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Stochastic chemical reaction networks for robustly approximating arbitrary probability distributions

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ABSTRACT

We show that discrete distributions on the d-dimensional non-negative integer lattice can be approximated arbitrarily well via the marginals of stationary distributions for various classes of stochastic chemical reaction networks. We begin by providing a class of detailed balanced networks and prove that they can approximate any discrete distribution to any desired accuracy. However, these detailed balanced constructions rely on the ability to initialize a system precisely, and are therefore susceptible to perturbations in the initial conditions. We therefore provide another construction based on the ability to approximate point mass distributions and prove that this construction is capable of approximating arbitrary discrete distributions for any choice of initial condition. In particular, the developed models are ergodic, so their limit distributions are robust to a finite number of perturbations over time in the counts of molecules.

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1. Introduction

Chemical reaction networks (CRNs) with mass-action kinetics [1,2] model the behavior of well-mixed chemical solutions and have a wide range of applications in science and engineering. In particular, they are used to study the behavior of natural, industrial, and biological processes. Thus, it is important to understand their mathematical foundations. There are two common choices for dynamical models of CRNs, *deterministic* and *stochastic*, and the choice of model depends on the properties of the system that one wishes to study. For systems where the counts of the relevant molecules are large and reactions are taking place nearly continuously, the randomness inherent in the timing and types of reactions taking place average out, and the state variables are the real-valued concentrations of molecular species, with dynamics expressed as ordinary differential equations. Since the trajectory of concentrations is uniquely determined by their initial values, these models are referred to as deterministic. Deterministic CRN models are well-studied and much is known about their stationary behavior [3]; moreover, their dynamics are known to be able to simulate arbitrary electrical and digital circuits [4,5]. Furthermore, it has been recently proved that deterministic CRNs are capable of universal computation [6]. Of increasing importance is the case of solutions with small volume and discrete counts, such as the interiors of biological cells and nanoscale engineered

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systems. In this case, the state variables are the integer counts of molecules, and dynamics are expressed as continuous-time, discrete-space stochastic processes [1,7–9]. These models are commonly referred to as the stochastic model of CRNs, which we adopt in the present document.

Stochastic models of CRNs are well studied. In particular, both their stationary and finite time dynamics are of interest and have been analyzed [1,8–33]. Moreover, their computational properties have been explored and it has been shown that they can simulate Turing machines, so long as an arbitrarily small probability of error is allowed [34–36]. They are in this sense capable of universal computation. However, there are known limitations on the dynamics exhibited by certain classes of stochastic CRNs [37,38] and the full repertoire of accessible behaviors has yet to be characterized.

A particular question is: what are the possible fluctuation sizes that can be seen in molecule counts for stochastic CRNs in stationarity? When used to model systems in thermodynamic equilibrium with particle reservoirs, i.e., models that are detailed balanced and have inflows and outflows of each species, the stationary distributions of stochastic CRNs take the form of the product of independent Poisson distributions [39]. Hence, in these cases, the magnitude of fluctuations in the population of each molecule type is equal to the square root of the mean, since the mean and variance of Poisson distributions are equal. In the physical sciences, it is typical to encounter systems with fluctuations with size of square root of the mean. This was stated by Schrödinger in *What is life?* when talking about the inaccuracy of physical laws and referred to it as the $\sqrt{n}$ law [40]. For more general detailed balanced systems, where the topology of the network restricts the set of states the process can reach, the stationary distributions continue to have product-Poisson form in the reachable space [39]. In fact, the occurrence of a stationary distribution that is a product of Poissons is equivalent to the model being *complex balanced*, which is a generalization of the detailed balanced condition [12,13]. For other well-known CRNs, such as models of gene regulation [11], the variance of particle counts meets or even exceeds their mean value. In other examples, CRN models of low-copy-number plasmid populations in bacterial cells, where variability due to replication and partitioning could have a disruptive effect, produce distributions where the variance is less than the mean [41]. It has remained an open question whether in general there exists a bound on the variance relative to the mean for stationary distributions of stochastic CRNs, though some results have been shown for specific classes of models [38].

The question that we address in this paper is more general than the one posed at the beginning of the previous paragraph: is there any limit on the shape of the stationary distributions of stochastic CRNs? We will show that *every distribution on the non-negative integer lattice can be approximated to desired precision with the stationary distribution of some stochastic CRN*. Note that, for example, this gives an answer to the open question posed at the end of the previous paragraph: there is no bound on the ratio between the variance and the mean of species at stationarity.

Remarkably, we will be able to approximate any distribution to any desired accuracy by restricting ourselves to two important classes of CRNs. The first class consists of detailed balanced models. These models in principle could be implemented physically as equilibrium systems that do not require the use of an external power supply [42–44]. However, for this class a specific initial condition must be utilized for the desired result to hold. The second class consists of CRNs that have a unique limit distribution (i.e., the models are ergodic), negating the need for special care with the initial conditions. However, physically implementing models from this class would require an external power supply, as they would be non-equilibrium systems [42–44]. Independence of initial conditions is a desirable feature for any model that would be physically implemented in a noisy environment. It is interesting to note how the networks in the intersection of the two classes above have limited expressive power in terms of their limit distributions, as these can only be product of Poisson distributions [39].

The constructions we use are mathematically motivated, and the resulting CRNs do not necessarily have correspondence to known physical systems. For example, we sometimes make use of reactions with arbitrarily high molecularity, such as $17V \to 16V$. However, in the case of constructions utilizing detailed balanced models, we show that CRNs with a more physical interpretation can be considered, such as CRNs where the reactants and products of each reaction contain at most two molecules (see Construction 2 and Remark 5). In fact, we expect that all the conclusions of our paper, namely, that the classes of detailed balanced and robust CRNs are universally approximating, will hold even if restricting the classes to suitable binary CRNs. Intuitively, this follows from the fact that the dynamics of high molecularity reactions can be approximated by the dynamics of a sequence of elementary reactions [45,46]. However, this claim awaits a rigorous proof and the resulting constructions may be more complex than the ones we present here. Moreover, the number of reactions and the number of species of the constructions we describe here both scale with the size of the support of the distribution we are approximating. Anticipating the question of descriptive complexity — namely, can complex distributions be approximated by simple CRNs? — we provide examples addressing it in Section 4. Finally, we note here that a fine tuning of the rate constant parameters is sometimes required to obtain the desired result, but not necessarily for all reactions: indeed, sometimes the desired behavior follows from a time-scale separation which does not depend on a precise regulation of the kinetic parameters. We will point out when this is the case in the paper.

While our work is not the first to explore the expressive power of CRNs in terms of their limit distributions, we are the first to consider the expression of a target distribution robustly with respect to the initial condition. Fett, Bruck, and Riedel [47] considered CRNs that make a stochastic choice among a fixed set of outcomes, with probabilities determined as a function of the counts of some input species. These CRNs require precise initial conditions, and settle to an absorbing state where no further reactions are possible. In contrast, our CRN constructions are ergodic and therefore “active” for all time. Thus, multiple observations over time would each have a distribution close to the limit distribution, enabling the CRN to be used for sampling. Poole et al. [48] show that stochastic CRNs are at least as powerful as the Boltzmann

machine model from statistical machine learning in terms of their ability to generate and sample different probability distributions. Cardelli, Kwiatkowska, and Laurenti [49], like us, consider the problem of programming a CRN to approximate an arbitrary multidimensional distribution, but their constructions require precise initial conditions and are not detailed balanced. Furthermore, as is the case in [47], their CRNs are fated to a state where no reactions can take place. Plesa et al. [50] do not consider arbitrary distributions, but develop methods for controlling noise while preserving the mean behavior of the model in a certain limit.

While our results are of independent interest as a characterization of the class of distributions that can be generated by CRNs, they may have implications for how biological cells, or engineered cell-scale molecular machines, can perform information processing in small volumes. In particular, a probability distribution can be considered as a representation of knowledge; a CRN with parameters chosen such that it generates a specific distribution can be considered to be storing said knowledge. It is therefore reasonable to ask how information stored in CRN distributions can be further processed, manipulated, and acted upon by other CRNs, or how the knowledge can be extracted by interaction with a (proto)cell's environment [48,51–53].

2. Preliminaries

2.1. Notation

Let us denote the sets of integers and reals with $\mathbb{Z}$ and $\mathbb{R}$, and their respective sets of nonnegative and positive elements using the subscripts ≥ 0 and > 0. In what follows, let $d \in \mathbb{Z}_{>0}$. For any set $K \subseteq \mathbb{R}$ of real numbers, we denote by K^d the set of vectors with d entries in K. We will often refer to the elements of $\mathbb{Z}^d_{\geq 0}$ as *states*. Let $u, v \in \mathbb{R}^d$ be vectors. We write vectors as rows $v = (v(1), \ldots, v(d))$, where $v(i)$ denotes the ith entry of v. For $i \in \{1, \ldots, d\}$ we define e_i to be the vector of $\mathbb{Z}^d_{\geq 0}$ with 1 in the ith entry and 0 otherwise, i.e. with $e_i(i) = 1$, and $e_i(j) = 0$, for $j \neq i$. If $u(i) \leq v(i)$, for all $i \in \{1, \ldots, d\}$, we write $u \leq v$. We define:

$$\mathbb{1}_{\{u \geq v\}} = \begin{cases} 1 & \text{if } u \geq v \\ 0 & \text{otherwise.} \end{cases}$$

Let $x \in \mathbb{Z}^d_{\geq 0}$. We define the following:

$$u^x = \prod_{i=1}^{d} u(i)^{x(i)}, \quad \text{and} \quad x! = \prod_{i=1}^{d} x(i)!,$$

with the convention that $0^0 = 1$. Let $f : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}$ be a function. We define the *infinity norm* as usual:

$$\|f\|_\infty = \sup_{x \in \mathbb{Z}^d_{\geq 0}} \{|f(x)|\}.$$

If f satisfies $f(x) \geq 0$, for each $x \in \mathbb{Z}^d_{\geq 0}$, and $\sum_{x \in \mathbb{Z}^d_{\geq 0}} f(x) = 1$, we say f is a *distribution*. We call the set $\{x \in \mathbb{Z}^d_{\geq 0} : f(x) > 0\}$ the *support* of f. Finally, we denote the cardinality of a set S with $|S|$.

2.2. Model

We are interested in the counts of molecules of different chemical species undergoing different chemical transformations. We use the standard model of stochastic chemical reaction networks in which the dynamics of the counts of the different chemical species is modeled as a continuous-time Markov chain. We begin with the definition of a reaction network, and then characterize the dynamics.

Definition 1. A *Chemical Reaction Network* (CRN) is a quadruple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ where $\mathcal{S}$, $\mathcal{C}$, $\mathcal{R}$, κ are defined as follows. $\mathcal{S}$ is a finite set of *species*. $\mathcal{C}$ is a finite set of *complexes*, which are linear combinations of species, with nonnegative integer coefficients. $\mathcal{R}$ is a finite set of *reactions*, that is a finite subset of $\mathcal{C} \times \mathcal{C}$ with the property that for any $y \in \mathcal{C}$ we have $(y, y) \notin \mathcal{R}$. Usually, a reaction (y, y') is denoted by $y \to y'$, and we adopt this notation. Finally, given an ordering for the reactions, κ is a vector in $\mathbb{R}^{|\mathcal{R}|}_{>0}$ that gives every reaction a *rate constant*. The rate constant of reaction $y \to y'$ will be denoted by $\kappa_{y \to y'}$.

Let $\mathcal{S} = \{A_1, \ldots, A_{|\mathcal{S}|}\}$ be an ordering of the species. Complexes will be regarded as vectors in $\mathbb{Z}^{|\mathcal{S}|}_{\geq 0}$ and we use the following notation for a complex y:

$$y = \sum_{i=1}^{|\mathcal{S}|} y(i) A_i.$$

A reaction $y \to y' \in \mathcal{R}$ is said to be *reversible* if $y' \to y \in \mathcal{R}$, and we write $y \rightleftharpoons y' \in \mathcal{R}$ for the pair of reactions. We say that a CRN is itself reversible if all of its reactions are reversible. We will often summarize the sets of complexes, reactions, and rate constants of a CRN in a *reaction diagram*, with reactions and their corresponding rate constants denoted in the following manner

$$\sum_{i=1}^{|\mathcal{S}|} y(i)A_i \xrightarrow{\kappa_{y\to y'}} \sum_{i=1}^{|\mathcal{S}|} y'(i)A_i, \quad \text{for } y \to y' \in \mathcal{R} \text{ such that } y' \to y \notin \mathcal{R}$$

$$\sum_{i=1}^{|\mathcal{S}|} y(i)A_i \underset{\kappa_{y'\to y}}{\overset{\kappa_{y\to y'}}{\rightleftharpoons}} \sum_{i=1}^{|\mathcal{S}|} y'(i)A_i, \quad \text{for } y \rightleftharpoons y' \in \mathcal{R}.$$

For example, consider the CRN with species $\mathcal{S} = \{A, B, C\}$, complexes $\mathcal{C} = \{0, A, C, 2A + B\}$, and reactions $\mathcal{R} = \{2A + B \to C, 0 \to A, A \to 0\}$. Assume all rate constants are unity, i.e. $\kappa = (1, 1, 1)$. The quadruple $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ forms a CRN. Moreover, the CRN includes the reversible pair $0 \to A$ and $A \to 0$, so we can write the set of reactions as $\mathcal{R} = \{2A + B \to C, 0 \rightleftharpoons A\}$. The reaction diagram of this CRN is:

$$2A + B \xrightarrow{1} C, \qquad 0 \underset{1}{\overset{1}{\rightleftharpoons}} A.$$

The usual *stochastic mass action model* of a CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ is defined as a continuous-time Markov chain (CTMC), denoted by $X(\cdot)$, where the propensity for reaction $y \to y'$ in state x is given by:

$$\lambda_{y\to y'}(x) = \kappa_{y\to y'} \frac{x!}{(x-y)!} \mathbb{1}_{\{x \geq y\}}.$$

For example, the propensity of the reaction $A + B \to C$ at state x is $\lambda_{A+B\to C}(x) = \kappa_{A+B\to C} x(1)x(2)$, where $x(1)$ and $x(2)$ represent the counts of species A and B, respectively. For any pair $(x, x') \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}|} \times \mathbb{Z}_{\geq 0}^{|\mathcal{S}|}$ the transition rate of the CTMC from x to x' is given by:

$$Q(x, x') = \sum_{\substack{y\to y' \in \mathcal{R} \\ x'-x = y'-y}} \lambda_{y\to y'}(x).$$

For an initial condition $x_0 \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}|}$, we use the following notation for the probability mass function:

$$P(x, t \mid x_0) = P(X(t) = x \mid X(0) = x_0).$$

2.3. Key concepts

If there is a $t > 0$ for which $P(x', t \mid x) > 0$ we say that x' is *reachable* from x. Note that if x' is reachable from x then it is possible to reach x' from x via a finite number of reactions. The *reachability class* of a state x_0 is the set of states that are reachable from x_0. If there is a distribution $\pi(\cdot \mid x_0)$ for which

$$\pi(x \mid x_0) = \lim_{t\to\infty} P(x, t \mid x_0), \quad \text{for all states } x, \tag{1}$$

then $\pi(\cdot \mid x_0)$ is said to be the *limit distribution* of the CRN for initial condition x_0. We note that limit distributions are stationary distributions for the models, i.e. distributions π such that $P(\cdot, t) = \pi(\cdot)$ for all $t \geq 0$ if $X(0)$ is distributed according to π. For a subset $\mathcal{V} \subseteq \mathcal{S}$ of species the *marginal* of $\pi(\cdot \mid x_0)$ onto $\mathcal{V}$ is:

$$\pi_{\mathcal{V}}(v \mid x_0) = \sum_{\substack{x' \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}|} \\ (x')_{\mathcal{V}} = v}} \pi(x' \mid x_0), \tag{2}$$

where $(x')_{\mathcal{V}} \in \mathbb{Z}_{\geq 0}^{|\mathcal{V}|}$ is the projection of x' onto the species in $\mathcal{V}$.

Definition 2. Let $\mathcal{U}$ be a set of CRNs. We say that $\mathcal{U}$ *approximates* a distribution $q : \mathbb{Z}_{\geq 0}^{d} \to [0, 1]$ if for every $\varepsilon > 0$ there exists a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa) \in \mathcal{U}$, an initial condition $x_0 \in \mathbb{Z}_{\geq 0}^{|\mathcal{S}|}$, and a subset of the species $\mathcal{V} \subseteq \mathcal{S}$, called the *visible* species, with $|\mathcal{V}| = d$, such that a limit distribution $\pi(\cdot \mid x_0)$ as in (1) exists and $\|\pi_{\mathcal{V}}(\cdot \mid x_0) - q\|_\infty < \varepsilon$. Species of $\mathcal{S}$ that are not visible may be called *hidden* species. If $\mathcal{U}$ approximates every distribution on $\mathbb{Z}_{\geq 0}^{m}$ for every $m \geq 1$, then we say that it is *universally approximating*.

Note that while in some cases better matches to the given distribution (i.e., lower ε) can be achieved using the same network structure $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and just changing the rate constants (κ), the notion defined above is more flexible in that it acknowledges that achieving a better match to the distribution may require additional species and reactions, or even an entirely different network structure.

