Analysis of stochastically modeled biochemical processes with applications to numerical methods

By

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Abstract

In this dissertation, we study stochastically modeled chemical reaction networks and associated simulation methods. The bulk of this dissertation focuses on three selected topics. Firstly, we present an efficient Runge-Kutta type simulation method and compare its weak error with those of other methods. In particular, we make a comparison with the usual Euler method, which is termed tau-leaping in the current context. The new method is found to be an order of magnitude more accurate than Euler's method, making it the first high-order numerical method for the models considered in this dissertation. Secondly, we study different coupling methods of stochastically modeled biochemical processes and provide an asymptotic relation between two such couplings found commonly in the literature. This work is motivated by the fact that variance reduction is a critical aspect of many computational methods, such as in finite difference schemes for the estimation of sensitivities and multi-level Monte Carlo algorithms for the estimation of expectations. Thirdly, we will prove a large population result on a class of chemical reaction networks which allow for reactions to have "interruptible" delay. The technique of the proof is similar in nature to that of Nancy Garcia's large population result on an S.I.R model with generally distributed infectious period, though this was not known at the time of writing. Finally, along with a package for the implementation of multi-level Monte Carlo for MATLAB, we present two miscellaneous results including: (i) a proof that complex balanced chemical reaction networks are non-explosive, and (ii) an application of the multi-level Monte Carlo algorithm for the purpose of sensitivity analysis, which produces the most efficient method for the approximation of sensitivities to date.

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Contents

Chapter 1

Introduction

1.1 Background

In 2004, geneticist John Venter and economist Daniel Cohen made the following famous quote: "If the 20th century was the century of physics, the 21st century will be the century of biology" [68]. One of the ultimate goals in the biological sciences, and in particular systems biology, is to predict and control the behaviors of cells and biochemical reactions. According to a recent report by the Japan Science and Technology Agency [34], today's frontier of this science mainly consists of two components: Bio-informatics and mathematical modeling. In Bio-informatics, one uses statistical methods to learn from raw data, in particular the so-called "omics"[1] data, the underlining network of reactions that governs the system. Hirai's work is a recent example of a network inference from metabolomics data [49]. In mathematical modeling, one constructs specific mathematical descriptions of the biological system and uses simulations or analytical techniques to study the dynamical properties of the processes, including their limiting behaviors. According to the JST [34], in both industry and academia alike, Bio-informatics was in the center of spotlight in the last decade. However, [34] also reports that the trend is slowly shifting toward mathematical modeling.

[1] omics stands for the group of chemical substances that ends in "-ome"; for example, genome, transcriptome, proteome, glycome, metabolonome, etc.

One may model the dynamics of a biochemical system deterministically or stochastically. There is a vast literature studying the qualitative properties of deterministically modeled systems. For just a small sample, the works of Feinberg, Horn, Jackson, Craciun, Sturmfels, Andersion, Shiu and others investigate the behavior of deterministically modeled systems using theories from ordinary differential equations, algebra, and geometry [2, 3, 5, 12, 21, 26, 27, 28, 29, 33, 43, 44, 45, 46, 59] . On the other hand, this dissertation studies (i) mathematical techniques to be used on models with stochastic dynamics, and (ii) computational methods of stochastic simulations for biological purposes.

Stochastic modeling of biological systems has dramatically increased in popularity over the last decade in the field of mathematical modeling. With the development of more efficient technologies to obtain "in vivo" data,[2] like fluorescent-activated cell sorting (FACS) to study the chemical dynamics within cells, biologists are finding ample evidence that intrinsic stochasticity within the cell system is affecting its behavior in pivotal ways. For example, Arkin and Adams [14] reports strong evidence that the developmental pathway of a phage infected E-coli cell is stochastically regulated. Lawson et al. [54] have shown that a model that includes spatial stochasticity describes the robust cell polarization much more accurately than the deterministic counterpart. Elowitz et al. [31] presented evidence that random fluctuations in gene expression contribute substantially to overall phenotypic variation.

[2]data from living cells, as opposed to artificial data ("in vitro")

While it is clear that stochastic models have a role to play in elucidating our understanding of biological phenomena, there are many aspects to stochastic models and their associated simulation methods that still need addressing. For example, there is a problem of scaling in that different constituent species may be available in significantly different abundances, and the rates of different reactions may vary by orders of magnitude. Stochasticity becomes especially important in the presence of chemical species in low abundances. In one of the first results aimed at describing how models with a given scaling behave, Kurtz introduced the notion of the "classical scaling," or the situation under which all species exist in the same scale and the reaction rates are proportional to that scale. He showed that the law of large numbers limit of the system takes the form of an ODE [52]. However, some chemical species can be present in the system in much greater abundances than others, and this motivates a multiscale analysis, where there has recently been significant research activity. For example, in [17], Ball, Kurtz, Popovic and Rempala developed some of the first multi-scale techniques applicable in the setting of biochemical processes, which utilized laws of large numbers and averaging methods in order to simplify the dynamics of multiple models, including a model of viral infection of a cell. Kurtz and Kang [48] specified a balance condition under which one can, with a particular time scale, simplify the dynamics of even more complicated models.

Simulation methods are still in their embryonic stage of development in the current setting: continuous efforts are being made to improve upon both the accuracy and the runtime of the different algorithms being developed. Gillespie is considered a pioneer in the field for the development of the stochastic simulation algorithm (SSA) [39] and the tau-leaping algorithm [40]. Up until recently, the main focus of the study of simulation methods had been in applications of the tau-leaping algorithm (which is the

usual Euler method in the present context) and on different exact stochastic simulation algorithms (SSA), and their improvements and extension in terms of bias reduction and speed. While extremely innovative and intuitive, the tau-leaping algorithm has multiple problems associated with it. For example, it, along with all forward in time simulation methods, can cause some populations to go negative in the course of a simulation, which is an issue that has garnered widespread attention. For example, the work of Cao et al. [23], Anderson [1], Chatterjee [25], Tian and Burrage [67] and others were all aimed at countering this negativity problem. Implicit methods [62], Runge-Kutta methods [22], midpoint methods [7], and trapezoidal methods [9], were also developed as improved variations of the tau-leaping algorithm. Conversely, E, Liu, and Vanden-Eijnden developed a method to simulate chemical systems with multiple time scales by algorithmically approximating the fast dynamics via homogenization methods [30], which had the effect of greatly increasing the speed of computing single realizations for a myriad of models at the cost of an unquantified bias.

The trend changed, however, with the advent of the multi-level Monte Carlo simulation algorithm (MLMC) by Mike Giles [38], which was developed in the context of stochastic differential equation driven by Brownian motions. In that context MLMC boasts an ability to produce highly precise, though still biased, estimates for expectations in a fraction of the time required by standard simulation methods such as Euler-Maruyama and Milstein's scheme together with standard Monte Carlo methods [38]. Later, in [8], Anderson and Higham extended the basic MLMC method to the setting of stochastically modeled chemical reaction networks in a manner that produced *unbiased estimators*, and which often produced its estimates in a fraction of the time required by exact simulation methods coupled with naive Monte Carlo. This new MLMC method

combines multiple SSA-generated paths and multiple approximated paths in a telescopic sum in a way that attempts to push the computational work away from highly precise paths, which detail every reaction, and towards coarse-grained approximations. These MLMC methods require tight couplings of the relevant simulated paths in order to work, and the coupling employed by Anderson and Higham is based off the random time change representation of Kurtz. However, this is not the only coupling available, and studying the properties of and relationships between different couplings is motivation for the material presented in Chapter 3 of this thesis.

1.1.1 Chapter outline

In this dissertation, we study simulation methods of stochastically modeled reaction networks and selected topics around stochastic modeling, including some results on non-Markovian systems. The dissertation is structured as follows.

In the remainder of the first chapter, we will introduce the specific stochastic models we consider (section 1.2) and the tools that will be useful in their analysis (section 1.3).

In Chapter 2, we will introduce a Runge-Kutta type method for Monte Carlo simulation, and analyze its weak error, or bias. We will show that this error scales like the square of the time-step, making it the first higher order method in the current context.

In Chapter 3, we will study two methods found in the computational literature for coupling processes. Coupling is a technique that is useful in any computational method where a reduction of variance is desired, such as in finite difference methods for sensitivity analysis and multi-level Monte Carlo for the computation of expectations. There are two leading methods in the literature to couple two processes tightly. We will show

a surprising relationship between the two by proving that a sequence of couplings of one type converges to the other coupling in a particular topology. In essence, the analysis shows that the coupling employed by Anderson and Higham in [8] maximizes the ability of the two process to re-couple during the course of a simulation.

In Chapter 4 we analyze a class of systems with a delay in the completion in one or more of their reactions. This problem was motivated by a series of conversations with Prof. Laurence Loewe in the University of Wisconsin Laboratory of Genetics and the Wisconsin Institute for Discovery. In particular, we assume that some reactions take a nontrivial time to complete, and this assumption causes the system to be non-Markovian. Such instances happen, for example, in gene transcription, a basic biological event necessary for the modeling of any genetic network. Previous results in the literature pertaining to biochemical models with delay detailed the expected behavior of the system [65] and the modeling of the system via delayed ordinary differential equations [18]. In this dissertation, we derive the law of large numbers limit under the classical scaling for a special class of stochastic models with delay in order to derive the correct delayed ODE model.

Finally, in Chapter 5 we conclude this dissertation with some miscellaneous results and a description of a software package written in the Python language that automatically generates MATLAB code for the implementation of multi-level Monte Carlo. Complexity of writing such code is one of the bottlenecks to the widespread implementation of MLMC. The package generates the code from simple inputs of the basic network stoichiometry, the system parameters, and an initial condition. Another result in this final chapter, and the one which is perhaps the most immediately applicable of the entire thesis, is the extension of the MLMC algorithm to the setting of sensitivity analysis

for stochastically modeled biochemical systems, thereby producing the most efficient method for sensitivities available today.

1.2 Mathematical Model

1.2.1 Base model and State Space

A chemical reaction network (CRN) consists of three components: a set of species $\mathcal{S}$, a set of complexes $\mathcal{C}$, and a set reactions $\mathcal{R}$. Each complex is a non-negative linear combination of the species, and each reaction transforms a reactant complex to a product complex. Each reaction has a corresponding reaction rate constant, which parametrizes the rate at which the reaction takes place. A CRN can be represented by a weighted digraph, with the complexes and the products serving as the nodes, and the reactions as the directed edges. For instance, the CRN with

$$\mathcal{S} = \{A, B, C, D, E\} \qquad \mathcal{C} = \{A + B, C, D, E\}$$

and reactions

$$\begin{aligned} A + B &\xrightarrow{r_1} C \\ A &\xrightarrow{r_2} A + B \\ C &\xrightarrow{r_3} \emptyset \\ A &\xrightarrow{r_4} C \\ D &\xrightarrow{r_5} 2E \end{aligned} \tag{1.1}$$

can be represented as the disconnected, weighted digraph given in Figure 1. Such a graph is typically termed a *reaction graph.*

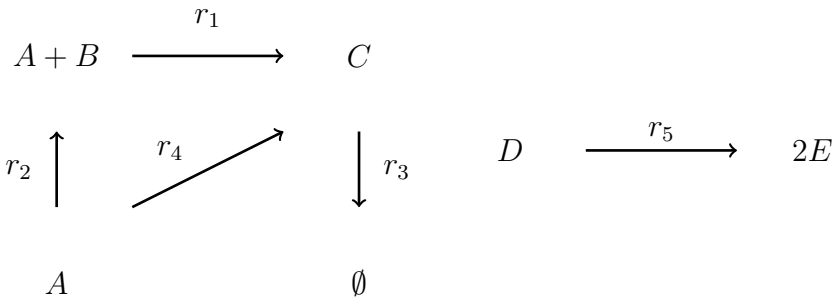

Figure 1: A graph representation of CRN (1.1).

Having a notion of a network, we turn to developing a dynamical system governing the behavior of the populations of the species. We may represent a state of the system by a vector in $\mathbb{R}^d$, where d is the number of species. In the case of (1.1), $d = 5$, and the coordinates 1 through 5 correspond to species A through E, respectively. If X is a state of the system, X_i represents the number of particles of the ith species present in the system. We associate with the reactions a set of vectors determining the net change in the composition of the system due to their occurrences, $\{\zeta_k; k = 1, ..., R\}$, with $\zeta_k \in \mathbb{Z}^d$. For the example (1.1) we have,

$$\zeta_1 = \begin{bmatrix} -1 \\ -1 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \ \zeta_2 = \begin{bmatrix} 0 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \ \zeta_3 = \begin{bmatrix} -1 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \ \zeta_4 = \begin{bmatrix} 0 \\ 0 \\ -1 \\ 0 \\ 0 \end{bmatrix}, \ \zeta_5 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ -1 \\ 2 \end{bmatrix} \tag{1.2}$$

For example, in the first reaction, one of the A particles and one of the B particles are consumed to make a C particle, and hence the entries in vector ζ_1. We can also associate

to each reaction the reactant complexes vector;

$$\nu_1 = \begin{bmatrix} 1 \\ 1 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \ \nu_2 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \ \nu_3 = \begin{bmatrix} 0 \\ 0 \\ 1 \\ 0 \\ 0 \end{bmatrix}, \ \nu_4 = \begin{bmatrix} 1 \\ 0 \\ 0 \\ 0 \\ 0 \end{bmatrix}, \ \nu_5 = \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1 \\ 0 \end{bmatrix} \tag{1.3}$$

The entries for ν_3 is zero everywhere except for the third coordinate, because the reactant complex of the third reaction is C. Associating to each reaction the product complex ν'_k, we see that $\zeta_k = \nu'_k - \nu_k$. Throughout the text, we will use d for the number of species, R for the number of reactions, and ζ_k for the kth reaction vector.

1.2.2 Dynamical System

Biologists are interested in the dynamics of the populations of chemical species over time. Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a CRN, with $\mathcal{R}$ consisting of $R > 0$ reactions. For $k = 1, ..., R$, we would like to define the reaction intensity (or rate/propensity) functions $\lambda_k : \mathbb{R}^d_{\geq 0} \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$, which represent the rates at which the reactions take place. If $X_i(t)$ represents the amount of the ith species in the system at time t, the natural deterministic model to consider would be the solution to the ODE

$$X(t) = X(0) + \sum_{k=1}^{R} \int_0^t \lambda_k(X(s), s) ds \zeta_k.$$

On the other hand, we can also consider the stochastic model

$$X(t) = X(0) + \sum_{k=1}^{R} N_k(t) \zeta_k \tag{1.4}$$

where N_k is a counting processes for the number of occurrences of the reaction k. For simplicity, we would like to use a Markovian model for now. That is, we will assume $\lambda_k : \mathbb{R}^d_{\geq 0} \to \mathbb{R}_{\geq 0}$ and

$$P(\text{Reaction } k \text{ occurs in } (t, t+\Delta t] | X_t) \cong \lambda_k(X(t))\Delta t \tag{1.5}$$

so that the likelihood for a specific reaction to take place in the next infinitesimal time frame depends only on the current state of the system. The assumption is indeed not perfect. No chemical reactions are processed instantly. In a strict sense, we must consider the delay within each reaction. We shall revisit this point later in Chapter 4. Let $\{Y_k; k = 1, ..., R\}$ be a set of unit rate Poisson process. The following model based on a random time change of Poisson process is in accord with (1.5), and is a critically important representation used throughout this thesis,

$$X(t) = X(0) + \sum_{k=1}^{R} Y_k \left(\int_0^t \lambda_k(X(s))ds \right) \zeta_k. \tag{1.6}$$

This model, however, is defined only up to $\tau_\infty \stackrel{def}{=} \lim_{n\to\infty} \tau_n$. Depending on the choice of propensity functions, the process might explode in that $\tau_\infty < \infty$. We will discuss this issue later in Chapter 5.

We have not yet discussed the choice of intensity function λ_k. The most common choice for both biologists and chemists is that of mass-action kinetics, and its usage dates back to the work of Guldberg and Waage [42] in 1864. Under mass action kinetics, intensity functions take the following form.

$$\lambda_k(x) = r_k \prod_{\ell=1}^{d} \binom{x_\ell}{x_\ell - \nu_{k\ell}}.$$

For example, for the model with reactions (1.1), the intensity functions are

$$r_1 X_A(t) X_B(t), \quad r_2 X_A(t), \quad r_3 X_C(t), \quad r_4 X_A(t), \quad r_5 X_D(t),$$

yielding the representation

$$\begin{aligned} X(t) =& X(0) + Y_1\left(\int_0^t r_1 X_A(s)X_B(s)ds\right)\zeta_1 + Y_2\left(\int_0^t r_2 X_A(s)ds\right)\zeta_2 \\ &+ Y_3\left(\int_0^t 3_1 X_C(s)ds\right)\zeta_3 + Y_4\left(\int_0^t r_4 X_A(s)ds\right)\zeta_4 + Y_5\left(\int_0^t r_5 X_D(s)ds\right)\zeta_5. \end{aligned} \tag{1.7}$$

1.3 Properties and characterizations of the stochastic models based on the random time change representation

In this section, we will discuss our stochastic model with more concreteness. We will describe its probability space and introduce properties that will become useful in this dissertation. The works in this section are organized from [10], [51], [57], the last of which is in French. We filled in the details which we deemed essential.

1.3.1 Probability Space of the Stochastic Model and the Meyer-Knight theorem

Let $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ be a CRN with d species and R reactions. Any path of our stochastic dynamical process X realized in the way of (1.4) (in particular of (1.6)) is determined completely by the set of counting processes $\{N_k; k = 1, ..., R\}$ that counts the number of reaction occurrences. Let $J[0, \infty)$ be the collection of non-negative integer valued càdlàg functions that are constant except for jumps of size 1. The probability space of our stochastic model will hence be $\Omega = J[0, \infty)^R$. We are going to derive the probability

measure for the process X given by a solution to

$$X(t \wedge \tau_n) = X(0) + \sum_{k=1}^{R} Y_k \left(\int_0^{t \wedge \tau_n} Z(s) ds \right) \tag{1.8}$$

with

$$\tau_n = \inf \left\{ r; \sum_{k=1}^{R} Y_k \left(\int_0^r Z(s) ds \right) = n \right\}. \tag{1.9}$$

where Z is a process adapted to the natural filtration of X. We will assume that $X(0)$ is deterministic. Because we are stopping the system at time τ_n this model never explodes.

To construct the desired probability measure, we will begin from the probability measure Q under which processes $\{N_k; k = 1, ..., R\}$ are mutually independent unit Poisson processes. We will suppose that the processes are adapted to the complete filtration $\mathcal{F}_t$. Based on Q, we will construct a measure $P \ll Q$ under which $\{N_k\}$ are equal in law to $\left\{ Y_k \left(\int_0^t Z(s) ds \right) \right\}$ in (1.8). Our main tool will be the Meyer-Knight theorem (theorem 1.8). The Meyer Knight theorem is a generalization of the Watanabe's characterization of the Poisson process, which states that a pure jump process N with jump size 1 is a Poisson process with rate λ if and only if $N(t) - \lambda t$ is a martingale with respect to the natural filtration of N.

When changing the measure, Bayes formula and the ensuing theorem become useful.

