MULTIPLE SCALING METHODS IN CHEMICAL REACTION NETWORKS

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Abstract

In this dissertation, we construct a general method of multiscale approximations in chemical reaction networks. We apply a continuous time Markov jump process to describe the state of the chemical reactions.

In general chemical reactions, the chemical species numbers and the chemical reaction rate constants will have various orders of magnitude. Therefore, we introduce two different scaling exponents to normalize the numbers of molecules of the chemical species and to scale the chemical reaction rate constants. Applying a time change, we have different time scales for the limiting processes in the reduced subsystems.

A systematic way to select the scaling exponents is suggested to make the normalized system have a nonzero finite limit. This method involves balance equations with the scaling exponents, which we call species and subnetwork balance conditions.

We investigate asymptotic methods used in multiscale approximations. The law of large numbers for Poisson processes is applied to approximate non-integer-valued processes. In each time scale, the slow processes act as constants and the fast processes are averaged out. Then the limit of the intermediate processes is obtained in terms of the averaged fast processes and the initial values of the slow processes.

We introduce a model of the heat shock response and apply the general method of multiscale approximations to this model. We analyze the system and obtain limiting processes in each simplified subsystem which approximate the normalized processes in the system with different time scales. We obtain error estimates of the difference between the normalized processes and the limiting processes. Simulation results are given to compare the evolution of the processes in the system and the evolution of the

approximated processes using the limiting processes in each simplified subsystem.

Applying the martingale central limit theorem and using averaging, we obtain a central limit theorem for deviation of the normalized processes from their limiting processes in the three species model and in the heat shock response model.

List of Tables

Contents

Chapter 1

Stochastic models for chemical reaction networks

1.1 Historical background

In this chapter, the historical background of the stochastic approaches to chemical reaction kinetics will be introduced. Chemical reactions are naturally stochastic. There have been various stochastic processes by which chemical reactions are approximately modeled since the 1960's [12].

In 1958, Bartholomay started to apply Markov process theory to chemical reactions [3]. He constructed stochastic Markov models for the linear birth and death population processes [3]. He used Q-matrix methods to relate the stochastic model and the classical deterministic model [3].

Then McQuarrie investigated chemical reaction kinetics in small systems such as several simple first order reactions [12]. He studied the effect of initial conditions on the expectation and the variance [12]. He extended his work to two binary reactions of $2A \rightarrow B$ and $A + B \rightarrow C$ and got the exact solutions to forward equations (master equation in the chemical literature) for these two separate reactions using generating functions [12].

Several approximate methods have also been developed since 1960. Bartholomay suggested a stochastic model for the Michaelis-Menten reaction in enzyme kinetics in 1962 [5]. He compared the system of ordinary differential equations of the classical mathematical model and the stochastic Markovian equations giving the rate of change in terms of the probability of the concentration [5]. Following [5], the deterministic differential equations may be obtained from the stochastic model by taking an expectation.

In 1972, Kurtz compared stochastic and deterministic models for chemical reactions. He suggested a format for stochastic rates in general chemical reaction networks and scaling in terms of the volume of the reaction system, and obtained the law of mass action as the limit of the stochastic models [9].

In 2003, Rao and Arkin suggested the quasi-steady-state assumption to reduce the complexity in stochastic simulation [13]. The quasi-steady-state assumption says that a subset of species is asymptotically at steady state in the specific time scale of interest in [13]. Later, in Section 5.2, we prove a rigorous limit theorem in the heat shock response model, and we prove that the quasi-steady-state assumption is justified.

Shortly after in 2006, Ball, Kurtz, Popovic and Rempala suggested multiscale approximations to chemical reaction networks using a continuous time Markov jump process [2]. In Section 5.1, we prove a central limit theorem for the three species model considered in [2]. Asymptotic methods of modeling chemical reaction networks used in [2] are based on [10] and [11] by Kurtz. In [10], he introduced strong approximation using the law of large numbers, diffusion approximation, and the central limit theorem of continuous time Markov chains. In [11], he gives stochastic averaging when there are two different time scales in a sequence of stochastic process; one is much faster than the other. The averaged generator is obtained in terms of the occupation measure of a sequence of components with much faster time scale.

1.2 Model description

We are interested in general chemical reaction networks involving n chemical reactions and m chemical species, $\{A_1, \cdots, A_m\}$.

$$\sum_{i=1}^{m} \nu_{ik} A_i \quad \rightarrow \quad \sum_{i=1}^{m} \nu'_{ik} A_i, \qquad k = 1, \cdots, n. \tag{1.1}$$

Here, ν_k is the vector indicating the number of molecules of each chemical species which are consumed in the kth reaction, and ν'_k is the vector indicating the number of molecules of each chemical species which are produced in the kth reaction. ν_{ik} and ν'_{ik} are the ith elements of ν_k and ν'_k, respectively.

Using a stochastic model, we would like to describe the evolution of the state of the chemical reaction network. Assuming the state of the chemical reaction network in the future only depends on the current state, we use a continuous-time Markov jump process to describe the chemical reaction network. Let $X(t)$ represent the state of the system at time t, where its ith component, $X_i(t)$, is the number of molecules of the ith chemical species at time t. Then $\nu'_{ik} - \nu_{ik}$ gives the jump size of the Markov process when the kth reaction occurs. If the kth reaction occurs at time t, the state satisfies

$$X(t) \quad = \quad X(t-) + (\nu'_k - \nu_k).$$

Let R_k be the counting process giving the number of times that the kth reaction occurs up to time t. The R_k will satisfy

$$R_k(t) \quad = \quad Y_k\Big(\int_0^t \lambda_k(X(s))\, ds\Big), \qquad k = 1, \cdots, n$$

where the Y_k are independent Poisson processes. $\lambda_k(X(t))$ is an intensity also called the propensity in the chemical literature. $\lambda_k(X(t))$ is the kth chemical reaction rate depending on the state of the system X at time t. Then the state of the chemical reaction system satisfies

$$\begin{aligned} X(t) &= X(0) + \sum_{k=1}^{m} R_k(t)({\nu'}_{ik} - \nu_{ik}) \\ &= X(0) + \sum_{k=1}^{m} Y_k(\int_0^t \lambda_k(X(s))\, ds)({\nu'}_{ik} - \nu_{ik}). \end{aligned}$$

Let x_i be a variable for X_i, the number of molecules of ith species, and x is a vector with x_i as its ith component. Let κ'_k be the kth reaction rate constant. Treating different chemical molecules as balls with different colors and viewing a chemical reaction as selecting balls to be consumed in the system, the chance of the kth reaction's occurrence during the interval $[t, t + \Delta t]$ is approximately proportional to

$$\prod_{i=1}^{m} \begin{pmatrix} x_i \\ \nu_{ik} \end{pmatrix} \Delta t \tag{1.2}$$

following Kurtz [9].

1.3 Classical scaling

In the chemical reaction setting, the amount of each chemical species is generally measured by a concentration in moles per liter [18]. In the deterministic approaches for chemical reaction kinetics, the instantaneous rate of the chemical reaction is generally considered as some product of powers of the concentrations of the chemical species to be consumed [18]. Theses powers are determined by ν_k, the numbers of molecules of chemical species consumed in the kth reaction. This law is *the mass-action kinetics* [18]. Following the mass-action kinetics, the chemical reaction system is described by a system of ordinary differential equations [18].

Now, we will derive mass-action kinetics for chemical reaction networks using stochastic modeling. Let N_0 be the volume of the system multiplied by Avogadro's number, so the number of molecules of chemical species normalized by N_0 would represent a concentration. For a binary reaction, the chance of a pair of molecules reacting during $[t, t + \Delta]$ is proportional to $\frac{1}{N_0}$ [9]. Similarly, for a reaction involving l molecules, the chance of l molecules reacting during $[t, t + \Delta]$ is proportional to $\frac{1}{N_0^{l-1}}$ [9]. Therefore, we express the rate in terms of the volume of the system.

Consider a general reaction $\sum_{i=1}^{m} \nu_{ik} A_i \xrightarrow{\kappa'_k} \sum_{i=1}^{m} \nu'_{ik} A_i$, for $k = 1, \cdots, n$. Using (1.2) and considering only the maximal order term in x, we approximate the kth reaction rate by

$$\lambda_k(x) \approx \kappa'_k \prod_{i=1}^{m} x_i^{\nu_{ik}} = N_0^{-\left(\sum_{i=1}^{m} \nu_{ik} - 1\right)} \kappa_k \prod_{i=1}^{m} x_i^{\nu_{ik}}. \tag{1.3}$$

Assuming that the number of molecules of each chemical species is large and has the same order of magnitude, we normalize the numbers of molecules of chemical species by N_0. The normalized number of molecules of the ith species is

$$z_i = \frac{x_i}{N_0} \tag{1.4}$$

and it represents the concentration of the ith species in the system. Plugging (1.4) in

(1.3), the approximate kth reaction rate parameterized by N_0 is written as

$$\begin{aligned}\lambda_k(x) &\approx N_0\kappa_k\prod_{i=1}^{m} z_i^{\nu_{ik}}\\ &\equiv N_0\tilde{\lambda}_k(z).\end{aligned}$$

Setting $Z^{N_0}(t) = \frac{X^N(t)}{N_0}$, a time change equation and its approximation is

$$\begin{aligned}Z^{N_0}(t) &= Z^{N_0}(0) + \sum_{k=1}^{m} N_0^{-1}Y_k\Big(\int_0^t \lambda_k(X^{N_0}(s))\,ds\Big)(\nu'_k - \nu_k)\\ &\approx Z^{N_0}(0) + \sum_{k=1}^{m} N_0^{-1}Y_k\Big(\int_0^t N_0\tilde{\lambda}_k(Z^{N_0}(s))\,ds\Big)(\nu'_k - \nu_k)\end{aligned}$$

where the initial value is defined as

$$Z^{N_0}(0) = \frac{1}{N_0}\Big[X(0)\Big].$$

By the law of large numbers for the Poisson process, $N_0^{-1}Y(N_0u) \approx u$, we have an approximation for the normalized system.

$$\begin{aligned}Z^{N_0}(t) &\approx Z^{N_0}(0) + \sum_{k=1}^{m}\int_0^t \tilde{\lambda}_k(Z^{N_0}(s))(\nu'_k - \nu_k)\,ds\\ &= Z^{N_0}(0) + \sum_{k=1}^{m}\int_0^t \kappa_k\prod_{i=1}^{m} Z_i^{N_0}(s)^{\nu_{ik}}(\nu'_k - \nu_k)\,ds.\end{aligned}$$

Since N_0 is large, we replace N_0 by N and define $Z^N(0) \equiv \frac{1}{N}\Big[\frac{X(0)N}{N_0}\Big]$. As $N \to \infty$, the limit of the system parameterized by N gives the deterministic law of mass action

$$\begin{aligned}\dot{Z}(t) &= \sum_{k=1}^{m}\kappa_k\prod_{i=1}^{m} Z_i(t)^{\nu_{ik}}(\nu'_k - \nu_k)\\ &\equiv F(Z(t))\end{aligned}$$

where $Z(t)$ represents a limit of $Z^N(t)$ as $N \to \infty$ [9]. Then the numbers of molecules of the chemical species are approximated as

$$X(t) \approx N_0 Z(t).$$

1.4 Multiple scaling

In the classical scaling, we assume that the orders of magnitude of all chemical species are the same. However, many chemical reaction networks have various ranges of orders of magnitude of chemical reaction rate constants and different ranges of orders of magnitude of the numbers of molecules of chemical species. Then the classical scaling does not capture the characteristics of the system well. Therefore, we need to consider different scaling exponents α_i for each chemical species and β_k for each chemical reaction rate constant. For each i and for each k, we will choose appropriate values for α_i and β_k so that the normalized values become $O(1)$.

In multiple scaling, N_0 is a fixed number used for scaling the number of molecules of chemical species and for scaling the chemical reaction rate constants in the system. Define Z as a vector for the normalized numbers of molecules of chemical species and κ's as the normalized chemical reaction rate constants.

$$Z_i(t) = \frac{X_i(t)}{N_0^{\alpha_i}} = O(1), \tag{1.5}$$

$$\kappa_k = \frac{\kappa'_k}{N_0^{\beta_k}} = O(1) \tag{1.6}$$

α_i are always nonnegative and β_k can be any number.

Consider a relationship between the chemical reaction rate constant κ'_k and the scaled reaction rate constant κ_k. As mentioned in (1.2), the kth reaction rate is proportional to

$$\prod_{i=1}^{m} \binom{x_i}{\nu_{ik}}.$$

Asymptotic behavior of the scaled reaction rate depends on x with the largest order. Considering only the maximal order term in x and substituting κ'_k and x_i by their scaled values, the approximated kth reaction rate is given by

$$\lambda_k(x) \approx \kappa'_k \prod_{i=1}^{m} x_i^{\nu_{ik}} \quad = \quad N_0^{\alpha\cdot\nu_k+\beta_k} \kappa_k \prod_{i=1}^{m} z_i^{\nu_{ik}}$$

where $z_i = \frac{x_i}{N_0^{\alpha_i}}$. Assuming N_0 is large and replacing N_0 by N, we obtain a parametric family of models.

$$Z_i^N(t) \quad = \quad Z_i^N(0) + N^{-\alpha_i} \sum_{k=1}^{m} Y_k\Big(\int_0^t N^{\alpha\cdot\nu_k+\beta_k} \lambda_k^N(Z^N(s))\, ds \Big)(\nu'_{ik} - \nu_{ik}) \qquad (1.7)$$

Now, we need to see how to set initial values for the parameterized family, $Z^N(0)$, using $X(0)$. Since X is an integer-valued Markov process, Z^N is also a Markov process with different jump size in each component. Considering $Z_i^N = \frac{X_i}{N^{\alpha_i}}$, the jump size of the ith component is $\frac{1}{N^{\alpha_i}}$. Therefore, set the normalized initial values as

$$Z_i^N(0) \quad \equiv \quad \frac{1}{N^{\alpha_i}} \left[\frac{X_i(0) N^{\alpha_i}}{N_0^{\alpha_i}} \right], \qquad i = 1, \cdots, n \qquad (1.8)$$

where $[\cdot]$ is a floor function which gives the greatest integer less or equal to the value inside $[\cdot]$. Then we have

$$\lim_{N\to\infty} Z_i^N(0) \quad = \quad Z_i(0) \equiv \frac{X_i(0)}{N_0^{\alpha_i}}. \qquad (1.9)$$

Moreover, an error is uniformly bounded.

$$|Z_i^N(0) - Z_i(0)| \leq \frac{1}{N^{\alpha_i}}. \tag{1.10}$$

Let $Z_i \equiv \lim_{N\to\infty} Z_i^N$. Then X is approximated as

$$X_i(t) \approx N_0^{\alpha_i} Z_i(t).$$

The classical scaling is one of the possible scalings setting $\alpha_i = 1$ and $\beta_k = -(\sum_{i=1}^m \nu_{ik} - 1)$.

1.5 Example

Consider again an example of two binary reactions $2A_1 \overset{\kappa_1'}{\to} A_1 + A_2$ and $A_1 + A_2 \overset{\kappa_2'}{\to} A_1 + A_3$. The state of the system is represented as

$$\begin{aligned}
X_1(t) &= X_1(0) - Y_1\Big(\int_0^t \kappa_1' X_1(s)(X_1(s)-1)\,ds\Big)\\
X_2(t) &= X_2(0) + Y_1\Big(\int_0^t \kappa_1' X_1(s)(X_1(s)-1)\,ds\Big) - Y_2\Big(\int_0^t \kappa_2' X_1(s)X_2(s)\,ds\Big)\\
X_3(t) &= X_3(0) + Y_2\Big(\int_0^t \kappa_2' X_1(s)X_2(s)\,ds\Big).
\end{aligned}$$

Reaction rates are written in two forms, the one before the scaling and the other after the scaling.

$$\begin{aligned}
\kappa_1' x_1(x_1 - 1) &= N^{2\alpha_1+\beta_1}\kappa_1 z_1(z_1 - \frac{1}{N^{\alpha_1}})\\
\kappa_2' x_1 x_2 &= N^{\alpha_1+\alpha_2+\beta_2}\kappa_2 z_1 z_2.
\end{aligned}$$

After scaling, the normalized system state of the two binary reactions is

$$
\begin{aligned}
Z_1^N(t) &= Z_1^N(0) - N^{-\alpha_1} Y_1\Big(\int_0^t N^{2\alpha_1+\beta_1}\kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N^{\alpha_1}})\,ds\Big) \\
Z_2^N(t) &= Z_2^N(0) + N^{-\alpha_2} Y_1\Big(\int_0^t N^{2\alpha_1+\beta_1}\kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N^{\alpha_1}})\,ds\Big) \\
&\quad - N^{-\alpha_2} Y_2\Big(\int_0^t N^{\alpha_1+\alpha_2+\beta_2}\kappa_2 Z_1^N(s) Z_2^N(s)\,ds\Big) \\
Z_3^N(t) &= Z_3^N(0) + N^{-\alpha_3} Y_2\Big(\int_0^t N^{\alpha_1+\alpha_2+\beta_2}\kappa_2 Z_1^N(s) Z_2^N(s)\,ds\Big).
\end{aligned} \tag{1.11}
$$

For the classical scaling, set $\alpha_1 = \alpha_2 = \alpha_3 = 1$ and $\beta_1 = \beta_2 = -1$. Then the normalized system becomes

$$
\begin{aligned}
Z_1^N(t) &= Z_1^N(0) - N^{-1} Y_1\Big(\int_0^t N\kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N})\,ds\Big) \\
Z_2^N(t) &= Z_2^N(0) + N^{-1} Y_1\Big(\int_0^t N\kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N})\,ds\Big) \\
&\quad - N^{-1} Y_2\Big(\int_0^t N\kappa_2 Z_1^N(s) Z_2^N(s)\,ds\Big) \\
Z_3^N(t) &= Z_3^N(0) + N^{-1} Y_2\Big(\int_0^t N\kappa_2 Z_1^N(s) Z_2^N(s)\,ds\Big).
\end{aligned}
$$

As $N \to \infty$, we get the limit of the normalized system which is a stochastic version of the mass-action kinetics.

$$
\begin{aligned}
Z_1(t) &= Z_1(0) - \int_0^t \kappa_1 Z_1(s)^2\,ds \\
Z_2(t) &= Z_2(0) + \int_0^t \big(\kappa_1 Z_1(s)^2 - \kappa_2 Z_1(s) Z_2(s)\big)\,ds \\
Z_3(t) &= Z_3(0) + \int_0^t \kappa_2 Z_1(s) Z_2(s)\,ds.
\end{aligned}
$$

Next, consider (1.11) with a different set of scaling exponents. Suppose that the numbers of molecules of A_1 and A_3 are much larger than that of A_2. Suppose than Reaction 2 is much faster than Reaction 1. Then we set $\alpha_1 = \alpha_3 = 1$, $\alpha_2 = 0$, $\beta_1 = -2$, and $\beta_2 = -1$. Then (1.11) becomes

$$\begin{aligned}
Z_1^N(t) &= Z_1^N(0) - N^{-1}Y_1\Big(\int_0^t \kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N})\, ds\Big) \\
Z_2^N(t) &= Z_2^N(0) + Y_1\Big(\int_0^t \kappa_1 Z_1^N(s)(Z_1^N(s) - \frac{1}{N})\, ds\Big) \\
&\quad - Y_2\Big(\int_0^t \kappa_2 Z_1^N(s) Z_2^N(s)\, ds\Big) \\
Z_3^N(t) &= Z_3^N(0) + N^{-1}Y_2\Big(\int_0^t \kappa_2 Z_1^N(s) Z_2^N(s)\, ds\Big).
\end{aligned} \tag{1.12}$$

In (1.12) have two time scales: the time scale for Z_1^N and Z_3^N is slower than that for Z_2^N. First, as $N \to \infty$, we obtain

$$\begin{aligned}
Z_1(t) &= Z_1(0) \\
Z_2(t) &= Z_2(0) + Y_1\Big(\int_0^t \kappa_1 Z_1(0)^2\, ds\Big) - Y_2\Big(\int_0^t \kappa_2 Z_1(0) Z_2(s)\, ds\Big) \\
Z_3(t) &= Z_3(0).
\end{aligned}$$

Now, to consider the behavior of the evolution of the processes in the later time scale, replace t by Nt. Let $Z_i'^N(t) = Z_i^N(Nt)$. Then using the change of variables, (1.12) becomes

$$Z_1'^N(t) = Z_1'^N(0) - N^{-1}Y_1\Big(\int_0^t \kappa_1 N Z_1'^N(s)(Z_1'^N(s) - \frac{1}{N})\, ds\Big) \tag{1.13}$$

$$\begin{aligned}
Z_2'^N(t) &= Z_2'^N(0) + Y_1\Big(\int_0^t \kappa_1 N Z_1'^N(s)(Z_1'^N(s) - \frac{1}{N})\, ds\Big) \\
&\quad - Y_2\Big(\int_0^t \kappa_2 N Z_1'^N(s) Z_2'^N(s)\, ds\Big)
\end{aligned} \tag{1.14}$$

$$Z_3'^N(t) = Z_3'^N(0) + N^{-1}Y_2\Big(\int_0^t \kappa_2 N Z_1'^N(s) Z_2'^N(s)\, ds\Big). \tag{1.15}$$

Dividing (1.14) by N and applying the law of large numbers for the Poisson process, we obtain

$$\int_0^t \kappa_2 Z_1'^N(s)\big(\frac{\kappa_1}{\kappa_2} Z_1'^N(s) - Z_2'^N(s)\big)\, ds \longrightarrow 0. \tag{1.16}$$

From (1.16), we have

$$\int_0^t \big(Z_2'^N(t) - \frac{\kappa_1}{\kappa_2} Z_1'^N(t)\big)\, ds \longrightarrow 0. \tag{1.17}$$

Using (1.17), as $N \to \infty$, we obtain

$$\begin{aligned} Z_1'(t) &= Z_1'(0) - \int_0^t \kappa_1 Z_1'(s)^2\, ds \\ Z_3'(t) &= Z_3'(0) + \int_0^t \kappa_1 Z_1'(s)^2\, ds \end{aligned}$$

1.6 The problem to be addressed

In Chapter 2, we construct a general method of multiscale approximations, which is an extension of the method developed by Ball, Kurtz, Popovic and Rempala [2]. We introduce a scaling exponent parameter γ for time change. A systematic way to select α's and β's is suggested to make the normalized system have the order of 1. This method involves balance equations with α_i and β_k, which we call species and subnetwork balance conditions.

In Chapter 3, we investigate asymptotic methods used in multiscale approximations. The law of large numbers for Poisson processes is applied to approximate non-integer-valued processes. The limit of the intermediate processes are obtained in terms of the averaged fast processes and the initial values of the slow processes.

In Chapter 4, we introduce a model of the heat shock response developed by Srivastava, Peterson, and Bentley [14]. We apply the general method of multiscale approximations to the heat shock response model. We analyze the system and obtain limiting processes in each simplified subsystem which approximate the normalized processes in the system with different time scales. We obtain error estimates of the difference between the normalized processes and the limiting processes.

In Chapter 5, applying the martingale central limit theorem and using averaging, we obtain a central limit theorem for deviation of the normalized processes from their limiting processes in the three species model introduced in [8] and in the heat shock response model.

Chapter 2

General scaling problem

2.1 Behavior of the system in different time

Since we treat the chemical reaction system as a network, we first define some terminologies borrowed from graph theory. A *graph* $G = \big(V(G), E(G)\big)$ consists of two finite sets: $V(G)$ the node set, often denoted by just V, which is a nonempty set of elements called the *nodes*, and $E(G)$, the edge set, often denoted by just E, which is a possibly empty set of elements called edges, such that each *edge* e in E is an *unordered* pair of nodes (u, v) [6]. A directed edge a is an *ordered* pair of nodes (u', v') in which u' is the initial node and v' is the terminal node [6]. Then a *directed graph* is a graph consisting of a directed edge set and a node set. Let H be a graph with the node set $V(H)$ and the edge set $E(H)$. Then H is a subgraph of G, if $V(H) \subseteq V(G)$ and $E(H) \subset E(G)$ [6]. Then a chemical reaction network gives a directed graph where the chemical species are the nodes and the chemical reactions are the directed edges. Each subnetwork is a subgraph of a directed graph. We will use these definitions in this chapter.

Consider again the general chemical reaction networks from (1.1)

$$\sum_{i=1}^{m} \nu_{ik} A_i \;\; \rightarrow \;\; \sum_{i=1}^{m} \nu'_{ik} A_i, \qquad i = 1, \cdots, n.$$

Then a parametric family of the normalized system is given from (1.7) in Section1.2.

$$Z_i^N(t) \;=\; Z_i^N(0) + N^{-\alpha_i} \sum_{k=1}^{m} Y_k\Big(\int_0^t N^{\alpha\cdot\nu_k+\beta_k} \lambda_k(Z^N(s))\, ds\Big)(\nu'_{ik} - \nu_{ik}) \qquad (2.1)$$

Let γ be a time change parameter. To apply the time change, replace t by $N^\gamma t$ and apply change of variables using $s = N^\gamma u$. Defining a new variable $V_i^N(u) = Z_i^N(N^\gamma u)$ and substituting Z_i^N by V_i^N in (2.1), we obtain

$$V_i^N(t) \;=\; V_i^N(0) + N^{-\alpha_i} \sum_{k=1}^{m} Y_k\Big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k} \lambda_k(V^N(u))\, du\Big)(\nu'_{ik} - \nu_{ik}). \qquad (2.2)$$

Taking $\gamma = 0$, there is no change on time. Choosing a positive value for γ, time is accelerated, while selecting a negative value for γ, time is decelerated.

We would like to understand the asymptotic behavior of the kth reaction term by comparing scaling exponents of N inside and outside of a counting process. There are three possible cases depending on values of γ.

$$\gamma + \alpha\cdot\nu_k + \beta_k \;<\; \alpha_i \qquad (2.3)$$

$$\gamma + \alpha\cdot\nu_k + \beta_k \;=\; \alpha_i \qquad (2.4)$$

$$\gamma + \alpha\cdot\nu_k + \beta_k \;>\; \alpha_i \qquad (2.5)$$

When (2.3) is satisfied, the kth reaction term $N^{-\alpha_i} Y_k\big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k}\lambda_k(V^N(s))\,ds\big)(\nu'_{ik} - \nu_{ik})$ is asymptotically zero. That is, the scaled number of kth reactions is asymptotically zero at the initial stage. When (2.4) is satisfied and $\alpha_i \neq 0$, applying the law of large numbers for the Poisson process, the kth reaction term satisfies

$$N^{-\alpha_i} Y_k\Big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k} \lambda_k(V^N(s))\, ds\Big)(\nu'_{ik} - \nu_{ik}) \;\approx\; \int_0^t \lambda_k(V^N(s))\, ds(\nu'_{ik} - \nu_{ik})$$

When (2.4) is satisfied and $\alpha_i = 0$, as $N \to \infty$, we anticipate that the kth reaction term converges to

$$Y_k\Big(\int_0^t \lambda_k(V(s))\,ds\Big)(\nu'_{ik} - \nu_{ik})$$

if certain conditions are satisfied. In both cases, when (2.4) is satisfied, nonzero finite limits of the scaled numbers of kth reactions are anticipated. When (2.5) is satisfied, the scaled numbers of kth reactions blow up as $N \to \infty$. Therefore, a necessary condition to prevent the kth reaction term blowing up is

$$\gamma + \alpha \cdot \nu_k + \beta_k \;\leq\; \alpha_i.$$

Now, we need to consider which conditions are necessary to prevent V_i^N blowing up. The natural time scale for V_i^N is determined by

$$\begin{aligned} \gamma &= \min_k \big(\alpha_i - (\alpha \cdot \nu_k + \beta_k)\big) \\ &= \alpha_i - \max_k(\alpha \cdot \nu_k + \beta_k) \end{aligned} \tag{2.6}$$

where the minimum in the first inequality is taken over reactions involved in the ith species. Then (2.6) is a necessary condition to prevent any term in the equation for V_i^N blowing up.

However, in some cases convergence may occur even though γ is larger than the value given in (2.6). For example, $V_2^{N,2}$ and $V_3^{N,2}$ converge when $\gamma = 2$ in the heat shock response model in Section 4.1.2, even though $\min_k \big(\alpha_2 - (\alpha \cdot \nu_k + \beta_k)\big) = \min_k \big(\alpha_3 - (\alpha \cdot \nu_k + \beta_k)\big) = 0$.

2.2 Balance conditions

2.2.1 Species balance conditions

Define Γ_i^+ to be the collection of reactions that produce the ith chemical species and Γ_i^- to be the collection of reactions that consume the ith chemical species. Then define the species balance equation as

$$\max_{k\in\Gamma_i^+}(\gamma+\alpha\cdot\nu_k+\beta_k) \quad = \quad \max_{k\in\Gamma_i^-}(\gamma+\alpha\cdot\nu_k+\beta_k). \tag{2.7}$$

Consider how (2.7) affects a limit of the normalized number of molecules of the ith species in different time scales. When

$$\gamma \; < \; \alpha_i - \max_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha\cdot\nu_k+\beta_k), \tag{2.8}$$

V_i^N should be asymptotically equal to $V_i^N(0)$ and have a nonzero finite limit, $V_i(0)$. (unless $V_i^N(0)=0$) When

$$\gamma \; = \; \alpha_i - \max_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha\cdot\nu_k+\beta_k), \tag{2.9}$$

V_i^N is asymptotically the same as the normalized number of species with reactions of both production and consumption of the same maximal orders of magnitude for the reaction rates. In this case, as $N\to\infty$, a nonzero finite limit should exist. If

$$\gamma \; > \; \alpha_i - \max_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha\cdot\nu_k+\beta_k), \tag{2.10}$$

both the maximal reaction rate of production and the maximal rate of consumption blow up to infinity as $N \to \infty$. However, in this chemical reaction networks, the consumption rates in the equation for the ith chemical species are proportional to the number of molecules of the ith chemical species, and the number of reactions of production and consumption occur at the asymptotically same rate. Therefore, the numbers of reaction of production and consumption are cancelled out, and as $N \to \infty$, a nonzero finite limit should exist.

