). \end{aligned} \tag{30}$$

Using the definitions of p_i, q_i and $\lambda_n^V(i)$, the first term in (30) becomes

$$-V^{-1}\sum_{i=i_0+1}^{V\tilde{x}^V}\left[\ln\left(\sum_{n\geq 0}\kappa_n\frac{(i-1)(i-2)\cdots\left(i-|\nu_n|\right)}{V^{|\nu_n|-1}}\right)-\ln\left(\sum_{n<0}\kappa_n\frac{i(i-1)\cdots\left(i-|\nu_n|+1\right)}{V^{|\nu_n|-1}}\right)\right].$$

Noting that this is a Riemann sum approximation, we have for $\tilde{x}^V \to \tilde{x} \in (0,\infty)$,

$$-V^{-1}\sum_{i=i_0+1}^{V\tilde{x}^V}\left[\ln\left(p_{i-1}\right)-\ln\left(q_i\right)\right] \to -\int_0^{\tilde{x}}\ln\left(\frac{\sum_{n\geq 0}\kappa_n u^{\nu_n}}{\sum_{n<0}\kappa_n u^{\nu_n}}\right)du \overset{\text{def}}{=} g_1(\tilde{x}), \tag{31}$$

as $V \to \infty$.

We next turn to the second term of (30). First, we consider the infinite series in equation (28). By (29), for $\epsilon > 0$ small enough there is an $m > 0$ so that if $i > mV$, then

$$\frac{p_{i-1}}{q_i} \leq (1+\epsilon)\frac{k_{n_u}}{k_{-n_d}}\frac{1}{m} \overset{\text{def}}{=} \beta < 1. \tag{32}$$

Let $m_V = \lfloor mV \rfloor + 1$. Hence, it follows that the tail of the partition function Z^V fulfills

$$\begin{aligned} \sum_{x=m_V}^{\infty}\prod_{i=i_0+1}^{x}\frac{p_{i-1}}{q_i} &= \left(\prod_{i=i_0+1}^{m_V}\frac{p_{i-1}}{q_i}\right)\sum_{x=m_V}^{\infty}\prod_{i=m_V+1}^{x}\frac{p_{i-1}}{q_i} \\ &\leq \left(\prod_{i=i_0+1}^{m_V}\frac{p_{i-1}}{q_i}\right)\sum_{x=m_V}^{\infty}\beta^{x-m_V} \\ &= \left(\prod_{i=i_0+1}^{m_V}\frac{p_{i-1}}{q_i}\right)\frac{1}{1-\beta}. \end{aligned} \tag{33}$$

Next we bound Z^V above, using (33),

$$\begin{aligned} Z^V &= \sum_{x=i_0}^{\infty} \prod_{i=i_0+1}^{x} \frac{p_{i-1}}{q_i} \\ &\le \sum_{x=i_0}^{m_V-1} \prod_{i=i_0+1}^{x} \frac{p_{i-1}}{q_i} + \left(\prod_{i=i_0+1}^{m_V} \frac{p_{i-1}}{q_i} \right) \frac{1}{1-\beta} \\ &= \sum_{x=i_0}^{m_V} \exp\left(\sum_{i=i_0+1}^{x} \left[\ln(p_{i-1}) - \ln(q_i) \right] - \delta_{m_V}(x) \ln(1-\beta) \right) \\ &\le \frac{1}{1-\beta} \sum_{x=i_0}^{m_V} \exp\left(\sum_{i=i_0+1}^{x} \left[\ln(p_{i-1}) - \ln(q_i) \right] \right), \end{aligned} \tag{34}$$

with the convention that the empty sum is zero, and where $\delta_a(x)$ is an indicator function that takes the value 1 if $x = a$, and is zero otherwise. In the last inequality we have used that $-\delta_a(x)\ln(1-\beta) \le -\ln(1-\beta)$.