Theorem 1.1. *(Bayes formula, generalized) Let L and Z be random variables on a probability space Ω. If $\mathcal{D}$ is a sigma algebra and $dP = LdQ$, then*

$$E^P[Z|\mathcal{D}] = \frac{E^Q[ZL|\mathcal{D}]}{E^Q[L|\mathcal{D}]}$$

Theorem 1.2. *Let M be a martingale with respect to a filtration $\mathcal{F}_t$ under Q. Also, let P be an absolutely continuous probability measure with respect to Q, and suppose $M(t)dQ|_{\mathcal{F}_t} = dP|_{\mathcal{F}_t}$. Then a process G is a P-martingale with respect to $\mathcal{F}_t$ if and only if GM is a Q-martingale with respect to $\mathcal{F}_t$.*

Proof. By Bayes formula, $E_Q[M(t+h)(G(t+h)-G(t))|\mathcal{F}_t] = 0$ if and only if $E_P[(G(t+h)-G(t))|\mathcal{F}_t] = 0$. Also, by the martingale property of M,

$$E_Q[M(t+h)G(t)|\mathcal{F}_t] = G(t)E_Q[M(t+h)|\mathcal{F}_t] = M(t)G(t)$$

Thus $E_Q[M(t+h)G(t+h)|\mathcal{F}_t] = M(t)G(t)$ if and only if $E_P[G(t+h)|\mathcal{F}_t] = G(t)$. □

Also, we will be using the following basic facts about martingales and stochastic integrals. For simplicity we denote $\int_0^t A(s)dB(s)$ by $(A \cdot B)(t)$.

Lemma 1.3. *A positive local martingale M_t with $E[M_t] = E[M_0]$ for all t is a martingale.*

Proof. Let τ_n be the localizing sequence of M. We know that $E[M_{t\wedge\tau_n}] = E[M_0]$, so

$$E[\lim_{n\to\infty} M_{t\wedge\tau_n}] = E[M_t] = E[M_0] = \lim_{n\to\infty} E[M_{t\wedge\tau_n}]$$

If $s \le t$ and $A \in \mathcal{F}_s$, by the martingale property of $M_{t\wedge\tau_n}$,

$$E[M_{t\wedge\tau_n}1_A] = E[M_{s\wedge\tau_n}1_A]$$

Now, use the generalized dominated convergence theorem to take $n \to \infty$ on both sides. □

Lemma 1.4. *If V is càdlàg and M is a positive square integrable martingale, then $V \cdot M$ is a martingale.*

Proof. Without loss of generality we may suppose that V is non-negative. This follows since any V can be written as the difference $V_+ - V_-$ of non-negative càdlàg functions, and a difference of two martingales is a martingale. Since V is locally bounded with some localizing sequence, $V \cdot M$ is a locally square integrable martingale. Let $V^C = V \wedge C$. Then clearly

$$E[(V^C \cdot M)(t)] = E[(V \cdot M)(0)].$$

By the monotone convergence theorem we obtain

$$E[(V \cdot M)(t)] = E[(V \cdot M)(0)].$$

By lemma 1.3, $V \cdot M$ is a martingale. □

Lemma 1.5. *Let N be a Poisson process adapted to $\mathcal{F}_t$, and let V be a càdlàg process adapted to $\mathcal{F}_t$. Denote by $\tilde{N}$ the compensated Poisson process. Then $V \cdot \tilde{N}$ is a martingale.*

Proof. Again without loss of generality assume V positive. Let $V^C = V \wedge C$. Then $V^C \cdot \tilde{N}$ is a martingale. If $A \in \mathcal{F}_s$, then by martingale property,

$$\begin{aligned} E[\{(V^C \cdot \tilde{N})_t - (V^C \cdot \tilde{N})_s\}1_A] &= 0 \\ E[(V^C \cdot N)_t 1_A] - E[(V^C \cdot N)_s 1_A] &= E\left[\int_s^t V^C(r)dr 1_A\right] \end{aligned} \tag{1.10}$$

By the Monotone convergence theorem applied to each expectation,

$$E[(V \cdot N)_t 1_A] - E[(V \cdot N)_s 1_A] = E\left[\int_s^t V(r)dr 1_A\right]$$

Implying that

$$E[((V \cdot \tilde{N})_t - (V \cdot \tilde{N})_s)1_A] = 0.$$

The claim follows. □

Now, let $\{N_i\}$ be Poisson processes on $(\Omega, \mathcal{F}, Q)$ and let $\{Z_i, i = 1, ..., R\}$ be processes with the following properties:

- $Z_i(t \wedge \tau_n)$ is càdlàg.
- $N_i(s) = N_i(s-)$ when $Z_i(s) = 0$.
- Z_i is adapted to $\mathcal{F}_t$.
- Z_i is non-negative.

In what follows, Z_i will serve as the reaction rate function for the reaction i, and N_i will be the counting process that counts the number of the occurrences of the reaction i. We need the first assumption to prevent the propensity from exploding with only a finite number of reactions. We need the second assumption because no reaction shall take place when the propensity is 0. We want the third assumption because we do not want the value of Z_i to depend on future information.

We define the Girsanov exponential Radon Nikodym Derivative based on Z as follows:

$$L(t) = \prod_{i=1}^{R} \exp\left(\int_0^t \ln(Z_i(s-))dN_i(s) - \int_0^t (Z_i(s) - 1)ds\right) \tag{1.11}$$

We then change the measure Q to the measure P defined by $dP = L(\tau_n)dQ$ on $\mathcal{F}_{\tau_n}$, where τ_n is as in (1.9). The following property of $L(t)$ ensures that our change of measure is a bona-fide change of probability measure.

Lemma 1.6. *$L(t)$ is a local martingale with localizing stopping time τ_n.*

Proof. By Ito's formula,

$$\begin{aligned} L(t) = L(0) &+ \sum_{i=1}^{R} \int_0^t L(s-) \ln(Z_i(s-)) dN_i(s) - \int_0^t L(s)(Z_i(s-) - 1) ds \\ &+ \frac{1}{2} \int_0^t L(s-) \ln(Z_i(s-)) dN_i(s) + \sum_{s \le t} (L(s) - L(s-)) \\ &- \sum_{s \le t} L(s-) \sum_i ln Z_i(s-)(N_i(s) - N_i(s-)) - \frac{1}{2} \sum_{s \le t} L(s-) \sum_{i=1}^{R} (N_i(s) - N_i(s-)) \end{aligned}$$

Now noting that

$$\sum_{s \le t} (L(s) - L(s-)) = \sum_{i=1}^{R} \int_0^t L(s-)(Z_i(s-) - 1) dN_i(s)$$

and that the first derivative and the second derivative terms cancel out, we see that

$$L(t) = 1 + \sum_{i=1}^{R} \int_0^t L(s-)(Z_i(s-) - 1) d(N_i - s).$$

Since $Z(t \wedge \tau_n)$ and $L(t \wedge \tau_n)$ are both càdlàg and positive, $L(t \wedge \tau_n)$ is a martingale by lemma 1.5 □

Lemma 1.7. *If $dP = L(\tau_n)dQ$, then this is a change of probability measure, and $dP = L(t \wedge \tau_n)dQ$ on $\mathcal{F}_{t \wedge \tau_n}$.*

Proof. We will use the method similar to theorem 1.12, which will mention later. Since we know that $Q(\tau_n < \infty) = 1$, $P(\tau_n < \infty) = 1$ as well by the absolute continuity of P with respect to Q. Therefore $P(L(\tau_n \wedge \infty) = L(\tau_n) < \infty) = 1$. By definition,

$$P(L(\tau_n) < K) = E^Q[L(\tau_n); L(\tau_n) < K]$$

Then applying monotone convergence theorem to the both sides, we see that

$$\begin{aligned} P(L(\tau_n) < \infty) &= E^Q[L(\tau_n); L(\tau_n) < \infty] \\ 1 &= E^Q[L(\tau_n)]. \end{aligned} \tag{1.12}$$

This shows that

$$1 = \lim_{t\to\infty} E^Q[L(t\wedge\tau_n)] = E^Q[\lim_{t\to\infty} L(t\wedge\tau_n)] = E^Q[L(\tau_n)].$$

Now, if $A \in \mathcal{F}_{t\wedge\tau_n}$, and $t < T$, then by optional sampling theorem

$$E[L(T\wedge\tau_n)1_A] = E[L(t\wedge\tau_n)1_A].$$

By the generalized dominated convergence theorem, as $T \uparrow \infty$ the left hand side converges to $E[L(\tau_n)1_A]$, and the claim follows. □

In the next subsection, as promised, we will finally show that the set of processes $\{N_k, k = 1, .., R\}$, which are independent unit Poisson under Q, are solutions to the system

$$N_k(t\wedge\tau_n) = Y_k\left(\int_0^{t\wedge\tau_n} Z_k(s)ds\right)$$

under the measure P with $dP = L(\tau_n)dQ$. To proceed, we need a theorem developed by Meyer based on the work of Knight [57].

1.3.2 The Meyer-Knight theorem

We need some definitions before introducing the Meyer-Knight theorem. Let X and Y be càdlàg processes which are both adapted to $\mathcal{F}_t$. Let us denote the quadratic covariation of X and Y by $[X, Y]$. The sharp bracket $\langle X, Y\rangle$ is defined as the unique predictable process such that

$$[X, Y] - \langle X, Y\rangle$$

is a martingale. We say X and Y are *orthogonal* if $\langle X, Y\rangle = 0$. Also, we say that a stopping time σ is *predictable* if there is a sequence of stopping times σ_n for which

$\sigma_n \to \sigma$. A stopping time τ is *totally inaccessible* if for any predictable stopping time σ,

$$P(\sigma = \tau < \infty) = 0.$$

In other words, *totally inaccessible* stopping time cannot be approximated by any increasing sequence of stopping times.

Theorem 1.8. ***(Meyer-Knight)*** *Suppose* $\{X_i\}_{i=1}^n$ *are mutually orthogonal (In the sense of sharp Bracket) purely discontinuous* [3] *martingales with totally inaccessible jumps of size* 1. *If*

$$\gamma(t) = \langle X_i, X_i \rangle$$

and

$$Q_i(t) = X_i(\gamma^{-1}(t)),$$

then $\{Q_i\}_{i=1}^n$ *is a set of mutually independent, compensated unit Poisson processes.*

We are going to use theorem 1.8 together with lemma 1.2 to prove the following;

Lemma 1.9. *Put*

$$U_i(t) = N_i(t) - \int_0^t Z_i(s)ds.$$

Then $U_i(t \wedge \tau_n)$ *is a martingale with respect to* P. *That is,*

$$\langle N_i(t \wedge \tau_n), N_i(t \wedge \tau_n) \rangle = \int_0^{t \wedge \tau_n} Z_i(s)ds.$$

Proof. With integration by parts,

$$\begin{aligned} L(t \wedge \tau_n)U_i(t \wedge \tau_n) = L(0)U_i(0) &+ \int_0^{t \wedge \tau_n} L(s-)dU_i(s) \\ &+ \int_0^{t \wedge \tau_n} U_i(s-)dL(s) + [U_i, L](t \wedge \tau_n) \end{aligned} \tag{1.13}$$

[3] *its quadratic variation is a pure jump process*

The third term is a martingale by lemma 1.4. Now the remaining terms simplify to

$$\begin{aligned}\int_0^{t\wedge\tau_n} L(s-)dU_i(s) + [U_i, L](t) &= \int_0^{t\wedge\tau_n} L(s-)(dN_i(s) - Z_i(s)ds)) \\ &\quad + \int_0^t L(s-)(Z_i(s)-1)dN_i(s) \\ &= \int_0^{t\wedge\tau_n} L(s-)Z_i(s)d(N_i - s)\end{aligned} \tag{1.14}$$

This is a martingale by lemma 1.5. Now seeing that $U_i(t\wedge\tau_n)$ is adapted to $\mathcal{F}_{\cdot\wedge\tau_n}$, we can apply lemma 1.2 with $M(t) = L(t\wedge\tau_n)$ together with lemma 1.7 to claim that $U_i(t\wedge\tau_n)$ is a martingale with respect to P. □

Now we are one step away from applying the Meyer-Knight theorem. We need to show that U_i has totally inaccessible jumps.

Lemma 1.10. *If G is a pure counting process for which $G-\gamma$ is a martingale for a continuous, monotonic γ, then G's jump times are totally inaccessible.*

Proof. By definition, a jump time τ is totally inaccessible if for any predictable stopping time σ, $P(\sigma = \tau < \infty) = 0$. Clearly, $\{G(\sigma) - G(\sigma-) > 0\}$ on the event $\{\sigma = \tau < \infty\}$. Therefore $P(\sigma = \tau) \leq P(G(\sigma) - G(\sigma-))$, and it suffices to show that, for any predictable stopping time σ, $E[G(\sigma) - G(\sigma-)] = 0$. Note that, since σ is predictable, there is an increasing sequence of stopping times σ_n such that $\lim_{n\to\infty}\sigma_n = \sigma$. By the monotone convergence theorem (MCT), we get

$$E[G(\sigma) - G(\sigma-)] = \lim_{n\to\infty} E[G(\sigma) - G(\sigma_n)] \tag{1.15}$$

By the optional stopping theorem, $E[G(\sigma_n)] = E[\gamma(\sigma_n)]$. Therefore again by the MCT and the continuity of γ,

$$\lim_{n\to\infty} E[G(\sigma) - G(\sigma_n)] = \lim_{n\to\infty} E[\gamma(\sigma) - \gamma(\sigma_n)] = 0 \tag{1.16}$$

□

With all of the above in mind, we finally have the following claim;

Theorem 1.11. *Let $dP = L(\tau_n)dQ$. Then $\{N_i\}$ under P is distributionally equal to the solution of*

$$\left\{ N_i(t \wedge \tau_n) = Y\left(\int_0^{t\wedge\tau_n} Z_i(s)ds \right) \right\}.$$

under P.

Proof. Put $G_i(t) = N_i(t \wedge \tau_n)$. By lemma 1.9,

$$\langle G_i(t), G_i(t) \rangle = \int_0^{t\wedge\tau_n} Z(s)ds$$

under P. That $\langle G_i(t), G_j(t) \rangle = 0$ for $i \neq j$ is obvious. Note that $\gamma_i(t) = \int_0^{t\wedge\tau_n} Z(s)ds$ is absolutely continuous, and this makes the jumps of G_i totally inaccessible. If $\gamma_i^{-1}(t) = \inf\{s; \gamma_i(s) \leq t\}$, the Meyer-Knight theorem tells us that $\{G_i(\gamma_i^{-1}(t))\}$ is a set of independent unit rate Poisson processes. Since $\gamma_i(t)$ is monotonically increasing for every event w, this tells us that

$$\begin{aligned} G_i(\gamma_i^{-1}(t)) &= Y(t) \\ G_i(t) &= Y(\gamma_i(t)) \\ N_i(t \wedge \tau_n) &= Y_i\left(\int_0^{t\wedge\tau_n} Z_i(s)ds \right) \end{aligned} \tag{1.17}$$

as desired. □

It is critical that we change the measure with $L(\tau_n)$ instead of $L(t)$ if the process is explosive. For example, suppose $R = 1$, and let Ω be the space of the set of all paths of a Poisson process. Consider a process N_1 which is a unit rate Poisson process under a

probability measure P_1, and a process N_2 which is a solution to

$$N_2(t) = Y\left(\int_0^t (1 + N_2^2(s))ds\right)$$

under another probability measure P_2. Then while $P_2|\mathcal{F}_{\cdot\wedge\tau_n} \ll P_1|\mathcal{F}_{\cdot\wedge\tau_n}$ holds, $P_2|\mathcal{F}_t \ll P_1|\mathcal{F}_t$ does not hold for any t. To see this, note that for each t, the event of explosion has positive measure with respect to P_2, while it has measure zero with respect to P_1.

Also, if N_3 is a Poisson process with constant rate 2 under the measure P_3, then while $P_3|\mathcal{F}_t \ll P_1|\mathcal{F}_t$ for all finite t, $P_3|\mathcal{F}_\infty$ is not absolutely continuous with respect to $P_1|\mathcal{F}_\infty$. To see this, note that the measure of the event on which $\lim_{t\to\infty} \frac{N(t)}{t} = 2$ is zero under P_1, while it is 1 under P_2.

On the other hand, If $P(\lim_{n\to\infty} \tau_n > T) = 1$, that is, if under P the process N up to T is not explosive, we hope to use $L(T)$ to change the measure Q on $\mathcal{F}_T$. When the process is non-explosive, we can appeal to the following very useful theorem.

Theorem 1.12. *Let $(\Omega, \mathcal{F})$ be a measurable space, and let P and Q be probability measures on $\mathcal{F}$. Suppose that $\mathcal{D}_n \subset \mathcal{D}_{n+1}$ and that for each n, $P|_{\mathcal{D}_n} \ll Q|_{\mathcal{D}_n}$. Put $L_n = \frac{dP}{dQ}\big|_{\mathcal{D}_n}$ and $\lim L_n(t) = L(t)$. Then $P \ll Q$ on $\mathcal{D} = \vee_n \mathcal{D}_n$ and $L(t)dQ = dP$ on $\mathcal{D}$ if and only if $P(\limsup_{n\to\infty} L_n < \infty) = 1$.*

Proof. It suffices to show that $E^Q[L(t)] = 1 = \lim E^Q[L_n(t)]$. To see this, note that with this assumption, we can use the generalized dominated convergence theorem to show $E^Q[L1_A] = \lim_{n\to\infty} E^Q[L_n 1_A] = E^Q[L_n(t)1_A]$ for any arbitrary n and for any $A \in \mathcal{D}_n(t)$. First, by Fatou's lemma $E^Q[L(t)] \leq 1$. This in particular means that $Q(\sup_n L_n(t) < \infty) = 1$. Next, using the dominated convergence theorem and the

monotone convergence theorem,

$$\begin{aligned} P(\sup_{n\leq N} L_n \leq K) &= E^Q[L_N 1(\sup_{n\leq N} L_n \leq K)] \\ P(\sup_n L_n \leq K) &= E^Q[L1(\sup_n L_n \leq K)] \\ 1 = P(\sup_n L_n < \infty) &= E^Q[L1(\sup_n L_n < \infty)] \\ &= E^Q[L]. \end{aligned} \tag{1.18}$$

□

Corollary 1.1. *Define $dP = L(\tau_n)dQ$ on $\mathcal{F}_{t\wedge\tau_n}$ as before, and suppose $P(\lim_{n\to\infty}\tau_n > T) = 1$. Then $P|\mathcal{F}_T \ll Q|\mathcal{F}_T$ with $L(T)dQ = dP$ on $\mathcal{F}_T$, and $\{N_i\}$ under $P|\mathcal{F}_T$ is a solution to*

$$\left\{ N_i(t\wedge T) = Y_i\left(\int_0^{t\wedge T} Z_i(s)ds\right)\right\}$$

under P.

Proof. Since $\lim\tau_n > T$ P-almost surely, $\sum_{i=1}^R N_i(T) < \infty$ P-almost surely. Also, since Z is càdlàg, $\int_0^T Z(s)ds < \infty$ as well. Thus by our assumption

$$L_n(T) < \prod_{i=1}^R \exp\left\{\int_0^T \log(Z_i(s-))dN_i(s) + \int_0^T Z_i(s)ds\right\} < \infty$$

for all n. We can therefore appeal to theorem 1.12, and use $L(t\wedge T)$ in place of $L(t\wedge\tau_n)$ everywhere in the arguments above. □

We will mention a condition of non-explosivity in Chapter 5. For the rest of this dissertation, we will consider non-explosive CRNs. We use the representation (1.6) in all other Chapters.

