Stochastically modeled reaction networks: positive recurrence and mixing times

By

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Abstract

Title : Stochastically modeled reaction networks: positive recurrence and mixing times.

For mathematical models of chemical reaction networks, randomness within molecular bonding may significantly affect the dynamical behavior of the associated system. In this case, we generally model the dynamics as a continuous-time Markov jump process with specific kinetics. One of major mathematical approaches for study of stochastically modeled reaction networks is to characterize network structure for qualitative behavior of the stochastic dynamics.

This type of mathematical approaches has been originally considered for long time for the deterministic system dynamics in which randomness is neglected by averaging out. In the literature of the deterministically modeled reaction networks, the relationships between network structural conditions and long-time behavior of the system dynamics have been considered as one of the most classical and challenging problems. Since the characterizations of network structures with respect to behaviors of system dynamics have tended to be made independently on system parameters which often remain unknown, this problem has attracted attentions of biologists, chemists and system bioengineers as well as mathematicians.

In a similar scheme, people in the literature of stochastically modeled reaction networks have studied network conditions independent on system parameters describing long time behavior of the associated Markov processes such as recurrence, existence of stationary distribution, explosion, mixing times and so on. In this thesis we provide

several network conditions for positive recurrence of the associated stochastic processes. We also provide results pertaining to mixing times of certain classes of reaction networks. The main tool is a generalization of the 'tier' style analysis which was originally introduced in [3, 4].

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Chapter 1

Introduction

A reaction network is a graphical configuration that models interaction systems with constituent **species**, **complexes** and **reactions**. These graphical configurations are used to model broad classes of interaction systems including signaling systems, viral infections, metabolism, neuronal networks, population models, etc. The figures below give several examples in which reaction networks are utilized.

$$S + E \leftrightharpoons SE \to S + P$$

Figure 1: Substrate-Enzyme kinetics

$$S + I \to 2I, \qquad I \to R$$

Figure 2: Susceptible, Infectious and Recovered epidemic model

$$\begin{aligned} &A \to 2A, \quad A + B \to 2B + A \\ &B \to \emptyset, \quad A + B \to B \end{aligned}$$

Figure 3: Lotka-Volterra population model

If the counts of the constituent species in a system associated with a reaction network are high, then their concentrations are typically modeled deterministically by a system of ordinary differential equation. However, if the abundances are low, then the randomness inherent in the molecular interactions is important to the system dynamics, and the abundances are modeled stochastically as a discrete-space, continuous-time Markov chain.

One of the most challenging issues facing researchers who study biological systems is the often extraordinarily complicated structure of their interaction networks such as the network in Figure 4.

$$\begin{array}{ll}
2A \xrightarrow{\kappa_1} A+B \underset{\kappa_2}{\overset{\kappa_3}{\rightleftarrows}} B, & \\
2D \underset{\kappa_4}{\overset{\kappa_5}{\rightleftarrows}} A \underset{\kappa_6}{\overset{\kappa_7}{\rightleftarrows}} 2C \xrightarrow{\kappa_8} B+C, & \\
2B \xrightarrow{\kappa_9} \emptyset \underset{\kappa_{10}}{\overset{\kappa_{11}}{\rightleftarrows}} D \underset{\kappa_{12}}{\overset{\kappa_{13}}{\rightleftarrows}} 2E, & \\
C \xrightarrow{\kappa_{13}} A+C \xrightarrow{\kappa_{14}} C+E, &
\end{array}$$

$$\begin{array}{ccccc}
B+E & \xleftarrow{\kappa_{15}} & A+D & \underset{\kappa_{16}}{\overset{\kappa_{17}}{\rightleftarrows}} & A+E \\
\downarrow \kappa_{18} & & & & \downarrow \kappa_{19} \\
F & \xrightarrow{\kappa_{20}} & B+F & \xrightarrow{\kappa_{21}} & 2F \\
\uparrow \kappa_{22} & & & & \downarrow \kappa_{23} \\
B+D & \underset{\kappa_{24}}{\overset{\kappa_{25}}{\rightleftarrows}} & A+F & \xleftarrow{\kappa_{26}} & D+F
\end{array}$$

Figure 4: An example of a large network

Thus, how to characterize network structures that induce emergent phenotypes (characteristic behaviors) of the systems' dynamics is one of the major open questions in systems biology.

The work presented in this thesis falls into the broad research area known as chemical reaction network theory, which dates back to at least [32, 33] where graphical characteristics of networks were shown to ensure uniqueness and local asymptotic stability of the steady states for deterministically modeled complex-balanced systems. Since that time, much of the focus of chemical reaction network theory has been related to discovering how the qualitative properties of deterministic models relate to their reaction networks [3, 4, 8, 11, 13, 15, 16, 21, 23, 22, 24, 29, 35, 40, 43]. However, with the advent of new technologies – most notably fluorescent proteins – there is now a large literature demonstrating that the fluctuations arising from the effective randomness of individual interactions in cellular systems can have significant consequences on the emergent behavior of the system [9, 12, 19, 34, 38, 44, 45]. Hence, analytic results related to stochastic models are essential if these systems are to be well understood, and attention is shifting in their direction.

In the deterministic modeling regime there are a number of network conditions that guarantee some sort of stability for the model. These conditions include weak reversibility and deficiency zero [21, 22, 23], weak reversibility and a single linkage class [3, 4], endotactic [17], strongly endotactic [29], tropically endotactic [14], etc. However, to the best of the author's knowledge, in the stochastic context there is only one such result: in [5] a model whose reaction network is weakly reversible and has a deficiency of zero is shown to be positive recurrent, and the stationary distribution is characterized as a product of Poissons. The paper [30] provides sufficient conditions for positive recurrence, but the provided conditions are analytic in nature and do not explicitly relate to the network structure of the model.

This thesis provides network conditions guaranteeing positive recurrence for stochastic processes associated to reaction networks. Positive recurrence is an equivalent condition for the existence of stationary distribution. Therefore this dynamical behavior for stochastic dynamics can be considered as an analogy of steady states for deterministic dynamics. In this thesis reaction networks we are interested in are restricted to be binary. Binary reaction networks only contain complexes consisting of at most two individual molecules, or species. Since three molecules rarely come together in the right configuration, the class of binary reaction networks broadly covers reaction networks in the literature. The network characterizations contained in this thesis for positive recurrence of stochastic dynamics associated to binary reaction networks are the followings: (i) models that are weakly reversible, have a single linkage class, and have in-flows and out-flows, (ii) a new category of networks we term "double-full", and (iii) models that are weakly reversible and have a single linkage class in which each species appears by itself. Our main analytic tools are Lyapunov functions and ideas related to "tier structures" as introduced in [3, 4], and also utilized in [29].

We also provide mixing times of the associated continuous-time Markov processes for the classes of reaction networks mentioned above. Mixing times of positive recurrent Markov processes indicate convergence rate of the distribution of the Markov process to its stationary distribution.

The outline of this thesis is as follows. In Chapter 2, we provide the relevant mathematical models, including the required terminology from chemical reaction network theory. In Chapter 3, we introduce our main analytic tool: "tiers" which were developed in [3, 4] for deterministic models associated with reaction networks and generalized for stochastic models in this thesis. In Chapter 4, we provide general results relating the tiers of a reaction network to positive recurrence of the Markov models. In Chapter 5, we introduce four main network conditions which guarantee positive recurrence of the associated Markov processes. In Chapter 6, we state results related to mixing times for the network classes introduced in Chapter 5. We provide basic probability knowledge for Markov chains and related theorems in Appendix A.1. We also show proofs of fundamental theorems used in this thesis in Appendices A.2 and A.3. Appendix A.4 shows the coupling inequality which will be used to estimate mixing times.

Chapter 2

Background: reaction networks and associated dynamical systems

In this chapter we will provide definitions for reaction networks and the associated dynamical models. In Section 2.1 the key definitions of reaction network and fundamental terminologies will be introduced. Furthermore, several important graph-topological properties of reaction networks are given along with a number of examples. In Section 2.2 we introduce dynamical systems used to model the behavior of reaction networks: stochastic dynamics and deterministic dynamics. In Section 2.3, we introduce the embedded discrete-time Markov chains for the associated continuous-time stochastic dynamics, which will be utilized for a network condition of reaction networks with a single linkage class in Section 5.4.

2.1 Reaction networks

A reaction network is a graphical construct that describes the set of possible interactions among the constituent species.

Definition 1 ***A reaction network*** *is given by a triple of finite sets* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *where:*

1. ***The species set*** $\mathcal{S} = \{S_1, S_2, \cdots, S_d\}$ *contains the species of the reaction network.*

2. ***The reaction set*** $\mathcal{R} = \{R_1, R_2, \cdots, R_r\}$ *consists of ordered pairs* $(y, y') \in \mathcal{R}$ *where*

$$y = \sum_{i=1}^{d} y_i S_i \quad \text{and} \quad y' = \sum_{i=1}^{d} y'_i S_i \tag{2.1}$$

and where the values $y_i, y'_i \in \mathbb{Z}_{\geq 0}$ *are the* ***stoichiometric coefficients****. We will often write reactions* (y, y') *as* $y \to y'$*.*

3. ***The complex set*** $\mathcal{C}$ *consists of the linear combinations of the species in (2.1). Specifically,* $\mathcal{C} = \{y \mid y \to y' \in \mathcal{R}\} \cup \{y' \mid y \to y' \in \mathcal{R}\}$*. For the reaction* $y \to y'$*, the complexes* y *and* y' *are termed the* ***source*** *and* ***product*** *complex of the reaction, respectively.*

Allowing for a slight abuse of notation, we will let y denote both the linear combination in (2.1) and the vector whose ith component is y_i, i.e. $y = (y_1, y_2, \cdots, y_d)^T \in \mathbb{Z}^d_{\geq 0}$. For example, when $\mathcal{S} = \{S_1, S_2, \ldots, S_d\}$, $2S_1 + S_2$ is associated with $(2, 1, 0, 0, \ldots, 0) \in \mathbb{Z}^d_{\geq 0}$.

Note that it is perfectly valid to have a linear combination of the form (2.1) with $y_i = 0$ for each i. In this case, we denote the complex by $\emptyset$.

It is most common to present a reaction network with a directed *reaction graph* in which the nodes are the complexes and the directed edges are given by the reactions. We present an example to solidify notation.

Example 2.1 Consider the reaction network with associated reaction graph

$$S + E \rightleftharpoons SE \to E + P,$$

which is a usual model for substrate-enzyme kinetics. For this reaction network, $\mathcal{S} = \{S, E, SE, P\}$, $\mathcal{C} = \{S + E, SE, E + P\}$ and $\mathcal{R} = \{S + E \to SE, SE \to S + E, SE \to E + P\}$. $\triangle$

Definition 2 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. The connected components of the associated reaction graph are termed* ***linkage classes****. We call a linkage class is* ***weakly reversible*** *if it is strongly connected, i.e. there is a directed path (reaction) for all pairs of complexes in the linkage class. If all linkage classes in a reaction network are weakly reversible, then the reaction network is said to be weakly reversible.*

Example 2.2 Consider the reaction network with associated reaction graph

$$2A \to B \rightleftharpoons A + C, \qquad \emptyset \to 2B, \qquad \begin{array}{ccc} A+B & \to & 2C. \\ \nwarrow & & \swarrow \\ & D & \end{array}$$

This network has three linkage classes. The right-most linkage class is weakly reversible, whereas the other two are not. △

We will denote by $\mathcal{S}(\mathcal{L}), \mathcal{C}(\mathcal{L})$, and $\mathcal{R}(\mathcal{L})$ the sets of species, complexes, and reactions involved in linkage class $\mathcal{L}$, respectively.

The following definitions related to possible network structures are required to state the main results in this thesis.

Definition 3 *A reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is called* ***binary*** *if $\sum_{i=1}^{d} y_i \leq 2$ for all $y \in \mathcal{C}$.*

Definition 4 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with $\mathcal{S} = \{S_1, S_2, \cdots, S_d\}$. The complex $\emptyset$ is termed the* ***zero complex****. Complexes of the form S_i are termed* ***unary complexes*** *and complexes of the form $S_i + S_j$ are termed* ***binary complexes****. Binary complexes of the form $2S_i$ are termed* ***double complexes****. If $2S_i \in \mathcal{C}$ for each $i = 1, 2, \ldots, d$, then the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is* ***double-full****.*

Definition 5 *We call the reactions* $\emptyset \to S$ *and* $S \to \emptyset$ *the* ***in-flow*** *and* ***out-flow*** *of* S*, respectively. We say a reaction network has* ***all in-flows and out-flows*** *if* $\emptyset \to S \in \mathcal{R}$ *and* $S \to \emptyset \in \mathcal{R}$ *for each* $S \in \mathcal{S}$*.*

2.2 Dynamical systems

In this section, we introduce two dynamical models for reaction networks. We begin with the usual Markov process model, and then present the deterministic model. Appendix A.1 contains probability background pertaining to the associated Markov processes.

We first introduce the invariant manifolds which are called stoichiometric compatibility classes on which the system dynamics is defined.

Definition 6 *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a reaction network. Let* $|S| = d$*. For a state* $x \in \mathbb{R}^d_{\geq 0}$*, the* ***stoichiometric compatibility class*** *is* $(x + span\{y' - y : y \to y' \in \mathcal{R}\}) \cap \mathbb{R}^d_{\geq 0}$*.*

For the usual Markov model associated to $(\mathcal{S}, \mathcal{C}, \mathcal{R})$, the vector $X(t) \in \mathbb{Z}^d_{\geq 0} = \{z = (z_1, z_2, \ldots, z_d) \in \mathbb{Z} : \; z_i \geq 0 \text{ for each } i\}$ gives the counts of the constituent species at time t, and the transitions are determined by the reactions in $\mathcal{R}$. In particular, for appropriate state-dependent intensity (or rate) functions $\lambda_{y \to y'} : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}_{\geq 0}$ we assume that for each $y \to y' \in \mathcal{R}$,

$$P(X(t + \Delta t) = x + y' - y \mid X(t) = x) = \lambda_{y \to y'}(x)\Delta t + o(\Delta t). \tag{2.2}$$

Note that the Markov process associated to a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ only jumps by $n(y' - y)$ with a reaction $y \to y' \in \mathcal{R}$ and a positive integer n, hence its state space $\mathbb{S}$ is a subset of the stoichiometric compatibility classes for $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. Moreover $X(t)$ is actually a non-negative integer valued vector, thus $\mathbb{S} \subset \mathbb{Z}^d_{\geq 0}$.

The generator $\mathcal{A}$ of the associated Markov process is [20]

$$\mathcal{A}V(x) = \sum_{y \to y' \in \mathcal{R}} \lambda_{y \to y'}(x)(V(x + y' - y) - V(x)), \tag{2.3}$$

for a function $V : \mathbb{Z}^d_{\geq 0} \to \mathbb{R}$. See Appendix A.1 for the general definition and derivation of the generator.

The usual choice of intensity is given by *stochastic mass-action kinetics*

$$\lambda_{y \to y'}(x) = \kappa_{y \to y'} \prod_{i=1}^{d} \frac{x_i!}{(x_i - y_i)!} \mathbf{1}_{\{x_i \geq y_i\}}, \tag{2.4}$$

where the positive constant $\kappa_{y \to y'}$ is the reaction rate constant. For example, letting $X = (X_1, X_2, \ldots, X_d)$ be a count vector for species $S_1, S_2, \ldots, S_d$,

$$\lambda_{S_1 \to S_3}(X) = \kappa_{S_1 \to S_3} X_1$$

$$\lambda_{S_1 + S_2 \to \emptyset}(X) = \kappa_{S_1 + S_2 \to \emptyset} X_1 X_2$$

$$\lambda_{2S_3 + 3S_4 \to S_1}(X) = \kappa_{2S_3 + 3S_4 \to S_1} X_3(X_3 - 1) X_4(X_4 - 1)(X_4 - 2).$$

Note that the intensity function for a reaction $y \to y'$ only depends on the source complex y.

We typically incorporate the rate constants into the reaction graphs by placing them next to the reaction arrow as in $y \xrightarrow{\kappa} y'$. Trajectories of this model are typically simulated via the Gillespie algorithm [26, 27] or the next reaction method [1, 25], or are approximated via tau-leaping [2, 28].

For the deterministic model, we let the vector $x(t) \in \mathbb{R}^d_{\geq 0}$ solve

$$\frac{d}{dt} x(t) = \sum_{y \to y'} \kappa_{y \to y'} x(t)^y (y' - y), \tag{2.5}$$

where for two vectors $u, v \in \mathbb{R}^d_{\geq 0}$, we define $u^v = \prod_{i=1}^{d} u_i^{v_i}$, with the convention $0^0 = 1$. The vector $x(t)$ then models the concentrations of the constituent species at time t.

See [6, 7, 36] for the connection between the stochastic and deterministic models. The choice of rate function, i.e. $\kappa_{y\to y'}x(t)^y$, is termed deterministic mass-action kinetics and the function $x(t)^y$ is called a deterministic rate function.

Recalling the discussion below Definition 1, we will sometimes write $x^{\sum_{i=1}^d y_i S_i}$ for $\prod_{i=1}^d x_i^{y_i}$. For example, we have $x^{2S_1+S_2} = x_1^2 x_2$.

2.3 Embedded Markov chains for the associated stochastic dynamics

The main idea for the network condition introduced in Section 5.4 is to utilize relations between the associated continuous-time Markov process and its embedded discrete-time Markov chain. In this section we provide theorems and lemmas stating relations between the associated Markov process and the embedded Markov chain.

Definition 7 *Let X be a continuous-time Markov process and τ_n be the first time of n-th jump of X for $n = 1, 2, \dots$. Then the discrete time Markov chain $\{\tilde{X}_n\} = \{X(\tau_n)\}$ is the embedded discrete time Markov chain of X.*

For any states i and j, let λ_{ij} be the intensity of transition from state i to j of a continuous-time Markov process X. That is,

$$P(X(t+\Delta t) = j \mid X(t) = i) = \lambda_{ij}\Delta t + o(\Delta t).$$

Then transition probabilities of the embedded discrete-time Markov chain $\tilde{X}$ are given as

$$\tilde{P}_i(\tilde{X}_1 = j) = \begin{cases} 0 & \text{if } \sum_\ell \lambda_{i\ell} = 0 \\ \frac{\lambda_{ij}}{\sum_\ell \lambda_{i\ell}} & \text{otherwise} \end{cases}, \tag{2.6}$$

where $\tilde{P}$ is the probability measure of $\tilde{X}$.

The following theorem shows that positive recurrence of the continuous-time Markov process can be guaranteed by positive recurrence of the embedded discrete-time Markov chain if we assume intensities of transitions for the continuous-time Markov process have a uniform lower bound away from zero.

Theorem 2.3.1 *Let X be a non-explosive continuous-time Markov process on discrete state space and $\tilde{X}$ be the embedded discrete time Markov chain of X. Let $\mathbb{S}$ be the state space of X. Furthermore, let λ_{ij} be the rate of transition from state i to j of X. In other words,*

$$P(X(t + \Delta t) = j | X(t) = i) = \lambda_{ij}\Delta t + o(\Delta t).$$

Suppose $\inf_i \sum_j \lambda_{ij} > 0$*. Then positive recurrence of $\tilde{X}$ implies positive recurrence of X.*

Proof. Positive recurrence of $\tilde{X}$ implies that there exists a stationary distribution of $\tilde{X}$. Let $\tilde{\pi}$ be a stationary distribution of $\tilde{X}$. Then

$$\sum_{j\in\mathbb{S}} \frac{\lambda_{ji}}{\sum_\ell \lambda_{j\ell}} \tilde{\pi}(j) - \sum_{j\in\mathbb{S}} \frac{\lambda_{ij}}{\sum_\ell \lambda_{i\ell}} \tilde{\pi}(i) = 0.$$

(See Definition 43). Thus if we put $\pi(i) = \frac{\tilde{\pi}(i)}{\sum_\ell \lambda_{i\ell}}$ for each $i \in \mathbb{S}$, then π satisfies

$$\sum_{i\in\mathbb{S}} \lambda_{ij}\pi(i) - \sum_{i\in\mathbb{S}} \lambda_{ji}\pi(j) = 0.$$

for each $i \in \mathbb{S}$. Since $\inf_i \sum_j \lambda_{ij} > 0$ and $\sum_i \tilde{\pi}(i) = 1$, we conclude that $\sum_i \pi(i) < \infty$. Thus by normalizing π, we obtain a stationary distribution of X (See Definition 42). Thus X is positive recurrent by Theorem A.2. □

The following lemmas shows the intensity function defined with mass-action kinetics (2.4) is uniformly bounded away from zero unless $X(0) = x$ is an absorbing state (i.e. $\lambda_{y\to y'}(x) = 0$ for all reactions $y \to y' \in \mathcal{R}$).

Lemma 8 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible reaction network with $|\mathcal{S}| = d$ and X be the associated continuous-time Markov process with state space $\mathbb{S}$. Let $\lambda_{y\to y'}$ be the intensity function associated with reaction $y \to y'$ defined with mass-action kinetics (2.4) and $\lambda_0(z) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(z)$ for each $z \in \mathbb{S}$. Suppose that $X(0) = x$ for a non-absorbing state x. Then*

$$\inf_{z\in\mathbb{S}} \lambda_0(z) > 0.$$

Proof. We show first that every state z in $\mathbb{S}$ is non-absorbing state. That is, we show for each state z, $\lambda_{y_z\to y'_z}(z) > 0$ for some reaction $y_z \to y'_z$. To do that, we will actaully show any state acheived by a single jump from a non-absorbing state is non-absorbing. Suppose w is a non-absorbing state and $X(t) = w$ for some t. Let $y_w \to y'_w \in \mathcal{R}$ be such that $\lambda_{y_w\to y'_w}(w) > 0$. By the definition of the stochastic mass-action kinetics, $w_j \geq (y_w)_j$ for all $j = 1, 2, \ldots, d$. Thus

$$w_j + (y'_w)_j - (y_w)_j \geq (y'_w)_j.$$

By weak reversibility, there is a reaction $y'_w \to y'' \in \mathcal{R}$ for some complex $y'' \in \mathcal{C}$. Therefore for $z = w + y'_z - y_z$

$$\lambda_{y'_w\to y''}(z) > 0$$

because $z_j = w_j + (y'_w)_j - (y_w)_j \geq (y'_w)_j$ for each $j = 1, 2, \ldots, d$. Thus z is non-absorbing since the reaction $y'_w \to y''$ has strictly positive intensity at z. We showed that any state achieved by a single jump from a non-absorbing state is non-absorbing. Since the initial point x is non-absorbing, every state of X is non-absorbing.