Consider the right side of (34). Let x_V be the value of $x \le m_V$ for which the sum attains it maximum. Hence, we have

$$Z^V \le \frac{m_V}{1-\beta} \exp\left(\sum_{i=i_0+1}^{x_V} \ln(p_{i-1}) - \ln(q_i) \right). \tag{35}$$

The sequence $V^{-1}x_V \in \left[0, V^{-1}m_V\right] \subseteq [0, m+1]$ has an accumulation point $\tilde{x}_{\max}$ in $[0, m+1]$ since the interval is compact. Using (31) and $m_V = \lfloor mV \rfloor + 1$, we obtain from (35)

$$\limsup_{V\to\infty} V^{-1} \ln\left(Z^V\right) \le \int_0^{\tilde{x}_{\max}} \ln\left(\frac{\sum_{n\ge 0} \kappa_n u^{\nu_n}}{\sum_{n<0} \kappa_n u^{\nu_n}} \right) du \stackrel{\text{def}}{=} g_0 . \tag{36}$$

Note that $\tilde{x}_{\max}$ is a global maximum of the integral on the entire $[0, \infty)$ (though it might not be unique): according to (32), the terms in the inner sum in (34) are negative for $x > x_V$.

To get a lower bound for Z^V, we choose a sequence of points $\tilde{x}^V \in \frac{1}{V}\mathbb{Z}_{\ge 0}$, such that $\tilde{x}^V \to \tilde{x}_{\max}$ as $V \to \infty$. Then, with $x_V = V\tilde{x}^V$,

$$Z^V \ge \frac{p_{i_0} \cdots p_{x_V - 1}}{q_{i_0+1} \cdots q_{x_V}},$$

and consequently,

$$\liminf_{V\to\infty} V^{-1}\ln\left(Z^V\right) \geq \int_0^{\tilde{x}_{\max}} \ln\left(\frac{\sum_{n\geq 0}\kappa_n u^{\nu_n}}{\sum_{n<0}\kappa_n u^{\nu_n}}\right) du = g_0, \tag{37}$$

by arguing as in (31). Combining (36) and (37) yields the desired result that $V^{-1}\ln(Z^V)\to g_0$ as $V\to\infty$.

Hence, we may conclude that the non-equilibrium potential converges to the function $g(\tilde{x}) = g_1(\tilde{x}) + g_0$, as stated in the theorem. To conclude the proof, we only need to confirm that g fulfills condition (2) in Definition 5, which we verify by differentiation,

$$\frac{d}{dt}g(x(t)) = g'(x(t))x'(t)$$

$$= -\ln\left(\frac{\sum_{n\geq 0}\kappa_n x^{\nu_n}}{\sum_{n<0}\kappa_n x^{\nu_n}}\right)\cdot\left(\sum_{n\geq 0}\kappa_n x^{\nu_n} - \sum_{n<0}\kappa_n x^{\nu_n}\right)$$

This is strictly negative unless

$$\sum_{n\geq 0}\kappa_n x^{\nu_n} - \sum_{n<0}\kappa_n x^{\nu_n} = 0,$$

in which case we are at an equilibrium. □

For this particular class of systems we have

$$\dot{x} = \sum_{n\geq 0}\kappa_n x^{\nu_n} - \sum_{n<0}\kappa_n x^{\nu_n},$$

so that the ratio in equation (27) is simply the ratio of the two terms in the equation above. The local minima and maxima of $g(\tilde{x})$ are therefore the equilibrium points of the deterministically modeled system. Further, by inspection, it can be seen that $g\left(\tilde{x}_{\max}\right) = 0$ and $g(\tilde{x})\to\infty$ as $\tilde{x}\to\infty$. If none of the extrema of $g(\tilde{x})$ are plateaus, then it follows that asymptotically stable and unstable equilibria must alternate and that the largest equilibrium point is asymptotically stable (Definition 5). Around each of the stable equilibria the function $g(\tilde{x})$ is a Lyapunov function.