3. Main results

3.1. Universal approximation with detailed balanced networks

Definition 3. Let the CRN $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ be reversible. If there exists a vector $c \in \mathbb{R}_{>0}^{|\mathcal{S}|}$ such that

$$\kappa_{y \to y'} c^y = \kappa_{y' \to y} c^{y'}, \tag{3}$$

for each reaction $y \to y' \in \mathcal{R}$, then we say that $\mathcal{N}$ is *detailed balanced*.

Remark 1. We employ one of multiple equivalent ways of defining detailed balance for CRNs. In the definition above the vector c is a vector of steady-state concentrations for the deterministic CRN with mass action kinetics that obeys the detailed balance condition [54]. The choice of c may not be unique. In particular, detailed balanced CRNs have the remarkable property that if one positive vector of steady-state concentrations satisfies the detailed balanced condition (3), then all other positive vectors of steady-state concentrations will also satisfy (3) [24, Theorem 3.10]. If one recognizes that concentrations correspond to $c_i = e^{-G_i/kT}$, where G_i plays the role of a free energy or chemical potential associated with the ith species, k is Boltzmann's constant, and T is temperature, the definition takes the form of the thermodynamic formula $\kappa_{y \to y'}/\kappa_{y' \to y} = e^{-\Delta G(y \to y')/kT}$, which relates the *equilibrium constant* $\kappa_{y \to y'}/\kappa_{y' \to y}$ to the *change in free energy* $\Delta G(y \to y') = \sum_{i=1}^{|\mathcal{S}|} G_i(y'(i) - y(i))$ associated with reaction $y \to y'$. Detailed balanced CRNs often arise as models of closed systems that will reach thermal equilibrium and thus a steady-state that on average consumes no further energy; more generally, they arise as models of open systems that exchange material with a reservoir that is in chemical equilibrium [42]. Note however that, here, G_i is purely a mathematical device and need not correspond to any physical free energy. For example, considered alone, the classical coarse-grained model of RNA synthesis and degradation in genetic regulatory networks, $DNA + RNAP \to DNA + RNAP + RNA$ and $RNA + RNase \to RNase$, despite that energy and material are consumed in RNA synthesis and degradation, has stochastic behavior identical to $0 \rightleftharpoons RNA$, which formally satisfies detailed balance for any choice of rate constants. △

The stationary distributions for detailed balanced CRNs are well known:

$$\pi(x \mid x_0) = \frac{1}{M_{x_0}} \frac{c^x}{x!}, \tag{4}$$

for each x in the reachability class of x_0, where M_{x_0} is the corresponding normalization constant. This result appears in, for example, Theorem 3.2 of Chapter 7 in [39], or, more recently, as a special case of Theorem 4.1 in [13]. However, versions of the theorem were published as early as 1958 in [55], and 1967 in [56].

The stationary distributions of detailed balanced CRNs consist exclusively of restrictions of products of Poisson distributions. Yet, as we will show, every distribution with finite support can be expressed as the marginal of the limit distribution of some detailed balanced CRN. We introduce three constructions that illustrate different design trade-offs (Fig. 1).

Construction 1 *(Full Indexed Network).* Let $d \geq 1$ and let $q : \mathbb{Z}_{\geq 0}^d \to [0, 1]$ be a distribution with finite support $\{v_1, \ldots, v_m\}$. Define the CRN $\texttt{Full}(q) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d, H_1, \ldots, H_m\}$. Note that there is one visible species V_i for each of the dimensions of $\mathbb{Z}_{\geq 0}^d$ and that there is one hidden species H_j for each of the points in the support of q.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$H_i + \sum_{k=1}^{d} v_i(k) V_k \underset{v_i!\, q(v_i)}{\overset{v_j!\, q(v_j)}{\rightleftharpoons}} H_j + \sum_{k=1}^{d} v_j(k) V_k, \tag{5}$$

for $i, j \in \{1, \ldots, m\}$, $i \neq j$. △

States of the associated continuous-time Markov chain reside in $\mathbb{Z}_{\geq 0}^{d+m}$, with the first d dimensions corresponding to the visible species V_i and the final m dimensions corresponding to the hidden species H_j. We will therefore write states as $x = (v, h)$, where $v \in \mathbb{Z}_{\geq 0}^d$ and $h \in \mathbb{Z}_{\geq 0}^m$.

Remark 2. Note that if the initial condition for Construction 1 is $x_0 = (\nu_1, e_1)$ (or, more generally, of the form (ν_i, e_i), for $i \in \{1, \dots, m\}$), then at any future time there is precisely one H_i species that has a count of one and the others have a count of zero. Moreover, the CRN is designed so that if the count of H_i is 1, then the counts of the $(V_1, \dots, V_d)$ are exactly ν_i. △

Lemma 1. *Let $d \geq 1$ and let $q : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be a distribution with finite support. Then, $\texttt{Full}(q)$ is detailed balanced and, for initial condition $x_0 = (\nu_1, e_1)$ and set of visible species $\mathcal{V} = \{V_1, \dots, V_d\}$, the marginal of the limit distribution satisfies $\pi_{\mathcal{V}}(\cdot \mid x_0) = q$.*

Proof. Let us denote the complexes of $\texttt{Full}(q)$ with:

$$y_i = H_i + \sum_{k=1}^{d} \nu_i(k) V_k,$$

for $i \in \{1, \dots, m\}$. Note that $c = (c^V, c^H) \in \mathbb{R}^{d+m}_{>0}$ given by

$$\begin{aligned} c^V_\ell &= 1, \quad \ell \in \{1, \dots, d\} \\ c^H_\ell &= \nu_\ell! q(\nu_\ell), \quad \ell \in \{1, \dots, m\} \end{aligned} \tag{6}$$

satisfies $\kappa_{y_i \to y_j} c^{y_i} = \nu_i! \nu_j! q(\nu_i) q(\nu_j) = \kappa_{y_j \to y_i} c^{y_j}$ for all $i, j \in \{1, \dots, m\}$. Hence, $\texttt{Full}(q)$ is detailed balanced. The reachability class of initial condition $x_0 = (\nu_1, e_1)$ is $\{(\nu_i, e_i) \mid 1 \leq i \leq m\}$. Hence, for initial condition x_0, the limit distribution (4) satisfies:

$$\pi((\nu_i, e_i) \mid x_0) = \frac{1}{M_{x_0}} \frac{c^{(\nu_i, e_i)}}{(\nu_i, e_i)!} = \frac{1}{M_{x_0}} \frac{c^H_i}{\nu_i!} = \frac{q(\nu_i)}{M_{x_0}}.$$

Notice that, since q is normalized, we have:

$$M_{x_0} = \sum_{i=1}^{m} q(\nu_i) = 1.$$

Therefore, for the set of visible species $\mathcal{V} = \{V_1, \dots, V_d\}$, the marginal of the distribution satisfies:

$$\pi_{\mathcal{V}}(\nu_i \mid x_0) = \pi((\nu_i, e_i) \mid x_0) = q(\nu_i), \tag{7}$$

for all $i \in \{1, \dots, m\}$, and it is 0 otherwise. □

Notice that if we modify the stoichiometry of the reactions in Construction 1, while preserving the net change of molecules of each reaction, the reachability class for the initial condition $x_0 = (\nu_1, e_1)$ is the same as before. Also, we can scale the rate constants of reversible pairs of reactions by the same factor without affecting the limit distribution. For example, if a state ν_i in the support of q has exactly one more molecule of V_k than another state ν_j in the support of q, we may use the reactions

$$H_i + V_k \underset{\nu_i(k)\, q(\nu_i)}{\overset{q(\nu_j)}{\rightleftharpoons}} H_j,$$

for that pair of states, instead of (5). With this choice of rate constants Lemma 1 remains true.

Let $d \geq 1$ and consider the set $\mathbb{Z}^d_{\geq 0}$ of states. We say that two states $x, x' \in \mathbb{Z}^d_{\geq 0}$ are *adjacent* if there exists $i \in \{1, \dots, d\}$ such that $|x(i) - x'(i)| = 1$, and $x(j) = x'(j)$ otherwise. Let $U \subseteq \mathbb{Z}^d_{\geq 0}$ be a set of states. If U induces a (possibly infinite) connected graph through the edge relation $\{(x, y) : x \text{ and } y \text{ are adjacent}\}$, then we say that U is a *cluster*. Then, if the support of a distribution is finite and also a cluster we can modify Construction 1 to use reactions that have at most two molecules in the reactants and similarly for the products, i.e. using only bimolecular reactions.

Construction 2 *(Bimolecular Indexed Network).* Let $d \geq 1$ and let $q : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be a distribution with finite support $\{\nu_1, \dots, \nu_m\}$. Suppose that the support is a finite cluster. Define the CRN $\texttt{Bimol}(q) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is the same as in Construction 1, i.e. $\mathcal{S} = \{V_1, \dots, V_d, H_1, \dots, H_m\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$H_i + V_k \underset{\nu_i(k)\, q(\nu_i)}{\overset{q(\nu_j)}{\rightleftharpoons}} H_j,$$

for $i, j \in \{1, \dots, m\}$, and $k \in \{1, \dots, d\}$ such that $\nu_i(k) = \nu_j(k) + 1$, and the components of ν_i and ν_j are otherwise equal. That is, when $\nu_i - \nu_j = e_k$. △

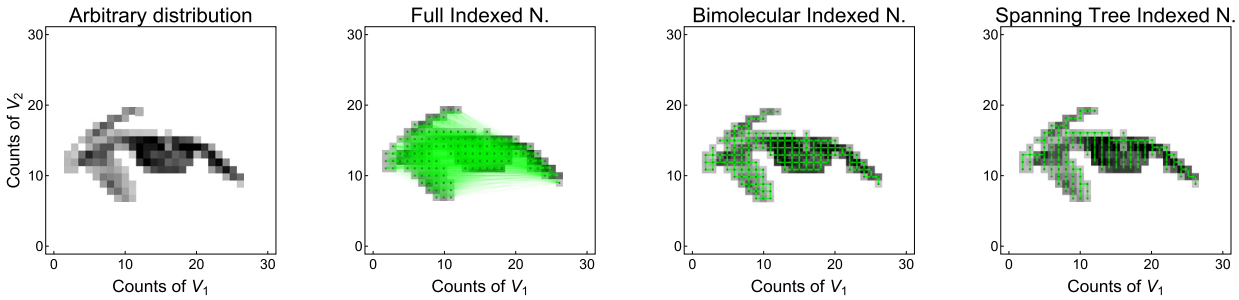


Fig. 1. Example of detailed balanced constructions. On the left we have a two-dimensional distribution with a finite cluster as support. For the Full Indexed Network every pair of elements of the support, indicated by a green edge connecting the pair, is assigned a reaction. For example, if $v_1 = (5, 3)$ and $v_2 = (13, 5)$, we have the reversible reaction pair $H_1 + 5V_1 + 3V_2 \rightleftharpoons H_2 + 13V_1 + 5V_2$. For the Bimolecular and Spanning Tree Indexed Networks we only consider reactions between adjacent states, indicated by green edges as well. For example, we assign to the pair $v_1 = (5, 3)$, $v_2 = (5, 4)$ the reversible reaction pair $H_1 \rightleftharpoons H_2 + V_2$. While the Bimolecular Indexed Network includes one reaction for every adjacent pair of elements of the support, the Spanning Tree Indexed Network includes only as many adjacent pairs as necessary to leave the support connected. (For interpretation of the colors in the figure(s), the reader is referred to the web version of this article.)

Remark 3. By an argument similar to the proof of Lemma 1, $\texttt{Bimol}(q)$ is detailed balanced with detailed balanced equilibrium c from (6). Moreover, for initial condition $x_0 = (v_1, e_1)$ and set of visible species $\mathcal{V} = \{V_1, \ldots, V_d\}$, the marginal of the limit distribution satisfies $\pi_{\mathcal{V}}(\cdot \mid x_0) = q$. △

We can further simplify Construction 2 by removing reactions but preserving the connectivity of the cluster. If we remove edges of a cluster until no edge can be removed without splitting it into two disconnected graphs, the graph that results is a spanning tree.

Let $U \subseteq \mathbb{Z}^d_{\geq 0}$ be a cluster, and let $G = (U, E)$ with $E \subseteq U \times U$ be a (possibly infinite) simple graph whose edges only connect adjacent states. If G is connected and it fails to be so when any edge from E is removed, we say that G is a *cluster spanning tree*.

Construction 3 *(Spanning Tree Indexed Network).* Let $d \geq 1$ and let $q : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be a distribution with finite support $U = \{v_1, \ldots, v_m\}$. Suppose that U is a finite cluster. Let $E \subseteq U \times U$ be a cluster spanning tree. Define the CRN $\texttt{SpanTree}(q, E) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d, H_1, \ldots, H_m\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$H_i + V_k \underset{v_i(k)\, q(v_i)}{\overset{q(v_j)}{\rightleftharpoons}} H_j,$$

for $i, j \in \{1, \ldots, m\}$, and $k \in \{1, \ldots, d\}$ such that $(v_i, v_j) \in E$, and $v_i(k) = v_j(k) + 1$. Notice that E consists of only edges between adjacent states so we must have that $v_i(\ell) = v_j(\ell)$ for $\ell \neq k$ since $v_i - v_j = e_k$. △

Remark 4. Notice that, similar to Construction 2, $\texttt{SpanTree}(q, E)$ is detailed balanced with detailed balanced equilibrium c from (6). Also, for initial condition $x_0 = (v_1, e_1)$ and set of visible species $\mathcal{V} = \{V_1, \ldots, V_d\}$, the marginal of the limit distribution satisfies $\pi_{\mathcal{V}}(\cdot \mid x_0) = q$. △

In Construction 1 the number of reactions is equal to $m(m-1) = \mathcal{O}(m^2)$, i.e. it is quadratic in the size of the support of q. By comparison, the number of reactions in Construction 2 is $\mathcal{O}(dm)$ since every point of the support has at most $2d$ adjacent states. Finally, the number of reactions in Construction 3 is equal to $2(m-1) = \mathcal{O}(m)$, i.e. it is linear in the size of the support of q.

Lemma 2. *Let $d \geq 1$, let $q : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be a distribution, and let $\varepsilon > 0$. Then, there exists a distribution $q' : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ with finite support that satisfies $\|q - q'\|_\infty < \varepsilon$.*

Proof. Consider an ordering of the states $\{x_1, x_2, \ldots\} = \mathbb{Z}^d_{\geq 0}$, that satisfies $q(x_i) \geq q(x_j)$, whenever $i \leq j$. Since we have $\sum_{i=1}^{\infty} q(x_i) = 1$, there is an m for which $\sum_{i=1}^{m} q(x_i) > 1 - \varepsilon$. Let $q' : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be the distribution given by:

$$q'(x_i) = \begin{cases} q(x_i), & i \in \{1, \ldots, m-1\} \\ \sum_{j=m}^{\infty} q(x_j), & i = m \\ 0, & i \in \{m+1, \ldots\} \end{cases} \tag{8}$$

Finally, notice that q' satisfies:

$$\|q - q'\|_\infty = |q'(x_m) - q(x_m)| = \sum_{i=m+1}^{\infty} q(x_i) < \varepsilon,$$

as desired. □

Theorem 3. *The set of all detailed balanced CRNs is universally approximating.*

Proof. For $d \geq 1$, let $q : \mathbb{Z}^d_{\geq 0} \to [0,1]$ be a distribution, and let $\varepsilon > 0$. By Lemma 2 we know that there exists a distribution $q' : \mathbb{Z}^d_{\geq 0} \to [0,1]$ with finite support that satisfies $\|q - q'\| < \varepsilon$. Consider the CRN $\texttt{Full}(q')$ as given in Construction 1. We know from Lemma 1 that for $\mathcal{V} = \{V_1, \ldots, V_d\}$ the marginal of the limit distribution for initial condition $x_0 = (v_1, e_1)$ satisfies $\pi_{\mathcal{V}}(\cdot \mid x_0) = q'$. Therefore, since q and ε were arbitrary, the set of Full Indexed Network CRNs is universally approximating. □

Remark 5. The proof of the theorem above can be carried out using Constructions 2 or 3 instead of 1. If the support of a distribution is not a cluster one may connect the disconnected components using a finite number of edges and distribute a sufficiently small amount of probability throughout the states along the edges that were added. △

In order for any of the above constructions to produce the appropriate limit distribution it is necessary to provide them with the right initial condition. Suppose instead that we wish to have a CRN whose limit distribution is independent of initial conditions. In particular, the process would be able to reach the support of its limit distribution from any state. Moreover, if the CRN satisfies detailed balance, then every state is reachable from every state due to reactions being reversible, a limit distribution exists [57], it is a product of Poisson distributions [39], and the marginalization onto any subset of species is also a product of Poisson distributions. Therefore, such a model could not be universally approximating if it satisfies detailed balance, and a new construction is needed if one wishes to dispose of the dependence on initial conditions.

3.2. Universal approximation with robust networks

We shift our attention to CRNs that have a unique limit distribution. In particular, for these CRNs, the limit distribution is independent of initial conditions and is robust to an arbitrary single perturbation in the counts of species at any time.

Definition 4. Let $\mathcal{N} = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ be a CRN. We say that $\mathcal{N}$ is *robust* if the limit distribution $\pi(\cdot \mid x_0)$ does not depend upon x_0. If $\mathcal{N}$ is robust, then we denote the limit distribution as $\pi(\cdot)$ and omit the initial condition.

