

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

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Abstract

We consider the relationship between stationary distributions for stochastic models of chemical reaction systems and Lyapunov functions for their deterministic counterparts. Specifically, we derive the well known Lyapunov function of chemical 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

This paper studies the connection between deterministic and stochastic models of (bio)chemical 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 [18, 19], the non-equilibrium potential of the stationary distribution of the scaled stochastic model converges to the standard Lyapunov function of deterministic chemical reaction network theory. Further, we extend this result to birth-death processes.

In 1972, Horn and Jackson [16] 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 [27, 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 [3], where Anderson, Craciun, and Kurtz showed that the stationary distribution for the class of complex balanced chemical 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 [18, 19, 20], 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,

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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 c — has a stationary distribution of product form,

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

where Γ is the state space of the stochastic model and $Z_\Gamma > 0$ is a normalizing constant [3]. On the other hand, in [4], 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 [3], and show that the usual Lyapunov function of Chemical Reaction Network Theory (CRNT),

$$\mathcal{V}(x) = \sum_i x_i (\ln(x_i) - \ln(c_i) - 1) + c_i, \quad (2)$$

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 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 [26]. See also [15] for recent mathematical work pertaining to the ergodicity of stochastically modeled chemical systems and [23] for earlier related work pertaining to the irreducibility and recurrence properties of stochastic models.

Before proceeding, we provide a key definition.

Definition 1. Let π be a probability distribution on a countable set Γ such that $\pi(x) > 0$ for all $x \in \Gamma$. The *non-equilibrium potential* of the distribution π is the function $\phi_\pi : \Gamma \rightarrow \mathbb{R}$ defined by

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

We close the introduction with an illustrative example.

Example 2. Consider the catalytic activation-inactivation network



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 κ_1 and κ_2 are the corresponding reaction rate constants for the forward and reverse reactions in (3). For a given total amount $M \stackrel{\text{def}}{=} x_A(0) + x_B(0) > 0$, these equations have a unique stable equilibrium

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

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, 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

$$\begin{aligned} \frac{d}{dt} p_\mu(x_A, x_B, t) &= \frac{\kappa_1}{V} (x_A + 1) x_A p_\mu(x_A + 1, x_B - 1, t) \\ &\quad + \frac{\kappa_2}{V} (x_A - 1) (x_B + 1) p_\mu(x_A - 1, x_B + 1, t) \\ &\quad - \left[\frac{\kappa_1}{V} x_A (x_A - 1) + \frac{\kappa_2}{V} x_A x_B \right] p_\mu(x_A, x_B, t), \end{aligned} \quad (4)$$

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 $\Gamma^V \stackrel{\text{def}}{=} \{(x_A, x_B) \in \mathbb{Z}_{\geq 0}^2 \mid x_A \geq 1, x_A + x_B = VM\}$, where $M > 0$ 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 (4) 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 [3] imply that for this particular system the stationary distribution is (almost) a binomial distribution and is of the form (1),

$$\pi^V(x_A, x_B) = \frac{1}{Z_V} \binom{VM}{x_A} \left(\frac{\kappa_2}{\kappa_1 + \kappa_2} \right)^{x_A} \left(\frac{\kappa_1}{\kappa_1 + \kappa_2} \right)^{x_B}, \quad (x_A, x_B) \in \Gamma^V, \quad (5)$$

where Z_V is the normalizing constant

$$Z_V \stackrel{\text{def}}{=} 1 - \left(\frac{\kappa_1}{\kappa_1 + \kappa_2} \right)^{VM}.$$

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 $\tilde{x}^V \stackrel{\text{def}}{=} V^{-1}x$. 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

$$\begin{aligned} -\frac{1}{V} \ln(\tilde{\pi}^V(\tilde{x}^V)) &= \frac{1}{V} \ln(Z_V) - \frac{1}{V} \ln((VM)!) + \frac{1}{V} \ln((V\tilde{x}_A^V)!) + \frac{1}{V} \ln((V\tilde{x}_B^V)!) \\ &\quad - \tilde{x}_A^V \ln \left(\frac{\kappa_2}{\kappa_1 + \kappa_2} \right) - \tilde{x}_B^V \ln \left(\frac{\kappa_1}{\kappa_1 + \kappa_2} \right). \end{aligned}$$

Stirling's formula says that

$$\ln(n!) = n \ln(n) - n + O(\ln(n)) \quad \text{for } n > 0. \quad (6)$$

Assuming that $\lim_{V \rightarrow \infty} \tilde{x}^V = \tilde{x} \in \mathbb{R}_{>0}^2$, and after some calculations, equation (6) yields

$$\begin{aligned} \lim_{V \rightarrow \infty} -\frac{1}{V} \ln(\tilde{\pi}^V(\tilde{x}^V)) &= \tilde{x}_A \left(\ln \tilde{x}_A - \ln \left(\frac{\kappa_2}{\kappa_1 + \kappa_2} \right) \right) \\ &\quad + \tilde{x}_B \left(\ln(\tilde{x}_B) - \ln \left(\frac{\kappa_1}{\kappa_1 + \kappa_2} \right) \right) - M \ln(M) \\ &\stackrel{\text{def}}{=} \mathcal{V}(\tilde{x}). \end{aligned}$$

