Accuracy of Multiscale Reduction for Stochastic Reaction Systems

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Abstract

Stochastic models of chemical reaction networks are an important tool to describe and analyze noise effects in cell biology. When chemical species and reaction rates in a reaction system have different orders of magnitude, the associated stochastic system is often modeled in a multiscale regime. It is known that multiscale models can be approximated with a reduced system such as mean field dynamics or hybrid systems, but the accuracy of the approximation remains unknown. In this paper, we estimate the probability distribution of low copy species in multiscale stochastic reaction systems under short-time scale. We also establish an error bound for this approximation. Throughout the manuscript, typical mass action systems are mainly handled, but we also show that the main theorem can extended to general kinetics, which generalizes existing results in the literature. Our approach is based on a direct analysis of the Kolmogorov equation, in contrast to classical approaches in the existing literature.

1 Introduction

Consider a reaction network with a discrete number of copies for each species, a problem of increasing importance in cell biology. The evolution of the copy number of each chemical species can be modeled using a continuous-time, discrete-space Markov process, and stochastic effects are well known to be present. The time evolution of this system can be computed by solving the so-called Kolmogorov equation, but this direct approach is rarely useful because of its high dimensionality. Therefore computational and analytic methods for estimating the distribution associated with a stochastic reaction network system have been developed [4, 7, 8, 14, 16, 17, 18, 19, 25, 26].

In a stochastic system, some chemical species can have much higher molecular counts that the others. Furthermore, the intensity of each reaction can also vary over several orders of magnitude. For example, suppose A and B are proteins interacting in the network system

$$A + B \underbrace{\stackrel{\kappa_1}{\overleftarrow{}}}_{\kappa_2 N} 2A \xleftarrow{\kappa_3} C, \tag{1}$$

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with the initial conditions A(0) = 1, B(0) = N and C(0) = 10. Here N is a large scaling parameter, and it could mean the Avogadro number 6×10^{23} , the total mass of the system, or the volume of the container where the reaction takes place. Letting X(t) = (A(t), B(t), C(t)) be the stochastic process associated with the reaction network at time t, we suppose that the intensities of the reactions $A + B \rightarrow 2A$, $2A \rightarrow A + B$ and $C \rightarrow 2A$ are $\lambda_{A+B\rightarrow 2A}(X(t)) = \kappa_1 A(t)B(t)$, $\lambda_{2A\rightarrow A+B}(X(t)) = \kappa_2 N A(t)(A(t) - 1)$ and $\lambda_{C\rightarrow 2A}(X(t)) = \kappa_3 C(t)$, respectively. Note that around t = 0, the intensity of $C \rightarrow \emptyset$ is much smaller than the intensities of the other reactions. Thus we can expect that reaction $C \rightarrow 2A$ is rarely fired and hence the copy number of C evolves in slow-time scale.

As shown in the example above, due to the size of intensities, the dynamics of each species in a reaction system can have different time scales. If the size of species and the size of intensities satisfy a particular balance condition, then the system can be decomposed into two or more subsystems, each of which converges to a lower dimensional system as the scaling parameter tends to infinity [4, 17]. Depending on the time scale, the limiting system of the subsystems could be either a stochastic, deterministic or piece-wise deterministic model [1, 4, 12, 16, 17].

In this paper, we show that a multiscale stochastic model under a short-term timescale converges in distribution to an associated reduced model. To illustrate this, we consider the toy model in (1). By modeling system (1) with a continuous time Markov process, the holding time for the next reaction is exponentially distributed with rate $\lambda_{A+B\to 2A}(X(t)) + \lambda_{2A\to A+B}(X(t)) + \lambda_{C\to 2A}(X(t))$. Hence the expected holding time until the next reaction around t = 0 is of order $\frac{1}{N}$. This indicates that the number of reactions fired within $[0, \frac{T}{N}]$ is of constant order on average for T > 0. This amount of transitions is substantial for the low copy species A and C, but it is too small to considerably fluctuate the concentration of B, $\frac{B(t)}{N}$, within $[0, \frac{T}{N}]$. In this vein, for the scaled process $(A(t)), \frac{B(t)}{N}, C(t))$, we can approximately freeze $\frac{B(t)}{N}$ at $\frac{B(0)}{N} = 1$. Then the dynamics of species A(t/N) in the original system (1) under the short-term timescale can be approximated with a reduced system $A \stackrel{\kappa_{1\lambda}}{\longrightarrow} 2A$.

In general, we show that for some $\theta_0 > 0$, the short-term distribution $p^N(t/N^{\theta_0})$ of the original network system converges to the distribution p(t) of the limiting reduced system for any t in a compact time interval [0, T], as the scaling parameter N tends to infinity. The main theoretic tools for this result rely on a direct calculation using the Kolmogorov equation, and this allows us to obtain the error bound

$$\sup_{t \in [0,T]} |p^N(U, t/N^{\theta_0}) - p(U, t)| \le \frac{c}{N^{\nu}}.$$
(2)

Here U is an arbitrary subset of the state space, and the constants c > 0 and $\nu \in (0,1)$ are independent of U.

For the main theorem and relevant lemmas, we assume that the associated stochastic system for a reaction system is under mass-action kinetics. However, the main result can be extended to general kinetics such as Michealis-Mentum kinetics and hill type functions. Furthermore since the proof of the main theorem does not require network structural restrictions, this convergence result holds not only for bimolecular chemical reaction systems, but also for higher order reaction systems with general kinetics. Instead of structural restrictions, we assume that the reduced reaction system admits a stationary distribution with a finite moment condition. Since the finite moment condition of the reduced network system guarantees the non-explosivity of the original multiscale model. Therefore the error bound (2) holds for any time T. By showing this error bound, this work provides a addition to previous related studies of multiscaling limits.

This manuscript has the following outline. In Section 2 we introduce the basic notions of a stochastic system for a reaction network. In the same section, we also provide a multiscale framework for the stochastic model and introduce the idea of network projection. Key lemmas and the main theorem of this paper including proofs are introduced in Section 3. In section 4, we discuss some extension of the main result for general kinetics. In Section 5, in order to demonstrate how the main theorem can be applied for practical models, we provide various examples of biological models such as a futile cycle, a system of yeast polarization, p53 response to DNA damage and a population model with three species. In Appendix A, a table of notations used in the entire paper is provided. In Appendix B proofs of some technical lemmas are given.

2 Preliminaries

2.1 Stochastic Reaction Networks

In this section, we provide a mathematical description of chemical reaction networks, with an emphasis on their associated stochastic dynamics. A *reaction network* is a graphical configuration consisting of constituent species, complexes (that is, combinations of species), and reactions between complexes. A triple (S, C, R) represents a reaction network where S, C and R are collections of species, complexes and reactions, respectively.

Definition 2.1. A reaction network is defined with a triple of finite sets (S, C, R) such that

- 1. the species set $S = \{S_1, S_2, \dots, S_d\}$ contains the species belonging to the reaction network,
- 2. the complex set $C = \{y_1, y_2, \ldots, y_c\}$ contains complexes y_k , where for each k,

$$y_k = \sum_{i=1}^d y_{ki} S_i$$
 for some non-negative integers y_{ik} , and

3. the reaction set $\mathcal{R} = \{R_1, R_2, \dots, R_r\}$ consists of ordered pairs (y, y') such that $y, y' \in \mathcal{C}$.

In the graphical configuration of a reaction network (S, C, \mathcal{R}) , we represent complexes $y, y, \ldots \in C$ by nodes, and we use directed edges $y \to y'$ to denote reactions $(y, y') \in \mathcal{R}$. In order to define a dynamical system associated with a reaction network (S, C, \mathcal{R}) , we denote a complex y_k by either a linear combination of species such as $\sum_{i=1}^{d} y_{ki}S_i$ or a *d*-dimensional vector $y_k = (y_{k1}, \ldots, y_{kd})^T$, interchangeably. In case $y_{ki} = 0$ for all *i*, the corresponding complex $y_k = \sum_{i=1}^{d} y_{ki}S_i$ is denoted by \emptyset in the graphical configuration of the reaction network.

Example 2.1. Consider the following reaction network describing a substrate-enzyme system with a protein dilution:

$$S + E \rightleftharpoons C \to E + P, \quad P \to \emptyset.$$

For this reaction network, $S = \{S, E, C, P\}$, $C = \{S + E, C, E + P, \emptyset\}$ and $\mathcal{R} = \{S + E \rightarrow C, C \rightarrow S + E, C \rightarrow E + P, P \rightarrow \emptyset\}$.

We now describe the stochastic dynamics of a reaction network using a continuous time, discrete state Markov process. At any time t, the counts of each species are given by a d-dimensional vector $X(t) = (X_1(t), \ldots, X_d(t)) \in \mathbb{Z}_{\geq 0}^d$. The transitions of the Markov process are determined by the given reactions. In order to define the transition probabilities, we use state-dependent intensity (or propensity) functions $\lambda_k : \mathbb{Z}_{\geq 0}^d \to \mathbb{R}_{\geq 0}$ of the reaction $y_k \to y'_k$. For example, the reaction $y_k \to y_k$ induces a transition from a given state z into the state $z + y_k - y_k$ with intensity $\lambda_k(z)$. More generally, we have

$$P(X(t + \Delta t) = z + y' - y \mid X(t) = z) = \sum_{\substack{y_k \to y'_k \in \mathcal{R} \\ y'_k - y_k = y' - y}} \lambda_k(z) \Delta t + o(\Delta t),$$
(3)

for each state z in the state space S of the associated Markov process X. The copy number of a species S at time t will be denoted by S(t). Let p(z,t) = P(X(t) = z), for a given state z and time t. Then p(z,t) solves the so-called Kolmogorov forward equation, also known as the chemical master equation:

$$\frac{d}{dt}p(z,t) = \sum_{k} \lambda_{k}(z - y'_{k} + y_{k})p(z - y'_{k} + y_{k}, t) - \sum_{k} \lambda_{k}(z)p(z,t),$$
(4)

where \sum_k denotes the sum over all reactions in \mathcal{R} . A stationary distribution π is a positive stationary solution of the Kolmogorov equation above such that $\sum_z \pi(z) = 1$.

The usual choice of intensity $\lambda_k(x)$ of a reaction $y_k \to y'_k$ in a network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ with rate constant κ_k is

$$\lambda_k(x) = \kappa_k x^{(y)},\tag{5}$$

where $n^{(k)} = n \cdot (n-1) \cdots (n-k+1)$ for non-negative integer vector n, k, $n^{(k)} = 0$ if n < k, and $u^{(v)} = \prod_{i=1}^{d} u_i^{(v_i)}$ for $u \in \mathbb{Z}^d, v \in \mathbb{Z}^d_{\geq 0}$. This choice of intensities is called *stochastic mass action kinetics*. An analogous *deterministic mass action kinetics* for a reaction $y_k \to y_k$ is x^{y_k} , where we define $u^v = \prod_{i=1}^{d} u_i^{v_i}$ for $u, v \in \mathbb{R}^d_{\geq 0}$.

The stochastic process X(t) also has another representation, so-called random time change representation. [21]

$$X(t) = X(0) + \sum_{k} Y_k \left(\int_0^t \lambda_k(X(s)) ds \right) (y'_k - y_k), \tag{6}$$

where Y_k 's are independent unit Poisson random variables.

In the graph associated to a reaction network, the rate constants κ typically appear next to the reaction arrow as in $y \xrightarrow{\kappa} y'$. Through this manuscript, we model a reaction system using massaction kinetics so that each reaction intensity $\lambda_k = \lambda_k(x) = \kappa_k x^{(y_k)}, k = 1, \ldots r$. For a given reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, we denote by \mathcal{K} the set of reaction intensities λ_k . We simply denote by $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$ the system associated with the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ with \mathcal{K} and call it a reaction system. Using this framework, the probabilities (3) describe the dynamics of the stochastic process X(t) associated with the reaction system $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$.