Now, consider the case that (2.7) is not satisfied. Then the reaction terms of production and consumption do not cancel as $N \to \infty$. We would like to prevent the possibility that one of the production or consumption rates has greater order of magnitude so that the limit, V_i, either blows up to infinity or converges to zero as $N \to \infty$. In other words, we do not want a case that one of the production or consumption reactions dominates. Then α_i is required to big enough to prevent the reaction term blowing up. That is,

$$\max_{k \in \Gamma_i^+ \cup \Gamma_i^-} (\gamma + \alpha \cdot \nu_k + \beta_k) \;\leq\; \alpha_i. \tag{2.11}$$

Solving (2.11) for γ, the time change exponent must satisfy

$$\gamma \;\leq\; \alpha_i - \max_{k \in \Gamma_i^+ \cup \Gamma_i^-} (\alpha \cdot \nu_k + \beta_k). \tag{2.12}$$

Combining (2.7) and (2.12), we define the species balance conditions as

$$C1.\,(i) \qquad \max_{k \in \Gamma_i^+}(\gamma + \alpha \cdot \nu_k + \beta_k) = \max_{k \in \Gamma_i^-}(\gamma + \alpha \cdot \nu_k + \beta_k) \tag{2.13}$$

or

$$(ii) \qquad \max_{k\in\Gamma_i^+}(\gamma+\alpha\cdot\nu_k+\beta_k) \neq \max_{k\in\Gamma_i^-}(\gamma+\alpha\cdot\nu_k+\beta_k)$$

and

$$\gamma \leq \alpha_i - \max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\alpha\cdot\nu_k+\beta_k) \qquad \text{for } i=1,\cdots,m \tag{2.14}$$

Now, apply the species balance conditions to simple reactions

$$A_1 \underset{\kappa_2'}{\overset{\kappa_1'}{\rightleftharpoons}} A_2.$$

Then the normalized time change equations for A_1 and A_2 after time change are

$$\begin{aligned} V_1^N(t) &= V_1^N(0)+N^{-\alpha_1}Y_2\Big(\int_0^t N^{\gamma+\alpha_2+\beta_2}\kappa_2 V_2^N(s)\,ds\Big) \\ &\quad -N^{-\alpha_1}Y_1\Big(\int_0^t N^{\gamma+\alpha_1+\beta_1}\kappa_1 V_1^N(s)\,ds\Big) \qquad (2.15) \\ V_2^N(t) &= V_2^N(0)+N^{-\alpha_2}Y_1\Big(\int_0^t N^{\gamma+\alpha_1+\beta_1}\kappa_1 V_1^N(s)\,ds\Big) \\ &\quad -N^{-\alpha_2}Y_2\Big(\int_0^t N^{\gamma+\alpha_2+\beta_2}\kappa_2 V_2^N(s)\,ds\Big). \qquad (2.16) \end{aligned}$$

The species balance equation for both A_1 and A_2 is

$$\gamma+\alpha_2+\beta_2 = \gamma+\alpha_1+\beta_1. \tag{2.17}$$

If (2.17) is not satisfied, then a scaling exponent of the species should be large enough to prevent the numbers of reaction of production and consumption of the species blowing up to infinity as $N\to\infty$. After rearrangement, it gives us a restriction on a time change scaling exponent. Applying (2.14), we have

$$\gamma+\alpha_2+\beta_2 \neq \gamma+\alpha_1+\beta_1 \tag{2.18}$$

$$\max(\gamma + \alpha_2 + \beta_2, \gamma + \alpha_1 + \beta_1) \leq \alpha_1 \tag{2.19}$$

$$\max(\gamma + \alpha_2 + \beta_2, \gamma + \alpha_1 + \beta_1) \leq \alpha_2. \tag{2.20}$$

Solving for γ, (2.19) and (2.20) require the time change scaling exponent to satisfy

$$\gamma \leq \min(\alpha_1, \alpha_2) - \max(\alpha_2 + \beta_2, \alpha_1 + \beta_1). \tag{2.21}$$

(2.21) means that the choice of α's and β's are valid for time scales up to

$$O\left(N^{\min(\alpha_1,\alpha_2)-\max(\alpha_2+\beta_2,\alpha_1+\beta_1)}\right).$$

For simplicity, assuming $\alpha_1 = \alpha_2$ and consider the limit in each case. First, assuming the species balance condition (2.17) is satisfied. Then using (2.17), we have $\beta_1 = \beta_2$. When $\gamma < -\beta_1$,

$$\begin{aligned} V_1(t) &\equiv \lim_{N\to\infty} V_2^N(t) = V_2(0) \\ V_2(t) &\equiv \lim_{N\to\infty} V_2^N(t) = V_2(0) \end{aligned}$$

where $V_1(0) \equiv \lim_{N\to\infty} V_1^N(0)$ and $V_2(0) \equiv \lim_{N\to\infty} V_2^N(0)$.

When $\gamma = -\beta_1$ and $\alpha_1 = \alpha_2 \neq 0$, using the law of large numbers for the Poisson process, we have

$$\begin{aligned} V_1(t) &= V_1(0) + \int_0^t \left(\kappa_2 V_2(s) - \kappa_1 V_1(s)\right) ds \\ V_2(t) &= V_2(0) + \int_0^t \left(\kappa_1 V_1(s) - \kappa_2 V_2(s)\right) ds. \end{aligned}$$

When $\gamma = -\beta_1$ and $\alpha_1 = \alpha_2 = 0$, we have

$$\begin{aligned} V_1(t) &= V_1(0) + Y_2\Big(\int_0^t \kappa_2 V_2(s)\,ds\Big) - Y_1\Big(\int_0^t \kappa_1 V_1(s)\,ds\Big) \\ V_2(t) &= V_2(0) + Y_1\Big(\int_0^t \kappa_1 V_1(s)\,ds\Big) - Y_2\Big(\int_0^t \kappa_2 V_2(s)\,ds\Big). \end{aligned}$$

When $\gamma > -\beta_1$, the numbers of reaction of production and consumption blow up as $N \to \infty$. However, the consumption rate in the equation for V_1^N is proportional to V_1^N and the consumption rate in the equation for V_2^N is proportional to V_2^N. Since both reaction rates have the same order of magnitude, the numbers of molecules of the chemical species are stabilized and as $N \to \infty$, a nonzero finite limit exist. Dividing (2.23) and (2.24) by $N^{\gamma+\beta_1}$ and applying the law of large numbers for the Poisson process, we obtain

$$\int_0^t \big(\kappa_1 V_1(s) - \kappa_2 V_2(s)\big)\,ds = 0$$

when $\alpha_1 = \alpha_2 \neq 0$. In case $\alpha_1 = \alpha_2 = 0$, both species are averaged out, and the averaged processes denoted $\bar{V}_1$ and $\bar{V}_2$ satisfy

$$\int_0^t \big(\kappa_1 \bar{V}_1(s) - \kappa_2 \bar{V}_2(s)\big)\,ds = 0.$$

Next, suppose that the species balance condition is not satisfied and we have (2.18) and (2.21). Without loss of generality, set $\beta_1 > \beta_2$. The the time change exponent should satisfy $\gamma \leq -\beta_1$. When $\gamma < -\beta_1$, we have

$$\begin{aligned} V_1(t) &= V_1(0) \\ V_2(t) &= = V_2(0) \end{aligned}$$

Then when $\gamma = -\beta_1$ and $\alpha_1 = \alpha_2 \neq 0$, the limits satisfy

$$\begin{aligned} V_1(t) &= V_1(0) - \int_0^t \kappa_1 V_1(s)\, ds \\ V_2(t) &= V_2(0) + \int_0^t \kappa_1 V_1(s)\, ds. \end{aligned}$$

In case $\gamma = -\beta_1$ and $\alpha_1 = \alpha_2 = 0$, we have

$$\begin{aligned} V_1(t) &= V_1(0) - Y_1\Big(\int_0^t \kappa_1 V_1(s)\, ds\Big) \\ V_2(t) &= V_2(0) + Y_1\Big(\int_0^t \kappa_1 V_1(s)\, ds\Big). \end{aligned}$$

2.2.2 Subnetwork balance conditions

Even though all species balance conditions are satisfied, additional conditions may be required to ensure the normalized system has nonzero finite limits. Consider the following example.

$$\emptyset \xrightarrow{\kappa_1'} A_1 \underset{\kappa_3'}{\overset{\kappa_2'}{\rightleftharpoons}} A_2 \xrightarrow{\kappa_4'} \emptyset. \tag{2.22}$$

Then the normalized time change equations for A_1 and A_2 after the time change are

$$\begin{aligned} V_1^N(t) &= V_1^N(0) + N^{-\alpha_1} Y_1\Big(\int_0^t N^{\gamma+\beta_1}\kappa_1\, ds\Big) + N^{-\alpha_1} Y_3\Big(\int_0^t N^{\gamma+\alpha_2+\beta_3}\kappa_3 V_2^N(s)\, ds\Big) \\ &\quad - N^{-\alpha_1} Y_2\Big(\int_0^t N^{\gamma+\alpha_1+\beta_2}\kappa_2 V_1^N(s)\, ds\Big) \qquad (2.23) \\ V_2^N(t) &= V_2^N(0) + N^{-\alpha_2} Y_2\Big(\int_0^t N^{\gamma+\alpha_1+\beta_2}\kappa_2 V_1^N(s)\, ds\Big) \qquad (2.24) \\ &\quad - N^{-\alpha_2} Y_3\Big(\int_0^t N^{\gamma+\alpha_2+\beta_3}\kappa_3 V_2^N(s)\, ds\Big) - N^{-\alpha_2} Y_4\Big(\int_0^t N^{\gamma+\alpha_2+\beta_4}\kappa_4 V_2^N(s)\, ds\Big). \end{aligned}$$

We would like to investigate when V_1^N and V_2^N have nonzero finite limits as $N \to \infty$. Suppose that $\beta_2 = \beta_3$ and they are larger than β_1 and β_4. We assume that each species satisfies the species balance conditions, (2.13) or (2.14). The species balance equations (2.13) are

$$\begin{aligned} \max(\beta_1, \alpha_2 + \beta_3) &= \alpha_1 + \beta_2 && (2.25) \\ \alpha_1 + \beta_2 &= \max(\alpha_2 + \beta_3, \alpha_2 + \beta_4). && (2.26) \end{aligned}$$

Using $\beta_2 = \beta_3$, $\alpha_1 \geq 0$, and $\beta_2 > \beta_1$, (2.25) is equivalent to $\alpha_1 = \alpha_2$. Using $\beta_2 = \beta_3 > \beta_4$, (2.26) is also equivalent to $\alpha_1 = \alpha_2$. Therefore, either both (2.25) and (2.26) are satisfied or both are not satisfied.

Now, assume that each species satisfies the species balance equations. Then using $\alpha_1 = \alpha_2$, consider the equation for $V_1^N + V_2^N$.

$$\begin{aligned} V_1^N(t) + V_2^N(t) &= V_1^N(0) + V_2^N(0) + N^{-\alpha_1} Y_1\Big(\int_0^t N^{\gamma+\beta_1}\kappa_1\, ds\Big) \\ &\quad - N^{-\alpha_1} Y_4\Big(\int_0^t N^{\gamma+\alpha_2+\beta_4}\kappa_4 V_2^N(s)\, ds\Big). && (2.27) \end{aligned}$$

To make $V_1^N + V_2^N$ have a non-zero finite limit, it is required that

$$\beta_1 = \alpha_2 + \beta_4. \qquad (2.28)$$

Assume that both species do not satisfy the species balance equations (2.14). Then we have $\alpha_1 \neq \alpha_2$ and the time change exponent γ must satisfy

$$\gamma \leq \min\Big(\alpha_1 - \max\big(\max(\beta_1, \alpha_2 + \beta_3), \alpha_1 + \beta_2\big),$$

$$\alpha_2 - \max\big(\alpha_1 + \beta_2, \max(\alpha_2 + \beta_3, \alpha_2 + \beta_4)\big)\Big). \tag{2.29}$$

Therefore as we see from (2.28) and (2.29), the maximal order of magnitude of collective reaction rates for inflow should be the same as the maximal order of magnitude of collective reaction rates of outflow in any subnetwork to make any collection of chemical species have a nonzero finite limit. In case the maximal order of magnitude of collective reaction rates for inflow and the maximal order of magnitude of collective reaction rates of outflow are different, the maximal exponent for the chemical species should be large enough to prevent the numbers of reactions with the maximal order blowing up.

Based on (2.28), we would like to generalize the conditions for collective rates involving a subset of chemical species. Consider chemical species and chemical reactions as nodes and directed graphs, respectively. Let G be the chemical species in the chemical reaction networks and let G_0 be any subset of G. Let $\Gamma^+_{G_0}$ be the collection of reactions that consume no chemical species in G_0 and produce at least one of chemical species in G_0. Similarly, $\Gamma^-_{G_0}$ is the set of reactions that produce no chemical species in G_0 and consume at least one of the chemical species in G_0. For each $G_0 \subset G$, define the subnetwork balance conditions as

$$C2.\,(i) \qquad \max_{k\in\Gamma^+_{G_0}}(\gamma + \alpha\cdot\nu_k + \beta_k) = \max_{k\in\Gamma^-_{G_0}}(\gamma + \alpha\cdot\nu_k + \beta_k), \tag{2.30}$$

or

$$(ii) \qquad \max_{k\in\Gamma^+_{G_0}}(\gamma + \alpha\cdot\nu_k + \beta_k) \neq \max_{k\in\Gamma^-_{G_0}}(\gamma + \alpha\cdot\nu_k + \beta_k),$$

and

$$\max_{k\in\Gamma^+_{G_0}\cup\Gamma^-_{G_0}}(\gamma + \alpha\cdot\nu_k + \beta_k) \le \max_{i\in G_0}\alpha_i. \tag{2.31}$$

Solving (2.31) for γ, the balance equations require the time change exponent to satisfy

$$\gamma \leq \min_{G_0 \subset G, G_0 \text{ unbalanced}} \left(\max_{i \in G_0} \alpha_i - \max_{k \in \Gamma^+_{G_0} \cup \Gamma^-_{G_0}} (\alpha \cdot \nu_k + \beta_k) \right). \tag{2.32}$$

In the subnetwork balance conditions, G_0 can consist of a single node. Therefore, the subnetwork balance condition contain the species balance conditions.

Assume that species and subnetwork balance conditions are all satisfied. Then, in general, we expect that any collection of the normalized numbers of chemical species in the system of chemical reaction networks has a nonzero finite limit as $N \rightarrow \infty$. However, a nonzero finite limit exceptionally may not exist for some cases.

For example, consider the following reaction networks.

$$\text{stuff} + A_2 \overset{\kappa_1'}{\rightarrow} 2A_2 \tag{2.33}$$

$$A_2 \overset{\kappa_2'}{\rightarrow} \emptyset \tag{2.34}$$

In (2.33), stuff represents a chemical species which we are not interested in and which exists in great amount in the system. In (2.34), $\emptyset$ represents a chemical species which we are not interested in. The normalized time change equation for the system after the time change is

$$\begin{aligned} V_2^N(t) &= V_2^N(0) + N^{-\alpha_2} Y_1\big(\int_0^t N^{\gamma+\alpha_2+\beta_1} \kappa_1 V_2^N(s)\, ds \big) \\ &\quad - N^{-\alpha_2} Y_2\big(\int_0^t N^{\gamma+\alpha_2+\beta_2} \kappa_2 V_2^N(s)\, ds \big). \end{aligned} \tag{2.35}$$

If we have

$$\alpha_2 + \beta_1 = \alpha_2 + \beta_2, \tag{2.36}$$

both the species balance conditions and the subnetwork balance conditions are satisfied. Still, V_2^N does not have a non-zero finite limit, in case we have $\kappa_1 \neq \kappa_2$ and $\gamma > -\beta_1$.

Now, we would like to obtain simpler conditions equivalent to the species balance conditions and the subnetwork balance conditions. First, define an *irreducible subnetwork* as a set of directed graphs in which any node can be reached from any other node. A *trivial irreducible subnetwork* means a subnetwork consisting of a single chemical species. Therefore, species balance conditions for each chemical species are equal to subnetwork balance conditions for trivial irreducible subnetworks.

Lemma 2.1 ensures that species and subnetwork balance equations are satisfied, if subnetwork balance conditions are satisfied for all irreducible subnetworks. For simplicity, we set

$$\rho_k = \alpha \cdot \nu_k + \beta_k,$$

and use this notation in Lemma 2.1.

Lemma 2.1. *Subnetwork balance equations are satisfied for each subnetwork in the system if and only if subnetwork balance equations are satisfied for each irreducible subnetwork. In other words,*

$$\max_{k\in\Gamma^+_{G_0}} \rho_k = \max_{k\in\Gamma^-_{G_0}} \rho_k, \qquad \textit{for all } G_0 \subset G \tag{2.37}$$

if and only if

$$\max_{k\in\Gamma^+_{G_1}} \rho_k = \max_{k\in\Gamma^-_{G_1}} \rho_k, \qquad \textit{for all irreducible } G_1 \subset G. \tag{2.38}$$

Proof of Lemma 2.1. If (2.37) holds, (2.38) is satisfied since the nodes involved in any irreducible subnetwork are in G. We need to prove that (2.38) implies (2.37). Suppose that (2.38) holds. Since a subnetwork with a single node is a trivial irreducible subnetwork, species balance conditions are satisfied.

Let G_2 be a subset of G in which the maximal irreducible subsets of the subnetwork are single nodes. Let $l_1 \in \Gamma^+_{G_2}$ satisfy

$$\rho_{l_1} = \max_{k \in \Gamma^+_{G_2}} \rho_k, \tag{2.39}$$

and let i_1 be any chemical species in G_2 produced by the l_1th chemical reaction. Then $l_1 \in \Gamma^+_{i_1}$ and using (2.39) we have

$$\max_{k \in \Gamma^+_{G_2}} \rho_k = \rho_{l_1} \leq \max_{k \in \Gamma^+_{i_1}} \rho_k. \tag{2.40}$$

If $\max_{k \in \Gamma^-_{i_1}} \rho_k = \max_{k \in \Gamma^-_{G_2}} \rho_k$, then using the species balance condition for the i_1th chemical species and (2.40), we obtain

$$\begin{aligned} \max_{k \in \Gamma^+_{G_2}} \rho_k &= \rho_{l_1} \leq \max_{k \in \Gamma^+_{i_1}} \rho_k \\ &= \max_{k \in \Gamma^-_{i_1}} \rho_k = \max_{k \in \Gamma^-_{G_2}} \rho_k \end{aligned} \tag{2.41}$$

and (2.41) gives

$$\max_{k \in \Gamma^+_{G_2}} \rho_k \leq \max_{k \in \Gamma^-_{G_2}} \rho_k. \tag{2.42}$$

If not, we recursively select l_j for $j = 2, \cdots, q$ in $\Gamma^-_{i_{j-1}}$ with $\rho_{l_j} = \max_{k \in \Gamma^-_{i_{j-1}}} \rho_k$

and set i_j for $j = 2, \cdots, q-1$ satisfying $i_j \in G_2$ and $l_j \in \Gamma^+_{i_j}$. Then we have

$$\max_{k\in\Gamma^-_{i_{j-1}}} \rho_k = \rho_{l_j} \leq \max_{k\in\Gamma^+_{i_j}} \rho_k. \tag{2.43}$$

We repeat selecting l_j and i_j until we find $l_q \in \Gamma^-_{i_{q-1}}$ satisfying

$$\max_{k\in\Gamma^-_{i_{n-1}}} \rho_k = \rho_{l_q} = \max_{k\in\Gamma^-_{G_2}} \rho_k. \tag{2.44}$$

Since G_2 has a finite number of nodes for chemical species and since maximal irreducible subsets of a subnetwork involved in G_2 are single nodes, there is no possibility that the same node is selected repeatedly as i_j and thus, q is finite. Then $\{l_j\}$ is a sequence of reactions with monotone increasing rates satisfying

$$\begin{aligned} \max_{k\in\Gamma^+_{G_2}} \rho_k &= \rho_{l_1} \leq \max_{k\in\Gamma^+_{i_1}} \rho_k = \max_{k\in\Gamma^-_{i_1}} \rho_k \\ &= \rho_{l_2} \leq \cdots \\ &= \rho_{l_q} = \max_{k\in\Gamma^-_{G_2}} \rho_k. \end{aligned} \tag{2.45}$$

Using (2.45), we get

$$\max_{k\in\Gamma^+_{G_2}} \rho_k \leq \max_{k\in\Gamma^-_{G_2}} \rho_k. \tag{2.46}$$

Using similar procedure, we also get

$$\max_{k\in\Gamma^-_{G_2}} \rho_k \leq \max_{k\in\Gamma^+_{G_2}} \rho_k. \tag{2.47}$$

By (2.46) and (2.47), we prove

$$\max_{k \in \Gamma^+_{G_2}} \rho_k = \max_{k \in \Gamma^-_{G_2}} \rho_k$$

where maximal irreducible subsets of a subnetwork involved in G_2 are single nodes.

Now, suppose that there exists a maximal irreducible subset of a subnetwork involved in G_2 which is not a single node. In this case, a subnetwork involving nodes in G_2 can be written as the unions of its maximal irreducible subspaces. We can treat each maximal irreducible subnetwork as a single nodes and (2.38) gives maximal irreducible subnetwork balance equations. Then we can apply the previous procedure given in the proof of subnetwork balance equations for any subnetwork containing no nontrivial irreducible subnetwork. □

2.2.3 α's depending of γ

Scaling exponents for the ith chemical species, α_i, may depend on the time change scaling exponent γ, since the numbers of molecules of each species evolve as time passes and thus α_i could be different for different time scales. In each time scale, we can define a different scaling exponent satisfying species balance conditions and subnetwork balance conditions. Actually, the restriction on the time change scaling exponent due to some of the unbalanced species and subnetwork balance equations indicates that we need to select a different set of scaling exponents satisfying species and subnetwork balance conditions. We will see α_i depending of γ in a heat shock response model in Section 4.1.1. Unlike α_i, we assume that β_k are independent of γ.

Chapter 3

Asymptotic methods in multiscale approximations

3.1 Law of large numbers

Applying the time change by replacing t with $N^\gamma t$, the normalized system becomes

$$V_i^N(t) \;=\; V_i^N(0) + \sum_k N^{-\alpha_i} Y_k\Big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k}\lambda_k(V^N(s))\,ds\Big)(\nu'_{ik} - \nu_{ik})$$

where $V_i^N(t) = N^{-\alpha_i}X_i(N^\gamma t)$. The law of large numbers for Poisson processes says, for each $u_0 > 0$,

$$\lim_{N\to\infty}\sup_{u\le u_0}\left|\frac{Y_k(Nu)}{N} - u\right| \;=\; 0 \quad \text{a.s.}$$

If $\alpha_i \neq 0$ and the time change exponent, γ, satisfies

$$\alpha_i \;=\; \max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\gamma + \alpha\cdot\nu_k + \beta_k), \tag{3.1}$$

we can apply the law of large numbers for Poisson processes to get the limiting process for the normalized number of molecules of the ith species provided that $\int_0^t \lambda_k(V^N(s))\,ds = O(1)$. Each counting process describing the number of times each chemical reaction occurs satisfying (3.1) is approximated by its intensity function. If we prove the intensity function of the counting process is $O(1)$, a non-zero limit for the counting process would be obtained when two scaling exponents inside and outside of the counting process have the same value. A natural time scale for V_i^N is a minimum of γ which would prevent all reactopm terms blowing up. Then each V_i^N satisfies

$$\gamma \;=\; \min_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha_i - \alpha\cdot\nu_k - \beta_k) = \alpha_i - \max_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha\cdot\nu_k + \beta_k).$$

Then the number of natural time scales of the processes in the system can be determined by

$$M \;\equiv\; \Big|\{\min_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha_i - \alpha\cdot\nu_k - \beta_k), i = 1, 2, \cdots, n\}\Big| \tag{3.2}$$

where n represents the number of chemical species in the system and where $|\cdot|$ is the number of elements in a set. However, the normalized numbers of molecules of some chemical species possibly do not satisfy the natural time scale. For example, we will see $V_2^{N,2}$ and $V_3^{N,2}$ have the time scale of $O(N^2)$, even though $\alpha_i - \max_{k\in\Gamma_i^+\bigcup\Gamma_i^-}(\alpha\cdot\nu_k+\beta_k) = 0$ for $i = 2, 3$ in the heat shock response model in Section 4.1.2.

Define a set of reactions having the maximal order of magnitude of reaction rates of production for each species

$$\Gamma_{i,0}^+ \equiv \{k' : \max_{k\in\Gamma_i^+}(\alpha\cdot\nu_k + \beta_k) = \alpha\cdot\nu_{k'} + \beta_{k'},\ k' \in \Gamma_i^+\} \tag{3.3}$$

and define a set of reactions having the maximal order of magnitude of reaction rates of consumption for each species

$$\Gamma_{i,0}^{-} \equiv \{k' : \max_{k\in\Gamma_i^-}(\alpha \cdot \nu_k + \beta_k) = \alpha \cdot \nu_{k'} + \beta_{k'},\ k' \in \Gamma_i^-\}. \tag{3.4}$$

Fix γ. Then γ would be one of the values in M defined in (3.2), since we are mostly interested in the evolution of the processes in different natural time scales.

In the subsystem for times of order N^γ, define index sets regarding processes with slow, intermediate, and fast time scales.

$$S \equiv \{i : \alpha_i > \max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\gamma + \alpha \cdot \nu_k + \beta_k)\} \tag{3.5}$$

$$I \equiv \{i : \alpha_i = \max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\gamma + \alpha \cdot \nu_k + \beta_k)\} \tag{3.6}$$

$$F \equiv \{i : \alpha_i < \max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\gamma + \alpha \cdot \nu_k + \beta_k)\}. \tag{3.7}$$

S gives indices for chemical species with time scale slower than $O(N^\gamma)$, I represents indices for chemical species with time scale equal to $O(N^\gamma)$, and F gives indices for chemical species with time scale faster than $O(N^\gamma)$. We split V^N and define collections of processes depending on time scales. Let

$$V^N|_S = \{V_i^N\}_{i\in S} \tag{3.8}$$

$$V^N|_I = \{V_i^N\}_{i\in I} \tag{3.9}$$

$$V^N|_F = \{V_i^N\}_{i\in F} \tag{3.10}$$

To obtain a limit of the system, we first need the stochastic boundedness of the intensity functions of the counting processes. The limiting behavior of the evolution of processes with time scale slower than $O(N^{\gamma})$ acts as constant and satisfy

$$\lim_{N\to\infty}\sup_{t\le T}\left|V^N|_S(t)-V|_S(0)\right| \;=\; 0, \qquad i\in S. \tag{3.11}$$

For $i \in F$, the behavior of the evolution of processes with time scale faster than $O(N^{\gamma})$ is averaged out and expressed in terms of the evolution of intermediate processes and slow processes. Let

$$\Gamma^{V^N|_F}\left(C\times[0,t)\right) \;=\; \int_0^t 1_C(V^N|_F(s))\,ds$$

and assume that $\left(V^N|_I, V^N|_S, \Gamma^{V^N|_F}\right) \Rightarrow \left(V|_I, V|_S, \Gamma^{V|_F}\right)$. Then the fast processes give the limiting equations

$$\sum_{k\in\Gamma^+_{i,0}\cup\Gamma^-_{i,0}} \int_{E^{V|_F}\times[0,t]} \lambda_k\big(z, V|_I(s), V|_S(s)\big)(\nu'_{ik}-\nu_{ik})\,\mu_s(dz)\,ds \;=\; 0. \qquad i\in F$$

where μ_s satisfies

$$\Gamma^{V|_F}\left(C\times[0,t)\right) \;=\; \int_{E^{V|_F}\times[0,t]} 1_C(V|_F(s))\mu_s(dz)\,ds$$

Then applying the law of large numbers for Poisson processes, the system of intermediate processes have a limit satisfying

$$\lim_{N\to\infty}\sup_{t\le T}\left|V^N|_I(t)-V|_I(t)\right| \;=\; 0$$

where

$$V_i(t) = V_i(0) + \sum_{\substack{k\in\Gamma^+_{i,0}\bigcup\Gamma^-_{i,0} \\ i\in I,\ \alpha_i\neq 0}} \int_{E^{V|_F}\times[0,t]} \lambda_k\big(z, V|_I(s), V|_S(s)\big)(\nu'_{ik} - \nu_{ik})\,\mu_s(dz)\,ds$$

In case $\alpha_i = 0$, we cannot apply the law of large numbers for Poisson processes and the limit is

$$V_i(t) = V_i(0) + \sum_{\substack{k\in\Gamma^+_{i,0}\bigcup\Gamma^-_{i,0} \\ i\in I,\ \alpha_i = 0}} Y_k\Big(\int_{E^{V|_F}\times[0,t]} \lambda_k\big(z, V|_I(s), V|_S(s)\big)\,\mu_s(dz)\,ds\Big)(\nu'_{ik} - \nu_{ik})$$

3.2 Averaging

In [16], quasi-steady-state approximation is used in deterministic modeling of chemical reaction networks by assuming that the fast processes have their equilibrium values instantaneously and the slow variables perform the slow dynamics in the slow subsystem [16]. Then the stationary points form an exponentially attracting manifold with conditions that all eigenvalues of the system of ODEs have all negative real parts [16]. On the stationary manifold of the system, slow limiting processes are obtained, and using quasi-steady-state approximation, fast processes approaching the continuum of the stationary points are approximated by projecting their trajectory vector on the invariant manifold [16]. Therefore, dynamics of the slow processes on the invariant surface dominate the slow subsystem with approximated fast dynamics onto the invariant surface [16].

Consider the normalized system V^N parameterized by N. Following (3.2), suppose that the system has M natural time scales. Arrange the natural time scale exponents in monotone decreasing orders

$$\gamma_1 > \gamma_2 > \cdots > \gamma_M. \tag{3.12}$$

Then we partition V^N into $\left(V^{N,\gamma_1}, V^{N,\gamma_2}, \cdots, V^{N,\gamma_M}\right)$ where each V^{N,γ_j} represents a collection of components of V^N in time scale $O(N^{\gamma_j})$ and V^{N,γ_j} consists of at least one normalized number of molecules of chemical species. We also define exponents $p_1, \cdots, p_M$ in monotone decreasing orders satisfying

$$p_1 > p_2 > \cdots > p_M \tag{3.13}$$

and

$$p_j \equiv \max_{V_i \in V^{N,\gamma_j}} \Big(\max_{k \in \Gamma_{i,0}^+ \bigcup \Gamma_{i,0}^-} (\alpha \cdot \nu_k + \beta_k) - \alpha_i \Big). \tag{3.14}$$

Actually, for any $V_i \in V^{N,\gamma_j}$, $p_j = \max_{k \in \Gamma_{i,0}^+ \bigcup \Gamma_{i,0}^-} (\alpha \cdot \nu_k + \beta_k) - \alpha_i$, since V^{N,γ_j} have the same natural time scale $O(N^{\gamma_j})$.

The generator of the system can be approximated by partial pieces of the generator depending on the order of magnitude of the scaling exponents in the reaction rates. Let v^i be a variable for V^{N,γ_i}, which is a collection of the components of V^N in time scale $O(N^{\gamma_i})$. Define $\mathbb{C}_s^{1,N}$ is generator having all reactions of the largest order of magnitude in the reaction rate. Then

$$N^{-\gamma-p_1}\left(\mathbb{B}_s^N g(v^1, v^2, \cdots, v^M) - \mathbb{C}_s^{N,1} g(v^1, v^2, \cdots, v^M)\right) \rightarrow 0. \tag{3.15}$$

Using $\mathbb{B}_s^N$, a martingale is defined as

$$
\begin{aligned}
M_g^N(t) &\equiv g\big(V^{N,\gamma_1}(t),\cdots,V^{N,\gamma_M}(t)\big)-g\big(V^{N,\gamma_1}(0),\cdots,V^{N,\gamma_M}(0)\big)\\
&\quad-\int_0^t \mathbb{B}_s^N g\big(V^{N,\gamma_1}(s),\cdots,V^{N,\gamma_M}(s)\big)\,ds\\
&= g\big(V^{N,\gamma_1}(t),\cdots,V^{N,\gamma_M}(t)\big)-g\big(V^{N,\gamma_1}(0),\cdots,V^{N,\gamma_M}(0)\big)\\
&\quad-\int_0^t \big(\mathbb{B}_s^N g\big(V^{N,\gamma_1}(s),\cdots,V^{N,\gamma_M}(s)\big)-\mathbb{C}_s^{N,1} g\big(V^{N,\gamma_1}(s),\cdots,V^{N,\gamma_M}(s)\big)\big)\,ds\\
&\quad-\int_0^t \mathbb{C}_s^{N,1} g\big(V^{N,\gamma_1}(s),\cdots,V^{N,\gamma_M}(s)\big)\,ds
\end{aligned}
\tag{3.16}
$$

Define an occupation measure of a set of the fastest species V^{N,γ_1} as

$$
\Gamma^{V^{N,\gamma_1}}\big(C\times[0,t]\big) = \int_0^t \mathbf{1}_C\big(V^{N,\gamma_1}(s)\big)\,ds
$$

Replace the integrals involving V^{N,γ_1} by the integrals against $\Gamma^{V^{N,\gamma_1}}$. Then the martingale is written as

$$
\begin{aligned}
M_g^N(t) &= g\big(V^{N,\gamma_1}(t),\cdots,V^{N,\gamma_M}(t)\big)-g\big(V^{N,\gamma_1}(0),\cdots,V^{N,\gamma_M}(0)\big)\\
&\quad-\int_{E^{V^{N,\gamma_1}}\times[0,t]}\Big(\mathbb{B}_s^N g\big(v^1,V^{N,\gamma_2}(s),\cdots,V^{N,\gamma_M}(s)\big)\\
&\qquad-\mathbb{C}_s^{N,1} g\big(v^1,V^{N,\gamma_2}(s),\cdots,V^{N,\gamma_M}(s)\big)\Big)\,\Gamma^{V^{N,\gamma_1}}\big(dv^1\times ds\big)\\
&\quad-\int_{E^{V^{N,\gamma_1}}\times[0,t]}\mathbb{C}_s^{N,1} g\big(v^1,V^{N,\gamma_2}(s),\cdots,V^{N,\gamma_M}(s)\big)\,\Gamma^{V^{N,\gamma_1}}\big(dv^1\times ds\big)
\end{aligned}
\tag{3.17}
$$

We assume that $\big(V^{N,\gamma_2},\cdots,V^{N,\gamma_M},\Gamma^{V^{N,\gamma_1}}\big)\Rightarrow\big(V^{\gamma_2 2},\cdots,V^{\gamma_M},\Gamma^{V^{\gamma_1}}\big)$ as $N\to\infty$. Dividing (3.17) by $N^{\gamma+p_1}$ and using (3.15), we obtain

$$
\int_{E^{V^{\gamma_1}}\times[0,t]}\mathbb{C}^{\infty,1}_{(V^{\gamma_2},\cdots,V^{\gamma_M})} g\big(v^1,V^{\gamma_2}(s),\cdots,V^{\gamma_M}(s)\big)\,\Gamma^{V^{\gamma_1}}\big(dv^1\times ds\big)
\tag{3.18}
$$

$$
\begin{aligned}
&= \int_{E^{V^{\gamma_1}} \times [0,t]} \mathbb{C}^{\infty,1}_{(V^{\gamma_2},\cdots,V^{\gamma_M})} g\big(v^1, V^{\gamma_2}(s), \cdots, V^{\gamma_M}(s)\big)\, \eta_s(dv^1)ds \\
&= 0
\end{aligned}
$$

where $\mathbb{C}^{\infty,1}_{(V^{\gamma_2},\cdots,V^{\gamma_M})}(\cdot)$ is a limit of $N^{-\gamma-p_1}\mathbb{C}^{1,N}_s(\cdot)$ as $N \to \infty$ satisfying

$$
\lim_{N\to\infty} \left(N^{-\gamma-p_1}\mathbb{C}^{N,1}_s g(v^1, v^2, \cdots, v^M) - \mathbb{C}^{\infty,1}_{(V^2,\cdots,V^M)} g(v^1, v^2, \cdots, v^M)\right) = 0 \quad (3.19)
$$

Suppose that for each $(v^2, \cdots, v^M)$, the solution $\mu_{(v^2,\cdots,v^M)} \in \mathcal{P}(E^{V^{\gamma_1}})$ of

$$
\int_{E^{V^{\gamma_1}}} \mathbb{C}^{\infty,1}_{(V^{\gamma_2},\cdots,V^{\gamma_M})} g\big(v_1, V^{\gamma_2}(s), \cdots, V^{\gamma_M}(s)\big)\, \eta^1_s(dv^1)ds = 0 \quad (3.20)
$$

is unique where $g \in \mathcal{D}$. Then

$$
\eta^1_s(dv^1) = \mu^1_{(V^{\gamma_2}(s),\cdots,V^{\gamma_M}(s))}(dv^1) \quad (3.21)
$$

(3.21) can be interpreted as the averaged behavior of processes in the fastest time scale $O(N^{\gamma_1})$ can be expressed by behavior of processes in time scales slower than $O(N^{\gamma_1})$.