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

$$\begin{aligned}\mathcal{V}(\tilde{x}) &= \tilde{x}_A \left(\ln \tilde{x}_A - \ln \left(\frac{M\kappa_2}{\kappa_1 + \kappa_2} \right) - 1 \right) - \frac{M\kappa_2}{\kappa_1 + \kappa_2} \\ &\quad + \tilde{x}_B \left(\ln \tilde{x}_B - \ln \left(\frac{M\kappa_1}{\kappa_1 + \kappa_2} \right) - 1 \right) - \frac{M\kappa_1}{\kappa_1 + \kappa_2}.\end{aligned}$$

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

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 Chemical reaction systems and previous results

2.1 Chemical reaction networks

We consider a system consisting of d chemical species, $\{S_1, \dots, S_d\}$, undergoing transitions due to a finite number, m , of chemical reactions. For the k th reaction, we denote by $\nu_k, \nu'_k \in \mathbb{Z}_{\geq 0}^d$ 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 $\mathcal{S} = \{S_1, \dots, S_d\}$, $\mathcal{C} = \{\nu_1, \nu'_1, \dots, \nu_m, \nu'_m\}$, and $\mathcal{R} = \{\nu_1 \rightarrow \nu'_1, \dots, \nu_m \rightarrow \nu'_m\}$ denote the sets of species, complexes, and reactions, respectively. The triple $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ is a *chemical reaction network*.

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

2.2 Dynamical system models

2.2.1 Stochastic models

The most common stochastic model for a chemical 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 k th 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 k th 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 *mass-action kinetics*, which states that the rate functions take the form

$$\lambda_k(x) = \kappa_k \prod_{i=1}^d \frac{x_i!}{(x_i - \nu_{ki})!}, \quad (7)$$

for some constant $\kappa_k > 0$, termed the rate constant, and where $\nu_k = (\nu_{k1}, \dots, \nu_{kd})^T$. 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 $X(t) \in (X(0) + S) \cap \mathbb{R}_{\geq 0}^d$.

The number of times that the k th 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 $\{Y_k, k \in \{1, \dots, m\}\}$ are independent unit-rate Poisson processes (see [5, 21], or [9, Chapter 6]). The state of the system then satisfies the equation $X(t) = X(0) + \sum_k R_k(t) \zeta_k$, or

$$X(t) = X(0) + \sum_k Y_k \left(\int_0^t \lambda_k(X(s)) ds \right) \zeta_k, \quad (8)$$

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

$$\frac{d}{dt} P_\mu(x, t) = \sum_k \lambda_k(x - \zeta_k) P_\mu(x - \zeta_k, t) - \sum_k \lambda_k(x) P_\mu(x, t), \quad (9)$$

where $P_\mu(x, t)$ represents the probability that $X(t) = x \in \mathbb{Z}_{\geq 0}^d$ given an initial distribution of μ and $\lambda_k(x - \zeta_k) = 0$ if $x - \zeta_k \notin \mathbb{Z}_{\geq 0}^d$. So long as the process is non-explosive, the two representations for the processes, the stochastic equation (8) and the Markov process with forward equation (9), are equivalent [5, 9].

It is of interest to characterize the long-term behavior of the process. Let $\Gamma \subset \mathbb{Z}_{\geq 0}^d$ 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

$$\sum_k \pi(x - \zeta_k) \lambda_k(x - \zeta_k) = \pi(x) \sum_k \lambda_k(x) \quad (10)$$

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 [17].

Solving equation (10) 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 (10) can be solved explicitly [3].

2.2.2 Deterministic models and complex balanced equilibria

For two vectors $u, v \in \mathbb{R}_{\geq 0}^d$ we define $u^v \stackrel{\text{def}}{=} \prod_i u_i^{v_i}$ 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

$$\dot{x}(t) = x(0) + \sum_k \left(\int_0^t f_k(x(s)) ds \right) (\nu'_k - \nu_k), \quad (11)$$

where

$$f_k(x) = \kappa_k x_1^{\nu_{k1}} x_2^{\nu_{k2}} \dots x_d^{\nu_{kd}} = \kappa_k x^{\nu_k}, \quad (12)$$

and $\kappa_k > 0$ is a constant. We say that the deterministic system (11) has *deterministic mass-action kinetics* if the rate functions f_k have the form (12). The system (11) is equivalent to the system of *ordinary differential equations* (ODEs) with a given initial condition $x_0 = x(0)$,

$$\dot{x} = \sum_k \kappa_k x^{\nu_k} (\nu'_k - \nu_k). \quad (13)$$

The trajectory given by x_0 is confined to the non-negative stoichiometric compatibility class $(x_0 + S) \cap \mathbb{R}_{\geq 0}^d$.

Some mass-action systems have complex balanced equilibria. An equilibrium point $c \in \mathbb{R}_{> 0}^d$ is said to be complex balanced if and only if for each complex $z \in \mathcal{C}$ we have

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

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 also [10, 14].

In [16] it is shown that if there exists a complex balanced equilibrium $c \in \mathbb{R}_{> 0}^d$ 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 [1, 2, 6, 7, 12, 22]. The local asymptotic stability is concluded by an application of the Lyapunov function (2).

2.2.3 Lyapunov functions

Definition 5. Let $E \subset \mathbb{R}_{> 0}^d$ be an open subset of $\mathbb{R}_{> 0}^d$ and let $f : \mathbb{R}_{> 0}^d \rightarrow \mathbb{R}$. A function $\mathcal{V} : E \rightarrow \mathbb{R}$ 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) $\mathcal{V}(x) > 0$ for all $x \neq x_0$, $x \in E$ and $\mathcal{V}(x_0) = 0$
- (2) $\nabla \mathcal{V}(x) \cdot f(x) \leq 0$, for all $x \in E$, with equality if and only if $x = x_0$, where $\nabla \mathcal{V}$ denotes the gradient of \mathcal{V} .