2.2 Multiscaling for Reaction Networks

In this section, we describe how to carry out a multiscaling procedure for a given stochastic reaction system. We use a similar notation as in the work by Kang and Kurtz [17]. Let N be a scaling parameter, which could be interpreted as either the volume of the system, Avogadro's number, or any biological parameter. We use the conventional big Θ notion: for a real-valued sequence a_n

$$a_n = \Theta(n^{\gamma})$$
 if and only if there exists $c > 0$ such that $\frac{1}{c} \le \frac{|a_n|}{n^{\gamma}} \le c$ for all n

Let $X^N(t) = (X_1^N(t), \dots, X_d^N(t))$ be a stochastic process associated with $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$. Assuming that each species may have a different magnitude of initial abundance, we scale $X^N(t)$ by using two sets of scaling exponents,

$$\{\alpha_i : S_i \in \mathcal{S}\}$$
 and $\{\beta_k : y_k \to y'_k \in \mathcal{R}\}.$ (7)

Each α_i represents the size of the abundance of species S_i such that $X_i^N(0) = \Theta(N^{\alpha_i})$. If $\alpha_i = 1$, then $N^{-\alpha_i}X_i(t)$ may represent the concentration of S_i at time t. For simplicity, we assume that $X_i^N(0) = N^{\alpha_i} z_i^0$ for some $z_i^0 \in \mathbb{R}_{\geq 0}$. We also assume that the rate constant of the reactions have different orders of magnitude so that we have scaled rate constants $N^{\beta_k} \kappa_k$ for each reaction $y_k \to y'_k \in \mathcal{R}$.

By the representation (6), the scaled process $Z_i^N(t) = N^{-\alpha_i} X_i(t), i = 1, 2, ..., d$, solves

$$Z_{i}^{N}(t) = Z_{i}^{N}(0) + \sum_{k} Y_{k} \left(\int_{0}^{t} N^{\beta_{k}} \lambda_{k}(X^{N}(s)) ds \right) \frac{(y_{k,i}' - y_{k,i})}{N^{\alpha_{i}}},$$
(8)

where Y_k 's are i.i.d. unit Poisson random variables.

For additional details on the definition and uses of multiscaling in stochastic and deterministic systems, see [4, 12, 16, 17, 28].

2.3 Order of reaction intensities under a short-term timescale

In this section we show that any multi-scale reaction system admits at most constant order of reaction intensities under a certain short-term timescale. For a multiscale process $X^N(t)$ associated with reaction system (S, C, R, K), let θ_0 be the maximum order of reaction intensities. That is,

$$\theta_0 = \max\{\theta_k : N^{\beta_k} \lambda_k(X^N(0)) = \Theta(N^{\theta_k})\} = \max_k \{\beta_k + y_k \cdot \alpha\},\tag{9}$$

where $\alpha = (\alpha_1, \ldots, \alpha_d)$.

We consider time-scaled model $Z_i^{N,\gamma}(t) := Z^N(N^{\gamma}t)$. Then by (8) with a change of variable, $Z^{N,\gamma}$ satisfies that

$$Z_{i}^{N,\gamma}(t) = Z^{N}(N^{\gamma}t) = Z^{N}(0) + \sum_{k} Y_{k} \left(\int_{0}^{N^{\gamma}t} \lambda_{k}^{N}(Z^{N}(s))ds \right) \frac{(y_{k,i}' - y_{k,i})}{N^{\alpha_{i}}}$$
$$= Z^{N,\gamma}(0) + \sum_{k} Y_{k} \left(\int_{0}^{t} \lambda_{k}^{N,\gamma}(Z^{N,\gamma}(s))ds \right) \frac{(y_{k,i}' - y_{k,i})}{N^{\alpha_{i}}}$$
(10)

where

$$\lambda_{k}^{N,\gamma}(z) = N^{\gamma+\beta_{k}} \prod_{i=1}^{d} N^{y_{k,i}\alpha_{i}} z_{i} \left(z_{i} - \frac{1}{N^{\alpha_{i}}}\right) \left(z_{i} - \frac{2}{N^{\alpha_{i}}}\right) \cdots \left(z_{i} - \frac{y_{k,i} - 1}{N^{\alpha_{i}}}\right)$$

$$= N^{\gamma+\beta_{k}+y_{k}\cdot\alpha} \prod_{i=1}^{d} z_{i} \left(z_{i} - \frac{1}{N^{\alpha_{i}}}\right) \left(z_{i} - \frac{2}{N^{\alpha_{i}}}\right) \cdots \left(z_{i} - \frac{y_{k,i} - 1}{N^{\alpha_{i}}}\right)$$

$$(11)$$

for $z \in \mathbb{R}^d_{\geq 0}$. Note that since $Z_i^{N,\gamma}(0) = \Theta(1)$ for each i, each scaled intensity $\lambda_k^N(Z^{N,\gamma}(0))$ is $\Theta(\gamma + \beta_k + y_k \cdot \alpha)$. For the set of intensities $\mathcal{K} = \{\lambda_k : y_k \to y'_k \in \mathcal{R}\}$ of the original system X, we associate the set of scaled intensities $\lambda_k^{N,\gamma}$ in (10) with $Z^{N,\gamma}$ and denote by $\mathcal{K}^{N,\gamma}$.

2.4 Projection of Multiscale Reaction Systmes

We can reduce (S, C, R, K^N) to consider only the dynamics of a subset of S by using network projection, which broadly speaking consists of the removal of species from the network as described for the example (1) in Introduction, and the subsequent merging of complexes if needed.

For a given system $(S, C, \mathcal{R}, \mathcal{K})$, to formally define the network projection we introduce two projection functions for complexes and reactions in (S, C, \mathcal{R}) . Let X^N be the stochastic process associated with $(S, C, \mathcal{R}, \mathcal{K})$. We decompose the set of species as $S = S_L \cup S_H$, where $S_L = \{S_i \in S : X_i^N(0) = \Theta(1)\}$ and $S_H = S \setminus S_L$ correspond to species with low and high initial counts, respectively. We enumerate them as $S_L = \{S_1, S_2, \ldots, S_d\}$ and $S_H = \{S_{d+1}, S_{d+2}, \ldots, S_{d+r}\}$. Let $q_L : \mathbb{Z}^{d+r} \to \mathbb{Z}^d$ and $q_H : \mathbb{Z}^{d+r} \to \mathbb{Z}^r$ be projection functions such that for each $v = (v_1, \ldots, v_d, v_{d+1}, \ldots, v_{d+r})^T \in \mathbb{Z}^{d+r}$,

$$q_L(v) = (v_1, v_2, \dots, v_d)^T \in \mathbb{Z}^d$$
 and $q_H(v) = (v_{d+1}, v_{d+2}, \dots, v_{d+r})^T \in \mathbb{Z}^r$. (12)

We demonstrate the usage of q_L and q_H with the network (1) for which we set $S_L = \{A, C\}$ and $S_H = \{B\}$. Since the associated vector for the complex y = A + B in (1) is $y = (1, 1, 0)^T$, we have $q_L(y) = (1, 0)$ and $q_H(y) = 1$. Using a slight abuse of notation, we also denote $q_L(A + B) = A$ and $q_H(A + B) = B$. In the same way, for the reaction $A + B \to \emptyset$, q_L defines the projected reaction $q_L(A + B) \to q_L(\emptyset)$, which is identical to $A \to \emptyset$.

Let $(S, C, \mathcal{R}, \mathcal{K}^N)$ be a given multiscale system. Then by using q_L and q_H we define the projected system $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$. Reactions in \mathcal{R}_L are chosen pertaining to the scale of the reaction intensities in \mathcal{K}^N because reactions of lower order intensities can be neglected. Let $Z^{N,\gamma}(t)$ be the stochastic process associated with $(S, C, \mathcal{R}, \mathcal{K}^N)$ and let θ_0 be the maximum reaction intensity order (9). Then we decompose

$$\mathcal{R} = \mathcal{R}_0 \cup \mathcal{R}_0^c \quad \text{where} \ \mathcal{R}_0 = \{ y_k \to y'_k : \lambda_k(Z^N(0)) = \Theta(\theta_0) \}, \tag{13}$$

and we define the set of projected reactions as

$$\mathcal{R}_L = \{q_L(y_k) \to q_L(y'_k) : y_k \to y'_k \in \mathcal{R}_0 \text{ and } q_L(y_k) \neq q_L(y'_k)\}.$$
(14)

The set of complexes of the projected network C_L is fully characterized with the complexes involved in the reactions in \mathcal{R}_L . To defined the reaction intensities of the scaled process $Z^{N,\gamma}(t)$ associated with the projected network, we first decompose the reaction intensities defined in (11) and then we fix the species in S_H at their initial state. For a given \mathcal{K}^N , each mass-action intensity $\lambda_k^{N,\gamma}$ for a reaction $y_k \to y'_k$ is decomposed as $\lambda_k^{N,\gamma}(z) = \kappa_k \lambda_{L,k}(q_L(z)) \lambda_{H,k}^{N,\gamma}(q_H(z))$ for each $z \in \mathbb{R}^{d+r}_{\geq 0}$, where

$$\lambda_{L,k}(z) = q_L(z)^{(q_L(y_k))}, \text{ and}$$

$$\lambda_{H,k}^{N,\gamma}(z) = N^{\gamma+\beta_k+y_k\cdot\alpha} \prod_{i=d+1}^{d+r} z_i \left(z_i - \frac{1}{N}\right) \cdots \left(z_i - \frac{y_{k,i} - 1}{N}\right).$$
(15)

Let $Z^{N,\gamma}(0) = z^0 = (z_\ell^0, z_h^0)$ such that $z_\ell^0 \in \mathbb{Z}_{\geq 0}^d$ and $z_h^0 \in \mathbb{R}_{\geq 0}^r$. Then by fixing $q_H(Z^{N,\gamma}(t))$ at z_h^0 , we define the reaction intensities of the projected system as

$$\mathcal{K}_L = \left\{ \bar{\lambda}_u(x) = \bar{\kappa}_u x^{(\bar{y}_u)} : \bar{y}_u \to \bar{y}'_u \in \mathcal{R}_L \right\},\tag{16}$$

where

$$\bar{\kappa}_u = \sum_{\substack{y_k \to y_k' \in \mathcal{R} \\ q_L(y_k) = \bar{y}_u, q_L(y_k') = \bar{y}_u'}} \kappa_k s_k, \quad \text{and} \quad s_k = \lim_{N \to \infty} \lambda_{H,k}^{N,\gamma}(z_h^0).$$

 $\bar{\kappa}_u$ serves a reaction rate constant of the projected system. Note that each $\bar{\lambda}_u$ in \mathcal{K}_L is scale-free.

Remark 2.1. The summation in the definition of $\bar{\kappa}_u$ is to consider the case that multiple reactions in \mathcal{R} are projected in to a single reaction $\bar{y}_u \to \bar{y}'_u$ in \mathcal{R}_L .

Remark 2.2. For each $x \in \mathbb{Z}_{\geq 0}^d$, by definition of $\lambda_{L,k}$ we have $x^{(\bar{y}_u)} = \lambda_{L,k}(x)$ for any k such that $q_L(y_k) = \bar{y}_u$. Hence letting k_u be such that $q_L(y_{k_u}) = \bar{y}_u$, \mathcal{K}_L can be represented differently as $\mathcal{K}_L = \{\bar{\lambda}_u(x) = \bar{\kappa}_u \lambda_{k_u}(x) : \bar{y}_u \to \bar{y}'_u \in \mathcal{R}_L\}.$

Remark 2.3. If $y_k \to y'_k \in \mathcal{R}_0$, then $-\theta_0 + \beta_k + y_k \cdot \alpha = 0$ by the definition of θ_0 in (9). Hence for $y_k \to y'_k \in \mathcal{R}_0$

$$s_{k} = \lim_{N \to \infty} \lambda_{H,k}^{N,-\theta_{0}}(q_{H}(Z^{N,-\theta_{0}}(0)))$$
$$= \lim_{N \to \infty} N^{-\theta_{0}+\beta_{k}+y_{k}\cdot\alpha} \prod_{i=1}^{r} z_{h,i}^{0} \left(z_{h,i}^{0} - \frac{1}{N}\right) \cdots \left(z_{h,i}^{0} - \frac{q_{H}(y_{k})_{i} - 1}{N}\right) = (z_{h}^{0})^{q_{H}(y_{k})}$$

If $y_k \to y'_k \in \mathcal{R}^c_0$, otherwise, then $s_k = 0$ since $-\theta_0 + \beta_k + y_k \cdot \alpha < 0$.