Example 10. Consider the following network which has three equilibria (for appropriate choice of rate constants), two of which may be stable,

$$\varnothing \underset{\kappa_{-1}}{\overset{\kappa_0}{\rightleftharpoons}} X,\quad 2X \underset{\kappa_{-3}}{\overset{\kappa_2}{\rightleftharpoons}} 3X\,.$$

The deterministic model satisfies

$$\dot{x} = \kappa_0 - \kappa_{-1}x + \kappa_2 x^2 - \kappa_{-3}x^3.$$

We have $n_u = 2$ and $n_d = 3$ such that condition (1) of Theorem 9 is fulfilled. Hence, the non-equilibrium potential converges to the function

$$g(\tilde{x}) = -\int_{\tilde{x}_{\max}}^{\tilde{x}} \ln\left(\frac{\kappa_0 + \kappa_2 x^2}{\kappa_{-1}x + \kappa_{-3}x^3}\right) dx. \tag{38}$$

The stationary distribution of the stochastically modeled system can be obtained in closed form [19],

$$\pi^V(x) = \pi^V(0) \prod_{i=1}^{x} \frac{B[(i-1)(i-2)+P]}{i(i-1)(i-2)+Ri},$$

where

$$B = \frac{\kappa_2}{\kappa_{-3}},\ R = \frac{\kappa_{-1}}{\kappa_{-3}},\ \text{and } P = \frac{\kappa_0}{\kappa_2}.$$

If $P = R$, then the distribution is Poisson with parameter B and, in fact, the system is complex balanced. In this case, $\tilde{x}_{\max} = \kappa_2/\kappa_{-3}$ and the Lyapunov function (38) reduces to

$$g(\tilde{x}) = \tilde{x}\ln(\tilde{x}) - \tilde{x} - \tilde{x}\ln\left(\frac{\kappa_2}{\kappa_{-3}}\right) + \frac{\kappa_2}{\kappa_{-3}},$$

in agreement with Theorem 8.

For a concrete example that is not complex balanced, consider the model with rate constants $\kappa_0 = 6,\ \kappa_{-1} = 11,\ \kappa_2 = 6,\ \kappa_{-3} = 1$. In this case

$$\dot{x} = 6 - 11x + 6x^2 - x^3 = -(x-1)(x-2)(x-3),$$

and there are two asymptotically stable equilibria at $c = 1, 3$ and one unstable at $c = 2$. Hence, the function $g(\tilde{x})$ is a Lyapunov function locally around $\tilde{x} = 1, 3$, and takes the form

$$\begin{aligned} g(\tilde{x}) = \tilde{x}\left(\ln\left(\frac{\tilde{x}\left(\tilde{x}^2+11\right)}{\tilde{x}^2+1}\right) - \ln(6) - 1\right) + 2\sqrt{11}\arctan\left(\frac{\tilde{x}}{\sqrt{11}}\right) - 2\arctan(\tilde{x}) \\ - 2\sqrt{11}\arctan\left(\frac{1}{\sqrt{11}}\right) + 1 + \frac{1}{2}\pi, \end{aligned} \tag{39}$$

where, for this example, $\tilde{x}_{\max} = 1$. In Figure 1, we demonstrate the convergence of the scaled non-equilibrium potential, $-\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right)$, of the scaled process to $g(\tilde{x})$ of (39).

Example 11. Consider the reaction network

$$X \xrightarrow{k} \varnothing\,,\ X \xrightarrow{k_1} 2X,$$

which is equivalent to a linear birth-death process with absorbing state 0. This model has $n_u = n_u = 1$, and so for a stationary distribution to exist the second condition of Theorem 9 must hold. If we put the death rate $\lambda_{-1}(1)$ to 0 and assume $\kappa_{-1} > \kappa_1$, then condition (2) is fulfilled and

$$g(\tilde{x}) = -\int_0^{\tilde{x}} \ln\left(\frac{\kappa_1 x}{\kappa_{-1} x}\right) dx = -\tilde{x}\ln\left(\frac{\kappa_1}{\kappa_{-1}}\right) \tag{40}$$

is a Lyapunov function. In fact, the stationary distribution of the modified system is proportional to

$$\pi^V(x) \propto \left(\frac{\kappa_1}{\kappa_{-1}}\right)^{x-1} \frac{1}{x},$$

which is independent of V. It follows that for $\tilde{x}^V \to \tilde{x}$,

$$\begin{aligned} -\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) &\approx -\left(\tilde{x}^V - \frac{1}{V}\right)\ln\left(\frac{\kappa_1}{\kappa_{-1}}\right) + \frac{1}{V}\ln\left(\tilde{x}^V\right) + \frac{1}{V}\ln(V) \\ &\to -\tilde{x}\ln\left(\frac{\kappa_1}{\kappa_{-1}}\right), \end{aligned}$$

in agreement with (40). In this particular case the deterministic system converges to zero – the absorbing state of the stochastic system – though this correspondence will not hold in general for systems with an absorbing state. □