This fact implies for each state z, we have $\lambda_0(z) > \lambda_{y_z \to y'_z}(z) > 0$ for some $y_z \to y'_z \in \mathcal{R}$. Note that λ_0 is a polynomial in $z \in \mathbb{S} \subset \mathbb{Z}^d_{\geq 0}$, so that it is increasing function, i.e.

$$\lambda_0(z') \geq \lambda_0(z) \quad \text{if} \quad z'_i \geq z_i \quad \text{for all} \quad i.$$

Therefore there exists a finite set K in $\mathbb{Z}^d_{\geq 0}$ such that $\inf_{z \in \mathbb{S}} \lambda_0(z) > \inf_{z \in K \cap \mathbb{S}} \lambda_0(z) > 0$. This completes the proof. $\square$

Chapter 3

The main analytic tools: Tier structures

In this chapter, the main analytic tool: tiers is introduced. This idea is a generalization of the tier structures for deterministically modeled reaction networks to stochastic models.

The tier idea for deterministic models of reaction networks was originally introduced in [3, 4] which was utilized to verify boundedness and persistence of deterministic dynamics for a weakly reversible reaction network that has a single linkage class. The next example briefly demonstrate the basic idea of tier structures and the motivation of two different types of tiers for stochastic models.

Example 3.1 Consider the reaction network in Figure 5. For a sequence $x_n = (n, 1)^T$

$$A + 2B \underset{1}{\overset{1}{\rightleftharpoons}} \emptyset \underset{1}{\overset{1}{\rightleftharpoons}} 3B$$

Figure 5: An example for the basic idea of tier structures.

for large n, we can think of the order of the size for the deterministic rate function x_n^y for each complex y. First, we compute all deterministic rate functions for complexes along the sequence $\{x_n\}$.

$$x_n^{A+2B} = n^1 1^2 = n$$

$$x_n^{3B} = n^0 1^3 = 1$$

$$x_n^{\emptyset} = n^0 1^0 = 1.$$

That is, $x_n^{A+2B} \geq x_n^{3B} \geq x_n^{\emptyset}$. Therefore along the sequence $\{x_n\}$, the reaction vector $(-1,-2)^T$ associated to the reaction $A + 2B \to \emptyset$ will be a dominating direction for the deterministic dynamics associated to the reaction network. We term the complex $A+2B$ as tier-1 complex along the sequence $\{x_n\}$. However, for a sequence $z_n = (1,n)^T$, we have $z_n^{3B} \geq z_n^{A+2B} \geq z_n^{\emptyset}$. In this case, the reaction $3B \to \emptyset$ will be a dominating reaction of the deterministic dynamics. We term the complex $3B$ as tier-1 complex along the sequence $\{z_n\}$. Note that with this idea of the tier structures, the behavior of the deterministic dynamics associated to the model can be understood at each region in the stoichiometric compatibility class of the reaction network.

However, the stochastic rate functions, $\lambda_{y\to y'}$, for each reaction $y \to y'$ may have a different tier structures from that of the deterministic rate functions. By the definition of the stochastic rate functions (2.4), we have

$$\lambda_{2A+B}(x_n) = n(n-1)\cdot 1 = n(n-1)$$

$$\lambda_{3B}(x_n) = 0 \quad \textit{since} \;\; 3 > 1 = x_{n,2}$$

$$\lambda_{\emptyset}(x_n) = 1.$$

Along the sequence $x_n = (n,1)^T$, therefore, we obtain

$$\lambda_{\emptyset\to 3B}(x_n) \leq \lambda_{A+2B\to\emptyset}(x_n) = \lambda_{3B\to\emptyset}(x_n).$$

$\triangle$

As demonstrated in Example 3.1, the general key difference between deterministic and stochastic dynamics is the following: deterministic dynamics does not touch the boundary as long as the initial point is located in the strict positive orthant, but the associated stochastic process can hit the boundary of the state space, where intensity functions can be zero.

This difference between deterministic rates and stochastic rates motivates us to think of the needs for a different type of tier structures with respect to stochastic rates and deterministic rates along a given sequence. In this thesis, therefore, we generalize the original tier structures introduced in [3, 4] by defining two different types of tier structures: D-type and S-type tiers.

We introduce some useful terminology.

1. For $x \in \mathbb{Z}^d$, we write $(x \vee 1)$ for the vector in $\mathbb{Z}^d$ with jth component $(x \vee 1)_j = x_j \vee 1 = \max\{x_j, 1\}$.

2. We will use the the phrase "for large n" for "for all n greater than some fixed constant N".

3. For each complex $y \in \mathcal{C}$, we define the stochastic rate function $\lambda_y(x)$ for each complex y as following,

$$\lambda_y(x) := \prod_{i=1}^{d} \frac{x_i!}{(x_i - y_i)!} \mathbf{1}_{\{x_i \geq y_i\}}, \qquad \text{for } x \in \mathbb{Z}^d.$$

Note that for a reaction $y \to y' \in \mathcal{R}$, we have $\lambda_{y \to y'}(x) = \kappa_{y \to y'} \lambda_y(x)$. That is, $\lambda_y(x)$ is the portion of the stochastic mass-action term that depends upon the source complex y.

3.1 Two types of tier structures

In this section we define D-type tiers and S-type tiers. We also provide some important lemmas pertaining to tiers that will be applied many times throughout this thesis.

Definition 9 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and let $\{x_n\}$ be a sequence in $\mathbb{R}^d_{\geq 0}$. We say that $\mathcal{C}$ has a* ***D-type partition along*** *$\{x_n\}$ if there exist a finite number of nonempty mutually disjoint subsets $T^{D,i}_{\{x_n\}} \subset \mathcal{C}$ such that $\cup_i T^{D,i}_{\{x_n\}} = \mathcal{C}$, and*

1. *if $y, y' \in T^{D,i}_{\{x_n\}}$, then there exists a $C \in (0, \infty)$ such that*
$$\lim_{n\to\infty} \frac{(x_n \vee 1)^y}{(x_n \vee 1)^{y'}} = C,$$
2. *if $y \in T^{D,i}_{\{x_n\}}$ and $y' \in T^{D,k}_{\{x_n\}}$ with $i < k$ then*
$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^{y}} = 0.$$

The mutually disjoint subsets $T^{D,i}_{\{x_n\}}$ are called ***D-type tiers along*** *$\{x_n\}$. We will say that y is in a higher tier than y' in the D-type partition along $\{x_n\}$ if $y \in T^{D,i}_{\{x_n\}}$ and $y' \in T^{D,j}_{\{x_n\}}$ with $i < j$. In this case, we will denote $y \succ_D y'$. If y and y' are in the same D-type tier, then we will denote this by $y \sim_D y'$.*

Note that $\mathcal{C}$ is well-ordered set with $\succ_D$ and $\sim_D$.

The terminology of saying tier $T^{D,1}_{\{x_n\}}$ is higher than the other tiers comes from point 2. in Definition 9.

Definition 10 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and let $\{x_n\}$ be a sequence in $\mathbb{R}^d_{\geq 0}$. We say that $\mathcal{C}$ has an* ***S-type partition along*** *$\{x_n\}$ if there exist a finite number of nonempty mutually disjoint subsets $T^{S,i}_{\{x_n\}} \subset \mathcal{C}$, with $i \in \{1, \dots, P, \infty\}$, such that $T^{S,1}_{\{x_n\}} \cup \cdots \cup T^{S,P}_{\{x_n\}} \cup T^{S,\infty}_{\{x_n\}} = \mathcal{C}$, and*

1. $y \in T^{S,\infty}_{\{x_n\}}$ *if and only if* $\lambda_y(x_n) = 0$ *for all* n,

2. $\lambda_y(x_n) \neq 0$ *for any* n *if* $y \in T^{S,i}_{\{x_n\}}$ *for* $i \in \{1, \dots, P\}$,

3. *if* $y, y' \in T^{S,i}_{\{x_n\}}$, *with* $i \in \{1, \dots, P\}$, *then there exists a* $C \in (0, \infty)$ *such that*

$$\lim_{n\to\infty} \frac{\lambda_y(x_n)}{\lambda_{y'}(x_n)} = C,$$

4. *if* $y \in T^{S,i}_{\{x_n\}}$ *and* $y' \in T^{S,k}_{\{x_n\}}$ *with* $1 \leq i < k \leq P$, *then*

$$\lim_{n\to\infty} \frac{\lambda_{y'}(x_n)}{\lambda_y(x_n)} = 0.$$

The mutually disjoint subsets $T^{S,i}_{\{x_n\}}$ *are called* ***S-type tiers along*** $\{x_n\}$. *We will say that* y *is in a higher tier than* y' *in the S-type partition along* $\{x_n\}$ *if* $y \in T^{S,i}_{\{x_n\}}$ *and* $y' \in T^{S,j}_{\{x_n\}}$ *with* $i < j$.

These two tier structures make hierarchies for the complexes with respect to the sizes of $(x_n \vee 1)^y$ and $\lambda_y(x_n)$ along a sequence $\{x_n\}$. In particular, S-type tiers are defined with asymptotic size of the intensity of each reaction along a sequence. Since the intensity of each reaction means how much likely the associated reaction is to be fired, we are able to know which reaction is the most likely reaction to be fired by the highest S-type tier along a sequence.

Definition 11 *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a reaction network and suppose that* $\{T^{D,i}_{\{x_n\}}\}$ *are the D-type tiers along a sequence* $\{x_n\}$. *We will call* $y \to y' \in \mathcal{R}$ *a* ***descending reaction*** *along* $\{x_n\}$ *if* $y \in T^{D,1}_{\{x_n\}}$ *and* $y' \in T^{D,i}_{\{x_n\}}$ *for some* $i > 1$. *We denote*

$$D_{\{x_n\}} := \{y \in \mathcal{C} \mid y \to y' \text{ is a descending reaction along } \{x_n\}\}.$$

We demonstrate the D-type tiers, the S-type tiers and descending reactions with the following example.

Example 3.2 Consider the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ in Figure 6.

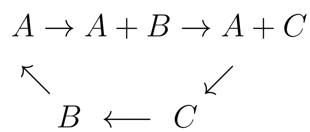

Figure 6: An example of the D-type, S-type tier structures and descending reactions.

Let $\{x_n\} = (n, 1, 0)^T$. Then we have the following tier structures.

1. $T^{D,1}_{\{x_n\}} = \{A, A+B, A+C\}$ *and* $T^{D,2}_{\{x_n\}} = \{B, C\}$.

2. $T^{S,1}_{\{x_n\}} = \{A, A+B\}$, $T^{S,1}_{\{x_n\}} = \{B\}$ *and* $T^{S,\infty}_{\{x_n\}} = \{C\}$

3. $A + C \to C$ is the only descending reaction. Hence $D_{\{x_n\}} = \{A + C\}$. $\triangle$

Weak reversibility of a reaction network implies existence of a descending reaction for any D-type partitions unless all reactions are in a single tier.

Lemma 12 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and suppose that $\mathcal{C}$ has a D-type partition along a sequence $\{x_n\}$. Suppose there are two complexes $y \in T^{D,1}_{\{x_n\}}$ and $y' \notin T^{D,1}_{\{x_n\}}$ such that there is a directed path within the reaction graph beginning with y and ending with y'. Then there is a descending reaction $y_0 \to y'_0$ along $\{x_n\}$ within the directed path.*

Proof. Let

$$y \to y'_1 \to y'_2 \to \cdots \to y'_k \to y'.$$

be the directed path from y to y'. If $y'_1 \notin T^{D,1}_{\{x_n\}}$, $y \to y'_1$ is a descending reaction. If $y_1 \in T^{D,1}_{\{x_n\}}$, either $y'_2 \in T^{D,1}_{\{x_n\}}$ or $y'_2 \notin T^{D,1}_{\{x_n\}}$. In the latter case, $y'_1 \to y'_2$ is a descending reaction. Otherwise we keep seeking a descending reaction by checking whether $y'_3 \in T^{D,1}_{\{x_n\}}$ or $y'_3 \notin T^{D,1}_{\{x_n\}}$. If $y'_l \in T^{D,1}_{\{x_n\}}$ for all $l = 1, \cdots, k$, then $y'_k \to y'$ must be a descending reaction because $y' \notin T^{D,1}_{\{x_n\}}$. □

Definition 13 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with $|\mathcal{S}| = d$. Let X be the Markov process associated to $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and let $\mathbb{S}$ be the state space of X. Then a sequence $\{x_n\}$ is called a* ***proper tier-sequence*** *of X if*

1. *$\{x_n\} \subset \mathbb{S}$,*

2. *$\lim_{n\to\infty} x_{n,i} \in [0, \infty]$ for all $i = 1, 2, \cdots, d$ and $\lim_{n\to\infty} x_{n,i} = \infty$ for at least one i, and*

3. *$\mathcal{C}$ has both a D-type partition and an S-type partition along $\{x_n\}$.*

If a sequence $\{x_n\}$ only satisfies the conditions 2 and 3 in Definition 13, we call $\{x_n\}$ is a **tier-sequence**.

The following lemma shows that for any sequence $\{x_n\}$, we can find a further subsequence that is a proper tier-sequence.

Lemma 14 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with $|\mathcal{S}| = d$. Let X be the Markov process associated to $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and $\mathbb{S}$ be the state space of X. For a sequence $\{x_n\} \subset \mathbb{S}$ such that $\lim_{n\to\infty} |x_n| = \infty$, there exists a subsequence of $\{x_n\}$ which is a proper tier-sequence.*

Proof. We can pick a subsequence $\{x_{n_k}\}$ of $\{x_n\}$ such that $\lim_{k\to\infty} x_{n_k,i} \in [0,\infty]$ for any $i = 1, 2, \cdots, d$. We first consider a further subsequence along which a D-type partition of $\mathcal{C}$ is defined. For the sake of brevity, we denote all subsequences as $\{x_{n_k}\}$ in this proof . Pick any two complexes $y_1, y_2 \in \mathcal{C}$ and find a subsequence $\{x_{n_k}\}$ so that $\lim_{k\to\infty} \frac{(x_{n_k}\vee 1)^{y_2}}{(x_{n_k}\vee 1)^{y_1}} = C_{12}$ for some $C_{12} \in [0,\infty]$. For another complex $y_3 \in \mathcal{C}$, we find a further subsequence $\{x_{n_k}\}$ so that the limits $\lim_{k\to\infty} \frac{(x_{n_k}\vee 1)^{y_3}}{(x_{n_k}\vee 1)^{y_2}} = C_{23} \in [0,\infty]$ and $\lim_{k\to\infty} \frac{(x_{n_k}\vee 1)^{y_3}}{(x_{n_k}\vee 1)^{y_1}} = C_{13} \in [0,\infty]$. Since there are finitely many complexes, we can repeat the same procedure for all complexes and finally find a subsequence x_{n_k} of $\{x_n\}$ for which the limit

$$\lim_{k\to\infty} \frac{(x_{n_k} \vee 1)^{y_i}}{(x_{n_k} \vee 1)^{y_j}} = C_{ij}$$

exists for some $C_{ij} \in [0,\infty]$ for all $i, j = 1, 2, \cdots, |\mathcal{C}|$. Therefore we can define a D-type partition on $\mathcal{C}$. In the same way, we can find a further subsequence of $\{x_{n_k}\}$ along which an S-type partition is defined on $\mathcal{C}$. □

The next lemma shows that for any tier-sequence $\{x_n\}$, the deterministic rate function associated with a complex belonging to $T^{D,1}_{\{x_n\}}$ goes infinity as $n \to \infty$.

Lemma 15 *Let $\{x_n\}$ be a tier-sequence of a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. If $y_0 \in T^{D,1}_{\{x_n\}}$, then $\lim_{n\to\infty}(x_n \vee 1)^{y_0} = \infty$.*

Proof. Let $I = \{i \mid \lim_{n\to\infty} x_{n,i} = \infty\}$ and let $y \in \mathcal{C}$ be such that $y_i \neq 0$ for some $i \in I$. By definition, if $y_0 \in T^{D,1}_{\{x_n\}}$ then

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{y}}{(x_n \vee 1)^{y_0}} = C$$

for some constant $C \geq 0$. Since $\lim_{n\to\infty}(x_n \vee 1)^{y} = \infty$, the result follows. □

In the next lemma, we provide a relationship between D-type partitions and S-type partitions.

Lemma 16 *Let $\{x_n\}$ be a tier-sequence of a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ and let $y \in \mathcal{C}$. Then*

$$\lim_{n\to\infty} \frac{\lambda_y(x_n)}{(x_n \vee 1)^y} = \begin{cases} 0 & \text{if} \quad y \in T^{S,\infty}_{\{x_n\}} \\ 1 & \text{if} \quad y \notin T^{S,\infty}_{\{x_n\}}. \end{cases}$$

Proof. If $y \in T^{S,\infty}_{\{x_n\}}$, then $\lambda_y(x_n) = 0$ for all n. If $y \notin T^{S,\infty}_{\{x_n\}}$, then $\lambda_y(x_n)$ and $(x_n \vee 1)^y$ are polynomials with the same degree and the same leading coefficient (of 1). □

The following corollary is used throughout this thesis and shows that for a complex y, if y is belonging to the highest D-type tier, then y is also belonging to the highest S-type tier as long as $y \notin T^{S,i}_{\{x_n\}}$ for any tier-sequence $\{x_n\}$.

Corollary 17 *Let $\{x_n\}$ be a tier-sequence of a reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. Suppose $y \notin T^{S,\infty}_{\{x_n\}}$ and $y \in T^{D,1}_{\{x_n\}}$. Then $y \in T^{S,1}_{\{x_n\}}$ and $\lim_{n\to\infty} \lambda_y(x_n) = \infty$.*

Proof. Let $y' \notin T^{S,\infty}_{\{x_n\}}$. Note that

$$\frac{\lambda_{y'}(x_n)}{\lambda_y(x_n)} = \frac{\lambda_{y'}(x_n)}{(x_n \vee 1)^{y'}} \cdot \frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^y} \cdot \frac{(x_n \vee 1)^y}{\lambda_y(x_n)}.$$

By Lemma 16, as $n \to \infty$ the first and third terms on the right of the above equation converge to 1. Therefore,

$$\lim_{n\to\infty} \frac{\lambda_{y'}(x_n)}{\lambda_y(x_n)} = \lim_{n\to\infty} \frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^y}.$$

Because $y \in T^{D,1}_{\{x_n\}}$, the last limit is either 0 (if $y' \notin T^{D,1}_{\{x_n\}}$) or some $C > 0$ (if $y' \in T^{D,1}_{\{x_n\}}$). Thus, y' cannot be in a higher tier than y in the S-type partition. Hence, $y \in T^{S,1}_{\{x_n\}}$.

Moreover, since $y \notin T^{S,\infty}_{\{x_n\}}$, by Lemma 15 and Lemma 16, we have $\lim_{n\to\infty} \lambda_y(x_n) = \infty$.
□

3.2 Tier structure for embedded Markov chains

Some network conditions for positive recurrence of the associated stochastic dynamics introduced in Section 5.4 will be derived from analyzing behavior of certain time points of the embedded Markov chain. More precisely speaking, for some positive integer k, we observe the discrete-time Markov chain $\tilde{X}_{kn}$ obtained from the embedded Markov chain $\tilde{X}_n$ at every k th time point. This leads us to consider tier structure of set of multiple complexes and reactions along a proper tier-sequence $\{x_n\}$. In this section we state important lemmas and definition of tier structures of multiple source complexes.

The following lemma states that for each proper tier-sequence, there exists at least one reaction whose source and product complex are not in a same D-type tier.

Lemma 18 *Let $(\mathcal{S},\mathcal{C},\mathcal{R})$ be a reaction network with $|\mathcal{S}| = d$. Let X be the Markov process associated to $(\mathcal{S},\mathcal{C},\mathcal{R})$ with $X(0) = x$. For a proper tier-sequence $\{x_n\}$ of X, there exists a reaction $y \to y' \in \mathcal{R}$ such that $y \in T^{D,i}_{\{x_n\}}$ and $y' \in T^{D,j}_{\{x_n\}}$ for some $i \neq j$.*

Note that if $\{x_n\}$ is just a tier-sequence, this lemma no longer holds. For example, consider the following reaction network

$$A \rightleftharpoons B.$$

Then along a tier-sequence $x_n = (n, n)$, both complexes A and B are belonging to $T^{D,1}_{\{x_n\}}$ because $(x_n \vee 1)^A = n = (x_n \vee 1)^B$. However the tier-sequence $\{x_n\}$ is not a proper tier-sequence because for any initial point x of the associated Markov process X, the state space $\mathbb{S}$ is a subset of the stoichiometric compatibility class, $(x + span\{(-1,1)^T\}) \cap \mathbb{R}^d_{\geq 0}$ which is a finite set, so that $\{x_n\} \not\subset\in \mathbb{S}$. Thus the condition 1 in Definition 13 is crucial for the proof of Lemma 18.

Proof. By Theorem 3.9 in [3], there is a vector $w \in \mathbb{R}^d$ such that (i) $w_i < 0$ if $(x_n \vee 1)_i \to \infty$, as $n \to \infty$, (ii) $w_i = 0$ if $(x_n \vee 1)_i < \infty$ and (ii) $\langle w, y' - y\rangle = 0$ for complexes y and y' such that $y, y' \in T^{D,i}_{\{x_n\}}$ for some i, where $\langle \cdot, \cdot \rangle$ is the usual inner product in $\mathbb{R}^d$.

Now suppose all complexes $y \in \mathcal{C}$ are in the same D-type tier along $\{x_n\}$. Then the vector w is orthogonal to all reaction vectors. Since $x_n \in \mathbb{S} \subset (x + span\{y' - y | y \to y' \in \mathcal{R}\})$ for all n,

$$\lim_{n\to\infty} \langle w, x_n \rangle = \langle w, x \rangle > -\infty.$$

However, $\{x_n\}$ is a proper sequence and hence $x_{n,i} \to \infty$, as $n \to \infty$ for at least one $i \in \{1, 2, \ldots, d\}$. This implies

$$\lim_{n\to\infty} \langle w, x_n \rangle < \lim_{n\to\infty} w_i x_{n,i} = -\infty.$$

This contradiction implies that there must exist at least one reaction whose source complex and product complex are in different D-type tiers along $\{x_n\}$. □

We need to observe how tier structures will change after k th jumps by reactions in order to handle the embedded Markov chain $\tilde{X}_{kn}$. The lemmas below describe how tier structures will be after shifting a proper tier-sequence by a reaction. In particular, Lemma 19 shows that the D-type partitions are preserved after shifting.

Lemma 19 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and let $y \to y' \in \mathcal{R}$. Assume that $\{x_n\}$ and $\{x_n + y' - y\}$ are proper tier-sequences of the associated Markov process. Let*

$\mathcal{C} = \cup_{j=1}^{P} T^{D,j}_{\{x_n\}}$. *Then there are also* P *D-type tiers along the sequence* $\{x_n + y' - y\}$ *and* $T^{D,j}_{\{x_n\}} = T^{D,j}_{\{x_n+y'-y\}}$ *for each* $j = 1, 2, \dots, P$.

Proof. The limits defined at 2 in Definition 9 do not change if we replace $\{x_n\}$ by $\{x_n + y' - y\}$ because $y' - y$ is a constant vector and $(x_n + y'y - \vee 1)_i \geq 1$ for each i and for all n. Therefore two D-type structures along $\{x_n\}$ and $\{x_n + y' - y\}$ are equal. □

The next technical lemma is utilized in Section 5.4.