If these two conditions are fulfilled then the equilibrium point x_0 is *asymptotically stable* [24]. 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, $\dot{\mathcal{V}}(x) > 0$, $x \neq x_0$, then the equilibrium point is *unstable* [24].

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 distributions

The following result from [3], utilized in (5), provides a characterization of the stationary distributions of complex balanced systems.

Theorem 6. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network and let $\{\kappa_k\}$ be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with a complex balanced equilibrium $c \in \mathbb{R}_{> 0}^d$. Then the stochastically modeled system with intensities (7) has a stationary distribution on $\mathbb{Z}_{> 0}^d$ consisting of the product of Poisson distributions,

$$\pi(x) = \prod_{i=1}^d \frac{c_i^{x_i}}{x_i!} e^{-c_i}, \quad \text{for } x \in \mathbb{Z}_{> 0}^d. \quad (14)$$

If $\mathbb{Z}_{\geq 0}^d$ is irreducible, then (14) is the unique stationary distribution. If $\mathbb{Z}_{\geq 0}^d$ is not irreducible, then the stationary distribution, π_Γ , of an irreducible component of the state space $\Gamma \subset \mathbb{Z}_{\geq 0}^d$ is

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

and $\pi_\Gamma(x) = 0$ 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 [3]. Note that since $\Gamma \subset \mathbb{Z}_{\geq 0}^d$, we always have that $Z_\Gamma \leq 1$.

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 [3], define $|\nu_k| = \sum_i \nu_{ki}$. Let $\{\kappa_k\}$ be a set of rate constants and define the scaled rate constants, κ_k^V , for the stochastic model in the following way,

$$\kappa_k^V = \frac{\kappa_k}{V^{|\nu_k|-1}} \quad (15)$$

(see [28, Chapter 6]). Let $x \in \mathbb{Z}_{\geq 0}^d$ 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 $\tilde{x} \stackrel{\text{def}}{=} V^{-1}x$ 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

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

where the final equality defines λ_k .

Denote the stochastic process determining the abundances by $X^V(t)$ (see (8)). Then, normalizing the original process X^V by V and defining $\tilde{X}^V \stackrel{\text{def}}{=} V^{-1}X^V$ yields

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

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

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

which is (13). For a precise formulation of the above scaling argument, termed the *classical scaling*, see [18, 19, 21].

The following is an immediate corollary to Theorem 6, and can also be found in [3]. 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 $\{\kappa_k^V\}$ of (15).

Theorem 7. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network and let $\{\kappa_k\}$ be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with a complex balanced equilibrium $c \in \mathbb{R}_{>0}^d$. For some $V > 0$, let $\{\kappa_k^V\}$ be related to $\{\kappa_k\}$ via (15). Then the stochastically modeled system with intensities (7) and rate constants $\{\kappa_k^V\}$ has a stationary distribution on $\mathbb{Z}_{\geq 0}^d$ consisting of the product of Poisson distributions,*

$$\pi^V(x) = \prod_{i=1}^d \frac{(Vc_i)^{x_i}}{x_i!} e^{-Vc_i}, \quad \text{for } x \in \mathbb{Z}_{\geq 0}^d. \quad (16)$$

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

$$\pi_\Gamma^V(x) = \frac{1}{Z_\Gamma^V} \prod_{i=1}^d \frac{(Vc_i)^{x_i}}{x_i!} e^{-Vc_i}, \quad \text{for } x \in \Gamma, \quad (17)$$

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

$$\tilde{\pi}^V(\tilde{x}^V) = \pi^V(V\tilde{x}^V), \quad \text{for } \tilde{x}^V \in \frac{1}{V}\mathbb{Z}_{\geq 0}^d. \quad (18)$$

3 Complex balanced systems

We are ready to state and prove our first result.

Theorem 8. Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical reaction network and let $\{\kappa_k\}$ be a choice of rate constants. Suppose that, modeled deterministically, the system is complex balanced with a complex balanced equilibrium $c \in \mathbb{R}_{>0}^d$. For $V > 0$, let $\{\kappa_k^V\}$ be related to $\{\kappa_k\}$ via (15).

Let π^V be given by (16) and let $\tilde{\pi}^V$ be as in (18). If $\tilde{x}^V \in \frac{1}{V}\mathbb{Z}_{\geq 0}^d$ is a sequence of points such that $\lim_{V \rightarrow \infty} \tilde{x}^V = \tilde{x} \in \mathbb{R}_{>0}^d$, then

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

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

Further, suppose $\Gamma^V \subset \mathbb{Z}_{\geq 0}^d$ is an irreducible component of the state space and that $\pi_{\Gamma^V}^V$ is given by (17). For $\tilde{x}^V \in \frac{1}{V}\Gamma^V$, define $\tilde{\pi}_{\Gamma^V}^V(\tilde{x}^V) \stackrel{\text{def}}{=} \pi_{\Gamma^V}^V(V\tilde{x}^V)$. If there exists a series of points $\tilde{x}^V \in \frac{1}{V}\Gamma^V$ such that $\lim_{V \rightarrow \infty} \tilde{x}^V = \tilde{x} \in \mathbb{R}_{>0}^d$, then

$$\lim_{V \rightarrow \infty} \left[-V^{-1} \ln(\tilde{\pi}_{\Gamma^V}^V(\tilde{x}^V)) - V^{-1} \ln(Z_\Gamma^V) \right] = \mathcal{V}(\tilde{x}),$$

where \mathcal{V} satisfies (2). In particular, \mathcal{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 $Z_\Gamma^V \equiv 1$.