Let $\lambda_k : J[0,\infty)^R \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ be a non-anticipating function; that is, $\lambda_k(x,s) = \lambda_k(x(\cdot \wedge s), s)$. Then we may use $\lambda(N,s)$ in place of Z, and we obtain the model (1.6). Also, if $\zeta_k \not\propto \zeta_k'$ for all $k \neq k'$, a path of X determines the paths of $\{N_k\}$ completely, and indeed vice versa. Therefore the natural filtration of $\{N_k\}$ agrees with that of X. For example, if

$$A \to 2A$$

is our CRN, and if $X_A(0) = 1$, then $\lambda_i(N,s) = N(s) + 1$.

In fact we can construct the process N from X under P forward in time. The construction not only justifies the condition (1.5), but also gives rise to a simulation algorithm known as the next reaction method ([58], [24]).

Algorithm 1.1. *Let $t = 0$ be the current time, and let T be the terminal time of the observation. First, assign $\tau_k = expo_k(1)$ for each $k = 1, \dots R$.*

1. *Compute $\lambda_k(X,t)$ for each $k = 1, \dots R$.*
2. *Compute $\tau = min(\{\tau_k/\lambda_k(X,t)\})$, and $win = \{k \ ; \ \tau_k/\lambda_k(X,t) = \tau\}$*
3. *update*
   (a) *$\tau_{win} = expo(1)$*
   (b) *Update t to be $t + \tau/\lambda_{win}(X(t))$. If $t > T$, break from the algorithm.*
   (c) *$X(t) = X(t) + \zeta_{win}$*
   (d) *return to 1.*

The algorithm also illuminates the fact that we are constructing the probability measure for the process from that of unit rate Poisson processes.

1.3.3 Intensity

The result of lemma 1.9 assures that

$$N_i(t \wedge \tau_n) = Y_i\left(\int_0^{t\wedge\tau_n} Z_i(s)ds\right) - \int_0^{t\wedge\tau_n} Z_i(s)ds$$

is a martingale with respect to the filtration $\mathcal{F}_{t\wedge\tau_n}$. In the context above, we say Z_i is the **intensity** of N_i.

With the definition of intensity, we can also discuss the concept of "thinning" a counting process. Let, for instance, R be a nonexplosive pure counting process with intensity $\lambda(R,s)$. If $p : \mathbb{Z}_{\geq 0} \to [0,1]$, we would like to construct a new counting process R_1 such that only when R jumps at time t, R_1 jumps with probability $p(R(t-))$. Let $\xi_0, \xi_1, ...$ be independent, uniform random variables. Also, for $n \geq 1$ let τ_n again be the nth jump time of R. Then we can define

$$R_1(t\wedge\tau_n) \stackrel{def}{=} \int_0^{t\wedge\tau_n} 1_{[0,p(R(s-))}(\xi_{R(s-)})dR(s) = \sum_{k=0}^{R((t\wedge\tau_n)-)} 1_{[0,p(R(s-))}(\xi_k). \tag{1.19}$$

If $\tilde{R}(t\wedge\tau_n) \stackrel{def}{=} R(t\wedge\tau_n) - \int_0^{t\wedge\tau_n}\lambda(R,s)ds$, then we see that

$$\begin{aligned} R_1(t\wedge\tau_n) - \int_0^{t\wedge\tau_n} p(R(s-))\lambda(R,s)ds = \int_0^{t\wedge\tau_n} & 1_{[0,p(R(s-)))}(\xi_{R(s-)}) - p(R(s-))dR_s \\ & + \int_0^{t\wedge\tau_n} p(R(s-))d\tilde{R}(s) \end{aligned} \tag{1.20}$$

is a martingale. We can therefore say that the intensity of R_1 is $p(R(s-))\lambda(R,s)$, and by the Meyer-Knight theorem, it is distributionally equal to $Y\left(\int_0^t p(R(s-))\lambda(R,s)ds\right)$

for a Poisson process Y.

The notion of thinning allows us to craft still another representation of (1.6). Let N be a pure counting process with intensity $\lambda_0(N,s) \stackrel{def}{=} \sum_{k=1}^{R} \lambda_k(N,s)$. Then we can decompose N into

$$N = \sum_{k=1}^{R} N_k,$$

with N_k such that whenever $N(t) - N(t-) = 1$, $N_k(t) - N_k(t-) = 1$ with probability $p_k(N, t-) = \frac{\lambda_k(N,t-)}{\lambda_0(N,t-)}$. By appealing to the Meyer-Knight theorem again, we see that X in (1.4) constructed from this set of N_k is equal in law to the solution of (1.6). As opposed to the next reaction method (1.1), this construction motivates the following method of generating the distribution of (1.6).

Algorithm 1.2. *Let $t = 0$ be the current time, and let T be the terminal time of the observation.*

1. *Compute $\lambda_0(X,t) = \sum_{k=1}^{R} \lambda_k(N,t)$.*
2. *Generate a categorical random variable $\eta(X(t))$ such that $\eta(X(t)) = \zeta_k$ with probability $\lambda_k(X,t)/\lambda_0(X,t)$.*
3. *update*
   (a) *$t = t + \tau$. If $t > T$, break from the algorithm.*
   (b) *$X(t) = X(t) + \eta(X(t))$*
   (c) *return to 1.*

This method is referred to as Gillespie's method, or the stochastic simulation algorithm (SSA) [39].

1.3.4 Martingale Problem

Lemma 1.9 tells us that, if X is given by (1.8), then

$$X(t \wedge \tau_n) - \sum_k \zeta_k \int_0^{t \wedge \tau_n} \lambda_k(X, s) ds \tag{1.21}$$

is a martingale with respect to its natural filtration. In fact X can satisfy another martingale property.

Let U be a Feller Markov process, and denote $E[f(U(t))|U(0) = u] = E_u[f(U(t))]$. Then we define

$$Af(u) = \lim_{\Delta t \to 0} \frac{E_u[f(U(t + \Delta t)] - E_u[f(U(t)]}{\Delta t}$$

to be the *generator* of X. Then

$$M(t) = f(U(t)) - \int_0^t Af(U(s)) ds$$

is a local martingale relative to the natural filtration of U [32]. Let $\overline{C}$ be the vector space of bounded continuous functions. We may associate the operator A with its graph $\mathcal{G}$, which is the completion of

$$\{(f, Af), f \in \overline{C}\}$$

in the uniform continuity norm. We say U is a solution to a local martingale problem for the closed graph $\mathcal{G}$ if for each $(f, g) \in \mathcal{G}$,

$$f(U(t)) - \int_0^t g(U(s)) ds$$

is a local martingale.

We would like to address the martingale problem for a process of type (1.6). Let us suppose that $\lambda_k(X, s)$ depends only on $X(s)$, that is, $\lambda_k : \mathbb{R}^d \to \mathbb{R}_{\geq 0}$ and we can write

$\lambda_k(X,s) = \lambda_k(X(s))$. Then we have a very simple formulation of the generator of X . Let $E = \mathbb{R}^d \cup \upsilon$ be the one point compactification of $\mathbb{R}^d$, and let

$$\tau_\infty = \inf\{t : X(t-) = \upsilon\}.$$

Next, for $f \in \overline{\mathcal{C}}$ vanishing off a finite subset of $\mathbb{Z}^d$, put

$$Af(x) = \begin{cases} \sum_{k=1}^R \lambda_k(x)(f(x+\zeta_k) - f(x)) & \text{if } x \in \mathbb{Z}^d \\ 0 & \text{if } x = \upsilon \end{cases} \tag{1.22}$$

Theorem 1.13. *Suppose X satisfies (1.6) with $X(t) = \nu$ for $t \geq \tau_\infty$. Then X is a solution of the local martingale problem for A. Moreover, if $\tilde{X}$ is another solution of the local martingale problem for A with càdlàg sample paths satisfying $\tilde{X}(t) = \nu$ for $t \geq \tau_\infty$, then $\tilde{X}$ is version of X.*

Ethier and Kurtz ([32], Chapter 6, section 4) provides a rigorous proof to this theorem using random time change theory. Although less rigorous, we also have an intuitive description of A as well. Note that

$$\begin{aligned} E[f(X(t+\delta t))|f(X(t))] &= \sum_{k=1}^R f(X(t)+\zeta_k)P(k\text{th reaction occurs in } [t,t+\delta t]) \\ &\quad + f(X(t))P(\text{no reaction occurs in } [t,t+\delta t]) \\ &\cong \sum_{k=1}^R f(X(t)+\zeta_k)\lambda_k(X(t)) + f(X(t))\left(1 - \sum_{k=1}^R \lambda_k(X(t))\right) \\ E[f(X(t+\delta t))|f(X(t)] - f(X(t)) &\cong Af(x)\delta t \end{aligned} \tag{1.23}$$

taking δt to 0, we obtain the expression in (1.22). When f is an identity function, we obtain (1.21). We note that $f(X)$ is a statistics of X, and its expectation is oftentimes a value of interest for Biologists.

1.3.5 Multiparameter Filtration

Sometime, it is useful to use the filtration of the unit rate Poisson processes in place of the natural filtration. The following definition becomes useful in Chapter 2 which considers the weak-analysis of Runge-Kutta type simulation methods. Let $u \in \mathbb{R}^R_{\geq 0}$. We define the multiparameter filtration $\tilde{\mathcal{F}}_u$ as follows:

$$\tilde{\mathcal{F}}_u = \sigma\{Y_k(s_k) : s_k \leq u_k, k = 1, ..., R\} \tag{1.24}$$

$$\tilde{\mathcal{F}}^k_u = \sigma\{Y_k(s_k) : s_k \leq u_k, Y_m(s_m), s_m < \infty\} \tag{1.25}$$

Also define

$$\eta_k(t) = \int_0^t \lambda_k(X(s))ds,$$

Lemma 1.14. *$\eta_k(t)$ is a stopping time with respect to $\tilde{\mathcal{F}}^k_u$.*

Proof. Define υ_k by

$$t = \int_0^{\upsilon_k(t)} \lambda_k(X(s))ds.$$

Then

$$\{\eta_k(t) < u\} = \{t < \upsilon_k(u)\}\tilde{\in}\mathcal{F}^k_u.$$

and the claim follows. □

Multiparameter filtrations are described in more detail in Chapter 6 of [32]. By the optional sampling theorem,

$$E[Y_k(\eta_k(t))] = E[\eta_k(t)]$$

Also, if

$$\eta(t) = \{\eta_1(t), \eta_2(t), ...\eta_R(t)\},$$

and $\zeta_k \not\propto \zeta'_k$ for all $k \neq k'$, then the natural filtration of X is $\tilde{\mathcal{F}}_{\eta(t)}$.

Chapter 2

Numerical methods for the weak analysis of biochemical processes

The content of this chapter has appeared in SIAM journal of multi-scale modeling and simulation [9]. If X is a càdlàg stochastic process in $\mathbb{R}^d$ describing the population dynamics of a chemical reaction network (CRN) as in (1.6), and if $J_{\mathbb{R}^d}[0,\infty)$ is the set of all càdlàg paths in $\mathbb{R}^d$, we often would like to know the value of $E[f(X)]$ for some function f mapping $J_{\mathbb{R}^d}[0,\infty)$ to $\mathbb{R}$. Since $E[f(X)]$ is determined by the distribution of X, its analysis can be referred to as "weak analysis." One way to approach this problem is to use Monte Carlo methods, which is a computational algorithm that relies on repeated sampling. If, for example, $\{X_i, i = 1, ..., N\}$ are independent samples of X, then

$$\frac{1}{N}\sum_{i=1}^{N} f(X_i) \tag{2.1}$$

serves as an unbiased estimator for $E[f(X)]$. As we introduced in the first chapter, we can simulate the continuous time Markov chain model of a CRN exactly by using Gillespie's algorithm (1.2) or the next reaction method (1.1). There is, however, a shortcoming associated with these exact algorithms in that they must simulate every transition of the Markov model. To be more specific, note that, in the Gillespie's algorithm, the time Δt between the jumps is an exponential random variable with a

parameter of $\sum_k \lambda_k(X(t))$. If

$$\sum_k \lambda_k(X(t)) \gg 1 \qquad \text{so that} \qquad \mathbb{E}\Delta t = \frac{1}{\sum_k \lambda_k(X(t))} \ll 1, \tag{2.2}$$

then the runtime needed to produce a single exact sample path can be prohibitive.

A straightforward resolution is to compromise bias in favor of runtime cost. In other words, we may reduce the complexity of the model and allow some bias. Munsky [61], for example, took the route of simplifying the system itself to a finite state space and then explicitly computing the solution to the forward equation

$$\frac{d}{dt}g(x,t) = Ag(x,t)$$

where $g(x,t) = E_x[f(X(t))]$ and A is the generator of X. This method is used, for example, in Marques-Lago's work [56]. Another approach is to use Euler/Runge-Kutta type algorithms. These algorithms discretize the continuous time Markov chain with a fixed time step and reduces the number of random variables to be generated per path. These numerical methods are oftentimes the most reasonable choices to aid in understanding the models in real time. Euler/Runge-Kutta type stochastic simulation algorithms are also referred as tau leaping methods [24].

In this chapter we provide a general framework for understanding the weak error of numerical approximation techniques in the setting of CRNs. We quantify how the errors of three different methods depend upon both the natural scalings within a given system and the step-size of the numerical method. Further, we will introduce a new Runge-Kutta type algorithm, the weak trapezoidal algorithm, which was developed originally

as an approximate method for diffusion processes [11] . We prove that the leading order of the bias of this new algorithm scales with the square of the time discretization, making it the first of the kind. As the cost per path is not appreciably more than that of the Euler's method, the new algorithm is an attractive choice.

2.1 Tau leaping methods

Throughout the chapter let X denote the solution to (1.6) in the first chapter. For approximate methods, we will sometimes consider an arbitrary method and will in such cases denote the solution as Z. Other times we will distinguish the Euler, midpoint, and Trapezoidal methods, by Z_E, Z_M, Z_{trap}, respectively. We will always begin the methods from the same initial condition, namely $X(0) = Z(0) = x_0$.

Remark 2.1. *Historically the time discretization parameter for the methods described in this dissertation has been τ, thus giving these methods the general name "τ-leaping methods." We choose to break from this tradition and denote our time-step by h so as not to confuse τ with a stopping time.*

2.1.1 Euler tau leaping

The approximate algorithm termed *explicit tau-leaping* was developed by Dan Gillespie in [40] in an effort to overcome the problem described above that Δt, the amount of time that must pass before the next reaction event, may be prohibitively small. The basic idea of tau-leaping is to hold the intensity functions fixed over the time interval $[t_n, t_n + h]$ at the values $\lambda_k(X(t_n))$, where $X(t_n)$ is the current state of the system, and, under this assumption, compute the number of times each reaction takes place

over this period. Note that this method will potentially yield lower runtimes only if $h \gg 1/\sum_k \lambda_k(X(t_n)) \approx \Delta t$. As the waiting times for the reactions are exponentially distributed this leads to the following algorithm, which simulates up to a time of $T > 0$. Below and in the sequel, for $x \geq 0$ we will write Poisson(x) for a Poisson random variable with a parameter of x.

Algorithm 2.1 (Euler tau-leaping)**.** *Fix $h > 0$. Set $Z_E(0) = x_0$, $t_0 = 0$, $n = 0$ and repeat the following until $t_{n+1} = T$:*

1. *Set $t_{n+1} = t_n + h$. If $t_{n+1} \geq T$, set $t_{n+1} = T$ and $h = T - t_n$.*
2. *For $k \in \{1, \ldots, R\}$, let $\Lambda_k = Poisson(\lambda_k(Z_E(t_n))h)$ be independent of each other and all previous random variables.*
3. *Set $Z_E(t_{n+1}) = Z_E(t_n) + \sum_k \Lambda_k \zeta_k$.*
4. *Set $n \leftarrow n + 1$.*

Several improvements and modifications have been made to the basic algorithm described above over the years. However, they are mainly concerned with how to choose the step-size adaptively [24, 41] and/or how to ensure that population values do not go negative during the course of a simulation [1, 23, 25], and are not explicitly relevant to the current discussion of convergence analysis.

Similar to (1.6), a path-wise representation of Euler tau-leaping defined for all $t \geq 0$ can be given through a random time change of Poisson processes:

$$Z_E(t) = Z_E(0) + \sum_k Y_k \left(\int_0^t \lambda_k(Z_E \circ \eta(s)) ds \right) \zeta_k, \tag{2.3}$$

where the Y_k are as before, and $\eta(s) \stackrel{def}{=} \left\lfloor \frac{s}{h} \right\rfloor h$. Thus, $Z_E(\eta(s)) = Z_E(t_n)$ if $t_n \leq s < t_{n+1}$. Noting that $\int_0^{t_{n+1}} \lambda_k(Z_E \circ \eta(s))ds = \sum_{i=0}^{n} \lambda_k(Z_E(t_i))(t_{i+1} - t_i)$ explains why this method is called "Euler tau-leaping." Defining the generator-like operator

$$(\mathcal{B}_z f)(x) \stackrel{def}{=} \sum_k \lambda_k(z)(f(x + \zeta_k) - f(x)), \tag{2.4}$$

we see that for $t > 0$

$$\mathbb{E}f(Z_E(t)) = \mathbb{E}f(Z_E \circ \eta(t)) + \mathbb{E}\int_{\eta(t)}^{t} (\mathcal{B}_{Z_E \circ \eta(t)} f)(Z_E(s))ds, \tag{2.5}$$

so long as the expectations exist. Equation (2.5) points out why we care about the associated operators for each of our approximate methods: they will be used to gain the necessary control over the difference $\mathbb{E}f(X(t)) - \mathbb{E}f(Z(t))$, called the *weak error* of the approximation, which is the focus of our dissertation.

2.1.2 Midpoint tau leaping

A midpoint type method was first described in [40][1] and analyzed in [7]. Define the function

$$\rho(z) \stackrel{def}{=} z + \frac{1}{2}h \sum_k \lambda_k(z)\zeta_k,$$

which computes an approximate midpoint for the system assuming the state of the system is z and the time-step is h. The following algorithm simulates up to a time of $T > 0$. Note that only step (ii) changes from Euler tau-leaping.

Algorithm 2.2 (Midpoint tau-leaping)**.** *Fix $h > 0$. Set $Z_M(0) = x_0$, $t_0 = 0$, $n = 0$ and repeat the following until $t_{n+1} = T$:*

[1]The midpoint method detailed in [40] is actually a slight variant of the method described here. In [40] the approximate midpoint, called $\rho(z)$ above, is rounded to the nearest integer value.

1. *Set* $t_{n+1} = t_n + h$. *If* $t_{n+1} \geq T$, *set* $t_{n+1} = T$ *and* $h = T - t_n$.

2. *For* $k \in \{1, \ldots, R\}$, *let* $\Lambda_k = Poisson(\lambda_k \circ \rho(Z_M(t_n))h)$ *be independent of each other and all previous random variables.*

3. *Set* $Z_M(t_{n+1}) = Z_M(t_n) + \sum_k \Lambda_k \zeta_k$.

4. *Set* $n \leftarrow n + 1$.

Similar to (1.6) and (2.3), $Z_M(t)$ constructed via Algorithm 2.2 can be represented for all $t \geq 0$ via a random time change of Poisson processes:

$$Z_M(t) = Z_M(0) + \sum_k Y_k \left(\int_0^t \lambda_k \circ \rho(Z_M(\eta(s)))ds \right) \zeta_k, \tag{2.6}$$

where $\eta(\cdot)$ is as before. For $\mathcal{B}_z$ defined via (2.4), any $t > 0$, and Z_M generated via (2.6) we have

$$\mathbb{E}f(Z_M(t)) = \mathbb{E}f(Z_M \circ \eta(t)) + \mathbb{E} \int_{\eta(t)}^t (\mathcal{B}_{\rho \circ Z_M \circ \eta(t)} f)(Z_M(s))ds,$$

so long as the expectations exist.