Remark 6. Notice that our definition of robustness corresponds to the definition of an ergodic stochastic processes in the probability theory literature. △

Unlike in the detailed balanced case considered in the previous section, we do not have a general form for the limit distribution of robust CRNs. Instead, we will provide a construction of a robust CRN that can approximate a given "point mass distribution". We will then "embed" this point mass construction in a larger robust CRN that is capable of approximating an arbitrary distribution.

Let $x \in \mathbb{Z}^d_{\geq 0}$. A *point mass distribution* centered at x, denoted by δ_x, is a distribution $\delta_x : \mathbb{Z}^d_{\geq 0} \to [0,1]$ that satisfies $\delta_x(x) = 1$, and, consequently, $\delta_x(x') = 0$ if $x' \neq x$.

Construction 4 *(Point mass network).* Let $d \geq 1$, $x \in \mathbb{Z}^d_{\geq 0}$, and $\varepsilon > 0$. Define the CRN $\texttt{PointMass}(x, \varepsilon) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$\begin{aligned} 0 &\xrightarrow{1} V_i && \text{for } i \in \{1, \ldots, d\} \text{ if } x(i) \neq 0, \\ (x(i)+1)V_i &\xrightarrow{2d/\varepsilon} x(i)V_i && \text{for } i \in \{1, \ldots, d\}, \\ 2V_i &\xrightarrow{1} 0 && \text{for } i \in \{1, \ldots, d\} \text{ if } x(i) = 0. \end{aligned}$$

△

Note that for every $i \in \{1, \ldots, d\}$, exactly one of the two reactions $0 \to V_i$ or $2V_i \to 0$ is present in Construction 4.

Lemma 4. *Let $d \geq 1$, $x \in \mathbb{Z}^d_{\geq 0}$, and $\varepsilon > 0$. Then, $\texttt{PointMass}(x, \varepsilon)$ is robust, with the unique limit distribution π satisfying $\|\pi - \delta_x\|_\infty < \varepsilon$.*

Proof. Notice that $\texttt{PointMass}(x, \varepsilon)$ consists of d decoupled subnetworks, each of which controls the counts of some V_i independently of all the others. We will therefore focus on one such subnetwork and later generalize. Let π_i be the stationary distribution of the subnetwork that keeps track of the counts of V_i. If $x(i) = 0$, then the subnetwork is

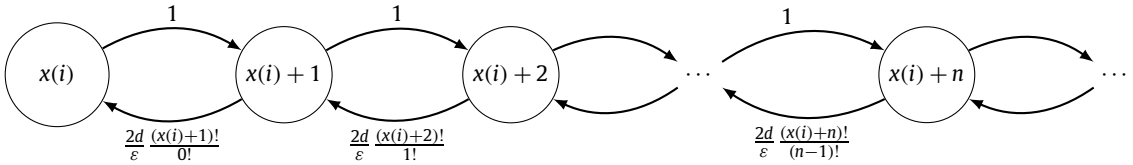
$$V_i \xrightarrow{2d/\varepsilon} 0, \qquad 2V_i \xrightarrow{1} 0,$$

and

$$\pi_i(0 \mid m) = \pi_i(0) = 1 \tag{9}$$

for all $m \geq 0$ and the result is shown.

Otherwise, we have $x(i) > 0$ and the subnetwork is a birth-death process when restricted to the closed set $\Upsilon = \{m \in \mathbb{Z} : m \geq x(i)\}$. Note that the set Υ is almost surely reached from any initial condition because of the reaction $0 \to V_i$. Within Υ, the CTMC for the subnetwork has the transition rates (propensities) shown below, which satisfy detailed balance within Υ:



Hence, we can compute the unique limit distribution explicitly: for any $m, n \geq 0$

$$\pi_i(n + x(i) \mid m) = \pi_i(n + x(i)) = \frac{1}{M_i}\left(\varepsilon^n (2d)^{-n} \prod_{j=1}^{n} \frac{(j-1)!}{(x(i)+j)!}\right), \tag{10}$$

with

$$M_i = \sum_{n=0}^{\infty} \varepsilon^n (2d)^{-n} \prod_{j=1}^{n} \frac{(j-1)!}{(x(i)+j)!}, \tag{11}$$

and $\pi_i(n' \mid m) = 0$, for $n' \leq x(i) - 1$.

Since the subnetworks behave independently, the joint limit probability will simply be the product of the marginal limit probabilities: for any $x', x_0 \in \mathbb{Z}_{\geq 0}$

$$\pi(x' \mid x_0) = \pi(x') = \prod_{i=1}^{d} \pi_i(x'(i) \mid x_0(i)) = \prod_{i=1}^{d} \pi_i(x'(i)). \tag{12}$$

We will now show that $\|\pi - \delta_x\|_\infty < \varepsilon$. Since $\|p - q\|_\infty \leq 2$ for any probability distributions p, q, we can assume that $\varepsilon < 2 \leq 2d$. Note that $|\pi(x) - \delta_x(x)| = 1 - \pi(x)$, and for all $x' \neq x$, $|\pi(x') - \delta_x(x')| = \pi(x')$. Also, notice that:

$$1 - \pi(x) = \sum_{x' \neq x} \pi(x') = \sum_{x' \neq x} |\pi(x')|,$$

so

$$\|\pi - \delta_x\|_\infty = 1 - \pi(x). \tag{13}$$

Utilizing equation (10) in the case $n = 0$ and (12), we deduce that $\pi(x) = 1/M$, where

$$M = \prod_{\substack{1 \leq i \leq d \\ x(i) \neq 0}} M_i.$$

From (11) we have

$$M_i \leq \sum_{n=0}^{\infty} \varepsilon^n (2d)^{-n} = \frac{1}{1 - \varepsilon/(2d)},$$

which implies

$$M \leq \frac{1}{(1-\varepsilon/(2d))^d}.$$

Recall that, in general, for variables a and b we have

$$a^d - b^d = (a-b)(a^{d-1} + a^{d-2}b + \ldots + b^{d-1})$$

so for $a = 1$ and $b = 1 - \varepsilon/(2d)$ we have

$$1 - \left(1 - \frac{\varepsilon}{2d}\right)^d = \frac{\varepsilon}{2d} \sum_{\ell=0}^{d-1} \left(1 - \frac{\varepsilon}{2d}\right)^\ell < \frac{\varepsilon}{2},$$

where the inequality is satisfied because $0 < (1-\varepsilon/(2d))^\ell < 1$ if $\varepsilon < 2d$, and there are d terms in the sum. Therefore, the following is true:

$$1 - \pi(x) = 1 - \frac{1}{M} \leq 1 - \left(1 - \frac{\varepsilon}{2d}\right)^d < \varepsilon,$$

which, when combined with (13), concludes the proof. □

Remark 7. Lemma 4 holds true (with an almost identical proof) if Construction 4 is replaced with

$$0 \xrightarrow{1} V_i \quad \text{for } i \in \{1, \ldots, d\},$$
$$(x(i)+1)V_i \xrightarrow{2d/\varepsilon} x(i)V_i \quad \text{for } i \in \{1, \ldots, d\},$$

where a distinction between null and positive entries of x is not made. However, if such a distinction is made, as in Construction 4, then the approximation of the target limit distribution is more accurate (since the marginal limit distributions of the null entries of x are *exactly* the point mass distribution at 0). Moreover, the reactions of type $2V_i \to 0$ utilized when $x(i) = 0$ provide a faster convergence to the limit distribution, which will be essential to obtain the main result of this paper, which is Theorem 5 (which in turn implies Theorem 6). More details on how the convergence rate is used to prove the result are given in the Appendix. △

Construction 5 *(Point Mass Mixing Network).* Let $d \geq 1$ and $q : \mathbb{Z}^d_{\geq 0} \to [0,1]$ be a distribution with finite support $\{v_1, v_2, \ldots, v_m\}$. Let $\delta > 0$. Define the CRN $\texttt{PointMassMix}(q, \delta) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d, H_1, \ldots, H_m\}$. In this case, each of the hidden species $H_1, \ldots, H_m$ will serve as a catalyst for a network that generates a point mass distribution centered at the corresponding element of the support
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$0 \underset{\delta}{\overset{\delta^2 q(v_i)}{\rightleftharpoons}} H_i, \quad \text{for } i \in \{1, \ldots, m\},$$
$$H_i \xrightarrow{1} H_i + V_j, \quad \text{for } i \in \{1, \ldots, m\}, \text{ if } v_i(j) \neq 0,$$
$$H_i + (v_i(j)+1)V_j \xrightarrow{2d/\delta} H_i + v_i(j)V_j, \quad \text{for } i \in \{1, \ldots, m\},\ j \in \{1, \ldots, d\},$$
$$H_i + 2V_j \xrightarrow{1} H_i \quad \text{for } i \in \{1, \ldots, m\}, \text{ if } v_i(j) = 0.$$ △

Remark 8. If δ is small enough, creation of catalyst species is much slower than destruction, and the probability that there is more than one catalyst species at any time can be made arbitrarily small. Furthermore, once a catalyst species is present, if the destruction rate δ is slow enough, the number of catalysts will remain unchanged long enough for the corresponding Point Mass Network to approach its limit distribution. △

Theorem 5. *Let $d \geq 1$ and let $q : \mathbb{Z}^d_{\geq 0} \to [0,1]$ be a distribution with finite support. Then, (i) for every $\delta > 0$ the CRN $\texttt{PointMassMix}(q, \delta)$ is robust, and (ii) for any $\varepsilon > 0$ there exists $\delta > 0$ such that, for the set of visible species $\mathcal{V} = \{V_1, \ldots, V_d\}$, the marginal of the unique limit distribution of $\texttt{PointMassMix}(q, \delta)$ satisfies $\|\pi_{\mathcal{V}} - q\|_\infty < \varepsilon$.*

The proof of Theorem 5 is given in Appendix A.6. Distributions generated by two Point Mass Networks and a Point Mass Mixing Network are illustrated in Fig. 2.

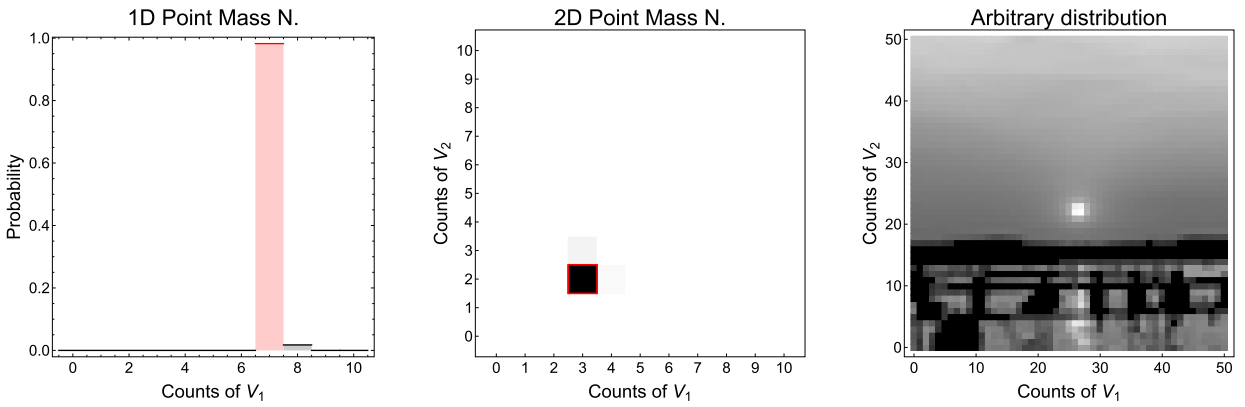


Fig. 2. Examples of robust constructions. In the first panel we see the limit distribution of Construction 4 for a 1-dimensional point mass distribution centered at $x = 7$. Similarly, the second panel shows the limit distribution for Construction 4, this time approximating a 2-dimensional point mass distribution centered at $x = (3, 2)$. The third panel shows an arbitrary 2-dimensional probability distribution. Each pixel in the picture has an associated Point Mass Network as prescribed by Construction 5.

Remark 9. As will be clear in the proof of Theorem 5, the result is based on the fact that the reactions of the form $0 \to H_i$ are much slower than the reactions of the form $H_i \to 0$, which in turn need to occur on a slower time scale than the reactions changing the visible species. Hence, while the ratios of the propensities of the reactions $0 \to H_i$ need careful tuning, the rate constants of other reactions do not need precise regulation. In particular, some rate constants only need to be of different orders of magnitude for the result to hold. This is a desired property, as rate parameters may be difficult to specify with precision in practice. △

We state and prove here an immediate important consequence of Theorem 5.

Theorem 6. *The set of all robust CRNs is universally approximating.*

Proof. Let $d \geq 1$, $q : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ be a distribution, and let $\varepsilon > 0$. By Lemma 2 we know that there exists a distribution $q' : \mathbb{Z}^d_{\geq 0} \to [0, 1]$ with finite support that satisfies $\|q - q'\|_\infty < \varepsilon$. Consider the CRN $\texttt{PointMassMix}(q', \varepsilon - \|q - q'\|_\infty)$. By Theorem 5 we have that for the set of visible species $\mathcal{V} = \{V_1, \ldots, V_d\}$:

$$\|\pi_{\mathcal{V}} - q'\|_\infty < \varepsilon - \|q - q'\|_\infty.$$

Finally, by the triangle inequality we have

$$\|\pi_{\mathcal{V}} - q\|_\infty \leq \|\pi_{\mathcal{V}} - q'\|_\infty + \|q - q'\|_\infty < \varepsilon.$$ □

4. More general constructions

In this section we explore generalizations of the constructions used in the previous sections. Theorem 5 states that by following Construction 5 we can design robust CRNs whose limit distribution approximates a given distribution, with any given accuracy and for any chosen distribution. Hence, the aim of generalizing Constructions 4 and 5 does not reside in exploring a larger set of distributions to approximate, but rather in comparing different CRNs with similar stationary distributions. As an example, let q be the Poisson distribution with mean κ. Using the construction provided above, we can design a robust CRN whose limit distribution is arbitrarily close to q, by truncating q to a finite support Υ as in Lemma 2, and by using Construction 5 to approximate the truncated q. Note that Construction 5 gives a CRN with $|\Upsilon| + 1$ species, $4|\Upsilon|$ reactions, and with high values of the molecularity (i.e. $\max_{y \in \mathcal{C}} \|y\|_1$) and of the logarithm of the rate constants, $|\log \kappa_{y \to y'}|$, to obtain its high accuracy. However, the distribution q can be obtained exactly as the limit distribution of the robust CRN

$$0 \underset{1}{\overset{\kappa}{\rightleftharpoons}} V.$$

Similarly, the marginal stationary distribution q of V is known for the CRN

$$2H_1 \xrightarrow{\kappa_1} H_1, \quad H_1 \underset{\kappa_3}{\overset{\kappa_2}{\rightleftharpoons}} H_2, \quad H_2 \xrightarrow{\kappa_4} H_2 + V, \quad V \xrightarrow{\kappa_5} 0,$$

and it is associated with a confluent hypergeometric equation [58–60], provided that the initial amount of molecules of the species H_1, H_2 is non-zero. The CRN is not robust but it could be made so by adding the reaction $0 \to H_1$ with a low reaction rate, so as to not perturb the stationary distribution too much. Using Construction 5 to approximate q would require more species and more reactions. Hence, natural questions in terms of *complexity* arise: given a distribution q and a parameter $\varepsilon > 0$, what is the minimal size of a robust CRN (in terms of number of species, number of reactions, and magnitude of the rate constants) whose limit distribution π satisfies $\|\pi - q\|_\infty < \varepsilon$?

We begin by formulating a generalization of Construction 4. The generalization, detailed in Construction 6 below, allows us to design robust CRNs whose limit distributions are arbitrarily close to the uniform distributions on d-dimensional intervals (see Proposition 7). The molecularity and the logarithm of the rate constants are similar to those of Construction 5, but the number of species utilized is only d, and the number of reactions is $2d$.

Definition 5. Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. We say that a probability distribution q on $\mathbb{Z}^d_{\geq 0}$ is *uniform* over

$$[a, b] \doteq [a(1), b(1)] \times [a(2), b(2)] \times \cdots \times [a(d), b(d)]$$

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

$$q(x) = \begin{cases} \displaystyle\prod_{i=1}^{d} \frac{1}{b(i) - a(i) + 1} & \text{if } a \leq x \leq b \\ 0 & \text{otherwise.} \end{cases}$$

Remark 10. Note that the point mass distribution at x is a particular case of the uniform distribution, as it can be regarded as the uniform distribution over $[x, x]$. △

Construction 6 *(Uniform Distribution Network).* Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. Let $\delta > 0$ and define the CRN $\texttt{MultiDimUnif}(a, b, \delta) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa^\delta)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$\begin{aligned} 0 &\xrightarrow{1} V_i && \text{for } i \in \{1, \ldots, d\} \text{ if } b(i) \neq 0, \\ (b(i)+1)V_i &\xrightarrow{2d/\delta} a(i)V_i && \text{for } i \in \{1, \ldots, d\}, \\ 2V_i &\xrightarrow{1} 0 && \text{for } i \in \{1, \ldots, d\} \text{ if } b(i) = 0. \end{aligned}$$

△

Remark 11. Note that $\texttt{PointMass}(x, \delta)$ can be regarded as a particular case of Construction 6. In particular, $\texttt{PointMass}(x, \delta) = \texttt{MultiDimUnif}(x, x, \delta)$ for all $x \in \mathbb{Z}^d_{\geq 0}$ and any $\delta > 0$. △

Proposition 7. *Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. Then, for any choice of $\delta > 0$ the CRN $\texttt{MultiDimUnif}(a, b, \delta)$ is robust. Moreover, if we denote by π^δ its limit distribution and by q the uniform distribution over $[a, b]$, we have*

$$\lim_{\delta \to 0} \frac{\|\pi^\delta - q\|_\infty}{\delta} \leq 1.$$

A proof of the proposition is given in Section A.3 in the Appendix, together with a sharper estimate on the distance between π^δ and q.