Similarly, we can get averaged behavior of processes in the time scale $O(N^{\gamma_j})$, $j = 2, \cdots, M$, using the appropriate generator. Define $\mathbb{C}^{j,N}_s$ to be the generator having all reactions of the largest order of magnitude involved in V^{N,γ_j}. Then

$$
N^{-\gamma-p_j}\big(\mathbb{B}^N_s g(v^j, \cdots, v^M) - \mathbb{C}^{N,j}_s g(v^j, \cdots, v^M)\big) \to 0. \quad (3.22)
$$

Using $\mathbb{B}^N_s$, a martingale is defined as

$$
M^N_g(t) \equiv g\big(V^{N,\gamma_j}(t), \cdots, V^{N,\gamma_M}(t)\big) - g\big(V^{N,\gamma_j}(0), \cdots, V^{N,\gamma_M}(0)\big)
$$

$$
\begin{aligned}
& - \int_0^t \mathbb{B}_s^N g\big(V^{N,\gamma_j}(s), \cdots, V^{N,\gamma_M}(s)\big)\, ds \\
= \; & g\big(V^{N,\gamma_j}(t), \cdots, V^{N,\gamma_M}(t)\big) - g\big(V^{N,\gamma_j}(0), \cdots, V^{N,\gamma_M}(0)\big) \\
& - \int_0^t \big(\mathbb{B}_s^N g\big(V^{N,\gamma_j}(s), \cdots, V^{N,\gamma_M}(s)\big) - \mathbb{C}_s^{N,j} g\big(V^{N,\gamma_j}(s), \cdots, V^{N,\gamma_M}(s)\big)\big)\, ds \\
& - \int_0^t \mathbb{C}_s^{N,2} g\big(V^{N,\gamma_j}(s), \cdots, V^{N,\gamma_M}(s)\big)\, ds \qquad (3.23)
\end{aligned}
$$

Define an occupation measure of a set of the fastest species V^{N,γ_j} as

$$
\Gamma^{V^{N,\gamma_j}}\big(C \times [0,t]\big) \;=\; \int_0^t \mathbf{1}_C(V^{N,\gamma_j}(s))\, ds \qquad (3.24)
$$

Replace the integrals involving V^{N,γ_j} by the integrals against $\Gamma^{V^{N,\gamma_j}}$. Then the martingale is written as

$$
\begin{aligned}
M_g^N(t) \;=\; & g\big(V^{N,\gamma_j}(t), \cdots, V^{N,\gamma_M}(t)\big) - g\big(V^{N,\gamma_j}(0), \cdots, V^{N,\gamma_M}(0)\big) \\
& - \int_{E^{V^{N,\gamma_j}} \times [0,t]} \Big(\mathbb{B}_s^N g\big(v^j, V^{N,\gamma_{j+1}}(s), \cdots, V^{N,\gamma_M}(s)\big) \\
& \qquad - \mathbb{C}_s^{N,j} g\big(v^j, V^{N,\gamma_{j+1}}(s), \cdots, V^{N,\gamma_M}(s)\big)\Big)\, \Gamma^{V^{N,\gamma_j}}\big(dv^j \times ds\big) \\
& - \int_{E^{V^{N,\gamma_j}} \times [0,t]} \mathbb{C}_s^{N,j} g\big(v^j, V^{N,\gamma_{j+1}}(s), \cdots, V^{N,\gamma_M}(s)\big)\, \Gamma^{V^{N,\gamma_j}}\big(dv^j \times ds\big) \qquad (3.25)
\end{aligned}
$$

We assume that $\big(V^{N,\gamma_{j+1}}, \cdots, V^{N,\gamma_M}, \Gamma^{V^{N,\gamma_j}}\big) \Rightarrow \big(V^{\gamma_{j+1}}, \cdots, V^{\gamma_M}, \Gamma^{V^{\gamma_j}}\big)$ as $N \to \infty$. Dividing (3.25) by $N^{\gamma + p_j}$ and using (3.22), we obtain

$$
\begin{aligned}
& \int_{E^{V^{\gamma_j}} \times [0,t]} \mathbb{C}^{\infty,j}_{(V^{\gamma_j}, \cdots, V^{\gamma_M})} g\big(v^j, V^{\gamma_{j+1}}(s), \cdots, V^{\gamma_M}(s)\big)\, \Gamma^{V^{\gamma_j}}\big(dv^j \times ds\big) \qquad (3.26) \\
= \; & \int_{E^{V^{\gamma_j}} \times [0,t]} \mathbb{C}^{\infty,j}_{(V^{\gamma_j}, \cdots, V^{\gamma_M})} g\big(v^j, V^{\gamma_{j+1}}(s), \cdots, V^{\gamma_M}(s)\big)\, \eta_s(dv^j) ds \\
= \; & 0
\end{aligned}
$$

where $\mathbb{C}^{\infty,j}_{(V^{\gamma_{j+1}},\cdots,V^{\gamma_M})}(\cdot)$ is a limit of $N^{-\gamma-p_j}\mathbb{C}^{j,N}_s(\cdot)$ as $N \to \infty$ satisfying

$$\lim_{N\to\infty}\Big(N^{-\gamma-p_j}\mathbb{C}^{N,j}_s g\big(v^j,\cdots,v^M\big) - \mathbb{C}^{\infty,j}_{(V^{j+1},\cdots,V^M)}g\big(v^j,\cdots,v^M\big)\Big) \;=\; 0 \qquad (3.27)$$

Note that $\mathbb{C}^{N,j}_s g\big(v^j,\cdots,v^M\big)$ possibly includes $V^{N,\gamma_1},\cdots,V^{N,\gamma_{j-1}}$ terms. Then terms related to $V^{N,\gamma_1},\cdots,V^{N,\gamma_{j-1}}$ are averaged out by terms related to $\big(V^{N,\gamma_j},\cdots,V^{N,\gamma_M}\big)$ using the generator $\mathbb{C}^{N,1}_s,\cdots,\mathbb{C}^{N,j-1}_s$. Therefore, as $N\to\infty$, $\mathbb{C}^{\infty,j}_{(V^{j+1},\cdots,V^M)}g\big(v^j,\cdots,v^M\big)$ only depends on $\mathbb{C}_{(V^{j+1},\cdots,V^M)}$.

Suppose that for each $(v^{j+1},\cdots,v^M)$, the solution $\mu_{(v^{j+1},\cdots,v^M)} \in \mathcal{P}(E^{V^{\gamma_j}})$ of

$$\int_{E^{V^{\gamma_j}}} \mathbb{C}^{\infty,j}_{(V^{\gamma_{j+1}},\cdots,V^{\gamma_M})}g\big(v_j, V^{\gamma_{j+1}}(s),\cdots,V^{\gamma_M}(s)\big)\,\eta^j_s(dv^j)ds \;=\; 0 \qquad (3.28)$$

is unique where $g \in \mathcal{D}$. Then

$$\eta^j_s(dv^j) \;=\; \mu^j_{(V^{\gamma_{j+1}}(s),\cdots,V^{\gamma_M}(s))}(dv^j) \qquad (3.29)$$

(3.29) can be interpreted as that averaged behavior of processes in the time scale $O(N^{\gamma_j})$ can be expressed by behavior of processes in time scales slower than $O(N^{\gamma_j})$.

Chapter 4

Heat shock response model

4.1 Analysis

4.1.1 Introduction of a heat shock response model

Borrowing a model of the heat shock response in *Escherichia coli* developed by Srivastava, Peterson, and Bentley [14], we apply multiple scaling methods as described in Chapter 2 and 3. Following [14], σ^{32} is a regulator against heat shock in *Escherichia coli*, and E is an holoenzyme stimulating synthesis of stress proteins FtsH, J, and GroEL [14].

There are three forms of σ^{32}: σ^{32} protein, Eσ^{32} (a complex of σ^{32} with holoenzyme), and J-σ^{32} (a complex of σ^{32} with the heat shock proteins). Holoenzyme E binds to σ^{32} and produces heat shock proteins which in turn reduce post heat shock stress rapidly [14]. Under normal condition, most σ^{32}'s are in a form of J-σ^{32} which acts as a reservoir of σ^{32} [14]. Then Eσ^{32} increases in a very small amount under heat shock, and only a very small amount of Eσ^{32} gives a huge effect to reduce post stress of heat shock [14]. All deterministic rate constants are given in [14].

Moreover, initial values for simulation (except for initial values of recombinant protein and for J-recombinant protein) in Table 9 are given by Srivastava, which are the same used in [14]. Nine species are involved in the heat shock response model and we will use the following notation of chemical species in the stochastic model.

Table 1: Species in a heat shock response model

ith	Chemical species
A_1	σ^{32} mRNA
A_2	σ^{32} protein
A_3	$E\sigma^{32}$
A_4	FtsH
A_5	GroEL
A_6	J (DnaJ+DnaK+GrpE)
A_7	J-σ^{32}
A_8	Recombinant protein
A_9	J-Recombinant protein

As mentioned in the previous paragraph, σ^{32} are in three forms: A_2, A_3, and A_7 in Table 1.

Chemical reaction networks in the heat shock response model are made up of eighteen reactions. As seen in Section 1.3, binary reaction rate constants can be redefined, which vary inversely to the volume. By dividing the binary reaction rate constants given in [14] by the cell volume $\times$ Avogadro's number ($= 9.033 \times 10^8$), we get newly defined binary reaction rate constants for the stochastic model. Arranging reactions in decreasing order of reaction rate constants, we express reactions in terms of the notation defined in Table 1.

Table 2: Reactions in a heat shock response model

	Reaction	Transition	Stoch constant
R_1	gene $\longrightarrow A_8$	Recombinant protein synthesis	4.00×10^0
R_2	$A_2 \longrightarrow A_3$	Holoenzyme association	7.00×10^{-1}
R_3	$A_3 \longrightarrow A_2$	Holoenzyme disassociation	1.30×10^{-1}
R_4	$\emptyset \xrightarrow{A_1} A_2$	σ^{32} translation	7.00×10^{-3}
R_5^{*1}	gene $+ A_3 \longrightarrow A_2 + A_5$	GroEL synthesis	6.30×10^{-3}
R_6^*	gene $+ A_3 \longrightarrow A_2 + A_4$	FtsH synthesis	4.88×10^{-3}
R_7^*	gene $+ A_3 \longrightarrow A_2 + A_6$	J-production	4.88×10^{-3}
R_8	$A_7 \longrightarrow A_2 + A_6$	σ^{32}-J-disassociation	4.40×10^{-4}
R_9^*	$A_2 + A_6 \longrightarrow A_7$	σ^{32}-J-association	3.62×10^{-4}
R_{10}^*	$A_6 + A_8 \longrightarrow A_9$	Recombinant protein-J association	3.62×10^{-4}
R_{11}	$A_8 \longrightarrow \emptyset$	Recombinant protein degradation	9.99×10^{-5}
R_{12}	$A_9 \longrightarrow A_6 + A_8$	Recombinant protein-J disassociation	4.40×10^{-5}
R_{13}	gene $\longrightarrow A_1$	σ^{32} transcription	1.40×10^{-5}
R_{14}	$A_1 \longrightarrow \emptyset$	σ^{32} mRNA decay	1.40×10^{-6}
R_{15}^*	$A_7 \xrightarrow{A_4} A_6$	σ^{32} degradation	1.42×10^{-6}
R_{16}	$A_5 \longrightarrow \emptyset$	GroEL degradation	1.80×10^{-8}
R_{17}	$A_6 \longrightarrow \emptyset$	J-disassociation	6.40×10^{-10}
R_{18}	$A_4 \longrightarrow \emptyset$	FtsH degradation	7.40×10^{-11}

Reactions R_5, R_6, R_7, R_9 R_{10}, and R_{15} are binary reactions, which are either

[1]Binary reactions are marked by *. Otherwise, reactions are unary.

$A+B \to C$ or $A+B \to C+D$. All others are unary reaction such as $A \to B$ or $A \to B+C$. In unary reactions, B could be $\emptyset$. In Table 2, $\emptyset$ represents chemical species which is out of our interest and which exists in great amount in the system.

Using the continuous time Markov jump process, we construct a stochastic model. After scaling the species numbers by N^{α_i}, scaling the reaction rate constants by N^{β_k}, and applying a time change by N^{γ}, we have the normalized system of chemical reaction in the heat shock response model.

$$
\begin{aligned}
V_1^N(t) &= V_1^N(0) + N^{-\alpha_1} Y_{13}\Big(\int_0^t \kappa_{13} N^{\gamma+\beta_{13}}\, ds\Big) - N^{-\alpha_1} Y_{14}\Big(\int_0^t \kappa_{14} N^{\gamma+\alpha_1+\beta_{14}} V_1^N(s)\, ds\Big) \\
V_2^N(t) &= V_2^N(0) + N^{-\alpha_2} Y_3\Big(\int_0^t \kappa_3 N^{\gamma+\alpha_3+\beta_3} V_3^N(s)\, ds\Big) + N^{-\alpha_2} Y_4\Big(\int_0^t \kappa_4 N^{\gamma+\alpha_1+\beta_4} V_1^N(s)\, ds\Big) \\
&\quad + N^{-\alpha_2} Y_5\Big(\int_0^t \kappa_5 N^{\gamma+\alpha_3+\beta_5} V_3^N(s)\, ds\Big) + N^{-\alpha_2} Y_6\Big(\int_0^t \kappa_6 N^{\gamma+\alpha_3+\beta_6} V_3^N(s)\, ds\Big) \\
&\quad + N^{-\alpha_2} Y_7\Big(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\, ds\Big) + N^{-\alpha_2} Y_8\Big(\int_0^t \kappa_8 N^{\gamma+\alpha_7+\beta_8} V_7^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_2} Y_2\Big(\int_0^t \kappa_2 N^{\gamma+\alpha_2+\beta_2} V_2^N(s)\, ds\Big) - N^{-\alpha_2} Y_9\Big(\int_0^t \kappa_9 N^{\gamma+\alpha_2+\alpha_6+\beta_9} V_2^N(s) V_6^N(s)\, ds\Big) \\
V_3^N(t) &= V_3^N(0) + N^{-\alpha_3} Y_2\Big(\int_0^t \kappa_2 N^{\gamma+\alpha_2+\beta_2} V_2^N(s)\, ds\Big) - N^{-\alpha_3} Y_3\Big(\int_0^t \kappa_3 N^{\gamma+\alpha_3+\beta_3} V_3^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_3} Y_5\Big(\int_0^t \kappa_5 N^{\gamma+\alpha_3+\beta_5} V_3^N(s)\, ds\Big) - N^{-\alpha_3} Y_6\Big(\int_0^t \kappa_6 N^{\gamma+\alpha_3+\beta_6} V_3^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_3} Y_7\Big(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\, ds\Big) \\
V_4^N(t) &= V_4^N(0) + N^{-\alpha_4} Y_6\Big(\int_0^t \kappa_6 N^{\gamma+\alpha_3+\beta_6} V_3^N(s)\, ds\Big) - N^{-\alpha_4} Y_{18}\Big(\int_0^t \kappa_{18} N^{\gamma+\alpha_4+\beta_{18}} V_4^N(s)\, ds\Big) \\
V_5^N(t) &= V_5^N(0) + N^{-\alpha_5} Y_5\Big(\int_0^t \kappa_5 N^{\gamma+\alpha_3+\beta_5} V_3^N(s)\, ds\Big) - N^{-\alpha_5} Y_{16}\Big(\int_0^t \kappa_{16} N^{\gamma+\alpha_5+\beta_{16}} V_5^N(s)\, ds\Big) \\
V_6^N(t) &= V_6^N(0) + N^{-\alpha_6} Y_7\Big(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\, ds\Big) + N^{-\alpha_6} Y_8\Big(\int_0^t \kappa_8 N^{\gamma+\alpha_7+\beta_8} V_7^N(s)\, ds\Big) \\
&\quad + N^{-\alpha_6} Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma+\alpha_9+\beta_{12}} V_9^N(s)\, ds\Big) + N^{-\alpha_6} Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma+\alpha_4+\alpha_7+\beta_{15}} V_4^N(s) V_7^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_6} Y_9\Big(\int_0^t \kappa_9 N^{\gamma+\alpha_2+\alpha_6+\beta_9} V_2^N(s) V_6^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_6} Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma+\alpha_6+\alpha_8+\beta_{10}} V_6^N(s) V_8^N(s)\, ds\Big) - N^{-\alpha_6} Y_{17}\Big(\int_0^t \kappa_{17} N^{\gamma+\alpha_6+\beta_{17}} V_6^N(s)\, ds\Big)
\end{aligned}
$$

$$
\begin{aligned}
V_7^N(t) &= V_7^N(0) + N^{-\alpha_7} Y_9\Big(\int_0^t \kappa_9 N^{\gamma+\alpha_2+\alpha_6+\beta_9} V_2^N(s) V_6^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_7} Y_8\Big(\int_0^t \kappa_8 N^{\gamma+\alpha_7+\beta_8} V_7^N(s)\, ds\Big) - N^{-\alpha_7} Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma+\alpha_4+\alpha_7+\beta_{15}} V_4^N(s) V_7^N(s)\, ds\Big) \\
V_8^N(t) &= V_8^N(0) + N^{-\alpha_8} Y_1\Big(\int_0^t \kappa_1 N^{\gamma+\beta_1}\, ds\Big) + N^{-\alpha_8} Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma+\alpha_9+\beta_{12}} V_9^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_8} Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma+\alpha_6+\alpha_8+\beta_{10}} V_6^N(s) V_8^N(s)\, ds\Big) - N^{-\alpha_8} Y_{11}\Big(\int_0^t \kappa_{11} N^{\gamma+\alpha_8+\beta_{11}} V_8^N(s)\, ds\Big) \\
V_9^N(t) &= V_9^N(0) + N^{-\alpha_9} Y_{10}\Big(\int_0^t \kappa_{10} N^{\gamma+\alpha_6+\alpha_8+\beta_{10}} V_6^N(s) V_8^N(s)\, ds\Big) \\
&\quad - N^{-\alpha_9} Y_{12}\Big(\int_0^t \kappa_{12} N^{\gamma+\alpha_9+\beta_{12}} V_9^N(s)\, ds\Big)
\end{aligned}
$$

In the heat shock response model, using Lemma 2.1, we need to consider balance conditions for each irreducible subnetwork. Since each trivial irreducible subnetwork represents a subnetwork involving a single chemical species, we additionally investigate the unnormalized equations for chemical species involved in each nontrivial irreducible subnetwork.

$$
\begin{aligned}
& N^{\alpha_2} V_2^N(t) + N^{\alpha_3} V_3^N(t) + N^{\alpha_7} V_7^N(t) = N^{\alpha_2} V_2^N(0) + N^{\alpha_3} V_3^N(0) + N^{\alpha_7} V_7^N(0) \\
&\qquad + Y_4\Big(\int_0^t \kappa_4 N^{\gamma+\alpha_1+\beta_4} V_1^N(s)\, ds\Big) - Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma+\alpha_4+\alpha_7+\beta_{15}} V_4^N(s) V_7^N(s)\, ds\Big) \\
& N^{\alpha_2} V_2^N(t) + N^{\alpha_3} V_3^N(t) = N^{\alpha_2} V_2^N(0) + N^{\alpha_3} V_3^N(0) + Y_4\Big(\int_0^t \kappa_4 N^{\gamma+\alpha_1+\beta_4} V_1^N(s)\, ds\Big) \\
&\qquad + Y_8\Big(\int_0^t \kappa_8 N^{\gamma+\alpha_7+\beta_8} V_7^N(s)\, ds\Big) - Y_9\Big(\int_0^t \kappa_9 N^{\gamma+\alpha_2+\alpha_6+\beta_9} V_2^N(s) V_6^N(s)\, ds\Big) \\
& N^{\alpha_2} V_2^N(t) + N^{\alpha_7} V_7^N(t) = N^{\alpha_2} V_2^N(0) + N^{\alpha_7} V_7^N(0) + Y_3\Big(\int_0^t \kappa_3 N^{\gamma+\alpha_3+\beta_3} V_3^N(s)\, ds\Big) \\
&\qquad + Y_4\Big(\int_0^t \kappa_4 N^{\gamma+\alpha_1+\beta_4} V_1^N(s)\, ds\Big) + Y_5\Big(\int_0^t \kappa_5 N^{\gamma+\alpha_3+\beta_5} V_3^N(s)\, ds\Big) \\
&\qquad + Y_6\Big(\int_0^t \kappa_6 N^{\gamma+\alpha_3+\beta_6} V_3^N(s)\, ds\Big) + Y_7\Big(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\, ds\Big) \\
&\qquad - Y_2\Big(\int_0^t \kappa_2 N^{\gamma+\alpha_2+\beta_2} V_2^N(s)\, ds\Big) - Y_{15}\Big(\int_0^t \kappa_{15} N^{\gamma+\alpha_4+\alpha_7+\beta_{15}} V_4^N(s) V_7^N(s)\, ds\Big) \\
& N^{\alpha_6} V_6^N(t) + N^{\alpha_7} V_7^N(t) + N^{\alpha_9} V_9^N(t) = N^{\alpha_6} V_6^N(0) + N^{\alpha_7} V_7^N(0) + N^{\alpha_9} V_9^N(0)
\end{aligned}
$$

$$
\begin{aligned}
&+Y_7(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\,ds) - Y_{17}(\int_0^t \kappa_{17} N^{\gamma+\alpha_6+\beta_{17}} V_6^N(s)\,ds)\\
&N^{\alpha_6}V_6^N(t) + N^{\alpha_9}V_9^N(t) = N^{\alpha_6}V_6^N(0) + N^{\alpha_9}V_9^N(0) + Y_7(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\,ds)\\
&+Y_8(\int_0^t \kappa_8 N^{\gamma+\alpha_7+\beta_8} V_7^N(s)\,ds) + Y_{15}(\int_0^t \kappa_{15} N^{\gamma+\alpha_4+\alpha_7+\beta_{15}} V_4^N(s)V_7^N(s)\,ds)\\
&-Y_9(\int_0^t \kappa_9 N^{\gamma+\alpha_2+\alpha_6+\beta_9} V_2^N(s)V_6^N(s)\,ds) - Y_{17}(\int_0^t \kappa_{17} N^{\gamma+\alpha_6+\beta_{17}} V_6^N(s)\,ds)\\
&N^{\alpha_6}V_6^N(t) + N^{\alpha_7}V_7^N(t) = N^{\alpha_6}V_6^N(0) + N^{\alpha_7}V_7^N(0) + Y_7(\int_0^t \kappa_7 N^{\gamma+\alpha_3+\beta_7} V_3^N(s)\,ds)\\
&+Y_{12}(\int_0^t \kappa_{12} N^{\gamma+\alpha_9+\beta_{12}} V_9^N(s)\,ds) - Y_{10}(\int_0^t \kappa_{10} N^{\gamma+\alpha_6+\alpha_8+\beta_{10}} V_6^N(s)V_8^N(s)\,ds)\\
&-Y_{17}(\int_0^t \kappa_{17} N^{\gamma+\alpha_6+\beta_{17}} V_6^N(s)\,ds)\\
&N^{\alpha_8}V_8^N(t) + N^{\alpha_9}V_9^N(t) = N^{\alpha_8}V_8^N(0) + N^{\alpha_9}V_9^N(0) + Y_1(\int_0^t \kappa_1 N^{\gamma+\beta_1}\,ds)\\
&-Y_{11}(\int_0^t \kappa_{11} N^{\gamma+\alpha_8+\beta_{11}} V_8^N(s)\,ds).
\end{aligned}
$$

Following the species balance arguments in Section 2.2.1, to make the normalized number of molecules of chemical species converge to nonnegative limits as $N \to \infty$, the maximal order of magnitude of reaction rates of production of each species should be the same as the maximal order of magnitude of reaction rates of consumption of each species.

$$
\max_{k\in\Gamma_i^+}(\gamma + \alpha\cdot\nu_k + \beta_k) \quad = \quad \max_{k\in\Gamma_i^-}(\gamma + \alpha\cdot\nu_k + \beta_k)
$$

Otherwise, the scaling exponent of the number of molecules of the chemical species must be big enough to prevent the normalized species number from blowing up, that is

$$
\max_{k\in\Gamma_i^+\cup\Gamma_i^-}(\gamma + \alpha\cdot\nu_k + \beta_k) \quad \leq \quad \alpha_i.
$$

The species balance equations are given in Table 3.

Table 3: Species balance equations

Species	Species balance equations
$\{A_1\}$	$\beta_{13} = \alpha_1 + \beta_{14}$
$\{A_2\}$	$\max(\alpha_3 + \beta_3, \alpha_1 + \beta_4, \alpha_3 + \beta_5, \alpha_3 + \beta_6, \alpha_3 + \beta_7, \alpha_7 + \beta_8)$
	$= \max(\alpha_2 + \beta_2, \alpha_2 + \alpha_6 + \beta_9)$
$\{A_3\}$	$\alpha_2 + \beta_2 = \max(\alpha_3 + \beta_3, \alpha_3 + \beta_5, \alpha_3 + \beta_6, \alpha_3 + \beta_7)$
$\{A_4\}$	$\alpha_3 + \beta_6 = \alpha_4 + \beta_{18}$
$\{A_5\}$	$\alpha_3 + \beta_5 = \alpha_5 + \beta_{16}$
$\{A_6\}$	$\max(\alpha_3 + \beta_7, \alpha_7 + \beta_8, \alpha_9 + \beta_{12}, \alpha_4 + \alpha_7 + \beta_{15})$
	$= \max(\alpha_2 + \alpha_6 + \beta_9, \alpha_6 + \alpha_8 + \beta_{10}, \alpha_6 + \beta_{17})$
$\{A_7\}$	$\alpha_2 + \alpha_6 + \beta_9 = \max(\alpha_7 + \beta_8, \alpha_4 + \alpha_7 + \beta_{15})$
$\{A_8\}$	$\max(\beta_1, \alpha_9 + \beta_{12}) = \max(\alpha_6 + \alpha_8 + \beta_{10}, \alpha_8 + \beta_{11})$
$\{A_9\}$	$\alpha_6 + \alpha_8 + \beta_{10} = \alpha_9 + \beta_{12}$

Similarly, following the subnetwork balance conditions in Section 2.2.2 and following Lemma 2.1, the maximal order of magnitude of the collective reaction rates of production for each nontrivial irreducible subnetwork involving $G_0 \subset G$ should be the same as the maximal order of magnitude of the collective reaction rates of consumption for each nontrivial irreducible subnetwork involving $G_0 \subset G$.

$$\max_{k \in \Gamma^+_{G_0}} (\gamma + \alpha \cdot \nu_k + \beta_k) \quad = \quad \max_{k \in \Gamma^-_{G_0}} (\gamma + \alpha \cdot \nu_k + \beta_k)$$

Otherwise, the maximal scaling exponent of the numbers of molecules of chemical species involved in each nontrivial irreducible subnetwork $G_0 \subset G$ must be large enough to prevent the normalized species numbers in the subnetwork from blowing up, that is

$$\max_{k \in \Gamma^+_{G_0} \cup \Gamma^-_{G_0}} (\gamma + \alpha \cdot \nu_k + \beta_k) \leq \max_{i \in G_0} \alpha_i.$$

The equations for chemical species involved in each nontrivial irreducible subnetwork will give balance equations in Table 4.

Table 4: Subnetwork balance equations for each nontrivial irreducible subnetwork

Nodes in each subnetwork	Subnetwork balance equations
$\{A_2, A_3, A_7\}$	$\alpha_1 + \beta_4 = \alpha_4 + \alpha_7 + \beta_{15}$
$\{A_2, A_3\}$	$\max(\alpha_1 + \beta_4, \alpha_7 + \beta_8) = \alpha_2 + \alpha_6 + \beta_9$
$\{A_2, A_7\}$	$\max(\alpha_3 + \beta_3, \alpha_1 + \beta_4, \alpha_3 + \beta_5, \alpha_3 + \beta_6, \alpha_3 + \beta_7)$
	$= \max(\alpha_2 + \beta_2, \alpha_4 + \alpha_7 + \beta_{15})$
$\{A_6, A_7, A_9\}$	$\alpha_3 + \beta_7 = \alpha_6 + \beta_{17}$
$\{A_6, A_9\}$	$\max(\alpha_3 + \beta_7, \alpha_7 + \beta_8, \alpha_4 + \alpha_7 + \beta_{15})$
	$= \max(\alpha_2 + \alpha_6 + \beta_9, \alpha_6 + \beta_{17})$
$\{A_6, A_7\}$	$\max(\alpha_3 + \beta_7, \alpha_9 + \beta_{12}) = \max(\alpha_6 + \alpha_8 + \beta_{10}, \alpha_6 + \beta_{17})$
$\{A_8, A_9\}$	$\beta_1 = \alpha_8 + \beta_{11}$

Next, we want to scale the numbers of chemical species and the reaction rate constants using a common scaling parameter N_0 with different exponents α's and β's. Considering the magnitude of the initial values in Table 9, let $N_0 = 100$. As defined in the general case in Chapter 2, we investigate a parametric family of models. Among the parametric family, we are interested in the specific system when $N = N_0$. Even though N_0 is not so large due to small initial values, the general case can be applied in this example.

We would like to get α_i and β_k satisfying as many balance equations as possible in Table 3 and Table 4 and to make α_i and β_k satisfying all balance conditions (conditions including inequalities). Since balance conditions in Table 3 and Table 4 include max functions, which make equations not so simple, we first reduce choices for α_i and β_k by solving balance equations in Table 3 and Table 4 by Maple. Maple gives us a general set of solutions which are not unique. After getting a general sense of the relationship among the α_i and β_k, we select α_i and β_k satisfying the balance conditions. In case we cannot get α_i and β_j satisfying all the equations, we will have restrictions on γ concerning unbalanced equations. We select scaling exponents β_k for the reaction rate constants κ'_k to make the normalized reaction rate constants κ have the order of 1.

$$\kappa_k = \frac{\kappa'_k}{N_0^{\beta_k}} = O(1)$$

Moreover, since reaction numbers are provided by arranging reactions based on the magnitude of κ'_k in decreasing order, the assumption that the β_k are monotone decreasing is plausible. We differentiate reaction rates of chemical reactions that consume one species in the system (unary reactions) and chemical reactions that consume two species in the system (binary reactions). In other words, β_k for the binary reactions are monotone decreasing and β_k for the unary reactions are monotone decreasing; however, monotonicity conditions are not required between unary reaction rates and binary reaction rates.