Lemma 20 *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a reaction network and let* $y \to y' \in \mathcal{R}$. *Assume that* $\{x_n\}$ *and* $\{x_n + y' - y\}$ *are proper tier-sequences of the associated Markov process and assume also that* $y \notin T^{S,\infty}_{\{x_n\}}$. *Then the followings hold.*

(i) $y' \notin T^{S,\infty}_{\{x_n+y'-y\}}$.

(ii) If $y' \in T^{D,1}_{\{x_n\}}$, *then* $y' \in T^{S,1}_{\{x_n+y'-y\}}$.

(iii) $T^{S,1}_{\{x_n+y'-y\}} \neq \emptyset$.

Proof. Let $\mathcal{S} = \{S_1, S_2, \dots, S_d\}$. Since $y \notin T^{S,\infty}_{\{x_n\}}$, $x_{n,j} \geq y_j$ for all $j = 1, 2, \dots, d$. This implies $x_{n,j} + y'_j - y_j \geq y'_j$. Thus $y' \notin T^{S,\infty}_{\{x_n+y'-y\}}$.

For (ii), suppose $y' \in T^{D,1}_{\{x_n\}}$. Then $y' \in T^{D,1}_{\{x_n+y'-y\}}$ by Lemma 19. Thus part (i) above and Corollary 17 imply $y' \in T^{S,1}_{\{x_n+y'-y\}}$.

We now show (iii). By weak reversibility, there is a reaction $y' \to y'' \in \mathcal{R}$ for some complex $y'' \in \mathcal{C}$. That is y' is a source complex for some reaction. Thus by (i) we showed above, $y' \notin T^{S,\infty}_{\{x_n+y'-y\}}$. Since $\mathcal{C} \neq T^{S,\infty}_{\{x_n+y'-y\}}$, at least one complex must belong to $T^{S,1}_{\{x_n+y'-y\}}$. □

Before we introduce the definitions for tier structures of multiple source complexes in Definition 21, we demonstrate its motivation with the following example.

Example 3.3 Let X be the associated Markov process for the reaction network in Figure 7. Consider a sequence $x_n = (n,0)^T$. This sequence is a proper tier-sequence for X with $X(0) = (1,0)^T$ by the following reasons.

$$\emptyset \rightleftharpoons A + B \rightleftharpoons A$$

Figure 7: An example for the motivation of Definition 21.

(i) The state space of X contain $(n,0)^T$ for all n because the counts of A can be infinitely increased with maintaining the counts of B by the reactions $\emptyset \to A+B \to A$ firing in that order.

(ii) $x_{n,1} = n \to \infty$, as $n \to \infty$, and

(iii) it is easy to check

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^{y}} \in [0,\infty] \quad \text{and} \quad \lim_{n\to\infty} \frac{\lambda_{y'}(x_n)}{\lambda_y(x_n)} \in [0,\infty]$$

for all pairs of complexes $y, y' \in \mathcal{C}$.

Note that for the reaction $A + B \leftarrow A$, the source complex A is belonging to $T^{S,1}_{\{x_n\}}$. This reaction is the most likely reaction to be fired because the probability of firing the reaction $\emptyset \to A+B$ is much smaller than the probability of firing the reaction $A+B \leftarrow A$ at $(n,0)^T$ and other two reactions cannot be fired since $\lambda_{A+B}(n,0) = 0$. After jumping by the reaction, $x_n = (n,0)^T$ is shifted to $(n,1)^T$, then $\emptyset \leftarrow A+B$ is one of the most likely reactions because $A+B \in T^{S,1}_{(n,1)^T}$.

Positive recurrence of a Markov chain is achieved when the Markov chain returns a finite set in its state space within finite amount of time in average. Thus we need to observe where the Markov chain jumps to by most likely reactions to be fired. Now let us describe how the Markov process will jumps by the two most likely reactions $A+B \leftarrow A$ and $\emptyset \leftarrow A+B$ subsequently. First by the reaction $A+B \leftarrow A$, the associated Markov process jumps to $(n,1)^T$. Note that by this jump, the Markov process does not get closer to a compact set around the origin. However, after the second jump $\emptyset \leftarrow A+B$, the Markov process reaches at $(n-1,1)^T$ so it eventually gets closer to a compact set around the origin.

Thus we conclude that the associated Markov chain need to have multiple most likely jumps in order to approach to the origin. $\triangle$

As shown in Example 3.3, we characterize a set of most likely reactions and their jump directions with tier structures for a set of source complexes.

Definition 21 *Let $(\mathcal{S},\mathcal{C},\mathcal{R})$ be a reaction network and $R = \{y_1 \to y_1', y_2 \to y_2', \dots, y_k \to y_k'\} \subset \mathcal{R}$ be an ordered set of reactions where we allow some of reactions to be same. Let $\{x_n\}$ be a sequence such that each of $\{x_n + \sum_{j=1}^{i-1}(y_i' - y_i)\}$ is a proper tier-sequence of X for each $i = 1,2,\dots,k$.*

(i) We denote $\{y_1,y_2,\dots,y_k\} \in \mathbb{D}_{\{x_n\},R}$ if $y_i \in T^{D,1}_{\{x_n+\sum_{j=1}^{i-1}(y_j'-y_j)\}}$ for each $i = 1,2,\dots,k$ and $y_\ell' \notin T^{D,1}_{\{x_n+\sum_{j=1}^{\ell-1}(y_j'-y_j)\}}$ for some $\ell \in \{1,2,\dots,k\}$.

(ii) We denote $\{y_1,y_2,\dots,y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R}$ if $y_i \in T^{S,1}_{\{x_n+\sum_{j=1}^{i-1}(y_j'-y_j)\}}$ for each $i = 1,2,\dots,k$.

Chapter 4

Main analytic theorems

In this section, we will introduce the main analytic theorems that provide sufficient conditions for positive recurrence of stochastic models associated to reaction networks with D-type and S-type tiers.

We first begin with the Foster-Lyapunov criteria which was introduced by Meyn and Tweedie [39]. Theorem 4.0.1 below is a version of a more general statement of the Foster-Lyapunov criteria that can be found at Theorem 4.2 in [39].

Theorem 4.0.1 (Foster-Lyapunov criteria) *Let X be a non-explosive continuous-time Markov process on a countable state space $\mathbb{S}$ with generator $\mathcal{A}$. Suppose there exists a finite set $K \subset \mathbb{S}$ and a positive function V on $\mathbb{S}$ such that*

$$\mathcal{A}V(x) \leq -1 \tag{4.1}$$

for all $x \in \mathbb{S} \setminus K$. Then the continuous-time Markov chain is positive recurrent.

One of the condition in Theorem 4.0.1 is non-explosion of the continuous-time Markov process. In Appendix A.3 we show that if the condition (4.1) holds with our main Lyapunov function that will be introduced at (4.2), then the associated Markov process X is non-explosive. Hence, in this chapter we mainly provide some tier structures guaranteeing that the condition (4.1) holds.

Theorem 4.2 in [39] assumes the Markov process X is non-explosive. However, on a countable state space, the condition (4.1) also implies non-explosion of the Markov process (See Appendix A.2). Thus we do not assume non-explosion in Theorem 4.0.1.

The statement of the Foster-Lyapunov criteria involves the Markov generator $\mathcal{A}$ (2.3) and a positive function V. As the definition of $\mathcal{A}$ with a positive function V in (2.3), $\mathcal{A}V$ is the averge of the directional derivative of X at x. Thus, as the Lyapunov function describes dynamical behavior of ordinary differential equations, the quantity $\mathcal{A}V(x)$ at each state x describes where the associated Markov process will jump to along the level sets of the function V at each state x. Therefore, if the Foster-Lyapunov criteria holds, then the strictly negative upper bound of $\mathcal{A}V(x)$ implies that the associated Markov process mainly jumps toward lower level sets of V which are finite sets, and thus positive recurrence of the associated Markov process follows. To find network conditions for positive recurrence, therefore, we will combine the tier structures we constructed in Chapter 3 and the Foster-Lyapunov criteria with our main Lyapunov function that will be introduced from (4.2).

In this thesis, our main Lyapunov function will be $V(x) = \sum_{i=1}^{d} v(x_i)$ where

$$v(x) = \begin{cases} x(\ln x - 1) + 1, & \text{if } x \in \mathbb{Z}_{\geq 0} \\ 0, & \text{otherwise,} \end{cases} \tag{4.2}$$

with the convention $0 \ln 0 = 0$. This function has been used widely to verify the stability of deterministic models of reaction networks. In particular, it played a significant role in the proof of the Deficiency Zero Theorem of chemical reaction network theory [21, 22, 23, 33].

4.1 Main theorem 1

We begin with a crucial lemma for an upper bound of $\mathcal{A}V(x_n)$ for a tier-sequence $\{x_n\}$ where $\mathcal{A}$ is the Markov generator introduced in (2.3).

Lemma 22 *Let $\mathcal{A}$ be the Markov generator (2.3) of the continuous-time Markov process associated to a reaction network $(\mathcal{S},\mathcal{C},\mathcal{R})$ with mass-action kinetics (2.4) and rate constants $\kappa_{y\to y'}$. Let V be the function defined in and around (4.2). For each tier sequence $\{x_n\}$ there is a constant $C>0$ for which*

$$\mathcal{A}V(x_n) \le \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'}\lambda_y(x_n)\Big(\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)+C\Big). \tag{4.3}$$

Proof. Let $I=\{i \mid x_{n,i}\to\infty, \quad \text{as} \quad n\to\infty\}$. Note that $I\neq\emptyset$ because $\{x_n\}$ is a tier-sequence. Then for a reaction $y\to y'\in\mathcal{R}$, there exists $C_{y\to y'}>0$ such that

$$\begin{aligned}
&V(x_n+y'-y)-V(x_n)\\
&\quad=\sum_{i\in I}[(x_{n,i}+y'_i-y_i)(\ln(x_{n,i}+y'_i-y_i)-1)-x_{n,i}(\ln(x_{n,i})-1)]\\
&\quad+\sum_{i\in I^c}[(x_{n,i}+y'_i-y_i)(\ln(x_{n,i}+y'_i-y_i)-1)-x_{n,i}(\ln(x_{n,i})-1)]\\
&\quad\le\sum_{i\in I}[(x_{n,i}+y'_i-y_i)(\ln(x_{n,i}+y'_i-y_i)-1)-x_{n,i}(\ln(x_{n,i})-1)]+C_{y\to y'}\\
&\quad=\sum_{i\in I}[x_{n,i}\ln\left(1+\frac{y'_i-y_i}{x_{n,i}}\right)+y_i-y'_i+\ln(x_{n,i}+y'_i-y_i)^{y'_i-y_i}]+C_{y\to y'},
\end{aligned}$$

where for the inequality in the middle, we simply grouped the second summation into the constant because each term in the summation is uniformly bounded. Using the fact that $\lim_{t\to\infty}(1+\frac{\alpha}{t})^t=e^\alpha$ for any α, we have that

$$x_{n,i}\ln\left(1+\frac{y'_i-y_i}{x_{n,i}}\right)+y_i-y'_i\to 0, \quad \text{as} \quad n\to\infty,$$

for each $i \in I$. Hence, there are $C'_{y\to y'} > 0$ for which

$$V(x_n + y' - y) - V(x_n) \le \sum_{i\in I}(y'_i - y_i)\ln(x_{n,i} + y'_i - y_i) + C'_{y\to y'} \quad \text{for each} \quad n. \tag{4.4}$$

Note that for $i \in I$,

$$\lim_{n\to\infty}\left(\ln(x_{n,i} + y'_i - y_i)^{y'_i - y_i} - \ln(x_{n,i}^{y'_i - y_i})\right) = (y'_i - y_i)\ln\left(1 + \lim_{n\to\infty}\frac{y'_i - y_i}{x_{n,i}}\right) = 0.$$

This combined with (4.4) implies the existence of a positive constant $C''_{y\to y'}$ for which

$$\begin{aligned}V(x_n + y' - y) - V(x_n) &\le \sum_{i\in I}\left(\ln(x_{n,i} + y'_i - y_i)^{y'_i - y_i} - \ln(x_{n,i}^{y'_i - y_i})\right) + \sum_{i\in I}\left(x_{n,i}^{y'_i - y_i}\right) + C_{y\to y'}\\ &\le \sum_{i\in I}\ln\left(x_{n,i}^{y'_i - y_i}\right) + C''_{y\to y'}.\end{aligned}$$

Since $x_{n,i}$ is uniformly bounded for each $i \in I^c$, we have

$$\ln\left(\prod_{i\in I}\frac{x_{n,i}^{y'_i}}{x_{n,i}^{y_i}}\right) \le \ln\left(\prod_{i\in I}\frac{(x_{n,i}\vee 1)^{y'_i}}{(x_{n,i}\vee 1)^{y_i}}\prod_{i\in I^c}\frac{(x_{n,i}\vee 1)^{y'_i}}{(x_{n,i}\vee 1)^{y_i}}\right) = \ln\left(\prod_{i=1}^{d}\frac{(x_{n,i}\vee 1)^{y'_i}}{(x_{n,i}\vee 1)^{y_i}}\right).$$

Thus we have a positive constant $C'''_{y\to y'}$ such that

$$V(x_n + y' - y) - V(x_n) \le \ln\left(\prod_{i=1}^{d}\frac{(x_{n,i}\vee 1)^{y'_i}}{(x_{n,i}\vee 1)^{y_i}}\right) + C'''_{y\to y'} = \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right) + C'''_{y\to y'}.$$

Hence,

$$\begin{aligned}\mathcal{A}V(x_n) &= \sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}\lambda_y(x_n)(V(x_n + y' - y) - V(x_n))\\ &\le \sum_{y\to y'\in\mathcal{R}}\kappa_{y\to y'}\lambda_y(x_n)\left(\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right) + C'''_{y\to y'}\right).\end{aligned}$$

The proof is completed by taking $C = \max_{y\to y'\in\mathcal{R}}\{C'''_{y\to y'}\}$. □

Note the on the right hand side of (4.3), the sign of each term can be determined by the ratio of the deterministic rate functions $(x_n \vee 1)^y$ and the size of each term can be determined by the stochastic rate function $\lambda_y(x_n)$ for each complex y. Therefore the following main analytic theorem of this thesis relates D-type and S-type partitions and the upper bound of $\mathcal{A}V$.

Theorem 4.1.1 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. Suppose that*

$$T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}} \neq \emptyset. \tag{4.5}$$

for any proper tier-sequence $\{x_n\}$, where $T^{S,i}_{\{x_n\}}$ are the S-type tiers and $D_{\{x_n\}}$ is the set of source complexes for the descending reactions along $\{x_n\}$. Then for any choice of rate constants the Markov process with intensity functions (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.

Note that the result in Theorem 4.1.1 holds whenever the tier condition is satisfied regardless of choice of rate constants. In practical experiments related to reaction networks, rate parameters often remain unknown. Thus such conditions depending solely network structures will be worth for practical problems.

Proof. Let $\mathbb{S}$ be the state space of the associated Markov process X. We will show there exists a finite set $K \subset \mathbb{S}$ such that $\mathcal{A}V(x) \le -1$ for all $x \in \mathbb{S} \setminus K$. An application of Theorem 4.0.1 then completes the proof. We proceed with an argument by contradiction. For ease of notation, the positive constant C appearing in different lines may vary.

Suppose, in order to find a contradiction, that there exists a sequence $\{x_n\}$ with $\lim_{n\to\infty} |x_n| = \infty$ and $\mathcal{A}V(x_n) > -1$ for all n. By Lemma 14, there exists a subsequence which is a proper tier-sequence. For simplicity, we also denote this proper tier-sequence by $\{x_n\}$. Denote the S-type tiers, D-type tiers, and source complexes for the descending reactions for this particular proper tier-sequence by $T^{S,i}_{\{x_n\}}, T^{D,i}_{\{x_n\}}$, and $D_{\{x_n\}}$, respectively.

Our main hypothesis (4.5) implies that there exists a reaction $y_0 \to y_0'$ such that $y_0 \in T^{D,1}_{\{x_n\}} \cap T^{S,1}_{\{x_n\}}$ and $y_0' \in T^{D,i}_{\{x_n\}}$ for some $i > 1$. Starting with an application of Lemma 22, we have the existence of a $C > 0$ for which

$$\begin{aligned}
\mathcal{A}V(x_n) &\le \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'}\lambda_y(x_n)\Big(\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)+C\Big)\\
&= \lambda_{y_0}(x_n)\Bigg(\underbrace{\sum_{\substack{y\to y'\in\mathcal{R}\\ y'\succ_D y}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)}\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)}_{I}+\underbrace{\sum_{\substack{y\to y'\in\mathcal{R}\\ y\succ_D y'}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)}\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)}_{II}\\
&\quad+\underbrace{\sum_{\substack{y\to y'\in\mathcal{R}\\ y\sim_D y'}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)}\ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)}_{III}+\underbrace{\sum_{y\to y'\in\mathcal{R}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)}C}_{IV}\Bigg).
\end{aligned} \tag{4.6}$$

First note that by Corollary 17, we know $\lambda_{y_0}(x_n) \to \infty$ as $n \to \infty$. To conclude the proof, we will show that term II will converge to $-\infty$, as $n \to \infty$, and that all the other terms remain uniformly bounded in n. One fact we will use repeatedly is the following: because $y_0 \in T^{D,1}_{\{x_n\}} \cap T^{S,1}_{\{x_n\}}$, there exists a constant $C' > 0$ such that for all complexes $y \in \mathcal{C}$ and all n large enough

$$\frac{\lambda_y(x_n)}{\lambda_{y_0}(x_n)} < C' \qquad \text{and} \qquad \frac{(x_n\vee 1)^{y}}{(x_n\vee 1)^{y_0}} < C'. \tag{4.7}$$

Note that (4.7) immediately implies that terms III and IV are uniformly bounded in n.

We turn to term I. By adding and subtracting appropriate log terms,

$$I = \sum_{\substack{y\to y'\in\mathcal{R}\\ y'\succ_D y}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y_0}}{(x_n\vee 1)^{y}}\right) + \sum_{\substack{y\to y'\in\mathcal{R}\\ y'\succ_D y}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y_0}}\right)$$

$$= \sum_{\substack{y\to y'\in\mathcal{R}\\ y'\succ_D y}} \left(\frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \frac{(x_n\vee 1)^{y_0}}{(x_n\vee 1)^{y}}\right) \frac{(x_n\vee 1)^{y}}{(x_n\vee 1)^{y_0}} \ln\left(\frac{(x_n\vee 1)^{y_0}}{(x_n\vee 1)^{y}}\right) \tag{4.8}$$

$$+ \sum_{\substack{y\to y'\in\mathcal{R}\\ y'\succ_D y}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y_0}}\right) \tag{4.9}$$

By Lemma 16, a part of term (4.8) can be shown to be bounded:

$$\lim_{n\to\infty} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \frac{(x_n\vee 1)^{y_0}}{(x_n\vee 1)^{y}} = \begin{cases} \kappa_{y\to y'}, & \text{if } y\notin T^{S,\infty}_{\{x_n\}} \\ 0, & \text{if } y\in T^{S,\infty}_{\{x_n\}}. \end{cases}$$

In addition, since $y_0\in T^{D,1}_{\{x_n\}}$ and $y\notin T^{D,1}_{\{x_n\}}$,

$$\lim_{n\to\infty} \frac{(x_n\vee 1)^{y}}{(x_n\vee 1)^{y_0}} \ln\left(\frac{(x_n\vee 1)^{y_0}}{(x_n\vee 1)^{y}}\right) = 0,$$

where we are utilizing $\lim_{t\to 0^+} t\ln(1/t) = 0$. We conclude that the term (4.8) converges to zero as $n\to\infty$. Finally, (4.7) shows that the term (4.9) is uniformly bounded in n.

We now turn to showing that term II converges to $-\infty$, as $n\to\infty$. We have

$$II = \sum_{\substack{y\to y'\in\mathcal{R}\\ y\succ_D y'}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right)$$

$$= \frac{\kappa_{y_0\to y_0'}\lambda_{y_0}(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}}\right) + \sum_{\substack{y\to y'\in\mathcal{R}\setminus\{y_0\to y_0'\}\\ y\succ_D y'}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right), \tag{4.10}$$

where we recall that y_0' is the product complex of the descending reaction $y_0\to y_0'$. Note that the first term on the right of (4.10), converges to $-\infty$ since $\kappa_{y_0\to y_0'} > 0$ and

$$\lim_{n\to\infty} \ln\left(\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}}\right) = -\infty.$$

The second term on the right of (4.10) may be an empty sum. However, if there are any terms in the sum, they must be less than or equal to zero for n large enough. Indeed, this follows because

$$\lim_{n\to\infty} \ln\left(\frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^{y}}\right) = -\infty,$$

and $\lambda_y(x_n) \geq 0$. Therefore, we conclude that the term II converges to $-\infty$, as $n \to \infty$.

Hence, we must conclude that $\lim_{n\to\infty} \mathcal{A}V(x_n) = -\infty$. However, this is in contradiction to the assumption that we made at the beginning of this proof, and the result is shown. □

We have following corollary of the Theorem 4.1.1.

Corollary 23 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network. Suppose that*

$$D_{\{x_n\}} \neq \emptyset \quad \textit{and} \quad T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}},$$

for any proper tier-sequence $\{x_n\}$. Then for any choice of rate constants the Markov process with intensity functions (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.

Proof. Note that $D_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$ by the definitions. Since $D_{\{x_n\}} \neq \emptyset$, $T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}} = T^{D,1}_{\{x_n\}} \cap D_{\{x_n\}} \neq$. Therefore by Theorem 4.1.1, the result follows. □

4.2 Main theorem 2

In this section we consider the analogous theorem of Theorem 4.1.1 pertaining to tier structures of the embedded Markov chain associated to our models. This theorem will be utilized to imply positive recurrence of the original continuous-time Markov processes associated to reaction networks.

Before we provide the key lemmas required for the proof of our theorem, we introduce some new notations. For an initial state x of the embedded Markov chain $\tilde{X}$ and a set of k reactions $\{y_1 \to y_1', \dots, y_k \to y_k'\}$, we denote the event $\{\tilde{X}_1 = x + y_1' - y_1, \tilde{X}_2 = x + y_2' - y_2 + y_1' - y_1, \dots, \tilde{X}_k = x + \sum_{i=1}^k (y_i' - y_i)\}$ by $x \xrightarrow{y_1'-y_1,\dots,y_k'-y_k} x + \sum_{j=1}^k (y_i' - y_i)$. We also use the convention $\sum_{i=1}^0 a_i = 0 \in \mathbb{Z}^d$ for any sequence $\{a_n\} \subset \mathbb{Z}^d$.

In the section, we use the tier structures $\mathbb{T}^{S,1}_{\{x_n\},R}$ and the notion $\mathbb{D}_{\{x_n\},R}$ for source complexes from a set of k reactions $R = \{y_1 \to y_1', \dots, y_k \to y_k'\}$ defined in Section 3.2. Moreover, note that reactions in the set R are not necessarily distinct.