Let $\{\tilde{x}^V\}$ be a sequence of points with $\tilde{x}^V \in \frac{1}{V}\Gamma^V$. Suppose that $\lim_{V \rightarrow \infty} \tilde{x}^V = \tilde{x} \in \mathbb{R}_{>0}^d$. We have

$$\begin{aligned} -V^{-1} \ln \left(Z_\Gamma^V \tilde{\pi}_{\Gamma^V}^V(\tilde{x}^V) \right) &= -V^{-1} \ln \left(\prod_{i=1}^d e^{-Vc_i} \frac{(Vc_i)^{V\tilde{x}_i^V}}{(V\tilde{x}_i^V)!} \right) \\ &= -V^{-1} \sum_{i=1}^d \left[-Vc_i + (V\tilde{x}_i^V) \ln(V) + (V\tilde{x}_i^V) \ln(c_i) - \ln \left((V\tilde{x}_i^V)! \right) \right]. \end{aligned}$$

Applying Stirling's formula (6) to the final term and performing some algebra yields

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

The sum is the usual Lyapunov function \mathcal{V} , and the result is shown after letting $V \rightarrow \infty$ and recalling that $\tilde{x}^V \rightarrow \tilde{x} \in \mathbb{R}_{>0}^d$. \square

The conditions of the theorem are clearly fulfilled for Example 2. In that case, as well as in many other cases, $V^{-1} \ln(Z_\Gamma^V)$ converges to 0 as $V \rightarrow \infty$, but we have not proven that $\lim_{V \rightarrow \infty} V^{-1} \ln(Z_\Gamma^V) = 0$ in general.

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 [17].

Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical 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 $nS \rightarrow n'S$ 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 the stochastically modeled reaction network can be considered as a birth-death process with birth and death rates

$$\begin{aligned} p_i &= \sum_{\{n|\zeta_n=(1)\}} \lambda_n^V(i) = \sum_{\{n \geq 0\}} \lambda_n^V(i), \\ q_i &= \sum_{\{n|\zeta_n=(-1)\}} \lambda_n^V(i) = \sum_{\{n < 0\}} \lambda_n^V(i), \end{aligned} \quad (19)$$

for $i \geq 0$, respectively.

If the stochastically modeled system has absorbing states 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



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_{\max} be the largest n for which κ_n is a non-zero reaction rate and similarly let n_{\min} be the largest n for which κ_{-n} is a non-zero rate constant. For the network (20), $n_{\max} = 4$ and $n_{\min} = 3$.

Theorem 9. *Let $\{\mathcal{S}, \mathcal{C}, \mathcal{R}\}$ be a chemical 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 (15). Then a stationary distribution for the modified system exists on the irreducible component $\Gamma = \{i | i \geq i_0\}$ if and only if either of the following holds,*

- (1) $n_{\min} > n_{\max}$, or
- (2) $n_{\min} = n_{\max}$ and $\kappa_{-n_{\min}} > \kappa_{n_{\max}}$,

in which case it exists for all $V > 0$. If a stationary distribution exists and $\tilde{x}^V \rightarrow \tilde{x} \in (0, \infty)$, then

$$\lim_{V \rightarrow \infty} -V^{-1} \ln(\pi^V(\tilde{x}^V)) = g(\tilde{x}) = - \int_0^{\tilde{x}} \ln \left(\frac{\sum_{n \geq 0} \kappa_n x^{\nu_n}}{\sum_{n < 0} \kappa_n x^{\nu_n}} \right) dx + \delta \left(\frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \right)^{1/\delta}, \quad (21)$$

where π^V is the stationary distribution for the model with parameter choice $V > 0$, and where $\delta = n_{\min} - n_{\max}$. If $\delta = 0$, the last term is taken to be zero. Further, the function $g(\tilde{x})$ fulfils 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 (19). 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, $\Gamma = \{i | i \geq i_0\}$ is irreducible and the stationary distribution, if it exists, is given by (see [17])

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

where the partition function Z^V satisfies

$$Z^V = \sum_{i=i_0}^{\infty} \frac{p_{i_0} \cdots p_{i-1}}{q_{i_0+1} \cdots q_i}.$$

Let $\delta = n_{\min} - n_{\max}$ and note that for large V , there exists constants $C_2 > C_1 > 0$ independent of V such that

$$C_2 \frac{V^\delta}{i^\delta} \frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \geq \frac{p_{i-1}}{q_i} \geq C_1 \frac{V^\delta}{i^\delta} \frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \quad \text{for } i \geq \max(i_0, 1).$$

Hence,

$$Z^V = \Theta \left(\sum_{i=i_0}^{\infty} \frac{V^{\delta i}}{(i!)^\delta} \left(\frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \right)^i \right), \quad (22)$$