We demonstrate the projection of a reaction system with an example.

Example 2.2. Consider a stochastic process $X^N(t)$ associated with a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R}, \mathcal{K})$ such that

$$A + B \xleftarrow[\kappa_2]{\kappa_1/N} 2B, \quad A + C \xrightarrow[\kappa_3]{\kappa_3} 2C, \quad 3C \xleftarrow[\kappa_4/N^2]{\kappa_5N} A, \quad B \xrightarrow[\kappa_6]{\kappa_6} \emptyset.$$

Suppose that $X_A^N(0) = X_B^N(0) = 2$ and $X_C^N(0) = 3N$. Then to reduce the scaled system Z^N , note that $S = S_L \cup S_H$ with $S_L = \{A, B\}$ and $S_H = \{C\}$. To find \mathcal{R}_L , note that $\theta_0 = 1$ and the reaction

intensities of $A + C \rightarrow 2C, 3C \rightleftharpoons A$ and $B \rightarrow \emptyset$ are belonging to \mathcal{R}_0 . Therefore, by projecting those reactions with q_L , we obtain

$$\mathcal{R}_L = \{ A \to \emptyset, \emptyset \to A, B \to \emptyset \},\$$

here note that two reactions $A + C \rightarrow 2C$ and $A \rightarrow 3C$ are merged into the same reaction $A \rightarrow \emptyset$. Finally, by (16)

$$\mathcal{K}_L = \{\bar{\lambda}_{A \to \emptyset}(x) = (s_3\kappa_3 + s_5\kappa_5)x_A, \bar{\lambda}_{\emptyset \to A}(x) = s_4\kappa_4, \bar{\lambda}_{B \to \emptyset}(x) = s_6\kappa_6x_B\}$$

can be defined for each $x = (x_A, x_B) \in \mathbb{Z}_{\geq 0}^2$ by freezing $Z_C^{N,-\theta_0}(t)$ at $Z_C^{N,-\theta_0}(0) = 3$. To compute s_3 , note that $\beta_3 = 0$ and $y_3 \cdot \alpha = 1$. Then as shown in Remark 2.3, for the initial condition $z^0 = (1, 2, 3)$ of the scaled process $Z^{N,-\theta_0}$

$$s_3 = q_H(z^0)^{q_H(y_3)} = 3, \quad s_4 = q_H(z^0)^{q_H(y_4)} = 27$$

$$s_5 = q_H(z^0)^{q_H(y_5)} = 1, \quad s_6 = q_H(z^0)^{q_H(y_6)} = 1.$$

Therefore $(\mathcal{S}_L, \mathcal{C}_L, \mathcal{R}_L, \mathcal{K}_L)$ is described with

$$A \xleftarrow{\frac{3\kappa_3 + \kappa_5}{27\kappa_4}} \emptyset \xleftarrow{\kappa_6} B$$

3 Main Results

In this section, we introduce our main results. In [4, 17], it was shown that if the scaling exponents α_i , β_k , and γ in (10) satisfy certain balance conditions, then species of high abundance follow a system of differential equations with random coefficients, and the species of low abundance follow a piece-wise deterministic Markov process. In this paper, for a given $X^N(t)$ with scaling parameters α_k , β_k , we consider $= Z^{N,-\theta_0}(t)$ under slow-timescale. Under this timescale, we show that the species in S_L approximately follow the projected system $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$ as the scaling parameter tends to infinity. We further investigate the accuracy of this approximation, which has not been investigated in the previous work.

3.1 Main Theorem

For a scaled process $Z^{N,-\theta_0}(t)$ associated with $(S, C, \mathcal{R}, \mathcal{K}^N)$, let Z(t) be the stochastic process associated with the projected system $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_{L,s})$ as defined in Section 2.4 such that $Z(0) = q_L(Z^{N,\gamma}(0))$. We denote by $p^N(\cdot, t)$ and $p(\cdot, t)$ the probability density of $Z^{N,-\theta_0}$ and Z, respectively. Throughout this paper, we always assume that $S = S_L \cup S_H$ such that $S_L = \{S_i \in S \mid X_i^N(0) = \Theta(1)\}$ and $S_H = \{S_i \in S \mid X_i^N(0) = \Theta(N)\}$. We further assume that the stochastic system Z(t) associated with the projected network $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$ is irreducible and admits a stationary distribution π such that

$$\sum_{x \in \mathbb{Z}_{\geq 0}^d} \sum_u \bar{\lambda}_u(x)^2 \pi(x) < \infty.$$
(17)

This condition is required to exclude irregular behavior of Z and in turn $Z^{N,-\theta_0}$ such as explosion.

Theorem 3.1. For each t, $Z^{N,-\theta_0}(t)$ converges to Z in distribution as $N \to \infty$. Furthermore, there exists constants c > 0 and $\nu \in (0,1)$ such that for any measurable set $A \subset \mathbb{R}^{d+r}_{\geq 0}$

$$\sup_{t \in [0,T]} \left| p^N(A,t) - p(A_L,t) \right| \le \frac{c \max\{1, T^2\}}{N^{\nu}} \quad \text{for any } T > 0.$$

where $A_L = \{q_L(z) \mid z \in A\}.$

Remark 3.1. *Two lemmas are required to complete the proof of Theorem 3.1. We introduce the lemmas in Section 3.2.*

Proof. Lemma 3.5 shows that for any M > 0 there exists a compact set $S_M = S_{L,M} \times S_{H,M}$ satisfying (i) $S_{L,M} \subset \mathbb{Z}_{\geq 0}^d$, $S_{H,M} \subset \mathbb{R}_{\geq 0}^r$ and (ii) for any t there exists $c_1 > 0$ such that

$$p^{N}(S_{M}^{c},t) \leq \frac{c_{1}\max\{1,t^{2}\}}{M^{2}} \text{ and } p(S_{L,M}^{c},t) \leq \frac{c_{1}\max\{1,t^{2}\}}{M^{2}}.$$
 (18)

By using this we split the set A as $A = (A \cap S_M) \cup (A \cap S_M^c)$. Thus we have

$$|p^{N}(A,t) - p(A_{L},t)| = |p^{N}(A \cap S_{M},t) + p^{N}(A \cap S_{M}^{c},t) - p(A_{L} \cap S_{L,M},t) - p(A_{L} \cap S_{L,M}^{c},t)| \le |p^{N}(A \cap S_{M},t) - p(A_{L} \cap S_{L,M},t)| + p^{N}(S_{M}^{c},t) + p(S_{L,M}^{c},t).$$

Lemma 3.7 shows that there exist positive constants c_2 and c_3 such that

$$|p^{N}(A \cap S_{M}, t) - p(A_{L} \cap S_{L,M}, t)| \le \frac{c_{2}M^{c_{3}}}{N} \max\{1, t^{2}\}$$
(19)

Thus if we choose $M = N^{\rho}$ for some $\rho < \frac{1}{c_3}$, then by (18) and (19), the result follows with $c = c_1 + c_2$ and $\nu = \min\{2\rho, 1 - \rho c_3\}$.

Figure 1 shows a schematic procedure of the proof of Theorem 3.1.

3.2 Lemmas

In this section, we provide two main lemmas (Lemma 3.5 and 3.7) used in the proof of Theorem 3.1. We further introduce additional lemmas required to proof the main lemmas. We use the usual ∞ -norm and 1-norm for vectors in \mathbb{Z}^m . That is, for $v \in \mathbb{Z}^m$

$$||v||_{\infty} = \max\{v_i : i = 1, 2, \dots, m\}$$
 and $||v||_1 = \sum_{i=1}^m |v_i|.$

Note that the state space of $Z^{N,-\theta_0}$ is a subset of $\mathbb{Z}_{\geq 0}^d \times \mathbb{R}_{\geq 0}^r$. Note further that the state space of $(Z_{d+1}^N, \ldots, Z_{d+r}^N)$ depends on the scaling parameter N, as $Z_i^{N,-\theta_0}(t) = \frac{X_i^N(t/N^{-\theta_0})}{N}$ for $i = d+1, \ldots, d+r$. We denote the state space of $Z^{N,-\theta_0}$ by $\mathbb{S}_\ell \times \mathbb{S}_h$ such that $\mathbb{S}_\ell \subseteq \mathbb{Z}_{\geq 0}^d$ and $\mathbb{S}_h \subseteq \mathbb{R}_{\geq 0}^r$, where $q_L(Z^{N,-\theta_0}(t)) \in \mathbb{S}_\ell$ and $q_H(Z^{N,-\theta_0}(t)) \in \mathbb{S}_h$.



Figure 1: A schematic description of the proof of the main theorem.

In the rest of this manuscript, for $z \in \mathbb{R}^{d+r}_{\geq 0}$ we denote $z_{\ell} = q_L(z)$ and $z_h = q_H(z)$. Then we define $S_M = S_{L,M} \times S_{H,M}$ such that

$$S_{L,M} = \{ z_{\ell} \in \mathbb{S}_{\ell} : ||z_{\ell}||_{\infty} \leq M \}, \text{ and}$$

$$S_{H,M} = \left\{ z_{h} \in \mathbb{S}_{h} : \left| \lambda_{H,k}^{N}(z_{h}) - s_{k} \right| \leq \frac{M}{N} \text{ for any } y_{k} \to y_{k}' \in \mathcal{R}_{0} \right\},$$
(20)

where $M = N^{\rho}$ for arbitrary $\rho \in (0, 1)$. As shown in Figure 1, one of the key ideas for the main theorem is to show that Z^N stays in the compact set S_M within a finite time interval [0, T] with high probability. In the following lemmas, we show that the probability of $Z^{N,-\theta_0}$ escaping S_M is low if N is sufficiently large.

Lemma 3.2. For each $y_k \to y'_k \in \mathcal{R}$, let $\bar{y}_u \to \bar{y}'_u \in \mathcal{R}_L$ such that $q_L(y_k) = \bar{y}_u$ and $q_L(y'_k) = \bar{y}'_u$. Then there exist $\nu_1, \nu_2, c > 0$ such that for any $z \in S_M$

$$\begin{array}{ll} (i) \quad \left| \lambda_k^{N,-\theta_0}(z) - \frac{s_k \kappa_k}{\bar{\kappa}_u} \bar{\lambda}_u(z_\ell) \right| \leq \kappa_k \lambda_{L,k}(z_\ell) \frac{1}{N^{\nu_1}} & \text{if } y_k \to y'_k \in \mathcal{R}_0, \\ (ii) \quad \lambda_k^{N,-\theta_0}(z) \leq \frac{c}{N^{\nu_2}} & \text{if } y_k \to y'_k \in \mathcal{R}_0^c, \text{ and} \\ (iii) \quad \left(1 - \frac{c}{N^{\nu_1}} \right) \sum_u \bar{\lambda}_u(z_\ell) \leq \sum_k \lambda_k^{N,-\theta_0}(z) \leq \left(1 + \frac{c}{N^{\nu_1}} \right) \sum_u \bar{\lambda}_u(z_\ell) + \frac{c}{N^{\nu_2}}. \end{array}$$

for N sufficiently large, where s_k and $\bar{\kappa}_u$ are defined as (16).

The following lemma shows that the number of transitions of Z by time t is on average less than $\max\{1, t^2\}$ assuming (17).

Lemma 3.3. Let J(t) be the number of jumps of Z by time t. If (17) holds, then there exists a constant c such that

$$E(J(t)^2) \le c \max\{1, t^2\} \quad \text{for any } t.$$

Remark 3.2. This guarantees that Z is non-explosive meaning that if we let T_n be the n the transition time of Z, then $\lim_{n\to\infty} T_n = \infty$ almost surely. Then Z does not transition infinitely many times on any finite time interval [0, T], which means Z is uniquely well-defined process satisfying (6) with the intensity functions $\overline{\lambda}_u$.