In the following Lemma 24, we consider probabilities of jumps of $\tilde{X}$ by k reactions whose source complexes are belonging to the highest S-type tiers. This is motivated from the following two observations. First, in order to establish the network conditions for positive recurrence which will be introduced in Section 5.4, we will observe $\{\tilde{X}_{kn}\}$ for some fixed positive integer k, i.e. we will observe every k th jump of the associated Markov process X (or the embedded Markov chain $\tilde{X}$). Second, we mainly consider k reactions whose sources are belonging to the highest S-type tier for our analysis as we showed in the proof of Theorem 4.1.1.

Lemma 24 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and let X be the associated continuous-time Markov process. Further let $\tilde{X}$ be the embedded discrete-time Markov chain of X and let $\tilde{P}$ be the probability measure of $\tilde{X}$. For an ordered set of k reactions $R = \{y_1 \to y_1', y_2 \to y_2', \dots, y_k \to y_k'\} \subset \mathcal{R}$, let $\{x_n\}$ be a sequence such that $\{x_n + \sum_{j=1}^{\ell-1}\}$ is a proper tier-sequence of X for each $\ell = 1, 2, \dots, k$. Then* *(i) if* $\{y_1, y_2, \ldots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R}$,

$$\lim_{n\to\infty} \tilde{P}_{x_n}\left(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \ldots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)\right) > 0, \quad \textit{and}$$

(ii) if $\{y_1, y_2, \ldots, y_k\} \notin \mathbb{T}^{S,1}_{\{x_n\},R}$,

$$\lim_{n\to\infty} \tilde{P}_{x_n}\left(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \ldots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)\right) = 0.$$

We can simply think of the results in (i) and (ii) with the definition of S-type partitions. First note that by the definition of S-type tiers and the transition probabilities of $\tilde{X}$ given at (2.6),

$$\lim_{n\to\infty} \tilde{P}_{\{x_n\}}(X_1 = x_n + y' - y) = \lim_{n\to\infty} \frac{\lambda_y(x_n)}{\lambda_0(x_n)} = \begin{cases} 1, & \text{if } \ y \in T^{S,1}_{\{x_n\}}, \\ 0, & \text{if } \ y \notin T^{S,1}_{\{x_n\}}, \end{cases}$$

where $\lambda_0(x) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x)$. Similarly, if all source complexes of reactions in R are belonging to the highest tiers, then the result in (i) holds. Otherwise, the result in (ii) will follow.

Proof. For each n, we denote $z_n(m) = x_n + \sum_{j=1}^{m}(y'_j - y_j)$ for $m = 1, 2, \ldots, k-1$ and $z_n(0) = x_n$. By the Markov property of $\tilde{X}$,

$$\begin{aligned} &\tilde{P}_{x_n}\left(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \ldots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)\right) \\ &= \tilde{P}_{z_n(0)}(\tilde{X}_1 = z_n(1), \tilde{X}_2 = z_n(2), \ldots, \tilde{X}_k = z_n(k)) \\ &= \prod_{m=1}^{k} \tilde{P}_{z_n(m-1)}\left(\tilde{X}_m = z_n(m)\right). \end{aligned} \tag{4.11}$$

For each $m = 1, 2, \ldots, k-1$,

$$\tilde{P}_{z_n(m-1)}\left(\tilde{X}_m = z_n(m) = z_n(m-1) + y'_m - y_m\right) = \frac{\lambda_{y_m\to y'_m}(z_n(m-1))}{\lambda_0(z_n(m-1))}$$

by (2.6), where $\lambda_0(x) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x)$.

Suppose first that $\{y_1, y_2, \dots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R}$. That is, $y_m \in T^{S,1}_{\{z_n(m-1)\}}$ for each $m = 1, 2, \dots, k$. Then by the definition of S-type tiers

$$\lim_{n\to\infty} \frac{\lambda_{y_m\to y'_m}(z_n(m-1))}{\lambda_0(z_n(m-1))} = \lim_{n\to\infty} \frac{\kappa_{y_m\to y'_m}}{\displaystyle\sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'}\lambda_y(z_n(m-1))/\lambda_{y_m}(z_n(m-1))} > 0.$$

for each $m = 1, 2, \dots, k$. Therefore statement (i) holds.

For (ii), suppose $y_\ell \notin T^{S,1}_{\{z_n(\ell-1)\}}$ for some $\ell \in \{1, 2, \dots, k\}$. If $y \in T^{S,\infty}_{\{z_n(\ell-1)\}}$ for all reactions $y \to y' \in \mathcal{R}$, the result follows because $\lambda_0(z_n(\ell-1)) = 0$ so that one of term in (4.11) is zero by (2.6). Thus we assume $y \in T^{S,1}_{\{z_n(\ell-1)\}}$ for some $y \to y' \in \mathcal{R}$. Then

$$\lim_{n\to\infty} \tilde{P}_{x_n}(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \dots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)) \tag{4.12}$$

$$\begin{aligned}
&\le \lim_{n\to\infty} \tilde{P}_{z_n(\ell-1)}\left(\tilde{X}_\ell = z_n(\ell)\right) \\
&= \lim_{n\to\infty} \frac{\lambda_{y_\ell\to y'_\ell}(z_n(\ell-1))}{\lambda_0(z_n(\ell-1))} \\
&\le \lim_{n\to\infty} \frac{\kappa_{y_\ell\to y'_\ell}\lambda_{y_\ell}(z_n(\ell-1))}{\kappa_{y\to y'}\lambda_y(z_n(\ell-1))}.
\end{aligned} \tag{4.13}$$

where the first inequality comes from (4.11), the equality in the middle is by the transition probabilities of $\tilde{X}$ given at (2.6) and the last inequality is by the definition of $\lambda_0(x) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x)$. Since $y_\ell \notin T^{S,1}_{\{z_n(\ell-1)\}}$, the limit on (4.13) is zero. Thus statement (ii) follows. □

Before we move on Lemma 25 and our second main theorem, Theorem 4.2.1, we consider a reaction network in Example 4.1 where (i) for a proper tier sequence $\{x_n\}$ no reaction is in $T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}$, however, (ii) there is an ordered set of k reactions $R = \{y_1 \to y'_1, \dots, y_k \to y'_k\}$ for some k such that $\{y_1, y_2, \dots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$.

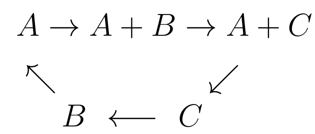

Figure 8: An example of tier structures for the embedded Markov chain.

Example 4.1 Consider the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ in Figure 8. Let X be the associated Markov process with $X(0) = (1, 1, 0)^T$. Then a sequence $x_n = (n, 1, 0)^T$ is a proper tier-sequence because

(i) species A can be infinitely produced with maintaining same counts of B and C by the reactions $A \to A + B \to A + C$ and $C \to B \to A$, hence $(n, 1, 0)^T$ is in the state space of X for any n,

(ii) $x_{n,1} = n \to \infty$, as $n \to \infty$, and

(iii) it is easy to check

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^{y}} \in [0, \infty] \quad \text{and} \quad \lim_{n\to\infty} \frac{\lambda_{y'}(x_n)}{\lambda_y(x_n)} \in [0, \infty]$$

for all pairs of complexes $y, y' \in \mathcal{C}$.

Note that $\lambda_A(x_n) = n$ and $\lambda_{A+B}(x_n) = n$ are the biggest stochastic rate functions among $\lambda_y(x_n)'s$ for all complexes y, and $A + C \to C$ is the only descending reaction. Thus there is no reaction belonging to $T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}$ because $T^{S,1}_{\{x_n\}} = \{A, A + B\}$, and $D_{\{x_n\}} = \{A + C\}$. Therefore the conditions in Theorem 4.1.1 are not fulfilled.

However, we will show that there are two most likely reactions by which the associated Markov chain started at $(n, 1, 0)^T$ can get closer to a compact set near the origin subsequently. For an ordered set of reactions $R = \{A + B \to A + C, A + C \to C\}$ where the associated reaction vector $(0,-1,1)^T$ for the first reaction $A+B \to A+C$, we have

$$A+B \in T^{S,1}_{\{x_n\}} \cap T^{D,1}_{\{x_n\}}, A+C \in T^{S,1}_{\{x_n+(0,-1,1)^T\}} \cap T^{D,1}_{\{x_n+(0,-1,1)^T\}} \text{ and } C \notin T^{D,1}_{\{x_n+(0,-1,1)^T\}}.$$

Therefore $\{A+B, A+C\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$. Note that the associated Markov chain stated at $(n,1,0)^T$ is shifted to $(n-1,0,1)^T$ by two reactions $A+B \to A+C$ and $A+C \to C$ which are in both highest S-type and D-type tiers. △

As we showed in Example 4.1, the associated Markov process X moves towards a compact set around the origin after two jumps. This will lead us to think of the embedded Markov chain $Z_n = \tilde{X}_{2n}$ which is obtained from the state of X after $2n$-th jump for $n = 1, 2, \dots$. The positive recurrence of Z will imply positive recurrence of $\tilde{X}$ and positive recurrence of $\tilde{X}$ will finally imply positive recurrence of X as we discussed in Section 2.3.

We will think of generalization of the idea above. For some fixed positive integer k, let Z be a discrete-time Markov chain such that

$$Z_n = \tilde{X}_{kn} \quad \text{for all} \quad n.$$

Based on Theorem 4.0.1 with the main Lyapunov function V defined as (4.2), the goal for showing positive recurrence of the discrete-time Markov chain Z is to characterize tier structures which guarantee

$$\mathbb{E}_x(V(Z_1)) - V(x) \le -1 \qquad \text{for all} \quad x \quad \text{but finitely many.} \tag{4.14}$$

The next lemma is required to find the asymptotic upper bound of the left hand side of (4.14) along a proper tier-sequence.

Lemma 25 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible reaction network and X be the associated Markov process with $X(0) = x$ for some non-absorbing state x. Suppose*

$$T^{S,1}_{\{z_n\}} \subset T^{D,1}_{\{z_n\}} \tag{4.15}$$

for any proper tier-sequence $\{z_n\}$ of X. Let $\tilde{X}$ be the embedded discrete-time Markov chain of X and $\tilde{P}$ be its probability measure. For an ordered set of k reactions $R = \{y_1 \to y_1, y_2 \to y_2', \ldots, y_k \to y_k'\} \subset \mathcal{R}$, let $\{x_n\}$ be a fixed sequence such that $\{x_n + \sum_{j=1}^{i-1}(y_j' - y_j)\}$ is a proper tier-sequence of X for each $i = 1, 2, \ldots, k$. Then, for the function V defined as (4.2)

(i) there is a constant $K > 0$ such that

$$\lim_{n\to\infty} \tilde{P}_{x_n}\left(x_n \xrightarrow{y_1'-y_1, y_2'-y_2, \ldots, y_k'-y_k} x_n + \sum_{j=1}^{k}(y_j' - y_j)\right) (V(x_n + \sum_{j=1}^{k}(y_j' - y_j)) - V(x_n)) \le K,$$

and

(ii) if $\{y_1, y_2, \ldots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$,

$$\lim_{n\to\infty} \tilde{P}_{x_n}\left(x_n \xrightarrow{y_1'-y_1, y_2'-y_2, \ldots, y_k'-y_k} x_n + \sum_{j=1}^{k}(y_j' - y_j)\right) (V(x_n + \sum_{j=1}^{k}(y_j' - y_j)) - V(x_n)) = -\infty.$$

Proof. For each $i = 1, 2, \ldots, k$ denote $z_n(m) = x_n + \sum_{j=1}^{m}(y_j' - y_j)$ for all n. As we showed in the proof of Lemma 22, there is a constant $C > 0$ such that

$$\begin{aligned} V(x_n + \sum_{j=1}^{k}(y_j' - y_j)) - V(x_n) &= V(z_n(k)) - V(z_n(0)) \\ &= \sum_{m=1}^{k} \left(V(z_n(m)) - V(z_n(m-1))\right) \\ &\le \ln\left(\prod_{m=1}^{k} \frac{(z_n(m) \vee 1)^{y_m'}}{(z_n(m-1) \vee 1)^{y_m}} \right) + C \end{aligned} \tag{4.16}$$

for large n.

Suppose $\{y_1, y_2, \ldots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$. Let $y'_\ell \notin T^{D,1}_{\{x_n\}}$ for some ℓ. Lemma 19 implies D-type tiers are invariant with respect to shifting the tier-sequence by finitely many reactions. Thus $\{y_1, y_2, \ldots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$ implies $y_i \in T^{D,1}_{\{z_n(i-1)\}}$ for $i = 1, 2, \ldots, k$ and $y'_\ell \notin T^{D,1}_{\{z_n(\ell-1)\}}$. Hence we have

$$\lim_{n\to\infty} \ln\left(\prod_{m=1}^{k} \frac{((z_n(i)) \vee 1)^{y'_m}}{((z_n(i-1)) \vee 1)^{y_m}}\right) + C = -\infty$$

This result combined with Lemma 24 completes (ii).

We now show part (i). Let $\lambda_0(x) = \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x)$. Suppose $y_\ell \in T^{S,\infty}_{\{z_n(\ell-1)\}}$ for some ℓ, then

$$\tilde{P}_{x_n}\left(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \ldots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)\right) = 0$$

thus the result (i) follows.

Now we suppose $y_i \notin T^{S,\infty}_{z_n(i-1)}$ for all i. Note that $\lambda_0(z) > 0$ for all $z \in \mathbb{S}$ by Lemma 8. That is, there is at least one complex $y \in T^{S,1}_{z_n(i-1)}$ for each i. From both (4.11) and (4.16), we have

$$\begin{aligned}
&\tilde{P}_{x_n}\left(x_n \xrightarrow{y'_1-y_1, y'_2-y_2, \ldots, y'_k-y_k} x_n + \sum_{j=1}^{k}(y'_j - y_j)\right)\left(V(x_n + \sum_{j=1}^{k}(y'_j - y_j)) - V(x_n)\right)\\
&\le \prod_{m=1}^{k} \tilde{P}_{z_n(m-1)}\left(\tilde{X}_m = z_n(m)\right)\left(\ln\left(\prod_{i=1}^{k} \frac{((z_n(i-1)) \vee 1)^{y'_i}}{((z_n(i-1)) \vee 1)^{y_i}}\right) + C\right)\\
&= \prod_{m=1}^{k} \frac{\kappa_{y_m\to y'_m}\lambda_{y_m}(z_n(m-1))}{\lambda_0(z_n(m))}\left(\ln\left(\prod_{i=1}^{k} \frac{((z_n(i-1)) \vee 1)^{y'_i}}{((z_n(i-1)) \vee 1)^{y_i}}\right) + C\right)
\end{aligned} \tag{4.17}$$

for large n. We denote

$$\psi_n = \prod_{i=1}^{k} \frac{((z_n(i-1)) \vee 1)^{y_i}}{\lambda_0(z_n(i-1))} \quad \text{and} \quad \phi_n = \prod_{i=1}^{k} \frac{((z_n(i-1)) \vee 1)^{y'_i}}{\lambda_0(z_n(i-1))}$$

Note that Lemma 16 implies that if $y \in T^{S,1}_{\{z_n(i-1)\}} \subset T^{D,1}_{\{z_n(i-1)\}}$ for each $i = 1, 2, \ldots, k$, then for any complex $\tilde{y} \in \mathcal{C}$,

$$\begin{aligned} \lim_{n\to\infty} \frac{(z_n(i-1)\vee 1)^{y'}}{\lambda_y(z_n(i-1))} &\leq \lim_{n\to\infty} \frac{(z_n(i-1)\vee 1)^{y'}}{\lambda_y(z_n(i-1))} \\ = \lim_{n\to\infty} \frac{(z_n(i-1)\vee 1)^{y'}}{(z_n(i-1)\vee 1)^{y}} \frac{(z_n(i-1)\vee 1)^{y}}{\lambda_y(z_n(i-1))} &< \infty \end{aligned} \tag{4.18}$$

The fact that there is at least one complex $y \in T^{S,1}_{z_n(i-1)}$ for each i and hypothesis (4.15) implies (4.18) holds for any complexes. Therefore there is a constant $C'' > 0$ such that

$$0 < \psi_n \leq C'' \quad \text{and} \quad 0 < \phi_n \leq C'' \quad \text{for all} \;\; n \tag{4.19}$$

Since $y_i \notin T^{S,\infty}_{\{x_n\}}$ for all i, by applying Lemma 16 again and (4.17), we have

$$\begin{aligned} &\tilde{P}_{x_n}\left(x_n \xrightarrow{y_1'-y_1, y_2'-y_2, \ldots, y_k'-y_k} x_n + \sum_{j=1}^{k}(y_j'-y_j)\right)\left(V(x_n + \sum_{j=1}^{k}(y_j'-y_j)) - V(x_n)\right) \\ \leq &\prod_{m=1}^{k} \frac{\kappa_{y_m\to y_m'}\lambda_{y_m}(z_n(m-1))}{\lambda_0(z_n(m))}\left(\ln\left(\prod_{i=1}^{k}\frac{((z_n(i-1))\vee 1)^{y_i'}}{((z_n(i-1))\vee 1)^{y_i}}\right) + C\right) \\ = &\lim_{n\to\infty}\prod_{m=1}^{k} \frac{\kappa_{y_m\to y_m'}\lambda_{y_m}(z_n(m-1))}{((z_n(m-1))\vee 1)^{y_m}}\psi_n\left(\ln\left(\frac{1}{\psi_n}\right) + \ln\phi_n + C\right) \\ \leq &(\max_{i=1,\ldots,k}\kappa_i)\lim_{n\to\infty}\psi_n\left(\ln\left(\frac{1}{\psi_n}\right) + \ln\phi_n + C\right), \end{aligned} \tag{4.20}$$

where the last inequality in (4.20) follows from the fact $\lambda_y(x) \leq (x \vee 1)^y$ for any complex y and state x.

By (4.19) and the fact that $t\ln(1/t)$ is bounded above when t is bounded above, we complete part (i). □

The following theorem is our main theorem for applying the embedded Markov chain to show positive recurrence of the associated continuous-time Markov process.

Theorem 4.2.1 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network and let X be the associated continuous-time Markov process with $X(0) = x$ and state space $\mathbb{S}$. Suppose for any proper tier sequence $\{x_n\}$,*

1. *$T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$, and*
2. *there is an ordered set of k reactions $R = \{y_1 \to y'_1, \ldots, y_k \to y'_k\} \subset \mathcal{R}$ satisfying the following conditions.*
   - *(i) $\{x_n + \sum_{j=1}^{i-1}(y'_j - y_j)\}$ is a proper tier-sequence for each $i = 1, 2, \ldots, k$, and*
   - *(ii) $\{y_1, y_2, \ldots, y_k\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$.*

Then the associated continuous-time Markov process X is positive recurrent.

Proof. If x is an absorbing state, then positive recurrence of X is obvious. Thus we suppose x is not an absorbing state.

For each $i = 1, 2, \ldots, k$, denote $z_n(i) = x_n + \sum_{j=1}^{i-1}(y'_j - y_j)$. Let $\tilde{X}$ be the embedded discrete-time Markov chain of X. Let Z be a discrete time Markov chain such that $Z_n = X_{kn}$ for all n. We denote by $\mathbb{E}$ and $\mathbb{P}$ for the expectation and the probability distribution of Z, respectively. By the definition of Z and $\tilde{X}$, for returning times $\tilde{T}_x = \inf\{n > 0 \ : \ \tilde{X}_n = x\}$ and $T_x = \inf\{n > 0 \ : \ Z_n = x\}$ for any state x,

$$P(\tilde{T}_x < T_x) = 1.$$

This is just because when Z hits x first, either $\tilde{X}$ hits x at the same time or $\tilde{X}$ already hit x. Hence

$$\tilde{E}_x(\tilde{T}_x) < \mathbb{E}_x(T_x).$$

Therefore positive recurrence of Z implies positive recurrence of $\tilde{X}$. This fact and Theorem 2.3.1 ensure that it is suffice to show positive recurrence of Z for the result.

We will apply Theorem 4.0.1 to Z with the main Lyapunov function V defined in (4.2). Let $\mathcal{A}_Z$ be the generator of Z (See Definition 45 for the generator of a discrete-time Markov chain). That is,

$$\mathcal{A}_Z V(x) = \mathbb{E}_X(V(Z_1)) - V(x).$$

Suppose that there is no finite set K such that $\mathcal{A}_Z V(x) < -1$ for all $x \in K^c$. Then, there exists a sequence $\{x_n\} \in \mathbb{Z}^d_{\geq 0}$ such that $\lim_{n\to\infty} |x_n| = \infty$ and $\mathcal{A}_Z V(x_n) \geq -1$ for all n. By Lemma 14, there is a subsequence of $\{x_n\}$ which is a proper tier-sequence. We denote this proper tier-sequence by $\{x_n\}$ for simplicity. By the hypotheses, there is a set of k reactions $R = \{y_1 \to y_1', \dots, y_k \to y_k'\} \subset \mathcal{R}$ for which conditions (i) and (ii) hold. Thus

$$\begin{aligned}
&\mathcal{A}_Z V(x_n) \\
=&\mathbb{E}_{x_n}(V(Z_1)) - V(x_n) \\
=&\sum_{\{\bar{y}_1 \to \bar{y}_1', \dots, \bar{y}_k \to \bar{y}_k'\} \subset \mathcal{R}} \mathbb{P}_{x_n}\left(x_n \xrightarrow{\bar{y}_1 \to \bar{y}_1', \dots, \bar{y}_k \to \bar{y}_k'} x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j)\right)\left(V(x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j)) - V(x_n)\right).
\end{aligned}$$

Note that for all k reactions $\{\bar{y}_1 \to \bar{y}_1', \dots, \bar{y}_k \to \bar{y}_k'\} \subset \mathcal{R}$, there exists a constant K such that

$$\lim_{n\to\infty} \mathbb{P}_{x_n}(x_n \xrightarrow{\bar{y}_1 \to \bar{y}_1', \dots, \bar{y}_k \to \bar{y}_k'} x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j))(V(x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j)) - V(x_n)) \leq K, \quad \text{and}$$

$$\lim_{n\to\infty} \mathbb{P}_{x_n}(x_n \xrightarrow{y_1 \to y_1', \dots, y_k \to y_k'} x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j))(V(x_n + \sum_{j=1}^k (\bar{y}_j' - \bar{y}_j)) - V(x_n)) = -\infty$$

by Lemma 25. Thus $\mathcal{A}_Z(x_n) \to -\infty$, as $n \to \infty$. This is a contradiction to the assumption $\mathcal{A}_Z(x_n) \geq -1$ for all n. Therefore Z is positive recurrent by Theorem 4.0.1.

□

Chapter 5

Network conditions guaranteeing positive recurrence

In this chapter we provide network conditions of binary reaction networks which imply that the associated Markov processes are positive recurrence so that stationary distributions exist. We introduce four classes of binary reaction networks for which the associated Markov process is guaranteed to be positive recurrent: 1) a network that has a single linkage class and all in-flows and out flows, 2) a double-full network with a path condition for each double complex, 3) a double-full networks with the path condition replaced by other conditions on unary complexes or double complexes , and 4) a network that has a single linkage class with each species appearing as a complex by itself.