Remark 12. As will be clear in the proof of Proposition 7, its validity does not depend on a fine tuning of the rate constants of the model, which as already observed in Remark 9 may be difficult to obtain in practice. Instead, the result is based on a time scale separation between the reactions creating and degrading V_i in Construction 6: as long as the reactions creating V_i are slower than those degrading it (when enough molecules are present), a uniform distribution over $[a, b]$ can be successfully approximated. The estimates found in Section A.3, however, may differ for different choices of rate constants. △

The second, and probably more important, generalization we deal with in this section is the following. In Construction 5 we combine different robust CRNs whose limit distributions are close to point mass distributions to obtain a new robust CRN whose limit distribution is close to a mixture of point mass distributions. In general, given a finite number of robust

CRNs with limit distributions π_i, we want to be able to design a new robust CRN that combines them, and whose limit distribution is arbitrarily close to the mixture of the distributions π_i. This can be accomplished under some general conditions, and the precise result is stated in Theorem 8. The assumptions of Theorem 8 have a slightly more technical nature than those of Theorem 5, which is a particular case. Note that by the known theory on detailed balanced CRNs, Lemma 4, and Proposition 7, it follows that robust CRNs whose limit distributions are arbitrarily close to a mixture of Poisson distributions, point mass distributions, and uniform distributions are readily available, and involve less species and reactions than those of Construction 5. The precise statement of the result is given in Theorem 9.

Before stating Theorem 8, we introduce a new construction (which is a generalization of Construction 5) and necessary concepts from the theory of stochastic processes.

Construction 7 *(Mixing Network).* Let $\mathcal{F} = \{\mathcal{N}_1, \dots, \mathcal{N}_m\}$ be a finite ordered set of m CRNs with the same set of species $\{V_1, \dots, V_d\}$. We denote by $\mathcal{R}_i$ the set of reactions of $\mathcal{N}_i$, and for each reaction $y \to y' \in \mathcal{R}_i$ we denote by $\kappa^i_{y\to y'}$ the corresponding rate constant. Let $\zeta \in \mathbb{R}^m_{>0}$ be such that $\sum_{i=1}^m \zeta(i) = 1$, and let $\delta > 0$. Define the CRN $\texttt{Mix}(\mathcal{F}, \zeta, \delta) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \dots, V_d, H_1, \dots, H_m\}$
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$0 \underset{\delta}{\overset{\delta^2\zeta(i)}{\rightleftharpoons}} H_i, \quad \text{for } i \in \{1, \dots, m\},$$

$$H_i + y \xrightarrow{\kappa^i_{y\to y'}} H_i + y', \quad \text{for } i \in \{1, \dots, m\},\ y \to y' \in \mathcal{R}_i. \qquad \triangle$$

Definition 6. Consider a robust CRN with d species, and let $\varepsilon > 0$. We define the *mixing time* at level ε to be the quantity

$$\tau^\varepsilon = \inf\left\{ t \geq 0 : \sup_{x_0 \in \mathbb{Z}^d_{\geq 0}} \|P(\cdot, s \mid x_0) - \pi\|_\infty < \varepsilon \quad \forall s \geq t \right\}.$$

The CRNs $\texttt{PointMass}(x, \delta)$ and $\texttt{MultiDimUnif}(a, b, \delta)$ have finite mixing times τ^ε, for any $\delta, \varepsilon > 0$. This is proven in Lemma A.2 in Section A.2 of the Appendix.

Definition 7. We say that a CRN is *explosive* if there exist an initial condition x_0 and a finite time $t \in \mathbb{R}_{>0}$ such that

$$P\left(\sup_{0\leq s\leq t} \|X(s)\|_\infty = \infty \,\middle|\, x_0 \right) > 0.$$

We say that the CRN is *non-explosive* otherwise.

Theorem 8. *Let $\mathcal{F} = \{\mathcal{N}_1, \dots, \mathcal{N}_m\}$ be a finite ordered set of m CRNs with the same set of species $\mathcal{V} = \{V_1, \dots, V_d\}$. Assume that each CRN $\mathcal{N}_i$ is robust, denote by π_i its limit distribution and by τ_i^ε its mixing time at level $\varepsilon > 0$. Let $\zeta \in \mathbb{R}^m_{>0}$ be such that $\sum_{i=1}^m \zeta(i) = 1$, and assume that for every $\varepsilon > 0$*

$$\max_{1\leq i\leq m} \tau_i^\varepsilon < \infty.$$

Moreover, assume that for every $\delta > 0$ the CRN $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$ is non-explosive. Then, for every $\delta > 0$ the CRN $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$ is robust, and, if we denote by π^δ the limit distribution of $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$, we have

$$\lim_{\delta\to 0} \left\| \pi^\delta_{\mathcal{V}} - \sum_{i=1}^m \zeta(i)\pi_i \right\|_\infty = 0.$$

In order to choose δ such that the distance

$$\left\| \pi^\delta_{\mathcal{V}} - \sum_{i=1}^m \zeta(i)\pi_i \right\|_\infty$$

is smaller than a given quantity, it is important to have upper bounds on the mixing times τ_i^ε. In Appendix B, such bounds are developed for the CRN $\texttt{PointMass}(x, \delta)$. We have seen in Theorem 5 (which is a consequence of Theorem 8) how a family of point mass networks can be used to construct a robust CRN whose limit distribution is arbitrarily close to a given distribution q.

However, the application of Theorem 8 does not need to be limited to point mass networks. Before stating the next result, which is more general than Theorem 5, we introduce a choice of CRN constructions with a product-form Poisson as limit distribution. Note that, due to [13], many different choices are possible. Here we choose one with a finite mixing time, so that Theorem 8 can be applied.

Construction 8. (Product-form Poisson Network) Let $c \in \mathbb{R}^d_{>0}$. Define the CRN $\texttt{ProdPois}(c) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \dots, V_d\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described by:

$$\begin{aligned} 0 &\xrightarrow{c(i)^2} V_i \quad \text{for } i \in \{1, \dots, d\} \\ V_i &\xrightarrow{c(i)} 2V_i \quad \text{for } i \in \{1, \dots, d\}, \\ 2V_i &\xrightarrow{1} 0 \quad \text{for } i \in \{1, \dots, d\}. \end{aligned}$$

△

Theorem 9. *Let $\{\pi_1, \dots, \pi_m\}$ be a family of distributions on $\mathbb{Z}^d_{\geq 0}$ such that there is a partition $\{I_1, I_2, I_3\}$ of $\{1, \dots, m\}$ satisfying the following:*

- *for all $i \in I_1$, π_i is a point mass distribution at some $v_i \in \mathbb{Z}^d_{\geq 0}$;*
- *for all $i \in I_2$, π_i is a uniform distribution over $[a(i), b(i)]$ for some $a(i) \leq b(i) \in \mathbb{Z}^d_{\geq 0}$;*
- *for all $i \in I_3$, π_i is a product-form Poisson distribution with mean $c_i \in \mathbb{R}^d_{>0}$.*

Let $\mathcal{F}^\delta = \{\mathcal{N}_1^\delta, \dots, \mathcal{N}_m^\delta\}$ be a family of CRNs with common set of species $\mathcal{V} = \{V_1, \dots, V_d\}$, such that

- *for all $i \in I_1$, $\mathcal{N}_i^\delta = \texttt{PointMass}(v_i, \delta)$;*
- *for all $i \in I_2$, $\mathcal{N}_i^\delta = \texttt{MultiDimUnif}(a(i), b(i), \delta)$;*
- *for all $i \in I_3$, $\mathcal{N}_i^\delta = \mathcal{N}_i = \texttt{ProdPois}(c_i)$.*

Let $\zeta \in \mathbb{R}^m_{>0}$ with $\sum_{i=1}^m \zeta(i) = 1$. Then, for any $\delta > 0$ the CRN $\texttt{Mix}(\mathcal{F}^\delta, \zeta, \delta)$ is robust. Moreover, if π^δ denotes its limit distribution, then

$$\lim_{\delta \to 0} \left\| \pi^\delta_{\mathcal{V}} - \sum_{i=1}^m \zeta(i) \pi_i \right\|_\infty = 0.$$

The proofs of Theorem 8 and Theorem 9 are given in Sections A.1 and A.5 of the Appendix, respectively. We note that much of the proof relies on time scale separation, hence, similarly to what we noted in Remarks 9 and 12, a precise regulation of all the rate constants is not necessary for the results to hold.

As a final remark, note that in Constructions 4, 6, and 8, the species do not interact (i.e. two different species are never involved in the same reaction). As a consequence, the counts of the different species evolve independently. It is therefore straightforward to obtain CRNs whose limit distribution approximates products of Poisson distributions and uniform distributions. It is indeed sufficient to consider different constructions for different species: consider for example the distribution q on $\mathbb{Z}^2_{\geq 0}$ given by $q(v_1, v_2) = q_1(v_1)q_2(v_2)$, where q_1 is uniform over $\{a, a+1, \dots, b\}$ (say with $1 \leq a \leq b$) and q_2 is Poisson with mean c. Then, q is approximated by the limit distribution of

$$\begin{aligned} &0 \xrightarrow{1} V_1 \\ &(b+1)V_1 \xrightarrow{2/\delta} aV_1 \\ &0 \xrightarrow{c^2} V_2 \\ &V_2 \xrightarrow{c} 2V_2 \\ &2V_2 \xrightarrow{1} 0. \end{aligned}$$

The design of the CRN in Fig. 3 follows this idea. Note however that Theorem 8 is considerably more general, in that the subnetworks $\mathcal{N}_i$ may be arbitrarily complex and may involve arbitrary interactions between the visible species (subject to the other conditions of the theorem). An apparent limitation of the theorem as stated is that the subnetworks $\mathcal{N}_i$ may not have their own hidden species; this is to ensure that when one subnetwork is "turned off" and another is "turned on", we can be assured (by robustness and finite mixing time) that all subnetwork species will be regulated within known bounds

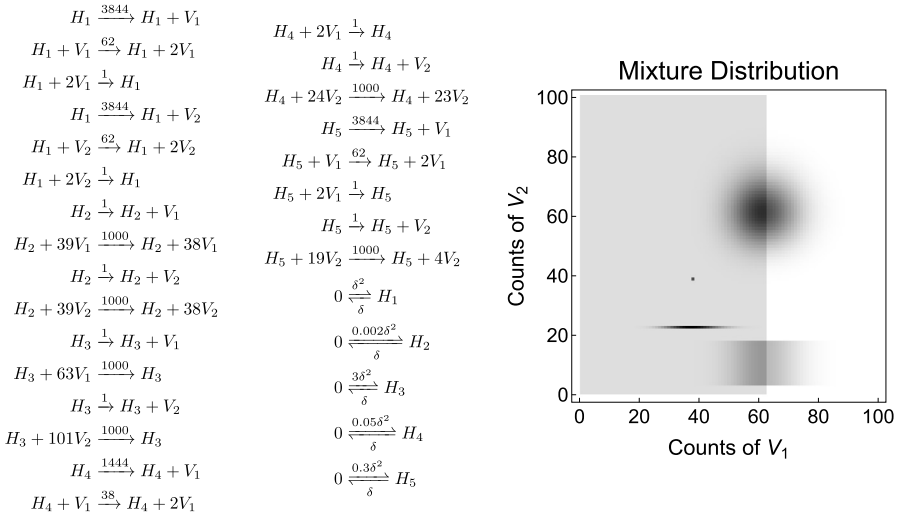


Fig. 3. Example of general mixing. The reaction diagram on the two left columns is an example of general mixing as given by Construction 7 with its target distribution on the right. Notice that whereas the CRN with limit distribution shown in the third panel of Fig. 2 has 6 reactions per pixel, giving a total of $6 \times 50 \times 50 = 1.5 \times 10^4$ reactions, the above distribution is generated using only 34 reactions despite the dimension of its support being larger, namely 100×100. In general, the size of the support of a distribution is not an indication of its complexity in terms of the CRNs that generate them. In this example $\delta = 0.01$.

– this would not be the case if different subnetworks had different sets of hidden species, for example. Since the use of hidden species has been critical for generating interesting marginal distributions, in this work and in prior work [48], it would desirable to also be able to mix distributions that were generated with the help of hidden species. Thankfully, it is straightforward to augment each $\mathcal{N}_i$ with degradation reactions for any hidden species that it was missing, thus obtaining a new set of $\mathcal{N}_i$ each of which use the same set of visible and hidden species and have unchanged marginal distributions on the visible species. Now Theorem 8 can be applied, renaming the subnetworks' visible and hidden species together as the theorem's "visible" species, and adding the theorem's new "hidden" species; the marginal of the resulting mixture distribution onto the subnetworks' original visible species will be as desired.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Proofs and estimates

The aim of this section is to provide a complete proof of Proposition 7, Theorem 5, Theorem 8, and Theorem 9. In particular, we will show how Theorem 5 follows from Theorem 9, which in turn follows from Theorem 8.

From the proof of Theorem 8 it will emerge how, for a fixed $\varepsilon > 0$, the choice of δ such that

$$\left\| \pi^{\delta}_{\mathcal{V}} - \sum_{i=1}^{m} \zeta(i)\pi_i \right\|_{\infty} < \varepsilon$$

depends on the mixing times of the CRNs $\mathcal{N}_1, \ldots, \mathcal{N}_m$. This holds in the particular case of Theorem 5 as well. Hence, to guide the design of networks that approximate a given distribution with accuracy ε, we will provide in Appendix B useful estimates on the mixing times of $\texttt{PointMass}(x, \delta)$.

A.1. Proof of Theorem 8

Proof. Denote by $X^\delta(\cdot)$ the continuous-time Markov chain associated with $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$. Define $X^\delta_{\mathcal{V}}(\cdot)$ and $X^\delta_{\mathcal{H}}(\cdot)$ as the projections of $X^\delta(\cdot)$ onto the components of the species in $\mathcal{V} = \{V_1, \ldots, V_d\}$ and $\mathcal{H} = \{H_1, \ldots, H_m\}$, respectively. Moreover, for convenience we will write a state of $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$ as

$$(v, h) \in \mathbb{Z}^{d+m}_{\geq 0},$$

with v and h indicating the components of the species in $\mathcal{V}$ and $\mathcal{H}$, respectively.

Note that $X^\delta_{\mathcal{H}}(\cdot)$ is a continuous-time Markov chain itself, and is distributed according to the subnetwork of $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$, which we will denote by $\mathcal{N}_{\mathcal{H}} = (\mathcal{H}, \mathcal{C}_{\mathcal{H}}, \mathcal{R}_{\mathcal{H}})$, given by

$$0 \underset{\delta}{\overset{\zeta(i)\delta^2}{\rightleftharpoons}} H_i \quad \text{for } 1 \leq i \leq m. \tag{A.1}$$

$\mathcal{N}_{\mathcal{H}}$ is detailed balanced with detailed balanced equilibrium $\delta\zeta$, and its state space is irreducible. It follows that $\mathcal{N}_{\mathcal{H}}$ admits a unique stationary distribution $\pi^\delta_{\mathcal{H}}$ defined by

$$\pi^\delta_{\mathcal{H}}(h) = e^{-\delta} \prod_{i=1}^{m} \frac{(\delta\zeta(i))^{h_i}}{h_i!} \tag{A.2}$$

for all $h \in \mathbb{Z}^m_{\geq 0}$.

Consider a vector $v \in \mathbb{Z}^d_{\geq 0}$ that is a positive recurrent state for at least one reaction system $\mathcal{N}_i$, $i \in \{1, \ldots, d\}$. Moreover, denote by $\sigma^\delta(v)$ the time of the first visit of $X^\delta(\cdot)$ to $(v, 0)$, defined as

$$\sigma^\delta(v) = \inf\{t \geq 0 : X^\delta(t) = (v, 0) \text{ and } X^\delta(s) \neq (v, 0) \text{ for some } 0 \leq s < t\}.$$

We prove that $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$ is robust by proving that for any $(v_0, h_0) \in \mathbb{Z}^{d+m}_{\geq 0}$

$$E[\sigma^\delta(v) \mid X^\delta(0) = (v_0, h_0)] < \infty. \tag{A.3}$$

Indeed, if (A.3) holds, then $(v, 0)$ is positive recurrent by definition, hence there exists a stationary distribution π^δ whose support coincides with the closed irreducible component that contains $(v, 0)$, and such stationary distribution is unique. Moreover, a unique closed irreducible set exists and it is eventually reached with probability 1 from all states of $\mathbb{Z}^{d+m}_{\geq 0}$, otherwise (A.3) could not hold.