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 $V > 0$. Since a stationary distribution exists if and only if Z^V is finite (see [17]), 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 infinite series in equation (22). We will first give bounds on the sum that allow us to conclude that $-V^{-1} \ln(1/Z^V)$ converges as $V \rightarrow \infty$. If $\delta = 0$ then Z^V is bounded between two positive constants that are independent of V , hence $-V^{-1} \ln(1/Z^V) \rightarrow 0$. For $\delta > 0$, let

$$x = V \left(\frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \right)^{1/\delta},$$

and note that

$$\sum_{i=i_0}^{\infty} \frac{V^{\delta i}}{(i!)^\delta} \left(\frac{\kappa_{n_{\max}}}{\kappa_{-n_{\min}}} \right)^i = \sum_{i=i_0}^{\infty} \frac{x^{\delta i}}{(i!)^\delta} \leq \left(\sum_{i=i_0}^{\infty} \frac{x^i}{i!} \right)^\delta \leq e^{\delta x}. \quad (23)$$

To get a lower bound we need Stirling's approximation again:

$$\sqrt{2\pi n} n^{n+0.5} e^{-n} \leq n! \leq e n^{n+0.5} e^{-n},$$

where $n \geq 1$ and e is the base of the natural logarithm. We first apply the second inequality to $i!$ and obtain

$$\frac{x^{\delta i}}{(i!)^\delta} \geq \frac{x^{\delta i}}{e^\delta (i^{i+0.5} e^{-i})^\delta} = \frac{\delta^{0.5}}{e^\delta i^{0.5(\delta-1)}} \cdot \frac{(\delta x)^{\delta i}}{(\delta i)^{\delta i + 0.5} e^{-\delta i}},$$

where the equality follows by simplifying the right hand side. Subsequently, we use the first inequality in Stirling's approximation to bound the right hand side in terms of $(\delta i)!$,

$$\frac{\delta^{0.5}}{e^\delta i^{0.5(\delta-1)}} \cdot \frac{(\delta x)^{\delta i}}{(\delta i)^{\delta i + 0.5} e^{-\delta i}} \geq \frac{\delta^{0.5} \sqrt{2\pi}}{e^\delta i^{0.5(\delta-1)}} \cdot \frac{(\delta x)^{\delta i}}{(\delta i)!} = \frac{K_1}{i^{0.5(\delta-1)}} \cdot \frac{(\delta x)^{\delta i}}{(\delta i)!}, \quad (24)$$

where K_1 are the terms that are independent of i .

The right hand side of (24) may further be bounded from below by

$$\frac{K_1}{i^{0.5(\delta-1)}} \cdot \frac{(\delta x)^{\delta i}}{(\delta i)!} \geq \frac{K_1 (\delta x)^{\delta i}}{(\delta(i+1))!} = \frac{K_1}{(\delta x)^\delta} \cdot \frac{(\delta x)^{\delta(i+1)}}{(\delta(i+1))!}. \quad (25)$$

The sum over i of the last expression is given on page 739, formula (8), in [25]. For our purposes it suffices to note that it can be bounded by the exponential function

$$\sum_{i=i_0+1}^{\infty} \frac{(\delta x)^{\delta i}}{(\delta i)!} \geq K_2 e^{\delta x}, \quad (26)$$

where $K_2 > 0$ is a constant independent of x . Putting (23)-(26) together yields

$$e^{\delta x} \geq \sum_{i=i_0}^{\infty} \frac{x^{\delta i}}{(i!)^{\delta}} \geq \frac{K_1 K_2}{(\delta x)^{\delta}} e^{\delta x},$$

which, recalling (22) and (23), implies that

$$-V^{-1} \ln(1/Z^V) \rightarrow \delta \left(\frac{\kappa_{n_{\max}}}{\kappa_{n_{\min}}} \right)^{1/\delta} \stackrel{\text{def}}{=} g_0. \quad (27)$$

Next we turn to the non-equilibrium potential. Letting $\tilde{x}^V = V^{-1}x$ with $x \geq i_0$, it takes the form

$$\begin{aligned} -V^{-1} \ln(\tilde{\pi}^V(\tilde{x}^V)) &= -V^{-1} \ln(\pi^V(V\tilde{x}^V)) \\ &= -V^{-1} \left[\sum_{i=i_0+1}^{V\tilde{x}^V} \ln(p_{i-1}) - \ln(q_i) \right] - V^{-1} \ln(1/Z^V). \end{aligned} \quad (28)$$

The last term converges for $V \rightarrow \infty$ as shown in (27). Using the definitions of p_i , q_i and $\lambda_n^V(i)$, the sum in the first term in (28) becomes

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

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

$$-V^{-1} \sum_{i=1}^{V\tilde{x}} [\ln(p_{i-1}) - \ln(q_i)] \rightarrow - \int_0^{\tilde{x}} \ln \left(\frac{\sum_{n \geq 0} \kappa_n x^{\nu_n}}{\sum_{n < 0} \kappa_n x^{\nu_n}} \right) dx \stackrel{\text{def}}{=} g_1(\tilde{x}),$$

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

$$\begin{aligned} \frac{d}{dt} g(x(t)) &= g'(x(t))x'(t) \\ &= - \ln \left(\frac{\sum_{n \geq 0} \kappa_n x^{\nu_n}}{\sum_{n < 0} \kappa_n x^{\nu_n}} \right) \cdot \left(\sum_{n \geq 0} \kappa_n x^{\nu_n} - \sum_{n < 0} \kappa_n x^{\nu_n} \right). \end{aligned}$$

This is strictly negative unless

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

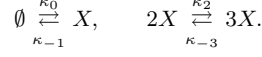
in which case we are at an equilibrium. \square

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 (21) 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 $g(0) = 0$ and $g(\tilde{x}) \rightarrow \infty$ as $\tilde{x} \rightarrow \infty$. 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,