One of the remarkable facts is that all the network conditions given in this thesis do not depend on rate constants i.e. system parameters which often remain unknown in practical experiments. Therefore we can predict dynamical behavior of the reaction networks in the long run as long as the network conditions provided in this chapter hold.

The main theorems provided in this chapter for positive recurrent will be several steps towards one of our goals that is proving 'Positive Recurrence Conjecture'.

Conjecture (Positive Recurrence Conjecture). *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a weakly reversible reaction network. Then, for any choice of rate constants, the Markov process with intensity* *function* (2.4) *associated to the reaction network* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *is positive recurrent.*

5.1 Single linkage class case

In this section we provide analogous results for stochastic dynamics pertaining to a network class considered in the papers [3, 4]. In those papers, it was shown that deterministic models of reaction networks with a single, weakly reversible linkage class were persistent (the dynamics does not touch the boundary of the positive orthant) and bounded. The principal ideas utilized in [3, 4] are tier structures on the set of complexes $\mathcal{C}$ by rates x_n^y along a sequence $\{x_n\}$ and the Lyapunov function style analysis with the main Lyapunov function V introduced in Equation 4.2. However the same approach does not always allow for the analysis of stochastically modeled systems. We demonstrate this with the following example.

Example 5.1 The reaction network in Figure 9 consists of a single, weakly reversible linkage class.

$$A + B \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} \emptyset \underset{\kappa_3}{\overset{\kappa_4}{\rightleftharpoons}} B$$

Figure 9: An example of weakly reversible single linkage class for which the main Lyapunov function approach does not work.

Consider the tier-sequence $x_n = (n, 0)^T$ which is exactly on the boundary of the stoichiometric compatibility class of the reaction network. Then $\mathcal{A}V(x_n) = \kappa_2(\ln(n + 1) + n\ln(\frac{n+1}{n}) - 2) - \kappa_4 \to \infty$, as $n \to \infty$.

For the deterministic model, however, the system dynamics never touches the boundary exactly. Therefore, instead of the sequence $\{x_n\}$, we will consider $z_n = (n, \epsilon)^T$ for some small $\epsilon > 0$. That is, the sequence $\{z_n\}$ is near the boundary of the stoichiometric compatibility class and the sequence $\{x_n\}$ lies on exactly the boundary of the stoichiometric compatibility class. Even though two sequences are very close each other, the deterministic dynamics and the stochastic dynamics associated to this reaction network behave very differently because along the sequence $\{z_n\}$, the reaction $A + B \to \emptyset$ offers the degradation of A in the deterministic model, but it was not fired along $\{x_n\}$ in the stochastic model since $\lambda_{A+B\to\emptyset}(x_n) = 0$ for all n. $\triangle$

As we mentioned at the beginning of Chapter 3 a key difference between behavior of deterministically modeled reaction networks and stochastically modeled reaction networks usually occur at the boundary of the state space. Stochastic intensity function $\lambda_{y\to y'}$ for a reaction $y \to y'$ can be exactly zero along a proper tier-sequence on the boundary but deterministic intensity $(x_n \vee 1)^y$ is always strictly positive.

To get around this issue, we add the out-flow of each species defined in Definition 5. The out-flows will play a role of degradation of some species on the boundary. We begin with a lemma.

Lemma 26 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a reaction network with $\mathcal{S} = \{S_1, S_2, \cdots, S_d\}$. Suppose $S_i \to \emptyset \in \mathcal{R}$ for some species S_i. Let $\{x_n\}$ be a proper tier-sequence. If $S_i \in T^{D,1}_{\{x_n\}}$, then*

$$S_i \in T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}. \tag{5.1}$$

Proof. Note that Lemma 15 implies $\emptyset \notin T^{D,1}_{\{x_n\}}$. Hence, $S_i \in D_{\{x_n\}}$. Because $\lambda_{S_i}(x_n) \neq 0$, Corollary 17 implies $S_i \in T^{S,1}_{\{x_n\}}$. $\square$

We now introduce our first result providing a network condition that guarantees positive recurrence of the associated continuous-time Markov model.

Theorem 5.1.1 *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a weakly reversible, binary reaction network that has a single linkage class. Let* $\widetilde{\mathcal{C}} = \mathcal{C} \cup \{\emptyset\} \cup \{S \mid S \in \mathcal{S}\}$ *and* $\widetilde{\mathcal{R}} = \mathcal{R} \cup_{S \in \mathcal{S}} \{\emptyset \to S, S \to \emptyset\}$*. Then, for any choice of rate constants, the Markov process with intensity functions* (2.4) *associated to the reaction network* $(\mathcal{S}, \widetilde{\mathcal{C}}, \widetilde{\mathcal{R}})$ *is positive recurrent.*

Proof. For concreteness, order the species as $\mathcal{S} = \{S_1, \ldots, S_d\}$.

First suppose $\mathcal{C}$ consists of either only binary complexes or only unary complexes. Then $(y' - y) \cdot \vec{1} = 0$ for all $y \to y' \in \mathcal{R}$, where $\vec{1} = (1, 1, \ldots, 1) \in \mathbb{Z}^d$. Let $\mathcal{A}$ be a generator of the Markov process associated to the reaction network $(\mathcal{S}, \widetilde{\mathcal{C}}, \widetilde{\mathcal{R}})$. Then for the function $W(x) = x_1 + x_2 + \cdots + x_d$, we have

$$\mathcal{A}W(x) = -\sum_{i=1}^{d} \kappa_{S_i \to \emptyset} x_i + \sum_{i=1}^{d} \kappa_{\emptyset \to S_i}$$

Thus, for an arbitrary sequence $\{x_n\} \in \mathbb{Z}^d_{\geq 0}$ such that $|x_n| \to \infty$, as $n \to \infty$,

$$\mathcal{A}W(x_n) \to -\infty.$$

This implies $\mathcal{A}W(x) < -1$ for all x but finitely many. An application of Theorem 4.0.1 would then finish the proof.

Now we suppose $\mathcal{C}$ does not contain only binary complexes or only unary complexes. Let $\{x_n\}$ be a proper tier-sequence. We will show that (4.5) holds for the expanded network $(\mathcal{S}, \widetilde{\mathcal{C}}, \widetilde{\mathcal{R}})$, in which case an application of Theorem 4.1.1 will complete the proof.

There are three cases to consider.

Case 1. Assume that all complexes in $\mathcal{C}$ are in $T^{D,1}_{\{x_n\}}$.

If there is no unary complex in $\mathcal{C}$, then we must have $\emptyset \in \mathcal{C}$ (since not all complexes are binary). However, by Lemma 15 we know $\emptyset \notin T^{D,1}_{\{x_n\}}$. Since this would contradict that all complexes in $\mathcal{C}$ are in $T^{D,1}_{\{x_n\}}$, it must be that at least one unary complex is in $\mathcal{C}$. Since a unary complex is in $T^{D,1}_{\{x_n\}}$, Lemma 26 implies $D_{\{x_n\}} \cap T^{S,1}_{\{x_n\}} \neq \emptyset$.

Case 2. Assume that some of the complexes in $\mathcal{C}$ are not in $T^{D,1}_{\{x_n\}}$, and one complex in $D_{\{x_n\}}$ is binary.

Since (i) not all complexes in $\mathcal{C}$ are in $T^{D,1}_{\{x_n\}}$, and (ii) $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is weakly reversible, there is a reaction $y_0 \to y_0'$ such that $y_0 \in T^{D,1}_{\{x_n\}}$ and $y_0' \notin T^{D,1}_{\{x_n\}}$. We assume that $y_0 = S_i + S_j$ for some $i, j \in \{1, 2, \ldots, d\}$ (where we allow $i = j$).

If $y_0 \in T^{S,1}_{\{x_n\}}$, then we may conclude the proof by an application of Theorem 4.1.1. Hence, we assume that $y_0 \notin T^{S,1}_{\{x_n\}}$, and must demonstrate the existence of a descending reaction $y \to y'$ such that $y \in T^{S,1}_{\{x_n\}}$.

By Corollary 17, we must have $y_0 \in T^{S,\infty}_{\{x_n\}}$. This means $i \neq j$, and, without loss of generality, $x_{n,j} = 0$ for all n. We further conclude from Lemma 15 that $x_{n,i} \to \infty$ as $n \to \infty$. Also, since $S_i + S_j \in T^{D,1}_{\{x_n\}}$, it must be that $S_i \in T^{D,1}_{\{x_n\}}$ since when $x_{n,j} = 0$, we have

$$(x_n \vee 1)^{S_i} = x_{n,i} = x_{n,i} \cdot (x_{n,j} \vee 1) = (x_n \vee 1)^{S_i + S_j}.$$

An application of Lemma 26 then completes the argument.

Case 3. Assume that some of the complexes in $\mathcal{C}$ are not in $T^{D,1}_{\{x_n\}}$, and one complex in $D_{\{x_n\}}$ is unary.

An application of Lemma 26 completes the argument. □

The example given below is one of applications of Theorem 5.1.1.

Example 5.2 Consider the reaction network in Figure 10.

$$S + E \underset{\kappa_1}{\overset{\kappa_2}{\rightleftharpoons}} SE \underset{\kappa_3}{\overset{\kappa_4}{\rightleftharpoons}} E + P,$$
$$S \underset{\kappa_5}{\overset{\kappa_6}{\rightleftharpoons}} \emptyset \underset{\kappa_7}{\overset{\kappa_8}{\rightleftharpoons}} E, \quad SE \underset{\kappa_9}{\overset{\kappa_{10}}{\rightleftharpoons}} \emptyset \underset{\kappa_{11}}{\overset{\kappa_{12}}{\rightleftharpoons}} P$$

Figure 10: Substrate-Enzyme kinetics with in-flows and out-flows for all species.

This reaction network consists of a single linkage class which is weakly reversible (the top linkage class), and in-flows and out-flows for all species. Therefore the associated Markov process for this reaction network is positive recurrent for any choice of rate constants $\kappa_1, \kappa_2, \dots, \kappa_{12}$. △

5.2 Double-full binary reaction networks

In this section, we drop the weak reversibility and a single linkage class assumption which is rarely seen in biology. However we add the 'double-full' condition for binary reaction networks. For this class of reaction network, we assume a path condition at each double complex for positive recurrence instead of weak reversibility of networks. We begin with a necessary lemma that captures the usefulness of the double-full assumption.

Lemma 27 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a double-full, binary reaction network with $\mathcal{S} = \{S_1, S_2, \dots, S_d\}$. Let $\{x_n\}$ be a proper tier-sequence of $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. Then the following holds:*

1. *If $S_i + S_j \in T^{D,1}_{\{x_n\}}$, then $2S_i, 2S_j \in T^{D,1}_{\{x_n\}}$. Thus, $\lim_{n\to\infty} \dfrac{(x_{n,i} \vee 1)}{(x_{n,j} \vee 1)} = C$ for some constant $C > 0$.*

2. $T^{D,1}_{\{x_n\}} \subset \{S_i + S_j \mid i,j = 1,2,\ldots,d\}$ *and* $2S_i \in T^{D,1}_{\{x_n\}}$ *for some* $i = 1,2\ldots,d$. *That is,* $T^{D,1}_{\{x_n\}}$ *consists of only binary complexes and always contains at least one double complex.*

3. $T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$.

Proof. Let $I = \{i \mid \lim_{n\to\infty} x_{n,i} = \infty\}$.

For the first claim, if $i = j$, then the result is trivial. Thus, let $i \neq j$. Suppose $2S_i \notin T^{D,1}_{\{x_n\}}$. Then

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{2S_i}}{(x_n \vee 1)^{S_i+S_j}} = \lim_{n\to\infty} \frac{(x_{n,i} \vee 1)}{(x_{n,j} \vee 1)} = 0.$$

Hence,

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{S_i+S_j}}{(x_n \vee 1)^{2S_j}} = \lim_{n\to\infty} \frac{(x_{n,i} \vee 1)}{(x_{n,j} \vee 1)} = 0.$$

This implies $2S_j \succ_D S_i + S_j$ which is in contradiction to the assumption $S_i + S_j \in T^{D,1}_{\{x_n\}}$. Therefore, $2S_i \in T^{D,1}_{\{x_n\}}$. In same way, we can show $2S_j \in T^{D,1}_{\{x_n\}}$.

We turn to the second claim. We will show that unary complexes and the zero complex cannot be in $T^{D,1}_{\{x_n\}}$. First $\emptyset \notin T^{D,1}_{\{x_n\}}$ follows by Lemma 15. Suppose now that $S_m \in T^{D,1}_{\{x_n\}}$ for some m. Then either $2S_m \succ_D S_m$ or $2S_k \succ_D S_m$ for some $k \in I$, because

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{S_m}}{(x_n \vee 1)^{2S_m}} = \lim_{n\to\infty} \frac{1}{x_{n,m}} = 0 \quad \text{if} \quad m \in I \quad \text{and,}$$
$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{S_m}}{(x_n \vee 1)^{2S_k}} = \lim_{n\to\infty} \frac{x_{n,m}}{x_{n,k}^2} = 0 \quad \text{if} \quad m \notin I.$$

Thus $S_m \notin T^{D,1}_{\{x_n\}}$. Part 1 shows that there is at least one i for which $2S_i \in T^{D,1}_{\{x_n\}}$.

For the last claim, we will first show that $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$. Let $y \in T^{S,1}_{\{x_n\}}$. By result 2, $2S_i \in T^{D,1}_{\{x_n\}}$ for some i. Note that, by Corollary 17, $2S_i \in T^{S,1}_{\{x_n\}}$ since Lemma 15 implies that $\lambda_{2S_i}(x_n) \neq 0$ for large n. Applying Lemma 16, we have

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{2S_i}}{(x_n \vee 1)^y} = \lim_{n\to\infty} \frac{\lambda_{2S_i}(x_n)}{\lambda_y(x_n)} = C \quad \text{for some constant } C > 0.$$

This means that $y \sim_D 2S_i$. Therefore $y \in T^{D,1}_{\{x_n\}}$ and we conclude that $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$. Now we will show $T^{D,1}_{\{x_n\}} \subset T^{S,1}_{\{x_n\}}$. Let $y \in T^{D,1}_{\{x_n\}}$. It is sufficient to show that $y \notin T^{S,\infty}_{\{x_n\}}$ by Corollary 17. By result 2, $y = S_i + S_j$ for some i and j (where we allow $i \neq j$), and $2S_i \in T^{D,1}_{\{x_n\}}$ and $2S_j \in T^{D,1}_{\{x_n\}}$. By Lemma 15, $x_{n,i} \to \infty$ and $x_{n,j} \to \infty$, as $n \to \infty$. Therefore $\lambda_y(x_n) \neq 0$ for large n and hence $y \notin T^{S,\infty}_{\{x_n\}}$. □

Lemma 27 concludes that $T^{D,1}_{\{x_n\}}$ and $T^{S,1}_{\{x_n\}}$ are always equal and consist of binary complexes for a double-full, binary reaction network. Now we show our second main network conditions for positive recurrence.

Theorem 5.2.1 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a binary reaction network satisfying the following two conditions:*

1. *the reaction network is double-full, and*

2. *for each double complex (of the form $2S_i$) there is a directed path within the reaction graph beginning with the double complex itself and ending with either a unary complex (of the form S_j) or the zero complex.*

Then, for any choice of rate constants, the Markov process with intensity functions (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.

Before we show the proof of Theorem 5.2.1, we provide here one of simple examples of reaction networks satisfying the conditions in Theorem 5.2.1. Consider a reaction network

$$2B \rightleftharpoons C \leftarrow A \leftarrow 2C \leftarrow 2A.$$

It is easy to check that it is binary and all double complexes $2A, 2B$ and $2C$ appear in this reaction network. Also each double complex has a directed path of reactions ending with the unary complex C. (i.e. $2A \to 2C \to C, 2C \to C$ and $2B \to C$) .

Proof. Let $\{x_n\}$ be a proper tier-sequence. Result 3 in Lemma 27 shows $T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$. Thus, so long as a descending reaction can be shown to exist, an application of Corollary 23 will complete the proof.

By result 2 in Lemma 27, there exists a double complex $2S_i \in T^{D,1}_{\{x_n\}}$ for some i. By our hypothesis, there exists a directed path from $2S_i$ to a unary or the zero complex y' in the reaction graph. According to result 2 in Lemma 27, $y' \notin T^{D,1}_{\{x_n\}}$. Therefore a descending reaction exists within the directed path from $2S_i$ to y'. □

We demonstrate Theorem 5.2.1 with an example.

Example 5.3 *The reaction network in Figure 11 contains* 5 *species,* 14 *complexes and* 14 *reactions. This binary reaction network is double-full. Moreover, for each double*

$$
\begin{aligned}
&2A \xrightarrow{\kappa_1} A + B \underset{\kappa_2}{\overset{\kappa_3}{\rightleftharpoons}} B \\
&2D \underset{\kappa_4}{\overset{\kappa_5}{\rightleftharpoons}} A \underset{\kappa_6}{\overset{\kappa_7}{\rightleftharpoons}} \quad 2C \xrightarrow{\kappa_8} B + C \\
&2B \xrightarrow{\kappa_9} \emptyset \underset{\kappa_{10}}{\overset{\kappa_{11}}{\rightleftharpoons}} D \underset{\kappa_{12}}{\overset{\kappa_{13}}{\rightleftharpoons}} 2E \\
&C \xrightarrow{\kappa_{13}} A + C \xrightarrow{\kappa_{14}} C + E.
\end{aligned}
$$

Figure 11: An example of double-full network satisfying the directed path conditions

complex ($2A$*,* $2B$*,* $2C$*,* $2D$*,* $2E$ *and* $2F$*), there is a directed path within the reaction graph beginning with the double complex itself and ending with either a unary complex or the zero complex. Therefore the conditions in Theorem 5.2.1 hold. Thus, the associated* *continuous time Markov chain is positive recurrence regardless of choice of the rate constants* $\kappa_1, \ldots, \kappa_{14}$. $\triangle$

5.3 More results on double-full, binary reaction networks

In this section, we provide classes of double-full, binary reaction networks for which condition 2 of Theorem 5.2.1 (the path condition) does not hold, but for which positive recurrence is still guaranteed.

We begin with a technical lemma.

Lemma 28 *Let* $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ *be a double-full, binary reaction network. Suppose the following:*

1. $\mathcal{L}$ *is a weakly reversible linkage class with* $S, \tilde{S} \in \mathcal{S}(\mathcal{L})$ *(where we allow* $S = \tilde{S}$*) such that* $S + \tilde{S} \in \mathcal{C}$.
2. *There is a directed path within the reaction graph beginning with* $S + \tilde{S}$ *and ending with a unary or the zero complex.*

Then for any proper tier-sequence $\{x_n\}$ *the following holds: if there is a complex* y *in the linkage class* $\mathcal{L}$ *(i.e.* $y \in \mathcal{C}(\mathcal{L})$*) that is in* $T^{D,1}_{\{x_n\}}$*, then* $D_{\{x_n\}} \neq \emptyset$.

We demonstrate the lemma with an example.

Example 5.4 Consider the reaction network in Figure 12.

Let $\mathcal{L}$ be the middle linkage class (i.e., $A + C \leftrightharpoons B + C$) in this reaction network. Then $A, B \in \mathcal{S}(\mathcal{L})$, and there is a directed path from $A+B$ to $\emptyset$, showing that conditions

$$\begin{aligned} &2A \leftrightharpoons 2B \leftrightharpoons 2C \leftrightharpoons 2D \\ &A + C \leftrightharpoons B + C \\ &A + B \leftrightharpoons 2F \leftrightharpoons \emptyset \to 2E. \end{aligned}$$

Figure 12: An example of a reaction network satisfying conditions in Lemma 28.

1 and 2 are met. Hence, we conclude that if $\{x_n\}$ is a proper tier-sequence and either $A + C$ or $B + C$ are in $T^{D,1}_{\{x_n\}}$, then we necessarily have that $D_{\{x_n\}} \neq 0$. In this case, the descending reaction could be in any of the three linkage classes (depending upon the particular sequence $\{x_n\}$). $\triangle$

Proof. Let $\mathcal{S} = \{S_1, S_2, \dots, S_d\}$. Assume that $\{x_n\}$ is a proper tier-sequence and that there is a $y \in \mathcal{C}(\mathcal{L})$ such that $y \in T^{D,1}_{\{x_n\}}$. We must show that $D_{\{x_n\}} \neq \emptyset$.

Case 1. If there is a complex $y' \in C(\mathcal{L})$ that is not in $T^{D,1}_{\{x_n\}}$, then there necessarily exits a descending reaction along $\{x_n\}$ by the weak reversibility of $\mathcal{L}$.

Case 2. Now suppose that all complexes in $C(\mathcal{L})$ are in $T^{D,1}_{\{x_n\}}$. We will show $S + \tilde{S} \in T^{D,1}_{\{x_n\}}$. We assume $S = S_i$ and $\tilde{S} = S_j$ for some i and j (where, again, we could have $i = j$). By result 2 in Lemma 27, $\mathcal{C}(\mathcal{L})$ contains only binary complexes. Thus $S_i + S_m \in \mathcal{C}(\mathcal{L})$ for some m. Indices i, j and m are not necessarily all distinct. By result 1 in Lemma 27, $\{2S_i, 2S_m, 2S_j\} \subset T^{D,1}_{\{x_n\}}$. Therefore

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{S_i+S_j}}{(x_n \vee 1)^{S_i+S_m}} = \lim_{n\to\infty} \frac{(x_{n,j} \vee 1)}{(x_{n,m} \vee 1)} = \sqrt{\lim_{n\to\infty} \frac{(x_n \vee 1)^{2S_j}}{(x_n \vee 1)^{2S_m}}} = C \quad \text{for some } C > 0.$$

Therefore $S_i + S_j \in T^{D,1}_{\{x_n\}}$. By hypothesis 2, there exists a directed path from $S_i + S_j$ to a unary complex or the zero complex within the reaction graph. Since only binary complexes can be in $T^{D,1}_{\{x_n\}}$ in a double-full reaction network, there exists a descending reaction along $\{x_n\}$ within the directed path. □

Theorem 5.3.1 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a double-full, binary reaction network with linkage classes $\mathcal{L}_1, \mathcal{L}_2, \ldots, \mathcal{L}_\ell$. Suppose there is an integer $m \in \{1, 2, \ldots, \ell - 1\}$ such that:*

1. *For $i \leq m$, $\mathcal{L}_i$ is weakly reversible and $\mathcal{C}(\mathcal{L}_i)$ contains only binary complexes.*
2. *For each $i \leq m$, there exists $S, \tilde{S} \in \mathcal{S}(\mathcal{L}_i)$ (where we allow $S \neq \tilde{S}$) such that*
   - *(i) $S + \tilde{S} \in \mathcal{C}$,*
   - *(ii) there is a directed path within the reaction graph beginning with $S + \tilde{S}$ and ending with a unary or the zero complex.*
3. *For each double complex $2S$, either $2S \in \mathcal{C}(\mathcal{L}_i)$ for some $i \leq m$ or there is a directed path within the reaction graph beginning with $2S$ and ending with a unary complex or the zero complex.*

Then, for any choice of rate constants, the Markov process with intensity function (2.4) *associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.*

Remark that the path condition for each double complex as mentioned in Theorem 5.2.1 is not assumed in Theorem 5.3.1. The path condition is actually replaced by another conditions on species in a linkage class that contains only double complexes.