Table 5 gives the stochastic reaction rate constants and the normalized stochastic reaction rate constants with scaling exponents.

Table 5: Scaling exponents of the reaction rates and normalized reaction rates

β_k	Scaling exponent	Stoch rate[2](κ'_k)	Scaled rate(κ_k)
β_1	0	4.00×10^{0}	4
β_2	0	7.00×10^{-1}	0.7
β_3	0	1.30×10^{-1}	0.13
β_4	-1	7.00×10^{-3}	0.7
β_5^{*}[3]	-1	6.30×10^{-3}	0.63
β_6^*	-1	4.88×10^{-3}	0.488
β_7^*	-1	4.88×10^{-3}	0.488
β_8	-2	4.40×10^{-4}	4.4
β_9^*	-2	3.62×10^{-4}	3.62
β_{10}^*	-2	3.62×10^{-4}	3.62
β_{11}	-2	9.99×10^{-5}	0.999
β_{12}	-2	4.40×10^{-5}	0.44
β_{13}	-2	1.40×10^{-5}	0.14
β_{14}	-2	1.40×10^{-6}	0.014

[2] It means Stochastic reaction rates.
[3] $*$ are binary reaction rate constants.

β^*_{15}	-3	1.42×10^{-6}	1.42
β_{16}	-2	1.80×10^{-8}	0.00018
β_{17}	-2	6.40×10^{-10}	0.0000064
β_{18}	-2	7.40×10^{-11}	0.00000074

From Table 5, normalized reaction rates κ_{14}, κ_{16}, κ_{17}, and κ_{18} are quite small compared to other κ_k's. However, we do not worry about those four cases, since they are involved in protein degradation which does not have a significant effect on the system.
We select α_i satisfying

$$V_i^{N,\gamma}(t) = \frac{X_i(N^\gamma t)}{N^{\alpha_i}} = O(1).$$

In case the balance equations are not satisfied, we get restrictions on γ as noted in Table 7 and Table 8. Table 6 gives our specific choice of the scaling exponents for the numbers of chemical species in this example.

The orders of magnitude of the number of species may have different values in different time scales, since the numbers of species evolve as time passes. In other words, the α's depend on the values of the time scale exponent γ. This dependence reflects the large growth in numbers of certain species. From now on, we set $V_i^{N,\gamma}$ as the normalized number of molecules of the ith species for times of $O(N^\gamma)$.

In the heat shock response model, α_1, α_2, and α_3 depend on γ. As seen in Table 7 and Table 8, $\alpha_1 = 1$, $\alpha_2 = \alpha_3 = 0$ are valid up to times of $O(1)$. Then, we change exponents to $\alpha_1 = 0$, $\alpha_2 = \alpha_3 = 0$, which are valid up to times of $O(N)$. After that, we select $\alpha_1 = 0$, $\alpha_2 = \alpha_3 = 1$ which are valid up to $O(N^2)$.

Table 6: Scaling exponents of the number of species

Scaling exponent	$\gamma = 0$	$\gamma = 1$	$\gamma = 2$
$\alpha_1^{\dagger 4}$	1	0	0
$\alpha_2^{\dagger}$	0	0	1
$\alpha_3^{\dagger}$	0	0	1
α_4	2	2	2
α_5	2	2	2
α_6	0	0	0
α_7	0	0	0
α_8	2	2	2
α_9	2	2	2

The balance equations in Table 3 should be either satisfied or each unbalanced one will give us a restriction on the time scale exponent γ.

$$\gamma \;\leq\; \alpha_i - \max_{k \in \Gamma_i^+ \cup \Gamma_i^-} (\alpha \cdot \nu_k + \beta_k)$$

Table 7 shows whether the species balance equations are satisfied in each time scale. In case the equation is not balanced, the restriction on γ is given.

Table 7: Species balance conditions

Species	$\alpha_1 = 1$	$\alpha_1 = 0$	$\alpha_1 = 0$

[4] α's depending on γ are marked by $\dagger$.

	$\alpha_2 = \alpha_3 = 0$	$\alpha_2 = \alpha_3 = 0$	$\alpha_2 = \alpha_3 = 1$
$\{A_1\}$	$\gamma \leq 2$	balanced	balanced
$\{A_2\}$	balanced	balanced	balanced
$\{A_3\}$	balanced	balanced	balanced
$\{A_4\}$	$\gamma \leq 2$	$\gamma \leq 2$	balanced
$\{A_5\}$	$\gamma \leq 2$	$\gamma \leq 2$	balanced
$\{A_6\}$	balanced	balanced	balanced
$\{A_7\}$	$\gamma \leq 1$	$\gamma \leq 1$	balanced
$\{A_8\}$	balanced	balanced	balanced
$\{A_9\}$	balanced	balanced	balanced

Similar to species balance equations, each nontrivial irreducible subnetwork gives a balance equation. Table 8 indicates whether the subnetwork balance equations are satisfied. In case the equation is unbalanced, the restriction on γ is given.

Table 8: Subnetworks balance conditions

Species in each nontrivial irreducible subnetwork	$\alpha_1 = 1$ $\alpha_2 = \alpha_3 = 0$	$\alpha_1 = 0$ $\alpha_2 = \alpha_3 = 0$	$\alpha_1 = 0$ $\alpha_2 = \alpha_3 = 1$
$\{A_2, A_3, A_7\}$	$\gamma \leq 0$	balanced	balanced
$\{A_2, A_3\}$	$\gamma \leq 0$	$\gamma \leq 1$	balanced
$\{A_2, A_7\}$	balanced	balanced	balanced
$\{A_6, A_7, A_9\}$	$\gamma \leq 3$	$\gamma \leq 3$	$\gamma \leq 2$
$\{A_6, A_9\}$	$\gamma \leq 3$	$\gamma \leq 3$	$\gamma \leq 2$
$\{A_6, A_7\}$	balanced	balanced	balanced

$\{A_8, A_9\}$	balanced	balanced	balanced

From Table 7 and Table 8, the importance of balance equations are found. A set of exponents in the second column is valid up to $\gamma = 0$. After the time scale with $\gamma = 0$, we need to use a different set of exponents. In conclusion, unbalanced equations give a restriction on γ, and validity of the set of exponents indicates when we need to use a different set of exponents.

4.1.2 Reduced systems in each time scale

In the heat shock response model with selected α_i and β_k satisfying the balance conditions, as $N \to \infty$, the system of chemical reactions can be approximated by three limiting subsystems with different time scales. Recall from (3.5) – (3.7) that in each time scale, the normalized numbers of species with time scale faster than the current time scale are fast processes. The normalized numbers of species with the current time scale are intermediate processes, and the normalized numbers of species with time scale slower than the current time scale are slow processes.

Behavior of the slow processes is approximately constant, since the slow processes have not started significantly moving in the current time scale yet [16]. Behavior of the intermediate processes is well captured by solving the reduced system with slow processes acting as parameters [16] and with fast processes averaged out and approximately expressed in terms of the intermediate and the slow processes.

Recall that the normalized system depends on γ, and that the normalized ith species in times of $O(N^\gamma)$ is represented by $V_i^{N,\gamma}$.

Times of order 1 (When $\gamma = 0$)

In the times of $O(1)$, $V_2^{N,0}$, $V_3^{N,0}$, and $V_6^{N,0}$ are intermediate processes

$$\begin{aligned}
V_2^{N,0}(t) &= V_2^{N,0}(0) + Y_3(\int_0^t \kappa_3 V_3^{N,0}(s)\,ds) + Y_4(\int_0^t \kappa_4 V_1^{N,0}(s)\,ds) \\
&\quad + Y_5(\int_0^t \kappa_5 N^{-1} V_3^{N,0}(s)\,ds) + Y_6(\int_0^t \kappa_6 N^{-1} V_3^{N,0}(s)\,ds) \\
&\quad + Y_7(\int_0^t \kappa_7 N^{-1} V_3^{N,0}(s)\,ds) + Y_8(\int_0^t \kappa_8 N^{-2} V_7^{N,0}(s)\,ds) \\
&\quad - Y_2(\int_0^t \kappa_2 V_2^{N,0}(s)\,ds) - Y_9(\int_0^t \kappa_9 N^{-2} V_2^{N,0}(s) V_6^{N,0}(s)\,ds)
\end{aligned} \tag{4.1}$$

$$\begin{aligned}
V_3^{N,0}(t) &= V_3^{N,0}(0) + Y_2(\int_0^t \kappa_2 V_2^{N,0}(s)\,ds) - Y_3(\int_0^t \kappa_3 V_3^{N,0}(s)\,ds) \\
&\quad - Y_5(\int_0^t \kappa_5 N^{-1} V_3^{N,0}(s)\,ds) - Y_6(\int_0^t \kappa_6 N^{-1} V_3^{N,0}(s)\,ds) \\
&\quad - Y_7(\int_0^t \kappa_7 N^{-1} V_3^{N,0}(s)\,ds)
\end{aligned} \tag{4.2}$$

$$\begin{aligned}
V_6^{N,0}(t) &= V_6^{N,0}(0) + Y_7(\int_0^t \kappa_7 N^{-1} V_3^{N,0}(s)\,ds) + Y_8(\int_0^t \kappa_8 N^{-2} V_7^{N,0}(s)\,ds) \\
&\quad + Y_{12}(\int_0^t \kappa_{12} V_9^{N,0}(s)\,ds) + Y_{15}(\int_0^t \kappa_{15} N^{-1} V_4^{N,0}(s) V_7^{N,0}(s)\,ds) \\
&\quad - Y_9(\int_0^t \kappa_9 N^{-2} V_2^{N,0}(s) V_6^{N,0}(s)\,ds) - Y_{10}(\int_0^t \kappa_{10} V_6^{N,0}(s) V_8^{N,0}(s)\,ds) \\
&\quad - Y_{17}(\int_0^t \kappa_{17} N^{-2} V_6^{N,0}(s)\,ds)
\end{aligned} \tag{4.3}$$

where

$$V_2^{N,0}(0) = X_2(0) \tag{4.4}$$

$$V_3^{N,0}(0) = X_3(0) \tag{4.5}$$

$$V_6^{N,0}(0) = X_6(0). \tag{4.6}$$

As $N \to \infty$, terms for Reaction 5, 6, 7, 8, 9, 15, and 17 converge to zero. The reduced system for times of $O(1)$ and the order of magnitude of an approximation error are obtained in Theorem 4.1.

Theorem 4.1. *In the times of* $O(1)$, $\{V_2^{N,0}, V_3^{N,0}, V_6^{N,0}\}$ *converge to* $\{V_2^0, V_3^0, V_6^0\}$ *as* $N \to \infty$, *which is a solution of*

$$\begin{aligned} V_2^0(t) &= V_2^0(0) + Y_3\Big(\int_0^t \kappa_3 V_3^0(s)\,ds\Big) + Y_4\Big(\int_0^t \kappa_4 V_1^0(0)\,ds\Big) \\ &\quad - Y_2\Big(\int_0^t \kappa_2 V_2^0(s)\,ds\Big) \end{aligned} \tag{4.7}$$

$$V_3^0(t) = V_3^0(0) + Y_2\Big(\int_0^t \kappa_2 V_2^0(s)\,ds\Big) - Y_3\Big(\int_0^t \kappa_3 V_3^0(s)\,ds\Big) \tag{4.8}$$

$$V_6^0(t) = V_6^0(0) + Y_{12}\Big(\int_0^t \kappa_{12} V_9^0(0)\,ds\Big) - Y_{10}\Big(\int_0^t \kappa_{10} V_6^0(s) V_8^0(0)\,ds\Big) \tag{4.9}$$

where

$$\begin{aligned} &V_2^0(0) = X_2(0), \quad V_3^0(0) = X_3(0), \quad V_6^0(0) = X_6(0), \\ &V_1^0(0) = \frac{X_1(0)}{N_0}, \quad V_8^0(0) = \frac{X_8(0)}{N_0^2}, \quad V_9^0(0) = \frac{X_9(0)}{N_0^2} = 0. \end{aligned}$$

An error between the normalized processes in the system and the limiting processes in the reduced system is $O(N^{-1})$.

$$\sup_{t \le T} \Big(E[|V_2^{N,0}(t) - V_2^0(t)|] + E[|V_3^{N,0}(t) - V_3^0(t)|] + E[|V_6^{N,0}(t) - V_6^0(t)|] \Big) \;\le\; O\left(N^{-1}\right).$$

Proof of Theorem 4.1. The reduced system consists of three stochastic equations. $\{V_2^0, V_3^0\}$ are independent of V_6^0. First, define errors regarding $V_1^{N,0}$, $V_2^{N,0}$, $V_3^{N,0}$, $V_6^{N,0}$,

$V_8^{N,0}$, and $V_9^{N,0}$.

$$
\begin{aligned}
\epsilon_{N,1}(t) &:= \sup_{u\le t}\int_0^u |V_1^{N,0}(0) - V_1^0(0) + N^{-1}Y_{13}(\int_0^v \kappa_{13}N^{-2}\,ds) \qquad (4.10)\\
&\quad -N^{-1}Y_{14}(\int_0^v \kappa_{14}N^{-1}V_1^{N,0}(s)\,ds)|\,dv,\\
\epsilon_{N,2}(t) &:= \sup_{u\le t}|Y_5(\int_0^u \kappa_5 N^{-1}V_3^{N,0}(s)\,ds) + Y_6(\int_0^u \kappa_6 N^{-1}V_3^{N,0}(s)\,ds) \qquad (4.11)\\
&\quad +Y_7(\int_0^u \kappa_7 N^{-1}V_3^{N,0}(s)\,ds) + Y_8(\int_0^u \kappa_8 N^{-2}V_7^{N,0}(s)\,ds)\\
&\quad -Y_9(\int_0^u \kappa_9 N^{-2}V_2^{N,0}(s)V_6^{N,0}(s)\,ds)|,\\
\epsilon_{N,3}(t) &:= \sup_{u\le t}|Y_5(\int_0^u \kappa_5 N^{-1}V_3^{N,0}(s)\,ds) + Y_6(\int_0^u \kappa_6 N^{-1}V_3^{N,0}(s)\,ds) \qquad (4.12)\\
&\quad +Y_7(\int_0^u \kappa_7 N^{-1}V_3^{N,0}(s)\,ds)|\\
\epsilon_{N,6}(t) &:= \sup_{u\le t}|Y_7(\int_0^u \kappa_7 N^{-1}V_3^{N,0}(s)\,ds) + Y_8(\int_0^u \kappa_8 N^{-2}V_7^{N,0}(s)\,ds) \qquad (4.13)\\
&\quad +Y_{15}(\int_0^u \kappa_{15} N^{-1}V_4^{N,0}(s)V_7^{N,0}(s)\,ds) - Y_9(\int_0^u \kappa_9 N^{-2}V_2^{N,0}(s)V_6^{N,0}(s)\,ds)\\
&\quad -Y_{17}(\int_0^u \kappa_{17} N^{-2}V_6^{N,0}(s)\,ds)|,\\
\epsilon_{N,8}(t) &:= \sup_{u\le t}|V_8^{N,0}(0) - V_8^0(0) + N^{-2}Y_1(\int_0^u \kappa_1\,ds) \qquad (4.14)\\
&\quad +N^{-2}Y_{12}(\int_0^u \kappa_{12}V_9^{N,0}(s)\,ds) - N^{-2}Y_{10}(\int_0^u \kappa_{10}V_6^{N,0}(s)V_8^{N,0}(s)\,ds)\\
&\quad -N^{-2}Y_{11}(\int_0^u \kappa_{11}V_8^{N,0}(s)\,ds)|^2\\
\epsilon_{N,9}(t) &:= \sup_{u\le t}\int_0^u |V_9^{N,0}(0) - V_9^0(0) + N^{-2}Y_{10}(\int_0^v \kappa_{10}V_6^{N,0}(s)V_8^{N,0}(s)\,ds) \qquad (4.15)\\
&\quad -N^{-2}Y_{12}(\int_0^v \kappa_{12}V_9^{N,0}(s)\,ds)|\,dv.
\end{aligned}
$$

Using the fact that $V_2^{N,0}(0) = V_2^0(0)$ and using (4.10) and (4.11), we have an upper bound for $E[|V_2^{N,0}(t) - V_2^0(t)|]$ by subtracting (4.7) from (4.1) and by taking an absolute value and an expectation.

$$
\begin{aligned}
E[|V_2^{N,0}(t) - V_2^0(t)|] \quad & \le E[\epsilon_{N,2}(t)] + E[|Y_3(\int_0^t \kappa_3 V_3^{N,0}(s)\,ds) - Y_3(\int_0^t \kappa_3 V_3^0(s)\,ds)|] \\
& + E[|Y_4(\int_0^t \kappa_4 V_1^{N,0}(s)\,ds) - Y_4(\int_0^t \kappa_4 V_1^0(0)\,ds)|] \\
& + E[|Y_2(\int_0^t \kappa_2 V_2^{N,0}(s)\,ds) - Y_2(\int_0^t \kappa_2 V_2^0(s)\,ds)|] \\
& = E[\epsilon_{N,2}(t)] + \int_0^t \Big(\kappa_3 E[|V_3^{N,0}(s) - V_3^0(s)|] + \kappa_4 E[|V_1^{N,0}(s) - V_1^0(0)|] \\
& + \kappa_2 E[|V_2^{N,0}(s) - V_2^0(s)|]\Big)\,ds \\
& \le \kappa_4 E[\epsilon_{N,1}(t)] + E[\epsilon_{N,2}(t)] \\
& + \int_0^t \Big(\kappa_3 E[|V_3^{N,0}(s) - V_3^0(s)|] + \kappa_2 E[|V_2^{N,0}(s) - V_2^0(s)|]\Big)\,ds
\end{aligned}
$$

The equality came by applying the optional sampling theorem.

Using the fact that $V_3^{N,0}(0) = V_3^0(0)$ and using (4.12), we have an upper bound for $E[|V_3^{N,0}(t) - V_3^0(t)|]$ by subtracting (4.8) from (4.2) and by taking an absolute value and an expectation.

$$
\begin{aligned}
E[|V_3^{N,0}(t) - V_3^0(t)|] \ \le \ & E[\epsilon_{N,3}(t)] + E[|Y_2(\int_0^t \kappa_2 V_2^{N,0}(s)\,ds) - Y_2(\int_0^t \kappa_2 V_2^0(s)\,ds)|] \\
& + E[|Y_3(\int_0^t \kappa_3 V_3^{N,0}(s)\,ds) - Y_3(\int_0^t \kappa_3 V_3^0(s)\,ds)|] \\
& = E[\epsilon_{N,3}(t)] + \int_0^t \Big(\kappa_2 E[|V_2^{N,0}(s) - V_2^0(s)|] + \kappa_3 E[|V_3^{N,0}(s) - V_3^0(s)|]\Big)\,ds
\end{aligned}
$$

The last equality came by applying the optional sampling theorem. By adding the inequalities for $E[|V_2^{N,0}(t) - V_2^0(t)|]$ and $E[|V_3^{N,0}(t) - V_3^0(t)|]$, we have

$$
\begin{aligned}
& E[|V_2^{N,0}(t) - V_2^0(t)|] + E[|V_3^{N,0}(t) - V_3^0(t)|] \\
\le \ & \kappa_4 E[\epsilon_{N,1}(t)] + E[\epsilon_{N,2}(t)] + E[\epsilon_{N,3}(t)]
\end{aligned}
$$

$$+\int_0^t (\kappa_2+\kappa_3)\Big(E[|V_2^{N,0}(s)-V_2^0(s)|]+\kappa_3 E[|V_3^{N,0}(s)-V_3^0(s)|]\Big)\,ds.$$

Then we get

$$\begin{aligned}&E[|V_2^{N,0}(t)-V_2^0(t)|]+E[|V_3^{N,0}(t)-V_3^0(t)|]\\&\qquad\le\Big(\kappa_4 E[\epsilon_{N,1}(t)]+E[\epsilon_{N,2}(t)]+E[\epsilon_{N,3}(t)]\Big)e^{(\kappa_2+\kappa_3)t}.\end{aligned}$$

Using Lemma 4.1, we have

$$\sup_{t\le T}\Big(\kappa_4 E[\epsilon_{N,1}(t)+E[\epsilon_{N,2}(t)]+E[\epsilon_{N,3}(t)]]\Big)\;\le\;O\left(N^{-1}\right).$$

Therefore, for each $T>0$

$$\sup_{t\le T}\Big(E[|V_2^{N,0}(t)-V_2^0(t)|]+E[|V_3^{N,0}(t)-V_3^0(t)|]\Big)\le O\left(N^{-1}\right).$$

Using the fact that $V_6^{N,0}(0)=V_6^0(0)$ and using (4.13), (4.14), and (4.15), we have an upper bound for $E[|V_6^{N,0}(t)-V_6^0(t)|]$ by subtracting (4.9) from (4.3) and by taking an absolute value and an expectation.

$$\begin{aligned}E[|V_6^{N,0}(t)-V_6^0(t)|]\;&\le\;E[\epsilon_{N,6}(t)]\\&+E[|Y_{10}(\int_0^t\kappa_{10}V_6^{N,0}(s)V_8^{N,0}(s)\,ds)-Y_{10}(\int_0^t\kappa_{10}V_6^0(s)V_8^0(0)\,ds)|]\\&+E[|Y_{12}(\int_0^t\kappa_{12}V_9^{N,0}(s)\,ds)-Y_{12}(\int_0^t\kappa_{12}V_9^0(0)\,ds)|]\\&=E[\epsilon_{N,6}(t)]+\int_0^t\Big(\kappa_{10}E[|V_6^{N,0}(s)V_8^{N,0}(s)-V_6^0(s)V_8^0(0)|]\\&+\kappa_{12}E[|V_9^{N,0}(s)-V_9^0(0)|]\Big)\,ds\\&\le E[\epsilon_{N,6}(t)]+\kappa_{12}E[\epsilon_{N,9}(t)]\end{aligned}$$

$$
\begin{aligned}
&+\int_0^t \left(\kappa_{10}E[V_6^{N,0}(s)|V_8^{N,0}(s)-V_8^0(0)|]+\kappa_{10}E[V_8^0(0)|V_6^{N,0}(s)-V_6^0(s)|]\right)ds \\
&\le E[\epsilon_{N,6}(t)]+\kappa_{12}E[\epsilon_{N,9}(t)]+\int_0^t \kappa_{10}(E[V_6^{N,0}(s)^2])^{1/2}(E[\epsilon_{N,8}(s)])^{1/2}\,ds \\
&+\int_0^t \kappa_{10}V_8^0(0)E[|V_6^{N,0}(s)-V_6^0(s)|]\,ds
\end{aligned}
$$

The first equality came by the optional sampling theorem. In the third inequality, Hölder's inequality is used. $V_8^0(0)$ is deterministic, so we take it outside the expectation in the third inequality. Using Lemma 4.1, we have

$$
\begin{aligned}
&\sup_{t\le T}\left(E[\epsilon_{N,6}(t)]+\int_0^t \left(\kappa_{12}E[\epsilon_{N,9}(t)]+\kappa_{10}E[V_6^{N,0}(s)^2]^{1/2}E[\epsilon_{N,8}(s)]^{1/2}\right)ds\right) \\
&\le O\left(N^{-1}\right).
\end{aligned}
$$

Therefore, for each $T>0$

$$
\sup_{t\le T}E[|V_6^{N,0}(t)-V_6^0(t)|] \;\le\; O\left(N^{-1}\right).
$$

□

In Theorem 4.1, the approximation error of $V_2^{N,0}$, $V_3^{N,0}$, and $V_6^{N,0}$ has the order of magnitude of $O\left(N^{-1}\right)$. In Lemma 4.1, we show the boundedness of the approximation error used in the proof of Theorem 4.1.

Lemma 4.1. *The error term used has an upper bound*

$$
\begin{aligned}
&\sup_{t\le T}\Big(\kappa_4E[\epsilon_{N,1}(t)]+E[\epsilon_{N,2}(t)]+E[\epsilon_{N,3}(t)]+E[\epsilon_{N,6}(t)] \\
&\qquad +\kappa_{12}E[\epsilon_{N,9}(t)]+\int_0^t \kappa_{10}E[V_6^{N,0}(s)^2]^{1/2}E[\epsilon_{N,8}(s)]^{1/2}\,ds\Big)\le O\left(N^{-1}\right).
\end{aligned}
$$

Proof of Lemma 4.1. Borrowing Theorem 7 in [1], we get an upper bound for the nth moment of the counting processes. Let τ be a stopping time for the process $\{X(t); t \geq 0\}$. $X(\cdot)$ is a process with stationary independent increments with zero mean. For $n \geq 2$ there exist constant C (finite and positive) depending on n and Ω such that if $E(\tau) < \infty$ and $\int |y|^{n-2}\Omega(dy) < \infty$ then

$$E|X(\tau)|^n \leq C \max\{E(\tau), E(\tau^{n/2})\}. \tag{4.16}$$

We have $E[\int_0^t \lambda_k(V^N(s))\,ds] < \infty$ since we will apply Theorem 7 in [1] to unary reaction rates and since we show that $\sup_{t\leq T} E[V_i^N(t)] < \infty$ in the proof of Lemma 4.1. Therefore using (4.16), we get upper bounds for the second and the forth moments of the counting processes.

$$\begin{aligned}
E\Big[\Big(Y_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big)\Big)^2\Big] &= E\Big[\Big(\tilde{Y}_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big) + \int_0^t \lambda_k(V^N(s))\,ds\Big)^2\Big] \\
&\leq 2E\Big[\Big(\tilde{Y}_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big)\Big)^2\Big] + 2E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^2\Big] \\
&\leq 2C_1 E\Big[\int_0^t \lambda_k(V^N(s))\,ds\Big] + 2E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^2\Big] \\
&\leq 2C_1 \int_0^t E\big[\lambda_k(V^N(s))\big]\,ds + 2t\int_0^t E\big[\lambda_k(V^N(s))^2\big]\,ds,
\end{aligned} \tag{4.17}$$

and

$$\begin{aligned}
E\Big[\Big(Y_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big)\Big)^4\Big] &= E\Big[\Big(\tilde{Y}_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big) + \int_0^t \lambda_k(V^N(s))\,ds\Big)^4\Big] \\
&\leq 8E\Big[\Big(\tilde{Y}_k\big(\int_0^t \lambda_k(V^N(s))\,ds\big)\Big)^4\Big] + 8E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^4\Big] \\
&\leq 8C_2 \max\Big(E\Big[\int_0^t \lambda_k(V^N(s))\,ds\Big], E\Big[\big(\int_0^t \lambda_k(V^N(s))\,ds\big)^2\Big]\Big) \\
&\quad + 8E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^4\Big]
\end{aligned}$$

$$
\begin{aligned}
&\leq 8C_2 E\Big[\int_0^t \lambda_k(V^N(s))\,ds\Big] + 8C_2 E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^2\Big] \\
&\quad +8E\Big[\Big(\int_0^t \lambda_k(V^N(s))\,ds\Big)^4\Big] \\
&\leq 8C_2 \int_0^t E\big[\lambda_k(V^N(s))\big]\,ds + 8C_2 t\int_0^t E\big[\lambda_k(V^N(s))^2\big]\,ds. \\
&\quad +8t^3\int_0^t E\big[\lambda_k(V^N(s))^4\big]\,ds
\end{aligned}
\tag{4.18}
$$

A difference between initial values of the normalized process and the limiting process is bounded

$$
\big|V_i^{N,0}(0) - V_i^0(0)\big| \;\leq\; N^{-\alpha_i}. \tag{4.19}
$$

Using (4.10) – (4.15), Hölder's inequality, and (4.17), we obtain upper bounds

$$
\begin{aligned}
E[\epsilon_{N,1}(t)] &\leq \sup_{u\leq t}\int_0^u \Big(N^{-1} + \kappa_{13}N^{-3}v + \int_0^v \kappa_{14}N^{-2}E[V_1^{N,0}(s)]\,ds\Big)\,dv, \\
E[\epsilon_{N,2}(t)] &\leq \sup_{u\leq t}\int_0^u \Big((\kappa_5+\kappa_6+\kappa_7)N^{-1}E[V_3^{N,0}(s)] + \kappa_8 N^{-2}E[V_7^{N,0}(s)] \\
&\quad +\kappa_9 N^{-2}E[V_2^{N,0}(s)^2]^{1/2}E[V_6^{N,0}(s)^2]^{1/2}\Big)\,ds, \\
E[\epsilon_{N,3}(t)] &\leq \sup_{u\leq t}\int_0^u (\kappa_5+\kappa_6+\kappa_7)N^{-1}E[V_3^{N,0}(s)]\,ds, \\
E[\epsilon_{N,6}(t)] &\leq \sup_{u\leq t}\int_0^u \Big(\kappa_7 N^{-1}E[V_3^{N,0}(s)] + \kappa_8 N^{-2}E[V_7^{N,0}(s)] \\
&\quad +\kappa_{15}N^{-1}E[V_4^{N,0}(s)^2]^{1/2}E[V_7^{N,0}(s)^2]^{1/2} + \kappa_9 N^{-2}E[V_2^{N,0}(s)^2]^{1/2}E[V_6^{N,0}(s)^2]^{1/2} \\
&\quad +\kappa_{17}N^{-2}E[V_6^{N,0}(s)]\Big)\,ds, \\
E[\epsilon_{N,8}(t)] &\leq \sup_{u\leq t} 5\Big(N^{-4} + N^{-4}\big(\kappa_1 u + \kappa_1^2 u^2\big) + N^{-4}\Big(\int_0^u \kappa_{12}E[V_9^{N,0}(s)]\,ds \\
&\quad +u\int_0^u \kappa_{12}^2 E[V_9^{N,0}(s)^2]\,ds\Big) + N^{-4}\Big(\int_0^u \kappa_{10}E[V_6^{N,0}(s)^2]^{1/2}E[V_8^{N,0}(s)^2]^{1/2}\,ds \\
&\quad +u\int_0^u \kappa_{10}^2 E[V_6^{N,0}(s)^4]^{1/2}E[V_8^{N,0}(s)^4]^{1/2}\,ds\Big)\Big),
\end{aligned}
$$

$$E[\epsilon_{N,9}(t)] \leq \sup_{u\leq t}\int_0^u \Big(N^{-2}+\int_0^v \kappa_{10}N^{-2}E[V_6^{N,0}(s)^2]^{1/2}E[V_8^{N,0}(s)^2]^{1/2}\,ds$$
$$+\int_0^v \kappa_{12}N^{-2}E[V_9^{N,0}(s)]\,ds\Big)\,dv.$$

We will show that for fixed $T>0$,

$$\sup_N\sup_{t\leq T}E[V_1^{N,0}(t)]<\infty,\quad \sup_N\sup_{t\leq T}E[V_2^{N,0}(t)^2]<\infty,\quad \sup_N\sup_{t\leq T}E[V_3^{N,0}(t)]<\infty,$$
$$\sup_N\sup_{t\leq T}E[V_4^{N,0}(t)^2]<\infty,\quad \sup_N\sup_{t\leq T}E[V_6^{N,0}(t)]<\infty,\quad \sup_N\sup_{t\leq T}E[V_6^{N,0}(t)^2]<\infty,$$
$$\sup_N\sup_{t\leq T}E[V_6^{N,0}(t)^4]<\infty,\quad \sup_N\sup_{t\leq T}E[V_7^{N,0}(t)]<\infty,\quad \sup_N\sup_{t\leq T}E[V_7^{N,0}(t)^2]<\infty,$$
$$\sup_N\sup_{t\leq T}E[V_8^{N,0}(t)^2]<\infty,\quad \sup_N\sup_{t\leq T}E[V_8^{N,0}(t)^4]<\infty,\quad \sup_N\sup_{t\leq T}E[V_9^{N,0}(t)]<\infty,$$
$$\sup_N\sup_{t\leq T}E[V_9^{N,0}(t)^2]<\infty.$$

The equation for $V_1^{N,0}$ is

$$\begin{aligned} V_1^{N,0}(t) &= V_1^{N,0}(0)+N^{-1}Y_{13}\Big(\int_0^t \kappa_{13}N^{-2}\,ds\Big) \\ &\quad -N^{-1}Y_{14}\Big(\int_0^t \kappa_{14}N^{-1}V_1^{N,0}(s)\,ds\Big). \end{aligned} \tag{4.20}$$