Now we investigate how many transitions are required for $Z^{N,-\theta_0}(t)$ to escape the set S_M . In the following lemmas, we use the floor function |x| that is the greatest integer less than x.

Lemma 3.4. Let τ_r^N be the first time for $\lfloor r \rfloor$ th transition of $Z^{N,-\theta_0}$. Then there exists a constant c > 0 such that $p^N(S_M^c, t) \le P(\tau_{cM}^N < t)$ for $M = N^{\rho}$ with arbitrary $\rho \in (0, 1)$ as long as N is sufficiently large.

Remark 3.3. Let τ_r be the first time for $\lfloor r \rfloor$ th transition of Z. Then as shown in the proof of Lemma 3.4, $\{z_{\ell} : |z_{\ell} - z_{\ell}^0| \leq c'''M\} \subseteq S_{L,M}$ for some c''' > 0. Therefore $p(S_{L,M}, t) \leq P(\tau_{c'''M} < t)$.

Now, Lemma 3.2 and Lemma 3.4 are combined to show (18). Before we introduce Lemma 3.5, we remind that Z(t) is irreducible. Therefore every state of Z is non-absorbing meaning that $\sum_{u} \bar{\lambda}_{u}(z_{\ell}) > 0$ for any state z. Since $\bar{\lambda}_{u}$ is a non-zero polynomial as defined in (16), it follows that

$$\min_{z_{\ell}} \sum_{u} \bar{\lambda}_{u}(z_{\ell}) > 0, \text{ and so } \min_{z} \sum_{k} \lambda_{k}^{N,-\theta_{0}}(z) > 0.$$
(21)

Lemma 3.5. For any t there exists c > 0 and $\nu_0 > 0$ that

$$p^{N}(S_{M}^{c},t) \leq \frac{c_{1}\max\{1,t^{2}\}}{N^{\nu_{0}}} \quad and \quad p(S_{L,M}^{c},t) \leq \frac{c_{1}\max\{1,t^{2}\}}{N^{\nu_{0}}}$$

Proof. Let the two stopping times τ_M^N and τ_M be defined as Lemma 3.4 and Remark 3.3. Then $p^N(S_M^c, t) \leq P(\tau_{cM}^N < t)$ and $p(S_{L,M}^c, t) \leq P(\tau_{cM} < t)$ for some c > 0. Hence we show the bounds for $P^N(\tau_{cM}^N < t)$ and $P(\tau_{cM} < t)$.

Let $Path_{M'}$ be a collection of all possible $\lfloor cM \rfloor = M'$ consecutive reactions in \mathcal{R} for Z^N started at $Z^N(0) = (z_{\ell}^0, z_h^0)$. Each element $\eta \in Path_{M'}$ is an ordered set of M' reactions in \mathcal{R} . That is,

$$\eta = \{y(\eta, 1) \to y'(\eta, 1), \dots, y(\eta, M') \to y'(\eta, M')\}$$

where $y(\eta, i) \to y'(\eta, i) \in \mathcal{R}$ for each *i*. We define $w(\eta, j)$ be a state after *j* consecutive jumps in η from $Z^{N,-\theta_0}(0) = (x_\ell, x_h)$. That is,

$$w(\eta, j) = Z^{N}(0) + \sum_{i=1}^{j} (y'(\eta, i) - y(\eta, i)) = (w(\eta, j)_{\ell}, w(\eta, j)_{h})$$
(22)

for j = 1, 2, ..., M', where

$$w(\eta, j)_{\ell} = \left(z_{\ell}^{0} + \sum_{i=1}^{j} q_{L}(y'(\eta, i) - y(\eta, i))\right) \text{ and}$$
$$w(\eta, j)_{h} = \left(z_{h}^{0} + \sum_{i=1}^{j} q_{H}(y'(\eta, i) - y(\eta, i))\right).$$

Note that $w(\eta, j) \in S_M$ since we choose c as $Z^{N,-\theta_0}$ needs at least M' transitions to escape S_M . Let $Path_{M',0} = \{\eta : y(\eta, i) \to y'(\eta, i) \in \mathcal{R}_0 \text{ for each } i\}$. Then for $\eta \in Path_{M',0}$ we denote by A_η represent the event of M' consecutive jumps for $Z^{N,-\theta_0}$ along the ordered reactions in $\eta \in Path_{M'}$. Let also \bar{A}_η the event of M' consecutive jumps for Z along the ordered reactions $q_L(y(\eta, 1)) \to q_L(y'(\eta, 1)), \ldots, q_L(y(\eta, M')) \to q_L(y'(\eta, M'))$.

We now show two key steps. First, conditioning on the event A_{η} , the stopping time τ_{cM}^{N} is sum of exponential distributions T_{i}^{N} with rate $\lambda^{N}(w(\eta, j))$ [27], where $\lambda^{N,-\theta_{0}}(z) = \sum_{k} \lambda_{k}^{N,-\theta_{0}}(z)$. More precisely,

$$P(\tau_{cM}^{N} < t | A_{\eta}) = P\left(\sum_{i=1}^{M'} T_{i}^{N} < t\right),$$
(23)

where T_i^N 's are independent exponential distributions with the rate $\lambda^{N,-\theta_0}(w(\eta,i))$. Lemma 3.2 (iii) implies that $\lambda^N(z) \leq 2\bar{\lambda}(z_\ell)$ for $z \in S_M$, where $\bar{\lambda}(z_\ell) = \sum_u \bar{\lambda}(z_\ell)$. Then this combined with (23) implies that

$$P(\tau_{cM}^{N} < t | A_{\eta}) \le P\left(\sum_{i=1}^{M'} T_{i} < t/2\right) = P\left(\tau_{cM} < t/2 | \bar{A}_{\eta}\right),$$
(24)

where T_i 's are independent exponential distributions with the rate $\sum_u \overline{\lambda}_u(w(\eta, i)_\ell)$.

Second, note that for each $\eta \in Path_{M'}$, the event A_{η} occurs if and only if the reaction $y(\eta, i) \rightarrow y'(\eta, i)$ fires at each state $w(\eta, i)$ among all reactions in \mathcal{R} . This implies that

$$P(A_{\eta}) = \prod_{i=1}^{M'} \frac{\lambda_{\eta,i}^{N,-\theta_0}(w(\eta,i))}{\lambda^{N,-\theta_0}(w(\eta,i))},$$

where $\lambda_{\eta,i}^N$ is the intensity function of the reaction $y(\eta, i) \to y'(\eta, i)$. Lemma 3.2 (i) and the fact that $\lambda_{L,k}(z_\ell) = \frac{1}{\bar{\kappa}_u} \bar{\lambda}_u(z_\ell)$ if $q_L(y_k) = \bar{y}_u$ imply that there exists c > 0 such that for each $\eta \in Path_{M',0}$

$$\lambda_{\eta,i}^{N,-\theta_0}(w(\eta,i)) \le \left(\frac{s_k \kappa_k}{\bar{\kappa}_u} + \frac{\kappa_k}{\bar{\kappa}_u N^{\nu_1}}\right) \bar{\lambda}_{\eta,i}(w(\eta,i)_\ell) \le \left(1 + \frac{c}{N^{\nu_1}}\right) \bar{\lambda}_{\eta,i}(w(\eta,i)_\ell)$$
(25)

for some c > 0, where $\bar{\lambda}_{\eta,i}$ denotes the intensity of $q_L(y(\eta, i)) \to q_L(y'(\eta, i))$. Then Lemma 3.2 (iii) and (25) further imply that there exists c > 0 such that for each $\eta \in Path_{M',0}$

$$P(A_{\eta}) \leq \left(\frac{\left(1 + \frac{c}{N^{\nu_{1}}}\right)}{\left(1 - \frac{c}{N^{\nu_{1}}}\right)}\right)^{cM} \prod_{i=1}^{M'} \frac{\bar{\lambda}_{\eta,i}(w(\eta, i)_{\ell})}{\bar{\lambda}(w(\eta, i)_{\ell})} = \left(\frac{\left(1 + \frac{c}{N^{\nu_{1}}}\right)}{\left(1 - \frac{c}{N^{\nu_{1}}}\right)}\right)^{cM} P(\bar{A}_{\eta}), \tag{26}$$

For $\eta \in Path_{M',0}^c$, a reaction $y(\eta, i) \to y'(\eta, i) \in \mathcal{R}_0^c$ for some i. Then

$$P\left(\bigcup_{\eta\in Path_{M',0}^{c}}A_{\eta}\right) \leq P(\text{a reaction in } R_{0}^{c} \text{ fires at a state lying in } S_{M})$$
$$\leq \max_{z\in S_{M}} \max_{y_{k} \to y_{k}' \in R_{0}^{c}} \frac{\lambda_{k}^{N,-\theta_{0}}(z)}{\lambda^{N,-\theta_{0}}(z)}.$$

Hence by Lemma 3.2 (ii) and (21)

$$P\left(\bigcup_{\eta\in Path_{M',0}^{c}}A_{\eta}\right) \leq \frac{c}{N^{\nu_{2}}}$$

$$(27)$$

for some c > 0.

Consequently, by (24), (26) and (27) there exists c > 0 such that

$$P(\tau_{cM}^{N} < t) = P\left(\tau_{cM}^{N} < t, \bigcup_{\eta \in Path_{M',0}} A_{\eta}\right) + P\left(\tau_{cM}^{N} < t, \bigcup_{\eta \in Path_{M',0}^{c}} A_{\eta}\right)$$
(28)

$$\leq \sum_{\eta \in Path_{M',0}} P(\tau_{cM}^{N} < t|A_{\eta})P(A_{\eta}) + \frac{c}{N^{\nu_{2}}}$$

$$\leq \left(\frac{\left(1 + \frac{c}{N^{\nu_{1}}}\right)}{\left(1 - \frac{c}{N^{\nu_{1}}}\right)}\right)^{cM} \sum_{\eta \in Path_{M',0}} P(\tau_{cM} < t/2|\bar{A}_{\eta})P(\bar{A}_{\eta}) + \frac{c}{N^{\nu_{2}}}$$

$$\leq \left(\frac{\left(1 + \frac{c}{N^{\nu_{1}}}\right)}{\left(1 - \frac{c}{N^{\nu_{1}}}\right)}\right)^{rM} P(\tau_{cM} < t/2) + \frac{c}{N^{\nu_{2}}}.$$
(29)

Finally, we let J(t) be the number of jumps of Z by time t as we define in Lemma 3.5. Then, applying the Chebyshev's inequality and the result of Lemma 3.5, we have

$$P(\tau_{cM} < t/2) \le P(J(t/2) > cM) \le \frac{E(J(t/2)^2)}{(cM)^2} \le \frac{c' \max\{1, t^2\}}{M^2},$$
(30)

for some c' > 0. Recall that $M = N^{\rho}$. Then we have

$$\lim_{N \to \infty} \left(\frac{\left(1 + \frac{c}{N^{\nu_1}}\right)}{\left(1 - \frac{c}{N^{\nu_1}}\right)} \right)^{rM} = 1,$$
(31)

because $\nu_1 = 1 - \rho$ as shown in the proof of Lemma 3.2. We further recall that ν_2 in Lemma 3.2 tends to 1, as $\rho \to 0$. Thus we choose ρ sufficiently small. Then by (29)–(31), the desired bounds follow with some ν_0 .

With Lemma 3.5, we can conclude that both $Z^{N,-\theta_0}$ and Z likely stay in S_M and $S_{L,M}$, respectively within [0, t] as long as N is sufficiently large. As the confined set S_M and $S_{L,M}$ have finitely many states, by using this advantage we can compare the probability densities of the two processes confined onto S_M and $S_{L,M}$, respectively. To compare the two probability densities, we use the following multi dimensional Gronwall's inequality [9].