2.1.3 Weak Trapezoidal tau leaping

We will now propose a trapezoidal type algorithm to approximate the solutions of (1.6). The method was originally introduced in the work of Anderson and Mattingly in the diffusive setting where it is best understood by using a path-wise representation that incorporates space-time white noise processes, see [11]. It can similarly be understood in the current setting of jump processes by using a representation that utilizes Poisson random measures.

In the algorithm below, which simulates a path up to a time $T > 0$, it is notationally convenient to define $[x]^+ = x \vee 0 = \max\{x, 0\}$.

Algorithm 2.3 (Weak trapezoidal method)**.** *Fix $h > 0$. Set $Z(0) = x_0$, $t_0 = 0$, and $n = 0$. Fixing a $\theta \in (0,1)$, we define*

$$\xi_1 \stackrel{def}{=} \frac{1}{2}\frac{1}{\theta(1-\theta)} \qquad \text{and} \quad \xi_2 \stackrel{def}{=} \frac{1}{2}\frac{(1-\theta)^2+\theta^2}{\theta(1-\theta)}\,. \tag{2.7}$$

We repeat the following steps until $t_{n+1} = T$, in which we first compute a θ-midpoint y^*, and then the new value $Z_{trap}(t_{n+1})$:

1. *Set $t_{n+1} = t_n + h$. If $t_{n+1} \geq T$, set $t_{n+1} = T$ and $h = T - t_n$.*
2. *For $k \in \{1, \ldots, R\}$, let $\Lambda_{k,1} = Poisson(\lambda_k(Z_{trap}(t_n))\theta h)$ be independent of each other and all previous random variables.*
3. *Set $y^* = Z_{trap}(t_n) + \sum_k \Lambda_{k,1}\zeta_k$.*
4. *For $k \in \{1, \ldots, R\}$, let $\Lambda_{k,2} = Poisson([\xi_1\lambda_k(y^*) - \xi_2\lambda_k(t_n)]^+(1-\theta)h)$ be independent of each other and all previous random variables.*
5. *Set $Z_{trap}(t_{n+1}) = y^* + \sum_k \Lambda_{k,2}\zeta_k$.*
6. *Set $n \leftarrow n + 1$.*

Remark 2.2. *Notice that on the $(n+1)$st-step, y^* is the Euler approximation to $X(nh+\theta h)$ starting from $Z_{trap}(t_n)$ at time nh.*

Remark 2.3. *Notice that for all $\theta \in (0,1)$ one has $\xi_1 > \xi_2$ and $\xi_1 - \xi_2 = 1$.*

We define the operator $\mathcal{B}_{z_1,z_2}$ by

$$(\mathcal{B}_{z_1,z_2}f)(x) \stackrel{def}{=} \sum_k [\xi_1\lambda_k(z_1) - \xi_2\lambda_k(z_2)]^+(f(x+\zeta_k) - f(x)).$$

Then, for $\eta(t) \leq t \leq \eta(t) + \theta h$, the process Z_{trap} satisfies

$$\mathbb{E}f(Z_{trap}(t)) = \mathbb{E}f(Z_{trap}(\eta(t))) + \mathbb{E}\int_{\eta(t)}^{t} (\mathcal{B}_{Z_{trap}(\eta(t))}f)(Z_{trap}(s))ds,$$

where we recall that $\mathcal{B}_z$ is defined via (2.4), and for $\eta(t) + \theta h \leq t \leq \eta(t) + h$, the process Z_{trap} satisfies

$$\mathbb{E}f(Z_{trap}(t)) = \mathbb{E}f(Z_{trap}(\eta(t) + \theta h)) + \mathbb{E}\int_{\eta(t)+\theta h}^{t} (\mathcal{B}_{Z_{trap}(\eta(t)+\theta h),Z_{trap}(\eta(t))}f)(Z_{trap}(s))ds.$$

2.1.4 Previous error analyses

Under the scaling $h \to 0$, Rathinam et al. performed a consistency check of Euler tau-leaping and found that the local truncation error was $O(h^2)$ for all moments [62]. They also showed that under this same scaling Euler tau-leaping is first order accurate in a weak sense in the case that the intensity functions λ_k are linear [62]. Li extended these results by showing that as $h \to 0$, Euler tau-leaping has a strong error (in the L^2 norm) of order $1/2$ and a weak error of order one [55], which agree with classical results pertaining to numerical analysis of SDEs driven by Brownian motions (see, for example, [50]).

Under the scaling $h \to 0$ it is readily seen that midpoint tau-leaping is no more accurate than Euler tau-leaping. This follows since midpoint tau-leaping consists of making an $O(h^2)$ correction to the intensity functions used in Euler tau-leaping. As $h \to 0$, this correction becomes negligible as Poisson processes "ignore" $O(h^2)$ corrections, and the accuracy of the two methods will be the same.

However, in many examples the midpoint method is readily seen to be more accurate than Euler's method in the discrete stochastic setting. In [7], Anderson, Ganguly, and Kurtz provided an error analysis of Euler's method and the approximate midpoint method under the assumptions that (i) the system of interest satisfies the classical scaling described in Section 2.2 below and (ii) the time discretization satisfies the requirement

$$h \gg \frac{1}{\sum_k \lambda_k(Z(t))}, \tag{2.8}$$

where $Z(t)$ is the state of the system at time t. The requirement (2.8) is reasonable as such approximation methods would only be used in a regime where $h \gg \Delta t$, where Δt is the expected amount of time between reactions, for otherwise an exact method would be performed. They proved that, in this specific setting, Euler's method is an order one method in both a weak and a strong (in the L^1 norm) sense. They proved that the strong error of the midpoint method falls between order one and two (see [7] for precise statements), and that the weak error of the midpoint method scales quadratically with the step-size *when condition* (2.8) *is satisfied*. The importance of the analysis in [7] is that it pointed out the need to incorporate the natural scales of the system into the analysis.

2.2 Scaled models

As discussed in and around (2.2), the approximate algorithms being considered are only useful on the class of models which satisfy $\sum_k \lambda_k(X(\cdot)) \gg 1$. There are at least two different ways this behavior can be achieved. The first is that there could be a large number of reactions, $R \gg 1$, in which case the approximate algorithms currently being discussed will not provide an appreciable improvement in terms of runtime over the

exact simulation methods. The other common way for $\sum_k \lambda_k(X(\cdot)) \gg 1$ to hold is to have either large abundances of certain species, or to have large rate constants, or both. We will study the behavior of the different algorithms under this latter assumption. To do so, we will introduce a scaling parameter, N, used to quantify the variations in the sizes of the abundances and parameters. We emphasize that the scaling detailed below is an analytical tool used to understand the behavior of the different processes, and that the actual simulations using the different methods make no use of, nor have need for, an understanding of N.

The specifics of the scaling used here have previously been used in [10, 17, 48]. Let $N \gg 1$. Assume that we are given a model of the form

$$X(t) = X(0) + \sum_k Y_k \left(\int_0^t \lambda'_k(X(s))ds \right) \zeta_k,$$

where the λ'_k are of the form

$$\lambda'_k(x) = \kappa'_k \prod_{i=1}^{d} \frac{x_i!}{(x_i - \nu_{ki})!},$$

and where we recall that $\zeta_k \stackrel{def}{=} \nu'_k - \nu_k$. For each species i, define the *normalized abundance* (or simply, the abundance) by

$$X_i^N(t) = N^{-\alpha_i} X_i(t),$$

where $\alpha_i \geq 0$ should be selected so that $X_i^N = O(1)$. Here X_i^N may be the species number ($\alpha_i = 0$) or the species concentration or something else.

Since the rate constants may also vary over several orders of magnitude, we write $\kappa'_k = \kappa_k N^{\beta_k}$ where the β_k are selected so that $\kappa_k = O(1)$. Note that for a binary reaction

$$\kappa'_k X_i X_j = N^{\beta_k + \alpha_i + \alpha_j} \kappa_k X_i^N X_j^N,$$

and we can write

$$\beta_k + \alpha_i + \alpha_j = \beta_k + \nu_k \cdot \alpha.$$

We also have,

$$\kappa_k' X_i = N^{\beta_k + \nu_k \cdot \alpha} \kappa_k X_i^N, \quad \kappa_k' X_i^N (X_i^N - 1) = N^{\beta_k + \nu_k \cdot \alpha} \kappa_k X_i^N (X_i^N - N^{-\alpha_i}),$$

where the source vectors are $\nu_k = e_i$ in the first example and $\nu_k = 2e_i$ in the second, with similar expressions for intensities involving higher order reactions. That is, under the mass-action kinetics assumption, we always have that $\lambda_k'(X(s)) = N^{\beta_k + \nu_k \cdot \alpha} \lambda_k(X^N(s))$, where λ_k is deterministic mass-action kinetics with rate constants κ_k. Note that for reactions of the form $2S_i \to *$, where $*$ represents an arbitrary linear combination of the species, the rate is $N^{\beta_k + 2\alpha_i} \kappa_k X_i^N(t)(X_i^N(t) - N^{-\alpha_i})$, so if $\alpha_i > 0$, we should write λ_k^N instead of λ_k, but to simplify notation, we will simply write λ_k. Our model has become

$$X_i^N(t) = X_i^N(0) + \sum_k N^{-\alpha_i} Y_k \left(\int_0^t N^{\beta_k + \nu_k \cdot \alpha} \lambda_k(X^N(s)) ds \right) \zeta_{ki}, \quad i \in \{1, \ldots, d\}. \quad (2.9)$$

Remark 2.4. *We emphasize that the models* (2.9) *and* (1.6) *are equivalent in that X^N is a scaled version of X. This scaling will allow us to quantify the behavior of the different algorithms, though plays no role in the simulation of the processes.*

Remark 2.5. *If $\beta_k + \nu_k \cdot \alpha = \alpha_i = 1$ for all i, k in* (2.9)*, then we have what is typically called the classical scaling. It was specifically this scaling that was used in the analyses of Euler and midpoint τ-leaping found in [7]. In this case it is natural to consider X^N as a vector whose ith component gives the concentration, in moles per unit volume, of the ith species.*

The focus of the dissertation will now shift from (1.6) to the equivalent (2.9). To

analyze how the different algorithms approximate X^N, we will need some terminology which we collect below.

2.2.1 Terminology and definitions

For any vector $w \in \mathbb{R}^d$, define w^N to be the vector with ith component

$$w_i^N \stackrel{def}{=} \frac{w_i}{N^{\alpha_i}},$$

and define

$$\mathbb{L}_N = \left\{ x^N \mid x \in \mathbb{Z}^d \right\}.$$

By construction, the process (2.9) lives in $\mathbb{L}_N$, and its generator is

$$\mathcal{A}^N f(x) = \sum_k N^{\beta_k + \nu_k \cdot \alpha} \lambda_k(x) (f(x + \zeta_k^N) - f(x)). \tag{2.10}$$

For $f : \mathbb{L}^N \to \mathbb{R}$ and any $t \geq 0$, Dynkin's formula is now

$$\mathbb{E}_{x_0} f(X^N(t)) = f(x_0) + \mathbb{E}_{x_0} \int_0^t \mathcal{A}^N f(X(s)) ds, \tag{2.11}$$

which holds so long as the expectations exist.

To quantify the natural time-scale of the system, define $\gamma \in \mathbb{R}$ via

$$\gamma \stackrel{def}{=} \max_{\{i,k \,:\, \zeta_{ki}^N \neq 0\}} \{\beta_k + \nu_k \cdot \alpha - \alpha_i\},$$

where we recall that ν_k is the source vector for the kth reaction. It is worth noting that $\gamma = 0$ if one assumes the system satisfies the classical scaling discussed in Remark 2.5. However, $\gamma = 0$ in many other settings as well. We will see that our main results are most useful when $\gamma \leq 0$.

Example 2.6. *As an instructive example, consider the system*

$$S_1 \underset{100}{\overset{100}{\longleftrightarrow}} S_2$$

with $X_1(0) = X_2(0) = 10{,}000$. *In this case, it is natural to take* $N = 10{,}000$ *and* $\alpha_1 = \alpha_2 = 1$. *As the rate constants are* $100 = \sqrt{10{,}000}$, *we take* $\beta_1 = \beta_2 = 1/2$ *and find that* $\gamma = 1/2$. *The equation governing the normalized process* X_1^N *is*

$$X_1^N(t) = X_1^N(0) - Y_1\left(N^{1/2}N\int_0^t X_1^N(s)ds\right)\frac{1}{N} + Y_2\left(N^{1/2}N\int_0^t (2 - X_1^N(s))ds\right)\frac{1}{N}$$

where we have used that $X_1^N + X_2^N \equiv 2$.

We define the operator ∇_k^N for the kth reaction via

$$\nabla_k^N f(x) \overset{def}{=} N^{\beta_k + \nu_k \cdot \alpha - \gamma}(f(x + \zeta_k^N) - f(x)). \tag{2.12}$$

In Example 2.6 above, we have

$$\nabla_1^N f(x) = N(f(x + (e_2 - e_1)/N) - f(x))$$
$$\nabla_2^N f(x) = N(f(x + (e_1 - e_2)/N) - f(x)),$$

where $S_1 \to S_2$ is arbitrarily labeled as the first reaction, and $e_i \in \mathbb{Z}^2$ is the vector of all zeros except with a one in the ith location.

Note that if f is globally Lipschitz, then by the definition of γ, $\nabla_k^N f(x)$ is uniformly bounded over k and x. We may now write (2.10) as

$$\mathcal{A}^N f(x) = \sum_k N^\gamma \lambda_k(x) \nabla_k^N f(x).$$

Defining the vector valued operators

$$\lambda \overset{def}{=} [\lambda_1, \ldots, \lambda_R], \quad \nabla^N \overset{def}{=} [\nabla_1^N, \ldots, \nabla_R^N], \tag{2.13}$$

where we recall that R is the number of reactions, we obtain

$$\mathcal{A}^N f(x) = (N^\gamma \lambda \cdot \nabla^N) f(x).$$

For $k \in \{1, \ldots, R\}$ we define

$$c_k \stackrel{def}{=} \beta_k + \nu_k \cdot \alpha - \gamma, \tag{2.14}$$

so that (2.12) becomes

$$\nabla_k^N f(x) = N^{c_k}(f(x + \zeta_k^N) - f(x)).$$

For $i \in \{1, \ldots, d\}$ and $k \in \{1, \ldots, R\}$, we define

$$m_k \stackrel{def}{=} \min\{\alpha_i \ : \ \zeta_{ki}^N \neq 0\},$$

so that $O(|\zeta_k^N|) = N^{-m_k}$. Note that $m_k \geq 0$, and by the choice of γ we have $c_k - m_k \leq 0$ for all k. Further, we point out that γ is chosen so that $c_k = 0$ for at least one k. Finally, we note that if $\|\nabla f\|_\infty$ is bounded, then $\nabla^N f$ is in $O(N^{c_k - m_k})$.

To obtain the analog of (2.11) for the approximate methods we first define the operator $\mathcal{B}_z^N$ by

$$\mathcal{B}_z^N f(x) \stackrel{def}{=} (N^\gamma \lambda(z) \cdot \nabla^N) f(x).$$

If Z_E^N represents the approximation to (2.9) via Euler's method, then for all $t > 0$

$$\mathbb{E} f(Z_E^N(t)) = \mathbb{E} f(Z_E^N(\eta(t))) + \mathbb{E} \int_{\eta(t)}^t (\mathcal{B}^N_{Z_E^N(\eta(t))} f)(Z_E^N(s)) ds,$$

so long as the expectations exist. If Z_M^N represents the approximation to (2.9) via the midpoint method, then for $t > 0$

$$\mathbb{E} f(Z_M^N(t)) = \mathbb{E} f(Z_M^N(\eta(t))) + \mathbb{E} \int_{\eta(t)}^t (\mathcal{B}^N_{\rho(Z_M^N \circ \eta(t))} f)(Z_M^N(s)) ds,$$

so long as the expectations exist, where now

$$\rho(z) = z + \frac{1}{2}h\sum_k N^{\beta_k+\nu_k\cdot\alpha}\lambda_k(z)\zeta_k^N.$$

While we should write ρ^N in the above, we repress the "N" in this case for ease of notation. Finally, define the operator $\mathcal{B}^N_{z_1,z_2}$ by

$$(\mathcal{B}^N_{z_1,z_2}f)(x) \stackrel{def}{=} (N^\gamma[\xi_1\lambda(z_1) - \xi_2\lambda(z_2)]^+\cdot\nabla^N)f(x),$$

where for some $\theta \in (0,1)$, ξ_1 and ξ_2 satisfy (2.7), and for $v \in \mathbb{R}^d$ the ith component of v^+ is $[v_i]^+ = \max\{v_i, 0\}$. Then, if Z^N_{trap} represents the approximation to (2.9) via the weak trapezoidal method, then for $\eta(t) \le t < \eta(t) + \theta h$

$$\mathbb{E}f(Z^N_{trap}(t)) = \mathbb{E}f(Z^N_{trap}(\eta(t))) + \mathbb{E}\int_{\eta(t)}^t (\mathcal{B}^N_{Z^N_{trap}(\eta(t))}f)(Z^N_{trap}(s))ds,$$

whereas for $\eta(t) + \theta h \le t < \eta(t) + h$

$$\mathbb{E}f(Z^N_{trap}(t)) = \mathbb{E}f(Z^N_{trap}(\eta(t) + \theta h)) + \mathbb{E}\int_{\eta(t)+\theta h}^t (\mathcal{B}^N_{Z^N_{trap}(\eta(t)+\theta h),Z^N_{trap}(\eta(t))}f)(Z^N_{trap}(s))ds.$$

As in [7], we modify the kinetics λ via multiplication by a C^∞ cutoff function, which sets the intensities to zero outside of our scaling region of interest. This has the effect of confining the dynamics to a compact subset of $\mathbb{L}_N$, which we denote by $\overline{\mathbb{L}}_N \subset \mathbb{R}^d_{\ge 0}$. Supposing the cutoff function were denoted $g \in C^\infty_c(\mathbb{R}^d, \mathbb{R}^R)$, we should technically henceforth write $g\lambda$, with the multiplication defined component-wise, as our intensity function. The function g is chosen so that $g\lambda(x) = \lambda(x)$ for all x in a region of interest in the interior of $\overline{\mathbb{L}}_N$. However, for ease of notation, we refrain from adding the cutoff function in the notation, and continue to solely write λ. Note that $\|\lambda\|_n$ is now bounded for all $n \ge 0$ where $\|\cdot\|_n$ is defined in (2.16). See Section 2.2 of [7] for a further discussion of the need for such a cutoff function.

For any function $f : \mathbb{R}^d \to \mathbb{R}$, we denote

$$\|f\|_\infty \stackrel{def}{=} \sup_{x \in \overline{\mathbb{L}}_N} \{|f(x)|\}.$$

We abuse notation this way because the processes X^N and Z^N have domain $\overline{\mathbb{L}}_N$ throughout our analysis.

2.3 Global error from local error

Throughout the section, we will denote the vector valued process whose ith component satisfies (2.9) by X^N, and denote an arbitrary approximate process via Z^N. Also, we define the following semigroup operators acting on $f \in C_0(\mathbb{L}_N, \mathbb{R})$ as follows

$$\mathcal{P}_t f(x) \stackrel{def}{=} \mathbb{E}_x f(X^N(t))$$
$$P_t f(x) \stackrel{def}{=} \mathbb{E}_x f(Z^N(t)),$$

where for ease of notation we choose not to incorporate the notation N into either $\mathcal{P}_t$ or P_t.