Proof. Let $\{x_n\}$ be a proper tier-sequence. Result 3 in Lemma 27 shows $T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$. Thus, so long as a descending reaction can be shown to exist, an application of Corollary 23 will complete the proof.

By result 2 in Lemma 27, $2S_j \in T^{D,1}_{\{x_n\}}$ for some j. If there is a directed path beginning with $2S_j$ and ending with a unary complex or the zero complex within the reaction graph, we have a descending reaction along $\{x_n\}$ within the directed path. Otherwise, $2S_j \in \mathcal{C}(\mathcal{L}_i)$ for some $i \leq m$ by the hypothesis, and hence $D_{\{x_n\}} \neq \emptyset$ by Lemma 28. $\square$

We demonstrate Theorem 5.3.1 with an example.

Example 5.5 The reaction network in Figure 13 is a double-full, binary reaction network for which the conditions in the Theorem 5.3.1 hold.

$$\begin{aligned}
&A + B \rightleftharpoons 2B \rightleftharpoons A + B \\
&2D \rightleftharpoons 2C \rightleftharpoons A + D \\
&2A \rightarrow B + C \rightleftharpoons A \\
&C + D \rightarrow \emptyset \rightleftharpoons D.
\end{aligned}$$

Figure 13: An application of Theorem 5.3.1.

Note that Theorem 5.2.1 stands silent on this model as there is no reaction path beginning with $2B$ and ending with a unary complex or $\emptyset$.

Let $\mathcal{L}_1, \mathcal{L}_2, \mathcal{L}_3$ and $\mathcal{L}_4$ be the linkage classes of this reaction network in order from top to bottom. We demonstrate that the assumptions of Theorem 5.3.1 are fulfilled with $m = 2$.

1. The linkage classes $\mathcal{L}_1$ and $\mathcal{L}_2$ contain only binary complexes and are weakly reversible.

2. (i) For linkage class $\mathcal{L}_1$, we take $S = \tilde{S} = A$, and note the path from $2A$ to A in $\mathcal{L}_3$.

   (ii) For linkage class $\mathcal{L}_2$, we take $S = C$ and $\tilde{S} = D$, and note the reaction $C + D \rightarrow \emptyset$ in $\mathcal{L}_4$.

3. We note $2B \in \mathcal{L}_1$ and $2C, 2D \in \mathcal{L}_2$. Also, there is a path from $2A$ to A in $\mathcal{L}_3$. $\triangle$

Since weak reversibility guarantees the existence of a directed path between two complexes within any linkage class, we can modify the conditions in Theorem 5.3.1.

Corollary 29 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible, double-full, binary reaction network with linkage classes $\mathcal{L}_1, \mathcal{L}_2, \ldots, \mathcal{L}_\ell$. Let $m \in \{1, \ldots, \ell - 1\}$ and suppose the following:*

1. *$\mathcal{C}(\mathcal{L}_i)$ contains only binary complexes for each $i \leq m$ and $\mathcal{C}(\mathcal{L}_i)$ contains at least one non-binary complex for each $i > m$.*
2. *For each $i \leq m$, there exist species $S, \tilde{S} \in \mathcal{C}(\mathcal{L}_i)$ such that $S + \tilde{S} \in \mathcal{C}(\mathcal{L}_j)$ for some $j > m$.*

Then, for any choice of rate constants, the Markov process with intensity function (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.

Now we will provide another class of double-full, binary reaction networks in which we will assume the existence of out-flows.

Theorem 5.3.2 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a double-full, binary reaction network with linkage classes $\mathcal{L}_1, \mathcal{L}_2, \ldots, \mathcal{L}_\ell$. Suppose there is an $m \in \{1, \ldots, \ell - 1\}$ such that the following three conditions hold:*

1. *For each $i \leq m$, $\mathcal{L}_i$ is weakly reversible and $\mathcal{C}(\mathcal{L}_i)$ contains only binary complexes.*
2. *For each $i > m$, $C(\mathcal{L}_i)$ contains no binary complex.*
3. *For each $i \leq m$, there exists an $S \in \mathcal{S}(\mathcal{L}_i)$ such that $S \to \emptyset \in \mathcal{R}$.*

Then, for any choice of rate constants, the Markov process with intensity functions (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is positive recurrent.

Proof. Let $\mathcal{S} = \{S_1, S_2, \ldots, S_d\}$ and for some $0 < \delta < 1$ let

$$T(x) = (x_1 + x_2 + \cdots + x_d)^{2+\delta} = (\vec{1} \cdot x)^{2+\delta},$$

where $\vec{1} = (1, 1, \cdots, 1)^T \in \mathbb{Z}^d_{\geq 0}$. Let $\{x_n\}$ be a proper tier-sequence of $(\mathcal{S}, \mathcal{C}, \mathcal{R})$. We will show that

$$\lim_{n\to\infty} \mathcal{A}(V + T)(x_n) = -\infty.$$

Then by Theorem 4.0.1, the associated Markov process is positive recurrence.

We begin by finding relevant upper bounds for $\mathcal{A}T(x_n)$ in a similar fashion as Lemma 22. First, we define

$$I = \{i \mid \lim_{n\to\infty} x_{n,i} = \infty\}, \quad U = \{i \mid S_i \to \emptyset \in \mathcal{R}\}, \quad \text{and} \quad V = \{i \mid \emptyset \to S_i \in \mathcal{R}\}.$$

Since $(1+h)^{2+\delta} = 1 + (2+\delta)h + o(h) \leq 1 + 3h$ for h small enough, there is a positive constant K such that, for large n

$$\begin{aligned}
\mathcal{A}T(x_n) &= \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x_n)\big((\vec{1}\cdot x_n + \vec{1}\cdot(y'-y))^{2+\delta} - (\vec{1}\cdot x_n)^{2+\delta}\big) \\
&= (\vec{1}\cdot x_n)^{2+\delta} \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x_n) \left(\left(1 + \frac{\vec{1}\cdot(y'-y)}{\vec{1}\cdot x_n}\right)^{2+\delta} - 1\right) \\
&\leq 3(\vec{1}\cdot x_n)^{2+\delta} \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x_n) \left(\frac{\vec{1}\cdot(y'-y)}{\vec{1}\cdot x_n}\right) \\
&= 3(\vec{1}\cdot x_n)^{1+\delta} \sum_{y\to y'\in\mathcal{R}} \lambda_{y\to y'}(x_n)(\vec{1}\cdot(y'-y)) \\
&= 3(\vec{1}\cdot x_n)^{1+\delta} \left(\sum_{i\in U} \lambda_{S_i\to\emptyset}(x_n)(-1) + \sum_{i\in V} \lambda_{\emptyset\to S_i}(x_n)\right) \\
&\leq 3(\vec{1}\cdot x_n)^{1+\delta} \left(-\sum_{i\in U\cap I} \kappa_{S_i\to\emptyset} x_{n,i} + K\right) \qquad (5.2)
\end{aligned}$$

Therefore, if there is $k \in U \cap I$ such that

$$\lim_{n\to\infty} \frac{(x_{n,k} \vee 1)}{(x_{n,i} \vee 1)} \quad \text{exists and} \quad \lim_{n\to\infty} \frac{(x_{n,k} \vee 1)}{(x_{n,i} \vee 1)} > 0$$

for all $i \in \{1, 2, 3, \ldots, d\}$, then there is a constant $K' > 0$ such that

$$\mathcal{A}T(x_n) \leq -K' x_{n,k}^{2+\delta} \tag{5.3}$$

for large n. Hence, we have found our bound on $\mathcal{A}T$, and we turn to $\mathcal{A}(T+V)$.

Note that by result 2 in Lemma 27 there is an i for which $2S_i \in T^{D,1}_{\{x_n\}}$. Without loss of generality, we assume $i = 1$ and $2S_1 \in \mathcal{C}(\mathcal{L}_1)$. There are two cases to consider: (i) $\mathcal{C}(\mathcal{L}_1) \subseteq T^{D,1}_{\{x_n\}}$ and (ii) there is a complex $y' \in \mathcal{C}(\mathcal{L}_1)$ such that $y' \notin T^{D,1}_{\{x_n\}}$.

Case 1. Suppose $\mathcal{C}(\mathcal{L}_1) \subseteq T^{D,1}_{\{x_n\}}$. Then by hypothesis 3, there exists a species, say S_k, such that $S_k \in \mathcal{S}(\mathcal{L}_1)$ and $S_k \to \emptyset \in \mathcal{R}$. Note that $S_k + S_j \in C(\mathcal{L}_1) \subseteq T^{D,1}_{\{x_n\}}$ for some j (where we allow $k = j$) because $C(\mathcal{L}_1)$ only contains binary complexes. By result 1 in Lemma 27, $2S_k \in T^{D,1}_{\{x_n\}}$ and hence $k \in U \cap I$ by Lemma 15. Since $2S_k \in T^{D,1}_{\{x_n\}}$ and the network is double-full, for all $i = 1, 2, 3, \ldots, d$ we have

$$\lim_{n\to\infty} \frac{(x_{n,k} \vee 1)}{(x_{n,i} \vee 1)} \quad \text{exists and} \quad \lim_{n\to\infty} \frac{(x_{n,k} \vee 1)}{(x_{n,i} \vee 1)} > 0.$$

Hence, by (5.3) there is a constant $K' > 0$ such that for large n,

$$\mathcal{A}T(x_n) \leq -K' x_{n,k}^{2+\delta} \tag{5.4}$$

We now turn to $\mathcal{A}V$. Note that $T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$ by result 3 in Lemma 27. Since $2S_k \in T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$ there is a constant $K'' > 0$ such that

$$\lim_{n\to\infty} \frac{\lambda_y(x_n)}{\lambda_{2S_k}(x)} \leq K'' \quad \text{and} \quad \lim_{n\to\infty} \frac{(x_n \vee 1)^y}{(x_n \vee 1)^{2S_k}} \leq K'' \tag{5.5}$$

for any complex $y \in \mathcal{C}$. Now applying Lemma 22 and (5.5), we may conclude that there are positive constants C and C' such that

$$\mathcal{A}V(x_n) \leq \sum_{y\to y'\in\mathcal{R}} \kappa_{y\to y'}\lambda_y(x_n)\left(\ln\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}} + C\right) \leq C'\lambda_{2S_k}(x_n)\ln\left(x_{n,k}^2\right)$$

for large n. Hence, combining our estimates for $\mathcal{A}T$ and $\mathcal{A}V$,

$$\mathcal{A}(V+T)(x_n) \leq C'\lambda_{2S_k}(x_n)\ln\left(x_{n,k}^2\right) - K'x_{n,k}^{2+\delta} \to -\infty, \quad \text{as} \quad n\to\infty.$$

Case 2. We now suppose that there is a complex $y' \in \mathcal{C}(\mathcal{L}_1)$ such that $y' \notin T^{D,1}_{\{x_n\}}$. Since $\mathcal{L}_1$ is weakly reversible, there exists a directed path beginning with $2S_1$ and ending with y'. Thus there is a descending reaction $y_0 \to y_0'$ along $\{x_n\}$ within the directed path. Note that $y_0 \in T^{S,1}_{\{x_n\}}$ because $T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$ by result 3 in Lemma 27 and, hence, $y_0 \in T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}$. Since terms I, III, IV in (4.6) are uniformly bounded in n and term II converges to $-\infty$, as $n\to\infty$,

$$\mathcal{A}V(x_n) \leq -\lambda_{y_0}(x_n) \quad \text{for large } n. \tag{5.6}$$

By Lemma 16 and the fact that $y_0 \in T^{D,1}_{\{x_n\}} = T^{S,1}_{\{x_n\}}$, there is a constant $C \geq 0$ such that for any $k \in I$,

$$\lim_{n\to\infty}\frac{x_{n,k}}{\sqrt{\lambda_{y_0}(x_n)}} = \lim_{n\to\infty}\sqrt{\frac{(x_{n,k}\vee 1)^{2S_k}}{\lambda_{y_0}(x_n)}} = \lim_{n\to\infty}\sqrt{\frac{(x_{n,k}\vee 1)^{2S_k}}{(x_n\vee 1)^{y_0}}}\sqrt{\frac{(x_n\vee 1)^{y_0}}{\lambda_{y_0}(x_n)}} = C.$$

Therefore, there is a constant $C' > 0$ such that

$$(\vec{1}\cdot x_n)^{1+\delta} = (x_{n,1} + x_{n,2} + \cdots + x_{n,d})^{1+\delta} \leq C''\lambda_{y_0}(x_n)^{(1+\delta)/2}. \tag{5.7}$$

Note that $\lambda_{y_0}(x_0) \to \infty$, as $n\to\infty$ by Corollary 17. Then by (5.2),(5.6) and (5.7), there are constants $C''' > 0$ such that

$$\mathcal{A}(V+T)(x_n) \leq -\lambda_{y_0}(x_n) + C'''\lambda_{y_0}(x_n)^{(1+\delta)/2} \to \infty, \quad \text{as} \quad n\to\infty,$$

because $\delta < 1$. □

We demonstrate Theorem 5.3.2 with an example.

Example 5.6 Consider the following double-full, binary reaction network in Figure 14 with 16 reactions.

$$2A \underset{\kappa_2}{\overset{\kappa_1}{\rightleftharpoons}} A + B \underset{\kappa_4}{\overset{\kappa_3}{\rightleftharpoons}} 2D$$

$$2B \underset{\kappa_6}{\overset{\kappa_5}{\rightleftharpoons}} A + D \underset{\kappa_8}{\overset{\kappa_7}{\rightleftharpoons}} C + B$$

$$C + D \underset{\kappa_{10}}{\overset{\kappa_9}{\rightleftharpoons}} 2C \underset{\kappa_{12}}{\overset{\kappa_{11}}{\rightleftharpoons}} A + C$$

$$B \xrightarrow{\kappa_{13}} \emptyset \underset{\kappa_{15}}{\overset{\kappa_{14}}{\rightleftharpoons}} C$$

$$A \xrightarrow{\kappa_{16}} D$$

Figure 14: An application of Theorem 5.3.2

Let $\mathcal{L}_1, \ldots, \mathcal{L}_5$ be the linkage classes of this reaction network in order from top to bottom. We verify the conditions of Theorem 5.3.2 with $m = 3$.

1. $\mathcal{L}_1$, $\mathcal{L}_2$, and $\mathcal{L}_3$ are weakly reversible and contain only binary complexes.

2. $\mathcal{L}_4$ and $\mathcal{L}_5$ do not contain binary complexes.

3. Note that species $B \in S(\mathcal{L}_1)$, $B \in S(\mathcal{L}_2)$ and $C \in S(\mathcal{L}_3)$ satisfy the third condition of the theorem.

Therefore the associate continuous-time Markov chain for this reaction network is positive recurrence for any choice of rate constants $\kappa_1, \kappa_2, \ldots, \kappa_{16}$. △

5.4 Another network condition for single linkage class cases: An application of the embedded Markov chains

In this section, we introduce another network condition for binary reaction networks with a single linkage class implying positive recurrence of the associated Markov process. As we stated in Section 2.3 and Section 3.2, we apply the embedded Markov chain introduced in Section 2.3 to derive positive recurrence of the associated continuous-time Markov processes. We begin with necessary lemmas. Two followup lemmas show that the two conditions in Theorem 4.2.1 hold for a binary reaction network that has a single linkage class and each species appears as either a unary complex or a double complex in the network.

The next lemma first shows that for the class of reaction networks mentioned above, the condition $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$ holds for any proper tier-sequence $\{x_n\}$ which we assumed in Theorem 4.2.1.

Lemma 30 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible, binary reaction network that has a single linkage class and X be the associated Markov process with $X(0) = x$ for a non-absorbing state x. Suppose for each $S \in \mathcal{S}$, either $S \in \mathcal{C}$ or $2S \in \mathcal{C}$. Let $\{x_n\}$ be a proper tier-sequence of X . Then $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$.*

Proof. Let $\mathcal{S} = \{S_1, S_2, \dots, S_d\}$. Since x is a non-absorbing state, Lemma 8 implies for each state z, there is a reaction $y \to y'$ such that $\lambda_{y\to y'}(z) > 0$. Therefore $T^{S,1}_{\{z_n\}} \neq \emptyset$ for any proper tier-sequence $\{z_n\}$ of X.

Let $y \in T^{S,1}_{\{x_n\}}$ and $\tilde{y} \in T^{D,1}_{\{x_n\}}$. We will show that $y \sim_D \tilde{y}$ and hence $y \in T^{D,1}_{\{x_n\}}$. There are two cases to consider : (i) $\tilde{y} \notin T^{S,\infty}_{\{x_n\}}$ and (ii) $\tilde{y} \in T^{S,\infty}_{\{x_n\}}$.

Case 1. Suppose $\tilde{y} \notin T^{S,\infty}_{\{x_n\}}$. Then $\tilde{y} \in T^{S,1}_{\{x_n\}}$ by Corollary 17. We will show following limit is equal to some positive constant to show $y \sim_D \tilde{y}$,

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{\tilde{y}}}{(x_n \vee 1)^{y}} = \lim_{n\to\infty} \frac{\lambda_{\tilde{y}}(x_n)}{\lambda_y(x_n)} \lim_{n\to\infty} \frac{(x_n \vee 1)^{\tilde{y}}}{\lambda_{\tilde{y}}(x_n)} \lim_{n\to\infty} \frac{\lambda_y(x_n)}{(x_n \vee 1)^{y}}. \tag{5.8}$$

The second and third limit on the right hand side is equal to 1 by Lemma 16. The first limit is equal to some positive constant because $y, \tilde{y} \in T^{S,1}_{\{x_n\}}$. Since $y \sim_D \tilde{y}$, we have $y \in T^{D,1}_{\{x_n\}}$.

Case 2. Suppose that $\tilde{y} \in T^{S,\infty}_{\{x_n\}}$. This implies that $\tilde{y} = S_m + S_\ell$ for some $m \neq \ell$ and $x_{n,\ell} = 0$ for all n without loss of generality. Furthermore, by Lemma 15, $x_{n,m} \to \infty$, as $n \to \infty$. By the hypothesis, either $S_m \in \mathcal{C}$ or $2S_m \in \mathcal{C}$.

First suppose $S_m \in \mathcal{C}$. Since $\lambda_{S_m}(x_n) = x_{n,m} = (x_n \vee 1)^{\tilde{y}}$ for large n and $y \in T^{S,1}_{\{x_n\}}$, then the fact that $y \in T^{S,1}_{\{x_n\}}$ implies

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{\tilde{y}}}{(x_n \vee 1)^{y}} = \lim_{n\to\infty} \frac{\lambda_{S_m}(x_n)}{\lambda_y(x_n)} \lim_{n\to\infty} \frac{\lambda_y(x_n)}{(x_n \vee 1)^{y}} < \infty$$

where the second limit on the right hand side is equal to 1 by Lemma 16. Thus we have either $y \succ_D \tilde{y}$ or $y \sim_D \tilde{y}$. However $\tilde{y} \in T^{D,1}_{\{x_n\}}$, hence we finally get $y \sim_D \tilde{y}$.

Now, suppose $2S_m \in \mathcal{C}$. Remind that $x_{n,m} \to \infty$, as $n \to \infty$ and $x_{n,\ell} = 0$ for all n. Then

$$\lim_{n\to\infty} \frac{(x_n \vee 1)^{\tilde{y}}}{(x_n \vee 1)^{2S_m}} = \lim_{n\to\infty} \frac{x_{n,m}}{x_{n,m}^2} = 0.$$

Therefore $2S_m \succ_d \tilde{y}$. This is a contradiction to the assumption $\tilde{y} \in T^{D,1}_{\{x_n\}}$. ☐

The next lemma shows for a weakly reversible reaction network consisting of a single linkage class, if $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$ for any proper tier-sequence, the the second condition in

Theorem 4.2.1 holds.

Lemma 31 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible reaction network that has a single linkage class. Let $r = |\mathcal{R}|$ and let X be the associated Markov process with $X(0) = x$ for some non-absorbing state x. Suppose*

$$T^{S,1}_{\{z_n\}} \subset T^{D,1}_{\{z_n\}} \tag{5.9}$$

for any proper tier-sequence $\{z_n\}$ of X. Let $\{x_n\}$ be a fixed proper tier-sequence of X. Then there exists a sub-sequence of $\{x_n\}$, denote $\{x_n\}$ for simplicity, for which there is an ordered set of reactions $R = \{y_1 \to y_1', y_2 \to y_2', \dots, y_k \to y_r'\} \subset \mathcal{R}$ satisfying the following conditions.

(i) For each $i = 1, 2, \dots, r$, $\{x_n + \sum_{j=1}^{i-1}(y_i' - y_i)\}$ is a proper tier-sequence of X, and

(ii) $\{y_1, y_2, \dots, y_r\} \in \mathbb{T}^{S,1}_{\{x_n\},R} \cap \mathbb{D}_{\{x_n\},R}$.

Proof. As we showed in the proof of Lemma 30, since x is a non-absorbing state, Lemma 8 implies for each state z, there is a reaction $y \to y'$ such that $\lambda_{y\to y'}(z) > 0$. Therefore $T^{S,1}_{\{z_n\}} \neq \emptyset$ for any proper tier-sequence $\{z_n\}$ of X. Then by the assumption of $T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}}$, we can pick $y_1 \in T^{D,1}_{\{x_n\}} \cap T^{S,1}_{\{x_n\}}$. We can also pick $\tilde{y} \notin T^{D,1}_{\{x_n\}}$ by Lemma 18.

By the weak reversibility of the reaction network, there is a sequence of reactions

$$y_1 \to y_2 \to \cdots \to \tilde{y}.$$

In the path of directed edge from y_1 to $\hat{y}$, we can find the first complex y_{k+1} not belonging to $T^{D,1}_{\{x_n\}}$ for some k. That is, we consider a path of directed edge

$$y_1 \to y_2 \to \cdots \to y_k \to y_{k+1}.$$

such that $y_i \in T^{D,1}_{\{x_n\}}$ for all $i = 1, 2, \ldots, k$ and $y_{k+1} \notin T^{D,1}_{\{x_n\}}$. We denote each reaction $y_i \to y_{i+1}$ by $y_i \to y'_i$ for $i = 1, 2, \ldots, k$. Note that $k \le r$. Since there are finitely many reaction vectors, as we showed in the proof of Lemma 14 we can find a sub-sequence of $\{x_n\}$, denote $\{x_n\}$ for simplicity, for which $\{x_n + \sum_{j=1}^{i}(y'_i - y_i)\}$ is a proper tier-sequence of X for each $i = 1, 2, \ldots, k$.