The deterministic model satisfies

$$\dot{x} = \kappa_0 - \kappa_{-1}x + \kappa_2x^2 - \kappa_{-3}x^3.$$

We have $n_{\max} = 2$ and $n_{\min} = 3$ such that condition (1) of Theorem 9 is fulfilled. Hence, the non-equilibrium potential converges to the function

$$g(\tilde{x}) = - \int_0^{\tilde{x}} \ln \left(\frac{\kappa_0 + \kappa_2x^2}{\kappa_{-1}x + \kappa_{-3}x^3} \right) dx + \frac{\kappa_2}{\kappa_{-3}}. \quad (29)$$

The stationary distribution of the stochastically modeled system can be obtained in closed form [11],

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

where

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

If $P = R$, then the distribution is Poisson with intensity B and, in fact, the system is complex balanced. In this case the Lyapunov function (29) 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 $\tilde{x} = 1, 3$. \square

Example 11. Consider the chemical reaction network



which is equivalent to a linear birth-death process with absorbing state 0. This model has $n_{\min} = n_{\max} = 1$, 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

$$g(\tilde{x}) = - \int_0^{\tilde{x}} \ln \left(\frac{\kappa_1x}{\kappa_{-1}x} \right) dx = -\tilde{x} \ln \left(\frac{\kappa_1}{\kappa_{-1}} \right) \quad (30)$$

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

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

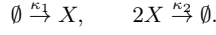
which is independent of V . It follows that for $\tilde{x}^V \rightarrow \tilde{x}$,

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

in agreement with (30). 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. \square

4.2 Other examples

Example 12. Consider the chemical reaction network,



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 (15) can be given in explicit form [8],

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

where $I_n(z)$ is the modified Bessel function of the n th kind. To evaluate the non-equilibrium potential we need two asymptotic results for the modified Bessel functions [13]:

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

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

where

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

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

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

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

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

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. \square

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



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 $\{\kappa_k^V\}$ be given accordingly. The deterministically modeled system takes the form

$$\dot{x} = 2\kappa_2 - \kappa_1 x \tag{31}$$

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

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

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 $V \rightarrow \infty$ with $\tilde{x}^V \rightarrow \tilde{x}$:

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

where

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

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

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

and zero if and only if $4a = x$. Comparing with (31) yields

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

and equality only if $x = 4a$. 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 (bio)chemical 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 [27]. Further, we showed the correspondence holds for a wider class of models including those birth and death systems that can be modeled via chemical reaction systems. It remains open just how wide the class of models satisfying this relationship is.

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SUPPORTING INFORMATION

Lyapunov Functions, Stationary Distributions, and Non-equilibrium Potential for Chemical Reaction Networks

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Example 13 in the Main text

In Example 13 in the main text we consider the following chemical reaction network:



The network is not weakly reversible, hence it cannot be complex balanced. Furthermore, the model is not a birth-death process as the ‘birth event’ creates two copies of X . Consequently, we cannot use the theory developed in the main text to determine whether the non-equilibrium potential converges to a Lyapunov function and in case it does, the form of the Lyapunov function.

Here we prove the claims made in the main text about the network. To be precise we will show that an equilibrium distribution exists and show that it can be given as the sum of two independent Poisson distributions. We will use this representation to argue that the non-equilibrium potential converges to a Lyapunov function and state its form.

Proposition 1. *Let N_t be the number of X molecules at time t in the network \mathcal{N} . Then the distribution of N_t is given as the convolution of two independent random variables,*

$$N_t = N_{1,t} + 2N_{2,t}, \quad N_{1,t} \sim Po\left(2\alpha V(1 - e^{-k_1 t})^2\right), \quad \text{and} \quad N_{2,t} \sim Po\left(\alpha V(1 - e^{-2k_1 t})\right).$$

Letting $t \rightarrow \infty$, we obtain the equilibrium distribution of X ,

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

where N_1 and N_2 are independent random variables.

Proof of Proposition 1. Let $\lambda = Vk_2$ and $\mu = k_1$ for convenience. Fix $t > 0$. The number of birth events that has occurred before time t is Poisson with rate λt . Assume a birth event happens at time $0 < u < t$. Then either zero, one or two of the X molecules might survive until time t , each with death rate μ . The probabilities of these events are

$$p_u(2) = e^{-2\mu(t-u)}, \quad p_u(1) = 2e^{-\mu(t-u)}(1 - e^{-\mu(t-u)}), \quad \text{and} \quad p_u(0) = 1 - p_u(1) - p_u(2), \quad (2)$$

where $p_t(i)$, $i = 0, 1, 2$, is the probability that i lineages survive. Given that N_t birth events have happened, each of the N_t events occur at a uniform random time in $(0, t)$. Hence, the probabilities in equation (2), averaged over time, become

$$P_t(i) = \frac{1}{t} \int_0^t p_u(i) du,$$

or

$$P_t(2) = \frac{1}{2\mu t}(1 - e^{-2\mu t}), \quad P_t(1) = \frac{1}{\mu t}(1 - e^{-\mu t})^2, \quad \text{and} \quad P_t(0) = 1 - P_t(1) - P_t(2).$$

It follows that the number of birth events for which both molecules survive is $N_{2,t} \sim \text{Po}(\lambda t P_t(2))$ and the number of birth events for which only one of the two molecules survive is $N_{1,t} \sim \text{Po}(\lambda t P_t(1))$, which coincide with those stated in the lemma. Since birth events occur independently of each other, $N_{1,t}$ and $N_{2,t}$ are independent random variables. Further, the number of molecules at time t is $N_t = N_{1,t} + 2N_{2,t}$, which proves the first part.