We will interpret the difference between the above two operators, for $t \in [0, T]$, as the *weak error* of the approximate process Z^N on the interval $[0, T]$. For our purposes, there will be a time discretization associated with Z^N, and we will then interpret $\mathcal{P}_h - P_h$ as the one step local error, as is common in the literature. These concepts are defined formally below.

Definition 2.7. *Let n be an arbitrary non-negative integer, and $\mathcal{M}$ be a m dimensional vector of $C(\mathbb{R}^d, \mathbb{R})$ valued operators on $C(\mathbb{R}^d, \mathbb{R})$, with its ℓth coordinate denoted by $\mathcal{M}_\ell$.*

Then we define

$$\|f\|_n^{\mathcal{M}} = \sup\left\{\left\|\left(\prod_{i=1}^{p}\mathcal{M}_{\ell_i}\right)f\right\|_\infty, 1 \le \ell_i \le m,\ p \le n\right\}.$$

For example, if $j,k,\ell \in \{1,...,R\}$ then

$$|(\nabla_j^N \nabla_k^N \nabla_\ell^N f)(x)| \le \|f\|_3^{\nabla^N},$$

where we recall that ∇^N is defined in (2.13). Note that, for any $\mathcal{M}$,

$$\|f\|_0^{\mathcal{M}} = \|f\|_0 = \|f\|_\infty. \tag{2.15}$$

Also note that, by definition, for $n \ge 0$

$$\|f\|_n^{\mathcal{M}} \le \|f\|_{n+1}^{\mathcal{M}}.$$

Definition 2.8. *Suppose* $\mathcal{M} : C(\mathbb{R}^d,\mathbb{R}) \to C(\mathbb{R}^d,\mathbb{R}^R)$ *and* $Q : C(\mathbb{R}^d,\mathbb{R}) \to C(\mathbb{R}^d,\mathbb{R})$ *are operators. Then define*

$$\|Q\|_{j\to\ell}^{\mathcal{M}} \stackrel{def}{=} \sup_{f\in C^j, f\neq 0} \frac{\|Qf\|_\ell^{\mathcal{M}}}{\|f\|_j^{\mathcal{M}}}.$$

The purpose of this dissertation can now be stated succinctly. We will derive bounds for the global weak error of the different approximate processes, which, due to (2.15), consists of deriving bounds for $\|(P_h^n - \mathcal{P}_{nh})\|_{m\to 0}^{\mathcal{M}}$, for an appropriately defined $\mathcal{M}$ and a reasonable choice of $m \ge 0$. Theorem 2.9 below quantifies how the global error $\|(P_h^n - \mathcal{P}_{nh})\|_{m\to 0}^{\mathcal{M}}$ can be bounded using the one-step local error $\|P_h - \mathcal{P}_h\|_{m\to 0}^{\mathcal{M}}$. As is common, we will denote by $O(h)$ a set of values bounded by a fixed constant multiple of h. Later, in Section 2.4, we will derive the requisite bounds for the local weak error.

Theorem 2.9. *Let $\mathcal{M}$ be a $C(\mathbb{R}^d, \mathbb{R}^R)$ valued operator on $C(\mathbb{R}^d, \mathbb{R})$. Then for any $n, m \geq 0$, and $h > 0$*

$$\|(P_h^n - \mathcal{P}_{nh})\|_{m\to 0}^{\mathcal{M}} = O(n \ \|P_h - \mathcal{P}_h\|_{m\to 0}^{\mathcal{M}} \max_{\ell \in \{1,\ldots,n\}} \{\|\mathcal{P}_{\ell h}\|_{m\to m}^{\mathcal{M}}\})$$

Proof. Let $f \in C_0(\mathbb{R}^d, \mathbb{R})$. Note that, since $\|g\|_0 = \|g\|_0^{\mathcal{M}}$ for any g,

$$\|P_h^{j-1}\|_{0\to 0}^{\mathcal{M}} \|P_h - \mathcal{P}_h\|_{m\to 0}^{\mathcal{M}} = \|P_h^{j-1}\|_{0\to 0} \|P_h - \mathcal{P}_h\|_{m\to 0}^{\mathcal{M}}.$$

With this in mind

$$\begin{aligned}
\|(P_h^n - \mathcal{P}_{nh})f\|_0 &= \Big\| \sum_{j=1}^{n} (P_h^j \mathcal{P}_{h(n-j)} - P_h^{j-1} \mathcal{P}_{h(n-j+1)}) f \Big\|_0 \\
&\leq \sum_{j=1}^{n} \|P_h^{j-1} (P_h - \mathcal{P}_h) \mathcal{P}_{h(n-j)} f\|_0 \\
&\leq \sum_{j=1}^{n} \|P_h^{j-1}\|_{0\to 0} \|P_h - \mathcal{P}_h\|_{m\to 0}^{\mathcal{M}} \|\mathcal{P}_{h(n-j)}\|_{m\to m}^{\mathcal{M}} \|f\|_m^{\mathcal{M}}.
\end{aligned}$$

Since P_h is a contraction, i.e. $\|P_h\|_{0\to 0} \leq 1$, the result is shown. □

From the proof of the above theorem, the following result is immediate with ∇^N in place of $\mathcal{M}$.

Corollary 2.1. *Under the same assumptions of Theorem 2.9 and with $f \in C_0^m(\mathbb{R}^d, \mathbb{R})$,*

$$\|(P_h^n - \mathcal{P}_{nh})f\|_0^{\nabla^N} = O(n \|P_h - \mathcal{P}_h\|_{m\to 0}^{\nabla^N} \max_{\ell \in \{1,\ldots,n\}} \{\|\mathcal{P}_{\ell h} f\|_m^{\nabla^N}\}).$$

The following generalization, which allows for variable step sizes, is straightforward.

Corollary 2.2. *For* $f \in C_0^m(\mathbb{R}^d, \mathbb{R})$

$$\|\mathbb{E}_x[f(Z_{t_n})] - \mathbb{E}_x[f(X_{t_n})]\|_\infty = O(n \max_{i=1,\dots,n}\{\|P_{h_i} - \mathcal{P}_{h_i}\|_{m\to 0}^{\nabla^N}\} \max_{\ell\in\{1,\dots,n\}}\{\|\mathcal{P}_{t_\ell} f\|_m^{\nabla^N}\}).$$

Thus, once we compute the local one step error $\|P_h - \mathcal{P}_h\|_{m\to 0}^{\nabla^N}$, we have a bound on the weak error of the algorithm that depends only on the semigroup $\mathcal{P}_t$ of the original process. We will delay discussion of $\|\mathcal{P}_t f\|_m^{\nabla^N}$ for now, as this term is independent of the numerical approximation method. Instead, in the next section we provide a bound of $\|P_h - \mathcal{P}_h\|_{m\to 0}^{\nabla^N}$ for each of the different algorithms.

2.4 Local errors

Section 2.4.1 will present some necessary analytic tools. Sections 2.4.2, 2.4.3, and 2.4.4 will present the local analysis of the Euler, midpoint, and weak trapezoidal tau-leaping, respectively.

2.4.1 Analytical tools

Definition 2.10. *Denote the* j*th directional derivative of* f *into the direction* $[v_1, v_2, ...v_j]$ *by* $f'[v_1, ..., v_j]$ *and*

$$\|f\|_j \stackrel{def}{=} \sup_x\{f'[v_1, ..., v_j](x), \|v\| = 1\} \tag{2.16}$$

Proposition 2.11. *For* $d, R \geq 0$*, let* $f \in C_0^1(\mathbb{R}^d, \mathbb{R}^R)$*. Then, for any* $k \in \{1, \dots, R\}$

$$\nabla_k^N f \in O(N^{c_k - m_k}\|f\|_1) \subset O(1).$$

In particular, $N^{-c_k}\nabla_k^N f$ *is bounded.*

Proof. The result follows from the fact that for any $w \in \mathbb{R}^d$

$$|f(x+w) - f(x)| \leq |w| \|f\|_1.$$

□

Define, for any multi-subset I of $\{1, ..., R\}$,

$$\nabla_I^N f \stackrel{def}{=} \left\{ (\prod_{i=1}^{|I|} \nabla_{\ell_i}^N) f \right\},$$

so that,

$$\|f\|_n^{\nabla^N} = \sup_{|I| \leq n} \|\nabla_I^N f\|_\infty.$$

Proposition 2.12. *For $d, R \geq 0$, let $f \in C_0^j(\mathbb{R}^d, \mathbb{R}^R)$. Then,*

$$\|f\|_j^{\nabla^N} = O(\|f\|_j).$$

Proof. The case $j = 1$ follows from Proposition 2.11. Now consider $\nabla_I^N f(x)$ for a multi-set I of $\{1, \ldots, R\}$, with $|I| = j \geq 2$. If $m_k > 0$ for all $k \in I$, the statement is clear. If on the other hand, $m_k = 0$ for some $k \in I$, then for this specific k, we have $c_k \leq 0$ and

$$\|\nabla_I^N f\|_\infty \leq 2N^{c_k} \|\nabla_{I \setminus k}^N f\|_\infty = O(\|f\|_{j-1}) = O(\|f\|_j),$$

where the second to last equality follows by an inductive hypothesis. □

We make some definitions associated with ∇^N. Let $g : \mathbb{R}^d \to \mathbb{R}^R$. For $i, j \in \{1, \ldots, R\}$

$$\begin{aligned} [D^N g(x)]_{ij} &\stackrel{def}{=} \nabla_j^N g_i(x) \\ [(\nabla^N)^2]_{ij} &\stackrel{def}{=} \nabla_i^N \nabla_j^N \\ diag(N^c) &\stackrel{def}{=} diag(N^{c_1}, ..., N^{c_R}). \end{aligned} \tag{2.17}$$

Also, we define $\mathbf{1}_R$ to be the R dimensional vector whose entries are all 1.

Lemma 2.13. *(Product Rule) Let $g, q : \mathbb{R}^d \to \mathbb{R}^R$ be vector valued functions. Then*

$$\nabla_k^N(g \cdot q)(x) = (\nabla_k^N g \cdot q)(x) + (g \cdot \nabla_k^N q)(x) + N^{-c_k}(\nabla_k^N g \cdot \nabla_k^N q)(x).$$

Also,

$$\nabla^N(g \cdot q)(x) = [D^N g]^T q(x) + [D^N q]^T g(x) + diag(N^c)^{-1}([D^N g]^T \times [D^N q]^T)(x)\mathbf{1}_R f.$$

Proof. Note that, for any k,

$$\begin{aligned}
\nabla_k^N(g \cdot q)(x) =& N^{c_k}(g(x + \zeta_k^N)q(x + \zeta_k^N) - g(x)q(x)) \\
&= N^{c_k}(g(x + \zeta_k^N) - g(x))q(x) + N^{c_k}(q(x + \zeta_k^N) - q(x))g(x) \\
&\quad + N^{-c_k}N^{c_k}(q(x + \zeta_k^N) - q(x))N^{c_k}(g(x + \zeta_k^N) - g(x)) \\
&= (\nabla_k^N g) \cdot q)(x) + (\nabla_k^N q \cdot g)(x) + N^{-c_k}(\nabla_k^N g \cdot \nabla_k^N q)(x),
\end{aligned}$$

verifying the first statement. To verify the second, one simply notes that the above calculation holds for every coordinate, and the result follows after simple bookkeeping. □

Corollary 2.3. *Let $\lambda : \mathbb{R}^d \to \mathbb{R}^R$ be a vector valued function, and $f : \mathbb{R}^d \to \mathbb{R}$. Then*

$$\nabla_k^N(\lambda \cdot \nabla^N f)(x) = (\nabla_k^N \lambda \cdot \nabla^N)f + \lambda \cdot \nabla^N \nabla_k^N f + N^{-c_k}\nabla_k^N \lambda \cdot \nabla^N \nabla_k^N f.$$

Also,

$$\nabla^N(\lambda \cdot \nabla^N f) = [D^N \lambda]^T \nabla^N f + [(\nabla^N)^2 f]\lambda + diag(N^c)^{-1}([D^N \lambda \times (\nabla^N)^2]\mathbf{1}_R f. \quad (2.18)$$

Proof. Simply put $g = \lambda$ and $q = \nabla^N f$, and recall that ∇^2 is symmetric. □

2.4.2 Euler's method

Throughout subsection 2.4.2, we let Z_E^N be the Euler approximation to X^N computed via Algorithm 2.1, and for $x \in \mathbb{L}_N$ let

$$P_{E,h}f(x) \stackrel{def}{=} \mathbb{E}_x f(Z_E^N(h)),$$

where h is the step-size taken in the algorithm. Below, we will assume $h < N^{-\gamma}$, which is a natural stability condition.

Theorem 2.14. *Suppose that the step size h satisfies $h < N^{-\gamma}$. Then*

$$\|P_{E,h} - \mathcal{P}_h\|_{2\to 0}^{\nabla^N} = O(N^{2\gamma}h^2).$$

Proof. For Euler's method with initial condition x_0,

$$P_{E,h}f(x_0) = f(x_0) + h\mathcal{B}_{x_0}^N f(x_0) + \frac{h^2}{2}(\mathcal{B}_{x_0}^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3), \tag{2.19}$$

where, noting $\nabla^N\lambda(x_0) = 0$ and using the product rule in Lemma 2.13, we have

$$\begin{aligned}
\mathcal{B}_{x_0}^N f &= N^\gamma \lambda(x_0)\cdot\nabla^N f \\
(\mathcal{B}_{x_0}^N)^2 f &= N^\gamma\lambda(x_0)\cdot\nabla^N(N^\gamma\lambda(x_0)\cdot\nabla^N f) \\
&= N^{2\gamma}\lambda(x_0)^T[(\nabla^N)^2 f]\lambda(x_0).
\end{aligned} \tag{2.20}$$

On the other hand, for the exact process (2.9),

$$\mathcal{P}_h f(x_0) = f(x_0) + h\mathcal{A}^N f(x_0) + \frac{h^2}{2}(\mathcal{A}^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3), \tag{2.21}$$

where, again,

$$\mathcal{A}^N f = N^\gamma\lambda\cdot\nabla^N f.$$

Noting that,

$$(\mathcal{A}^N)^2 f(x) = N^{2\gamma}(\lambda \cdot \nabla^N(\lambda \cdot \nabla^N f(x)))$$
$$= N^{2\gamma}\lambda^T([D^N\lambda]^T\nabla^N f(x) + [(\nabla^N)^2 f]\lambda(x) + N^{2\gamma}\lambda^T(diag(N^{-c})[D^N\lambda \times (\nabla)^2]1_R f) \tag{2.22}$$

and defining

$$a(x) \stackrel{def}{=} N^{2\gamma}\lambda^T[D^N\lambda]^T\nabla^N f(x)$$
$$b(x) \stackrel{def}{=} N^{2\gamma}\lambda^T[(\nabla^N)^2 f]\lambda(x)$$
$$c(x) \stackrel{def}{=} N^{2\gamma}\lambda^T[diag(N^{-c})[D^N\lambda \times (\nabla^N)^2]1_R f(x)],$$

we can write

$$\mathcal{P}_h f(x_0) = f(x_0) + h\mathcal{A}^N f(x_0) + \frac{h^2}{2}(a(x_0) + b(x_0) + c(x_0)) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3).$$

Note that $\mathcal{B}^N_{x_0} f(x_0) = \mathcal{A}^N f(x_0)$ and $b(x_0) = (\mathcal{B}^N_{x_0})^2 f(x_0)$. We may then compare (2.19) and (2.21)

$$(P_{E,h} - \mathcal{P}_h)f(x_0) = \frac{h^2}{2}((\mathcal{B}^N_{x_0})^2 f(x_0) - (a(x_0) + b(x_0) + c(x_0))) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3)$$
$$= \frac{h^2}{2}(-a(x_0) - c(x_0)) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3).$$

The term $a(x) + c(x) = O(N^{2\gamma}\|f\|_2^{\nabla^N})$ is clearly non-zero in general, giving the desired result. □

2.4.3 Approximate midpoint method

Throughout subsection 2.4.3, we let Z^N_M be the midpoint method approximation to X^N computed via Algorithm 2.2, and for $x \in \mathbb{L}_N$ let

$$P_{M,h} f(x) \stackrel{def}{=} \mathbb{E}_x f(Z^N_M(h)),$$

where h is the step-size taken in the algorithm. As before, we will assume $h < N^{-\gamma}$, which is a natural stability condition.

Theorem 2.15. *Suppose that the step size h satisfies $h < N^{-\gamma}$. Then*

$$\|(P_{M,h} - \mathcal{P}_h)\|_{3\to 0}^{\nabla^N} = O(N^{3\gamma}h^3 + N^{2\gamma - \min\{m_k\}}h^2).$$

Remark 2.16. *Theorem 2.15 predicts that the midpoint method behaves locally like a third order method and globally like a second order method if h is in a regime satisfying $N^\gamma h \gg N^{-\min\{m_k\}}$, or equivalently if $h \gg N^{-\gamma-\min\{m_k\}}$. This agrees with the result found in [7] pertaining to the midpoint method, which had $\gamma = 0$, $m_k \equiv 1$, and the running assumption that $h \gg 1/N$.*

Proof. (of Theorem 2.15) Let ζ^N denote the matrix with kth column ζ_k^N, i.e.

$$[\zeta^N] = [\zeta_1^N, \zeta_2^N, ..., \zeta_R^N].$$

Recall that ρ is defined via

$$\rho(z) = z + \frac{h}{2}N^\gamma \sum_k \lambda_k(z) N^{c_k}\zeta_k^N.$$

After some algebra, we have

$$\begin{aligned}\mathcal{B}_{\rho(x_0)}^N f(x) &= N^\gamma(\lambda(x_0 + \frac{h}{2}N^\gamma \sum_k \lambda_k(x_0)N^{c_k}\zeta_k^N)) \cdot \nabla^N f(x) \\ &= N^\gamma \lambda(x_0)\cdot \nabla^N f(x) + w(x_0) + O(N^{2\gamma}\|f\|_1^{\nabla^N} h^2).\end{aligned}$$

where

$$w(x) \stackrel{def}{=} N^{2\gamma}\frac{h}{2}[D\lambda(x_0)][\zeta^N] diag(N^c)\lambda(x_0)\cdot\nabla^N f(x).$$

Next, using the product rule (2.18), we see

$$\begin{aligned}(\mathcal{B}^N_{\rho(x_0)})^2 f(x) &= N^\gamma \lambda(x_0 + \frac{h}{2}[\zeta^N] diag(N^c)\lambda(x_0)) \cdot \nabla^N (N^\gamma \lambda(x_0 + \frac{h}{2}[\zeta^N] diag(N^c)\lambda(x_0)) \cdot \nabla^N f)(x) \\ &= N^{2\gamma} \lambda(x_0 + \frac{h}{2}[\zeta^N] diag(N^c)\lambda(x_0))^T [(\nabla^N)^2 f] \lambda(x_0 + \frac{h}{2}[\zeta^N] diag(N^c)\lambda(x_0)) \cdot \nabla^N f)(x) \\ &= g(x_0) + O(N^{2\gamma} \|f\|_2^{\nabla^N} h),\end{aligned}$$

where

$$g(x_0) \stackrel{def}{=} N^{2\gamma} \lambda(x_0)^T [(\nabla^N)^2 f(x)] \lambda(x_0).$$

Therefore, since $N^\gamma \lambda(x_0) \cdot \nabla^N f(x_0) = \mathcal{A}^N f(x_0)$,

$$\begin{aligned}P_{M,h} f(x_0) &= f(x_0) + h\mathcal{B}^N_{\rho(x_0)} f(x_0) + \frac{h^2}{2} (\mathcal{B}^N_{\rho(x_0)})^2 f(x_0) + O(N^{3\gamma} \|f\|_3^{\nabla^N} h^3) \\ &= f(x_0) + h \left(\mathcal{A}^N f(x_0) + w(x_0) + O(N^{2\gamma} \|f\|_2^{\nabla^N} h^2) \right) \\ &\quad + \frac{h^2}{2} \left(g(x_0) + O(N^{2\gamma} \|f\|_2^{\nabla^N} h) \right) + O(N^{3\gamma} \|f\|_3^{\nabla^N} h^3).\end{aligned}$$

Recall that

$$(\mathcal{A}^N)^2 f(x) = a(x) + b(x) + c(x),$$

where

$$\begin{aligned}a(x) &= N^{2\gamma} \lambda^T [D^N \lambda]^T \nabla^N f(x), \\ b(x) &= N^{2\gamma} \lambda^T [(\nabla^N)^2 f] \lambda(x), \\ c(x) &= N^{2\gamma} \lambda^T [diag(N^{-c})[D^N \lambda \times (\nabla^N)^2] 1_R f(x)],\end{aligned} \tag{2.23}$$

and

$$\mathcal{P}_h f(x_0) = f(x_0) + h\mathcal{A}^N f(x_0) + \frac{h^2}{2}(a(x_0) + b(x_0) + c(x_0)) + O(N^{3\gamma} \|f\|_3^{\nabla^N} h^3).$$

Noting that $b(x_0) = g(x_0)$, we see

$$\begin{aligned}(P_{M,h} - \mathcal{P}_h)f(x_0) &= hw(x_0) + \frac{h^2}{2}\left(g(x_0) - (a(x_0) + b(x_0) + c(x_0))\right) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3) \\ &= (hw(x_0) - \frac{h^2}{2}a(x_0)) - \frac{h^2}{2}c(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3).\end{aligned} \tag{2.24}$$

We will now gain control over the terms $(hw(x_0) - \frac{h^2}{2}a(x_0))$ and $\frac{h^2}{2}c(x_0)$, separately.