We need to prove (A.3). Let $e_i \in \mathbb{Z}^m_{\geq 0}$ be the ith vector of the canonical basis, namely the vector with 1 in the ith entry and 0 in the other components. We have that (A.1) is positive recurrent and irreducible, and that $X^\delta(\cdot)$ is non-explosive and therefore well-defined for all times greater than 0. Hence, given $X^\delta(0) = (v_0, h_0)$, the chain will satisfy $X^\delta_{\mathcal{H}}(t) = e_i$ after a time with finite expectation. Assume $X^\delta_{\mathcal{H}}(t) = e_i$, and let u be the time until the next change in copy-numbers of the species $\{H_1, \ldots, H_m\}$. Then, u is exponentially distributed with rate $\delta + \delta^2$, independently of the value of $X^\delta_{\mathcal{V}}(t)$. It follows that there is a positive probability $\varphi_i(\delta, v)$ that $u > \tau^{\pi_i(v)/2}$, where

$$\tau^\eta = \max_{1 \leq i \leq m} \tau^\eta_i$$

is finite by assumption for all $\eta > 0$. Moreover, by definition of mixing times,

$$P\left(X^\delta(t+u) = (v, 0) \;\middle|\; X^\delta_{\mathcal{H}}(t) = e_i, u > \tau^{\pi_i(v)/2}, X^\delta_{\mathcal{V}}(t) = v'\right) \geq \frac{\pi_i(v)}{2} > 0,$$

independently of $v' \in \mathbb{Z}^d_{\geq 0}$. Hence, the number of times the chain satisfies $X^\delta_{\mathcal{H}}(t) = e_i$ before visiting $(v, 0)$ is stochastically bounded from above by a geometric random variable with mean $\left(\varphi_i(\delta, v)\pi_i(v)/2\right)^{-1}$. Moreover, the expected time between two visits of (A.1) to e_i is finite. Hence, (A.3) holds.

For all $\delta > 0$ we have

$$\pi^\delta_{\mathcal{V}}(v) - \pi^\delta(v, 0) = \sum_{h \in \mathbb{Z}^m_{\geq 0} \setminus \{0\}} \pi^\delta(v, h),$$

which implies

$$0 \leq \pi^{\delta}_{\mathcal{V}}(v) - \pi^{\delta}(v,0) \leq \sum_{h \in \mathbb{Z}^m_{\geq 0} \setminus \{0\}} \pi^{\delta}_{\mathcal{H}}(h) = 1 - e^{-\delta}. \tag{A.4}$$

For any $v \in \mathbb{Z}^d_{\geq 0}$, let $Y^{\delta}_v(t)$ be the time $X^{\delta}(\cdot)$ spends in state $(v,0) \in \mathbb{Z}^{d+m}_{\geq 0}$ by time t, that is

$$Y^{\delta}_v(t) = \int_0^t \mathbb{1}_{\{(v,0)\}}(X^{\delta}(s))ds.$$

By classical Markov chain theory and by robustness of $\texttt{Mix}(\mathcal{F}, \zeta, \delta)$ we have that

$$\lim_{t\to\infty} \frac{Y^{\delta}_v(t)}{t} = \pi^{\delta}(v,0)$$

almost surely, for any initial condition $X^{\delta}(0)$.

We now assume that for any $v \in \mathbb{Z}^d_{\geq 0}$ and any $\varepsilon > 0$, there exists $\delta^{\varepsilon,v}$ such that if $\delta \leq \delta^{\varepsilon,v}$ then

$$\left| \lim_{t\to\infty} \frac{Y^{\delta}_v(t)}{t} - \sum_{i=1}^m \zeta(i)\pi_i(v) \right| < \frac{3}{4}\varepsilon \tag{A.5}$$

almost surely, independently on the initial condition $X^{\delta}(0)$. For δ small enough, both $\delta \leq \delta^{\varepsilon,v}$ and $1 - e^{-\delta} < \varepsilon/4$ hold. Hence, by (A.4), (A.5), and the triangular inequality

$$\left| \pi^{\delta}_{\mathcal{V}}(v) - \sum_{i=1}^m \zeta(i)\pi_i(v) \right| < \varepsilon.$$

For any $\varepsilon > 0$, there exists a compact set $K^{\varepsilon} \subset \mathbb{Z}^d_{\geq 0}$ such that for any $v \notin K^{\varepsilon}$

$$\pi^{\delta}_{\mathcal{V}}(v) + \sum_{i=1}^m \zeta(i)\pi_i(v) < \varepsilon.$$

Since K^{ε} is compact, the minimum $\delta^{\varepsilon} = \min_{v\in K^{\varepsilon}} \delta^{\varepsilon,v}$ exists and is positive. Hence, for all $v \in \mathbb{Z}^d_{\geq 0}$ and for all δ small enough such that $\delta \leq \delta^{\varepsilon}$ and $1 - e^{-\delta} < \varepsilon/4$, we have

$$\left| \pi^{\delta}_{\mathcal{V}}(v) - \sum_{i=1}^m \zeta(i)\pi_i(v) \right| < \begin{cases} \varepsilon & \text{if } v \in K^{\varepsilon} \\ \pi^{\delta}_{\mathcal{V}}(v) + \sum_{i=1}^m \zeta(i)\pi_i(v) < \varepsilon & \text{if } v \notin K^{\varepsilon} \end{cases}$$

and the proof is concluded. Hence, it suffices to show (A.5).

Let $t_0 = 0$ and define recursively

$$t_j = \inf\{t \geq t_{j-1} : X^{\delta}_{\mathcal{H}}(t) = 0 \text{ and } X^{\delta}_{\mathcal{H}}(s) \neq 0 \text{ for some } t_{j-1} < s < t\}$$

for $j \geq 1$. That is, t_j with $j \geq 1$ is the time of the jth visit to a state with no molecules of species $H_1, \ldots, H_m$.

For any $j \geq 1$, let s_j denote the holding time in the state with no molecules of $\{H_1, \ldots, H_m\}$, measured from time t_j. Then, s_j is exponentially distributed with rate

$$\sum_{y \to y' \in \mathcal{R}_{\mathcal{H}}} \lambda_{y\to y'}(0) = \sum_{i=1}^m \delta^2 \zeta(i) = \delta^2.$$

It follows from classical renewal theory and from (A.2) that for any $j \geq 1$

$$E[t_{j+1} - t_j] = \frac{1}{\pi^{\delta}_{\mathcal{H}}(0) \sum_{y\to y' \in \mathcal{R}_{\mathcal{H}}} \lambda_{y\to y'}(0)} = \frac{e^{\delta}}{\delta^2}.$$

It follows that, with probability 1, $\lim_{j\to\infty} t_j = \infty$. This in turn implies that almost surely

$$\lim_{t\to\infty} \frac{Y^{\delta}_v(t)}{t} = \lim_{j\to\infty} \frac{Y^{\delta}_v(t_j)}{t_j}.$$

For all $j \geq 1$, independently of the value of $X^{\delta}_{\mathcal{V}}(t_j)$, a molecule of H_i is produced at time $t_j + s_j$ with probability $\zeta(i)$. Let u_j denote the molecule lifetime. Note that with probability

$$\frac{\delta}{\delta+\delta^2}=\frac{1}{1+\delta}$$

the molecule of H_i is degraded before another molecule of a species in $\mathcal{H}$ is produced. For convenience, denote this event by A_j. Given that A_j occurs, u_j is the minimum between the degradation of the H_i molecule (exponentially distributed with rate δ) and the time until the production of another molecule of a species in $\mathcal{H}$ (exponentially distributed with rate δ^2). Hence, given that A_j occurs, u_j is exponentially distributed with rate $\delta+\delta^2$. It follows that

$$P(u_j > \tau^{\varepsilon/2} \mid A_j) = e^{-(\delta+\delta^2)\tau^{\varepsilon/2}}.$$

Given that $u_j > \tau^{\varepsilon/2}$, all the reactions of the system $\mathcal{N}_i$ can take place for a time longer than $\tau^{\varepsilon/2}$, and these are the only reactions that can occur. Thus, by the definition of mixing times,

$$\pi_i(v)-\frac{\varepsilon}{2} \le P\left(X^\delta_{\mathcal{V}}(t_{j+1})=v \;\middle|\; X^\delta_{\mathcal{H}}(t_j+s_j)=H_i, A_j, u_j>\tau^{\varepsilon/2}, X^\delta_{\mathcal{V}}(t_j)=v'\right) \le \pi_i(v)+\frac{\varepsilon}{2}$$

for all $v, v' \in \mathbb{Z}^d_{\ge 0}$. Note that the bounds do not depend on $X^\delta_{\mathcal{V}}(t_j)=v'$. In conclusion, by conditioning and by using the probabilities of the conditioning events calculated above, we obtain

$$\begin{aligned} P\left(X^\delta_{\mathcal{V}}(t_{j+1})=v \mid X^\delta_{\mathcal{V}}(t_j)=v'\right) &\ge \sum_{i=1}^{m}\left(\pi_i(v)-\frac{\varepsilon}{2}\right)\zeta(i)\frac{1}{1+\delta}e^{-(\delta+\delta^2)\tau^{\varepsilon/2}} \\ &\doteq b^\delta(v) \qquad \text{(A.6)} \\ P\left(X^\delta_{\mathcal{V}}(t_{j+1})=v \mid X^\delta_{\mathcal{V}}(t_j)=v'\right) &\le \sum_{i=1}^{m}\left(\pi_i(v)+\frac{\varepsilon}{2}\right)\zeta(i)\frac{1}{1+\delta}e^{-(\delta+\delta^2)\tau^{\varepsilon/2}}+\frac{\delta}{1+\delta}+\frac{1}{1+\delta}\left(1-e^{-(\delta+\delta^2)\tau^{\varepsilon/2}}\right) \\ &\doteq B^\delta(v). \qquad \text{(A.7)} \end{aligned}$$

The sequence $D^\delta(j)=X^\delta_{\mathcal{V}}(t_j)$ for $j\in\mathbb{Z}_{\ge 0}$ defines a discrete time Markov chain. Since $X^\delta(\cdot)$ is robust, $D^\delta(\cdot)$ has a unique closed irreducible set Υ, and for any $v'\in\mathbb{Z}^d_{\ge 0}$ we have

$$\lim_{j\to\infty} P(D^\delta(j)\in\Upsilon \mid D^\delta(0)=v')=1.$$

Moreover, (A.6) and (A.7) give a lower and upper bound on the transition probabilities to a state v from a state v', which does not depend on v'. Hence, for small enough ε and small enough δ such that $b^\delta(v)>0$, $D^\delta(\cdot)$ restricted to Υ is aperiodic and positive recurrent. It follows that there exists a limit distribution γ such that for any $v, v'\in\mathbb{Z}^d_{\ge 0}$

$$\lim_{j\to\infty} P(D^\delta(j)=v \mid D^\delta(0)=v')=\gamma(v),$$

independently of v'. Furthermore, since the argument of the limit is bounded from below by $b^\delta(v)$ and from above by $B^\delta(v)$, we have

$$b^\delta(v)\le\gamma(v)\le B^\delta(v).$$

If $W_j(v)$ is the number of visits of $D^\delta(\cdot)$ to v up to step j (included), we have that with probability 1 $\lim_{j\to\infty} W_j(v)=\infty$, and

$$\lim_{j\to\infty}\frac{W_j(v)}{j}=\gamma(v).$$

By the strong law of large numbers, we have that almost surely

$$\begin{aligned} \lim_{j\to\infty}\frac{Y^\delta_v(t_j)}{t_j} &= \lim_{j\to\infty}\frac{Y^\delta_v(t_1)}{t_j}+\lim_{j\to\infty}\frac{t_j-t_1}{t_j}\cdot\frac{Y^\delta_v(t_j)-Y^\delta_v(t_1)}{t_j-t_1} \\ &= 0+\lim_{j\to\infty}\frac{t_j-t_1}{t_j}\cdot\frac{\sum_{i=1}^{W_{j-1}(v)}s_i}{\sum_{i=2}^{j}(t_i-t_{i-1})} \\ &= \lim_{j\to\infty}\frac{t_j-t_1}{t_j}\cdot\frac{\sum_{i=1}^{W_{j-1}(v)}s_i}{W_{j-1}(v)}\cdot\frac{W_{j-1}(v)}{j-1}\cdot\frac{j-1}{\sum_{i=2}^{j}(t_i-t_{i-1})} \\ &= 1\cdot\frac{1}{\delta^2}\cdot\gamma(x)\cdot\frac{\delta^2}{e^\delta}=\gamma(x)e^{-\delta}. \end{aligned}$$

Hence,

$$e^{-\delta} b^{\delta}(v) \leq \lim_{j\to\infty} \frac{Y_v^{\delta}(t_j)}{t_j} \leq e^{-\delta} B^{\delta}(v).$$

If δ is small enough,

$$e^{-\delta} b^{\delta}(v) \geq \sum_{i=1}^{m} \Big(\zeta(i)\pi_i(v)\Big) - \frac{3}{4}\varepsilon$$
$$e^{-\delta} B^{\delta}(v) \leq \sum_{i=1}^{m} \Big(\zeta(i)\pi_i(v)\Big) + \frac{3}{4}\varepsilon,$$

which proves (A.5) and concludes the proof. □

A.2. Analysis of Constructions 4 and 6

In this section, we study the limit distributions and the mixing times of a construction that generalize slightly Constructions 4 and 6, by allowing for a more general choice of rate constants. We also give explicit bounds on the distance between the uniform distribution and the limit distribution of the construction presented here. The bounds provided here are in general sharper than those presented in the main text.

Construction 6′ *(General Uniform Distribution Network).* Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. Define the CRN $\texttt{MultiDimUnif}'(a, b, \kappa) = (\mathcal{S}, \mathcal{C}, \mathcal{R}, \kappa)$ as follows.

- The set of species is $\mathcal{S} = \{V_1, \ldots, V_d\}$.
- The sets of complexes, reactions, and rate constants are given by the reaction diagram described below:

$$\begin{aligned} 0 &\xrightarrow{\kappa_1^i} V_i \quad \text{for } i \in \{1,\ldots,d\} \text{ if } b(i) \neq 0,\\ (b(i)+1)V_i &\xrightarrow{\kappa_2^i} a(i)V_i \quad \text{for } i \in \{1,\ldots,d\},\\ 2V_i &\xrightarrow{\kappa_3^i} 0 \quad \text{for } i \in \{1,\ldots,d\} \text{ if } b(i) = 0. \end{aligned}$$

△

In what follows, we will denote by $X^{\kappa}(\cdot)$ the continuous-time Markov chain associated with the CRN $\texttt{MultiDimUnif}'(a, b, \kappa)$, and we will use the notation $r_i = b(i) - a(i) + 1$ for all $i \in \{1, \ldots, d\}$. Further, we will denote by $X^{\kappa}(\cdot, i)$ the ith component of $X^{\kappa}(\cdot)$. Note that the components $X^{\kappa}(\cdot, i)$ are distributed as independent continuous-time Markov chains. In particular, $X^{\kappa}(\cdot, i)$ is distributed as the process associated with the subnetwork of $\texttt{MultiDimUnif}'(a, b, \kappa)$ given by the reactions changing the species V_i. We will denote by $A^{\kappa,i}$ the generator of $X^{\kappa}(\cdot, i)$ (see [61]). We define $\sigma^{\kappa,i}$ and $\sigma^{\kappa,i}_{v(i)}$ as the hitting times of $[a(i), b(i)]$ and of $v(i) \in \mathbb{Z}_{\geq 0}$, respectively:

$$\sigma^{\kappa,i} = \inf\{t > 0 : X^{\kappa}(t, i) \in [a(i), b(i)]\},$$
$$\sigma^{\kappa,i}_{v(i)} = \min\{t > 0 : X^{\kappa}(t, i) = v(i) \text{ and } X^{\kappa}(s, i) \neq v(i) \text{ for some } s < t\}.$$

Finally, we denote by $E^{\kappa,i}_{v_0(i)}[\cdot]$ the expectation with respect to the distribution of $X^{\kappa}(\cdot, i)$ given $X^{\kappa}(0, i) = v_0(i)$

Lemma A.1. *Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. Consider the function $L(\cdot)$, defined as $L(v(i)) = v(i)$ for all $v(i) \in \mathbb{Z}_{\geq 0}$. Then, $\lim_{v(i)\to\infty} L(v(i)) = \infty$. Moreover, for any $\kappa > 0$ and any $i \in \{1, \ldots, d\}$, there exists $\alpha_i \in \mathbb{R}_{>0}$ and a compact set $K_i \subset \mathbb{Z}_{\geq 0}$ such that*

$$A^{\kappa,i} L(v(i)) \leq -\alpha_i L^2(v(i)) \quad \text{for all } v(i) \notin K_i.$$

Proof. Clearly, $\lim_{v(i)\to\infty} L(v(i)) = \infty$. Now assume that $b(i) = 0$. Then, for all $v(i) \geq 2$ we have

$$A^{\kappa,i} L(v(i)) = -\kappa_2^i v(i) - 2\kappa_3^i v(i)(v(i) - 1),$$

which implies that for $v(i)$ big enough $A^{\kappa,i} L(v(i)) \leq -\kappa_3^i v(i)^2 = -\kappa_3^i L^2(v(i))$, and the result holds.