4.2 Other examples

Example 12. Consider the reaction network,

$$\varnothing \xrightarrow{\kappa} X,\ 2X \xrightarrow{\kappa_2} \varnothing\,,$$

The network is not complex balanced, nor is it a birth-death process, hence the theory developed in the previous sections is not applicable. The stationary distribution with scaled rate constants as in (18) can be given in explicit form [14],

$$\pi(x) = \frac{1}{\sqrt{2}I_1(2\sqrt{2}aV)}\frac{(aV)^x}{x!}I_{x-1}(2aV),\ x \in \mathbb{Z}_{\geq 0},\ \text{and } a = \sqrt{\frac{\kappa_1}{\kappa_2}},$$

where $I_n(z)$ is the modified Bessel function of the nth kind. To evaluate the non-equilibrium potential we need two asymptotic results for the modified Bessel functions [22]:

$$I_1(z) \propto \frac{1}{\sqrt{2\pi z}}e^z,\ \text{for large } z,$$

$$I_n(nz) \propto \frac{1}{\sqrt{2\pi n}}\frac{e^{\eta n}}{\left(1+z^2\right)^{1/4}}\left(1+\sum_{k=1}^{\infty}\frac{u_k(t)}{n^k}\right),\ \text{for large } n$$

where

$$\eta = \sqrt{1+z^2} + \ln\left(\frac{z}{1+\sqrt{1+z^2}}\right),\ t = \frac{1}{\sqrt{1+z^2}},$$

and $u_k(t)$, $k \geq 1$, are functions of t. Note that the sum involving $u_k(t)$ decreases proportionally to $n^{-1}u_1(t)$ as n gets large (the other terms vanish faster than $\frac{1}{n}$).

After some cumbersome calculations using the asymptotic relationships for the modified Bessel function, we obtain that the non-equilibrium potential satisfies

$$-\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) \to g(\tilde{x}),\ \text{for } \tilde{x}^V \to \tilde{x} \text{ as } V \to \infty,$$

where $g(\tilde{x})$ is defined by

$$g(\tilde{x}) = 2\sqrt{2}a - 2\tilde{x}\ln(a) + \tilde{x}\ln(\tilde{x}) - \tilde{x}(1+\ln(2)) - \sqrt{\tilde{x}^2+4a^2} + \tilde{x}\ln\left(\tilde{x}+\sqrt{\tilde{x}^2+4a^2}\right).$$

Another straightforward, but likewise cumbersome, calculation, shows that $g(\tilde{x})$ in fact fulfils condition (2) in Definition 5. By differentiation twice with respect to x, we find that $g''(\tilde{x}) > 0$, hence $g(\tilde{x})$ is a Lyapunov function. □

Example 13. As a last example consider the reaction network:

$$X \xrightarrow{\kappa} \varnothing,\ \varnothing \xrightarrow{\kappa_2} 2X.$$

It is not weakly reversible, hence not complex balanced for any choice of rate constants. It is not a birth-death process either, as two molecules are created at each “birth” event. It is similar to Example 12, but with the reactions going in the opposite direction.