Lemma 3.6. Suppose for any vector $u_0 \in \mathbb{R}^n_{>0}$ with $||u_0||_1 = 1$, a system of differential equation

$$\begin{cases} \frac{d}{dt}u(t) = Au, \\ u(0) = u_0, \end{cases}$$
(32)

admits a unique solution $u(t) \in \mathbb{R}^n_{\geq 0}$ such that $u_i(t) \geq 0$ for each i and $||u(t)||_1 = 1$ for any t. Suppose v satisfies $\frac{d}{dt}v(t) \leq Av(t) + b$ for some $b \in \mathbb{R}^n$. Then for each t,

$$v(t) \le tb + t^2 \bar{A}b,$$

where \bar{A} is an $n \times n$ matrix such that $\bar{A}_{ij} = \max_{k,m} A_{km}$.

As two probability densities p^N and p solve two similar systems of ordinary differential equation, respectively, Lemma 3.6 helps finding the distance between the two densities.

Lemma 3.7. For any t and for any $A \subset \mathbb{R}^{d+r}_{\geq 0}$, there exist c > 0, c' > 0 and $\nu'_0 > 0$ such that

$$|p^{N}(A \cap S_{M}, t) - p(A_{L} \cap S_{L,M}, t)| \le \frac{cM^{c'} \max\{1, t^{2}\}}{N^{\nu'_{0}}},$$

where $A_L = \{q_L(z) : z \in A\}.$

Proof. The probability density $p(z_{\ell}, t)$ of Z(t) satisfies the Kolomogorov forward equation (chemical master equation) (4)

$$\frac{d}{dt}p(z_{\ell},t) = \sum_{u} \bar{\lambda}_{u}(z_{\ell} - \bar{y}'_{u} + \bar{y}_{u})p(z_{\ell} - \bar{y}'_{u} + \bar{y}_{u},t) - \sum_{u} \bar{\lambda}_{u}(z_{\ell})p(z_{\ell},t).$$
(33)

By considering $p(t) = \{p(z, t)\}_{z_{\ell} \in S_{L,M}}$ as a column vector, (33) is equivalent to

$$\frac{d}{dt}p(t) = \mathcal{L}^M p(t) + b_{in}^M - b_{out}^M, \tag{34}$$

where L^M is an $|S_{L,M}| \times |S_{L,M}|$ matrix, and b_{out}^M and b_{in}^M are column vectors. The ij entry $L^M(i, j)$ with $i \neq j$ is the transition rate from the j th state to the i th state in $S_{L,M}$, and $L^M(i, i) = -\sum_j L^M(i, j)$. The the vector b_{in}^M represents the in-flow from $S_{L,M}^c$ to $S_{L,M}$, and hence it is defined as for the i the state $z_\ell \in S_{L,M}$, the i th entry is

$$b_{in}^{M}(i) = \sum_{\substack{\bar{y}_{u} \to \bar{y}'_{u} \\ z_{\ell} - \bar{y}'_{u} + \bar{y}_{u} \in S_{L,M}^{c}}} \bar{\lambda}_{u}(z_{\ell} - \bar{y}'_{u} + \bar{y}_{u})p(z_{\ell} - \bar{y}'_{u} + \bar{y}_{u}, t)$$
(35)

For any $z_{\ell} \in S_{L,M}$, the state $z_{\ell} - \bar{y}'_u + \bar{y}_u$ belongs to $S_{L,rM}$ for some r > 1. Hence $\bar{\lambda}_u(z_{\ell} - \bar{y}'_u + \bar{y}_u) \leq cM^{\max_k} \|\bar{y}_u\|_1$ because $\bar{\lambda}_u$ is a polynomial of degree $\|\bar{y}_u\|_1$. Moreover, by applying Lemma 3.4 and Lemma 3.5 for rM instead of M, we have $p(z_{\ell} - \bar{y}'_u + \bar{y}_u, t) \leq c\frac{\max\{1, t^2\}}{N^{\nu_3}}$ for some $\nu_0 \in (0, 1)$. Therefore with a sufficiently small ρ , each entry $b_{in}^M(i)$ is less than $\frac{c}{N^{\nu_3}}$ for some c > 0 and $\nu_3 \in (0, 1)$. In the same way, we can show also that there exist c > 0 and $\nu_4 \in (0, 1)$ such that $b_{out}^M(i) \leq \frac{c}{N^{\nu_4}}$ for each i. Hence we have the following componentwise inequality from (34):

$$\mathcal{L}^{M}p(t) - b_1^N \le \frac{d}{dt}p(t) \le \mathcal{L}^{M}p(t) + b_1^N,$$
(36)

where b_1^N is a column vector with each entry $\frac{c}{N^{\nu_3}}$.

Now we turn to the Kolomogorov forward equation for $p^N(z,t)$. We first recall that as defined in (10), the reaction vector of $Z^{N,-\theta_0}$ is scaled so that the transition for each entry is $\frac{y'_{k,i}-y_{k,i}}{N^{\alpha_i}}$. Thus we denote this scaled reaction vector by $y'^N_k - y^N_k$. Then for each $z \in S_M$, the distribution $p^N(z,t)$ satisfies

$$\frac{d}{dt}p^{N}(z,t) = \sum_{k} \lambda_{k}^{N,-\theta_{0}}(z-y_{k}^{\prime N}-y_{k}^{N})p^{N}(z-y_{k}^{\prime N}+y_{k}^{N},t) - \sum_{k} \lambda_{k}^{N,-\theta_{0}}(z)p^{N}(z,t).$$
(37)

Then we show that the two differential equations (37) and (33) are similar with Lemma 3.2. Note that as we discussed above, some state $z - y'_k + y_k$ in (37) may be outside S_M . However, such states can be encompassed by S_{rM} for some r > 1, and Lemma 3.2 still holds for S_{rM} with different constant c. Hence we can apply Lemma 3.2 for each $z - y'_k + y_k \in S_M^c$.

Let $p_L^N(z_\ell, t) = \sum_{\substack{z \in A \cap S_M \\ q_L(z) = z_\ell}} p^N(z, t)$, which represents the probability density of the projected

process $q_L(Z^N(t))$. For each $z \in S_{rM}$, if $y_k \to y'_k \in \mathcal{R}_0$, then Lemma 3.2 (i) implies that $\lambda_k^{N,-\theta_0}(z) \leq \frac{s_k \kappa_k}{\bar{\kappa}_u} \bar{\lambda}_u(z_\ell) + \kappa_k \lambda_{L,k}(z_\ell) \frac{1}{N^{\nu_1}}$. Since $\lambda_{L,k}(z_\ell) \leq (cM)^{\max_k \|y_k\|_{\infty}}$ for any $z_\ell \in S_{L,rM}$, there exists c > 0 such that for any $z_\ell \in S_{L,rM}$,

$$\sum_{\substack{z \in A \cap S_M \\ q_L(z) = z_\ell}} \sum_{y_k \to y'_k \in \mathcal{R}_0} \lambda_k^N (z - {y'}_k^N - y_k^N) p^N (z - {y'}_k^N - y_k^N, t)$$

$$\leq \sum_u \bar{\lambda}_u (z_\ell - \bar{y}'_u + \bar{y}_u) p_L^N (z_\ell - \bar{y}'_u + \bar{y}_u, t) + c \frac{M^{\max_k \|y_k\|_\infty}}{N^{\nu_1}}.$$
(38)

Lemma 3.2 (ii) further implies that

$$\sum_{\substack{z \in A \cap S_M \\ q_L(z) = z_\ell}} \sum_{y_k \to y'_k \in \mathcal{R}^c_0} \lambda_k^{N, -\theta_0}(z) p^N(z, t) \le \frac{c M^{\max_k \|y_k\|_\infty}}{N^{\nu_2}}$$
(39)

Hence by using (38) and (39), we take $\sum_{\substack{z \in A \cap S_M \\ q_L(z) = z_\ell}} in$ (37) to show that for sufficiently small ρ there exists c > 0 and $\nu_4 \in (0, 1)$ such that for any $z_\ell \in S_{L,M}$

$$\frac{d}{dt} p_L^N(z_{\ell}, t) = \sum_{\substack{z \in A \cap S_M \\ q_L(z) = z_{\ell}}} \left(\sum_k \lambda_k^{N, -\theta_0} (z - y'_k^N - y^N) p^N (z - y'_k^N + y_k^N, t) - \sum_k \lambda_k^{N, -\theta_0} (z) p^N (z, t) \right) \\
\leq \sum_u \bar{\lambda}_u (z_{\ell} - \bar{y}_u + \bar{y}_u) p^N (z_{\ell} - \bar{y}'_u + \bar{y}_u, t) - \sum_u \bar{\lambda}_u (z_{\ell}) p^N (z_{\ell}, t) + \frac{c}{N^{\nu_4}}.$$

Hence as we derived (36), we have the following componentwise inequality for the column vector $p_L^N(t) = \{p_L^N(z_\ell, t)\}_{z_\ell \in S_{L,M}}$: for some c > 0 and $\nu_5 \in (0, 1)$

$$\mathcal{L}^M p_L^N(t) - b_2^N \le \frac{d}{dt} p_L^N(t) \le \mathcal{L}^M p_L^N(t) + b_2^N,$$

where b_2^N is a column vetor with each entry $\frac{c}{N^{\nu_4}}$. By combining these inequalities with (36), we have

$$\mathcal{L}^{M}(p_{L}^{N}(t) - p(t)) - b^{N} \leq \frac{d}{dt}(p_{L}^{N}(t) - p(t)) \leq \mathcal{L}^{M}(p_{L}^{N}(t) - p(t)) + b^{N},$$
(40)

with a vector b^N such that each entry $b^N(i)$ is $\frac{c}{N^{\nu_5}}$ for some c > 0 and $\nu_5 \in (0, 1)$.

Then we complete this proof applying Lemma 3.6 for (40). Note first that a system of differential equation

$$\begin{cases} \frac{d}{dt}u(t) = \mathcal{L}^M u\\ u(0) = u_0, \end{cases}$$

admits a unique solution u(t) when $||u_0||_1 = 1$ because we can regard \mathcal{L}^M as the transition rate matrix of a continuous time Markov chain defined on $\mathcal{S}_{L,M}$. Hence applying Lemma 3.6 for (40) with $v(t) = p_L^N(t) - p(t)$ and $v(t) = p(t) - p_L^N(t)$ respectively, we have

$$|p_L^N(t) - p(t)| \le tb^N + t^2 |S_{L,M}| \mathcal{L}_{max}^M b^N,$$

where \mathcal{L}_{max}^{M} is the maximum entry of \mathcal{L}^{M} . Each entry of \mathcal{L}^{M} is either the reaction intensity $\bar{\lambda}_{u}(z_{\ell})$ or finite sum of $\bar{\lambda}_{u}(z_{\ell})$ at some $z_{\ell} \in S_{L,M}$. Hence \mathcal{L}_{max}^{M} can be bound by $cM^{\max_{u}} \|\bar{y}_{u}\|_{1}$ for some c > 0 because $\max_{u} \max_{z_{\ell} \in S_{L,M}} \bar{\lambda}_{u}(z_{\ell}) \leq cM^{\max_{u}} \|\bar{y}_{u}\|_{1}$ for some c > 0. Furthermore note that $|S_{L,M}| \leq M^{d}$ and each entry of b^{N} is $\frac{c}{N^{\nu_{4}}}$. Hence for each $z_{\ell} \in S_{L,M}$, we have

$$|p^{N}(A \cap S_{M}, t) - p(A_{L} \cap S_{L,M}, t)| \le \sum_{z_{\ell} \in S_{L,M}} |p_{L}^{N}(z_{\ell}, t) - p(z_{\ell}, t)| \le \frac{cM^{c'} \max\{1, t^{2}\}}{N^{\nu'_{0}}}$$

with sufficiently small ρ and some $\nu'_0 \in (0, 1)$.

4 Theorem **3.1** with general kinetics

Theorem 3.1 can hold for a reaction system under general kinetics as long as the scaled reaction intensities (11) satisfy the following conditions.