Assume that $b(i) \neq 0$. For all $v(i) \geq b(i) + 1$ we have

$$A^{\kappa,i}L(v(i)) = \kappa_1^i - \kappa_2^i \frac{v(i)!}{(v(i) - b(i) - 1)!},$$

which is smaller than or equal to $-\frac{\kappa_2^i}{2}L^2(v(i))$ for $v(i)$ large enough. The proof is then concluded. □

Lemma A.2. *Let $d \geq 1$ and let $a, b \in \mathbb{Z}^d_{\geq 0}$ be such that $a \leq b$. For any $\kappa > 0$, $\texttt{MultiDimUnif}'(a, b, \kappa)$ is robust and the support of its limit distribution is*

$$\Theta = \{v \in \mathbb{Z}^d_{\geq 0} : v \geq a \quad \text{and} \quad v(i) = 0 \quad \text{if} \quad b(i) = 0\} = \left(\bigtimes_{\substack{1 \leq i \leq d \\ b(i)=0}} \{0\} \right) \times \left(\bigtimes_{\substack{1 \leq i \leq d \\ b(i)\neq 0}} \{v(i) : v(i) \geq a(i)\} \right).$$

Moreover, for any $\kappa > 0$ and any $\varepsilon > 0$, the mixing time of $\texttt{MultiDimUnif}'(a, b, \kappa)$ at level ε is finite.

Proof. In order to prove the existence of a unique limit distribution and argue that the mixing times are finite, we will make use of Foster-Lyapunov criteria discussed by Meyn and Tweedy in [62]. In particular, we will use the concept of super Lyapunov function, developed by Athreya, Kolba, and Mattingly in [63], to which Appendix C is devoted.

Since the components $X^\kappa(\cdot, i)$ are distributed as independent continuous-time Markov chains, in order to prove robustness of $X^\kappa(\cdot)$ it is sufficient to prove it for all its components separately. The same holds for the description of the irreducible closed sets of $X^\kappa(\cdot)$, which are necessarily Cartesian products of closed and irreducible sets of the components $X^\kappa(\cdot, i)$. Finally, the mixing times of $X^\kappa(\cdot)$ at level $\varepsilon > 0$ are finite for all $\varepsilon > 0$, if and only if the mixing times $\tau^{\varepsilon,i}$ of $X^\kappa(\cdot, i)$ at level $\varepsilon > 0$ are finite for all $\varepsilon > 0$ and for all $i \in \{1, \ldots, d\}$.

If $b(i) = 0$, then the process $X^\kappa(\cdot, i)$ is the continuous-time Markov chain associated with the CRN with reaction diagram

$$V_i \xrightarrow{\kappa_2^i} 0, \qquad 2V_i \xrightarrow{\kappa_3^i} 0.$$

As such, $X^\kappa(\cdot, i)$ can only decrease. It follows that the set $\{0\}$ is closed and irreducible for $X^\kappa(\cdot, i)$. Moreover, it is the only closed and irreducible set, since the reaction $V_i \to 0$ can always take place as long as there is at least one molecule of V_i.

If $b(i) \neq 0$, then the process $X^\kappa(\cdot, i)$ is the continuous-time Markov chain associated with the CRN with reaction diagram

$$0 \xrightarrow{\kappa_1^i} V_i, \qquad (b(i) + 1)V_i \xrightarrow{\kappa_2^i} a(i)V_i.$$

Hence, the process $X^\kappa(\cdot, i)$ can always increase by 1, and decrease by r_i if and only if at least $b(i) + 1 = r_i + a(i)$ molecules of V_i are available. Hence, the set $\Theta(i) = \{v(i) \in \mathbb{Z}_{\geq 0} \mid v(i) \geq a(i)\}$ is the only closed and irreducible set of $X^\kappa(\cdot, i)$.

In both cases, we can conclude that $X^\kappa(\cdot, i)$ is robust by showing that a unique limit distribution exists. This, together with the fact that the mixing times $\tau^{\varepsilon,i}$ are finite, follows from Lemma A.1 and Theorem C.2. □

In Lemma A.2 we proved that $X^\kappa(\cdot)$ is robust, which holds if and only if each process $X^\kappa(\cdot, i)$ is robust. We denote by π^κ the unique limit distribution of $X^\kappa(\cdot)$, and by $\pi^{\kappa,i}$ the unique limit distribution of $X^\kappa(\cdot, i)$. Since the components of $X^\kappa(\cdot)$ are independent, it follows that

$$\pi^\kappa(v) = \prod_{i=1}^d \pi^{\kappa,i}(v(i)) \quad \text{for all } v \in \mathbb{Z}_{\geq 0}.$$

Hence, in order to study π^κ it is sufficient to study the distributions $\pi^{\kappa,i}$, for $i \in \{1, \ldots, d\}$, and this is what we will do.

Lemma A.3. *Let $i \in \{1, \ldots, d\}$ with $b(i) = 0$. Then, $\pi^{\kappa,i}$ is the point mass distribution at 0.*

Proof. The result follows from the fact that $X^\kappa(\cdot, i)$ is robust, and $\{0\}$ is its only closed irreducible set, as proven in Lemma A.2. □

Lemma A.4. *Let $i \in \{1, \ldots, d\}$ with $b(i) \geq 1$. Let $v_0(i) \geq b(i) + 1$. Assume that*

$$\kappa_2^i r_i (b(i) + 1)! > \kappa_1^i. \tag{A.8}$$

Then

$$E^{\kappa,i}_{v_0(i)}[\sigma^{\kappa,i}] \leq \frac{v_0(i)}{\kappa_2^i r_i (b(i) + 1)! - \kappa_1^i}.$$

Proof. Let $L(v(i)) = v(i)$ for all $v(i) \in \mathbb{Z}_{\geq 0}$. By Dynkin's formula we have that for all $t > o$

$$\begin{aligned} E^{\kappa,i}_{v_0(i)}[L(X^\kappa(\min\{t,\sigma^{\kappa,i}\},i))] &= L(v_0(i)) + E^{\kappa,i}_{v_0(i)}\left[\int_0^{\min\{t,\sigma^{\kappa,i}\}} A^{\kappa,i}L(X^\kappa(s,i))ds\right] \\ &\leq v_0(i) + E^{\kappa,i}_{v_0(i)}\left[\int_0^{\min\{t,\sigma^{\kappa,i}\}} (\kappa_1^i - \kappa_2^i r_i(b(i)+1)!)ds\right] \\ &= v_0(i) + (\kappa_1^i - \kappa_2^i r_i(b(i)+1)!)E^{\kappa,i}_{v_0(i)}[\min\{t,\sigma^{\kappa,i}\}]. \end{aligned}$$

By (A.8) and since for all times $t > 0$ we have $E^{\kappa,i}_{v_0(i)}[L(X^\kappa(\min\{t,\sigma^{\kappa,i}\},i))] \geq 0$, we may conclude

$$E^{\kappa,i}_{v_0(i)}[\min\{t,\sigma^{\kappa,i}\}] \leq \frac{x_0(i)}{\kappa_2^i r_i(b(i)+1)! - \kappa_1^i}.$$

We may use the monotone convergence theorem to conclude the proof. □

Lemma A.5. *Let $i \in \{1,\dots,d\}$ with $b(i) \geq 1$, and assume (A.8) holds. Then,*

$$0 \leq \frac{1}{r_i} - \pi^{\kappa,i}(b(i)) \leq \frac{1}{(r_i)^2} \cdot \frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)! + \kappa_1^i}\left(\frac{b(i)+2}{\kappa_2^i r_i(b(i)+1)! - \kappa_1^i} + \frac{b(i)-a(i)}{\kappa_1^i}\right).$$

Proof. By classical theory on continuous-time Markov chains it is known that

$$\pi^{\kappa,i}(b(i)) = \frac{1/\kappa_1^i}{E^{\kappa,i}_{b(i)}[\sigma^{\kappa,i}_{b(i)}]},$$

where $1/\kappa_1^i$ is the expected holding time of $X^\kappa(\cdot,i)$ in the state $b(i)$. By conditioning on the first two steps, we have

$$\begin{aligned} E^{\kappa,i}_{b(i)}[\sigma^{\kappa,i}_{b(i)}] &= \frac{1}{\kappa_1^i} + E^{\kappa,i}_{b(i)+1}[\sigma^{\kappa,i}_{b(i)}] \\ &= \frac{1}{\kappa_1^i} + \frac{1}{\kappa_2^i(b(i)+1)! + \kappa_1^i} + \frac{\kappa_2^i(b(i)+1)!}{\kappa_2^i(b(i)+1)! + \kappa_1^i}E^{\kappa,i}_{a(i)}[\sigma^{\kappa,i}_{b(i)}] + \frac{\kappa_1^i}{\kappa_2^i(b(i)+1)! + \kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}] \\ &= \frac{1}{\kappa_1^i} + \frac{1}{\kappa_2^i(b(i)+1)! + \kappa_1^i} + \frac{\kappa_2^i(b(i)+1)!}{\kappa_2^i(b(i)+1)! + \kappa_1^i} \cdot \frac{b(i)-a(i)}{\kappa_1^i} + \frac{\kappa_1^i}{\kappa_2^i(b(i)+1)! + \kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}] \\ &= \frac{r_i}{\kappa_1^i} + \frac{\kappa_1^i}{\kappa_2^i(b(i)+1)! + \kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]. \end{aligned}$$

Hence,

$$\begin{aligned} \frac{1}{r_i} - \pi^{\kappa,i}(b(i)) &= \frac{1}{r_i}\left(1 - \frac{r_i}{\kappa_1^i E^{\kappa,i}_{b(i)}[\sigma^{\kappa,i}_{b(i)}]}\right) = \frac{1}{r_i}\left(\frac{\frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)!+\kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]}{r_i + \frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)!+\kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]}\right) \\ &= \frac{1}{(r_i)^2}\left(\frac{\frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)!+\kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]}{1 + \frac{(\kappa_1^i)^2}{r_i\kappa_2^i(b(i)+1)!+r_i\kappa_1^i}E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]}\right) \leq \frac{1}{(r_i)^2} \cdot \frac{(\kappa_1^i)^2 E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}]}{\kappa_2^i(b(i)+1)! + \kappa_1^i}. \end{aligned}$$

From the first two equalities we have $\frac{1}{r_i} - \pi^{\kappa,i}(b(i)) \geq 0$, which is the first part of the lemma. Moreover,

$$E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}_{b(i)}] \leq E^{\kappa,i}_{b(i)+2}[\sigma^{\kappa,i}] + \frac{b(i)-a(i)}{k_1^i},$$

where the second term bounds from above the expected time to reach $b(i)$ from within the set $\{a(i),\dots,b(i)\}$. Hence, by Lemma A.4,

$$\frac{1}{r_i} - \pi^{\kappa,i}(b(i)) \leq \frac{1}{(r_i)^2} \cdot \frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)! + \kappa_1^i} \left(\frac{b(i)+2}{\kappa_2^i r_i (b(i)+1)! - \kappa_1^i} + \frac{b(i)-a(i)}{\kappa_1^i} \right),$$

which concludes the proof. □

Lemma A.6. *Let $i \in \{1, \dots, d\}$ with $b(i) \geq 1$, and assume (A.8) holds. Let $w \in \mathbb{Z}_{\geq 0}$ such that $w \in [2, r_i]$. Then,*

$$\pi^{\kappa,i}(b(i)+w) \leq \left(\frac{\kappa_1^i}{\kappa_2^i} \right)^w C(i,w),$$

where

$$C(i,w) = \frac{\prod_{j=1}^w (j-1)!}{\prod_{j=1}^w (j+b(i))!} \leq \frac{1}{(b(i)+1)!(b(i)+2)!}.$$

Proof. To simplify the notation, denote

$$\phi_i(v(i)) = \frac{v(i)!}{(v(i)-b(i)-1)!}$$

for all integers $v(i)$ that are greater than or equal to $b(i)+1$, so that the transition rate from $v(i)$ to $v(i)-r_i$ is given by $\kappa_2^i \phi_i(v(i))$. Then, by using again classical Markov chain theory we have

$$\pi^{\kappa,i}(b(i)+w) = \frac{1}{\kappa_2^i \phi_i(b(i)+w) + \kappa_1^i} \cdot \frac{1}{E^{\kappa,i}_{b(i)+w}[\sigma^{\kappa,i}_{b(i)+w}]}, \tag{A.9}$$

where the first factor is the expectation of the holding time of $X^\kappa(\cdot, i)$ in the state $b(i)+w$. By performing first step analysis on $E^{\kappa,i}_{b(i)+w}[\sigma^{\kappa,i}_{b(i)+w}]$, we have

$$\begin{aligned} E^{\kappa,i}_{b(i)+w}[\sigma^{\kappa,i}_{b(i)+y}] &= \frac{\kappa_2^i \phi_i(b(i)+w)}{\kappa_2^i \phi_i(b(i)+w) + \kappa_1^i} E^{\kappa,i}_{a(i)+w-1}[\sigma^{\kappa,i}_{b(i)+w}] + \frac{\kappa_1^i}{\kappa_2^i \phi_i(b(i)+w) + \kappa_1^i} E^{\kappa,i}_{b(i)+w+1}[\sigma^{\kappa,i}_{b(i)+w}] \\ &\geq \frac{\kappa_2^i \phi_i(b(i)+w)}{\kappa_2^i \phi_i(b(i)+w) + \kappa_1^i} E^{\kappa,i}_{a(i)+w-1}[\sigma^{\kappa,i}_{b(i)+w}]. \end{aligned} \tag{A.10}$$

We will then study $E_{a(i)+w-1}[\sigma^{\kappa,i}_{b(i)+w}]$. Note that $a(i)+w-1 \in [a(i), b(i)]$, because $2 \leq w \leq r_i$ by assumption.

From each state $v(i) \in [a(i), b(i)]$, it takes at least one exponential time with rate κ_1^i to reach the state $b(i)+1$. From $b(i)+1$, we reach the state $b(i)+w$ without hitting $[a(i), b(i)]$ with probability

$$p_w^{\kappa,i} = \frac{(\kappa_1^i)^{w-1}}{(\kappa_2^i)^{w-1} \prod_{j=1}^{w-1} [\phi_i(j+b(i)) + (\kappa_1^i/\kappa_2^i)]}.$$

Hence, if we let $G_w^{\kappa,i}$ be a geometric random variable with parameter $p_w^{\kappa,i}$, we have

$$E_{a(i)+w-1}[\sigma^{\kappa,i}_{b(i)+w}] \geq \frac{1}{\kappa_1^i} E[G_w^{\kappa,i}] = \frac{1}{\kappa_1^i p_w^{\kappa,i}} = \frac{(\kappa_2^i)^{w-1} \prod_{j=1}^{w-1} [\phi_i(j+b(i)) + (\kappa_1^i/\kappa_2^i)]}{(\kappa_1^i)^w}. \tag{A.11}$$

Hence, by combining (A.9), (A.10), and (A.11), we have

$$\begin{aligned} \pi^{\kappa,i}(b(i)+w) &\leq \frac{1}{\kappa_2^i \phi_i(b(i)+w) E^{\kappa,i}_{b(i)+w+1}[\sigma^{\kappa,i}_{b(i)+w}]} \\ &\leq \frac{(\kappa_1^i)^w}{(\kappa_2^i)^w \phi_i(b(i)+w) \prod_{j=1}^{w-1} [\phi_i(j+b(i)) + (\kappa_1^i/\kappa_2^i)]} \\ &\leq \frac{(\kappa_1^i)^w}{(\kappa_2^i)^w \prod_{j=1}^{w} \phi_i(j+b(i))}, \end{aligned}$$

which concludes the proof. □

Finally, we are ready to prove the following result:

Theorem A.7. *Let $i \in \{1, \dots, d\}$, and assume (A.8) holds. Let q_i be the uniform distribution on the set $\{a(i), \dots, b(i)\}$. Then, for any integer $v(i) \in [a(i), b(i)]$ we have*

$$0 \leq q_i(v(i)) - \pi^{\kappa,i}(v(i)) \leq \frac{\kappa_1^i}{\kappa_2^i} \mathbb{1}_{\{b(i)\geq 1\}} D(\kappa, i),$$

where

$$\begin{aligned} D(\kappa, i) = &\frac{1}{(b(i)+1)!}\left(\frac{1}{r_i} + \mathbb{1}_{\{r_i\geq 2\}}\frac{1}{b(i)+2}\right) \\ &+ \frac{\kappa_1^i}{\kappa_2^i}\left(\frac{1}{(r_i)^2}\cdot\frac{b(i)+2}{[(b(i)+1)!]^2 - (\kappa_1^i/\kappa_2^i)^2} + \mathbb{1}_{\{r_i\geq 3\}}\frac{1}{(b(i)+1)!(b(i)+2)!}\cdot\frac{1-(\kappa_1^i/\kappa_2^i)^{r_i-2}}{1-(\kappa_1^i/\kappa_2^i)}\right). \end{aligned} \tag{A.12}$$

Moreover,

$$\|\pi^{\kappa,i} - q_i\|_\infty < \frac{\kappa_1^i}{\kappa_2^i}\mathbb{1}_{\{b(i)\geq 1\}} r_i D(\kappa, i).$$

Proof. By Lemma A.3, if $b(i) = 0$ then $\pi^{\kappa,i} = q_i$, hence the statement holds. We now assume $b(i) \geq 1$.