Handling $\frac{h^2}{2}c(x_0)$ first, we simply note that by the discussion surrounding (2.14), we have that $\nabla^N\lambda_k \in O(N^{c_k - m_k})$, and so

$$c(x_0) = O(N^{2\gamma - \min\{m_k\}}\|f\|_2^{\nabla^N}).$$

Next, we will show that

$$hw(x_0) - \frac{h^2}{2}a(x_0) = O(N^{2\gamma - \min\{m_k\}}\|f\|_1^{\nabla^N}h^2).$$

We have

$$\begin{aligned}hw(x_0) - \frac{h^2}{2}a(x_0) &= \frac{h^2}{2}N^{2\gamma}[D\lambda(x_0)][\zeta^N]diag(N^c)\lambda(x_0)\cdot\nabla^N f(x_0) - \frac{h^2}{2}N^{2\gamma}\lambda^T[D^N\lambda]^T\nabla^N f(x) \\ &= \frac{h^2}{2}N^{2\gamma}\Big([D\lambda(x_0)][\zeta^N]diag(N^c) - [D^N\lambda(x_0)]\Big)\lambda(x_0)\cdot\nabla^N f(x_0).\end{aligned} \tag{2.25}$$

By Proposition 2.12, $\nabla^N f(x)$ is bounded by $\|f\|_1^{\nabla^N}$. Therefore, we just need to show that the difference between the two square matrices

$$[D^N\lambda(x_0)] \qquad \textit{and} \qquad [D\lambda(x_0)][\zeta^N]diag(N^c) \tag{2.26}$$

is $O(N^{-\min\{m_k\}})$. Recalling the definitions in (2.17), the (i,j)th entry of the left side of (2.26) is

$$N^{c_j}(\lambda_i(x_0 + \zeta_j^N) - \lambda_i(x_0))$$

whereas that of the right side of (2.26) is

$$N^{c_j}\nabla\lambda_i \cdot \zeta_j^N.$$

Also, note that, for $\lambda \in C_c^2(\mathbb{R}^d, \mathbb{R})$,

$$((\lambda(x+v) - \lambda(x)) - \nabla\lambda(x)\cdot v) \in O(|v|^2\|\lambda\|_2).$$

where

$$\|\lambda\|_2 = \sup\{\|\lambda\|_\infty, \|\partial_{x_i}\lambda\|_\infty, \|\partial_{x_j}\partial_{x_\ell}\lambda\|_\infty, i,j,k \le d.\}$$

Since $\|\lambda_k\|_2$ is bounded for any k, the difference between the (i,j)th entries of the two expressions in (2.26) is hence

$$O(N^{c_j}N^{-2m_j})$$

Also, recall that $c_j - m_j \le 0$ by our choice of γ, with equality at at least one j. Thus the above is also

$$O(N^{-\min\{m_k\}}).$$

Therefore (2.25) is of order

$$O(N^{2\gamma-\min\{m_k\}}h^2\|f\|_1^{\nabla^N}),$$

as desired. Combining the above with (2.24) gives us

$$\begin{aligned}\|(\mathcal{P}_h - P_{M,h})f\|_0 &= O(N^{2\gamma-\min\{m_k\}}\|f\|_1^{\nabla^N}h^2 + N^{2\gamma-\min\{m_k\}}\|f\|_2^{\nabla^N}h^2 + N^{3\gamma}\|f\|_3^{\nabla^N}h^3) \\ &= O(\|f\|_3^{\nabla^N}[N^{3\gamma}h^3 + N^{2\gamma-\min\{m_k\}}h^2]),\end{aligned} \tag{2.27}$$

implying

$$\|P_{M,h} - \mathcal{P}_h\|_{3\to 0}^{\nabla^N} = O(N^{3\gamma}h^3 + N^{2\gamma-\min\{m_k\}}h^2),$$

as desired. □

We can strengthen Theorem 2.15 slightly. Suppose that f explicitly depends only on a subset of species $S_0 \subset S$. More precisely, suppose that

$$S_0(f) = \{i \in \{1,..,d\} \ : \ f(x + \epsilon e_i) \neq f(x) \quad \text{for some } x \text{ and } e_i \in \mathbb{R}^d, \epsilon \in \mathbb{R} \ \}.$$

Next define R_0 to be the subset of all reactions that affect any element in S_0; that is,

$$R_0(f) = \{k \in \{1,..,R\} \ : \ \zeta_{ki} \neq 0 \quad \text{for some } i \in S_0\}.$$

Therefore,

$$\nabla_k^N f = 0 \qquad \forall k \notin R_0. \tag{2.28}$$

Finally, define

$$R_{00}(f) = \{k \in \{1,..,R\} \ : \ \lambda_\ell(x + \zeta_k) \neq \lambda_\ell(x), \text{ for some } \ell \in R_0 \text{ and some } x \in \mathbb{L}_N\}$$

Thus, by construction, the set R_{00} corresponds to those reactions that affect those of R_0, which in turn affect S_0.

Corollary 2.4. *For a given f, define $S_0(f)$, $R_0(f)$,and $R_{00}(f)$ as above. Then if $h < N^{-\gamma}$,*

$$\|(P_{M,h} - \mathcal{P}_h)f\|_\infty = O\left((N^{3\gamma}h^3 + N^{2\gamma - \min_{k \in R_{00}(f)}\{m_k\}}h^2)\|f\|_3^{\nabla^N}\right).$$

Proof. Returning to the proof of Theorem 2.15, we consider again (2.24). First we handle

$$c(x_0) = N^{2\gamma}\lambda^T[diag(N^{-c})[D^N\lambda \times (\nabla^N)^2]1_R f(x_0)].$$

By (2.28), $\nabla_i^N \nabla_j^N f(x_0) = 0$ if either $i \notin R_0(f)$ or $j \notin R_0(f)$. Thus, in the matrix $D^N\lambda \times (\nabla^N)^2$, the only non-zero entries are those with indices $i, j \in R_0(f)$. Further, by

construction

$$[D^N\lambda]_{i,j} = \nabla_j\lambda_i \neq 0 \qquad \text{only if} \qquad i \in R_0(f), j \in R_{00}(f).$$

Therefore, after recalling that $\nabla_j\lambda_i(x_0) \in N^{c_j - m_j}$ we have that,

$$c(x_0) \in N^{2\gamma - \min_{k\in R_{00}(f)}\{m_k\}}.$$

By similar arguments,

$$hw(x_0) - \frac{h^2}{2}a(x_0) \in O(N^{2\gamma - \min_{k\in R_{00}(f)}\{m_k\}}\|f\|_1^{\nabla^N}h^2),$$

and the remainder of the argument proceeds in exactly the same manner as the proof of Theorem 2.15. □

Definition 2.17. *The system* (1.6) *is called a* first order system *if each* λ_k *is linear.*

Noting that it is always possible to solve for the means of first order systems, see [35], the following is pointed out for completeness.

Corollary 2.5. *If* X^N *is the solution of a first order system, and if* f *is linear, then*

$$\|(P_{M,h} - \mathcal{P}_h)f\|_\infty = O(N^{3\gamma}h^3).$$

Proof. It is sufficient to show that $c(x_0)$ in (2.23) and the right hand side of (2.25) are both zero. The fact that $c(x_0) = 0$ follows immediately from the linearity of f, as $(\nabla^N)^2 f = 0$. Moreover, by the linearity of the intensity functions,

$$D^N\lambda(\cdot) = [D\lambda(\cdot)][\zeta^N]diag(N^c),$$

showing the right hand side of (2.25) is zero. □

2.4.4 Weak trapezoidal method

Throughout subsection 2.4.4, we let Z^N_{trap} be the approximation to X^N computed via Algorithm 2.3, and for $x \in \mathbb{L}_N$ let

$$P_{trap,h} f(x) \stackrel{def}{=} \mathbb{E}_x f(Z^N_{trap}(h)),$$

where h is the size of the time discretization. We will again only consider the case $h < N^{-\gamma}$, which is a natural stability condition.

We make the standing assumption that for all $x \in \overline{\mathbb{L}}_N$ and $k, j \in \{1, \ldots, R\}$, we have

$$\xi_1 \lambda_k(x + \zeta_j) - \xi_2 \lambda_k(x) \geq 0, \tag{2.29}$$

where $\xi_1 > \xi_2$ are defined in (2.7) for some $\theta \in (0, 1)$.

Theorem 2.18. *Suppose that the step size h satisfies $h < N^{-\gamma}$. Then*

$$\|(P_{trap,h} - \mathcal{P}_h)\|^{\nabla^N}_{3 \to 0} = O(N^{3\gamma} h^3).$$

Proof. Consider one step of the method with a step-size of size h and with initial value x_0. Note that the first step of the algorithm produces a value y^* that is distributionally equivalent to one produced by a Markov process with generator B^N_1 given by

$$B^N_1 f(x) = N^\gamma \lambda(x_0) \cdot \nabla^N f(x).$$

Next, given both x_0 and y^*, step 2 produces a value which is distributionally equivalent to one produced by a Markov process with generator

$$B^N_2 f(x) = N^\gamma [\xi_1 \lambda(y^*) - \xi_2 \lambda(x_0)]^+ \cdot \nabla^N f(x). \tag{2.30}$$

Recall that for the exact process,

$$\mathcal{P}_h f(x_0) = f(x_0) + h\mathcal{A}^N f(x_0) + \frac{h^2}{2}(\mathcal{A}^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3).$$

For the approximate process we have,

$$\begin{aligned} P_{trap,h} f(x_0) &= \mathbb{E}_{x_0}[\mathbb{E}_{x_0}[f(Z^N_{trap}(h))|y^*]] \\ &= \mathbb{E}_{x_0} f(y^*) + (1-\theta)h\mathbb{E}_{x_0}[B_2^N f(y^*)] + \frac{(1-\theta)^2 h^2}{2}\mathbb{E}_{x_0}[(B_2^N)^2 f(y^*)] + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3). \end{aligned} \tag{2.31}$$

We will expand each piece of (2.31) in turn. Noting that $B_1^N f(x_0) = \mathcal{A}^N f(x_0)$, the first term is

$$\begin{aligned} \mathbb{E}_{x_0} f(y^*) &= f(x_0) + \mathbb{E}_{x_0}\left[\int_0^{\theta h} B_1^N f(Z_s) ds\right] \\ &= f(x_0) + \theta h \mathcal{A}^N f(x_0) + \frac{\theta^2 h^2}{2}(B_1^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^3). \end{aligned}$$

We turn attention to the second term, $(1-\theta)h\mathbb{E}_{x_0}[B_2^N f(y^*)]$, and begin by making the following definition:

$$g(y^*) \stackrel{def}{=} B_2^N f(y^*) = N^\gamma[\xi_1\lambda(y^*) - \xi_2\lambda(x_0)]^+ \cdot \nabla^N f(y^*),$$

so that $g(x) = N^\gamma([\xi_1\lambda(x) - \xi_2\lambda(x_0)]^+ \cdot \nabla^N) f(x)$. Because $\xi_1 - \xi_2 = 1$, we have

$$g(x_0) = N^\gamma \lambda(x_0) \cdot \nabla^N f(x_0) = \mathcal{A}^N f(x_0).$$

By our standing assumption (2.29)

$$g(x_0 + \zeta_k) - g(x_0) = N^\gamma(\xi_1\lambda(x_0+\zeta_k) - \xi_2\lambda(x_0)) \cdot \nabla^N f(x_0+\zeta_k) - N^\gamma\lambda(x_0)\cdot\nabla^N f(x_0).$$

After some algebra

$$\begin{aligned} B_1^N g(x_0) = N^\gamma(\lambda(x_0)\cdot\nabla^N g)(x_0) &= N^\gamma \sum_k N^{c_k}\lambda_k(x_0)[g(x_0+\zeta_k)-g(x_0)] \\ &= \xi_1 N^\gamma \lambda(x_0)\cdot\nabla^N(N^\gamma\lambda\cdot f)(x_0) - \xi_2 N^\gamma\lambda(x_0)\cdot\nabla^N(\lambda(x_0)\cdot f)(x_0) \\ &= \xi_1(B_1^N\mathcal{A}^N f(x_0)) - \xi_2((B_1^N)^2 f)(x_0). \end{aligned}$$

Thus,

$$\begin{aligned} \mathbb{E}_{x_0}[B_2^N f(y^*)] = \mathbb{E}_{x_0}[g(y^*)] &= g(x_0) + \theta h B_1^N g(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^2) \\ &= \mathcal{A}^N f(x_0) + \theta h\left[\xi_1(B_1^N\mathcal{A}^N f)(x_0) - \xi_2(B_1^N)^2 f(x_0)\right] + O(N^{3\gamma}\|f\|_2^{\nabla^N} h^2) \\ &= \mathcal{A}^N f(x_0) + \theta h\left[\xi_1(\mathcal{A}^N)^2 f(x_0) - \xi_2(B_1^N)^2 f(x_0)\right] + O(N^{3\gamma}\|f\|_3^{\nabla^N} h^2), \end{aligned}$$

where the last line follows since $B_1^N f(x_0) = \mathcal{A}^N f(x_0)$ for any f.

Finally, we turn the the last term in (2.31). Define

$$\begin{aligned} q(y^*) &\stackrel{def}{=} (B_2^N)^2 f(y^*) \\ &= [\xi_1\lambda(y^*) - \xi_2\lambda(x_0)]^+\cdot\nabla^N([\xi_1\lambda(y^*) - \xi_2\lambda(x_0)]^+\nabla^N f)(y^*), \end{aligned}$$

so that

$$q(x) = [\xi_1\lambda - \xi_2\lambda(x_0)]^+\cdot\nabla^N([\xi_1\lambda - \xi_2\lambda(x_0)]^+\nabla^N f)(x).$$

By our standing assumption (2.29) we have

$$\begin{aligned} \mathbb{E}_{x_0}[(B_2^N)^2 f(y^*)] &= \mathbb{E}_{x_0}[q(y^*)] \\ &= q(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h) \\ &= (B_1^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N} h). \end{aligned} \tag{2.32}$$

Noting that

$$(1-\theta)\theta\xi_1 = \frac{1}{2} \qquad \text{and} \qquad (1-\theta)\theta\xi_2 = \frac{(1-\theta)^2+\theta^2}{2},$$

we may conclude the following from the above calculations

$$\begin{aligned}\mathbb{E}_{x_0}[f(Z^N_{trap,h})] &= \mathbb{E}_{x_0}f(y^*) + (1-\theta)h\mathbb{E}_{x_0}[B_2^N f(y^*)] + \frac{(1-\theta)^2h^2}{2}\mathbb{E}_{x_0}[(B_2^N)^2 f(y^*)] \\ &\quad + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3) \\ &= f(x_0) + \theta h\mathcal{A}^N f(x_0) + \frac{\theta^2h^2}{2}(B_1^N)^2 f(x_0) \\ &\quad + (1-\theta)h\mathcal{A}^N f(x_0) + \frac{h^2}{2}(\mathcal{A}^N)^2 f(x_0) - \frac{h^2}{2}[(1-\theta)^2+\theta^2](B_1^N)^2 f(x_0) \\ &\quad + \frac{(1-\theta)^2h^2}{2}(B_1^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3) \\ &= f(x_0) + \mathcal{A}^N f(x_0) + \frac{h^2}{2}(\mathcal{A}^N)^2 f(x_0) + O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3).\end{aligned}$$

Thus

$$\|(P_{trap,h} - \mathcal{P}_h)f\|_0 \in O(N^{3\gamma}\|f\|_3^{\nabla^N}h^3),$$

and the proof is complete. □

2.5 Bound on $\|\mathcal{P}_t f\|_n^{\nabla^N}$

In this section we will provide a bound on $\|\mathcal{P}_t f\|_n^{\nabla^N}$ for any nonnegative n. We point out, however, that for any process X^N for which $\mathcal{P}_t$ is well behaved, in that $\|\mathcal{P}_t\|_{n\to 0}^{\nabla^N}$ is bounded without any N dependence, the following results are not needed, and, in fact, would most likely be a *least optimal* bound, as the bound grows exponentially in $N^\gamma t$. Note that any system satisfying the classical scaling has $\gamma = 0$.

For $t \geq 0$ and $x \in \mathbb{L}_N$, We define

$$v(t,x) \stackrel{def}{=} \mathcal{P}_t f(x) = \mathbb{E}_x[f(X_t^N)].$$

Theorem 2.19. *If* $\|f\|_n^{\nabla^N} < \infty$, *then*

$$\|v(t,\cdot)\|_n^{\nabla^N} = \|\mathcal{P}_t f\|_n^{\nabla^N} \leq \|f\|_n^{\nabla^N} e^{N^\gamma C_n t}$$

where

$$C_n = 2\left(\|\lambda\|_1^{\nabla^N} n\ R + R(n-1)\|\lambda\|_n^{\nabla^N}\right). \tag{2.33}$$

We delay the proof of Theorem 2.19 until the following Lemma is shown, the proof of which is similar to that found in [47], which itself was an extension of the proof of Lemma 4.3 in [7].