(CD1) The scaled reaction intensity for $Z^{N,\gamma}(t)$ is also decomposed as following: for z such that $q_L(z) \in \mathbb{Z}_{\geq 0}^d$ and $Nq_H(z) \in \mathbb{Z}_{\geq 0}^r$

$$\lambda_k^{N,\gamma}(z) = \kappa_k \lambda_{L,k}(q_L(z)) \lambda_{H,k}^{N,\gamma}(q_H(z)).$$

(CD2) $\lambda_{L,k}$ grows polynomially: for any k, there exist positive constants c_1 such that

$$\lambda_{L,k}(z_\ell) \le c_1 \|z_\ell\|_{\infty}^{c_2} \quad \text{for any } z_\ell \in \mathbb{Z}^d_{\ge 0}.$$

(CD3) The limit $\lim_{N\to\infty} \lambda_{H,k}^{N,\gamma}(z_h)$ exists for each $z_h \in \mathcal{R}_{\geq 0}^r$ and we denote this limit by $\bar{\lambda}_{H,k}(z_h)$. Furthermore if $|z - z^0| \leq \frac{M}{N}$, then

$$|\bar{\lambda}_{H,k}(z_h) - s_k| \leq rac{M}{N} \quad ext{and} \quad |\lambda_{H,k}^{N,\gamma}(z_h) - \bar{\lambda}_{H,k}(z_h)| \leq rac{1}{N},$$

where $s_k = \lim_{N \to \infty} \lambda_{H,k}^{N,\gamma}(z_h^0)$ with an initial condition $z_h^0 \in \mathcal{R}_{\geq 0}^r$,

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Remark 4.1. Conditions (CD1)–(CD3) hold under the stochastic mass action kinetics (5).

Remark 4.2. Polynomials, MichaelisMenten kinetics, hill functions and logarithms satisfy (CD2) and (CD3).

Note that Lemma 3.4 can be proved by using conditions (CD1)–(CD3) without properties of mass action kinetics. The other lemmas still hold without further modifications in the proofs. Thus for general kinetics satisfying conditions (CD1)–(CD3), Theorem (3.1) holds.

5 Examples

We apply Theorem 3.1 for several multiscale biological systems. In the follow examples, the probability density of low order species in S_L can be approximated with explicit forms.

5.1 Futile Cycle

A futile cycle system (41) appears in [11, 22] as an example for computing rare event probabilities. In the system, species S_2 is transformed to S_5 through intermediate species S_3 , and this transformation is catalyzed with S_1 . In the opposite way, S_4 catalyzes the transform of S_5 to S_2 with the intermediate form S_6 . We added synthesis and degradation of the catalysts S_1 and S_6 to the original model.

$$S_{1} + S_{2} \xrightarrow{\kappa_{1}} S_{3}, \quad S_{3} \xrightarrow{\kappa_{2}} S_{1} + S_{2}, \quad S_{3} \xrightarrow{\kappa_{3}} S_{1} + S_{5}$$

$$S_{4} + S_{5} \xrightarrow{\kappa_{4}} S_{6}, \quad S_{6} \xrightarrow{\kappa_{5}} S_{4} + S_{5}, \quad S_{6} \xrightarrow{\kappa_{6}} S_{4} + S_{2},$$

$$\emptyset \xrightarrow{\kappa_{7}}_{\kappa_{8}} S_{1}, \quad \emptyset \xrightarrow{\kappa_{9}}_{\kappa_{10}} S_{6}.$$

$$(41)$$

Let N be the scaling parameter. We set the initial copies of the species as S_2 , S_3 , S_5 and S_6 have initially high copies and S_1 and S_4 have initially low copies. In particular, $X_i^N(0) = N$ for $i = 2, 5, 6, X_3^N(0) = 2N, X_1^N(0) = 2$ and $X_4^N(0) = 1$. Hence $S_L = \{S_1, S_4\}$ and $S_H = \{S_2, S_3, S_5, S_6\}$. We choose the same rate constants as used in [11, 22], and we assume that the scaling parameter $\beta_k = 0$ for all the reaction rate constants so that $\kappa_i = 0.1$ for i = 3, 6 and $\kappa_i = 1$ otherwise.

Under the mass-action kinetics, the initial reaction intensities are $\lambda_1(X^N(0)) = \kappa_1 X_1^N(0) X_2^N(0) = \kappa_1 2N, \ \lambda_2(X^N(0)) = \kappa_2 X_3^N(0) = \kappa_2 2N, \ \text{and so on. Note}$ that $\lambda_k(X^N(0)) = \Theta(N)$ for each $y_k \to y'_k \in \mathcal{R}_0$, so the maximum order of the initial reaction intensity is $\theta_0 = 1$. By definition of \mathcal{R}_0 (13), the reactions are classified into \mathcal{R}_0 and \mathcal{R}_0^c where \mathcal{R}_0^c contains the 7 and 8 th reactions, and the other reactions belong to \mathcal{R}_0 .

We consider the scaled process $Z^{N,-\theta_0}(t)$ such that $Z^{N,-\theta_0}(t) = N^{-\alpha_i}X^N(N^{-\theta_0}t)$. We also consider the projected system $(\mathcal{S}_L, \mathcal{C}_L, \mathcal{R}_L, \mathcal{K}_L)$. By fix all the species \mathcal{S}_H at their initial values, we obtain the parameter s_k for the projected system such that

$$s_1 = \lim_{N \to \infty} \lambda_{H,1}^{N,-\theta_0}(Z^{N,-\theta_0}(0)) = \lim_{N \to \infty} \frac{N^{\beta_1 + y_1 \cdot \alpha}}{N^{\theta_0}} \frac{X_2^N(0)}{N} = 1,$$

and so on. Thus as shown in Section 2.4 the projected system $(\mathcal{S}_L, \mathcal{C}_L, \mathcal{R}_L, \mathcal{K}_L)$ is defined as

$$S_1 \xrightarrow[]{\kappa_1} \emptyset \xrightarrow[]{\kappa_5 + \kappa_6} S_4.$$
(42)

Both S_1 and S_4 in (42) follow a simple birth-death process and hence the stationary distribution of Z is a Poisson distribution so that the condition (17) holds. Furthermore, unlikely in the original model (41), probability densities of species S_1 and S_5 at time t are analytically tractable as it is shown in [15] that the time evolution of the probabilities for a linear birth-death process is a convolution of Poisson distributions and multinomial distributions. Thus we can analytically approximate the dynamics of the species in S_L of the original system (41). Figure 2A displays the density function of S_1 for $Z^{N,-\theta_0}(10)$ and the reduced system Z(10) with N = 100. Figure 2B displays the accuracy of the approximation indicating the convergence rate in the scaling parameter N as proved in Theorem 3.1.

5.2 Yeast Polarization

In this section, we consider a signal-transduction pathway (43), which was introduced in [11]. In the system, species G, so-called 'G-proten', serves an important role in yeast polarization [24]. G goes through a separation-dephosphorylation-rebind cycle, as the 5th,6th and 7th reactions describe in (43), respectively. And this cycle is activated by ligand-receptor binding.

$$\emptyset \xrightarrow{\kappa_1/N}_{\kappa_2/N} R, \quad L + R \xrightarrow{\kappa_3/N} RL + L, \quad RL \xrightarrow{\kappa_4/N} R,,$$

$$RL + G \xrightarrow{\kappa_5} G_a + G_{bg} \quad G_a \xrightarrow{\kappa_6/N} G_d,$$

$$G_d + G_{bg} \xrightarrow{\kappa_7} G, \quad \emptyset \xrightarrow{\kappa_8} RL.$$
(43)

We model this yeast polarization system with a multiscale stochastic mass-action system. Let N be the scaling parameter. We suppose that the initial copies of ligand L, protein G and its subunit G_{bg} are $\Theta(1)$, and other species have the copy numbers of order N. More precisely, for a multiscale process $X^N(t)$ associated with (43), we set $X^N_R(0) = N, X^N_L(0) = 2, X^N_{RL}(0) = N, X^N_G(0) = 5, X^N_{G_{\alpha}}(0) = N, X^N_{G_{bg}}(0) = 5$ and $X^N_{G_d}(0) = N$. As described in (43), we scale the rate constants (see the caption of Figure 2 for the values of κ_i 's). Then by computing the reaction intensities at $X^N(0)$, we have the maximum order of reaction intensity θ_0 and then we classify the reactions into $\mathcal{R}_0 = \{y_k \to y'_k : k = 5, 7\}$ and \mathcal{R}^c_0 . We approximate the scaled process $Z^{N,-\theta_0}(t)$ under slow-timescale with the projected system

We approximate the scaled process $Z^{N,-\theta_0}(t)$ under slow-timescale with the projected system $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$. The parameters s_k defined around (16) are

$$s_5 = \lim_{N \to \infty} \lambda_{H,5}^{N,-\theta_0} = \lim_{N \to \infty} N^{-\theta_0 + \beta_5 + y_5 \cdot \alpha} Z_{RL}^{N,-\theta_0}(0) = 1,$$

$$s_7 = \lim_{N \to \infty} \lambda_{H,7}^{N,-\theta_0} = \lim_{N \to \infty} N^{-\theta_0 + \beta_7 + y_7 \cdot \alpha} Z_{G_d}^{N,-\theta_0}(0) = 1.$$

Then the projected system is

$$G \underset{\kappa_7}{\underbrace{\underset{\kappa_7}{\leftarrow}}} G_{bg}. \tag{44}$$

The stochastic process $Z(t) = (Z_G(t), Z_{G_{bg}}(t))$ associated with (44) admits a finite state space as the total quantity of G and G_{bg} is preserved. Hence (17) hold. Furthermore the probability density function can be analytically derived as $p(t) = \mu e^{-Qt}$ where Q is the transition matrix of Z defined on $\{(z_1, z_2) : z_1 + z_2 = Z_G(0) + Z_{G_{bg}}(0) = 10\}$ and μ is the initial distribution of Z such that $\mu(5,5) = 1$. We show model reduction in Figure 2CD with almost the same rate constants used in [11]. In Figure 2C, letting N = 1000, we compare the probability densities of G_{bg} of $Z^{N,-\theta_0}$ associated with (43) and its reduced system Z associated with (44) at time t = 10. Figure 2D furthermore shows the convergence rate of the approximation.

5.3 p53 response to DNA damage

Network (45) describes signaling pathway and negative feedback for activating p53 proteins in damages DNA, which is introduced in [5]. When DNA is damages, signaling kinases (S) such as ATM and Chk2 convert inactive p53 protein (P_0) to active p53 protein (P). The p53 protein also represses itself by the negative feedback loop with the Mdm2 protein (M). Another negative feedback loop between p53, the signal and inhibitor (I) is also present in this system. See a schematic description of this system in [5, Figure 1B]

$$P_{0} + S \xrightarrow{N\kappa_{1}} P + S,$$

$$P_{0} + M \xrightarrow{\kappa_{2}} M, \qquad P + M \xrightarrow{\kappa_{3}} M,$$

$$P \xrightarrow{\kappa_{4}} P + M, \qquad P \xrightarrow{\kappa_{5}} P + I,$$

$$S + M \xrightarrow{\kappa_{6}/N} S, \qquad S + I \xrightarrow{\kappa_{7}} I,$$

$$P \xrightarrow{\kappa_{8}} \emptyset \xrightarrow{\kappa_{10}} M, \qquad S \xrightarrow{\kappa_{12}} \emptyset \xleftarrow{\kappa_{14}} I.$$

$$(45)$$

To match the initial setting used in [5], we assume that the inhibitor has low copies at the beginning. Furthermore we assume that P_0 and P have also initially low copies. Precisely, $X_{P_0}^N(0) = 5, X_{P_0}^N(0) = 0, X_I^N(0) = 1, X_N^N(0) = N$ and $X_S^N(0) = 5N$. Hence $S_L = \{P_0, P, I\}$ and $S_H = \{M, S\}$. For each state $x = (x_{P_0}, x_P, x_S, x_M, x_I)$, the reaction intensities λ_1 and λ_7 contain hill-functions as

$$\lambda_1(x) = N\kappa_1 x_{P_0} \frac{x_S}{x_S + c_1}, \quad \text{and} \quad \lambda_7(x) = \kappa_7 x_S \frac{x_I}{x_I + c_2},$$

for some positive constants c_1 and c_2 . The other intensities follow the mass-action kinetics (5). Under the scaled rate constants shown in (45). Then the maximum order θ_0 of the intensities is 1 so that \mathcal{R}_0 contains reaction 1, 2, 3, 6, 7, 9, 11 and 12. For the process $Z^{N,-\theta_0}(t)$ under slowtimescale, the associated projected network $(\mathcal{S}_L, \mathcal{C}_L, \mathcal{R}_L, \mathcal{K}_L)$ is

$$\begin{array}{c} P_0 \xrightarrow{s_1 \kappa_1} & P \\ s_8 \kappa_8 \swarrow & s_2 \kappa_2 & \swarrow & s_3 \kappa_3 \\ \emptyset & & & & & & & & \\ \end{array}$$

where the parameters s_k 's are defined as in (16). Especially for the non-mass action intensity $\lambda_1^N(Z^{N,-\theta_0}(0))$ we have

$$s_1 = \lim_{N \to \infty} \lambda_{H,1}^{N,-\theta_0}(q_H(Z^{N,-\theta_0}(0)) = N^{-\theta_0+\beta_1} \frac{N}{N+c_1} = 1.$$