By Lemma A.2, $X^\kappa(\cdot, i)$ is non-explosive, hence the forward Kolmogorov equation holds true [64]. It follows that, provided that $r_i \geq 2$ (which is equivalent to $b(i) \geq a(i)+1$), for any integer $v(i) \in [a(i)+1, b(i)]$

$$\kappa_1^i \pi^{\kappa,i}(v(i)) = \kappa_1^i \pi^{\kappa,i}(v(i)-1) + \kappa_2^i \frac{(v(i)+r_i)!}{(v(i)-a(i))!}\pi^{\kappa,i}(v(i)+r_i).$$

From $v(i) \in [a(i)+1, b(i)]$ it follows $v(i)+r_i \in [b(i)+2, b(i)+r_i]$. Hence, by Lemma A.6 we have

$$0 \leq \pi^{\kappa,i}(v(i)) - \pi^{\kappa,i}(v(i)-1) \leq \frac{1}{(b(i)+1)!(b(i)+2)!}\cdot\frac{(v(i)+r_i)!}{(v(i)-a(i))!}\left(\frac{\kappa_1^i}{\kappa_2^i}\right)^{v(i)-a(i)}.$$

Hence, by applying the above inequality iteratively, we have that for any two integers $v_1(i) \leq v_2(i) \in [a(i), b(i)]$

$$\begin{aligned} 0 \leq \pi^{\kappa,i}(v_2(i)) - \pi^{\kappa,i}(v_1(i)) &\leq \pi^{\kappa,i}(b(i)) - \pi^{\kappa,i}(a(i)) \leq \frac{1}{(b(i)+1)!(b(i)+2)!}\sum_{j=a(i)+1}^{b(i)}\frac{(j+r_i)!}{(j-a(i))!}\left(\frac{\kappa_1^i}{\kappa_2^i}\right)^{j-a(i)} \\ &= \mathbb{1}_{\{r_i\geq 2\}}\frac{\kappa_1^i}{\kappa_2^i}\cdot\frac{1}{(b(i)+2)!} + \left(\frac{\kappa_1^i}{\kappa_2^i}\right)^2\cdot\frac{1}{(b(i)+1)!(b(i)+2)!}\sum_{j=0}^{r_i-3}\left(\frac{\kappa_1^i}{\kappa_2^i}\right)^j \\ &= \mathbb{1}_{\{r_i\geq 2\}}\frac{\kappa_1^i}{\kappa_2^i}\cdot\frac{1}{(b(i)+2)!} + \mathbb{1}_{\{r_i\geq 3\}}\left(\frac{\kappa_1^i}{\kappa_2^i}\right)^2\frac{1}{(b(i)+1)!(b(i)+2)!}\cdot\frac{1-(\kappa_1^i/\kappa_2^i)^{r_i-2}}{1-(\kappa_1^i/\kappa_2^i)}. \end{aligned} \tag{A.13}$$

By Lemma A.2, for any integer $v(i) < a(i)$ we have $\pi^{\kappa,i}(v(i)) = q_i(v(i)) = 0$. By Lemma A.5 and (A.13), for any integer $v(i) \in [a(i), b(i)]$

$$\begin{aligned} 0 \leq q_i(v(i)) - \pi^{\kappa,i}(v(i)) &= \frac{1}{r_i} - \pi^{\kappa,i}(b(i)) + \pi^{\kappa,i}(b(i)) - \pi^{\kappa,i}(v(i)) \\ &\leq \frac{1}{(r_i)^2}\cdot\frac{(\kappa_1^i)^2}{\kappa_2^i(b(i)+1)! + \kappa_1^i}\left(\frac{b(i)+2}{\kappa_2^i r_i(b(i)+1)! - \kappa_1^i} + \frac{b(i)-a(i)}{\kappa_1^i}\right) \\ &\quad + \mathbb{1}_{\{r_i\geq 2\}}\frac{\kappa_1^i}{\kappa_2^i}\cdot\frac{1}{(b(i)+2)!} + \mathbb{1}_{\{r_i\geq 3\}}\left(\frac{\kappa_1^i}{\kappa_2^i}\right)^2\frac{1}{(b(i)+1)!(b(i)+2)!}\cdot\frac{1-(\kappa_1^i/\kappa_2^i)^{r_i-2}}{1-(\kappa_1^i/\kappa_2^i)} \\ &\leq \frac{\kappa_1^i}{\kappa_2^i}D(\kappa, i), \end{aligned} \tag{A.14}$$

where $D(\kappa, i)$ is as in (A.12). Finally, from (A.14) it follows that

$$\begin{aligned}\sum_{v(i)=b(i)+1}^{\infty}\pi^{\kappa,i}(v(i)) &= 1-\sum_{v(i)=a(i)}^{b(i)}\pi^{\kappa,i}(v(i))\\ &= \sum_{v(i)=a(i)}^{b(i)}\Big(q_i(v(i))-\pi^{\kappa,i}(v(i))\Big)\\ &\leq \frac{\kappa_1^i}{\kappa_2^i}r_i D(\kappa,i).\end{aligned}$$

Hence, for any $v(i)\geq b(i)+1$

$$|\pi^{\kappa,i}(v(i))-q_i(v(i))| = \pi^{\kappa,i}(v(i)) \leq \frac{\kappa_1^i}{\kappa_2^i}r_i D(\kappa,i),$$

which concludes the proof. □

A.3. Proof of Proposition 7

Proof. The CRN $\texttt{MultiDimUnif}(a,b,\delta)$ is equal to $\texttt{MultiDimUnif}'(a,b,\kappa^\delta)$, with κ^δ as described in Construction 6. The quantity $D(\kappa^\delta,i)$ defined in (A.12) becomes

$$D(\kappa^\delta,i) = \frac{1}{(b(i)+1)!}\left(\frac{1}{r_i}+\mathbb{1}_{\{r_i\geq 2\}}\frac{1}{b(i)+2}\right)+\frac{\delta}{2d}g_i(\delta),$$

where $g_i(\delta)$ is a continuous function satisfying

$$\lim_{\delta\to 0} g_i(\delta) = \frac{1}{[(b(i)+1)!]^2}\left(\frac{1}{(r_i)^2}+\mathbb{1}_{\{r_i\geq 3\}}\frac{1}{b(i)+2}\right).$$

Hence, by Theorem A.7 for any $v\in\mathbb{Z}^d_{\geq 0}$ such that $a\leq v\leq b$ we have

$$\begin{aligned}|\pi^\delta(v)-q(v)| = q(v)-\pi^\delta(v) &= \prod_{i=1}^d\Big[\pi^{\kappa^\delta,i}(v(i))+\Big(q_i(v(i))-\pi^{\kappa^\delta,i}(v(i))\Big)\Big]-\prod_{i=1}^d\pi^{\kappa^\delta,i}(v(i))\\ &\leq \prod_{i=1}^d\left[\frac{1}{r_i}+\frac{\delta}{2d}\mathbb{1}_{\{b(i)\geq 1\}}D(\kappa^\delta,i)\right]-\prod_{i=1}^d\frac{1}{r_i}\\ &\leq \frac{\delta}{2d}\left(\frac{1}{\prod_{i=1}^d r_i}\sum_{i=1}^d\mathbb{1}_{\{b(i)\geq 1\}}\frac{1}{(b(i)+1)!}\left(1+\mathbb{1}_{\{r_i\geq 2\}}\frac{r_i}{b(i)+2}\right)\right)+\delta^2 G(\delta),\end{aligned}$$

where $G(\delta)$ is a continuous function satisfying $\lim_{\delta\to 0}G(\delta)<\infty$. If $v\in\mathbb{Z}^d_{\geq 0}$ does not satisfy $v\geq a$, then by Lemma A.2 we have $\pi^\delta(v)=0=q(v)$. Finally, for all $v\in\mathbb{Z}^d_{\geq 0}$ with $v\geq a$ and $v\not\leq b$, we have

$$\begin{aligned}|\pi^\delta(v)-q(v)| = \pi^\delta(v) &\leq \sum_{v'\geq a,\,v'\not\leq b}\pi^\delta(v') = 1-\sum_{a\leq v'\leq b}\pi^\delta(v') = \sum_{a\leq v'\leq b}\Big(q(v')-\pi^\delta(v')\Big)\\ &\leq \frac{\delta}{2d}\sum_{i=1}^d\mathbb{1}_{\{b(i)\geq 1\}}\frac{1}{(b(i)+1)!}\left(1+\mathbb{1}_{\{r_i\geq 2\}}\frac{r_i}{b(i)+2}\right)+\delta^2 G(\delta)\prod_{i=1}^d r_i.\end{aligned}$$

The proof is concluded by noting that $r_i<b(i)+2$. □

A.4. Analysis of Construction 8

Let $X(\cdot)$ be the continuous-time Markov chain associated with $\texttt{ProdPois}(c)$. Note that the different components $X(\cdot,i)$ are independent continuous-time Markov chains, each one associated with the subnetwork of $\texttt{ProdPois}(c)$ governing the changes of the species V_i. We state and prove the following results concerning Construction 8.

Lemma A.8. *Let $d\geq 1$ and let $c\in\mathbb{R}^d_{>0}$. Consider the function $L(\cdot)$, defined as $L(v(i))=v(i)$ for all $v(i)\in\mathbb{Z}_{\geq 0}$. Then, $\lim_{v(i)\to\infty}L(v(i))=\infty$. Moreover, for any $i\in\{1,\ldots,d\}$, there exists $\alpha_i\in\mathbb{R}_{>0}$ and a compact set $K\subset\mathbb{Z}_{\geq 0}$ such that*

$$A^i L(v(i)) \leq -\alpha_i L^2(v(i)) \quad \text{for all } v(i) \notin K,$$

where A^i is the generator of $X(\cdot, i)$.

Proof. It is clear that $\lim_{v(i)\to\infty} L(v(i)) = \infty$. Moreover,

$$A^i L(v(i)) = c(i)^2 + c(i)v(i) - 2v(i)\Big(v(i) - 1\Big).$$

Hence, if $v(i)$ is large enough we have

$$A^i L(v(i)) \leq -v(i)^2 = -L^2(v(i)),$$

which concludes the proof. □

Proposition A.9. *The CRN* `ProdPois`(c) *is robust, with limit distribution π given by*

$$\pi(v) = \prod_{i=1}^{d} e^{-c(i)} \frac{(c(i))^{v(i)}}{v(i)!} \quad \text{for all } v \in \mathbb{Z}^d_{\geq 0}. \tag{A.15}$$

Moreover, the mixing times of `ProdPois`(c) *are finite at any level $\varepsilon > 0$.*

Proof. Since the components $X(\cdot, i)$ are independent, the state space of $X(\cdot)$ is irreducible if and only if the same holds for each $X(\cdot, i)$. This is the case, since the molecules of a species V_i can always increase by 1, and to decrease by 2 whenever at least 2 molecules are available.

The CRN `ProdPois`(c) is *complex balanced* with complex balanced equilibrium c, in the sense of [54]. Indeed, for any complex $y \in \mathcal{C}$ it holds that

$$\sum_{\substack{y' \in \mathcal{C} \\ y' \to y \in \mathbb{R}}} \kappa_{y' \to y} c^{y'} = \sum_{\substack{y' \in \mathcal{C} \\ y \to y' \in \mathbb{R}}} \kappa_{y \to y'} c^{y}.$$

Hence, due to [57] the associated continuous-time Markov chain $X(\cdot)$ is non-explosive, and due to [13] and to the fact that the state space is irreducible, the limit distribution satisfies (A.15).

Finally, the mixing times of $X(\cdot)$ are finite at any level, if and only if the mixing times of any component $X(\cdot, i)$ are finite at any level. The latter is implied by Lemma A.8 and Theorem C.2, hence the proof is concluded. □

A.5. Proof of Theorem 9

Proof. Let $X^\delta(\cdot)$ be the continuous-time Markov chain associated with `Mix`$(\mathcal{F}, \zeta, \delta)$. By Lemma 4, Proposition 7, and Proposition A.9, all the networks $\mathcal{N}_i^\delta$ are robust, for all $\delta > 0$. Let π_i^δ denote the limit distribution of $\mathcal{N}_i^\delta$. By Lemma 4, Proposition 7, and Proposition A.9 we have

$$\|\pi_i^\delta - \pi_i\|_\infty \leq \delta \quad \text{for all } i \in I_1; \tag{A.16}$$

$$\|\pi_i^\delta - \pi_i\|_\infty \leq \delta + o(\delta) \quad \text{for all } i \in I_2; \tag{A.17}$$

$$\|\pi_i^\delta - \pi_i\|_\infty = 0 \quad \text{for all } i \in I_3, \tag{A.18}$$

where $o(\delta)$ is a function with the property

$$\lim_{\delta \to 0} \frac{o(\delta)}{\delta} = 0.$$

Furthermore, Constructions 4 and 6 are special cases of Construction 6′, hence by Lemma A.2 and Proposition A.9 it follows that the mixing times of any network $\mathcal{N}_i^\delta$ are finite at any level $\varepsilon > 0$, for any $\delta > 0$.

If we can show that `Mix`$(\mathcal{F}, \zeta, \delta)$ is non-explosive for any $\delta > 0$, we can conclude the proof by Theorem 8 and by triangular inequality, using (A.16), (A.17), and (A.18).

Let $X^\delta_{\mathcal{H}}(\cdot)$ be the projection of $X^\delta(\cdot)$ onto the species $\{H_1, \ldots, H_m\}$. Note that $X^\delta_{\mathcal{H}}(\cdot)$ is a continuous-time Markov chain, associated with the CRN

$$0 \underset{\delta}{\overset{\delta^2 \zeta(i)}{\rightleftharpoons}} H_i, \quad \text{for } i \in \{1, \ldots, m\}.$$

The above CRN is detailed balanced, with detailed balanced equilibrium $\delta\zeta \in \mathbb{R}^m_{>0}$. Hence, due to [57] $X^\delta_{\mathcal{H}}(\cdot)$ is non-explosive. If $X^\delta(\cdot)$ were explosive, then infinitely many transitions of $X^\delta(\cdot)$ would occur while $X^\delta_{\mathcal{H}}(\cdot)$ is fixed at a state h.

Note that given $X^{\delta}_{\mathcal{H}}(\cdot) \equiv h$, the components of $X^{\delta}(\cdot)$ relative to the species $\{V_1, \ldots, V_d\}$ are independent continuous-time Markov chains. Let $X^{\delta,h}(\cdot, j)$ denote the component of $X^{\delta}(\cdot)$ relative to species V_j, given that $X^{\delta}_{\mathcal{H}}(\cdot) \equiv h$. If $X^{\delta}(\cdot)$ were explosive, then a process $X^{\delta,h}(\cdot, j)$ would be explosive, for some $h \in \mathbb{Z}^m_{\geq 0}$ and some $j \in \{1, \ldots, d\}$. We will conclude the proof by showing that this is not possible.

Let $A^{\delta,i}$ be the generator of $\mathcal{N}^{\delta}_i$. Then, the generator of $X^{\delta,h}(\cdot, j)$ is given by

$$A^{\delta,h} = \sum_{i=1}^{m} h(i) A^{\delta,i}.$$

From Lemma A.1 and Lemma A.8, it follows that if $L(v(j)) = v(j)$ for all $v(j) \in \mathbb{Z}_{\geq 0}$, then for each $i \in \{1, \ldots, m\}$ and for each $\delta \in \mathbb{R}_{>0}$, there exist $\alpha^{\delta,i} \in \mathbb{R}_{>0}$ and a compact set $K^{\delta,i} \subset \mathbb{Z}_{\geq 0}$ such that

$$A^{\delta,i} L(v(j)) \leq -\alpha^{\delta,i} L^2(v(j)) \quad \text{for all } v(j) \notin K^{\delta,i}, i \in \{1, \ldots, m\}.$$

Hence, if

$$K^{\delta} = \bigcup_{i=1}^{m} K^{\delta,i} \quad \text{and} \quad \alpha^{\delta} = \min_{1 \leq i \leq m} h(i) \alpha^{\delta,i},$$

then

$$A^{\delta,h} L(v(j)) = \sum_{i=1}^{m} h(i) A^{\delta,i} L(v(j)) \leq -\alpha^{\delta} L^2(v(j)) \quad \text{for all } v(j) \notin K^{\delta}.$$

The proof is then concluded by Theorem C.2. □

A.6. Proof of Theorem 5

Proof. If q has finite support $\{v_1, \ldots, v_m\}$, then we have

$$q = \sum_{i=1}^{m} q(v_i) \delta_{v_i}.$$

Note that $\texttt{PointMassMix}(q, \delta) = \texttt{Mix}\{\mathcal{F}, \zeta, \delta\}$, if we let $\mathcal{N}^{\delta}_i = \texttt{PointMass}(v_i, \delta)$ and $\zeta(i) = q(v_i)$ for all $i \in \{1, \ldots, m\}$. Hence, the proof is concluded by Theorem 9. □

Appendix B. Bounds for the mixing times of $\texttt{PointMass}(x, \delta)$

Here we give some useful bounds on the mixing times of a generalization of one-dimensional $\texttt{PointMass}(x, \delta)$, where the choice of rate constants is not constrained.