To obtain the equilibrium distribution we let $t \rightarrow \infty$ and obtain $N_1 \sim \text{Po}(2\alpha V)$ and $N_2 \sim \text{Po}(\alpha V)$, where α is as defined in the lemma. \square

The probability distribution of N in Lemma 1 is given by

$$\begin{aligned} P(N = n) &= \sum_{k,m: k+2m=n} \frac{(2V\alpha)^k}{k!} e^{-2V\alpha} \frac{(V\alpha)^m}{m!} e^{-V\alpha} \\ &= e^{-3V\alpha} \sum_{k,m: k+2m=n} \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!}, \end{aligned} \quad (3)$$

where the sum is over all positive integers k, m such that $k + 2m = n$. The sum does not seem easy to manipulate further.

To evaluate $\frac{1}{V} \ln(P(N = n))$ as $V \rightarrow \infty$ and $n/V \rightarrow x$, we need a version of Laplace's method for approximating integrals of the form $\int e^{Vf(x)} dx$. To state the method, we first look at the sum in (3). Each term is rewritten by taking the exponential and the logarithm to the term, and subsequently applying Stirling's approximation,

$$\sqrt{2\pi} n^{n+\frac{1}{2}} e^{-n} \leq n! \leq e n^{n+\frac{1}{2}} e^{-n} \quad \text{for} \quad n \geq 1 \quad (e \approx 2.71),$$

to provide an upper and a lower bound:

$$\begin{aligned} \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!} &= \exp\{k \ln(2V\alpha) - \ln(k!) + m \ln(V\alpha) - \ln(m!)\} \geq \frac{\sqrt{2\pi}}{V} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{Vf_x(u)} \\ \frac{(2V\alpha)^k}{k!} \frac{(V\alpha)^m}{m!} &= \exp\{k \ln(2V\alpha) - \ln(k!) + m \ln(V\alpha) - \ln(m!)\} \leq \frac{e}{V} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{Vf_x(u)}, \end{aligned} \quad (4)$$

where $x = \frac{n}{V}$, $u = \frac{m}{V}$, and $k, m > 0$, such that $u > 0$ and $x - 2u > 0$, and

$$f_x(u) = -u \ln(u) - (x - 2u) \ln(x - 2u) + (x - u)(\ln(\alpha) + 1) + (x - 2u) \ln(2).$$

Note that $x - 2u = \frac{k}{V}$, $x - u = \frac{k+m}{V}$ and $0 < u < \frac{x}{2}$. Only the cases $m = 0$ and $k = 0$ cannot be bound in this way.

Consider $f_x(u)$ as a function on the open interval $(0, \frac{x}{2})$ into \mathbb{R} . The derivative of $f_x(u)$ with respect to u is

$$f'_x(u) = -\ln(u) + 2\ln(x - 2u) - 2\ln(2) - \ln(\alpha),$$

which is decreasing in u . The function $f_x(u)$ attains its maximum for

$$u^* = \frac{1}{2}(x + \alpha - \sqrt{\alpha(\alpha + 2x)}),$$

which fulfills

$$0 < u^* < \frac{x}{2} \quad \text{for } x > 0.$$

The second derivative of $f_x(u)$ is always negative; hence $f_x(u)$ is convex and strictly increasing for $u < u^*$ and strictly decreasing for $u > u^*$.

Let (a, b) be an open interval in \mathbb{R} with a, b potentially infinite.

Theorem 1. (Laplace's method) *Assume $h: (a, b) \rightarrow \mathbb{R}$ and $f(u): (a, b) \rightarrow \mathbb{R}$ are two functions, such that $h(u)$ is continuous and $h(z) > 0$ for all $u \in (a, b)$, and $f(u)$ is twice continuously differentiable with a unique (global) maximum $u^* \in (a, b)$, such that $f''(u^*) < 0$. Further, assume $h(u)e^{Vf(u)}$ is integrable on (a, b) for all $V \geq 0$.*

Then,

$$\int_a^b h(u)e^{Vf(u)} du \approx \sqrt{\frac{2\pi}{V|f''(u^*)|}} h(u^*)e^{Vf(u^*)} \quad \text{as } V \rightarrow \infty,$$

where the approximation means that the ratio of the two terms goes to one.

Lemma 1. *Let $P(N = n)$ be the probability in (3). Then*

$$\lim_{V \rightarrow \infty} -\frac{1}{V} \ln(P(N = xV)) = 3\alpha - f_x(u^*),$$

where u^* , which depends on u , is the unique maximum of $f_x(u)$.

Proof of Lemma 1. We assume the notation and definitions introduced above. Consider the sum over all k, m , such that $k + 2m = n$ and $k, m > 0$:

$$S = \sum_{u=\frac{1}{V}}^{\frac{n'}{V}} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{Vf_x(u)},$$

where $n' = \frac{n-1}{2}$, if n is odd and $n' = \frac{n}{2} - 1$, if n is even. We split the sum S into three parts:

$$\sum_{u < \epsilon} + \sum_{\frac{x}{2} - \epsilon < u} + \sum_{\epsilon \leq u \leq \frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V\tilde{f}_x(u)}$$

for some (small) $\epsilon > 0$. The sum of the first two terms can be bounded downwards by 0 and upwards by

$$d_1 V^{\frac{1}{2}} e^{V d_2},$$

where $d_1 > 0$ and $d_2 \in \mathbb{R}$. Indeed, using the properties of $f_x(u)$, we have $d_2 = \max(f_x(\epsilon), f_x(\frac{x}{2} - \epsilon))$, and d_1 is a number such that $d_1 V^{\frac{1}{2}} > \max\left(\frac{1}{u^{1/2}(x-2u)^{1/2}} | u \leq \epsilon \text{ or } \frac{x}{2} - \epsilon \leq u\right)$.