Solving (4.20) for $E[V_1^{N,0}(t)]$, we have

$$E[V_1^{N,0}(t)] = \Big(E[V_1^{N,0}(0)]-\frac{\kappa_{13}}{\kappa_{14}}N^{-1}\Big)e^{-\kappa_{14}N^{-2}t}+\frac{\kappa_{13}}{\kappa_{14}}N^{-1}.$$

Using (4.20) and (4.17), we have

$$\begin{aligned} E[V_1^{N,0}(t)^2] &\leq 2E[V_1^{N,0}(0)^2]+2E\Big[\Big(N^{-1}Y_{13}\Big(\int_0^t \kappa_{13}N^{-2}\,ds\Big)\Big)^2\Big] \\ &\leq 2E[V_1^{N,0}(0)^2]+4C_1\kappa_{13}N^{-4}t+4\kappa_{13}^2N^{-6}t^2. \end{aligned}$$

Using (4.20) and (4.18), we have

$$\begin{aligned} E[V_1^{N,0}(t)^4] &\leq 8E[V_1^{N,0}(0)^4] + 8E\Big[\Big(N^{-1}Y_{13}(\int_0^t \kappa_{13}N^{-2}\,ds)\Big)^4\Big] \\ &\leq 8E[V_1^{N,0}(0)^4] + 64C_2\kappa_{13}N^{-6}t + 64C_2\kappa_{13}^2N^{-8}t^2 + 64\kappa_{13}^4N^{-12}t^4 \end{aligned}$$

The equation for $V_2^{N,0} + V_3^{N,0} + V_7^{N,0}$ is

$$\begin{aligned} V_2^{N,0}(t) + V_3^{N,0}(t) + V_7^{N,0}(t) &= V_2^{N,0}(0) + V_3^{N,0}(0) + V_7^{N,0}(0) \\ &\quad + Y_4(\int_0^t \kappa_4 V_1^{N,0}(s)\,ds) - Y_{15}(\int_0^t \kappa_{15}N^{-1}V_4^{N,0}(s)V_7^{N,0}(s)\,ds). \end{aligned} \tag{4.21}$$

Eliminating the negative term and taking an expectation, we have an upper bound

$$\begin{aligned} E[V_2^{N,0}(t)] + E[V_3^{N,0}(t)] + E[V_7^{N,0}(t)] &\leq E[V_2^{N,0}(0)] + E[V_3^{N,0}(0)] + E[V_7^{N,0}(0)] \\ &\quad + \int_0^t \kappa_4 E[V_1^{N,0}(s)]\,ds. \end{aligned}$$

Using (4.21) and (4.17), we also have

$$\begin{aligned} E\Big[\big(V_2^{N,0}(t) + V_3^{N,0}(t) + V_7^{N,0}(t)\big)^2\Big] &\leq 2E\Big[\big(V_2^{N,0}(0) + V_3^{N,0}(0) + V_7^{N,0}(0)\big)^2\Big] \\ &\quad + 2E\Big[\Big(Y_4(\int_0^t \kappa_4 V_1^{N,0}(s)\,ds)\Big)^2\Big] \\ &\leq 2E\Big[\big(V_2^{N,0}(0) + V_3^{N,0}(0) + V_7^{N,0}(0)\big)^2\Big] \\ &\quad + 4C_1\int_0^t \kappa_4 E[V_1^{N,0}(s)]\,ds + 4t\int_0^t \kappa_4^2 E[V_1^{N,0}(s)^2]\,ds. \end{aligned}$$

Using (4.21) and (4.18), we also have

$$E\Big[\big(V_2^{N,0}(t) + V_3^{N,0}(t) + V_7^{N,0}(t)\big)^4\Big] \leq 8E\Big[\big(V_2^{N,0}(0) + V_3^{N,0}(0) + V_7^{N,0}(0)\big)^4\Big]$$

$$
\begin{aligned}
&+8E\Big[\Big(Y_4\big(\int_0^t \kappa_4 V_1^{N,0}(s)\,ds\big)\Big)^4\Big] \\
&\le 8E\Big[\big(V_2^{N,0}(0)+V_3^{N,0}(0)+V_7^{N,0}(0)\big)^4\Big] \\
&\quad +64C_2\int_0^t \kappa_4 E[V_1^{N,0}(s)]\,ds + 64C_2 t\int_0^t \kappa_4^2 E[V_1^{N,0}(s)^2]\,ds. \\
&\quad +64t^3\int_0^t \kappa_4^4 E[V_1^{N,0}(s)^4]\,ds
\end{aligned}
$$

The equation for $V_6^{N,0}+V_7^{N,0}+N^2V_9^{N,0}$ is

$$
\begin{aligned}
V_6^{N,0}(t)+V_7^{N,0}(t)+N^2V_9^{N,0}(t) &= V_6^{N,0}(0)+V_7^{N,0}(0) \\
&\quad +Y_7\big(\int_0^t \kappa_7 N^{-1}V_3^{N,0}(s)\,ds\big) - Y_{17}\big(\int_0^t \kappa_{17}N^{-2}V_6^{N,0}(s)\,ds\big).
\end{aligned}
\tag{4.22}
$$

Eliminating the negative term and taking an expectation, we have an upper bound

$$
\begin{aligned}
E[V_6^{N,0}(t)]+E[V_7^{N,0}(t)]+N^2E[V_9^{N,0}(t)] &\le E[V_6^{N,0}(0)]+E[V_7^{N,0}(0)] \\
&\quad +\int_0^t \kappa_7 N^{-1}E[V_3^{N,0}(s)]\,ds.
\end{aligned}
$$

Using (4.22) and (4.17), we also have

$$
\begin{aligned}
E\Big[\big(V_6^{N,0}(t)+V_7^{N,0}(t)+N^2V_9^{N,0}(t)\big)^2\Big] &\le 2E\Big[\big(V_6^{N,0}(0)+V_7^{N,0}(0)\big)^2\Big] \\
&\quad +2E\Big[\Big(Y_7\big(\int_0^t \kappa_7 N^{-1}V_3^{N,0}(s)\,ds\big)\Big)^2\Big] \\
&\le 2E\Big[\big(V_6^{N,0}(0)+V_7^{N,0}(0)\big)^2\Big]+4C_1\int_0^t \kappa_7 N^{-1}E[V_3^{N,0}(s)]\,ds \\
&\quad +4t\int_0^t \kappa_7^2 N^{-2}E[V_3^{N,0}(s)^2]\,ds.
\end{aligned}
$$

Using (4.22) and (4.18), we also have

$$\begin{aligned} E\Big[\big(V_6^{N,0}(t)+V_7^{N,0}(t)+N^2V_9^{N,0}(t)\big)^4\Big] &\le 8E\Big[\big(V_6^{N,0}(0)+V_7^{N,0}(0)\big)^4\Big] \\ &\quad +8E\Big[\Big(Y_7(\int_0^t \kappa_7 N^{-1}V_3^{N,0}(s)\,ds)\Big)^4\Big] \\ &\le 8E\Big[\big(V_6^{N,0}(0)+V_7^{N,0}(0)\big)^4\Big] \\ &\quad +64C_2\int_0^t \kappa_7 N^{-1}E[V_3^{N,0}(s)]\,ds+64C_2 t\int_0^t \kappa_7^2N^{-2}E[V_3^{N,0}(s)^2]\,ds \\ &\quad +64t^3\int_0^t \kappa_7^4 N^{-4}E[V_3^{N,0}(s)^4]\,ds. \end{aligned}$$

The equation for $V_8^{N,0}+V_9^{N,0}$ is

$$\begin{aligned} V_8^{N,0}(t)+V_9^{N,0}(t) &= V_8^{N,0}(0)+N^{-2}Y_1(\int_0^t \kappa_1\,ds) \\ &\quad -N^{-2}Y_{11}(\int_0^t \kappa_{11}V_8^{N,0}(s)\,ds). \end{aligned} \tag{4.23}$$

Eliminating the negative term and taking an expectation, we have an upper bound

$$E[V_8^{N,0}(t)]+E[V_9^{N,0}(t)] \le E[V_8^{N,0}(0)]+\kappa_1 N^{-2}t.$$

Using (4.23) and (4.17), we also have

$$\begin{aligned} E\Big[\big(V_8^{N,0}(t)+V_9^{N,0}(t)\big)^2\Big] &\le 2E[V_8^{N,0}(0)^2]+2E\Big[\Big(N^{-2}Y_1(\int_0^t \kappa_1\,ds)\Big)^2\Big] \\ &\le 2E[V_8^{N,0}(0)^2]+4C_1\kappa_1N^{-4}t+4\kappa_1^2N^{-4}t^2. \end{aligned}$$

Using (4.23) and (4.18), we also have

$$E\Big[\big(V_8^{N,0}(t)+V_9^{N,0}(t)\big)^4\Big] \le 8E[V_8^{N,0}(0)^4]+8E\Big[\Big(N^{-2}Y_1(\int_0^t \kappa_1\,ds)\Big)^4\Big]$$

$$\leq 8E[V_8^{N,0}(0)^4] + 64C_2\kappa_1 N^{-8}t + 64C_2\kappa_1^2 N^{-8}t^2 + 64\kappa_1^4 N^{-8}t^4.$$

□

Times of order N (When $\gamma = 1$)

In the times of $O(N)$, $V_7^{N,1}$ is the only intermediate process

$$\begin{aligned} V_7^{N,1}(t) &= V_7^{N,1}(0) + Y_9(\int_0^t \kappa_9 N^{-1} V_2^{N,1}(s) V_6^{N,1}(s)\, ds) \\ &\quad -Y_8(\int_0^t \kappa_8 N^{-1} V_7^{N,1}(s)\, ds) - Y_{15}(\int_0^t \kappa_{15} V_4^{N,1}(s) V_7^{N,1}(s)\, ds) \end{aligned} \tag{4.24}$$

where

$$V_7^{N,1}(0) = X_7(0). \tag{4.25}$$

Terms for Reaction 8 and 9 converge to zero as $N \to \infty$ in (4.24). The reduced system in the time of $O(N)$ and the order of magnitude of an approximation error are obtained in Theorem 4.2.

Theorem 4.2. *In the times of $O(N)$, $V_7^{N,1}$ converges to V_7^1 as $N \to \infty$, which is a solution of*

$$V_7^1(t) = V_7^1(0) - Y_{15}(\int_0^t \kappa_{15} V_4^1(0) V_7^1(s)\, ds) \tag{4.26}$$

where

$$V_7^1(0) = X_7(0). \tag{4.27}$$

An error between the normalized process in the system and the limiting process in the reduced system is $O\left(N^{-1}\right)$.

$$\sup_{t\leq T} E\left[|V_7^{N,1}(t) - V_7^1(t)|\right] \;\leq\; O\left(N^{-1}\right).$$

Proof of Theorem 4.2. The reduced system consists of a stochastic equation for V_7^1, which is a death process. First, define errors regarding $V_4^{N,1}$ and $V_7^{N,1}$.

$$\begin{aligned}
\epsilon_{N,4}(t) &:= \sup_{u\leq t} |V_4^{N,1}(0) - V_4^1(0) + N^{-2}Y_6(\int_0^u \kappa_6 V_3^{N,1}(s)\,ds) \\
&\quad -N^{-2}Y_{18}(\int_0^u \kappa_{18} N V_4^{N,1}(s)\,ds)|^2
\end{aligned} \tag{4.28}$$

$$\begin{aligned}
\epsilon_{N,7}(t) &:= \sup_{u\leq t} |V_7^{N,1}(0) - V_7^1(0) + Y_9(\int_0^u \kappa_9 N^{-1} V_2^{N,1}(s) V_6^{N,1}(s)\,ds) \\
&\quad -Y_8(\int_0^u \kappa_8 N^{-1} V_7^{N,1}(s)\,ds)|.
\end{aligned} \tag{4.29}$$

Using (4.28) and (4.29), we have an upper bound for $E[|V_7^{N,1}(t) - V_7^1(t)|]$ by subtracting (4.26) from (4.24) and by taking an absolute value and an expectation:

$$\begin{aligned}
E[|V_7^{N,1}(t) - V_7^1(t)|] &\leq E[\epsilon_{N,7}(t)] \\
&\quad +E[|Y_{15}(\int_0^t \kappa_{15} V_4^{N,1}(s) V_7^{N,1}(s)\,ds) - Y_{15}(\int_0^t \kappa_{15} V_4^1(0) V_7^1(s)\,ds)|] \\
&= E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15} E[|V_4^{N,1}(s) V_7^{N,1}(s) - V_4^1(0) V_7^1(s)|])\,ds \\
&\leq E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15} E[V_7^{N,1}(s)|V_4^{N,1}(s) - V_4^1(0)|]\,ds \\
&\qquad + \int_0^t \kappa_{15} E[V_4^1(0)|V_7^{N,1}(s) - V_7^1(s)|]\,ds \\
&\leq E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15} (E[V_7^{N,1}(s)^2])^{1/2} (E[\epsilon_{N,4}(s)])^{1/2}\,ds \qquad (4.30) \\
&\quad + \int_0^t \kappa_{15} V_4^1(0) E[|V_7^{N,1}(s) - V_7^1(s)|]\,ds
\end{aligned}$$

The first equality comes by the optional sampling theorem. In the third inequality, Hölder's inequality is used. $V_7^1(0)$ is deterministic, so we take it outside the expectation in the third inequality. Then, using (4.30), we get

$$\begin{aligned} E[|V_7^{N,1}(t) - V_7^1(t)|] \;\leq\; & \left(E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15}(E[V_7^{N,1}(s)^2])^{1/2}(E[\epsilon_{N,4}(s)])^{1/2}\, ds\right) \\ & \times e^{\kappa_{15} V_4^1(0))t} \end{aligned}$$

By Lemma 4.2, we have

$$\sup_{t\leq T}\left(E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15} E[V_7^{N,1}(s)^2]^{1/2} E[\epsilon_{N,4}(s)]^{1/2}\, ds\right) \;\leq\; O\left(N^{-1}\right).$$

Therefore, for each $T > 0$

$$E[|V_7^{N,1}(t) - V_7^1(t)|] \;\leq\; O\left(N^{-1}\right).$$

□

In Theorem 4.2, the moment of the approximation error of $V_7^{N,1}$ has the order of magnitude of $O\left(N^{-1}\right)$. In Lemma 4.2, we show the boundedness of the approximation error used in the proof of Theorem 4.2.

Lemma 4.2. *The error term used has an upper bound*

$$\sup_{t\leq T}\left(E[\epsilon_{N,7}(t)] + \int_0^t \kappa_{15} E[V_7^{N,1}(s)^2]^{1/2} E[\epsilon_{N,4}(s)]^{1/2}\, ds\right) \;\leq\; O\left(N^{-1}\right).$$

Proof of Lemma 4.2. Using (4.28), (4.29), Hölder's inequality, and (4.17), we obtain upper bounds

$$
\begin{aligned}
E[\epsilon_{N,4}(t)] &\leq \sup_{u\leq t} 3\Big(N^{-4} + N^{-4}\Big(\int_0^u \kappa_6 E[V_3^{N,1}(s)]\,ds \\
&\quad + u\int_0^u \kappa_6^2 E[V_3^{N,1}(s)^2]\,ds\Big) + N^{-4}\Big(\int_0^u \kappa_{18} N E[V_4^{N,1}(s)]\,ds \\
&\quad + u\int_0^u \kappa_{18}^2 N^2 E[V_4^{N,1}(s)^2]\,ds\Big)\Big), \\
E[\epsilon_{N,7}(t)] &\leq \sup_{u\leq t}\Big(\int_0^u \kappa_9 N^{-1} E[V_2^{N,1}(s)^2]^{1/2} E[V_6^{N,1}(s)^2]^{1/2}\,ds \\
&\quad + \int_0^u \kappa_8 N^{-1} E[V_7^{N,1}(s)]\,ds\Big).
\end{aligned}
$$

We will show that for fixed $T > 0$,

$$
\begin{aligned}
&\sup_N \sup_{t\leq T} E[V_2^{N,1}(t)^2] < \infty, \quad \sup_N \sup_{t\leq T} E[V_3^{N,1}(t)] < \infty, \quad \sup_N \sup_{t\leq T} E[V_3^{N,1}(t)^2] < \infty, \\
&\sup_N \sup_{t\leq T} E[V_4^{N,1}(t)] < \infty, \quad \sup_N \sup_{t\leq T} E[V_4^{N,1}(t)^2] < \infty, \quad \sup_N \sup_{t\leq T} E[V_6^{N,1}(t)^2] < \infty, \\
&\sup_N \sup_{t\leq T} E[V_7^{N,1}(t)] < \infty, \quad \sup_N \sup_{t\leq T} E[V_7^{N,1}(t)^2] < \infty.
\end{aligned}
$$

The equation for $V_1^{N,1}$ is

$$
V_1^{N,1}(t) = V_1^{N,1}(0) + Y_{13}\Big(\int_0^t \kappa_{13} N^{-1}\,ds\Big) - Y_{14}\Big(\int_0^t \kappa_{14} N^{-1} V_1^{N,1}(s)\,ds\Big). \quad (4.31)
$$

Solving (4.31) for $E[V_1^{N,1}(t)]$, we have

$$
E[V_1^{N,1}(t)] = \Big(E[V_1^{N,1}(0)] - \frac{\kappa_{13}}{\kappa_{14}}\Big)e^{-\kappa_{14}N^{-1}t} + \frac{\kappa_{13}}{\kappa_{14}}.
$$

Using (4.31) and (4.17), we have

$$
E[V_1^{N,1}(t)^2] \leq 2E[V_1^{N,1}(0)^2] + 2E\Big[\Big(Y_{13}\Big(\int_0^t \kappa_{13} N^{-1}\,ds\Big)\Big)^2\Big]
$$

$$\leq \ 2E[V_1^{N,1}(0)^2] + 4C_1\kappa_{13}N^{-1}t + 4\kappa_{13}^2N^{-2}t^2.$$

$V_2^{N,1} + V_3^{N,1} + V_7^{N,1}$ satisfies

$$\begin{aligned} V_2^{N,1}(t) + V_3^{N,1}(t) + V_7^{N,1}(t) &= V_2^{N,1}(0) + V_3^{N,1}(0) + V_7^{N,1}(0) \\ &+Y_4\Big(\int_0^t \kappa_4 V_1^{N,1}(s)\,ds\Big) - Y_{15}\Big(\int_0^t \kappa_{15}V_4^{N,1}(s)V_7^{N,1}(s)\,ds\Big). \end{aligned} \tag{4.32}$$

Eliminating the negative term and taking expectation, we have

$$\begin{aligned} E[V_2^{N,1}(t)] + E[V_3^{N,1}(t)] + E[V_7^{N,1}(t)] &\leq E[V_2^{N,1}(0)] + E[V_3^{N,1}(0)] + E[V_7^{N,1}(0)] \\ &+ \int_0^t \kappa_4 E[V_1^{N,1}(s)]\,ds. \end{aligned}$$

Using (4.32) and (4.17), we have

$$\begin{aligned} E\Big[\big(V_2^{N,1}(t) + V_3^{N,1}(t) + V_7^{N,1}(t)\big)^2\Big] &\leq 2E\Big[\big(V_2^{N,1}(0) + V_3^{N,1}(0) + V_7^{N,1}(0)\big)^2\Big] \\ &+2E\Big[\Big(Y_4\Big(\int_0^t \kappa_4 V_1^{N,1}(s)\,ds\Big)\Big)^2\Big] \\ &\leq 2E\Big[\big(V_2^{N,1}(0) + V_3^{N,1}(0) + V_7^{N,1}(0)\big)^2\Big] \\ &+4C_1\int_0^t \kappa_4 E[V_1^{N,1}(s)]\,ds + 4t\int_0^t \kappa_4^2 E[V_1^{N,1}(s)^2]\,ds. \end{aligned}$$

The equation for $V_4^{N,1}$ is

$$\begin{aligned} V_4^{N,1}(t) &= V_4^{N,1}(0) + N^{-2}Y_6\Big(\int_0^t \kappa_6 V_3^{N,1}(s)\,ds\Big) \\ &-N^{-2}Y_{18}\Big(\int_0^t \kappa_{18}NV_4^{N,1}(s)\,ds\Big). \end{aligned} \tag{4.33}$$

Eliminating the negative term and taking expectations, we have

$$E[V_4^{N,1}(t)] \;\leq\; E[V_4^{N,1}(0)] + \int_0^t \kappa_6 N^{-2} E[V_3^{N,1}(s)]\, ds.$$

Using (4.33) and (4.17), we have

$$\begin{aligned} E[V_4^{N,1}(t)^2] &\leq 2E[V_4^{N,1}(0)^2] + 2E\Big[\Big(N^{-2}Y_6\big(\int_0^t \kappa_6 V_3^{N,1}(s)\, ds\big)\Big)^2\Big] \\ &\leq 2E[V_4^{N,1}(0)^2] + 4C_1 \int_0^t \kappa_6 N^{-2} E[V_3^{N,1}(s)]\, ds + 4t \int_0^t \kappa_6^2 N^{-4} E[V_3^{N,1}(s)^2]\, ds. \end{aligned}$$

The equation for $V_6^{N,1} + V_7^{N,1} + N^2 V_9^{N,1}$ is

$$\begin{aligned} V_6^{N,1}(t) + V_7^{N,1}(t) + N^2 V_9^{N,1}(t) &= V_6^{N,1}(0) + V_7^{N,1}(0) \\ &\quad + Y_7\big(\int_0^t \kappa_7 V_3^{N,1}(s)\, ds\big) - Y_{17}\big(\int_0^t \kappa_{17} N^{-1} V_6^{N,1}(s)\, ds\big). \end{aligned} \tag{4.34}$$

Eliminating the negative term and taking expectations, we have

$$\begin{aligned} E[V_6^{N,1}(t)] + E[V_7^{N,1}(t)] + E[N^2 V_9^{N,1}(t)] &\leq E[V_6^{N,1}(0)] + E[V_7^{N,1}(0)] \\ &\quad + \int_0^t \kappa_7 E[V_3^{N,1}(s)]\, ds. \end{aligned}$$

Using (4.34) and (4.17), we have

$$\begin{aligned} E\Big[\big(V_6^{N,1}(t) + V_7^{N,1}(t) + N^2 V_9^{N,1}(t)\big)^2\Big] &\leq 2E\Big[\big(V_6^{N,1}(0) + V_7^{N,1}(0)\big)^2\Big] \\ &\quad + 2E\Big[\Big(Y_7\big(\int_0^t \kappa_7 V_3^{N,1}(s)\, ds\big)\Big)^2\Big] \\ &\leq 2E\Big[\big(V_6^{N,1}(0) + V_7^{N,1}(0)\big)^2\Big] \\ &\quad + 4C_1 \int_0^t \kappa_7 E[V_3^{N,1}(s)]\, ds + 4t \int_0^t \kappa_7^2 E[V_3^{N,1}(s)^2]\, ds. \end{aligned}$$

□

In Lemma 4.3, for each $t \geq 0$, the quasi-stationary distribution of the fast processes $V_2^1(t)$, $V_3^1(t)$, and $V_6^1(t)$ are obtained.

Lemma 4.3. *In times of $O(N)$, for each $t \geq 0$, $\left(V_2^{N,1}(t), V_3^{N,1}(t), V_6^{N,1}(t)\right)$ converges in distribution to $\left(\hat{V}_2^1(t), \hat{V}_3^1(t), \hat{V}_6^1(t)\right)$ satisfying $\left(\hat{V}_2^1(t), \hat{V}_3^1(t)\right)$ conditioned on $\hat{V}_2^1(t) + \hat{V}_3^1(t)$ has a binomial distribution with parameter*

$$\frac{\kappa_3}{\kappa_2+\kappa_3}, \qquad \frac{\kappa_2}{\kappa_2+\kappa_3},$$

respectively, that is,

$$P\left\{\hat{V}_2^1(t) = k | \hat{V}_2^1(t) + \hat{V}_3^1(t) = n\right\} = C(n,k)\left(\frac{\kappa_3}{\kappa_2+\kappa_3}\right)^k \left(\frac{\kappa_2}{\kappa_2+\kappa_3}\right)^{n-k} \quad (4.35)$$

$$P\left\{\hat{V}_3^1(t) = k | \hat{V}_2^1(t) + \hat{V}_3^1(t) = n\right\} = C(n,k)\left(\frac{\kappa_2}{\kappa_2+\kappa_3}\right)^k \left(\frac{\kappa_3}{\kappa_2+\kappa_3}\right)^{n-k} \quad (4.36)$$

$\hat{V}_6^1(t)$ has a Poisson distribution with parameter

$$\frac{\kappa_{12} V_9^1(0)}{\kappa_{10} V_8^1(0)}.$$

Proof of Lemma 4.3. Define

$$\begin{aligned} A^N_{(V_1^{N,1}(s), V_4^{N,1}(s), V_7^{N,1}(s), V_8^{N,1}(s), V_9^{N,1}(s))} g(x,y,z) &= \kappa_2 x\big(g(x-1,y+1,z) - g(x,y,z)\big) \\ &+ \kappa_3 y\big(g(x+1,y-1,z) - g(x,y,z)\big) + \kappa_{10} z V_8^{N,1}(s)\big(g(x,y,z-1) - g(x,y,z)\big) \\ &+ \kappa_{12} V_9^{N,1}(s)\big(g(x,y,z+1) - g(x,y,z)\big) + O\left(N^{-1}\right). \end{aligned}$$

Then

$$M_g^N(t) \equiv g(V_2^{N,1}(t), V_3^{N,1}(t), V_6^{N,1}(t)) - g(V_2^{N,1}(0), V_3^{N,1}(0), V_6^{N,1}(0)) \tag{4.37}$$
$$-N\int_0^t A^N_{(V_1^{N,1}(s),V_4^{N,1}(s),V_7^{N,1}(s),V_8^{N,1}(s),V_9^{N,1}(s))} g(V_2^{N,1}(s), V_3^{N,1}(s), V_6^{N,1}(s))\, ds$$

is a martingale. Define am occupation measure for $\left(V_2^{N,1}, V_3^{N,1}, V_6^{N,1}\right)$ by

$$\Gamma^N(C \times D \times E \times [0,t]) = \int_0^t 1_C(V_2^{N,1}(s))1_D(V_3^{N,1}(s))1_E(V_6^{N,1}(s))\, ds. \tag{4.38}$$

Using (4.38), we rewrite (4.37)

$$M_g^N(t) = g(V_2^{N,1}(t), V_3^{N,1}(t), V_6^{N,1}(t)) - g(V_2^{N,1}(0), V_3^{N,1}(0), V_6^{N,1}(0)) \tag{4.39}$$
$$-N\int_{(\mathbb{Z}+)^3\times[0,t]} A^N_{(V_1^{N,1}(s),V_4^{N,1}(s),V_7^{N,1}(s),V_8^{N,1}(s),V_9^{N,1}(s))} g(x,y,z)\,\Gamma^N(dx \times dy \times dz \times ds)$$

We can show relatively compactness of Γ^N using the boundedness of $\sup_{t\le T} E[V_2^{N,1}(t)]$, $\sup_{t\le T} E[V_3^{N,1}(t)]$, and $\sup_{t\le T} E[V_6^{N,1}(t)]$. Let $\Gamma^N \Rightarrow \Gamma$. Dividing (4.39) by N and letting $N \to \infty$, we have

$$\int_0^t A_{(V_8^1(0),V_9^1(0))} g(x,y,z)\,\Gamma(dx \times dy \times dz \times ds) = 0. \tag{4.40}$$

where

$$A_{(V_8^1(0),V_9^1(0))} g(x,y,z) = \kappa_2 x\big(g(x-1,y+1,z) - g(x,y,z)\big) \tag{4.41}$$
$$+\kappa_3 y\big(g(x+1,y-1,z) - g(x,y,z)\big) + \kappa_{10} z V_8^1(0)\big(g(x,y,z-1) - g(x,y,z)\big)$$
$$+\kappa_{12} V_9^1(0)\big(g(x,y,z+1) - g(x,y,z)\big).$$

Differentiating (4.40) with respect to t, for almost every t, $\left(V_2^{N,1}(t), V_3^{N,1}(t), V_6^{N,1}(t)\right) \Rightarrow \left(\hat{V}_2^1(t), \hat{V}_3^1(t), \hat{V}_6^1(t)\right)$ satisfying

$$\begin{aligned}\int \Big[&\kappa_2 x\big(g(x-1,y+1,z)-g(x,y,z)\big)+\kappa_3 y\big(g(x+1,y-1,z)-g(x,y,z)\big) \\ &+\kappa_{10} z V_8^1(0)\big(g(x,y,z-1)-g(x,y,z)\big) \\ &+\kappa_{12} V_9^1(0)\big(g(x,y,z+1)-g(x,y,z)\big)\Big]\mu^{236}(dx,dy,dz)=0.\end{aligned} \tag{4.42}$$

Using (4.42), $(\hat{V}_2^1(t), \hat{V}_3^1(t))$ conditioned on $\hat{V}_2^1(t)+\hat{V}_3^1(t)$ has a binomial distribution with parameter $\frac{\kappa_3}{\kappa_2+\kappa_3}$ and $\frac{\kappa_2}{\kappa_2+\kappa_3}$, respectively, that is,

$$\begin{aligned} P\Big\{\hat{V}_2^1(t)=k|\hat{V}_2^1(t)+\hat{V}_3^1(t)=n\Big\} &= C(n,k)\Big(\frac{\kappa_3}{\kappa_2+\kappa_3}\Big)^k\Big(\frac{\kappa_2}{\kappa_2+\kappa_3}\Big)^{n-k} \\ P\Big\{\hat{V}_3^1(t)=k|\hat{V}_2^1(t)+\hat{V}_3^1(t)=n\Big\} &= C(n,k)\Big(\frac{\kappa_2}{\kappa_2+\kappa_3}\Big)^k\Big(\frac{\kappa_3}{\kappa_2+\kappa_3}\Big)^{n-k}\end{aligned}$$

$\hat{V}_6^1(t)$ is independent of $(\hat{V}_2^1(t), \hat{V}_3^1(t))$ and it has a Poisson distribution with parameter $\frac{\kappa_{12}V_9^1(0)}{\kappa_{10}V_8^1(0)}$.