Proposition B.1. *Consider the CRN*

$$V \xrightarrow{\kappa_1} 0$$
$$2V \xrightarrow{\kappa_2} 0$$

Then, the CRN is robust with unique limit distribution π being the point mass distribution centered at 0. Moreover, for any choice of rate constants κ_1, κ_2, and for all $\varepsilon > 0$,

$$\tau^{\varepsilon} \leq \frac{1}{\varepsilon} \sum_{v=1}^{\infty} \frac{1}{\kappa_1 v + \kappa_2 v(v-1)} < \infty.$$

Proof. Robustness of the CRN and the fact that the limit distribution is the point mass distribution at 0 follows from Lemma A.3. Let $X(\cdot)$ denote the continuous-time Markov chain associated with the CRN. Let

- $\sigma = \inf\{t \geq 0 : X(t) = 0\}$;
- $Y(\cdot)$ be the embedded discrete time Markov chain of $X(\cdot)$: $Y(0) = X(0)$ and for each $n \geq 1$, $Y(n)$ is defined as the value of the process $X(\cdot)$ after n jumps;
- $M = \inf\{n \geq 0 : Y(n) = 0\}$.

Let $X(0) = v_0$. Note that since the process $X(\cdot)$ decreases at least by one unit at each jump, necessarily $M \leq v_0$. Denote by $(\mathcal{E}_v)_{v=0}^{\infty}$ a sequence of independent exponential random variables with rates $\kappa_1 v + \kappa_2 v(v-1)$. Then,

$$\sigma = \sum_{n=0}^{M-1} \mathcal{E}_{Y(n)} \leq \sum_{v=1}^{v_0} \mathcal{E}_v$$

Then, by Markov inequality,

$$P(0,t \mid v_0) = P(\sigma \leq t \mid v_0) \geq 1 - \frac{1}{t} \sum_{v=1}^{v_0} \frac{1}{\kappa_1 v + \kappa_2 v(v-1)} \geq 1 - \frac{1}{t} \sum_{v=1}^{\infty} \frac{1}{\kappa_1 v + \kappa_2 v(v-1)}.$$

The proof is then concluded by noting that in this case

$$\begin{aligned} \| P(\cdot, t \mid v_0) - \pi \|_{\infty} &\leq \max \left\{ |P(0,t \mid v_0) - \pi(0)|, \sum_{v=1}^{\infty} |P(v,t \mid v_0) - \pi(v)| \right\} \\ &= \max \left\{ 1 - P(0,t \mid v_0), \sum_{v=1}^{\infty} P(v,t \mid v_0) \right\} \\ &= 1 - P(0,t \mid v_0). \end{aligned}$$

□

Proposition B.2. *Consider an integer $x \geq 1$, and consider the CRN*

$$0 \xrightarrow{\kappa_1} V$$
$$(x+1)V \xrightarrow{\kappa_2} xV$$

Then, the CRN is robust. Let π be its unique limit distribution. Moreover, assume that

$$\varepsilon > \max \left\{ \frac{\kappa_1^2 (x+2)}{\kappa_2^2 [(x+1)!]^2 - \kappa_1^2}, 1 - e^{-\frac{\kappa_1}{x! \cdot x}} \right\} \qquad \text{if } \kappa_2^2 [(x+1)!]^2 > \kappa_1^2 \tag{B.1}$$

$$\varepsilon > \max \left\{ \frac{2\kappa_1}{\kappa_2}, 1 - e^{-\frac{\kappa_1}{x! \cdot x}} \right\} \qquad \text{if } \kappa_2^2 [(x+1)!]^2 \leq \kappa_1^2. \tag{B.2}$$

Then

$$\tau^{2\varepsilon} \leq \max \left\{ \frac{e^{-\frac{\kappa_1}{x! \cdot x}}}{\kappa_2 (e^{-\frac{\kappa_1}{x! \cdot x}} - 1 + \varepsilon) x! \cdot x}, \frac{x}{\kappa_1 \varepsilon} \right\}.$$

Proof. First, the CRN is robust due to Lemma A.2. Note that by Lemma A.5 and Lemma 4, it follows from (B.1) and (B.2) that

$$\varepsilon > \max \left\{ 1 - \pi(x), 1 - e^{-\frac{\kappa_1}{x! \cdot x}} \right\}. \tag{B.3}$$

Let $X(\cdot)$ be the process associated with the CRN, and let

$$\sigma = \inf\{t \geq 0 : X(t) = x\}.$$

Since $\{X(t) = x\} \subseteq \{\sigma \leq t\}$, we have that for any $v_0 \in \mathbb{Z}_{\geq 0}$

$$P(x,t \mid v_0) = P(X(t) = x, \sigma \leq t \mid X(0) = v_0) = P(X(t) = x \mid \sigma \leq t, X(0) = v_0) P(\sigma \leq t \mid X(0) = v_0).$$

By monotonicity of birth and death processes [65, Section 2] and by strong Markov property we have

$$P(X(t) = n \mid \sigma < t, X(0) = v_0) \geq \pi(x).$$

Hence,

$$P(x,t \mid v_0) \geq \pi(x) P(\sigma \leq t \mid X(0) = v_0).$$

There are three cases:

1. If $v_0 < x$, and if we denote by $\Gamma(k, \theta)$ the sum of k independent exponential random variables with mean θ, then by Markov inequality

$$\begin{aligned} P(\sigma \leq t \mid X(0) = v_0) &= P\left(\Gamma\left(x - v_0, \frac{1}{\kappa_1}\right) \leq t\right) \\ &\geq P\left(\Gamma\left(x, \frac{1}{\kappa_1}\right) \leq t\right) \\ &\geq 1 - \frac{x}{\kappa_1 t} \end{aligned}$$

2. If $v_0 = x$, then $P(\sigma < t \mid X(0) = v_0) = 1$ for all $t \geq 0$.
3. If $v_0 > x$, then

$$P(\sigma \leq t \mid X(0) = v_0) \geq P(\sigma \leq t \mid A_{v_0}, X(0) = v_0) P(A_{v_0} \mid X(0) = v_0),$$

where

$$A_{v_0} = \{\text{the first } v_0 - x \text{ jumps of } X(\cdot) \text{ point downwards}\}.$$

For notational convenience, let

$$\phi^x(v) = \frac{v!}{(v - x - 1)!} \quad \text{for } v \geq x + 1,$$

and denote by $(\mathcal{E}_v)_{v=x+1}^{\infty}$ a sequence of independent exponential random variables with rates $\kappa_2 \phi^x(v)$. Then, by Markov inequality,

$$\begin{aligned} P(\sigma \leq t \mid A_{v_0}, X(0) = v_0) &= P\left(\sum_{v=x+1}^{v_0} \mathcal{E}_v \leq t\right) \\ &\geq 1 - \frac{1}{\kappa_2 t} \sum_{v=x+1}^{v_0} \frac{1}{\phi^x(v)} \\ &\geq 1 - \frac{1}{\kappa_2 t} \sum_{v=x+1}^{\infty} \frac{1}{\phi^x(v)}. \end{aligned}$$

In order to express better the last series, note that

$$\begin{aligned} \sum_{v=x}^{\infty} \frac{(v-x)!}{v!} &= \frac{1}{x!} + \sum_{v=x+1}^{\infty} (v - x) \frac{(v - x - 1)!}{v!} \\ &= \frac{1}{x!} + \sum_{v=x}^{\infty} \frac{(v-x)!}{v!} - x \sum_{v=x+1}^{\infty} \frac{(v - x - 1)!}{v!} \end{aligned}$$

It follows that

$$\sum_{v=x+1}^{\infty} \frac{1}{\phi^x(v)} = \sum_{v=x+1}^{\infty} \frac{(v - x - 1)!}{v!} = \frac{1}{x! \cdot x}$$

and

$$P(\sigma \leq t \mid A_{v_0}, X(0) = v_0) \geq 1 - \frac{1}{x! \cdot x \kappa_2 t}.$$

Moreover,

$$\begin{aligned} P(A_{v_0} \mid X(0) = v_0) &= \prod_{v=x+1}^{v_0} \frac{\phi^x(v)}{\kappa_1 + \phi^x(v)} \\ &= e^{-\sum_{v=x+1}^{v_0} \log\left(1 + \frac{\kappa_1}{\phi^x(v)}\right)} \\ &\geq e^{-\sum_{v=x+1}^{\infty} \frac{\kappa_1}{\phi^x(v)}} \\ &= e^{-\frac{\kappa_1}{x! \cdot x}}, \end{aligned}$$

which implies

$$P(\sigma \leq t \mid X(0) = v_0) \geq e^{-\frac{\kappa_1}{x!\cdot x}} \left(1 - \frac{1}{x! \cdot x \kappa_2 t}\right)$$

Hence, independently on the initial condition v_0 and provided that

$$\varepsilon > 1 - e^{-\frac{\kappa_1}{x!\cdot x}},$$

if

$$t \geq \max\left\{\frac{e^{-\frac{\kappa_1}{x!\cdot x}}}{\kappa_2(e^{-\frac{\kappa_1}{x!\cdot x}} - 1 + \varepsilon)x! \cdot x}, \frac{x}{\kappa_1 \varepsilon}\right\}$$

then

$$P(x, t \mid v_0) \geq (1 - \varepsilon)\pi(x).$$

Hence, since $\varepsilon > 1 - \pi(x)$ by (B.3), it follows that

$$|P(x, t \mid v_0) - \pi(x)| \leq \varepsilon.$$

Moreover, for any $v \neq x$ we have

$$\begin{aligned} |P(v, t \mid v_0) - \pi(v)| &\leq \max\{P(v, t \mid v_0), \pi(v)\} \\ &\leq \max\{1 - P(x, t \mid v_0), 1 - \pi(x)\} \\ &\leq 1 - \pi(x) + \varepsilon\pi(x) < 2\varepsilon, \end{aligned}$$

which concludes the proof. □

Appendix C. Super Lyapunov functions

The theory we develop here was mostly developed in [63], for a specific family of stochastic differential equations. The concept and the terminology of "super Lyapunov function" themselves were also introduced in [63]. We are interested in an adaptation of [63, Lemma 6.1], which we state here as Theorem C.1 and whose proof we repeat for completeness.

Definition C.1. Let $X(\cdot)$ be a continuous-time Markov chain on $\mathbb{Z}^d_{\geq 0}$, with generator A. We say that a function $L\colon \mathbb{Z}^d_{\geq 0} \to \mathbb{R}_{\geq 0}$ is a *super Lyapunov function* if the following holds true:

- $\lim_{x\to\infty} L(x) = \infty$
- there exists a compact set K and real numbers $\alpha > 0$ and $\gamma > 1$ such that

$$AL(x) \leq -\alpha L^{\gamma}(x) \quad \text{for all } x \notin K. \tag{C.1}$$

Remark C.1. If (C.1) holds for $\gamma = 1$, then the function L is a standard Lyapunov function. While the existence of such a function implies that the process $X(\cdot)$ is non explosive and that a limit distribution exists for any initial condition [62], in general it does not imply that the mixing times are finite. △

Remark C.2. Equation (C.1) is equivalent to the existence of real numbers $\alpha, \beta \geq 0$ and $\gamma > 1$ such that

$$AL(x) \leq -\alpha L^{\gamma}(x) + \beta \quad \text{for all } x \in \mathbb{Z}^d_{\geq 0}. \tag{C.2}$$

Indeed, it is sufficient to consider $b = \max_{x\in K} |AL(x)|$. △

Theorem C.1. *Let $X(\cdot)$ be a continuous-time Markov chain on $\mathbb{Z}^d_{\geq 0}$, and let $L(\cdot)$ be a super Lyapunov function. Then,*

$$E[L(X(t)) \mid X(0) = x_0] \leq \max\left\{\left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}, \left(\frac{2}{\alpha(\gamma - 1)t}\right)^{\frac{1}{\gamma-1}}\right\} \quad \textit{for all } t \geq 0, x_0 \in \mathbb{Z}^d_{\geq 0},$$

where α, β, γ are as in (C.2).

Proof. For simplicity, denote

$$z_{x_0}(t) = E[L(X(t)) \mid X(0) = x_0].$$

Moreover, for any real number $M > 0$ let ρ^M be the stopping time

$$\rho^M = \inf\{t \geq 0 : L(V(t)) \geq M\}.$$

By Dynkin's formula, (C.2) and Jensen's inequality, for any $M > L(x_0)$ we have

$$\begin{aligned} z_{x_0}(\max\{t, \rho^M\}) &= L(x_0) + E\left[\int_0^{\max\{t,\rho^M\}} AL(X(s))ds \;\middle|\; X(0) = x_0 \right] \\ &\leq L(x_0) + \beta t - \alpha \int_0^t \left(z_{x_0}(s)\right)^\gamma ds. \end{aligned}$$

By taking the limit for M going to infinity we have

$$z_{x_0}(t) \leq L(x_0) + \beta t - \alpha \int_0^t \left(z_{x_0}(s)\right)^\gamma ds.$$

Since the latter holds for any initial condition x_0, we must have

$$\frac{d}{dt} z_{x_0}(t) \leq \beta - \alpha \left(z_{x_0}(t)\right)^\gamma \leq -\frac{\alpha}{2} \left(z_{x_0}(t)\right)^\gamma \quad \text{for } z_{x_0}(t) \geq \left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}. \tag{C.3}$$

Since the latter is strictly negative, it follows that as soon as we have $z_{x_0}(t) \leq \left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}$ for some $t \geq 0$, then the same holds for all times afterwards. In particular, if this holds for $t = 0$, then the proof is complete. We can therefore assume that $z_{x_0}(0) \geq \left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}$. By (C.3), it follows that as long as $z_{x_0}(t) \geq \left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}$, then $z_{x_0}(t) \leq u_{x_0}(t)$ where $u_{x_0}(t)$ is the solution to

$$\frac{d}{dt} u_{x_0}(t) = -\frac{\alpha}{2} \left(u_{x_0}(t)\right)^\gamma, \quad u_{x_0}(0) = z_{x_0}(0) \geq \left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}.$$

The latter can be explicitly calculated, and we have

$$u_{x_0}(t) = \left(\frac{\alpha(\gamma-1)t}{2} + u_{x_0}(0)^{1-\gamma}\right)^{\frac{1}{1-\gamma}} \leq \left(\frac{2}{\alpha(\gamma-1)t}\right)^{\frac{1}{\gamma-1}},$$

which concludes the proof. □

Theorem C.2. *Let $X(\cdot)$ be a continuous-time Markov chain on $\mathbb{Z}^d_{\geq 0}$, and let $L(\cdot)$ be a super Lyapunov function. Then, $X(\cdot)$ is non-explosive. Moreover, if there exists a unique closed irreducible set, then $X(\cdot)$ has a unique limit distribution and the mixing times at any level are finite.*

Proof. $X(\cdot)$ is non-explosive and admits a unique limit distribution π (when a unique closed irreducible set exists) due Foster-Lyapunov theory [62] (see Remark C.1). Hence, we only need to prove that the mixing times are finite. Let τ^ε be the mixing time at level ε, and for any $x \in \mathbb{Z}^d_{\geq 0}$ let

$$\tau_x^{\frac{\varepsilon}{2}} = \inf\left\{t \geq 0 : \|P(\cdot, s \mid x) - \pi\|_\infty < \frac{\varepsilon}{2} \quad \text{for all } s \geq t\right\}.$$

Note that since π is a limit distribution, for any $x \in \mathbb{Z}^d_{\geq 0}$ we have $\tau_x^{\frac{\varepsilon}{2}} < \infty$. Let

$$M^\varepsilon = \frac{4}{\varepsilon}\left(\frac{2\beta}{\alpha}\right)^{\frac{1}{\gamma}}.$$

The set $\Xi^\varepsilon = \{x \in \mathbb{Z}^d_{\geq 0} : L(x) \leq M^\varepsilon\}$ is finite, because $\lim_{x\to\infty} L(x) = \infty$. Hence,

$$R^{\varepsilon} \doteq \max_{x \in \Xi^{\varepsilon}} \tau_x^{\frac{\varepsilon}{2}} < \infty.$$

Finally, let

$$T = \frac{2}{\alpha(\gamma - 1)} \left(\frac{\alpha}{2\beta} \right)^{\frac{\gamma - 1}{\gamma}}$$

By Theorem C.1, we have that for any $x_0 \in \mathbb{Z}^d_{\geq 0}$

$$E[L(X(T)) \mid X(0) = x_0] \leq \left(\frac{2\beta}{\alpha} \right)^{\frac{1}{\gamma}},$$

and by Markov inequality we have that for any $x_0 \in \mathbb{Z}^d_{\geq 0}$

$$P(X(T) \notin \Xi^{\varepsilon} \mid x_0) = P(L(X(T)) > M^{\varepsilon} \mid x_0) \leq \frac{E[L(X(T)) \mid X(0) = x_0]}{M^{\varepsilon}} \leq \frac{\varepsilon}{4}.$$

Hence, by Markov property and by definition of R^{ε}, for any $s \geq T + R^{\varepsilon}$ and any $x_0 \in \mathbb{Z}^d_{\geq 0}$ we have

$$\| P(\cdot, s \mid x_0) - \pi \|_{\infty} \leq \frac{\varepsilon}{4} \cdot 2 + \max_{x \in \Xi^{\varepsilon}} \| P(\cdot, s - T \mid x) - \pi \|_{\infty} \leq \varepsilon.$$

It follows that $\tau^{\varepsilon} \leq T + R^{\varepsilon}$, which concludes the proof. □

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