The last sum can be approximated by an integral. For this, consider the function

$$h(u) = \frac{1}{u^{1/2}(x-2u)^{1/2}}$$

and let u_0 be given. Since $f_x(u_0 + \frac{1}{V}) \approx f_x(u_0) + \frac{1}{V} f'_x(u_0)$ to order $\frac{1}{V}$, we have

$$a_1 V \int_{u_0}^{u_0 + \frac{1}{V}} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} du \leq h(u_0) e^{V f_x(u_0)} \leq a_2 V \int_{u_0}^{u_0 + \frac{1}{V}} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} du,$$

for two constants $a_1, a_2 > 0$. The functions $h(u)$, $f_x(u)$ and $f'_x(u)$ are continuous and bounded on $[\epsilon, \frac{x}{2} - \epsilon]$, hence a_1, a_2 can be chosen such that they are independent of $u \in [\epsilon, \frac{x}{2} - \epsilon]$. Consequently, the bounds hold for all $u \in [\epsilon, \frac{x}{2} - \epsilon]$ and we obtain

$$\begin{aligned} a_1 V \int_{\epsilon}^{\frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} du &\leq \sum_{\epsilon \leq u \leq \frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} \\ &\leq a_2 V \int_{\epsilon}^{\frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} du. \end{aligned}$$

Using Theorem 1, the sum can further be approximated by a single term for large V . Since $h(u) e^{V f_x(u)}$ is bounded on $[\epsilon, \frac{x}{2} - \epsilon]$ for fixed V , the conditions for using Theorem 1 are fulfilled and we obtain,

$$b_1 V^{\frac{1}{2}} e^{V f_x(u^*)} \leq \sum_{\epsilon \leq u \leq \frac{x}{2} - \epsilon} \frac{1}{u^{1/2}(x-2u)^{1/2}} e^{V f_x(u)} \leq b_2 V^{\frac{1}{2}} e^{V f_x(u^*)}.$$

for some new constants $b_1, b_2 > 0$.

Consider now $P(N = n)$. We have from the equation (3) and the definition of S that

$$P(N = n) = S e^{-3\alpha V} + P(N = n, N_1 = 0) + P(N = n, N_2 = 0).$$

Depending on whether n is odd or even, $P(N = n, N_1 = 0)$ might be zero. Using Stirling's approximation we obtain

$$P(N = n, N_2 = 0) \approx e^{-3\alpha V} e^{V f_x(0)} x^{-\frac{1}{2}} V^{-\frac{1}{2}},$$

and

$$P(N = n, N_2 = 0) \approx e^{-3\alpha V} e^{V f_x(\frac{x}{2})} \left(\frac{x}{2}\right)^{-\frac{1}{2}} V^{-\frac{1}{2}},$$

where the \approx means the ratio of the two terms goes to one as $V \rightarrow \infty$.

Putting all terms in $P(N = n)$ together, using that $S e^{-3\alpha V}$ is to a higher power in V than the other terms, yields

$$\lim_{V \rightarrow \infty} -\frac{1}{V} \ln(P(N = xV)) = \lim_{V \rightarrow \infty} -\frac{1}{V} \ln(S e^{-3\alpha V}) = 3\alpha - f_x(u^*),$$

which proves the claim of the lemma. □

Proposition 2. *The function*

$$g(x) = 3\alpha - f_x(u^*), \quad \text{with } u^* = \frac{1}{2}(x + \alpha - \sqrt{\alpha(\alpha + 2x)})$$

is a Lyapunov function for the network in (1). Further, $g(x)$ might be written as

$$g(x) = \int_0^x \ln\left(\sqrt{1 + \frac{2u}{\alpha}} - 1\right) du - \ln(2)x,$$

as stated in the main text.

Proof of Proposition 2. From (1) we have $\dot{x} = 2k_2 - k_1x$. Recall that $\alpha = \frac{k_2}{2k_1}$, hence the sign of \dot{x} is the same as the sign of

$$\frac{\dot{x}}{k_1} = 4\alpha - x. \tag{5}$$

We consider the function $g(x)$ as a function $\tilde{g}(x, u) = -3\alpha + f_x(u)$ of two variables (x, u) evaluated in (x, u^*) . Hence the derivative of $g(x)$ with respect to x is

$$g'(x) = \frac{\partial \tilde{g}}{\partial u}(x, u^*) \frac{du^*}{dx} + \frac{\partial \tilde{g}}{\partial x}(x, u^*) = -\frac{\partial f_x}{\partial u}(u^*) \frac{du^*}{dx} - \frac{\partial f_x}{\partial x}(u^*).$$

The first term on the right side is 0 by definition of u^* . Evaluating the second term yields

$$g'(x) = \ln\left(\sqrt{1 + \frac{2x}{\alpha}} - 1\right) - \ln(2),$$

which fulfills

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

and zero only when $4\alpha = x$. Comparing with (5) gives

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

and equality only if $x = 4\alpha$. Hence $g(x)$ is a Lyapunov function for the network (1). □