We see more details about the existence of the averaged generator and quasi-stationary distribution in [11]. □

Remark 4.4. *Since $V_9^1(0) = 0$ in this example, there is no meaning in the quasi-stationary distribution for $V_6^{N,1}$ in Lemma 4.3. However, when $V_9^1(0) \neq 0$, it will give us a quasi-stationary distribution for $V_6^{N,1}$.*

Times of order N^2 (When $\gamma = 2$)

In times of $O(N^2)$, $V_1^{N,2}$, $V_2^{N,2} + V_3^{N,2}$,$V_4^{N,2}$, $V_5^{N,2}$, $V_8^{N,2}$, and $V_9^{N,2}$ are intermediate processes.

$$\begin{aligned}
V_1^{N,2}(t) &= V_1^{N,2}(0) + Y_{13}(\int_0^t \kappa_{13}\, ds) - Y_{14}(\int_0^t \kappa_{14} V_1^{N,2}(s)\, ds) &(4.43)\\
V_2^{N,2}(t) &+ V_3^{N,2}(t) = V_2^{N,2}(0) + V_3^{N,2}(0) + N^{-1}Y_4(\int_0^t \kappa_4 N V_1^{N,2}(s)\, ds) &(4.44)\\
&+N^{-1}Y_8(\int_0^t \kappa_8 V_7^{N,2}(s)\, ds) - N^{-1}Y_9(\int_0^t \kappa_9 N V_2^{N,2}(s) V_6^{N,2}(s)\, ds)\\
V_4^{N,2}(t) &= V_4^{N,2}(0) + N^{-2}Y_6(\int_0^t \kappa_6 N^2 V_3^{N,2}(s)\, ds) &(4.45)\\
&-N^{-2}Y_{18}(\int_0^t \kappa_{18} N^2 V_4^{N,2}(s)\, ds)\\
V_5^{N,2}(t) &= V_5^{N,2}(0) + N^{-2}Y_5(\int_0^t \kappa_5 N^2 V_3^{N,2}(s)\, ds) &(4.46)\\
&-N^{-2}Y_{16}(\int_0^t \kappa_{16} N^2 V_5^{N,2}(s)\, ds)\\
V_8^{N,2}(t) &= V_8^{N,2}(0) + N^{-2}Y_1(\int_0^t \kappa_1 N^2\, ds) + N^{-2}Y_{12}(\int_0^t \kappa_{12} N^2 V_9^{N,2}(s)\, ds) &(4.47)\\
&-N^{-2}Y_{10}(\int_0^t \kappa_{10} N^2 V_6^{N,2}(s) V_8^{N,2}(s)\, ds) - N^{-2}Y_{11}(\int_0^t \kappa_{11} N^2 V_8^{N,2}(s)\, ds)\\
V_9^{N,2}(t) &= V_9^{N,2}(0) + N^{-2}Y_{10}(\int_0^t \kappa_{10} N^2 V_6^{N,2}(s) V_8^{N,2}(s)\, ds) &(4.48)\\
&-N^{-2}Y_{12}(\int_0^t \kappa_{12} N^2 V_9^{N,2}(s)\, ds).
\end{aligned}$$

where

$$\begin{aligned}
&V_1^{N,1}(0) = X_1(0),\\
&V_2^{N,2}(0) = \frac{X_2(0)}{N}, \qquad V_3^{N,2}(0) = \frac{X_3(0)}{N} &(4.49)\\
&V_4^{N,2}(0) = \frac{1}{N^2}\left[\frac{X_4(0)N^2}{N_0^2}\right], \qquad V_5^{N,2}(0) = \frac{1}{N^2}\left[\frac{X_5(0)N^2}{N_0^2}\right],
\end{aligned}$$

$$V_8^{N,2}(0) = \frac{1}{N^2}\left[\frac{X_8(0)N^2}{N_0^2}\right], \qquad V_9^{N,2}(0) = \frac{1}{N^2}\left[\frac{X_9(0)N^2}{N_0^2}\right] = 0.$$

Here, we define $V_2^N(0)$ and $V_3^N(0)$ differently from others to prevent the boundary layer problem. Using the equation for V_3^N,

$$\begin{aligned} V_3^{N,2}(t) &= V_3^{N,2}(0) + N^{-1}Y_2(\int_0^t \kappa_2 N^3 V_2^{N,2}(s)\,ds) - N^{-1}Y_3(\int_0^t \kappa_3 N^3 V_3^{N,2}(s)\,ds) \\ &-N^{-1}Y_5(\int_0^t \kappa_5 N^2 V_3^{N,2}(s)\,ds) - N^{-1}Y_6(\int_0^t \kappa_6 N^2 V_3^{N,2}(s)\,ds) \\ &-N^{-1}Y_7(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds), \end{aligned} \tag{4.50}$$

and dividing (4.50) by N^2, we have

$$\int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right) = O\left(N^{-1}\right). \tag{4.51}$$

After passing short amount of time from $t = 0$, V_2^N and V_3^N satisfy (4.51). Therefore, we set up initial values as ones in (4.49)

Letting $N \to \infty$, the term for Reaction 8 converges to zero. Applying the law of large numbers for Poisson processes, for each $u_0 > 0$,

$$\lim_{N\to\infty} \sup_{u \le u_0} \left|\frac{Y_k(Nu)}{N} - u\right| = 0 \qquad a.s.$$

Fast processes $V_2^{N,2}$, $V_3^{N,2}$, and $V_6^{N,2}$ are involved in the terms for Reaction 5, 6, 9, and 10. Behavior of the fast processes is either projected or averaged by the processes in the current time scale. The reduced system in the time of $t \sim O(N^2)$ and an error between the normalized processes in the system and the limiting processes in the reduced system are summarized in Theorem 4.3.

Theorem 4.3. *In times of* $O(N^2)$, $\{V_1^{N,2}, V_2^{N,2}, V_3^{N,2}, V_4^{N,2}, V_5^{N,2}, V_8^{N,2}, V_9^{N,2}\}$ *converges to* $\{V_1^2, V_2^2, V_3^2, V_4^2, V_5^2, V_8^2, V_9^2\}$ *as* $N \to \infty$, *which is a solution of*

$$\begin{aligned}
V_1^2(t) &= V_1^2(0) + Y_{13}\Big(\int_0^t \kappa_{13}\, ds\Big) - Y_{14}\Big(\int_0^t \kappa_{14} V_1^2(s)\, ds\Big) && (4.52)\\
V_2^2(t) &= V_2^2(0) && (4.53)\\
&\quad + \int_0^t \frac{\kappa_3}{\kappa_2+\kappa_3}\cdot\Big(\kappa_4 V_1^2(s) - \frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3}\big(V_2^2(s)+V_3^2(s)\big)\cdot\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\Big)\, ds\\
V_3^2(t) &= V_3^2(0) && (4.54)\\
&\quad + \int_0^t \frac{\kappa_2}{\kappa_2+\kappa_3}\cdot\Big(\kappa_4 V_1^2(s) - \frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3}\big(V_2^2(s)+V_3^2(s)\big)\cdot\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\Big)\, ds\\
V_4^2(t) &= V_4^2(0) + \int_0^t \big(\kappa_6 V_3^2(s) - \kappa_{18} V_4^2(s)\big)\, ds && (4.55)\\
V_5^2(t) &= V_5^2(0) + \int_0^t \big(\kappa_5 V_3^2(s) - \kappa_{16} V_5^2(s)\big)\, ds && (4.56)\\
V_8^2(t) &= V_8^2(0) + \int_0^t \big(\kappa_1 - \kappa_7 V_3^2(s) - \kappa_{11} V_8^2(s)\big)\, ds && (4.57)\\
V_9^2(t) &= V_9^2(0) + \int_0^t \kappa_7 V_3^2(s)\, ds && (4.58)
\end{aligned}$$

where

$$\begin{aligned}
&V_1^2(0) = X_1(0), \quad V_2^2(0) = 0, \quad V_3^2(0) = 0,\\
&V_4^2(0) = \frac{X_4(0)}{N_0^2}, \qquad V_5^2(0) = \frac{X_5(0)}{N_0^2},\\
&V_8^2(0) = \frac{X_8(0)}{N_0^2}, \qquad V_9^2(0) = \frac{X_9(0)}{N_0^2}.
\end{aligned}$$

An error between the normalized processes in the system and the limiting processes in the reduced system is $O\left(N^{-1/2}\right)$.

$$\sup_{t\le T}\Big(|V_2^{N,2}(t) - V_2^2(t)| + |V_3^{N,2}(t) - V_3^2(t)| + |V_4^{N,2}(t) - V_4^2(t)| \qquad (4.59)$$

$$+|V_5^{N,2}(t)-V_5^2(t)|+|V_8^{N,2}(t)-V_8^2(t)|+|V_9^{N,2}(t)-V_9^2(t)|\Big)$$
$$\leq\ O\left(N^{-1/2}\right).$$

Proof of Theorem 4.3. We prove a central limit theorem in Theorem 5.3 in Section 5.2. The proof of Theorem 5.3 and $V_1^{N,2}(t)=V_1^2(t)$ give (4.59). □

In Lemma 4.5, we obtain the right form of the limit of $\int_0^t V_2^{N,2}(s)V_6^{N,2}(s)\,ds$ as $N\to\infty$.

Lemma 4.5.

$$\int_0^t\left(V_2^{N,2}(s)V_6^{N,2}(s)-\frac{\kappa_3}{\kappa_2+\kappa_3}\left(V_2^{N,2}(s)+V_3^{N,2}(s)\right)\frac{\kappa_7V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right)ds$$
$$=O\left(N^{-1}\right) \tag{4.60}$$

Proof of Lemma 4.5. Split $\int_0^t V_2^{N,2}(s)V_6^{N,2}(s)\,ds$ into two terms.

$$\begin{aligned}\int_0^t V_2^{N,2}(s)V_6^{N,2}(s)\,ds &= \frac{\kappa_3}{\kappa_2+\kappa_3}\int_0^t\left(V_2^{N,2}(s)+V_3^{N,2}(s)\right)V_6^{N,2}(s)\,ds \\ &\quad+\frac{1}{\kappa_2+\kappa_3}\int_0^t\left(\kappa_2V_2^{N,2}(s)-\kappa_3V_3^{N,2}(s)\right)V_6^{N,2}(s)\,ds\end{aligned} \tag{4.61}$$

Since the two split terms in (4.61) contain $V_6^{N,2}$, which is a fast process in times of $O\left(N^2\right)$, we need to get averaged processes as limits.

First, calculate $V_2^NV_6^N$ and $V_3^NV_6^N$ using Ito's formula.

$$\begin{aligned}V_2^{N,2}(s)V_6^{N,2}(s) &= V_2^{N,2}(0)V_6^{N,2}(0)+\int_0^t V_2^{N,2}(s-)d\tilde{V}_6^{N,2}(s) \\ &\quad+\int_0^t V_6^{N,2}(s-)d\tilde{V}_2^{N,2}(s)+[V_2^{N,2},V_6^{N,2}]_t \\ &\quad+N^2\int_0^t V_2^{N,2}(s)\left(\kappa_7V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)-\kappa_{10}V_6^{N,2}(s)V_8^{N,2}(s)\right)ds\end{aligned} \tag{4.62}$$

$$+N^2\int_0^t V_6^{N,2}(s)\big(\kappa_3 V_3^{N,2}(s)-\kappa_2 V_2^{N,2}(s)\big)\,ds+\int_0^t O(N)\,ds$$

and

$$\begin{aligned}V_3^{N,2}(s)V_6^{N,2}(s) &= V_3^{N,2}(0)V_6^{N,2}(0)+\int_0^t V_3^{N,2}(s-)d\tilde{V}_6^{N,2}(s) \\ &+\int_0^t V_6^{N,2}(s-)d\tilde{V}_3^{N,2}(s)+[V_3^{N,2},V_6^{N,2}]_t \\ &+N^2\int_0^t V_3^{N,2}(s)\big(\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)-\kappa_{10}V_6^{N,2}(s)V_8^{N,2}(s)\big)\,ds \\ &+N^2\int_0^t V_6^{N,2}(s)\big(\kappa_2 V_2^{N,2}(s)-\kappa_3 V_3^{N,2}(s)\big)\,ds+\int_0^t O(N)\,ds.\end{aligned} \tag{4.63}$$

We also have

$$\begin{aligned}[V_2^{N,2},V_6^{N,2}]_t &= N^{-1}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big)+N^{-1}\tilde{Y}_8\Big(\int_0^t \kappa_8 V_7^{N,2}(s)\,ds\Big) \\ &+N^{-1}\tilde{Y}_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big) \\ &+\int_0^t \big(\kappa_7 N V_3^{N,2}(s)+\kappa_8 N^{-1}V_7^{N,2}(s)+\kappa_9 V_2^{N,2}(s)V_6^{N,2}(s)\big)\,ds\end{aligned} \tag{4.64}$$

and

$$[V_3^{N,2},V_6^{N,2}]_t = -N^{-1}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big)-\int_0^t \kappa_7 N V_3^{N,2}(s)\,ds. \tag{4.65}$$

Comparing the exponents inside and outside the centered counting processes, we have

$$\begin{aligned}N^{-2}\int_0^t V_2^{N,2}(s)d\tilde{V}_6^{N,2}(s)+N^{-2}\int_0^t V_6^{N,2}(s)d\tilde{V}_2^{N,2}(s) &= O\left(N^{-1}\right) \\ N^{-2}\int_0^t V_3^{N,2}(s)d\tilde{V}_6^{N,2}(s)+N^{-2}\int_0^t V_6^{N,2}(s)d\tilde{V}_3^{N,2}(s) &= O\left(N^{-1}\right).\end{aligned}$$

We know that $N^{-2}\big(V_2^{N,2}(t)+V_3^{N,2}(t)\big)V_6^{N,2}(t) \to O\left(\frac{1}{N^2}\right)$ and $N^{-2}\big(V_2^{N,2}(0)+V_3^{N,2}(0)\big)V_6^{N,2}(0) \to O\left(\frac{1}{N^2}\right)$. Then, adding (4.62) and (4.63), dividing by N^2, and considering (4.64) and (4.65), we have

$$\int_0^t \big(V_2^{N,2}(s)+V_3^{N,2}(s)\big)\big(\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)-\kappa_{10}V_6^{N,2}(s)V_8^{N,2}(s)\big)\,ds, \\ = O\left(N^{-1}\right). \tag{4.66}$$

$V_8^{N,2}(0)\neq 0$ and we can take the finite time interval in which $V_8^{N,2}t$ is strictly positive. Since $V_8^{N,2}$ is an intermediate process in times of $O\left(N^2\right)$, using Lemma 4.6, (4.66) implies

$$\int_0^t \big(V_2^{N,2}(s)+V_3^{N,2}(s)\big)\left(V_6^{N,2}(s)-\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right)ds \;=\; O\left(N^{-1}\right) \tag{4.67}$$

Now, multiplying (4.62) by κ_2 and multiplying (4.63) by κ_3, we subtract one from the other. Dividing by N^2 and using the similar way in (4.66), we have

$$\int_0^t \big(\kappa_2 V_2^{N,2}(s)-\kappa_3 V_3^{N,2}(s)\big) \\ \times\big(\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)-(\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s))V_6^{N,2}(s)\big)\,ds \\ = O\left(N^{-1}\right). \tag{4.68}$$

Since $V_8^{N,2}$ is an intermediate process in times of $O\left(N^2\right)$, using Lemma 4.6, (4.68) implies

$$\int_0^t \big(\kappa_2 V_2^{N,2}(s)-\kappa_3 V_3^{N,2}(s)\big)\left(V_6^{N,2}(s)-\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)}\right)ds \\ = O\left(N^{-1}\right). \tag{4.69}$$

In (4.69), since $V_2^{N,2}$, $V_3^{N,2}$, $V_8^{N,2}$, and $V_9^{N,2}$ are intermediate processes in times of $O\left(N^2\right)$, using Lemma 4.6 and (4.51), we have

$$\int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right) \frac{\kappa_7 V_3^{N,2}(s) + \kappa_{12} V_9^{N,2}(s)}{\kappa_2 + \kappa_3 + \kappa_{10} V_8^{N,2}(s)}\, ds$$
$$= O\left(N^{-1}\right). \tag{4.70}$$

Then using (4.69) and (4.70), we obtain

$$\int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right) V_6^{N,2}(s)\, ds = O\left(N^{-1}\right). \tag{4.71}$$

Using (4.61), (4.67), and (4.71), we prove (4.60). □

Lemma 4.6. *If for any* $t > 0$,

$$\sup_n \int_0^t |u_n(s)|\, ds \quad < \quad \infty, \tag{4.72}$$
$$\int_0^t u_n(s)\, ds \quad \to \quad \int_0^t u(s)\, ds, \tag{4.73}$$
$$\sup_{s\le t} |v_n(s) - v(s)| \quad \to \quad 0 \text{ in } \mathcal{D}_{\mathbb{R}}[0,\infty), \tag{4.74}$$

then

$$\int_0^t u_n(s) v_n(s)\, ds \to \int_0^t u(s) v(s)\, ds. \tag{4.75}$$

Proof of Lemma 4.6. The absolute difference between the terms in (4.75) is given as follows.

$$\left| \int_0^t \left(u_n(s) v_n(s) - u(s) v(s)\right)\, ds \right|$$
$$= \left| \int_0^t \left((u_n(s) - u(s)) v(s) + u_n(s)(v_n(s) - v(s))\right)\, ds \right| \tag{4.76}$$

$$\leq \left|\int_0^t (u_n(s) - u(s))\, v(s)\, ds\right| + \int_0^t u_n(s)\, |v_n(s) - v(s)|\, ds$$
$$\leq \left|\int_0^t (u_n(s) - u(s))\, v(s)\, ds\right| + \sup_{0\leq s\leq t} |v_n(s) - v(s)| \int_0^t u_n(s)\, ds$$

In (4.76), $u_n \geq 0$ is used. Since $\sup_{s\leq t} |v_n(s) - v(s)| \longrightarrow 0$, using $\int_0^t u_n(s)\, ds < \infty$,

$$\sup_{s\leq t} |v_n(s) - v(s)| \int_0^t u_n(s)\, ds \quad \longrightarrow \quad 0.$$

Since $v \in \mathcal{D}_{\mathbb{R}}[0, \infty)$, there exists a step function

$$\sum_{i=1}^{M_m} a_i^m 1_{[\frac{i-1}{2^m}, \frac{i}{2^m})} \quad \longrightarrow \quad v$$

as $m \to \infty$. Then

$$\left|\int_0^t (u_n(s) - u(s)) \sum_{i=1}^{M_m} a_i^m 1_{[\frac{i-1}{2^m}, \frac{i}{2^m})}(s)\, ds\right| \leq \sum_{i=1}^{M_m} |a_i^m| \left|\int_{\frac{i-1}{2^m}\wedge t}^{\frac{i}{2^m}\wedge t} (u_n(s) - u(s))\; ds\right| \tag{4.77}$$

Using (4.73) and letting $n \to \infty$,

$$\left|\int_{\frac{i-1}{2^m}\wedge t}^{\frac{i}{2^m}\wedge t} (u_n(s) - u(s))\; ds\right| \quad \longrightarrow \quad 0. \tag{4.78}$$

In (4.77), we have

$$\int_0^t (u_n(s) - u(s)) \sum_{i=1}^{M_m} a_i^m 1_{[\frac{i-1}{2^m}, \frac{i}{2^m})}\, ds \quad \longrightarrow \quad \int_0^t (u_n(s) - u(s))\, v(s)\, ds \tag{4.79}$$

as $m \to \infty$. Therefore, using (4.77), (4.78), and (4.79) and letting $n \to \infty$, we have

$$\left|\int_0^t (u_n(s) - u(s))\, v(s)\, ds\right| \quad \longrightarrow \quad 0$$

in (4.76). Therefore,

$$\int_0^t u_n(s)v_n(s)\,ds \longrightarrow \int_0^t u(s)v(s)\,ds.$$

$\square$

4.1.3 Calculation of quasi-steady-state distributions using averaged generator in the times of $O\left(N^2\right)$

In Lemma 4.7, the quasi-stationary distributions of the fast processes, $V_6^{N,2}$ and $V_7^{N,2}$, are obtains in terms of the intermediate processes.

Lemma 4.7. *In times of $O\left(N^2\right)$, for almost every t, $\left(V_6^{N,2}(t), V_7^{N,2}(t)\right)$ converges in distribution to $\left(\hat{V}_6^2(t), \hat{V}_7^2(t)\right)$ where $\hat{V}_6^2(t)$ has a Poisson distribution with parameter*

$$\frac{\kappa_7 V_3^2(t) + \kappa_{12} V_9^2(t)}{\kappa_{10} V_8^2(t)}$$

and where $\hat{V}_7^2(t)$ has a Poisson distribution with parameter

$$\frac{\kappa_9 V_2^2(t)\left(\kappa_7 V_3^2(t) + \kappa_{12} V_9^2(t)\right)}{\kappa_{10}\kappa_{15} V_4^2(t) V_8^2(t)}.$$

Proof of Lemma 4.7. Full generator of the heat shock response model in the times of $O\left(N^2\right)$ is

$$\mathbb{A}^N f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9) \tag{4.80}$$

$$\kappa_1 N^2\big(f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8 + N^{-2}, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_2 N^3 v_2\big(f(v_1, v_2 - N^{-1}, v_3 + N^{-1}, v_4, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_3 N^3 v_3\big(f(v_1, v_2 + N^{-1}, v_3 - N^{-1}, v_4, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_4 N v_1\big(f(v_1, v_2 + N^{-1}, v_3, v_4, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_5 N^2 v_3\big(f(v_1, v_2 + N^{-1}, v_3 - N^{-1}, v_4, v_5 + N^{-2}, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_6 N^2 v_3\big(f(v_1, v_2 + N^{-1}, v_3 - N^{-1}, v_4 + N^{-2}, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_7 N^2 v_3\big(f(v_1, v_2 + N^{-1}, v_3 - N^{-1}, v_4, v_5, v_6 + 1, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_8 v_7\big(f(v_1, v_2 + N^{-1}, v_3, v_4, v_5, v_6 + 1, v_7 - 1, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_9 N v_2 v_6\big(f(v_1, v_2 - N^{-1}, v_3, v_4, v_5, v_6 - 1, v_7 + 1, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{10} N^2 v_6 v_8\big(f(v_1, v_2, v_3, v_4, v_5, v_6 - 1, v_7, v_8 - N^{-2}, v_9 + N^{-2}) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{11} N^2 v_8\big(f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8 - N^{-2}, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{12} N^2 v_9\big(f(v_1, v_2, v_3, v_4, v_5, v_6 + 1, v_7, v_8 + N^{-2}, v_9 - N^{-2}) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{13}\big(f(v_1 + 1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{14} v_1\big(f(v_1 - 1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{15} N v_4 v_7\big(f(v_1, v_2, v_3, v_4, v_5, v_6 + 1, v_7 - 1, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{16} N^2 v_5\big(f(v_1, v_2, v_3, v_4, v_5 - N^{-2}, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{17} v_6\big(f(v_1, v_2, v_3, v_4, v_5, v_6 - 1, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big)$$

$$+\kappa_{18} N^2 v_4\big(f(v_1, v_2, v_3, v_4 - N^{-2}, v_5, v_6, v_7, v_8, v_9) - f(v_1, v_2, v_3, v_4, v_5, v_6, v_7, v_8, v_9)\big).$$

Let us define generator with respect to the fast processes, $V_6^{N,2}$ and $V_7^{N,2}$ in terms of $V_2^{N,2}$, $V_3^{N,2}$, $V_4^{N,2}$, $V_8^{N,2}$, and $V_9^{N,2}$ in the times of $O(N^2)$. x and y are the variables regarding $V_6^{N,2}$ and $V_7^{N,2}$, respectively. The generator is

$$\begin{aligned}
\mathbb{B}_s^N g(x,y) &= \kappa_7 N^2 V_3^{N,2}(s)\big(g(x+1,y) - g(x,y)\big) \\
&\quad + \kappa_8 y\big(g(x+1,y-1) - g(x,y)\big) \\
&\quad + \kappa_9 N V_2^{N,2}(s) x\big(g(x-1,y+1) - g(x,y)\big) \\
&\quad + (\kappa_{10} N^2 V_8^{N,2}(s) x + \kappa_{17} x)\big(g(x-1,y) - g(x,y)\big)
\end{aligned}$$

$$+\kappa_{12}N^2V_9^{N,2}(s)\big(g(x+1,y)-g(x,y)\big)$$
$$+\kappa_{15}NV_4^{N,2}(s)y\big(g(x+1,y-1)-g(x,y)\big).$$

Then,

$$\begin{aligned} M_g^N(t) &\equiv g(V_6^{N,2}(t),V_7^{N,2}(t))-g(V_6^{N,2}(0),V_7^{N,2}(0)) \\ &\quad -\int_0^t \mathbb{B}_s^N g(V_6^{N,2}(s),V_7^{N,2}(s))\,ds \end{aligned} \tag{4.81}$$

is a martingale. Let us define the occupation measure Γ^N for $V_6^{N,2}$ and $V_7^{N,2}$ by

$$\Gamma^N(C\times D\times[0,t]) = \int_0^t 1_C(V_6^{N,2}(s))1_D(V_7^{N,2}(s))\,ds \tag{4.82}$$

Using (4.82), we rewrite (4.81) as

$$\begin{aligned} M_g^N(t) &\equiv g(V_6^{N,2}(t),V_7^{N,2}(t))-g(V_6^{N,2}(0),V_7^{N,2}(0)) \\ &\quad -\int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{B}_s^N g(x,y)\,\Gamma^N(dx\times dy\times ds). \end{aligned}$$

Splitting $\mathbb{B}_s^N(x,y)$ into three parts based on the scaling exponent in each term, we have $\mathbb{C}_s^{N,1}$ and $\mathbb{C}_s^{N,2}$ with each term of $O(1)$ and $\mathbb{C}_s^{N,3}$ with each terms of $O(1)$ or of smaller order.

$$\mathbb{B}_s^N g(x,y) = N^2\mathbb{C}_s^{N,1}g(x,y)+N\mathbb{C}_s^{N,2}g(x,y)+\mathbb{C}_s^{N,3}g(x,y)$$

where

$$\mathbb{C}_s^{N,1}g(x,y) = \kappa_7V_3^{N,2}(s)\big(g(x+1,y)-g(x,y)\big)$$

$$+\kappa_{10}V_8^{N,2}(s)x\big(g(x-1,y)-g(x,y)\big)$$
$$+\kappa_{12}V_9^{N,2}(s)\big(g(x+1,y)-g(x,y)\big),$$

$$\mathbb{C}_s^{N,2}g(x,y) \;=\; \kappa_9 V_2^{N,2}(s)x\big(g(x-1,y+1)-g(x,y)\big)$$
$$+\kappa_{15}V_4^{N,2}(s)y\big(g(x+1,y-1)-g(x,y)\big),$$

and

$$\mathbb{C}_s^{N,3}g(x,y) \;=\; \kappa_8 y\big(g(x+1,y-1)-g(x,y)\big)$$
$$+\kappa_{17}x\big(g(x-1,y)-g(x,y)\big).$$

In Lemma 4.8, we show that Γ^N is relatively compact. We use Theorem 2.1. in [11]. Let $\Gamma^N \Rightarrow \Gamma$ as $N \to \infty$. Then we will get

$$\lim_{N\to\infty}\left(\mathbb{C}_s^{N,1}g_1(x) - \mathbb{C}^{\infty,1}_{(V_8^2(s),V_9^2(s))}g_1(x)\right) \;=\; 0$$

where

$$\mathbb{C}^{\infty,1}_{(V_3^2(s),V_8^2(s),V_9^2(s))}g_1(x) \;=\; \kappa_7 V_3^2(s)\big(g(x+1)-g(x)\big) \tag{4.83}$$
$$+\kappa_{10}V_8^2(s)x\big(g_1(x-1)-g_1(x)\big)$$
$$+\kappa_{12}V_9^2(s)\big(g_1(x+1)-g_1(x)\big).$$

Then

$$M_{g_1}^N(t) \;\equiv\; g_1(V_6^{N,2}(t)) - g_1(V_6^{N,2}(0)) - N^2\int_{(\mathbb{Z}^+)^2\times[0,t]}\mathbb{C}_s^{N,1}g_1(x)\,\Gamma^N(dx\times dy\times ds)$$

$$-N\int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{C}_s^{N,2} g_1(x)\,\Gamma^N(dx\times dy\times ds)$$
$$-\int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{C}_s^{N,3} g_1(x)\,\Gamma^N(dx\times dy\times ds)$$

is a martingale. By dividing by N^2 and letting $N\to\infty$, we get

$$\int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{C}^{\infty,1}_{(V_3^2(s),V_8^2(s),V_9^2(s))} g_1(x)\,\Gamma(dx\times dy\times ds)=0.$$

Using (4.83), for each $t\geq 0$, $V_6^{N,2}(t)$ converges in distribution to $\hat{V}_6^2(t)$ where $\hat{V}_6^2(t)$ has a Poisson distribution with parameter

$$\frac{\kappa_7 V_3^2(t)+\kappa_{12}V_9^2(t)}{\kappa_{10}V_8^2(t)}.$$

Let's apply generator to the function of w. Then,

$$\lim_{N\to\infty}\left(\mathbb{C}_s^{N,2}g_2(w)-\mathbb{C}^{\infty,2}_{(V_2^2(s),V_3^2(s),V_4^2(s),V_8^2(s),V_9^2(s))}g_2(w)\right) \;=\; 0$$

where

$$\begin{aligned}\mathbb{C}^{\infty,2}_{(V_2^2(s),V_3^2(s),V_4^2(s),V_8^2(s),V_9^2(s))}g_2(y) &= \kappa_9 V_2^2(s)\frac{\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\big(g_2(y+1)-g_2(y)\big)\\ &\quad+\kappa_{15}V_4^2(s)y\big(g_2(y-1)-g_2(y)\big).\end{aligned}\tag{4.84}$$

Then

$$\begin{aligned}M_{g_2}^N(t) &\equiv g_2(V_7^{N,2}(t))-g_2(V_7^{N,2}(0))\\ &\quad -N\int_{(\mathbb{Z}^+)^2\times[0,t]}\mathbb{C}_s^{N,2}g_2(y)\,\Gamma^N(dx\times dy\times ds)\end{aligned}$$

$$- \int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{C}_s^{N,3} g_2(y)\, \Gamma^N(dx \times dy \times ds)$$

is a martingale. By dividing by N and let $N \to \infty$, we get

$$\int_{(\mathbb{Z}^+)^2\times[0,t]} \mathbb{C}^{\infty,2}_{(V_2^2(s),V_3^2(s),V_4^2(s),V_8^2(s),V_9^2(s))} g_2(y)\, \Gamma(dx \times dy \times ds) \;=\; 0$$

Using (4.84), for almost every t, $V_7^{N,2}(t)$ converges in distribution to $\hat{V}_7^2(t)$ where $\hat{V}_7^2(t)$ has a Poisson distribution with parameter

$$\frac{\kappa_9 V_2^2(t)\big(\kappa_7 V_3^2(t) + \kappa_{12} V_9^2(t)\big)}{\kappa_{10}\kappa_{15} V_4^2(t) V_8^2(t)}.$$

□

In Lemma 4.8, we prove the relative compactness of $V_6^{N,2}$ and $V_7^{N,2}$.

Lemma 4.8. *In the times of $O(N^2)$, Γ^N is relatively compact.*

Proof of Lemma 4.8. Γ^N is defined

$$\begin{aligned} &\Gamma^N(C \times D \times [0,t]) \\ =\;& \int_0^t 1_C(V_6^{N,2}(s)) 1_D(V_7^{N,2}(s))\, ds. \end{aligned} \tag{4.85}$$

To show relatively compactness of Γ^N, we only need to show that $V_6^{N,2}$ and $V_7^{N,2}$ are relatively compact. The equation for $V_6^{N,2} + V_7^{N,2}$ is

$$\begin{aligned} V_6^{N,2}(t) + V_7^{N,2}(t) \;&=\; V_6^{N,2}(0) + V_7^{N,2}(0) + Y_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\, ds\Big) \\ &+ Y_{12}\Big(\int_0^t \kappa_{12} N^2 V_9^{N,2}(s)\, ds\Big) - Y_{10}\Big(\int_0^t \kappa_{10} N^2 V_6^{N,2}(s) V_8^{N,2}(s)\, ds\Big) \\ &- Y_{17}\Big(\int_0^t \kappa_{17} V_6^{N,2}(s)\, ds\Big). \end{aligned} \tag{4.86}$$

Dividing (4.86) by N^2 and taking the expectation, we have

$$\begin{aligned}\int_0^t \kappa_{10} E[V_6^{N,2}(s)V_8^{N,2}(s)]\,ds &\le N^{-2}E[V_6^{N,2}(0)] + N^{-2}E[V_7^{N,2}(0)] \\ &\quad + \int_0^t \kappa_7 E[V_3^{N,2}(s)]\,ds.\end{aligned} \tag{4.87}$$

We will show that $V_3^{N,2}$ is uniformly bounded. The equation for $V_2^{N,2} + V_3^{N,2} + N^{-1}V_7^{N,2}$ is

$$\begin{aligned}V_2^{N,2}(t) + V_3^{N,2}(t) + N^{-1}V_7^{N,2}(t) &= V_2^{N,2}(0) + V_3^{N,2}(0) + N^{-1}V_7^{N,2}(0) \\ +N^{-1}Y_4\Big(\int_0^t \kappa_4 N V_1^{N,2}(s)\,ds\Big) &- N^{-1}Y_{15}\Big(\int_0^t \kappa_{15} N V_4^{N,2}(s)V_7^{N,2}(s)\,ds\Big).\end{aligned} \tag{4.88}$$

Eliminating the negative term and taking the expectation, we have

$$\begin{aligned}E[V_2^{N,2}(t)] + E[V_3^{N,2}(t)] + N^{-1}E[V_7^{N,2}(t)] &\le E[V_2^{N,2}(0)] + E[V_3^{N,2}(0)] \\ &\quad +N^{-1}E[V_7^{N,2}(0)] + \int_0^t \kappa_4 E[V_1^{N,2}(s)]\,ds.\end{aligned} \tag{4.89}$$

The equation for $V_1^{N,2}$ is

$$V_1^{N,2}(t) = V_1^{N,2}(0) + Y_{13}\Big(\int_0^t \kappa_{13}\,ds\Big) - Y_{14}\Big(\int_0^t \kappa_{14} V_1^{N,2}(s)\,ds\Big). \tag{4.90}$$

Solving (4.90) for $E[V_1^{N,2}(t)]$, we have

$$E[V_1^{N,2}(t)] = \Big(E[V_1^{N,2}(0)] - \frac{\kappa_{13}}{\kappa_{14}}\Big)e^{-\kappa_{14}t} + \frac{\kappa_{13}}{\kappa_{14}}.$$

Therefore, $V_1^{N,2}$ and $V_3^{N,2}$ are uniformly bounded and using (4.87), we have

$$\sup_N E\Big[\int_0^t V_6^{N,2}(s)V_8^{N,2}(s)\,ds\Big] < \infty. \tag{4.91}$$

We have

$$\int_0^t 1_{[k,\infty)}(V_6^{N,2}(s))\,ds \;\leq\; \int_0^t \frac{V_6^{N,2}(s)}{k}\,ds \tag{4.92}$$

and taking the probability in both sides of (4.92), for fixed $\delta > 0$, we get

$$\begin{aligned} &\sup_N P\Big\{\int_0^t \frac{V_6^{N,2}(s)}{k}\,ds > \delta\Big\} \qquad (4.93)\\ \leq\;& \sup_N P\Big\{\inf_{s\leq t} V_8^{N,2}(s) \leq \epsilon\Big\} + \sup_N P\Big\{\int_0^t V_6^{N,2}(s)V_8^{N,2}(s)\,ds > \delta k\epsilon\Big\}\\ \leq\;& \sup_N P\Big\{\inf_{s\leq t} V_8^{N,2}(s) \leq \epsilon\Big\} + \sup_N \frac{E\Big[\int_0^t V_6^{N,2} s V_8^{N,2}(s)\,ds\Big]}{\delta k\epsilon}. \end{aligned}$$

Since $V_8^{N,2}(0) \neq 0$ and (4.92), we can take $\epsilon > 0$ small enough and k large enough to make both terms in the right side of (4.93). Therefore, $V_6^{N,2}$ is relatively compact.