Since $y_i \in T^{D,1}_{\{x_n\}}$ for $i = 2, 3, \ldots, k$ and since D-type tiers are preserved after jumps as shown in Lemma 19,

$$y_i = y'_{i-1} \in T^{D,1}_{\{x_n + \sum_{j=1}^{i-2}(y'_j - y_j)\}} \quad \text{for} \quad i = 2, 3, \ldots, k.$$

Then (ii) in Lemma 20 combined with hypothesis (5.9), for $i = 2, 3, \ldots, k$

$$y_i \in T^{D,1}_{\{x_n + \sum_{j=1}^{i-1}(y'_j - y_j)\}} \cap T^{S,1}_{\{x_n + \sum_{j=1}^{i-1}(y'_j - y_j)\}}.$$

Furthermore, since D-type tiers are preserved after jumps as shown in Lemma 19,

$$y_{k+1} = y'_k \notin T^{D,1}_{\{x_n + \sum_{j=1}^{k-1}(y'_j - y_j)\}}.$$

If $k = r$, then the proof is complete with $R = \{y_1 \to y'_1, y_2 \to y'_2, \ldots, y_k \to y'_k\}$.

Now, suppose $k < r$. Remind that $T^{S,1}_{\{z_n\}} \neq \emptyset$ for any proper tier-sequence $\{z_n\}$. Hypothesis (5.9) allows us to choose a reaction $y_{k+1} \to y'_{k+1}$ such that

$$y_{k+1} \in T^{D,1}_{\{x_n + \sum_{j=1}^{k}(y'_j - y_j)\}} \cap T^{S,1}_{\{x_n + \sum_{j=1}^{\ell}(y'_j - y_j)\}}.$$

We can also find a further sub-sequence of $\{x_n\}$ for which $\{x_n + \sum_{j=1}^{k}(y'_j - y_j)\}$ is a proper tier-sequence. By iterating this, we can find reactions $y_{k+\ell} \to y'_{k+\ell}$ such that $\{x_n + \sum_{j=1}^{k+\ell}(y'_j - y_j)\}$ is a proper tier-sequence of X and

$$y_{k+\ell} \in T^{D,1}_{\{x_n + \sum_{j=1}^{\ell+j-1}(y'_j - y_j)\}} \cap T^{S,1}_{\{x_n + \sum_{j=1}^{\ell+j-1}(y'_j - y_j)\}}$$

for $\ell = 1, 2, \ldots, r-j$. Note that for the set of reactions $\{y_1 \to y_1', \ldots, y_r \to y_r'\}$,

$$y_i \in T^{S,1}_{\{x_n + \sum_{j=1}^{i-1}(y_j' - y_j)\}} \cap T^{D,1}_{\{x_n + \sum_{j=1}^{i-1}(y_j' - y_j)\}}$$

for each $i = 1, 2, \ldots, r$ and $y_k' \notin T^{D,1}_{\{x_n + \sum_{j=1}^{k-1}(y_j' - y_j)\}}$. Thus the proof is completed. $\square$

Now we show that Lemma 30, Lemma 31 and Theorem 4.2.1 imply positive recurrence of the continuous-time Markov process associated to a weakly reversible, binary reaction network that has single linkage class and in which each species appearing as either a unary complex or a double complex.

Theorem 5.4.1 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a weakly reversible, binary reaction network that has a single linkage class. Suppose for each $S \in \mathcal{S}$, either $S \in \mathcal{C}$ or $2S \in \mathcal{C}$. Let X be the associated Markov process with mass-action (2.4) kinetics for which $X(0) = x$ for some non-absorbing state x. Then, for any choice of rate constants, X is positive recurrent.*

Proof. By Lemma 30, we have

$$T^{S,1}_{\{x_n\}} \subset T^{D,1}_{\{x_n\}} \tag{5.10}$$

for any proper tier-sequence $\{x_n\}$. Note that (5.10) is the first condition in Theorem 4.2.1. Moreover, since the reaction network consists of only a weakly reversible single linkage class, (5.10) implies the second condition in Theorem 4.2.1 by Lemma 31. Because both conditions in Theorem 4.2.1 hold, the associated Markov process is positive recurrent. $\square$

The following example demonstrates Theorem 5.4.1.

Example 5.7 Consider a weakly reversible, binary reaction network with a single linkage class below.

$$
\begin{array}{ccccccccc}
\emptyset & \underset{\kappa_1}{\overset{\kappa_2}{\rightleftharpoons}} & D & \overset{\kappa_3}{\longrightarrow} & A + C & \overset{\kappa_4}{\longrightarrow} & C + D & \underset{\kappa_5}{\overset{\kappa_6}{\rightleftharpoons}} & B \\
 & & \uparrow \kappa_7 & & & & \downarrow \kappa_8 & & \\
 & & C & \overset{\kappa_9}{\longleftarrow} & A + D & \overset{\kappa_{10}}{\longleftarrow} & 2A & &
\end{array}
$$

Figure 15: An application of Theorem 5.4.1.

We can observe that there are four species, A, B, C, and D. We can also observe that $2A, B, C, D \in \mathcal{C}$. That is, each species appears as a unary or a double complex in this reaction network. Therefore, by Theorem 5.4.1, for any choice of system parameters $\kappa_1, \kappa_2, \ldots, \kappa_{10}$, the associated Markov process for the reaction network in Figure 15 is positive recurrent. $\triangle$

Chapter 6

Mixing Times

When stochastically modeled reaction networks admit a stationary distribution for the associcated Markov processes, one of the natural followup questions is how fast the distribution of the Markov processes converges to the stationary distribution. In this thesis, we are particularly interested in how the rate of convergence varies with respect to initial states of the associated Markov processes. The rate of convergence regarding to initial counts of species can be described by mixing times of Markov processes. In this chapter we state two theorems pertaining to Lyapunov functions for mixing times of Markov processes. Using these theorems we will compute mixing times for two network classes introduced in Theorem 5.1.1 and Theorem 5.3.1

Mixing times indicate how fast the distribution of a positive recurrent Markov process converges to its stationary distribution. In many discrete stochastic models, one can be interested in dependence of the number of states for mixing times. In this thesis, however, we are interested in dependence of mixing times on initial counts of Markov processes associated to reaction networks. Therefore, for reaction networks, we define a mixing time of the associated Markov process X with a stationary distribution π as the following. For a small positive number $\epsilon < 1$ and a state x,

$$\tau_x^\epsilon = \inf\{t \geq 0 : \|P^t(x, \cdot) - \pi(\cdot)\|_{tv} \leq \epsilon\} \tag{6.1}$$

where $P^t(x, A) = P(X(t) \in A | X(0) = x)$ and $\| \cdot \|_{tv}$ is the total variation norm defined as $\|\mu\|_{tv} = \sup_{A\in\mathcal{F}}\{|\mu(A)|\}$ for a signed measure μ on a σ-algebra $\mathcal{F}$.

Mixing time and convergence rate of distribution of the associated Markov model may have many applications. For example, certain types of estimation methods for stationary distributions, such as the stationary Finite State Projection method [31], require the distribution of the associated Markov process to be converging to its stationary distribution exponentially fast.

We use the 'big O' notation in this chapter: $f(x) = O(g(x))$ if and only if there are positive constants x_0 and M such that $|f(x)| \leq Mg(x)$ for all $|x| \geq x_0$.

6.1 Exponential ergodicty and mixing times for single linkage class cas

In this section we introduce the theorem of stronger Foster-Lyapunov criteria which guarantees exponential ergodicty introduced in Definition 32. Then, applying that theorem, we prove that mixing time $\tau_x^\epsilon = O(\ln|x|)$ for reaction networks satisfying the conditions in Theorem 5.1.1: a single linkage class with the in-flow and the out-flow for each species. We begin with the definition of exponential ergodicity.

Definition 32 *A continuous-time Markov process X is* ***exponentially ergodic*** *if*

1. *X admits a unique stationary distribution and*
2. *for any x in its state space there exist positive constant η and positive function B such that*

$$\|P^t(x,\cdot) - \pi(\cdot)\|_{tv} \leq B(x)e^{-\eta t}$$

where $P^t(x,\cdot) = P^t(x,A) = P(X(t) \in A | X(0) = x)$ *and* π *is the stationary distribution of* X*.*

The next theorem is a version of Theorem 6.1 in [39] stating sufficient conditions for exponential ergodicity.

Theorem 6.1 *Let* X *be a continuous-time Markov chain on a countable state space* $\mathbb{S}$ *with generator* $\mathcal{A}$*. Suppose there exists a positive function* V *on* $\mathbb{S}$ *satisfying the followings.*

1. $V(x) \to \infty$ *as* $|x| \to \infty$*, and*

2. *There are positive constants* a *and* b *such that*

$$\mathcal{A}V(x) \leq -aV(x) + b \quad \text{for all} \ \ x \in \mathbb{S}. \tag{6.2}$$

Then X *is exponentially ergodic. Moreover for all* x *in its state space, there exists positive constants* η *and* C *such that*

$$\|P^t(x,\cdot) - \pi(\cdot)\|_{tv} \leq C(V(x)+1)e^{-\eta t}.$$

Note that if a continuous-time Markov process X satisfies the conditions in Theorem 6.1 with the main Lyapunov function V defined from (4.2), mixing time $\tau_x^\epsilon \leq \frac{1}{\eta}\ln\left(\frac{C(V(x)+1)}{\epsilon}\right) = O(\ln|x|)$. Thus $\tau_x^\epsilon = O(\ln|x|)$.

In the next theorem, we show the Markov processes associated to the class of reaction networks introduced in Theorem 5.1.1 satisfies the conditions in Theorem 6.1.

Theorem 6.2 *Let* $(\mathcal{S},\mathcal{C},\mathcal{R})$ *be a weakly reversible, binary reaction network that has a single linkage class. Let* $\widetilde{\mathcal{C}} = \mathcal{C} \cup \{\emptyset\} \cup \{S \mid S \in \mathcal{S}\}$ *and* $\widetilde{\mathcal{R}} = \mathcal{R} \cup_{S\in\mathcal{S}} \{\emptyset \to S, S \to \emptyset\}$*.*

Then, for any choice of rate constants, the Markov process X with intensity functions (2.4) *associated to the reaction network* $(\mathcal{S}, \widetilde{\mathcal{C}}, \widetilde{\mathcal{R}})$ *is exponentially ergodic. Moreover for all x in its state space, there exist positive constants η and C such that*

$$\|P^t(x,\cdot) - \pi(\cdot)\|_{tv} \le C(V(x)+1)e^{-\eta t}$$

where $P^t(x,\cdot) = P^t(x,A) = P(X(t) \in A | X(0) = x)$*, π is a stationary distribution of X and $V(x)$ is the main Lyapunov function defined in* (4.2)*. Therefore the mixing time* $\tau_x^\epsilon = O(\ln|x|)$*.*

The basic idea of the proof of Theorem 6.2 is to utilize the upper bound of $\mathcal{A}V(x_n)$ shown in the proof of Theorem 4.1.1 for a tier-sequence $\{x_n\}$. The leading term of the upper bound of $\mathcal{A}V(x_n)$ is the term II in the proof for large n. Thus we show the right hand side of (6.2) can be obtained from the term II.

Proof. Let $|\mathcal{S}| = d$ and $\mathbb{S}$ be the state space of X. We will claim first that there exists a finite set $K \subset \mathbb{S}$ such that for some positive constant a,

$$\mathcal{A}V(x) \le -aV(x) \quad \text{for all} \quad x \in \mathbb{S} \setminus K \tag{6.3}$$

If this claim holds, then we take $b = (a+1)\min_{x\in K} V(x)$ so that the result follows as (6.2) holds with a and b. We prove the claim by contradiction. Suppose the claim does not hold. Then there exists a sequence $\{x_n\} \subset \mathbb{S}$ such that

$$\lim_{n\to\infty} |x_n| = \infty \quad \text{and} \quad AV(x_n) \ge -\frac{1}{n}V(x_n) \quad \text{for all} \quad n. \tag{6.4}$$

By Lemma 14, we let $\{x_n\}$ be a proper tier-sequence. We also can assume that there is a maximal coordinate of x_n by considering a further subsequence. Without loss of generality, we assume $x_{n,1}$ be a maximal coordinate of x_n. That is, there exists a positive constant C' such that for each $i = 1, 2, \dots, d$

$$x_{n,i} \le C' x_{n,1} \quad \text{for large} \quad n.$$

Note that for a proper tier-sequence $\{x_n\}$, we showed in Theorem 5.1.1 that the reaction network with conditions in Theorem 6.2 admits a reaction $y_0 \to y_0' \in T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}$.

As we have shown in the proof of Theorem 4.1.1, for all n

$$\mathcal{A}V(x_n) \le \alpha \lambda_{y_0}(x_n) II$$

for some positive constant α, where

$$II = \sum_{\substack{y \to y' \in \mathcal{R} \\ y \succ_D y'}} \frac{\kappa_{y \to y'} \lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln \left(\frac{(x_n \vee 1)^{y'}}{(x_n \vee 1)^{y}} \right).$$

Note that for the out-flow $S_1 \to \emptyset$, it is true that $\emptyset \prec_D S_1$ and each term in II is negative for large n. Thus we have

$$\mathcal{A}V(x_n) \le \alpha \lambda_{y_0}(x_n) II \le -\alpha \kappa_{S_1 \to \emptyset} \lambda_{S_1}(x_n) \ln x_{n,1}.$$

However, since we assumed $x_{n,1}$ is a maximal coordinate of x_n and $\lim_{n \to \infty} x_{n,1} = \infty$ by the definition of a tier-sequence, we can find some positive constant β such that $V(x_n) \le \beta x_{n,1} \ln x_{n,1}$ for large n. Therefore for large n,

$$\begin{aligned} \mathcal{A}V(x_n) &\le \alpha \lambda_{y_0}(x_n) II \\ &\le -\alpha \kappa_{S_1 \to \emptyset} \lambda_{S_1}(x_n) \ln x_{n,1} \\ &\le \frac{-\alpha \kappa_{S_1 \to \emptyset}}{\beta} V(x_n). \end{aligned}$$

This is contraction to (6.4). Thus the claim (6.3) holds, so the result follows. $\square$

6.2 Uniform ergodicity and mixing times for double-full binary reaction networks

In this section we introduce the 'super Lyapunov function' condition originally provided in [10] for uniform ergodicity of Markov processes. We begin with the definition of uniform ergodicity and the theorem related to the super Lyapunov condition.

Definition 33 *For a continuous-time Markov process X, X is* ***uniformly ergodic*** *if*

1. *X admits a unique stationary distribution and*

2. *for any x in its state space there exist positive constants η and B such that*

$$\|P^t(x,\cdot) - \pi(\cdot)\|_{tv} \leq Be^{-\eta t}$$

   where $P^t(x,\cdot) = P^t(x,A) = P(X(t) \in A|X(0) = x)$ and π is the stationary distribution of X.

The next theorem is a version of Theorem 3.2 in [10].

Theorem 6.3 *Let X be a continuous-time Markov chain on a countable state space $\mathbb{S}$ with generator $\mathcal{A}$. Suppose there exists a positive function V on $\mathbb{S}$ satisfying the followings.*

1. *$V(x) \to \infty$ as $|x| \to \infty$, and*

2. *There are positive constants a, b and δ such that*

$$\mathcal{A}V(x) \leq -aV^{1+\delta}(x) + b \quad \textit{for all} \;\; x \in \mathbb{S}. \tag{6.5}$$

Then X is uniformly ergodic.

The positive function V satisfying the conditions in Theorem 6.3 is called **super Lyapunov function**. Note that if continuous time Markov process X is uniformly ergodic, the mixing time $\tau_x^\epsilon \leq \frac{1}{\eta}\ln\frac{B}{\epsilon} = O(1)$. Thus $\tau_x^\epsilon = O(1)$.

In the following theorem, we will show that it can be shown that the main Lyapunov function defined at (4.2) for double-full, binary reaction networks with the path condition provided in Theorem 5.2.1 is a super Lyapunov function. Then the associated Markov process for the class of reaction networks is uniformly ergodic and its mixing time $\tau_x^\epsilon = O(1)$ for any initial state x. This uniform boundedness of the mixing time means very interesting property of the associated Markov process: wherever it starts at, the time taken for the distribution of the stochastic process to converge to its stationary distribution is uniformly bounded.

Theorem 6.4 *Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a binary reaction network satisfying the following two conditions:*

1. *the reaction network is double-full, and*

2. *for each double complex (of the form $2S_i$) there is a directed path within the reaction graph beginning with the double complex itself and ending with either a unary complex (of the form S_j) or the zero complex.*

Then, for any choice of rate constants, the Markov process with intensity functions (2.4) associated to the reaction network $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ is uniformly ergodic. Therefore its mixing time $\tau_x^\epsilon = O(1)$.

Proof. We will mimic the proof of Theorem 6.2, but the double-full condition of the reaction network enables us to obtain the stronger upper bound from the term II in the proof of Theorem 6.2. Let $|\mathcal{S}| = d$ and let $\mathbb{S}$ be the state space of the associated Markov process X. We will claim first that there exists a finite set $K \subset \mathbb{S}$ such that for some positive constant a,

$$\mathcal{A}V(x) \le -aV^{1.5}(x) \quad \text{for all} \quad x \in \mathbb{S} \setminus K, \tag{6.6}$$

where V is the main Lyapunov function defined at (4.2). If this claim holds, then we take $b = (a+1)\min_{x\in K} V(x)$ so that the result follows as (6.5) holds with a,b and $\delta = 1/2$. We prove the claim by contradiction. Suppose the claim does not hold. Then there exists a sequence $\{x_n\} \subset \mathbb{S}$ such that

$$\lim_{n\to\infty} |x_n| = \infty \quad \text{and} \quad AV(x_n) \ge -\frac{1}{n}V^{1+1/2}(x_n) \;\; \text{for all} \;\; n. \tag{6.7}$$

By Lemma 14, we let $\{x_n\}$ be a proper tier-sequence. We also can assume that there is a maximal coordinate of x_n by considering a further subsequence. Without loss of generality, we assume $x_{n,1}$ be a maximal coordinate of x_n. That is, there exists a positive constant C' such that for each $i = 1, 2, \dots, d$

$$x_{n,i} \le C' x_{n,1} \quad \text{for large} \quad n.$$

Note that for a proper tier-sequence $\{x_n\}$, we showed in Theorem 5.1.1 that the reaction network with conditions in Theorem 6.2 admits a reaction $y_0 \to y_0' \in T^{S,1}_{\{x_n\}} \cap D_{\{x_n\}}$. Note also the followings

i) $y_0 = S_i + S_j$ for some i and j (not necessarily $i \neq j$) by part 1 in Lemma 27, and

ii) since the reaction network is double-full, $2S_1 \in \mathcal{C}$. Thus

$$\lim_{n\to\infty} \frac{\lambda_{y_0}(x_n)}{\lambda_{2S_1}(x_n)} = \lim_{n\to\infty} \frac{\lambda_{y_0}(x_n)}{x_{n,1}(x_{n,1}-1)} < \infty,$$

because $y_0 \in T^{S,1}_{\{x_n\}}$.

Therefore there exists a positive constant C'' such that

$$\lambda_{2S_1}(x_n) \leq C''\lambda_{y_0}(x_n). \tag{6.8}$$

As we have shown in the proof of Theorem 4.1.1, for all n

$$\mathcal{A}V(x_n) \leq \alpha\lambda_{y_0}(x_n)II$$

for some positive constant α, where

$$II = \sum_{\substack{y\to y'\in\mathcal{R}\\ y\succ_D y'}} \frac{\kappa_{y\to y'}\lambda_y(x_n)}{\lambda_{y_0}(x_n)} \ln\left(\frac{(x_n\vee 1)^{y'}}{(x_n\vee 1)^{y}}\right).$$

Since every term in II is negative for large n, we have for large n

$$\begin{aligned}
\mathcal{A}V(x_n) &\leq \alpha\lambda_{y_0}(x_n)II \\
&\leq \alpha\kappa_{y_0\to y_0'}\lambda_{y_0}(x_n)\ln\left(\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}}\right) \\
&\leq \alpha\kappa_{y_0\to y_0'}C''\lambda_{2S_1}(x_n)\ln\left(\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}}\right)
\end{aligned} \tag{6.9}$$

The third inequality above holds because of (6.8) and $\ln\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}} < 0$ for large n.

However, there exists a positive constant C''' such that for large n,

$$V^{1.5}(x_n) \leq C'''(x_{n,1}\ln x_{n,1})^{1+1/2} \leq C'''\lambda_{2S_1}(x_n) = C'''x_{n,1}(x_{n,1}-1), \tag{6.10}$$

since $x_{n,1}$ is a maximal coordinate of x_n and $\lim_{n\to\infty} x_{n,1} = \infty$ by the definition of a tier-sequence. Lastly note that for large n we have

$$\ln\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}} \leq -1. \tag{6.11}$$

Therefore from (6.9), (6.10) and (6.11), for large n

$$\mathcal{A}V(x_n) \leq \alpha\kappa_{y_0\to y_0'}C''\lambda_{2S_1}(x_n)\ln\frac{(x_n\vee 1)^{y_0'}}{(x_n\vee 1)^{y_0}} \leq -\frac{\alpha\kappa_{y_0\to y_0'}C''}{C'''}V^{1.5}(x_n).$$

This contradicts to (6.7). Thus the claim (6.6) holds, so the desired result follows. □

We demonstrate Theorem 6.4 with the following reaction network and the graph of its stochastic dynamics.

Example 6.5 For the binary, double-full reaction network in Figure 16, there is a directed path of reaction from each double complex to a single complex or the zero complex. i.e. $2A \to A+B \to B$, $A \leftarrow 2C$ and $2B \to \emptyset$. Therefore the network satisfies all conditions in Theorem 6.4. Let π be the stationary distribution of the associated Markov X.

$$2A \xrightarrow{1} A+B \underset{1}{\overset{1}{\rightleftharpoons}} B$$
$$A \underset{1}{\overset{1}{\rightleftharpoons}} \quad 2C \xrightarrow{1} B+C$$
$$2B \xrightarrow{1} \emptyset$$
$$C \xrightarrow{1} A+C$$

Figure 16: An example of reaction works admiting uniformly bounded mixing times

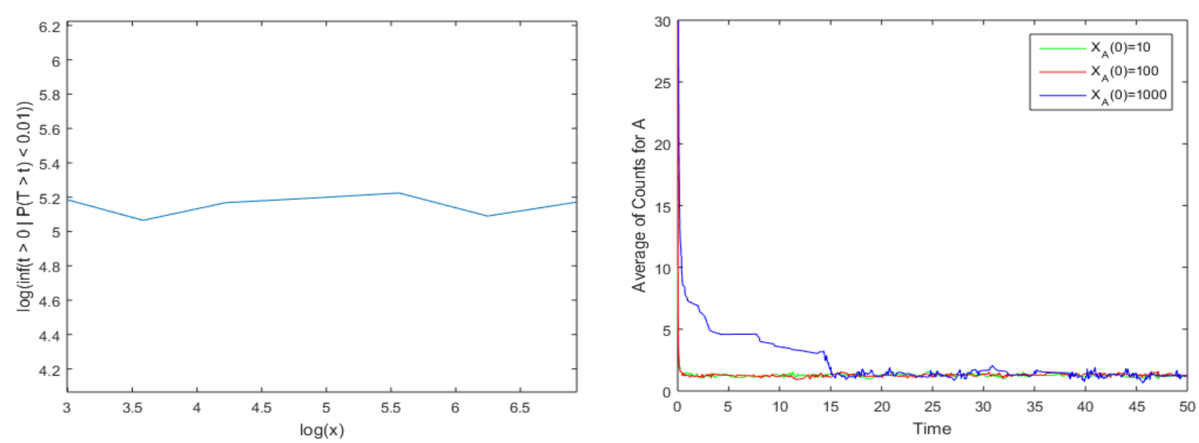

Figure 17: Estimation of mixing times (Left) and graph of mean for species A for different initial counts (Right) for the reaction network in Figure 16.