Figure 2: AB. Model reduction for the futile system (41). Parameters are $\kappa_3 = 0.1$ and $\kappa_6 = 0.1$, and $\kappa_i = 1$ otherwise. The probability density of the original model is calculated with 10^5 times of Gillespie's simulations [13]. A. Comparison of the distributions $P(S_1^{N,-\theta_0}(t) = z_\ell)$ and $P(S_1(t) = z_\ell)$ at t = 100 with $N = 10^4$. B. Convergence $d(N) = |P(Z^{N,-\theta_0}(t))| \in$ $A) - P(Z(t) \in A)$ as N increases for $A = \{S_1 = 3 \text{ or } 4\}$ at t = 100. CD. Model reduction for the yeast polarization system (43). Parameters are $\kappa_1 = 3.8, \kappa_2 = 40, \kappa_3 = 42, \kappa_4 =$ $10, \kappa_5 = 0.011, \kappa_6 = 10, \kappa_7 = 1$ and $\kappa_8 = 3.21$. The probability density of the original model is calculated with 10^7 times of Gillespie's simulations. C. Comparison of the distribu-tions $P(G_{bg}^{N,-\theta_0}(t) = z_\ell)$ and $P(G_{bg}(t) = z_\ell)$ at t = 10 with $N = 10^3$. D. Convergence of $d(N) = |P(Z^{N,-\theta_0}(t) \in A) - P(Z(t) \in A)|$ as N increases for $A = \{S_1 = 3 \text{ or } 4\}$ at t = 100. EF. Model reduction for the system of p53 response (45). The parameters κ_i are 1.1, 0.6, 0.3, 0.3, 3.4, 4.5, 4.1, 0.6, 1.1, 0.9, 1.9, 3.2, 3.2, and 3.0 for i = 1, 2..., 14, respectively. Furthermore $c_1 = 4.7$ and $c_2 = 1.9$. Each parameter is sampled uniformly in [0, 5]. 10⁷ Gillespie's simulations are used to estimate the probability densities of the original and reduced models. E. Comparison of the distributions $P(P_1^{N,-\theta_0}(t) = z_\ell)$ and $P(P(t) = z_\ell)$ at t = 100 with $N = 10^5$. F. Convergence $d(N) = |P(P^{N, -\theta_0}(t) \in A) - P(P(t) \in A)|$ as N increases for $A = \{P = 3 \text{ or } 4\}$ at t = 100. **GH.** Model reduction for the population model (46). The parameters κ_i are 0.5, 1.7, 3.9, 4.6, 2.7, 1.9, 6.1, 2.4, and 1.5 for i = 1, 2..., 9, respectively. Each parameter is sampled uniformly in [0, 5]. We sampled 10^5 trajectories with Gillespie's algorithm to estimate the probability densities of the original and reduced models. G. Comparison of the distributions $P(B^{N,-\theta_0}(t) = z_\ell)$ and $P(B(t) = z_\ell)$ at t = 150 with $N = 10^5$. H. Convergence $d(N) = |P(B^{N,-\theta_0}(t) \in U) - P(B(t) \in U)|$ as N increases for $U = \{B \ge 10\}$ at t = 150. The yellow straight lines in **BDFH** indicate that the convergence rate of d(N) to 0 is in $\Theta(\frac{1}{N^{\nu}})$ for some $\nu \in (0, 1)$.

Note that these intensities under non-mass action kinetics satisfy (CD1)–(CD3). Let Z(t) be the stochastic process associated with $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$. The time evolution of the probability density of Z(t) is analytically intractable. However, it can be shown that the probability density converges

to a unique stationary distribution, which can be explicitly derived. $(S_L, C_L, \mathcal{R}_L, \mathcal{K}_L)$ satisfies special network structure, so-called *zero deficiency* and *weakly reversible*, and hence its stationary distribution is a product form of Poisson distributions [2, Theorem 6.1]. See Appendix for more details.

Figure 2E displays the probability distribution of the original and reduced models along with Poisson distribution of rate $\mu = 2.4$, which is the average of P in $(S_L, C_L, \mathbb{R}_L, \mathcal{K}_L)$. A commodity machine was used to simulate the samples in parallel (parfor in Matlab with 6 workers) and took 317 sec for the original model and 2.4 sec for the reduced model. We also show the convergence of the original model in Figure 2E.

5.4 Three species Lotka-Volterra model with migration

We consider a multiscale Lotka-Volterra population model (46) with the scailing parameter N. There exists three species in the network where A is the lowest level prey, B is the middle level species, and C is the top level predator.

$$B \stackrel{\kappa_1}{\underset{\kappa_2}{\longleftarrow}} \emptyset, \quad A \stackrel{\kappa_3/N}{\underset{\kappa_4}{\longleftarrow}} \emptyset, \quad C \stackrel{\kappa_5}{\underset{\kappa_6}{\longleftarrow}} \emptyset,$$

$$A \stackrel{\kappa_7/N}{\underset{\kappa_7}{\longrightarrow}} 2A, \quad A + B \stackrel{\kappa_8/N}{\underset{\kappa_8}{\longrightarrow}} 2B, \quad B + C \stackrel{\kappa_9}{\underset{\kappa_9}{\longrightarrow}} 2C.$$
(46)

We use non-mass action kinetics for the reactions $A + B \rightarrow 2B$ and $B + C \rightarrow 2C$ to model 'weak hunting' of B and C such that for each $x = (x_A, x_B, x_C)$,

$$\lambda_8(x) = \frac{\kappa_8}{N} x_A \sqrt{x_B}$$
 and $\lambda_9(x) = \kappa_9 \log(x_B x_C + 1).$

The other reaction intensities obey the mass-action kinetics. We assume that $S_L = \{B, C\}$ and $S_H = \{A\}$ as $X_A^N(0) = N$, $X_B^N(0) = 10$ and $X_C^N(0) = 10$. Under the scaled rate constants shown in (46), the maximum order of the reaction intensities θ_0 is 0, and every reaction belongs to \mathcal{R}_0 . Note that we assumed that slow birth and slow degradation of A so that the associated reaction rate constants for the 3rd and 7th reactions are of order $\frac{1}{N}$.

For the scaled process $Z^{N,-\theta_0}(t)$, the scaled reaction intensities are decomposed as defined in (15), especially for each $z = (z_A, z_B, z_C) \lambda_{H,8}^{N,-\theta_0} = N^{\beta_8+y_8\cdot\alpha} z_A, \lambda_{L,8} = \kappa_8 \sqrt{z_B}, \lambda_{H,9}^{N,-\theta_0} = 1$ and $\lambda_{L,9} = \kappa_9 \log(z_B z_C + 1)$. Hence (CD1)–(CD3) hold.

Now we consider the projected system. As the the reaction $A+B \rightarrow 2B$ obeys non-mass action kinetics involving $A \in S_H$, parameter the s_8 is especially computed as $s_8 = \lim_{N\to\infty} \lambda_{H,8}^N(Z^{N,-\theta_0}(0)) =$ 1. Hence the projected system is

$$B \underset{\kappa_2}{\overset{\kappa_1}{\underset{\kappa_2}{\longleftarrow}}} \emptyset, \quad C \underset{\kappa_6}{\overset{\kappa_5}{\underset{\kappa_6}{\longleftarrow}}} \emptyset \quad B \xrightarrow{\kappa_8} 2B, \quad B + C \xrightarrow{\kappa_9} 2C.$$
(47)

Let Z(t) be the stochastic process associated with (47) In Appendix, we show how to use the Foster-Lyapunov criterion [23] to verify that a stationary distribution π of Z exists and how π meets the condition (17). The approximation and convergence rates of species B is shown in Figure 2G and H. A commodity machine was used to approximate the probability densities in parallel (parfor in Matlab with 6 workers) and took 174 sec for the original model and 70 sec for the reduced model.

6 Discussion

When a stochastic biochemical reaction system contains species with different orders of abundance, one can model the system using a multiscaling approach. We have shown in this paper that a multiscale stochastic reaction a short-term timescale can be approximated using a reduced stochastic system with a specific error bound.

The scaling regime we considered in this paper is a special case of the scaling under the socalled species balance condition, which was introduced in [17]. More general multiscaling limits of stochastic reactions introduced by Kurtz and others rely on the law of large numbers and relative compactness of probability measures in a metric spaces [1, 4, 17, 21]. This general framework covers a wide range of multiscaling limits, but the convergence rate in the general case remains unknown. Instead of the classical methods, here we have used a direct analysis of the Kolmogorov forward equation, and we also use the state space truncation through FSP to exploit the distance between two probability measures more explicitly.

One of the key steps for the main result was to show that the concentrations of the order N species are confined near the initial concentrations. To do this, we showed that the multiscale model is non-explosive by assuming that the reduced system admits a stationary distribution satisfying a finite moment condition. Indeed, this assumption implies the tightness of the family of multiscale stochastic processes, which in turn implies the relative compactness of the sequence of probability measures. This assumption is also closely related to some technical conditions on stoichiometric coefficients such as the binary or unary conditions assumed in [1, 17].

We can generalize the rate of the convergence in the main result if all the moments of the stationary distribution π in 17 are finite. Based on a suggestion by Chaojie Yuan for this case, we used the BurkholderDavisGundy inequality [6] and were able to prove inductively the alternative result that $E(J(t)^m) \leq ct^m$ in Lemma 3.3. By combining this result with the other lemmas with slight modifications, it follows that

$$|p^N(A, \mathbb{R}^r_{\geq 0}, t) - p(A, t)| \le \frac{c \max\{1, t^m\}}{N^{\nu}} \quad \text{for any } \nu \in (0, 1).$$

The main result in this paper can shed light on the applicability of multiscaling model approximations for the analysis of stochastic reaction systems. In the analysis that we proposed for the multiscale model reduction, the convergence of the probability measure has been exhibited more explicitly than in the existing literature. The main result can also strengthen the applicability of this theoretical framework to practical problems in systems biology such as rational circuit design and the study of absolute robustness [20].