Now, consider relatively compactness of $V_7^{N,2}$. The equation for $V_7^{N,2}$ is

$$\begin{aligned} V_7^{N,2}(t) \;=\;& V_7^{N,2}(0) + Y_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big) - Y_8\Big(\int_0^t \kappa_8 V_7^{N,2}(s)V_6^{N,2}(s)\,ds\Big)\\ &-Y_{15}\Big(\int_0^t \kappa_{15} N V_4^{N,2}(s)V_7^{N,2}(s)\,ds\Big). \end{aligned} \tag{4.94}$$

Using (4.94), we have

$$Y_{15}\Big(\int_0^t \kappa_{15} N V_4^{N,2}(s)V_7^{N,2}(s)\,ds\Big) \leq V_7^{N,2}(0) + Y_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big). \tag{4.95}$$

Dividing (4.96) by N and using $\frac{Y_k(Nu)-Nu}{N} \approx \frac{1}{\sqrt{N}} W(u)$, for large N, we have

$$\int_0^t \kappa_{15} V_4^{N,2}(s) V_7^{N,2}(s)\, ds \leq \frac{V_7^{N,2}(0)}{N} + Y_9\Big(\int_0^t \kappa_9 V_2^{N,2}(s) V_6^{N,2}(s)\, ds\Big) + O\left(N^{-1/2}\right). \tag{4.96}$$

Taking the probability in both sides and the lim sup, we have

$$\begin{aligned} &\limsup_{N\to\infty} P\Big\{ \int_0^t \kappa_{15} V_4^{N,2}(s) V_7^{N,2}(s)\, ds > k' \Big\} \qquad (4.97)\\ &\leq \limsup_{N\to\infty} P\Big\{ \int_0^t \kappa_9 V_2^{N,2}(s) V_6^{N,2}(s)\, ds > k' \Big\} \\ &\leq \limsup_{N\to\infty} P\Big\{ \int_0^t \kappa_9 V_6^{N,2}(s) V_8^{N,2}(s)\, ds > \frac{k'}{m} \Big\} + \limsup_{N\to\infty} P\Big\{ \sup_{s\leq t} \frac{V_2^{N,2}(s)}{V_8^{N,2}(s)}\, ds > m \Big\} \\ &\leq \limsup_{N\to\infty} \frac{mE\Big[\int_0^t \kappa_9 V_6^{N,2}(s) V_8^{N,2}(s)\, ds\Big]}{k'} + \limsup_{N\to\infty} P\Big\{ \sup_{s\leq t} \frac{V_2^{N,2}(s)}{V_8^{N,2}(s)}\, ds > m \Big\} \end{aligned}$$

Using (4.91) and taking k' large enough, we can make the first term on the right side of (4.97) small. Since $V_2^{N,2}$ and $V_8^{N,2}$ converge to their limits as $N \to \infty$ and since $V_8^{N,2}(0) \neq 0$, we can take m large to make the second term small.

Next, similar to (4.93), we show the relatively compactness of $V_7^{N,2}$ using (4.97).

$$\int_0^t 1_{[k'',\infty)}(V_7^{N,2}(s))\, ds \;\; \leq \;\; \int_0^t \frac{V_7^{N,2}(s)}{k''}\, ds \tag{4.98}$$

Taking the probability and $\sup_N$, we have

$$\begin{aligned} &\sup_N P\Big\{ \int_0^t \frac{V_7^{N,2}(s)}{k''}\, ds > \delta' \Big\} \qquad (4.99)\\ \leq \;\; &\sup_N P\Big\{ \inf_{s\leq t} V_4^{N,2}(s) \leq \epsilon' \Big\} + \sup_N P\Big\{ \int_0^t V_4^{N,2}(s) V_7^{N,2}(s)\, ds > \delta' k'' \epsilon' \Big\} \end{aligned}$$

Since $V_4^{N,2}(0) \neq 0$ and (4.98), we can take $\epsilon' > 0$ small enough to make the first term in the right side of (4.99). Using (4.97), $V_7^{N,2}$ is relatively compact. $\square$

4.2 Simulations

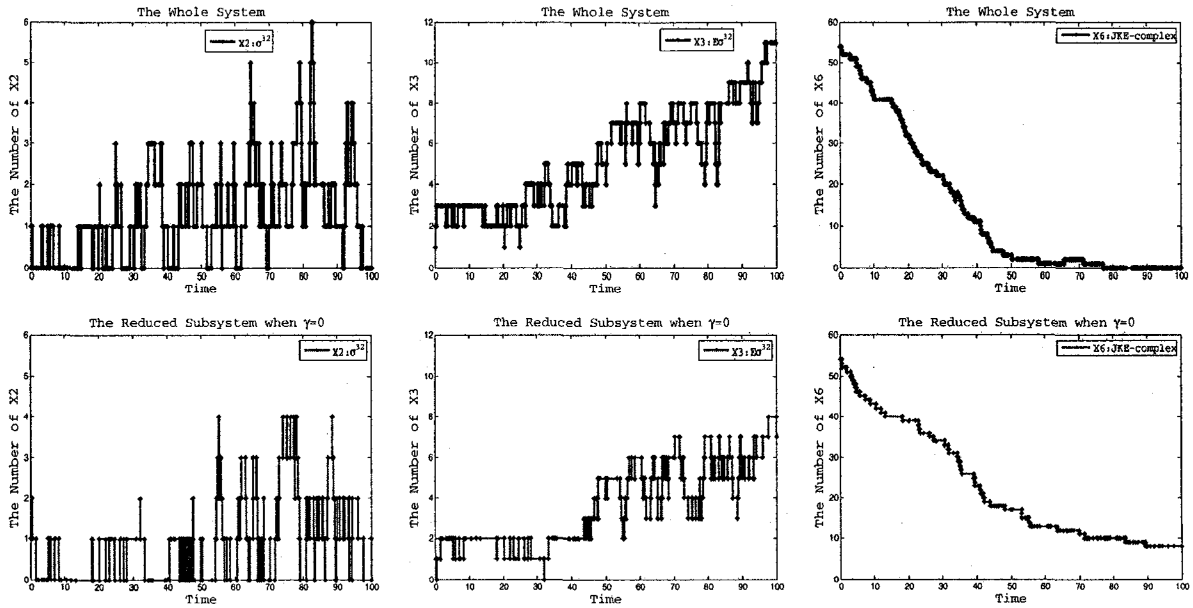
For stochastic simulation, we use Exact SSA (Gillespie's Stochastic Simulation Algorithm). To get behavior of the whole system, we used SSA with nine species and 18 reactions. Resulst are located in the figure with black graphs. Next, to get approximated behavior of the processes, we use systems of limiting processes in three diffeent time scales. We compare the behavior of processes in the whole system and the behavior of approximated processes in the reduced system.

Table 9: Initial values used in simulation

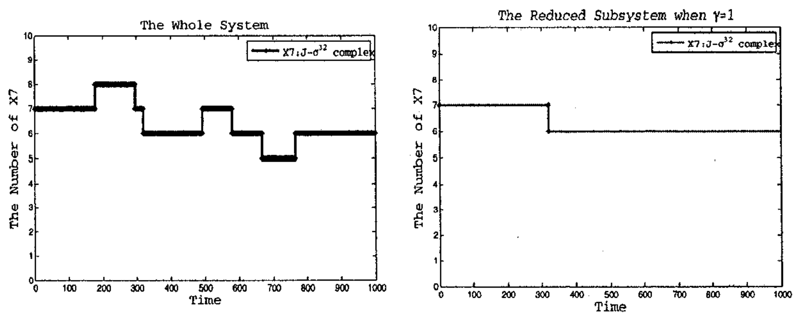
ith	Initial value
A_1	10
A_2	1
A_3	1
A_4	93
A_5	172
A_6	54
A_7	7
A_8	$50^{\ddagger}$[5]
A_9	$0^{\ddagger}$

[5]Initial values with ‡ are assumed based on the heat shock response model in [14]. Others are given in [14].

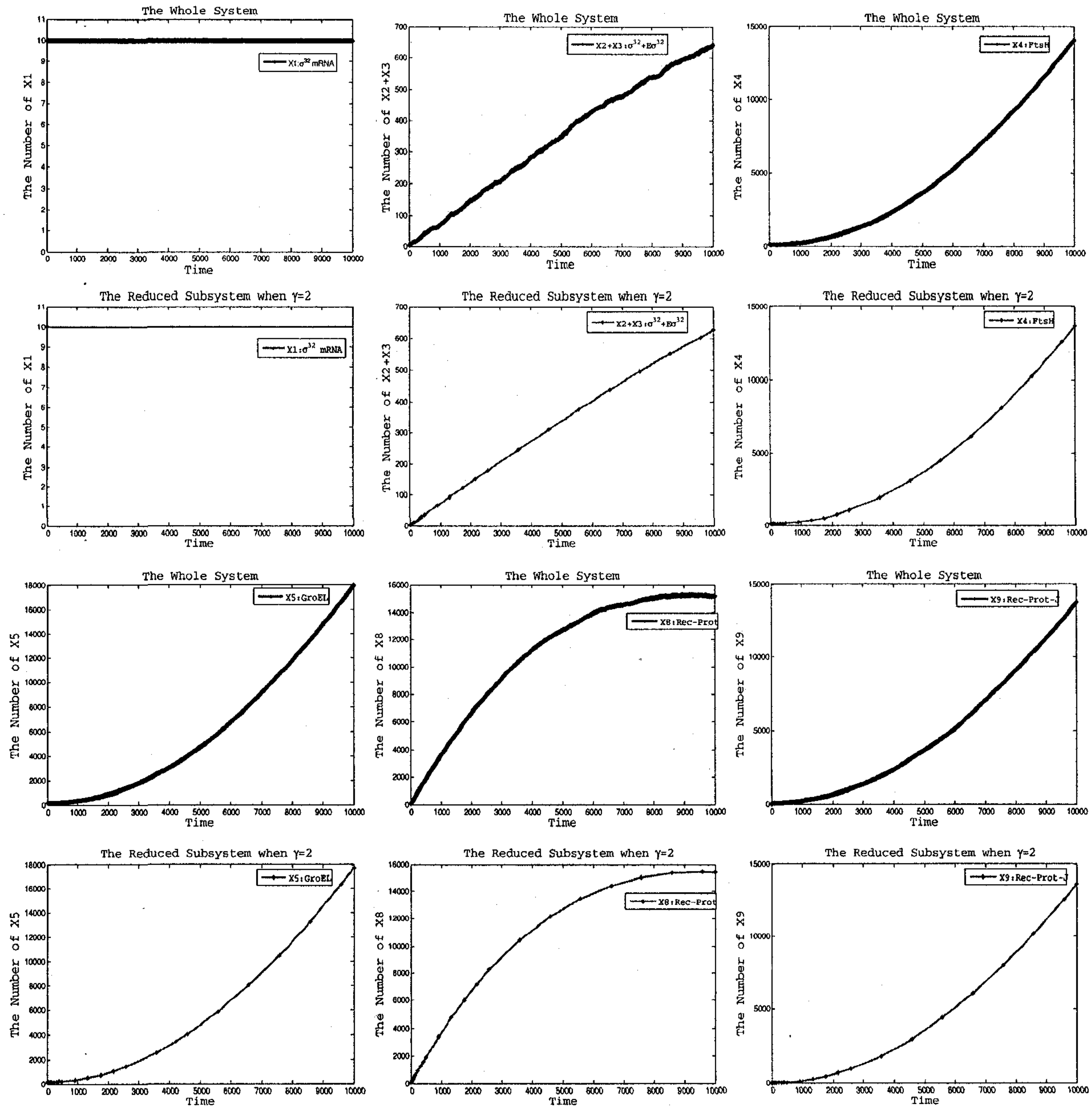
First, we obtain behavior of $V_2^{N,0}$, $V_3^{N,0}$, and $V_6^{N,0}$ in the times of $O\,(1)$ when $\gamma = 0$.



Next, we obtain behavior of $V_7^{N,1}$in the times of $O\,(N^1)$ when $\gamma = 1$.



Last, we obtain behavior of $V_1^{N,2}$, $V_2^{N,2} + V_3^{N,2}$, $V_4^{N,2}$, $V_5^{N,2}$, $V_8^{N,2}$ and $V_9^{N,2}$ in the times of $O\left(N^2\right)$ when $\gamma = 2$.



Chapter 5

Central limit theorem

5.1 Three species model

We consider a model of an intracellular viral infection which is given in [15] and studied further by [8] and [2]. There are three species: the viral template, the viral genome, and the structural protein denoted species 1, 2, and 3. We would like to investigate the normalized asymptotic behavior of the evolution of the number of molecules of species with slower time scales centered by its limit. In Theorem 5.1, we will show that the normalized asymptotic behavior of the process converges to a solution of stochastic integral equation with a time changed Brownian motion. Both limits of the centered counting processes and their intensities approximated by some martingale contribute to the time changed Brownian motion.

$X_i(t)$ represents the number of the ith species at time t and a time change equation is

$$X_1(t) = X_1(0) + Y_b\Big(\int_0^t \kappa_2' X_2(s)\,ds\Big) - Y_d\Big(\int_0^t \kappa_4' X_1(s)\,ds\Big) \tag{5.1}$$

$$\begin{aligned} X_2(t) &= X_2(0) + Y_a\Big(\int_0^t \kappa_1' X_1(s)\,ds\Big) - Y_b\Big(\int_0^t \kappa_2' X_2(s)\,ds\Big) \\ &\quad - Y_f\Big(\int_0^t \kappa_6' X_2(s) X_3(s)\,ds\Big) \\ X_3(t) &= X_3(0) + Y_c\Big(\int_0^t \kappa_3' X_1(s)\,ds\Big) - Y_e\Big(\int_0^t \kappa_5' X_3(s)\,ds\Big) \end{aligned} \tag{5.2}$$

$$-Y_f\Big(\int_0^t \kappa_6' X_2(s)X_3(s)\,ds\Big). \tag{5.3}$$

Let N_0 be equal to 1000. Table 13 indicates scaling exponents for each number of molecules of the chemical species, and Table 14 indicates both stochastic rate constants as given in [15] and normalized stochastic rate constants.

Table 13: Scaling exponents for the numbers of molecules in the three species model

α_i	Scaling exponent
α_1	0
α_2	2/3
α_3	1

Table 14: Stochastic rates and their scaling exponents in the three species model

β_k	Scaling exponent	Stoch rate (κ_k')	Scaled rate (κ_k)
β_1	0	1	1
β_2	$-2/3$	0.025	2.5
β_3	1	1000	1
β_4	0	0.25	0.25
β_5	0	2	2
β_6	$-5/3$	7.5×10^{-6}	0.75

Applying the multiscale methods to (5.1) – (5.3) and letting

$$V_i^N(t) \;=\; N^{-\alpha_i} X_i(N^{2/3}t),$$

the normalized system in the times of $O\left(N^{2/3}\right)$ is

$$\begin{aligned}
V_1^N(t) &= V_1^N(0) + Y_b\Big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\Big) - Y_d\Big(\int_0^t \kappa_4 N^{2/3} V_1^N(s)\,ds\Big) \qquad (5.4)\\
V_2^N(t) &= V_2^N(0) + N^{-2/3} Y_a\Big(\int_0^t \kappa_1 N^{2/3} V_1^N(s)\,ds\Big) - N^{-2/3} Y_b\Big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\Big)\\
&\quad - N^{-2/3} Y_f\Big(\int_0^t \kappa_6 N^{2/3} V_2^N(s) V_3^N(s)\,ds\Big) \qquad (5.5)\\
V_3^N(t) &= V_3^N(0) + N^{-1} Y_c\Big(\int_0^t \kappa_3 N^{5/3} V_1^N(s)\,ds\Big) - N^{-1} Y_e\Big(\int_0^t \kappa_5 N^{5/3} V_3^N(s)\,ds\Big)\\
&\quad - N^{-1} Y_f\Big(\int_0^t \kappa_6 N^{2/3} V_2^N(s) V_3^N(s)\,ds\Big). \qquad (5.6)
\end{aligned}$$

The time scale for V_2^N is much slower than that for V_1^N and V_3^N. In the times of $O\left(N^{2/3}\right)$, the fast processes $\{V_1^N, V_3^N\}$ are averaged out and they contribute to the evolution of the intermediate process V_2^N.

Consider a limiting process of V_2^N as $N \to \infty$. In (5.5), centering counting processed by their intensities, the equation for V_2^N becomes

$$\begin{aligned}
V_2^N(t) &= V_2^N(0) + N^{-2/3} \tilde{Y}_a\Big(\int_0^t \kappa_1 N^{2/3} V_1^N(s)\,ds\Big) - N^{-2/3} \tilde{Y}_b\Big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\Big)\\
&\quad - N^{-2/3} \tilde{Y}_f\Big(\int_0^t \kappa_6 N^{2/3} V_2^N(s) V_3^N(s)\,ds\Big) \qquad (5.7)\\
&\quad + \int_0^t \big(\kappa_1 V_1^N(s) - \kappa_2 V_2^N(s) - \kappa_6 V_2^N(s) V_3^N(s)\big)\,ds.
\end{aligned}$$

The centered counting processes in (5.7) converge to zero as $N \to \infty$. Following [2], dividing (5.4) and (5.6) by $-\kappa_4 N^{2/3}$ and $-\kappa_5 N^{2/3}$, respectively, as $N \to \infty$, gives

$$\int_0^t \big(V_1^N(s) - \frac{\kappa_2}{\kappa_4} V_2^N(s)\big)\, ds \;\to\; 0 \tag{5.8}$$

$$\int_0^t \big(V_3^N(s) - \frac{\kappa_3}{\kappa_5} V_1^N(s)\big)\, ds \;\to\; 0. \tag{5.9}$$

Using (5.8) and (5.9), fast processes $\{V_1^N, V_3^N\}$ are averaged by V_2^N.

$$\int_0^t \big(V_1^N(s) - \frac{\kappa_2}{\kappa_4} V_2^N(s)\big)\, ds \;\to\; 0 \tag{5.10}$$

$$\int_0^t \big(V_3^N(s) - \frac{\kappa_2\kappa_3}{\kappa_4\kappa_5} V_2^N(s)\big)\, ds \;\to\; 0. \tag{5.11}$$

Therefore, following [2], V_2^N converges to V_2 which is a solution of

$$V_2(t) \;=\; V_2(0) + \int_0^t \Big((\frac{\kappa_1\kappa_2}{\kappa_4} - \kappa_2) V_2(s) - \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5} V_2(s)^2 \Big)\, ds. \tag{5.12}$$

Using (5.7) and (5.12), we will get the asymptotic behavior of $N^{1/3}\big(V_2^N - V_2\big)$ in the following theorem.

Theorem 5.1. $D^N(t) \equiv N^{1/3}\big(V_2^N(t) - V_2(t)\big)$ *converges to* $D(t)$ *where* D *is a Gaussian Ornstein Uhlenbeck process which is a solution of a stochastic integral equation*

$$\begin{aligned} D(t) \;&=\; D(0) + W_b\Big(\int_0^t \big(\big(a_1 V_2(s)^3 + a_2 V_2(s)^2 + a_3 V_2(s)\big)\, ds\Big) \\ &\quad + \int_0^t D(s)\big(\frac{\kappa_1\kappa_2}{\kappa_4} - \kappa_2 - \frac{2\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5} V_2(s)\big)\, ds \end{aligned} \tag{5.13}$$

where

$$a_1 \;=\; 2\kappa_2 \left(\frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}\right)^2 \tag{5.14}$$

$$\begin{aligned} a_2 &= \kappa_2 \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}\left(3 - 4\frac{\kappa_1}{\kappa_4}\right) \\ a_3 &= 2\kappa_2\left(\frac{\kappa_1}{\kappa_4}\right)^2 - \kappa_2\left(\frac{\kappa_1}{\kappa_4}\right) + \kappa_2 \end{aligned}$$

and where W_b is a standard Brownian motion.

Proof of Theorem 5.1. Subtracting (5.12) from (5.7) and multiplying both sides by $N^{1/3}$, we have

$$\begin{aligned} &N^{1/3}\big(V_2^N(t) - V_2(t)\big) \qquad (5.15)\\ = \;& N^{1/3}\Big[V_2^N(0) + N^{-2/3}\tilde{Y}_a\big(\int_0^t \kappa_1 N^{2/3} V_1^N(s)\,ds\big) - N^{-2/3}\tilde{Y}_b\big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\big) \\ &-N^{-2/3}\tilde{Y}_f\big(\int_0^t \kappa_6 N^{2/3} V_2^N(s)V_3^N(s)\,ds\big) \\ &+\int_0^t \big(\kappa_1 V_1^N(s) - \kappa_2 V_2^N(s) - \kappa_6 V_2^N(s)V_3^N(s)\big)\,ds\Big] \\ &-N^{1/3}\Big[V_2(0) + \int_0^t \Big(\big(\frac{\kappa_1\kappa_2}{\kappa_4} - \kappa_2\big)V_2(s) - \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2(s)^2\Big)\,ds\Big]. \end{aligned}$$

Using D^N, (5.15) becomes

$$\begin{aligned} D^N(t) = D^N(0) &+ N^{-1/3}\tilde{Y}_a\big(\int_0^t \kappa_1 N^{2/3} V_1^N(s)\,ds \qquad (5.16)\\ &-N^{-1/3}\tilde{Y}_b\big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\big) - N^{-1/3}\tilde{Y}_f\big(\int_0^t \kappa_6 N^{2/3} V_2^N(s)V_3^N(s)\,ds\big) \\ &+\int_0^t N^{1/3}\big(\kappa_1 V_1^N(s) - \frac{\kappa_1\kappa_2}{\kappa_4}V_2^N(s) + \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s)^2 - \kappa_6 V_2^N(s)V_3^N(s)\big)\,ds \\ &+\int_0^t D^N(s)\big(\frac{\kappa_1\kappa_2}{\kappa_4} - \kappa_2 - \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}(V_2^N(s) + V_2(s))\big)\,ds. \end{aligned}$$

In (5.16),

$$N^{-1/3}\tilde{Y}_a\big(\int_0^t \kappa_1 N^{2/3} V_1^N(s)\,ds\big) - N^{-1/3}\tilde{Y}_b\big(\int_0^t \kappa_2 N^{2/3} V_2^N(s)\,ds\big)$$

$$-N^{-1/3}\tilde{Y}_f\Big(\int_0^t \kappa_6 N^{2/3} V_2^N(s)V_3^N(s)\,ds\Big)$$

is a martingale. We will show that

$$\int_0^t N^{1/3}\big(\kappa_1 V_1^N(s) - \frac{\kappa_1\kappa_2}{\kappa_4}V_2^N(s) + \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s)^2 - \kappa_6 V_2^N(s)V_3^N(s)\big)\,ds \tag{5.17}$$

in (5.16) can be approximated by a martingale. Let $f(x,y,z)$ be

$$f(x,y,z) \equiv \frac{\kappa_1}{\kappa_4}x - \frac{\kappa_6}{\kappa_5}yz - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}xy \tag{5.18}$$

Using the generator defined in (5.32), we have

$$\begin{aligned}
\mathbb{A}^N f(x,y,z) &= \frac{\kappa_1}{\kappa_4}\Big(\kappa_2 N^{2/3}y((x+1)-x) + \kappa_4 N^{2/3}x((x-1)-x)\Big) \\
&\quad -\frac{\kappa_6}{\kappa_5}\Big(\kappa_1 N^{2/3}x((y+N^{-2/3})z - yz) + \kappa_2 N^{2/3}y((y-N^{-2/3})z - yz) \\
&\quad +\kappa_3 N^{5/3}x(y(z+N^{-1}) - yz) + \kappa_5 N^{5/3}z(y(z-N^{-1}) - yz) \\
&\quad +\kappa_6 N^{2/3}yz((y-N^{-2/3})(z-N^{-1}) - yz)\Big) \\
&\quad -\frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}\Big(\kappa_1 N^{2/3}x(x(y+N^{-2/3}) - xy) + \kappa_2 N^{2/3}y((x+1)(y-N^{-2/3}) - xy) \\
&\quad +\kappa_4 N^{2/3}x((x-1)y - xy) + \kappa_6 N^{2/3}yz(x(y-N^{-2/3}) - xy)\Big) \\
&= -N^{2/3}\big(\kappa_1 x - \frac{\kappa_1\kappa_2}{\kappa_4}y + \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}y^2 - \kappa_6 yz\big) + O(1)
\end{aligned} \tag{5.19}$$

and hence

$$M^N(t) \equiv f(V^N(t)) - f(V^N(0)) - \int_0^t \mathbb{A}^N f(V^N(s))\,ds \tag{5.20}$$

is a martingale. Then using (5.19) and (5.20), (5.17) is expressed in terms of M^N and some errors

$$\begin{aligned}
&\int_0^t N^{1/3}\big(\kappa_1 V_1^N(s) - \frac{\kappa_1\kappa_2}{\kappa_4}V_2^N(s) + \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s)^2 - \kappa_6 V_2^N(s)V_3^N(s)\big)\,ds \\
&= N^{-1/3}M^N(t) + \int_0^t O\left(N^{-1/3}\right)\,ds \\
&-N^{-1/3}\big(\frac{\kappa_1}{\kappa_4}V_1^N(t) - \frac{\kappa_6}{\kappa_5}V_2^N(t)V_3^N(t) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(t)V_2^N(t)\big) \\
&+N^{-1/3}\big(\frac{\kappa_1}{\kappa_4}V_1^N(0) - \frac{\kappa_6}{\kappa_5}V_2^N(0)V_3^N(0) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(0)V_2^N(0)\big).
\end{aligned} \tag{5.21}$$

Substituting (5.21) in (5.16), we have

$$\begin{aligned}
D^N(t) = D^N(0) &+ N^{-1/3}\tilde{Y}_a\big(\int_0^t \kappa_1 N^{2/3}V_1^N(s)\,ds \\
&-N^{-1/3}\tilde{Y}_b\big(\int_0^t \kappa_2 N^{2/3}V_2^N(s)\,ds\big) - N^{-1/3}\tilde{Y}_f\big(\int_0^t \kappa_6 N^{2/3}V_2^N(s)V_3^N(s)\,ds\big) \\
&+N^{-1/3}M^N(t) + \int_0^t O\left(N^{-1/3}\right)\,ds \\
&-N^{-1/3}\big(\frac{\kappa_1}{\kappa_4}V_1^N(t) - \frac{\kappa_6}{\kappa_5}V_2^N(t)V_3^N(t) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(t)V_2^N(t)\big) \\
&+N^{-1/3}\big(\frac{\kappa_1}{\kappa_4}V_1^N(0) - \frac{\kappa_6}{\kappa_5}V_2^N(0)V_3^N(0) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(0)V_2^N(0)\big) \\
&+\int_0^t D^N(s)\big(\frac{\kappa_1\kappa_2}{\kappa_4} - \kappa_2 - \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}(V_2^N(s) + V_2(s))\big)\,ds.
\end{aligned} \tag{5.22}$$

Now, we will show that $N^{-1/3}M^N$ is approximated by centered counting processes in the equation for $f(V_1^N, V_2^N, V_3^N)$. Applying Ito's formula to $f(V_1^N, V_2^N, V_3^N)$, we have

$$\begin{aligned}
&\frac{\kappa_1}{\kappa_4}V_1^N(t) - \frac{\kappa_6}{\kappa_5}V_2^N(t)V_3^N(t) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(t)V_2^N(t) \\
= \;&\frac{\kappa_1}{\kappa_4}V_1^N(0) - \frac{\kappa_6}{\kappa_5}V_2^N(0)V_3^N(0) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(0)V_2^N(0) \\
&+\frac{\kappa_1}{\kappa_4}\int_0^t dV_1^N(s) - \frac{\kappa_6}{\kappa_5}\int_0^t V_2^N(s-)\,dV_3^N(s) - \frac{\kappa_6}{\kappa_5}\int_0^t V_3^N(s-)\,dV_2^N(s)
\end{aligned}$$

$$-\frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}\int_0^t V_1^N(s-)\,dV_2^N(s) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}\int_0^t V_2^N(s-)\,dV_1^N(s)$$
$$-\frac{\kappa_6}{\kappa_5}[V_2^N, V_3^N]_t - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}[V_1^N, V_2^N]_t \tag{5.23}$$

Covariations in (5.23) are

$$-\frac{\kappa_6}{\kappa_5}[V_2^N, V_3^N]_t = -\frac{\kappa_6}{\kappa_5}N^{-5/3}Y_f\Big(\int_0^t \kappa_6 N^{2/3}V_2^N(s)V_3^N(s)\,ds\Big) \tag{5.24}$$
$$-\frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}[V_1^N, V_2^N]_t = \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}Y_b\Big(\int_0^t \kappa_2 N^{2/3}V_2^N(s)\,ds\Big). \tag{5.25}$$

Replacing dV_1^N, dV_2^N, and dV_3^N by terms in (5.4) – (5.6) and using (5.24), and (5.25), we rewrite (5.23) after rearrangement.

$$\begin{aligned}
&\tfrac{\kappa_1}{\kappa_4}V_1^N(t) - \tfrac{\kappa_6}{\kappa_5}V_2^N(t)V_3^N(t) - \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(t)V_2^N(t)\\
&= \tfrac{\kappa_1}{\kappa_4}V_1^N(0) - \tfrac{\kappa_6}{\kappa_5}V_2^N(0)V_3^N(0) - \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_1^N(0)V_2^N(0)\\
&\left.\begin{aligned}
&+\textstyle\int_0^t\big(-\tfrac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) - \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-)\big)\,dY_a\big(\int_0^s \kappa_1 N^{2/3}V_1^N(u)\,du\big)\\
&+\textstyle\int_0^t\big(\tfrac{\kappa_1}{\kappa_4} + \tfrac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) + \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-) - \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-) + \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}\big)\\
&\qquad\qquad \times dY_b\big(\textstyle\int_0^s \kappa_2 N^{2/3}V_2^N(u)\,du\big)\\
&+\textstyle\int_0^t\big(-\tfrac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-)\big)\,dY_c\big(\int_0^s \kappa_3 N^{5/3}V_1^N(u)\,du\big)\\
&+\textstyle\int_0^t\big(-\tfrac{\kappa_1}{\kappa_4} + \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-)\big)\,dY_d\big(\int_0^s \kappa_4 N^{2/3}V_1^N(u)\,du\big)\\
&+\textstyle\int_0^t \tfrac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-)\,dY_e\big(\int_0^s \kappa_5 N^{5/3}V_3^N(u)\,du\big)\\
&+\textstyle\int_0^t\big(\tfrac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-) + \tfrac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) + \tfrac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-) - \tfrac{\kappa_6}{\kappa_5}N^{-5/3}\big)\\
&\qquad\qquad \times dY_f\big(\textstyle\int_0^s \kappa_6 N^{2/3}V_2^N(u)V_3^N(u)\,du\big)
\end{aligned}\right\}(**)
\end{aligned}$$

Since $\int_0^t \mathbb{A}f(V^N(s))\,ds$ in (5.20) is equal to the intensities in $(**)$, the jumps in $N^{-1/3}M^N$ are asymptotically the same as those in $(**)$ divided by $N^{1/3}$.