We simulate two Markov processes, X and Y, associated to the reaction network in Figure 16 for which $X(0) = x$ and $P(Y(0) = y) = \pi(y)$ for each y. That is, Y is the associated Markov process associated with its initial distribution being the stationary distribution π. Let T_x be the coupling time of X and Y as described in Appendix A.4. By the coupling inequality in Theorem A.5, we have $\tau_\epsilon^x \le \inf\{t > 0 : \ P(T_x > t) < \epsilon\}$. The left graph in Figure 17 shows uniform boundedness of τ_ϵ^x for the reaction network by simulating $\inf\{t > 0 : \ P(T_x > t) < \epsilon\}$ versus various initial points x of X.

The right graph in Figure 17 shows average counts $\mathbb{E}(X_A(t))$ of A in time with initial counts $X_A(0) = 10, 100$ and 1000 for the reaction network in Figure 16. See $\mathbb{E}(X_A(t)) \to \sum_{x=(x_1,x_2,x_3)} x_1\pi(x)$ where π is the stationary distribution. All three graphs converge to $\sum_{x=(x_1,x_2,x_3)} x_1\pi(x)$ by $t = 20$. This is because the mixing time is uniformly bounded in initial state $X(0)$. $\triangle$

Appendix A

Appendix

A.1 Appendix A.1: Probability background

Definitions in this section come from [18] and [42].

Definition 34 *A **probability space** is a triple, $\{\Omega, \mathcal{F}, P\}$, such that Ω is a set, $\mathcal{F}$ is a σ-algebra of Ω and P is a positive measure on $\mathcal{F}$ such that $P(\Omega) = 1$. For a topological space Ω, $\mathcal{B}$ is called a **Borel σ-algebra** of Ω if $\mathcal{B}$ is smallest σ-algebra of Ω containing all open sets.*

Definition 35 *A random variable is a measurable function $X : \{\Omega, \mathcal{F}\} \to \{\mathbb{S}, \mathcal{S}\}$. $\{\Omega, \mathcal{F}\}$ is called the **sample space** and $\{\mathbb{S}, \mathcal{S}\}$ is called the **state space**.*

In this thesis we consider the state space $\{\mathbb{S}, \mathcal{B}\}$ where $\mathbb{S} \subseteq \mathbb{Z}^d_{\geq 0}$ for some d.

Definition 36 *A stochastic process, $\{X(t) : t \in \mathcal{I}\}$, is a collection of random variables from a sample space to a state space. $\mathcal{I}$ is an index set.*

In this thesis the index set $\mathcal{I}$ will typically be $\mathbb{R}_{\geq 0} = \{t \in \mathbb{R} | t \geq 0\}$ or $\mathbb{Z}_{\geq 0} = \{n \in \mathbb{Z} | n \geq 0\}$. Thus we assume that $\mathcal{I}$ is an ordered index set.

Definition 37 *A stochastic process $\{X\}_{t \in \mathcal{I}}$ is called Markov process if for any $0 \leq s_0 <$*

$s_1 < \cdots < s_n < s$,

$$P(X(t+s) = y | X(s) = x, X(s_n) = x_n, \ldots, X(s_0) = x_0) = P(X(t) = y | X(s) = x).$$

If $\mathcal{I} = \mathbb{R}_{\geq 0}$, we call X a continuous-time Markov process. If $\mathcal{I} = \mathbb{Z}_{\geq 0}$, we call X a discrete-time Markov chain and we typically denote $X(n) = \tilde{X}_n$ for each $n \in \mathbb{Z}_{\geq 0}$.

Definition 38 *Let X be a continuous-time Markov process on a discrete state space $\mathbb{S}$ such that for any $x, y \in \mathbb{S}$*

$$P(X(t + \Delta t) = y | X(t) = x) = \lambda_{xy} \Delta t + o(\Delta)$$

*for some $\lambda_{xy} \geq 0$. Then a state x is termed an **absorbing state** if*

$$\lambda_{xy} = 0 \quad \text{for all} \quad y \in \mathbb{S}.$$

*A state x is termed a **non-absorbing state** if it is not an absorbing state.*

Definition 39 *Let X be a continuous time Markov chain on a discrete state space $\mathbb{S}$. Let $\{O_m\}_{m=1}^{\infty}$ be a family of finite sets such that $O_{m-1} \subset O_m$ for all $m = 1, 2, \cdots$ and $\cup_{m=1}^{\infty} O_m = \mathbb{S}$. Let P_x be a probability distribution of the Markov process X with initial state x. For $\mathcal{T}_m = \inf\{t > 0 \mid X_t \in O_m^c\}$, if $\lim_{m \to \infty} \mathcal{T}_m = \infty$ P_x - a.s. for all x, then X is **non-explosive**.*

Definition 40 *For a Markov process X, its state space $\mathbb{S}$ is irreducible if for any $x, y \in \mathbb{S}$*

$$P(X(t) = y | X(0) = x) > 0 \quad \text{for some} \quad t.$$

Let E_x denote expectation of random variable X with $X(0) = x$.

Definition 41 *A Markov process X with its irreducible state space $\mathbb{S}$ is* ***positive recurrent*** *if for each $x \in \mathbb{S}$,*

$$E_x(T_x) < \infty$$

where $T_x = \inf\{t > 0 | X(t) = x\}$.

Definition 42 *Let X be a continuous-time Markov process on a discrete state space $\mathbb{S}$ such that for any $x, y \in \mathbb{S}$*

$$P(X(t + \Delta t) = y | X(t) = x) = \lambda_{xy}\Delta t + o(\Delta)$$

for some $\lambda_{xy} \geq 0$. Then probability measure π is a ***stationary distribution*** *if for each $y \in \mathbb{S}$*

$$\sum_{x \in \mathbb{S}} \lambda_{xy}\pi(x) - \sum_{x \in \mathbb{S}} \lambda_{yx}\pi(y) = 0.$$

Definition 43 *Let $\tilde{X}$ be a discrete-time Markov process on a discrete state space $\mathbb{S}$. Then probability measure $\tilde{\pi}$ is a* ***stationary distribution*** *if for each $y \in \mathbb{S}$*

$$\sum_{x \in \mathbb{S}} P(\tilde{X}_{n+1} = y | \tilde{X}_n = x)\tilde{\pi}(x) - \sum_{x \in \mathbb{S}} P(\tilde{X}_{n+1} = x | \tilde{X}_n = y)\tilde{\pi}(y) = 0.$$

The following theorem says stationary distribution of Markov process X is the limiting distribution.

Theorem A.1 *Let X be a non-explosive continuous-time Markov process on an irreducible discrete state space $\mathbb{S}$. If π is a stationary distribution of X, then*

$$\lim_{n \to \infty} P(X(t) = y | X(0) = x) = \pi(y) \quad \textit{for all} \;\; y \in \mathbb{S}.$$

The next theorem comes from Theorem 3.5.3 (for continuous-time case) and Theorem 1.7.7 (for discrete-time case) in [41].

Theorem A.2 *Let X be a non-explosive continuous-time Markov process (discrete-time Markov chain) on an irreducible state space $\mathbb{S}$. Then X is positive recurrent if and only if a stationary distribution π exists.*

We now introduce the definition of the Markov generator $\mathcal{A}$ which is used in main analytic theorems of this thesis. We first introduce the generator of a continuous-time Markov process.

Definition 44 *Let X be a continuous-time Markov process on a discrete state space $\mathbb{S}$ such that for each pair of states $x, y \in \mathbb{S}$*

$$P(X(t+\Delta t) = y | X(t) = x) = \lambda_{xy}\Delta t + o(\Delta)$$

*for some $\lambda_{xy} \geq 0$. Then **the Markov generator** $\mathcal{A}$ is an operator such that for a function $f : \mathbb{S} \to \mathbb{R}$,*

$$\mathcal{A}f(x) = \lim_{h \to 0} \frac{E_x(f(X(h)) - f(x)}{h} = \sum_{y \in \mathbb{S}} \lambda_{xy}(f(y) - f(x)),$$

when $\mathcal{A}f(x)$ is well defined for each $x \in \mathbb{S}$.

We also introduce the generator of a discrete-time Markov chain.

Definition 45 *Let X be a discrete-time Markov process on a discrete state space $\mathbb{S}$. Then **the Markov generator** $\mathcal{A}$ is an operator such that for a function $f : \mathbb{S} \to \mathbb{R}$,*

$$\mathcal{A}f(x) = E_x(f(X_1)) - x,$$

when $\mathcal{A}f(x)$ is well defined for each $x \in \mathbb{S}$.

The following theorem states the Dynkin's formula (Theorem 7.4.1 in [42]) which will be employed in Appendix A.3.

Theorem A.3 (Dynkin's formula) *Let X be a continuous-time Markov process. Let $f \in C_0^2(\mathbb{R}^d)$, i.e. f is compactly supported function whose second derivative is continuous. Suppose τ is a stopping time such that $E_x(\tau) < \infty$. Then*

$$E_x(f(X_\tau)) = f(x) + E_x\left(\int_0^\tau \mathcal{A}f(X(s))ds\right).$$

A.2 Appendix A.2: Non-explosion of X

The main analytic theorem of this thesis, Theorem 4.1.1, shows that some tier conditions of reaction networks imply that the associated Markov process fulfills the Foster-Lyapunov criteria introduced in Theorem 4.0.1. One of conditions in Theorem 4.0.1 is non-explosion of the Markov process. In this section we show that if the condition (4.1) holds with a positive function $V(x)$ such that $V(x) \to \infty$, as $|x| \to \infty$, then the corresponding continuous-time Markov process on discrete state space is non-explosive.

Indeed, a weaker condition is required for non-explosion by Theorem 2.1 in [39]. We first introduce a truncated Markov process and its generator. Let X be a continuous-time Markov process on its state space $\mathbb{S}$. Let $\{O_m\}_{m=1}^\infty$ be a family of finite sets such that $\cup_{m=1}^\infty O_m = \mathbb{S}$ and $\mathcal{T}_m = \inf\{t > 0 \mid X_t \in O_m^c\}$ be a first time of X to hit O_m^c for each m. We define truncated Markov process $X_m(t)$ of $X(t)$ as below,

$$X_m(t) = \begin{cases} X(t) & \text{if } \ t < \mathcal{T}_m \\ c_m & \text{if } \ t \geq \mathcal{T}_m \end{cases} \tag{A.1}$$

where c_m is to be chosen at any state in O_m^c. We will denote $\mathcal{A}_m$ for the Markov generator of X_m.

The next theorem, Theorem 2.1 in [39], states the Foster-Lyapunov criteria for non-explosion of Markov processes.

Theorem A.2.1 *Let X be a continuous-time Markov process on a countable state space $\mathbb{S}$. Let X_m be the truncated Markov process defined from (A.1) and $\mathcal{A}_m$ be its Markov generator. Suppose there exists a positive function V on $\mathbb{S}$ satisfying the followings.*

1. *$V(x) \to \infty$ as $|x| \to \infty$*
2. *There are positive constants a and b such that $\mathcal{A}_m V(x) \leq aV(x) + b$ for all x and for all $m = 1, 2, \cdots$*

Then X is non-explosive.

Proposition A.4 *Let X be a continuous time Markov process on discrete state space $\mathbb{S}$. Suppose that there exist a positive function $V(x)$ defined on $\mathbb{S}$ and a finite set $K \subset \mathbb{S}$ such that*

1. *$V(x) \to \infty$ as $|x| \to \infty$*
2. *$\mathcal{A}V(x) < -1$ for all $x \in \mathbb{S} \setminus K$.*

Then, for some constant $M > 0$, $\mathcal{A}_m V(x) < M\mathbf{1}_{\{x\in K\}} - \mathbf{1}_{\{x\in\mathbb{S}\setminus K\}}$ for all m and $x \in \mathbb{S}$. Moreover, the continuous-time Markov chain X is non-explosive.

Proof. Let X_m be the truncated Markov process defined from (A.1). We choose c_m to be equal to a minimizing state for V on O_m^c. That is, $V(c_m) = \min_{x\in O_m^c} V(x)$. This

c_m always exists for each m because the state space $\mathbb{S}$ is discrete and $V(x) \to \infty$ as $|x| \to \infty$. Note that, since $X(t)$ is a continuous-time Markov process, its jump time is distributed exponentially. Let T_2 be the first time for the second jump of $X(t)$. Then, $P(h \geq T_2|X(0) = x) = o(h)$ for h small enough and $x \in \mathbb{S}$. From this, we can drive relations of jump probabilities between $X_m(h)$ and $X(h)$ with h small enough as the followings.

$$\begin{aligned}
P(X_m(h) = c_m|X_m(0) = x) &= P(\mathcal{T}_m < h|X(0) = x) \\
&= P(\mathcal{T}_m < h < T_2|X(0) = x) + P(\mathcal{T}_m < h, h \geq T_2|X(0) = x) \\
&\leq P(X(h) \in O_m^c|X(0) = x) + o(h) \\
&= \sum_{y \in O_m^c} P(X(h) = y|X(0) = x) + o(h)
\end{aligned}$$

and for $y \in O_m$,

$$\begin{aligned}
P(X_m(h) = y|X_m(0) = x) &= P(X_m(h) = y, h < \mathcal{T}_m|X(0) = x) \\
&= P(X(h) = y, h < \mathcal{T}_m|X(0) = x) \\
&\leq P(X(h) = y|X(0) = x)
\end{aligned}$$

Then

$$
\begin{aligned}
&\mathcal{A}_m V(x)\\
=&\lim_{h\to 0}\frac{E_x(V(X_m(h))-V(x)}{h}\\
=&\lim_{h\to 0}\frac{1}{h}\left(V(c_m)P(X_m(h)=c_m)|X_m(0)=x)+\sum_{y\in O_m}V(y)P(X_m(h)=y|X_m(0)=x)-V(x)\right)\\
\le&\lim_{h\to 0}\frac{1}{h}\left(\sum_{y\in O_m^c}V(c_m)P(X(h)=y|X(0)=x)+\sum_{y\in O_m}V(y)P(X(h)=y|X(0)=x)-V(x)\right)\\
=&\lim_{h\to 0}\frac{1}{h}\left(\sum_{y\in \mathbb{S}}V(y)P(X(h)=y|X(0)=x)-V(x)\right)\\
=&\mathcal{A}V(x)<(\max_{x\in K}\mathcal{A}V(x))\mathbf{1}_{\{x\in K\}}-\mathbf{1}_{\{x\in K^c\}} \qquad \text{for all } \ m \ \text{ and } \ x\in\mathbb{S}
\end{aligned}
$$

Letting $M := \max_{x\in K}\mathcal{A}V(x)$, we have

$$\mathcal{A}_m V(x) < M\mathbf{1}_{\{x\in K\}} - \mathbf{1}_{\{x\in \mathbb{S}\setminus K\}}$$

for all m and $x \in \mathbb{S}$. This means that the conditions in the Theorem A.2.1 hold. Hence, X is non-explosive. □

A.3 Appendix A.3: Proof of Theorem 4.0.1

In this section we provide a short version of proof of Theorem 4.0.1 for especially the case that the state space of the coninuous-time Markov process is discrete. For general topological state space, the proof of Foster-Lyapunov criteria (4.1) is very long. For discrete state space, however, we can simply prove Theorem 4.0.1 using Ergodic Theorem (Theorem 3.8.1 [41]).

Theorem A.3.1 (Ergodic Theorem) *Let X be a continuous time Markov process on a discrete state space $\mathbb{S}$ such that for each pair of states i, j*

$$P(X(t+\Delta t) = j | X(t) = i) = \lambda_{ij}\Delta t + o(t) \tag{A.2}$$

for some $\lambda_{ij} \geq 0$. Let $\lambda_i(x) := \sum_{j\in\mathbb{S}} \lambda_{ij}(x)$. Then

$$P\Big(\frac{1}{t}\int_0^t \mathbf{1}_{\{X(s)=i\}}\, ds \to \frac{1}{q_i\lambda_i} \quad \text{as } t\to\infty\Big) = 1 \tag{A.3}$$

where $q_i = \mathbb{E}_i(T_i)$ and $T_i = \inf\{t > 0 | X(t) = i\}$. For the case of $q_i = \infty$, we use the convention $\frac{1}{\infty} = 0$.

Now we prove Theorem 4.0.1.

Proof of Theorem 4.0.1. We suppose $X(0) = x$ for some x in an irreducible state space $\mathbb{S}$. Assume that X is not positive recurrent. Then $q_i = \mathbb{E}_i(T_i) = \infty$ for any $i \in \mathbb{S}$. Let X_m, $\mathcal{T}_m$ and $\mathcal{A}_m$ be a truncated continuous time Markov chain of $X(t)$, first hitting time into O_m^c and generator of X_m, respectively as introduced around (A.1). Note that

$$\lim_{m\to\infty} X_m(t) = \lim_{m\to\infty} X(t\wedge \mathcal{T}_m) = X(t) \quad \text{a.s.}$$

for each t since X is non-explosive, i.e. $\lim_{m\to\infty}\mathcal{T}_m = \infty$ a.s.. Then, for the finite set K,

$$\lim_{t\to\infty}\lim_{m\to\infty} \mathbb{E}_x\Big(\frac{1}{t}\int_0^t \mathbf{1}_{\{X_m(s)\in K\}}\, ds\Big) = \lim_{t\to\infty}\lim_{m\to\infty}\sum_{i\in K}\mathbb{E}_x\Big(\frac{1}{t}\int_0^t \mathbf{1}_{\{X_m(s)=i\}}\, ds\Big) \tag{A.4}$$

$$= \sum_{i\in K}\mathbb{E}_x\Big(\lim_{t\to\infty}\lim_{m\to\infty}\frac{1}{t}\int_0^t \mathbf{1}_{\{X_m(s)=i\}}\, ds\Big) \tag{A.5}$$

$$= \sum_{i\in K}\mathbb{E}_x\Big(\lim_{t\to\infty}\frac{1}{t}\int_0^t \mathbf{1}_{\{X(s)=i\}}\Big)$$

$$= \sum_{i\in K}\frac{1}{q_i\lambda_i} = 0 \tag{A.6}$$

by the Theorem A.3.1, where $\lambda_i = \sum_{j\in\mathbb{S}} \lambda_{ij}$. Note that $\sup_t |\frac{1}{t}\int_0^t \mathbf{1}_{\{x\in K\}}| \le 1$ so that (A.4) and (A.5) follow from the Dominated Convergence Theorem. By Proposition A.4, there exists $M > 0$ such that

$$\begin{aligned}\mathcal{A}_m V(x) &< -\mathbf{1}_{\{x\in K^c\}} + M\mathbf{1}_{\{x\in K\}} \\ &= -1 + (M+1)\mathbf{1}_{\{x\in K\}}\end{aligned}$$

for all $x \in \mathbb{S}$. Since the state space of X_m is finite, the Dynkin's formula in Theorem A.3 holds for the positive function $V(x)\mathbf{1}_{O_m}(x)$. Therefore

$$\begin{aligned}0 \le \mathbb{E}_x(V(X_m(t)) &= V(x) + \mathbb{E}_x\Big(\int_0^t \mathcal{A}V(X(s))\, ds\Big) \\ &\le V(x) + \mathbb{E}_x\Big(\int_0^t -1 + (M+1)\mathbf{1}_{\{X_m(s)\in K\}}\Big) \\ &= V(x) - t + (M+1)\mathbb{E}_x\Big(\int_0^t (M+1)\mathbf{1}_{\{X+m(s)\in K\}}\Big)\end{aligned}$$

After simple algebra, dividing both sides by t and taking limits over m and t, we have

$$\frac{1}{M+1} = \lim_{t\to\infty}\lim_{m\to\infty}\frac{t-V(x)}{(M+1)t} \le \lim_{t\to\infty}\lim_{m\to\infty}\mathbb{E}_x\Big(\frac{1}{t}\int_0^t \mathbf{1}_{\{X_m(s)\in K\}}\Big) = 0$$

where the last equality follows by (A.6). Since it is a contradiction, the continuous time Markov chain $X(t)$ must be positive recurrent. □

A.4 Appendix A.4: The coupling inequality

In this section we introduce the coupling inequality which will be utilized for estimating mixing times of Markov processes. The following terms and theorems related to the coupling inequality come from [37]. Let $X : \Omega \to \mathbb{S}^{\mathbb{R}_{\ge 0}}$ and $Y : \Omega \to \mathbb{S}^{\mathbb{R}_{\ge 0}}$ be Markov processes on probability spaces $(\Omega, \mathcal{F}, P^X)$ and $(\Omega, \mathcal{F}, P^Y)$. Then we defined a joint probability measure P for $(X, Y) : \Omega \to \mathbb{S}^{\mathbb{R}_{\ge 0}} \times \mathbb{S}^{\mathbb{R}_{\ge 0}}$ as following,

1. $P((X,Y) \in A \times \mathbb{S}^{\mathbb{R}_{\geq 0}}) = P^X(A)$ and $P((X,Y) \in \mathbb{S}^{\mathbb{R}_{\geq 0}} \times A) = P^Y(A)$ for each $A \in \mathcal{F}$, and

2. for the coupling time $T = \inf\{t > 0 : \; X(t) = Y(t)\}$,

$$P(X(t) = x, Y(t) = y \mid t < T) = P^X(X(t) = x)P^Y(Y(t) = y) \text{ for each } x, y \in \mathbb{S}$$
$$\text{and} \quad P(X(t) = Y(t) \mid t \geq T) = 1. \tag{A.7}$$

This definition means that X and Y move independently before the coupling time T and stay together after T when they encounter at a state. In the case $P^Y(Y(0) = y) = \pi(y)$ for each $y \in \mathbb{S}$ where π is a stationary distribution of Y, we denote $T_x = T$ for a coupling time for (X,Y) such that $X(0) = x$.

For this coupling we have the coupling inequality. In the next theorem, we introduce a version of the coupling inequality provided from Theorem 5.2 in [37].

Theorem A.5 *Let $X : \Omega \to \mathbb{S}^{\mathbb{R}_{\geq 0}}$ and $Y : \Omega \to \mathbb{S}^{\mathbb{R}_{\geq 0}}$ be Markov processes in probability spaces $(\Omega, \mathcal{F}, P^X)$ and $(\Omega, \mathcal{F}, P^Y)$. Suppose $X(0) = x$ and $P^T(Y(0) = y) = \pi(y)$ for each $y \in \mathbb{S}$ where π is a stationary distribution of Y. Let (X,Y) be a pair of X and Y satisfying (A.7) with the coupling time T_x. Then*

$$\|P^X(X(t) \in \cdot) - \pi(\cdot)\|_{tv} \leq P(T_x > t).$$

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