Lemma 2.20. *Given a multiset I of $\{1, \cdots, R\}$, there exists a function $q_I(x)$ that is a linear function of terms of the form $\nabla_J^N v(t,x)$ with $|J| < |I|$, so that*

$$\partial_t \nabla_I^N v(t,x) = N^\gamma(\lambda \cdot \nabla^N)\nabla_I^N v(t,x) + N^\gamma \sum_{i=1}^{|I|}(\beta_i \cdot \nabla^N)\nabla_{I\setminus \ell_i} v(t, x+\zeta_{\ell_i}) + N^\gamma q_I(x),$$

where $\beta_i = \nabla_{\ell_i}^N \lambda$. Further, q_I consists of at most $R(|I|-1)$ terms of the form $\nabla_J^N v(t,x)$, each of whose coefficients are bounded above by $\|\lambda\|_{|I|}^{\nabla^N}$.

Proof. This goes by induction. For $|I| = 0$, the statement follows because

$$\partial_t v(t,x) = N^\gamma(\lambda \cdot \nabla^N)v(t,x). \tag{2.34}$$

Note that in this case, there are no β_i or q terms. It is instructive to perform the $|I| = 1$ case. We have

$$\begin{aligned}
\partial_t \nabla_k^N v(t,x) &= \nabla_k^N \partial_t v(t,x) \\
&= \nabla_k^N (N^\gamma \lambda \cdot \nabla^N v(t,x)) \\
&= N^\gamma(\nabla_k^N \lambda \cdot \nabla^N)v(t,x) + N^\gamma \lambda \cdot \nabla_k^N \nabla^N v(t,x) + N^\gamma(N^{-c_k}\nabla_k^N \lambda \cdot \nabla_k^N \nabla^N v(t,x)).
\end{aligned}$$

Note that for any $g : \mathbb{R}^d \to \mathbb{R}$

$$(\nabla_k^N \lambda \cdot \nabla^N)g(x) + (N^{-c_k}\nabla_k^N \lambda \cdot \nabla^N)\nabla_k^N g(x) = (\nabla_k^N \lambda \cdot \nabla^N)g(x+\zeta_k). \tag{2.35}$$

Therefore, with $g(x) = v(t,x)$ in the above, we have

$$\partial_t \nabla_k^N v(t,x) = N^\gamma(\lambda(x)\cdot\nabla^N)\nabla_k^N v(t,x) + N^\gamma(\nabla_k^N\lambda(x)\cdot\nabla^N)v(t,x+\zeta_k).$$

Now assume that it holds for a set of size $\leq |I|$. Then, using the inductive hypothesis, Lemma 2.18, and equation (2.35) yields

$$\begin{aligned}
&\partial_t \nabla_k^N \nabla_I^N v(t,x) \\
&\quad = \nabla_k^N \partial_t \nabla_I^N v(t,x) \\
&\quad = N^\gamma \nabla_k^N \left[(\lambda\cdot\nabla^N)\nabla_I^N v(t,x) + \sum_{i=1}^{|I|} (\beta_i\cdot\nabla^N)\nabla_{I\setminus\ell_i} v(t,x+\zeta_{\ell_i}) + q_I(x) \right] \\
&\quad = N^\gamma \left[(\lambda\cdot\nabla^N)\nabla_{I\cup k}^N v(t,x) + (\nabla_k^N\lambda\cdot\nabla^N)\nabla_I^N v(t,x+\zeta_k) \right] \\
&\qquad + N^\gamma \sum_{i=1}^{|I|} \left[(\beta_i\cdot\nabla^N)\nabla_k^N\nabla_{I\setminus\ell_i}^N v(t,x+\zeta_{\ell_i}) + (\nabla_k^N\beta_i\cdot\nabla^N)\nabla_{I\setminus\ell_i}^N v(t,x+\zeta_{\ell_i}+\zeta_k) \right] \\
&\qquad + N^\gamma \nabla_k^N q_I(x) \\
&\quad = N^\gamma(\lambda\cdot\nabla^N)\nabla_{I\cup k}^N v(t,x) + N^\gamma \left[(\nabla_k^N\lambda\cdot\nabla^N)\nabla_{I\cup k\setminus k}^N v(t,x+\zeta_k) + \sum_{i=1}^{|I|} (\beta_i\cdot\nabla^N)\nabla_{I\cup k\setminus\ell_i}^N v(t,x+\zeta_{\ell_i}) \right] \\
&\qquad + N^\gamma \left[\nabla_k^N q_I(x) + (\nabla_k^N\beta_i\cdot\nabla^N)\nabla_{I\setminus\ell_i}^N v(t,x+\zeta_{\ell_i}+\zeta_k) \right],
\end{aligned}$$

showing the result. □

Proof. (*of Theorem 2.19*)

Let $n \geq 0$. Define

$$U_n(t) \stackrel{def}{=} \max_{x\in\mathbb{L}_N, |I|\leq n} |\nabla_I^N v(t,x)| = \|v\|_n^{\nabla^N}.$$

Each $\nabla_I^N v(t,x)$ is a continuously differentiable function with respect to t. Therefore, the maximum above is achieved at some (I^*, x^*) for all $t \in [0, t_1]$ where $t_1 > 0$. Fixing

this choice of (I^*, x^*), we have

$$U_n(t) = \nabla^N_{I^*} v(t, x^*)$$

for all $t < t_1$.

Note that

$$\begin{aligned}
[(\lambda \cdot \nabla^N)\nabla^N_{I^*} v(t, x^*)]\nabla^N_{I^*} v(t, x^*) &= \sum_k \lambda_k(x)(\nabla^N_k \nabla^N_{I^*} v(t, x^*))\nabla^N_{I^*} v(t, x^*) \\
&= \sum_k N^{c_k} \lambda_k(x)(\nabla^N_{I^*} v(t, x^* + \zeta_k) - \nabla^N_{I^*} v(t, x^*))\nabla^N_{I^*} v(t, x^*) \qquad (2.36) \\
&\leq 0,
\end{aligned}$$

where the final inequality holds by the specific choice of I^* and x^*. Also note that for any $\ell_i \in I^*$ and any choice of $x \in \overline{\mathbb{L}}_N$

$$|\nabla^N \nabla^N_{I^* \setminus \ell_i} v(t, x)| \leq \sum_{k=1}^{R} |\nabla_k \nabla^N_{I^* \setminus \ell_i} v(t, x)| \leq R |\nabla^N_{I^*} v(t, x^*)|. \qquad (2.37)$$

From Lemma 2.20 and equations (2.36) and (2.37), we have

$$\begin{aligned}
\frac{1}{2}\partial_t (\nabla^N_{I^*} v(t, x^*))^2 &= (\partial_t \nabla^N_{I^*} v(t, x^*))\nabla^N_{I^*} v(t, x^*) \\
&= N^\gamma \left[(\lambda \cdot \nabla^N)\nabla^N_{I^*} v(t, x^*) + \sum_{i=1}^{|I^*|} (\beta_i \cdot \nabla^N)\nabla_{I^* \setminus \ell_i} v(t, x^* + \zeta_{\ell_i}) + q_{I^*}(x^*) \right] \nabla^N_{I^*} v(t, x^*) \qquad (2.38) \\
&\leq N^\gamma \left[\|\lambda\|_1^{\nabla^N} |I^*| \; R \; |\nabla^N_{I^*} v(t, x^*)|^2 + R(|I^*| - 1)\|\lambda\|^{\nabla^N}_{|I^*|} |\nabla^N_{I^*} v(t, x^*)|^2 \right],
\end{aligned}$$

where we have used the fact that each $\beta_i = \nabla_{\ell_i} \lambda$ for $\ell_i \in I^*$. Setting

$$C_n = 2 \left(\|\lambda\|_1^{\nabla^N} n \; R + R(n-1)\|\lambda\|_n^{\nabla^N} \right), \qquad (2.39)$$

we see by an application of Gronwall's inequality that the conclusion of the theorem holds for all $t < t_1$. That is, for $t < t_1$

$$U_n(t) \leq \|f\|_n^{\nabla^N} e^{N^\gamma C_n t}.$$

To continue, repeat the above argument on the interval $[t_1, t_2)$, with I^*, x^* again chosen to maximize U_n on that interval, and note that

$$U_n(t_1) \leq \|f\|_n^{\nabla^N} e^{N^\gamma C_n t_1},$$

so that we may conclude that for $t_1 \leq t < t_2$,

$$U_n(t) \leq \|f\|_n^{\nabla^N} e^{N^\gamma C_n t_1} e^{N^\gamma C_n (t-t_1)} = \|f\|_n^{\nabla^N} e^{N^\gamma C_n t}.$$

Continuing on, we see that $t_i \to \infty$ as $i \to \infty$ by the boundedness of the time derivatives of $v(t,x)$, thereby concluding the proof. □

Remark 2.21. *In the theorem above, $C_n \in \|\lambda\|_n^{\nabla^N}$.*

Combining all of the above results, we have the following theorems.

Theorem 2.22. ***(Global bound for the Euler method)***

For Algorithm 2.1, suppose that the step size h satisfies $h < N^{-\gamma}$, and $T = nh$. Then

$$\|(P_{E,h}^n - \mathcal{P}_{nh})\|_{2\to 0}^{\nabla^N} = O(N^{2\gamma} h e^{C_2 N^\gamma T})$$

where $C_2 \in O(\|\lambda\|_2^{\nabla^N})$ is defined in (2.33).

Theorem 2.23. ***(Global bound for the midpoint tau-leap method)***

For Algorithm 2.2, suppose that the step size h satisfies $h < N^{-\gamma}$, and $T = nh$. Then

$$\|(P_{M,h}^n - \mathcal{P}_{nh})\|_{3\to 0}^{\nabla^N} = O([N^{3\gamma} h^2 + N^{2\gamma - \min\{m_k\}} h] e^{C_3 N^\gamma T})$$

where $C_3 \in O(\|\lambda\|_3^{\nabla^N})$ is defined in (2.33).

The following immediate corollary to the theorem above recovers the result in [7].

Corollary 2.6. *Under the additional condition* $h > N^{-\gamma-\min\{m_k\}}$ *in Theorem* (2.23)*, the leading order of the error of midpoint tau-leaping is* $O(h^2)$*.*

Theorem 2.24. ***(Global bound for the weak trapezoidal method)***

For Algorithm 2.3, suppose that the step size h *satisfies* $h < N^{-\gamma}$*, and* $T = nh$*. Then*

$$\|P_h^n - \mathcal{P}_{nh}\|_{3\to 0}^{\nabla^N} = O(h^2 N^{3\gamma} e^{N^\gamma C_3 T})$$

where $C_3 \in O(\|\lambda\|_3^{\nabla^N})$ *is defined in* (2.33)*.*

Thus, we see that the weak trapezoidal method detailed in Algorithm 2.3 is the only method that boasts a global error of second order in the stepsize h in an honest sense. That is, it is a second order method for the multiple scalings regardless of the relation of h with respect to N. This is in contrast to the midpoint tau leaping method, Algorithm 2.2, which has second order accuracy only when the step-size h is larger than $N^{-\gamma-\min\{m_k\}}$.

Chapter 3

A connection between two commonly used couplings

3.1 Introduction

We saw in the introductory chapter that the dynamics of a chemical reaction network under a Markovian assumption can be modeled with a purely discontinuous stochastic process X in the form of (1.8)

$$X(t) = X(0) + \sum_k N_k(t)\zeta_k \tag{3.1}$$

built from the counting processes N_k with intensity functions $\lambda_k(X, s)$, where $\lambda_k : J[0,\infty) \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}$ are non-anticipating. We would like to consider another process Z given as

$$Z(t) = Z(0) + \sum_k \tilde{N}_k(t)\zeta_k \tag{3.2}$$

with $\tilde{N}_k(t)$ built from a different set of intensity functions $\tilde{\lambda}_k$, and assess the ways to couple X and Z on the same probability space. Coupling is often useful as a means to reduce the computational complexity of numerical experiments. For an elementary example, consider an experiment of throwing a dice and a coin. If the objective of the experiment is only to sample a fixed number of outcomes, we can reduce the number of

experiments by using a dice alone; if the outcome of the dice is even, we can take the outcome of the coin to be heads, and if the dice is odd you take the coin to be tails.

For our case, we will be specifically interested in coupling X and Z of (3.1) and of (3.2) in order to reduce the variance of $X - Z$. We can thereby decrease the number of samples required to estimate its expectation with a desired precision. Rathinam, Sheppard, and Khammash [60] used a coupling called the common reaction path (CRP) method to improve upon finite difference schemes for the approximation of parametric sensitivity.

On the other hand, in the same context of sensitivity analysis, Anderson [4] used another specific coupling introduced by Kurtz [52] to further reduce the complexity of finite difference methods. For a reason that will become clear in its construction, we would like to call this coupling the "split coupling." Anderson and Higham also applied the split coupling in the development of a variation of the multi-level Monte Carlo (MLMC) method [38], which was originally invented for Brownian diffusion processes, and extended the result to the setting of population processes [8]. Motivation for the work presented in this chapter is that there is no clear analytical basis of selecting a coupling, and no studies have been done to analyze relationships amongst different couplings.

In this chapter, we will introduce different coupling methods and make an analytical connection between the split coupling and the CRP coupling. In particular, we will introduce a new coupling called the "local CRP coupling", and create a sequence of local CRP couplings that limits to the CRP coupling in one extreme, and converges weakly to the split coupling under an appropriate topology in another extreme. The analysis demonstrates that the split coupling maximizes the ability of the two processes

to re-couple during the course of a simulation.

3.1.1 Motivation (Sensitivity Analysis)

As we analyze stochastic models, we come across many situations in which we must compare different, but closely related, stochastic processes. For example, when $\{X_\theta\}$ is a family of stochastic processes parametrized by θ on a state space E and if $f : E \to \mathbb{R}$ is a statistic, one might aim to evaluate

$$\frac{E[f(X_{\theta+h}(t))] - E[f(X_\theta(t))]}{h} \cong \frac{d}{d\theta} E[f(X_\theta(t)] \tag{3.3}$$

as a measurement of the sensitivity of $X_\theta(t)$ with respect to a parameter θ. More specifically, in the setting of the previous section, we are interested in the case of

$$\lambda_k(\cdot) = \eta_k(\theta, \cdot), \qquad \tilde{\lambda}_k(\cdot) = \eta_k(\theta + \epsilon, \cdot),$$

where for each k, $\{\eta_k(\theta, \cdot) : \mathbb{R}^d \to \mathbb{R}^+\}$ is a parametric family of functions about θ so that using the notation from the previous section we have

$$X = X_{\theta+h}, \qquad Z = X_\theta.$$

We would then like to empirically evaluate the left hand side of (3.3). In order to achieve the required confidence interval with as small a number of simulations as possible, it is essential to couple X and Z tightly to control the variance of $X - Z$, and therefore of $f(X) - f(Z)$. Anderson, Rawlings, and Srivastava compared different coupling methods in the context of finite difference method sensitivity analysis, and concluded that split coupling is the most versatile and efficient coupling as of today [66].

3.1.2 Motivation (MLMC)

In [38], Mike Giles introduced the multi-level Monte Carlo (MLMC) method to efficiently approximate expected values of smooth functions of diffusion processes. MLMC is a method which cleverly uses telescopic sums to reduce the overall computational complexity required to estimate $E[f(X)]$ for a stochastic process X. If $\{Z_n\}$ are approximation processes of X (Euler tau-leap processes with different time discretization parameter, for example) for which larger n implies greater computational complexity in return for less bias, we may write

$$E[f(X)] = E[f(X)-f(Z_{n-1})]+E[f(Z_{n-1})-f(Z_{n-2})]+\cdots+E[f(Z_1)-f(Z_0)]+E[f(Z_0)].$$

Let us denote $X = Z_n$ for now. If the pair (Z_k, Z_{k+1}) in each term above are tightly coupled, then we may put most of the computational burden on $E[f(Z_0)]$ and simulate other costly processes only a small number of times. This will decrease the overall complexity of the simulation, because the tightly coupled terms will contribute only a small portion to the overall variance of the estimator. For the details of the algorithm, refer to [38]. However, if each pair is not coupled tightly, then the cost of the intermediate terms might outweigh the benefit of the tail terms. Anderson and Higham [8] incorporated the split coupling to establish what seems to be the "correct" analogue of the MLMC as in [38] for our systems of interest (1.4).

A "good coupling," however, still appears to depend on situations. Indeed, there are numerous ways to couple X and Z. Even for the elementary example of the dice and the coin in the introduction, we can couple the coin and the dice differently by considering the outcome $1 \sim 3$ as heads instead of using its parity. Our case is obviously not so simple. In [4], Anderson also reports a case in which the finite difference method

performed better with the CRP coupling than with the split coupling. This motivates our study of the connections among different ways of coupling.

3.2 Different Couplings

Throughout this section, let X be the counting process in (1.4) with intensity functions λ_k, and Z the counting process (1.4) with intensity functions $\tilde{\lambda}_k$. Let us use ζ for an element in $\mathbb{R}^d$, where $d > 0$ is a positive integer.

3.2.1 Split coupling

We will first introduce the split coupling in [53]. Let R and L be càdlàg processes on $\mathbb{R}^d$, and define

$$r_1(\lambda, \tilde{\lambda}, R, L)(s) = \lambda(R, s) - \lambda(R, s) \wedge \tilde{\lambda}(L, s)$$

$$r_2(\lambda, \tilde{\lambda}, R, L)(s) = \lambda(L, s) - \lambda(R, s) \wedge \tilde{\lambda}(L, s)$$

$$r_3(\lambda, \tilde{\lambda}, R, L)(s) = \lambda(R, s) \wedge \tilde{\lambda}(L, s)$$

The split coupling of X and Z is given by the solution of

$$\begin{aligned} X_o(t) = X(0) + \sum_{k=1}^{R} \Bigg\{ & Y_{3k}\left(\int_0^t r_3(\lambda_k, \tilde{\lambda}_k, X_o, Z_o)(s)ds\right) \\ & + Y_{1k}\left(\int_0^t r_1(\lambda_k, \tilde{\lambda}_k, X_o, Z_o)(s)ds\right)\Bigg\}\zeta_k \\ Z_o(t) = X(0) + \sum_{k=1}^{R} \Bigg\{ & Y_{3k}\left(\int_0^t r_3(\lambda_k, \tilde{\lambda}_k, X_o, Z_o)(s)ds\right) \\ & + Y_{2k}\left(\int_0^t r_2(\lambda_k, \tilde{\lambda}_k, X_o, Z_o)(s)ds\right)\Bigg\}\zeta_k. \end{aligned} \tag{3.4}$$

Note that X_o and Z_o share the same Y_{3k} channel. "o" stands for ordinary, because this coupling was a good coupling in most of the situations we encountered. In [19], Beth Wolf cleverly introduces what seems to be the right analogue of the split coupling for more than three processes. For the coupling of n processes in the form of

$$\left\{ X_i(t) = X_i(0) + \sum_{k=1}^{R} Y_{ik} \left(\int_0^t \lambda_k^i(X, s)ds \right) \zeta_k \right\}_{i=1^n}, \tag{3.5}$$

one needs to consider minimums of all 2^n subsets of $\{\lambda_k^i\}_{i=1}^n$ and consequently we need

$$\left(\sum_{j=1}^{n} 2^n \right) * R = 2^{n+1} * R$$

many Poisson processes all together to construct the coupling in [19].