Let the rate constants $\{\kappa_k\}$ be given and let the scaled rates $\left\{\kappa_k^V\right\}$ be given accordingly. The deterministically modeled system takes the form

$$\dot{x} = 2\kappa_2 - \kappa_1 x \tag{41}$$

such that there is a unique equilibrium at $C = \frac{2\kappa_2}{\kappa_1}$. Let $a \overset{\text{def}}{=} \frac{\kappa_2}{2\kappa_1}$ so that $c = 4a$. The stationary distribution exists for all reaction rates and is most easily characterized in the following way (see Supporting Information):

$$N = N_1 + 2N_2,\ N_1 \sim \text{Po}(2aV),\ \text{and}\ N_2 \sim \text{Po}(aV),$$

where N_1 and N_2 are two independent Poisson random variables with intensities $2aV$ and aV, respectively. Hence, the stationary distribution can be written as

$$\pi(x) = e^{-3Va} \sum_{k,m:\, x = k + 2m} \frac{(2Va)^k}{k!} \frac{(Va)^m}{m!}.$$

In the Supporting Information it is shown that the limit of the non-equilibrium potential exists as $V \to \infty$ with $\tilde{x}^V \to \tilde{x}$:

$$\lim_{V \to \infty} -\frac{1}{V} \ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right) = g(\tilde{x}),$$

where

$$g(\tilde{x}) = \int_0^{\tilde{x}} \ln\left(\sqrt{1 + \frac{2x}{a}} - 1\right) dx - \ln(2)\tilde{x}$$

(the integral can be solved explicitly, see Supporting Information). The first derivative of g fulfils

$$g'(x) > 0 \text{ if and only if } 4a < x,$$

and zero if and only if $4a = x$. Comparing with (41) yields

$$g'(x)\dot{x} \leq 0 \text{ for all } x > 0,$$

and equality only if $4a = x$. The second derivative of g is positive for all x. Hence, $g(x)$ is a Lyapunov function.

5 Discussion

We have demonstrated a relationship between the *stochastic* models for reaction systems and an important Lyapunov function for the corresponding *deterministic* models. In particular, we showed that this relationship holds for the class of complex balanced systems, which contains the class of detailed balanced systems that have been well studied in both the physics and probability literature [44]. Further, we showed the correspondence holds for a wider class of models including those birth and death systems that can be modeled via reaction systems. It remains open just how wide the class of models satisfying this relationship is.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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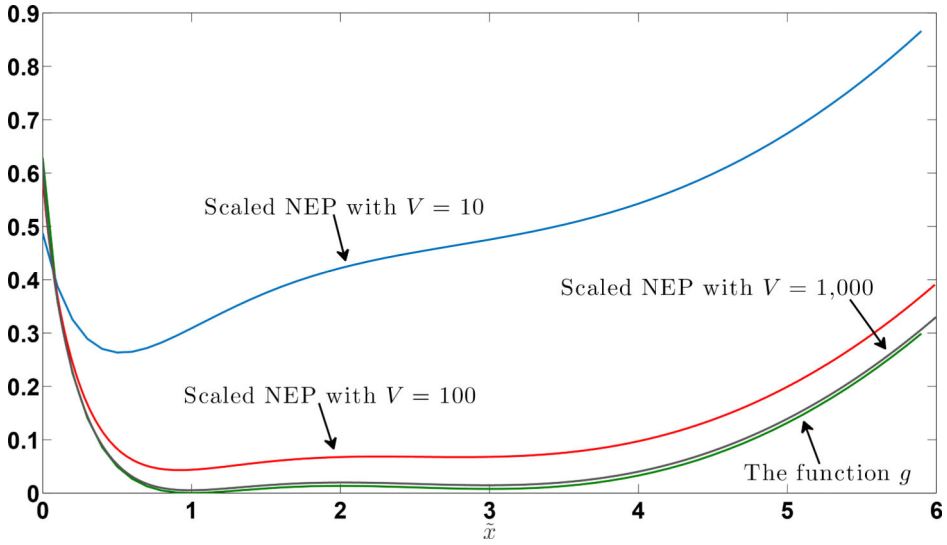

Figure 1:

Plots of the scaled non-equilibrium potential (NEP), $-\frac{1}{V}\ln\left(\tilde{\pi}^V\left(\tilde{x}^V\right)\right)$, of the scaled birth-death process of Example 10 are given for $V \in \{10, 10^2, 10^3\}$, as is the function $g(\tilde{x})$ of (39).