We will calculate quadratic variation of the martingale in (5.22) and will apply the martingale central limit theorem to obtain limiting behavior. Since quadratic variation of centered counting processes are counting processes themselves, using (**), quadratic variation of the martingale in (5.22) is

$$
\begin{aligned}
&\Big[N^{-1/3}\tilde{Y}_a - N^{-1/3}\tilde{Y}_b - N^{-1/3}\tilde{Y}_f + N^{-1/3}M^N\Big]_t \\
= &\int_0^t N^{-2/3}\Big(-\frac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-) + 1\Big)^2 \\
&\qquad \times dY_a\Big(\int_0^s \kappa_1 N^{2/3}V_1^N(u)\,du\Big) \\
&+\int_0^t N^{-2/3}\Big(\frac{\kappa_1}{\kappa_4} + \frac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) + \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-) - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-) \\
&\qquad + \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3} - 1\Big)^2 \times dY_b\Big(\int_0^s \kappa_2 N^{2/3}V_2^N(u)\,du\Big) \\
&+\int_0^t N^{-2/3}\Big(-\frac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-)\Big)^2 dY_c\Big(\int_0^s \kappa_3 N^{5/3}V_1^N(u)\,du\Big) \\
&+\int_0^t N^{-2/3}\Big(-\frac{\kappa_1}{\kappa_4} + \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-)\Big)^2 dY_d\Big(\int_0^s \kappa_4 N^{2/3}V_1^N(u)\,du\Big) \\
&+\int_0^t N^{-2/3}\Big(\frac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-)\Big)^2 dY_e\Big(\int_0^s \kappa_5 N^{5/3}V_3^N(u)\,du\Big) \\
&+\int_0^t N^{-2/3}\Big(\frac{\kappa_6}{\kappa_5}N^{-1}V_2^N(s-) + \frac{\kappa_6}{\kappa_5}N^{-2/3}V_3^N(s-) + \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}N^{-2/3}V_1^N(s-) \\
&\qquad - \frac{\kappa_6}{\kappa_5}N^{-5/3} - 1\Big)^2 \times dY_f\Big(\int_0^s \kappa_6 N^{2/3}V_2^N(u)V_3^N(u)\,du\Big) \qquad (5.26)
\end{aligned}
$$

Eliminate low order terms converging to zero. Then using (5.10) and (5.11) and using V_2^N is regular, a limit of quadratic variation is addition of the following limits.

$$
N^{-2/3}Y_a\Big(\int_0^t \kappa_1 N^{2/3}V_1^N(s)\,ds\Big) \to \int_0^t \frac{\kappa_1\kappa_2}{\kappa_4}V_2(s)\,ds, \qquad (5.27)
$$

$$
\begin{aligned}
&N^{-2/3}\int_0^t \big(\frac{\kappa_1}{\kappa_4} - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-) - 1\big)^2 dY_b\Big(\int_0^s \kappa_2 N^{2/3}V_2^N(u)\,du\Big) \\
&\quad \to \int_0^t \kappa_2 V_2(s)\big(\frac{\kappa_1}{\kappa_4} - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2(s) - 1\big)^2, \qquad (5.28) \\
&N^{-2/3}\int_0^t \big(-\frac{\kappa_1}{\kappa_4} + \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2^N(s-)\big)^2 dY_d\Big(\int_0^s \kappa_4 N^{2/3}V_1^N(u)\,du\Big) \\
&\quad \to \int_0^t \kappa_2 V_2(s)\big(\frac{\kappa_1}{\kappa_4} - \frac{\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2(s)\big)^2\,ds. \qquad (5.29)
\end{aligned}
$$

$$N^{-2/3}Y_f\Big(\int_0^t \kappa_6 N^{2/3}V_2^N(s)V_3^N(s)\,ds\Big) \to \int_0^t \frac{\kappa_2\kappa_3\kappa_6}{\kappa_4\kappa_5}V_2(s)^2\,ds \tag{5.30}$$

Adding (5.27) – (5.30), quadratic variation of the martingale in (5.22) converges to

$$a_1V_2(s)^3 + a_2V_2(s)^2 + a_3V_2(s) \tag{5.31}$$

where a_1, a_2, and a_3 are defined in (5.14). Then applying the martingale central limit theorem given in Theorem 5.2, (5.22) converges to (5.13) as $N \to \infty$. □

Remark 5.1. *The generator for V^N is*

$$\begin{aligned}
\mathbb{A}^N f(x,y,z) &= \kappa_1 N^{2/3}x\big(f(x,y+N^{-2/3},z) - f(x,y,z)\big) \\
&\quad +\kappa_2 N^{2/3}y\big(f(x+1,y-N^{-2/3},z) - f(x,y,z)\big) \\
&\quad +\kappa_3 N^{5/3}x\big(f(x,y,z+N^{-1}) - f(x,y,z)\big) \\
&\quad +\kappa_4 N^{2/3}x\big(f(x-1,y,z) - f(x,y,z)\big) \\
&\quad +\kappa_5 N^{5/3}z\big(f(x,y,z-N^{-1}) - f(x,y,z)\big) \\
&\quad +\kappa_6 N^{2/3}yz\big(f(x,y-N^{-2/3},z-N^{-1}) - f(x,y,z)\big)
\end{aligned} \tag{5.32}$$

where x, y, and z are the variables for V_1^N, V_2^N, and V_3^N, respectively.

The martingale central limit theorem is used to prove Theorem 5.1 is borrow from [7].

Theorem 5.2 (Vector-valued version). *Let M_n be a $\mathbb{R}^d$-valued martingale such that for each $1 \le i \le d$*

$$\lim_{n\to\infty} E[\sup_{s\le t}|M_n^i(s) - M_n^i(s-)|] = 0$$

and for each $1 \leq i, j \leq d$ and for all $t \geq 0$,

$$[M_n^i, M_n^j]_t \quad \rightarrow \quad h_{ij}(t)$$

in probability where h is continuous. Then $M_n \Rightarrow W \circ h$, where W is d-dimensional standard Brownian motion satisfying $E[W \circ h(t)\, W \circ h(t)^T] = h(t) = ((h_{ij}(t)))$.

Proof. See Ethier and Kurtz [7]. □

5.2 Heat shock response model

We will see asymptotic behavior of the intermediate processes in the times of $O(N^2)$ centered by their limiting processes and multiplied by $N^{1/2}$. Define

$$F_i^N(t) \quad \equiv \quad N^{1/2}\big(V_i^{N,2}(t) - V_i^2(t)\big). \tag{5.33}$$

Recall that $\{V_1^2, V_2^2, V_3^2, V_4^2, V_8^2, V_9^2\}$ is a solution of the reduced system in times of $O(N^2)$ in (4.52) – (4.58). Then F^N converges to a solution of a stochastic integral equation with a time-changed Brownian motion. Unlike the three species model in Section 5.1, the intensities of counting processes do not contribute to the time-changed Brownian motion, since the intensities of the counting processes are approximated by a martingale with quadratic variation converging to zero.

Theorem 5.3. *$F^N(t)$ converges to $F(t)$ where F is a solution of*

$$\begin{aligned} F_2(t) \quad &= \quad F_2(0) + \frac{\kappa_3^2\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \big(F_2(s)+F_3(s)\big)\frac{\kappa_7 V_3^2(s) + \kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2}\, ds \\ &+ \frac{\kappa_3^2\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \frac{V_2^2(s)+V_3^2(s)}{\kappa_{10}V_8^2(s)}\big(\kappa_7 F_3(s) + \kappa_{12}F_9(s)\big)\, ds \end{aligned} \tag{5.34}$$

$$
\begin{aligned}
&-\frac{\kappa_3^2\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \big(V_2^2(s)+V_3^2(s)\big)\big(\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)\big)\frac{F_8(s)}{\kappa_{10}V_8^2(s)^2}\,ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}W_{b'}\bigg(\int_0^t \Big(\kappa_4V_1^2(s)+\kappa_9V_2^2(s)\cdot\frac{\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\Big)\,ds\bigg)\\
F_3(t) &= F_3(0)+\frac{\kappa_2\kappa_3\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \big(F_2(s)+F_3(s)\big)\frac{\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2}\,ds\\
&+\frac{\kappa_2\kappa_3\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \frac{V_2^2(s)+V_3^2(s)}{\kappa_{10}V_8^2(s)}\big(\kappa_7F_3(s)+\kappa_{12}F_9(s)\big)\,ds\\
&-\frac{\kappa_2\kappa_3\kappa_9}{(\kappa_2+\kappa_3)^2}\int_0^t \big(V_2^2(s)+V_3^2(s)\big)\big(\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)\big)\frac{F_8^N(s)}{\kappa_{10}V_8^2(s)^2}\,ds\\
&+\frac{\kappa_2}{\kappa_2+\kappa_3}W_{b'}\bigg(\int_0^t \Big(\kappa_4V_1^2(s)+\kappa_9V_2^2(s)\cdot\frac{\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\Big)\,ds\bigg)\\
F_4(t) &= F_4(0)+\int_0^t \big(\kappa_6F_3(s)-\kappa_{18}F_4(s)\big)\,ds,\\
F_5(t) &= F_5(0)+\int_0^t \big(\kappa_5F_3(s)-\kappa_{16}F_5(s)\big)\,ds,\\
F_8(t) &= F_8(0)+\int_0^t \big(-\kappa_7F_3(s)-\kappa_{11}F_8(s)\big)\,ds,\\
F_9(t) &= F_9(0)+\int_0^t \kappa_7F_3(s)\,ds
\end{aligned}
$$

where

$$F_2(0)=F_3(0)=F_4(0)=F_5(0)=F_8(0)=F_9(0) \;=\; 0 \tag{5.35}$$

and where $W_{b'}$ is a standard Brownian motion.

Proof of Theorem 5.3. The equation for $V_2^{N,2}+V_3^{N,2}$ is

$$
\begin{aligned}
V_2^{N,2}(t)+V_3^{N,2}(t) &= V_2^{N,2}(0)+V_3^{N,2}(0)+N^{-1}Y_4\Big(\int_0^t \kappa_4NV_1^{N,2}(s)\,ds\Big) \qquad (5.36)\\
&+N^{-1}Y_8\Big(\int_0^t \kappa_8V_7^{N,2}(s)\,ds\Big)-N^{-1}Y_9\Big(\int_0^t \kappa_9NV_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big),
\end{aligned}
$$

and the equation for $V_2^2 + V_3^2$ is

$$\begin{aligned} V_2^2(t) + V_3^2(t) &= V_2^2(0) + V_3^2(0) \\ &+ \int_0^t \left(\kappa_4 V_1^2(s) - \frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3}(V_2^2(s) + V_3^2(s))\frac{\kappa_7 V_3^2(s) + \kappa_{12} V_9^2(s)}{\kappa_{10} V_8^2(s)}\right) ds. \end{aligned} \tag{5.37}$$

Subtract (5.37) from (5.36) and multiply by $N^{1/2}$. Center the terms regarding Reaction 4, 7, and 9 by their intensity and remove $\int_0^t \kappa_4 N^{1/2}|V_1^{N,2}(s) - V_1^2(s)|\, ds$ since $V_1^{N,2}(t) = V_1^2(t)$. Then, we have the equation for $F_2^N + F_3^N$.

$$\begin{aligned} F_2^N(t) + F_3^N(t) &= F_2^N(0) + F_3^N(0) \\ &-N^{1/2}\int_0^t \kappa_9\Big(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^2(s) + V_3^2(s))\frac{\kappa_7 V_3^2(s) + \kappa_{12} V_9^2(s)}{\kappa_{10} V_8^2(s)}\Big)\, ds \\ &+N^{-1/2}\int_0^t \kappa_8 V_7^{N,2}(s)\, ds + N^{-1/2}\tilde{Y}_4\Big(\int_0^t \kappa_4 N V_1^{N,2}(s)\, ds\Big) \\ &+N^{-1/2}\tilde{Y}_8\Big(\int_0^t \kappa_8 V_7^{N,2}(s)\, ds\Big) - N^{-1/2}\tilde{Y}_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s) V_6^{N,2}(s)\, ds\Big). \end{aligned} \tag{5.38}$$

Then we have

$$\left|\kappa_2 F_2^N(t) - \kappa_3 F_3^N(t)\right| \le O\left(\frac{1}{\sqrt{N}}\right). \tag{5.39}$$

Then, if a limit of $F_2^N + F_3^N$ exists ($\equiv F_2 + F_3$), we have

$$F_2(t) = \frac{\kappa_3}{\kappa_2+\kappa_3}\big(F_2(t) + F_3(t)\big) \tag{5.40}$$

$$F_3(t) = \frac{\kappa_2}{\kappa_2+\kappa_3}\big(F_2(t) + F_3(t)\big). \tag{5.41}$$

Now, we split

$$N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^2(s)+V_3^2(s))\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\right) ds$$

into three terms and express using F^N. Adding and subtracting terms, we have

$$\begin{aligned}
&N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^2(s)+V_3^2(s))\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\right) ds \qquad (5.42)\\
&= N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^{N,2}(s)+V_3^{N,2}(s))\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right) ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}N^{1/2}\int_0^t \Big(\big(V_2^{N,2}(s)-V_2^2(s)\big)+\big(V_3^{N,2}(s)-V_3^2(s)\big)\Big)\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}} ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}N^{1/2}\int_0^t \frac{V_2^2(s)+V_3^2(s)}{\kappa_{10}V_8^{N,2}(s)}\Big(\kappa_7\big(V_3^{N,2}(s)-V_3^2(s)\big)+\kappa_{12}\big(V_9^{N,2}(s)-V_9^{N,2}(s)\big)\Big) ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}N^{1/2}\int_0^t \big(V_2^2(s)+V_3^2(s)\big)\big(\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)\big)\left(\frac{1}{\kappa_{10}V_8^{N,2}(s)}-\frac{1}{\kappa_{10}V_8^2(s)}\right) ds
\end{aligned}$$

Using F^N, (5.42) is rewritten as

$$\begin{aligned}
&N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^2(s)+V_3^2(s))\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\right) ds\\
&= N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^{N,2}(s)+V_3^{N,2}(s))\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right) ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}\int_0^t \big(F_2^N(s)+F_3^N(s)\big)\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}} ds\\
&+\frac{\kappa_3}{\kappa_2+\kappa_3}\int_0^t \frac{V_2^2(s)+V_3^2(s)}{\kappa_{10}V_8^{N,2}(s)}\big(\kappa_7F_3^N(s)+\kappa_{12}F_9^N(s)\big) ds\\
&-\frac{\kappa_3}{\kappa_2+\kappa_3}\int_0^t \big(V_2^2(s)+V_3^2(s)\big)\big(\kappa_7V_3^2(s)+\kappa_{12}V_9^2(s)\big)\frac{F_8^N(s)}{\kappa_{10}V_8^{N,2}(s)V_8^2(s)} ds. \qquad (5.43)
\end{aligned}$$

The first term on the right side of (5.42) is expressed as

$$N^{1/2}\int_0^t \left(V_2^{N,2}(s)V_6^{N,2}(s) - \frac{\kappa_3}{\kappa_2+\kappa_3}(V_2^{N,2}(s)+V_3^{N,2}(s))\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right) ds$$

$$\left.\begin{cases} = \frac{\kappa_3}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(V_2^{N,2}(s) + V_3^{N,2}(s)\right)\left(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right) ds \\ +\frac{1}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right)\left(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)}\right) ds \end{cases}\right\} (*)$$

$$+\frac{1}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right)\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)} ds.$$

We have

$$\begin{aligned} &\frac{1}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right)\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)} ds \\ = \;& \int_0^t O\left(\frac{1}{\sqrt{N}}\right) ds. \end{aligned} \tag{5.44}$$

In Lemma 5.2, we show that $(*)$ is approximated by the martingale with quadratic variation converging to zero. Therefore,the first term on the right side of (5.42) does not contribute to a time-changed Brownian motion in the limit of $F_2^N + F_3^N$.

Rewriting (5.38) and using (5.43), (5.44), and Lemma 5.2, we obtain

$$\begin{aligned} &F_2^N(t) + F_3^N(t) = F_2^N(0) + F_3^N(0) \\ &+\frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(V_2^{N,2}(s) + V_3^{N,2}(s)\right)\left(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\right) ds \\ &+\frac{\kappa_9}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \left(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\right)\left(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)}\right) ds \\ &+\frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3} \int_0^t \left(F_2^N(s) + F_3^N(s)\right)\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}} ds \\ &+\frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3} \int_0^t \frac{V_2^2(s)+V_3^2(s)}{\kappa_{10}V_8^{N,2}(s)}\left(\kappa_7 F_3^N(s) + \kappa_{12}F_9^N(s)\right) ds \\ &-\frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3} \int_0^t \left(V_2^2(s)+V_3^2(s)\right)\left(\kappa_7 V_3^2(s) + \kappa_{12}V_9^2(s)\right)\frac{F_8^N(s)}{\kappa_{10}V_8^{N,2}(s)V_8^2(s)} ds \\ &+\int_0^t O\left(\frac{1}{\sqrt{N}}\right) ds + N^{-1/2}\tilde{Y}_4\left(\int_0^t \kappa_4 N V_1^{N,2}(s)\, ds\right) \\ &+N^{-1/2}\tilde{Y}_8\left(\int_0^t \kappa_8 V_7^{N,2}(s)\, ds\right) - N^{-1/2}\tilde{Y}_9\left(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\, ds\right). \end{aligned} \tag{5.45}$$

Using Lemma 5.2, calculate quadratic variation of the martingale terms in (5.45).

$$
\begin{aligned}
&\Big[\frac{\kappa_3\kappa_9}{\kappa_2+\kappa_3}N^{1/2}\int_0^t \big(V_2^{N,2}(s)+V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s)-\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\Big)\,ds\\
&+\frac{\kappa_9}{\kappa_2+\kappa_3}N^{1/2}\int_0^t \big(\kappa_2 V_2^{N,2}(s)-\kappa_3 V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s)-\frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)}\Big)\,ds\\
&+N^{-1/2}\tilde{Y}_4\Big(\int_0^t \kappa_4 N V_1^{N,2}(s)\,ds\Big)+N^{-1/2}\tilde{Y}_8\Big(\int_0^t \kappa_8 V_7^{N,2}(s)\,ds\Big)\\
&+N^{-1/2}\tilde{Y}_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big)\Big]_t\\
&\quad\approx N^{-1}Y_4\Big(\int_0^t \kappa_4 N V_1^{N,2}(s)\,ds\Big)+N^{-1}Y_9\Big(\int_0^t \kappa_9 N V_2^{N,2}(s)V_6^{N,2}(s)\,ds\Big)\\
&\quad\to \int_0^t \Big(\kappa_4 V_1^2(s)+\kappa_9 V_2^2(s)\cdot\frac{\kappa_7 V_3^2(s)+\kappa_{12}V_9^2(s)}{\kappa_{10}V_8^2(s)}\Big)\,ds
\end{aligned}
\tag{5.46}
$$

The equation for $V_4^{N,2}$ is

$$
\begin{aligned}
V_4^{N,2}(t) &= V_4^{N,2}(0)+N^{-2}Y_6\Big(\int_0^t \kappa_6 N^2 V_3^{N,2}(s)\,ds\Big)\\
&\quad -N^{-2}Y_{18}\Big(\int_0^t \kappa_{18}N^2 V_4^{N,2}(s)\,ds\Big)
\end{aligned}
\tag{5.47}
$$

and the equation for V_4^2 is

$$
V_4^2(t) = V_4^2(0)+\int_0^t \big(\kappa_6 V_3^2(s)-\kappa_{18}V_4^2(s)\big)\,ds. \tag{5.48}
$$

Subtracting (5.48) from (5.47) and multiplying by $N^{1/2}$, we have

$$
\begin{aligned}
&N^{1/2}\big(V_4^{N,2}(t)-V_4^2(t)\big) \qquad (5.49)\\
&= N^{1/2}\Big[V_4^{N,2}(0)+N^{-2}Y_6\Big(\int_0^t \kappa_6 N^2 V_3^{N,2}(s)\,ds\Big)-N^{-2}Y_{18}\Big(\int_0^t \kappa_{18}N^2 V_4^{N,2}(s)\,ds\Big)\Big]
\end{aligned}
$$

$$-N^{1/2}\left[V_4^2(0)+\int_0^t \left(\kappa_6 V_3^2(s)-\kappa_{18}V_4^2(s)\right)ds\right]$$

We center the terms regarding Reaction 6 and 18 by their intensity in (5.49). Then using F^N, (5.49) is rewritten as

$$\begin{aligned} F_4^N(t) &= F_4^N(0)+\int_0^t \left(\kappa_6 F_3^N(s)-\kappa_{18}F_4^N(s)\right)ds \qquad (5.50)\\ &+N^{-3/2}\tilde{Y}_6\Big(\int_0^t \kappa_6 N^2 V_3^{N,2}(s)\,ds\Big)-N^{-3/2}\tilde{Y}_{18}\Big(\int_0^t \kappa_{18}N^2 V_4^{N,2}(s)\,ds\Big). \end{aligned}$$

Similar to how we get F_4^N, using $V_5^{N,2}$ and V_5^2, we get F_5^N.

$$\begin{aligned} F_5^N(t) &= F_5^N(0)+\int_0^t \left(\kappa_5 F_3^N(s)-\kappa_{16}F_5^N(s)\right)ds \qquad (5.51)\\ &+N^{-3/2}\tilde{Y}_5\Big(\int_0^t \kappa_5 N^2 V_3^{N,2}(s)\,ds\Big)-N^{-3/2}\tilde{Y}_{16}\Big(\int_0^t \kappa_{16}N^2 V_5^{N,2}(s)\,ds\Big) \end{aligned}$$

The equation for $V_8^{N,2}$ is

$$\begin{aligned} V_8^{N,2}(t) &= V_8^{N,2}(0)+N^{-2}Y_1\Big(\int_0^t \kappa_1 N^2\,ds\Big)+N^{-2}Y_{12}\Big(\int_0^t \kappa_{12}N^2 V_9^{N,2}(s)\,ds\Big) \qquad (5.52)\\ &-N^{-2}Y_{10}\Big(\int_0^t \kappa_{10}N^2 V_6^{N,2}(s)V_8^{N,2}(s)\,ds\Big)-N^{-2}Y_{11}\Big(\int_0^t \kappa_{11}N^2 V_8^{N,2}(s)\,ds\Big) \end{aligned}$$

and the equation for V_8^2 is

$$V_8^2(t) = V_8^2(0)+\int_0^t \left(\kappa_1-\kappa_7 V_3^2(s)-\kappa_{11}V_8^2(s)\right)ds. \qquad (5.53)$$

First, we will get an approximate term for

$$N^{-2}Y_{12}\Big(\int_0^t \kappa_{12}N^2 V_9^{N,2}(s)\,ds\Big)-N^{-2}Y_{10}\Big(\int_0^t \kappa_{10}N^2 V_6^{N,2}(s)V_8^{N,2}(s)\,ds\Big). \qquad (5.54)$$

From the equation for $V_6^{N,2} + V_7^{N,2}$ dividing by N^2, we get

$$\begin{aligned}
& N^{-2}Y_{12}\Big(\int_0^t \kappa_{12}N^2V_9^{N,2}(s)\,ds\Big) - N^{-2}Y_{10}\Big(\int_0^t \kappa_{10}N^2V_6^{N,2}(s)V_8^{N,2}(s)\,ds\Big) \qquad (5.55)\\
= & \int_0^t \Big(- \kappa_7 V_3^{N,2}(s) + \kappa_{17}N^{-2}V_6^{N,2}(s)\Big)\,ds \\
& + N^{-2}\big(V_6^{N,2}(t) + V_7^{N,2}(t)\big) - N^{-2}\big(V_6^{N,2}(0) + V_7^{N,2}(0)\big) \\
& - N^{-2}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big) + N^{-2}\tilde{Y}_{17}\Big(\int_0^t \kappa_{17}V_6^{N,2}(s)\,ds\Big).
\end{aligned}$$

Subtract (5.53) from (5.52) and substitute (5.54) in (5.52). Then multiply the equation by $N^{1/2}$, we have

$$\begin{aligned}
& N^{1/2}\big(V_8^{N,2}(t) - V_8^2(t)\big) \qquad (5.56)\\
= \;& N^{1/2}\Big[V_8^{N,2}(0) + \int_0^t \big(- \kappa_7 V_3^{N,2}(s) + \kappa_{17}N^{-2}V_6^{N,2}(s)\big)\,ds \\
& + N^{-2}\big(V_6^{N,2}(t) + V_7^{N,2}(t)\big) - N^{-2}\big(V_6^{N,2}(0) + V_7^{N,2}(0)\big) \\
& - N^{-2}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big) + N^{-2}\tilde{Y}_{17}\Big(\int_0^t \kappa_{17}V_6^{N,2}(s)\,ds\Big) \\
& + N^{-2}Y_1\Big(\int_0^t \kappa_1 N^2\,ds\Big) - N^{-2}Y_{11}\Big(\int_0^t \kappa_{11}N^2V_8^{N,2}(s)\,ds\Big)\Big] \\
& - N^{1/2}\Big[V_8^2(0) + \int_0^t \big(\kappa_1 - \kappa_7 V_3^2(s) - \kappa_{11}V_8^2(s)\big)\,ds\Big].
\end{aligned}$$

We center the terms regarding Reaction 1 and 11 by their intensity in (5.56). Then using F^N, (5.54) is rewritten as

$$\begin{aligned}
F_8^N(t) = \;& F_8^N(0) + \int_0^t \big(- \kappa_7 F_3^N(s) - \kappa_{11}F_8^N(s) + \kappa_{17}N^{-3/2}V_6^{N,2}(s)\big)\,ds \qquad (5.57)\\
& + N^{-3/2}\big(V_6^{N,2}(t) + V_7^{N,2}(t)\big) - N^{-3/2}\big(V_6^{N,2}(0) + V_7^{N,2}(0)\big) \\
& - N^{-3/2}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big) + N^{-3/2}Y_{17}\Big(\int_0^t \kappa_{17}V_6^{N,2}(s)\,ds\Big)
\end{aligned}$$

$$+N^{-3/2}\tilde{Y}_1\Big(\int_0^t \kappa_1 N^2\,ds\Big) - N^{-3/2}\tilde{Y}_{11}\Big(\int_0^t \kappa_{11} N^2 V_8^{N,2}(s)\,ds\Big).$$

Similar to how we get F_8^N, using $V_9^{N,2}$, V_9^2, and (5.55), we get F_9^N.

$$\begin{aligned} F_9^N(t) &= F_9^N(0) + \int_0^t \big(\kappa_7 F_3^N(s) - \kappa_{17} N^{-3/2} V_6^{N,2}(s)\big)\,ds \\ &\quad - N^{-3/2}\big(V_6^{N,2}(t) + V_7^{N,2}(t)\big) + N^{-3/2}\big(V_6^{N,2}(0) + V_7^{N,2}(0)\big) \\ &\quad + N^{-3/2}\tilde{Y}_7\Big(\int_0^t \kappa_7 N^2 V_3^{N,2}(s)\,ds\Big) - N^{-3/2}\tilde{Y}_{17}\Big(\int_0^t \kappa_{17} V_6^{N,2}(s)\,ds\Big) \end{aligned} \tag{5.58}$$

Following from (5.45), (5.40), (5.41) (5.50), (5.51), (5.57), and (5.58), applying the martingale central limit theorem given in Theorem 5.2, and using (5.46), as $N \to \infty$, F^N converges to F satisfying (5.34). □

In Lemma5.2, we show that $(*)$ is approximated by a martingale with quadratic variation converging to zero.

Lemma 5.2.

$$\begin{aligned} &\frac{\kappa_3}{\kappa_2+\kappa_3} N^{1/2} \int_0^t \big(V_2^{N,2}(s) + V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s) + \kappa_{12} V_9^{N,2}(s)}{\kappa_{10} V_8^{N,2}(s)}\Big)\,ds \\ &+ \frac{1}{\kappa_2+\kappa_3} N^2 \int_0^t \big(\kappa_2 V_2^{N,2}(s) - \kappa_3 V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s) + \kappa_{12} V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10} V_8^{N,2}(s)}\Big)\,ds \end{aligned} \tag{5.59}$$

is approximated by a martingale with quadratic variation converging to zero.

Proof. As we see in (2.2), V^N is a continuous time Markov process written as

$$V_i^N(t) = V_i^N(0) + N^{-\alpha_i} \sum_{k=1}^m Y_k\Big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k} \lambda_k(V^N(s))\,ds\Big)(\nu'_{ik} - \nu_{ik}). \tag{5.60}$$

Then the generator of V^N is defined as

$$\mathbb{A}^N g(v) = \sum_{k=1}^{m} N^{\gamma+\alpha\cdot\nu_k+\beta_k}\lambda_k(v)\big(g(v+l_k^N)-g(v)\big) \tag{5.61}$$

where v is a variable for V^N and the ith component of l_k^N, l_{ik}^N, represents a jump size of the ith component of V^N when the kth reaction occurs. l_{ik}^N is written as

$$l_{ik}^N = N^{-\alpha_i}(\nu'_{ik}-\nu_{ik}).$$

Set

$$R_k(t) = Y_k\Big(\int_0^t N^{\gamma+\alpha\cdot\nu_k+\beta_k}\lambda_k(V^N(s))\,ds\Big). \tag{5.62}$$

Then we can interpret the equation for V^N in terms of a martingale and its generator or in terms of a jump process with counting processes.

$$\begin{aligned} g(V^N(t)) &= g(V^N(0)) + \sum_{k=1}^{m}\int_0^t \big(g(V^N(s-)+l_k^N) - g(V^N(s-))\big)\,dR_k(s) \\ &= g(V^N(0)) + \int_0^t \mathbb{A}^N g(V^N(s))\,ds + M_g^N(t). \end{aligned} \tag{5.63}$$

We find a function g satisfying

$$\begin{aligned} &\int_0^t \mathbb{A}^N g(V^N(s))\,ds \\ &= -\frac{\kappa_3}{\kappa_2+\kappa_3}N^2\int_0^t \big(V_2^{N,2}(s)+V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_{10}V_8^{N,2}(s)}\Big)\,ds \\ &-\frac{1}{\kappa_2+\kappa_3}N^2\int_0^t \big(\kappa_2 V_2^{N,2}(s)-\kappa_3 V_3^{N,2}(s)\big)\Big(V_6^{N,2}(s) - \frac{\kappa_7 V_3^{N,2}(s)+\kappa_{12}V_9^{N,2}(s)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(s)}\Big)\,ds \\ &+\int_0^t O(N)\,ds, \end{aligned}$$

where g is

$$g(V_2^{N,2}(t), V_3^{N,2}(t), V_6^{N,2}(t), V_8^{N,2}(t)) \tag{5.64}$$
$$= \frac{\kappa_3}{\kappa_2+\kappa_3} \frac{\big(V_2^{N,2}(t)+V_3^{N,2}(t)\big)V_6^{N,2}(t)}{\kappa_{10}V_8^{N,2}(s)} + \frac{1}{\kappa_2+\kappa_3} \frac{\big(\kappa_2 V_2^{N,2}(t) - \kappa_3 V_3^{N,2}(t)\big)V_6^{N,2}(t)}{\kappa_2+\kappa_3+\kappa_{10}V_8^{N,2}(t)}.$$

Dividing (5.63) by $N^{3/2}$, we have

$$N^{-3/2}g(V^N(t)) \to 0, \quad N^{-3/2}g(V^N(0)) \to 0.$$

Consider the exponents inside and outside the martingale $N^{-3/2}\sum_{k=1}^m \int_0^t \big(g(V^N(s-)+l_k^N)-g(V^N(s-))\big)\,dR_k(s)$ using the generator $\mathbb{A}^N$ in (4.80) in Section 4.1.3. Then without calculation, we get

$$\left[N^{-3/2}\sum_{k=1}^m \int_0^t \big(g(V^N(s-)+l_k^N)-g(V^N(s-))\big)\,dR_k(s)\right]_t \to 0.$$

Since the jumps of $N^{-3/2}M_g^N$ is the same as those in $N^{-3/2}\sum_{k=1}^m \int_0^t \big(g(V^N(s-)+l_k^N)-g(V^N(s-))\big)\,dR_k(s)$, (5.59) is approximated by the martingale $N^{-3/2}M_g^N$ with quadratic variation converging to zero. $\square$

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