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Appendix A: Table of symbols

Symbol	Meaning
$\mathcal{S}, \mathcal{C}, \mathcal{R} \text{ and } \mathcal{K}$	Set of species, complexes, reaction and reaction intensities, respectively
$X_i(t)$	The count of i th species at time t
$X^N(t)$	A multiscale stochastic model associated with a reaction network
$Z^{N,\gamma}(t)$	A scaled process
d	Number of species of low initial copies
r	Number of species of high initial copies
$\mathbb{Z}^d_{\geq 0}$	$\{x \in \mathbb{Z}^d : x_i \ge 0 \text{ for each } i\}$
$\mathcal{R}_{>0}^{\overline{r}}$	$\{z \in \mathbb{R}^r : z_i \ge 0 \text{ for each } i\}$
$p^{N}(\bar{\cdot},t)$	Probability density function of $Z^{N,-\theta_0}(t)$
$p(\cdot,t)$	Probability density function of $Z(t)$
$n^{(k)}$	$n(n-1)\cdots(n-k+1)\mathbb{1}_{n\geq k}$ for non-negative integers n and k
$u^{(v)}$	$\prod_{i=1}^{d} u_i^{(v_i)}$ for $u, v \in \mathbb{Z}_{\geq 0}^d$
u^v	$\prod_{i=1}^{d} u_i^{v_i}$ for $u, v \in \mathbb{R}_{\geq 0}^{\overline{d}}$
\mathcal{S}_L	Set of species such that $X_i(0) = \Theta(1)$
\mathcal{S}_{H}	Set of species such that $X_i(0) = \Theta(N)$
λ_k	Reaction intensity of X^N associated with the k th reaction.
$\lambda_k^{N,\gamma}$	Reaction intensity of $Z^{N,\gamma}$ associated with the k th reaction (11).
$\lambda_{L,k}, \lambda_{H,k}^{N,\gamma}$	Decomposition of $\lambda_k^{N,\gamma}$ (15).
$y'^N - y^N$	The scaled reaction vector with the <i>i</i> th component $\frac{y'_{k,i}-y_{k,i}}{N^{\alpha_i}}$

Appendix B: Proof of Lemmas in Section 3.2

Proof of Lemma 3.2. Suppose first that $y_k \to y'_k \in \mathcal{R}_0$. As defined in (15), we use the decomposition of $\lambda_k^{N,-\theta_0}(z) = \kappa_k \lambda_{L,k}(z_\ell) \lambda_{H,k}^{N,-\theta_0}(z_h)$. As we discussed in Remark 2.2, the intensities of Z can be calculated as $\bar{\lambda}_u(z_\ell) = \bar{\kappa}_u(z_\ell)^{(\bar{y}_u)} = \bar{\kappa}_u \lambda_{L,k}(z_\ell)$ if $q_L(y_k) = \bar{y}_u$. Hence by definition of S_M in (20),

$$\begin{aligned} \left| \lambda_k^{N,-\theta_0}(z) - \frac{s_k \kappa_k}{\bar{\kappa}_u} \bar{\lambda}_u(z_\ell) \right| &= \kappa_k \lambda_{L,k}(z_\ell) \left| \lambda_{H,k}^{N,-\theta_0}(z_h) - s_k \right| \\ &\leq \kappa_k \lambda_{L,k} \frac{M}{N} = \kappa_k \lambda_{L,k} \frac{1}{N^{1-\rho}}, \end{aligned}$$
(48)

for each $z \in S_M$. Therefore (i) follows with $\nu_1 = 1 - \rho$.

To show (ii), we recall that $-\theta_0 + \beta_k + y_k \cdot \alpha < 0$ for each $y_k \to y'_k \in \mathcal{R}^c_0$, which implies that for $Z^{N,-\theta_0}(0) = z^0$

$$s_k = \lim_{N \to \infty} N^{-\theta_0 + \beta_k + y_k \cdot \alpha} \prod_{i=d+1}^{d+r} z_i^0 \left(z_i^0 - \frac{1}{N} \right) \cdots \left(z_i^0 - \frac{y_i - 1}{N} \right) = 0.$$

Thus (ii) follows with $\nu_2 = 1 - \rho(\max_k ||q_L(y_k)||_{\infty} + 1)$ by choosing sufficiently small $\rho \in (0, 1)$

for $M = N^{\rho}$ because for $z \in S_M$

$$\lambda_k^{N,-\theta_0}(z) \le \kappa_k \lambda_{L,k(z_\ell)} \frac{M}{N} \le \kappa_k M^{\|q_L(y_k)\|_{\infty}} \frac{M}{N} = \kappa_k \frac{1}{N^{\nu_2}}$$

Lastly, to show that (iii) we note that $\sum_{y \to y' \in \mathcal{R}_0} s_k \kappa_k \lambda_{L,k}(z) = \sum_u \kappa_u \bar{\lambda}_u(z)$. Then by (i) and (ii) there exists c > 0 such that for any $z \in S_M$

$$\begin{split} \sum_{k} \lambda_{k}^{N,-\theta_{0}}(z) &= \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \lambda_{k}^{N,-\theta_{0}}(z) + \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}^{c}} \lambda_{k}^{N,-\theta_{0}}(z) \\ &\leq \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \left| \lambda_{k}^{N,-\theta_{0}}(z) - \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell}) \right| + \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell}) \\ &+ \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \lambda_{k}^{N,-\theta_{0}}(z) \\ &\leq \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{\kappa_{k}\lambda_{L,k}(z_{\ell})}{N^{\nu_{1}}} + \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell}) + \frac{c}{N^{\nu_{2}}} \\ &\leq \frac{c}{N^{\nu_{1}}}\sum_{u} \bar{\lambda}_{u}(z_{\ell}) + \sum_{u} \bar{\lambda}_{u}(z_{\ell}) + \frac{c}{N^{\nu_{2}}} = \left(1 + \frac{c}{N^{\nu_{1}}}\right)\sum_{u} \bar{\lambda}_{u}(z_{\ell}) + \frac{c}{N^{\nu_{2}}}. \end{split}$$

Then by (21), the upper bound of $\sum_k \lambda_k^{N,-\theta_0}(z)$ follows. The lower bound also holds as

$$\sum_{k} \lambda_{k}^{N,-\theta_{0}}(z) \geq \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \lambda_{k}^{N,-\theta_{0}}(z)$$

$$\geq \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \left(\lambda_{k}^{N,-\theta_{0}}(z) - \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell}) \right) + \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell})$$

$$\geq -\sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{\kappa_{k}\lambda_{L,k}(z_{\ell})}{N^{\nu_{1}}} + \sum_{y_{k} \to y_{k}' \in \mathcal{R}_{0}} \frac{s_{k}\kappa_{k}}{\bar{\kappa}_{u}}\bar{\lambda}_{u}(z_{\ell})$$

$$\geq \left(-\frac{c}{N^{\nu_{1}}} + 1\right)\sum_{u}\bar{\lambda}_{u}(z_{\ell})$$

Proof of Lemma 3.3. By the random-time representation (6), $J(t) = \sum_{\bar{y}_u \to \bar{y}'_u \in \mathcal{R}_L} Y_u \left(\int_0^t \bar{\lambda}_u(Z(s)) ds \right), \text{ where } Y_u \text{ are independent unit Poisson random variables.}$ Note that for each u,

$$Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right) - \int_0^t \bar{\lambda}_u(Z(s))ds$$

is a Martingale process [3]. We denote by $M_u(t)$ this Martingale. Then the quadratic variation of $M_u(t)$ is $[M_u](t) = Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right)$. Since $M_u^2(t) - [M_u](t)$ is a martingale [3], we have that by using Jansen's inequality

$$E\left(Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right)^2\right) \le 2E(M_u(t)^2) + 2E\left(\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right)^2\right)$$
$$\le 2E([M_u](t)) + 2tE\left(\int_0^t \bar{\lambda}_u(Z(s))^2ds\right)$$
(49)

For a fixed initial value $Z(0) = z^0$, there exists c > 0 such that $P(Z(s) = z) \le c\pi(z)$ for any z because

$$\pi(z) = \sum_{x} P(Z(s) = z \mid Z(0) = x) \pi(x) \ge P(Z(s) = z) \pi(z^{0}).$$

This implies that by 17, we have

$$E([M_u](t)) = E\left(Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))\right)\right) = \int_0^t \sum_x \sum_u \bar{\lambda}_u(x)P(Z(s) = x)ds$$
$$\leq c_1 \sum_x \bar{\lambda}_u(x)\pi(x)t \leq c'_1 t,$$

with some positive constants c_1 and c'_1 . Similarly,

$$E\left(\int_0^t \bar{\lambda}_u(Z(s))^2 ds\right) = \int_0^t \sum_x \bar{\lambda}_u(x)^2 P(X(s) = x) ds$$
$$\leq c_2' \int_0^t \sum_x \bar{\lambda}_u(x)^2 \pi(x) ds \leq c_2 t,$$

with some positive constants c_2 and c'_2 . Applying these to (49), it follows that

$$E\left(Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right)^2\right) \le c'\max\{1,t^2\},$$

with some positive constant c'.

Finally the result follows since by Jansen's inequality we have that there exists a positive constant *c* such that

$$E(J(t)^2) \le |\mathcal{R}_L| \sum_u E\left(\left(Y_u\left(\int_0^t \bar{\lambda}_u(Z(s))ds\right)\right)^2\right) \le c \max\{1, t^2\},$$

 \square

Proof of Lemma 3.4. It is suffice to show that at least cM transitions are required for $Z^{N,-\theta_0}(t)$ to escape S_M . Let $Z^{N,-\theta_0}(0) = z^0$ be the initial state. We first show that $\{z_h : |z_h - z_h^0| < c\frac{M}{N}\} \subseteq$

 $S_{H,M}$ for some c > 0. Note that if $y_k \to y'_k \in \mathcal{R}_0$, then $s_k = (z_h^0)^{q_H(y_k)}$ and $-\theta_0 + \beta_k + y_k \cdot \alpha = 0$. Then there exist c' > 0 and c'' > 0 such that for any $y_k \to y'_k \in \mathcal{R}_0$ if $z_h = z_h^0 + \eta$ with $|\eta| \le c' \frac{M}{N}$, then

$$\begin{aligned} |z_{h}^{q_{H}(y_{k})} - s_{k}| &= |(z_{h}^{0} + \eta)^{q_{H}(y_{k})} - s_{k}| \leq c'' |\eta| \leq \frac{M}{2N}, \quad \text{and} \\ \left| z_{h}^{q_{H}(y_{k})} - \lambda_{H,k}^{N,-\theta_{0}}(z_{h}) \right| &= \left| \prod_{i=1}^{r} z_{h,i}^{y_{k,d+i}} - \prod_{i=1}^{r} z_{h,i} \left(z_{h,i} - \frac{1}{N} \right) \cdots \left(z_{h,i} - \frac{y_{k,d+i} - 1}{N} \right) \right| \\ &\leq \frac{c''}{N}. \end{aligned}$$

This implies that for $y_k \to y'_k \in \mathcal{R}_0$ if $|z_h - z_h^0| \le c' \frac{M}{N}$ then

$$\left|\lambda_{H,k}^{N,-\theta_{0}}(z_{h})-s_{k}\right| \leq \left|z_{h}^{q_{H}(y_{k})}-s_{k}\right| + \left|z_{h}^{q_{H}(y_{k})}-\lambda_{H,k}^{N,-\theta_{0}}(z_{h})\right| \leq \frac{M}{N},$$

for sufficiently large N. Hence $\{z_h : |z_h - z_h^0| < c_N^M\} \subseteq S_{H,M}$. Furthermore $\{z_\ell : |z_\ell - z_\ell^0| \le c'''M\} \subseteq S_{L,M}$ for some c''' > 0 when N is sufficiently large. Therefore

$$\{z_{\ell} : |z_{\ell} - z_{\ell}^{0}| \le c'M\} \times \left\{z_{h} : |z_{h} - z_{h}^{0}| < c'''\frac{M}{N}\right\} \subset S_{M}$$

Since the transition size for each entry $Z_i^{N,-\theta_0}$ of the scaled process transitions by a single reaction is $\Theta(N^{-\alpha_i})$, this implies that $Z^{N,-\theta_0}(t)$ needs at least $\lfloor cM \rfloor$ transitions for some c > 0 to escape S_M .

Proof of Lemma 3.6. $\frac{d}{dt}v(t) \leq Av(t) + b$ can be written as

$$v(t) \le tb + \int_0^t Av(s)ds$$

allowing that the inequality holds component-wisely. Then by the multivariable Gronwall's inequality [10],

$$v(t) \le tb + t \int_{s}^{t} V(t,s)Abds$$

where V(t, s) satisfies

$$V(t,s) = I + \int_{s}^{t} AV(x,s)dx$$

allowing the equality holds component-wisely. By taking time-derivative, we notice that i th column of V(t,s) is a solution u of the system of differential equation (32) with $u_i(s) = 1$ and $u_j(s) = 0$ if $j \neq i$. Therefore by the hypothesis in the statement, each column of V(t,s) is a positive vector and the sum of the entries is equal to 1 for $t \geq s$. Hence it implies that $V(t,s)Ab \leq \bar{A}b$ for $t \geq s$. Thus for each t, the result follows.

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