3.2.2 Common Random Number (CRN) coupling

In CRN coupling, we will construct the processes using the idea of thinning; the idea which we introduced in the first chapter along with the Gillespie algorithm (1.2). Let us denote

$$\lambda_0(x, s) = \sum_{k=1}^{R} \lambda_k(x, s) \quad \tilde{\lambda}_0(x) = \sum_{k=1}^{R} \tilde{\lambda}_k(x, s),$$

and let $\{U_i\}_{i=0}^{\infty}$ be a sequence of uniform random variables. Now, if $\eta : \mathbb{R}_{\geq 0}^R \times [0, 1] \to \mathbb{Z}^d$ is a function such that

$$\eta(c_1, ..., c_R, u) = \zeta_k \quad \text{if} \quad \frac{\sum_{i=1}^{k-1} c_i}{\sum_{i=1}^{R} c_i} \leq u \leq \frac{\sum_{i=1}^{k} c_i}{\sum_{i=1}^{R} c_i},$$

then $\nu(c_1, ..., c_R, U)$ is a categorical random variable that takes the vector value ζ_k with probability $\frac{c_k}{\sum_{i=1}^{R} c_i}$. Now, for a common unit rate Poisson process Y, we consider the following system:

$$
\begin{aligned}
R_x(t) &= Y\left(\int_0^t \lambda_0(X_r, s)ds\right) \\
R_z(t) &= Y\left(\int_0^t \tilde{\lambda}_0(Z_r, s)ds\right) \\
X_r(t) &= X(0) + \int_0^t \eta(\lambda_1(X_r, s), ..., \lambda_R(X_r, s), U_{R_x(s-)})dR_x(s) \\
Z_r(t) &= Z(0) + \int_0^t \eta(\lambda_1(Z_r, s), ..., \lambda_R(Z_r, s), U_{R_z(s-)})dR_z(s)
\end{aligned}
\tag{3.6}
$$

The solution to this system exists by construction. In particular, we just construct X and Z using the Gillespies algorithm with the common set of uniform random variables U_i. We also note that, while the representations are different, the processes X_r and X_o are weakly the same, while (X_r, Z_r) and (X_o, Z_o) are obviously not so. For the details of the CRN coupling, refer to [66] and [60].

3.2.3 Common Reaction Path (CRP) coupling and local CRP coupling

In the common reaction path coupling, X and Z are given by the solution of

$$
\begin{aligned}
X_c(t) &= X(0) + \sum_{k=1}^{R}\left\{Y_k\left(\int_0^t \lambda_k(X_c, s)ds\right)\right\}\zeta_k \\
Z_c(t) &= X(0) + \sum_{k=1}^{R}\left\{Y_k\left(\int_0^t \tilde{\lambda}_k(Z_c, s)ds\right)\right\}\zeta_k
\end{aligned}
\tag{3.7}
$$

where the Y_k are independent unit rate Poisson processes. Numerical experiments have shown that this coupling is not very tight (that is, $var(X_c(t) - Z_c(t))$ is large) in many situations with large value of t [66], [4].

We postulate that the CRP coupling is not as good because of its inability to fix a "decoupling" once it occurs. For example, given $X_c(t_0)$ and $Z_c(t_0)$ for some $t_0 > 0$, if

$$\int_0^{t_0} \tilde{\lambda}_k(Z_c, s)ds \ll \int_0^{t_0} \lambda_k(X_c, s)ds \tag{3.8}$$

for all k, then by the strong Markov property the time until the next jump of X is nearly independent from the time until the next jump of Z. Once the process stumbles into the situation of $\lambda_k(X_c(s)) \ll \tilde{\lambda}_k(Z_c(s))$, then the probability of escaping the trap (3.8) in any finite time can be very small, depending on the choice of the intensity functions. This does not happen to the split coupling, since the next jump time of X and Z are always correlated via the purely counting processes with the intensity

$$\lambda_k(X, s) \wedge \lambda_k(Z, s).$$

This motivates us to "reset" the Poisson process at each small time interval, so that we may overcome the problem of X and Z quickly decoupling from each other. We will elaborate on this strategy. Let $\pi = \{0 = s_0 < s_1 \cdots < s_N = T\}$ be a partition of $[0, T]$. Also let $\{Y_{km} : k = 1, ..., R, m = 0, 1, 2, ...\}$ be a set of independent, unit rate Poisson processes. Then we define the local CRP coupling over $[0, T]$ with respect to π as the solution of

$$\begin{aligned} X_c^\pi(t) &= X_0 + \sum_{k=1}^{R} \sum_{m=0}^{\infty} Y_{km} \left(\int_{t \wedge s_m}^{t \wedge s_{m+1}} \lambda_k(X_c^\pi, s)ds \right) \zeta_k \\ Z_c^\pi(t) &= X_0 + \sum_{k=1}^{R} \sum_{m=0}^{\infty} Y_{km} \left(\int_{t \wedge s_m}^{t \wedge s_{m+1}} \tilde{\lambda}_k(Z_c^\pi, s)ds \right) \zeta_k \end{aligned} \tag{3.9}$$

We remark that, irrespective of π, the marginal distribution of X_c^π and X_o^π are the same as that of X, and the same goes for Z_c^π, Z_o^π and Z. Also, when π is a trivial

partition with $N = 1$, the coupling of (3.9) becomes the CRP coupling of (3.7). In the next section, we will consider the limit of taking $N \to \infty$. By doing so, we will make a connection between the local CRP coupling and split coupling.

3.3 Limit of the local CRP vs the split coupling

Before we begin this section, we would like to clarify some notation. First, when X and Z are stochastic processes on $(\Omega, \mathcal{F}, P)$, with Ω being the set of all càdlàg processes in $\mathbb{R}^d$, by $(X, Z)(s)$ we mean $(X(s), Z(s))$, a $2d$ dimensional vector. Also, when $\mathbf{t}$ is a K dimensional vector of time points, we denote

$$X(\mathbf{t}) = [X(t_1), ..., X(t_K)]$$

which is just the time series of X sampled at points $t_1, ..., t_k$.

We also make the standing assumption throughout the rest of the chapter that the intensities λ_k and $\tilde{\lambda}_k$ are continuous function on $\mathbb{R}^d_{\geq 0}$. That is, $\lambda_k(N, s) = \lambda_k(N(s))$ and $\tilde{\lambda}_k(N, s) = \tilde{\lambda}_k(N(s))$.

3.3.1 Weak convergence at finite coordinates

We first have to articulate on what we mean by taking N to ∞ in the context of the last section. We first introduce the concept of a mesh, which is a definition that appears frequently in the construction of an integral.

Definition 3.1. *Let $\pi = \{0 = s_0 < s_1 \cdots < s_N = T\}$ be a partition of $[0, T]$. Then let*

$$\Delta_m \pi = s_{m+1} - s_m.$$

We define the mesh of π *as*

$$mesh(\pi) = \max_m \{\Delta_m \pi\}$$

We want to take the limit of $mesh(\pi)$ to 0. First, we will show the weak convergence of X_c^π to X_o over finite coordinates.

Proposition 3.1. *Let* $(X_o(t), Z_o(t))$ *be coupled in the way of* (3.4)*, and suppose that neither* X *nor* Z *explode in* $[0,T]$ *almost surely. Further, let*

$$\pi_n = \{0 = s_0 \leq s_1 \leq \cdots \leq s_{N(n)} = T\}$$

be a sequence of partitions such that $mesh(\pi_n) \to 0$ *as* $n \uparrow \infty$*. Then for any* $K \in \mathbb{Z}_{\geq 0}$ *and* $\mathbf{t} \in [0,T]^K$*, and any bounded Lipshitz* $f : (\mathbb{R}^d \times \mathbb{R}^d)^K \to \mathbb{R}$*,*

$$E[f((X_c^{\pi_n}, Z_c^{\pi_n})(\mathbf{t}))] \to E[f((X_o, Z_o)(\mathbf{t}))] \quad \text{as } n \uparrow \infty \ .$$

Before the proof , we require some additional notation. For a fixed n, let

$$\{Y_{ikm}^n; \quad i = 1,2,3 \quad k = 1,...,R \quad m = 0,1,2,...\} \tag{3.10}$$

and

$$\{Y_{km}^n; \quad k = 1,...,R \quad m = 0,1,2,...\} \tag{3.11}$$

be two sets of independent unit rate Poisson processes. We do not specify the set (3.10) and the set (3.11) to be mutually independent. In fact, we will couple the two sets.

Consider the systems

$$\begin{aligned} X_o^{\pi_n}(t) = X_o(t) + \sum_{m=0}^{\infty}\sum_{k=1}^{R}\Bigg\{ & Y_{3km}^n\left(\int_{s_m\wedge t}^{s_{m+1}\wedge t} r_3(\lambda_k,\tilde{\lambda}_k,X_o^{\pi_n},Z_o^{\pi_n})(s)ds\right) \\ & + Y_{1km}^n\left(\int_{s_m\wedge t}^{s_{m+1}\wedge t} r_1(\lambda_k,\tilde{\lambda}_k,X_o^{\pi_n},Z_o^{\pi_n})(s)ds\right)\Bigg\}\zeta_k \\ Z_o^{\pi_n}(t) = X_o(0) + \sum_{m=0}^{\infty}\sum_{k=1}^{R}\Bigg\{ & Y_{3km}^n\left(\int_{s_m\wedge t}^{s_{m+1}\wedge t} r_3(\lambda_k,\tilde{\lambda}_k,X_o^{\pi_n},Z_o^{\pi_n})(s)ds\right) \\ & + Y_{2km}^n\left(\int_{s_m\wedge t}^{s_{m+1}\wedge t} r_2(\lambda_k,\tilde{\lambda}_k,X_o^{\pi_n},Z_o^{\pi_n})(s)ds\right)\Bigg\}\zeta_k. \end{aligned} \tag{3.12}$$

along with

$$\begin{aligned} X_c^{\pi_n}(t) &= X_0 + \sum_{m=0}^{\infty}\sum_{k=1}^{R} Y_{km}^n\left(\int_{t\wedge s_m}^{t\wedge s_{m+1}} \lambda_k(X_c^{\pi}(s))ds\right)\zeta_k \\ & \%labellocalCRP \\ Z_c^{\pi_n}(t) &= X_0 + \sum_{m=0}^{\infty}\sum_{k=1}^{R} Y_{km}^n\left(\int_{t\wedge s_m}^{t\wedge s_{m+1}} \tilde{\lambda}_k(Z_c^{\pi}(s))ds\right)\zeta_k \end{aligned} \tag{3.13}$$

Note that the generator of (X_o, Z_o) is the same as $(X_o^{\pi_n}, Z_o^{\pi_n})$, so $(X_o, Z_o) \sim (X_o^{\pi_n}, Z_o^{\pi_n})$ irrespective of n. We will first generate $(X_c^{\pi_n}, Z_c^{\pi_n})$ up to a fixed time, and couple (3.10) to (3.11) in a particular way based on the outcome. We will then show that the coupling of $(X_o^{\pi_n}, Z_o^{\pi_n})$ and $(X_c^{\pi_n}, Z_c^{\pi_n})$ created thus will satisfy

$$\lim_{n\to\infty} P(\max_{i=0,\ldots,K} |(X_o^{\pi_n}(t_i), Z_o^{\pi_n}(t_i)) - (X_c^{\pi_n}(t_i), Z_c^{\pi_n}(t_i))| > \gamma) = 0 \tag{3.14}$$

for any $\gamma > 0$. We can then appeal to a standard Portmanteau type argument. Let $\epsilon > 0$, and consider any bounded continuous map $f : (E \times E)^K \to \mathbb{R}$ with Lipshitz

constant L. Then

$$\begin{aligned}
&|Ef((X_o, Z_o)(\mathbf{t}) - Ef((X_c^{\pi_n}, Z_c^{\pi_n})(\mathbf{t})| \\
&\quad = |Ef((X_o^{\pi_n}, Z_o^{\pi_n})(\mathbf{t}) - Ef((X_o^{\pi_n}, Z_o^{\pi_n})(\mathbf{t})| \\
&\quad \leq LE[|(X_o^{\pi_n}, Z_o^{\pi_n})(\mathbf{t}) - (X_c^{\pi_n}, Z_c^{\pi_n})(\mathbf{t})|] \\
&\quad \leq LK\gamma + L\ P(\max_{i=0,...,K} |(X_o^{\pi_n}(t_i), Z_o^{\pi_n}(t_i)) - (X_c^{\pi_n}(t_i), Z_c^{\pi_n}(t_i))| > \gamma)
\end{aligned} \tag{3.15}$$

We can choose $\gamma < \epsilon/2LK$. With this γ fixed, we may choose n large enough so that the second piece can be bounded by $\epsilon/2$, and we will achieve the claim.

Let us therefore describe the coupling of $(X_c^{\pi_n}, Z_c^{\pi_n})$ and$(X_o^{\pi_n}, Z_o^{\pi_n})$ which will make (3.14) possible. For each n, let us prepare the following infinite series of Poisson processes:

$$\{Y_{km}^n, Y_{ikm}^{n,aug}, i = 1, 2, 3,\ k = 1, ..., R,\ m = 0, 1, 2, ...\} \tag{3.16}$$

We will generate (3.10) out of (3.11). We need some notational preparation to proceed. First, as promised above, we generate $(X_c^{\pi_n}, Z_c^{\pi_n})$ up to time T. Fix this n. We then define

$$\begin{aligned}
\mathcal{T}_{ikm} &\stackrel{def}{=} r_{ikm}(\lambda_k, \tilde{\lambda}_k, X_o^{\pi_n}, Z_o^{\pi_n})(s_m) \cdot \Delta_m(\pi_n) \\
T_{ikm}^o &\stackrel{def}{=} \int_{s_m}^{s_{m+1}} r_{ikm}(\lambda_k, \tilde{\lambda}_k, X_o^{\pi_n}, Z_o^{\pi_n})(s) ds
\end{aligned} \tag{3.17}$$

$$T_{km}^c \stackrel{def}{=} \left(\int_{s_m}^{s_{m+1}} \lambda(X_c^{\pi_n}(s)) ds\right) \vee \left(\int_{s_m}^{s_{m+1}} \tilde{\lambda}(Z_c^{\pi_n}(s)) ds\right) \tag{3.18}$$

We have omitted n from the definitions above to avoid notational overflow, since we will create the coupling between (3.11) and (3.10) for each fixed n.

Inductively arguing on m, suppose that we have seen $(X_o^{\pi_n}, Z_o^{\pi_n})$ up to time s_m in (3.12). At this point, we are yet to generate $Y_{ik\tilde{m}}$ for any $\tilde{m} > m$. We will define Y_{3km}^n as the jump process for which

$$\begin{aligned} Y_{3km}^n(s) &= Y_{km}^n(s) \qquad \text{for} \quad s \le \mathcal{T}_{3km} \\ Y_{3km}^n(s) - Y_{3km}(\mathcal{T}_{3km}) &= Y_{3km}^{n,aug}(s) \qquad \text{for} \quad s \ge \mathcal{T}_{3km} \end{aligned} \tag{3.19}$$

Next, if $\lambda(X_o(s_m)) < \lambda(X_o(s_m))$, let Y_{1km}^n be the jump process such that

$$\begin{aligned} Y_{1km}^n(s) &= Y_{km}^n(s + \mathcal{T}_{3km}) - Y_{km}^n(\mathcal{T}_{3km}) \qquad \text{for} \quad s \le \mathcal{T}_{1km} \\ Y_{1km}^n(s) - Y_{1km}^n(\mathcal{T}_{1km}) &= Y_{1km}^{n,aug}(s) \qquad \text{for} \quad s \ge \mathcal{T}_{1km} \end{aligned} \tag{3.20}$$

and $Y_{2km}^n = Y_{2km}^{n,aug}$. If $\lambda(X_o^{\pi_n}(s_m)) \ge \lambda(X_o^{\pi_n}(s_m))$, then we will interchange the role of $1km$ with $2km$.

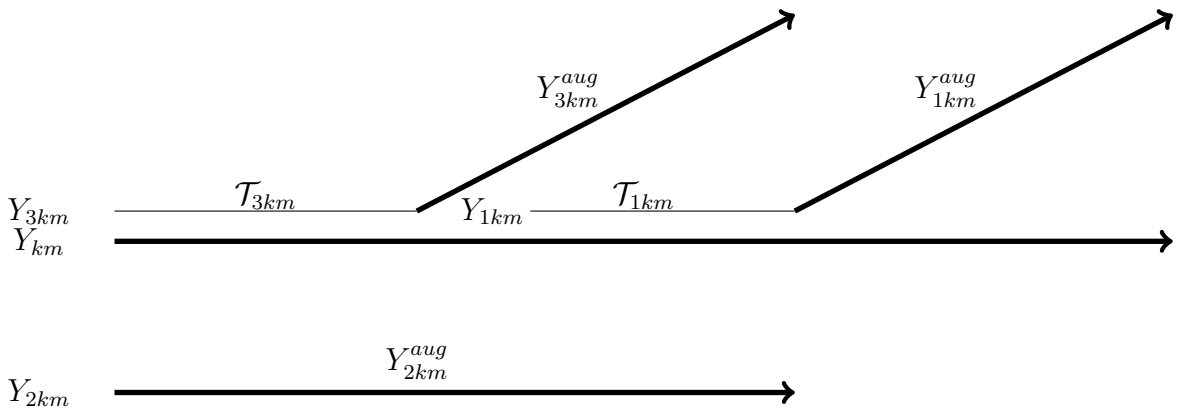

Figure 2: A pictorial image of coupling (3.10) to (3.11) in the case of $\lambda(Z_o(s_m)) < \lambda(X_o(s_m))$.

We would emphasize that $\mathcal{T}_{ikm}$ are values independent from Y^n_{km}. By the Markov property of Y^n_{km}, $\{Y^n_{ikm}\}$ constructed this way is a set of independent Poisson processes. By generating $(X^{\pi_n}_o, Z^{\pi_n}_o)$ from this $\{Y^n_{ikm}\}$, we establish a coupling between $(X^{\pi_n}_o, Z^{\pi_n}_o)$ and $(X^{\pi_n}_c, Z^{\pi_n}_c)$. We would like to make few observations before we proceed further.

Lemma 3.2. *Fix n, and let $m \in \mathbb{N}$. If*

$$\sum_{k=1}^{R}\sum_{i=1}^{3} Y^n_{ikm}(\mathcal{T}_{ikm} \vee T^o_{ikm}) = 1 \tag{3.21}$$

then there is a unique $j \in \{1,2,3\}$ and $\ell \in \{1,...,R\}$ for which

$$Y^n_{j\ell m}(\mathcal{T}_{j\ell m} \wedge T^o_{j\ell m}) = 1.$$

Note the difference between $\wedge$ and $\vee$.

Proof. For each (i,k), let

$$Q_{ik}(t) \stackrel{def}{=} Y^n_{ikm}\left(\int_{s_m}^{t+s_m} r_{ik}(\lambda_k, \tilde{\lambda}_k, X^{\pi_n}_o, Z^{\pi_n}_o)(s)ds\right)$$

be a counting process on E. First, (3.21) implies that $Y^n_{j\ell m}(\mathcal{T}_{j\ell m} \vee T^o_{j\ell m}) = 1$ for some j and ℓ and $Y^n_{ikm}(\mathcal{T}_{ikm} \vee T^o_{ikm}) = 0$ for all $(i,k) \neq (j,\ell)$. This in particular means that $Q_{j\ell m}$ is the first one among all $\{Q_{ikm}\}$ to jump. This is because, for all (i,k), $r_{ik}(\lambda_k, \tilde{\lambda}_k, X^{\pi_n}_o, Z^{\pi_n}_o)(s)$ won't change from $r_{ik}(\lambda_k, \tilde{\lambda}_k, X^{\pi_n}_o, Z^{\pi_n}_o)(s_m)$ until the first jump of $(X^{\pi_n}_o, Z^{\pi_n}_o)$. If $Q_{j\ell m}$ marks the first jump at time $t = \alpha$, $Y^n_{j\ell m}$ must mark the first jump at some t_0 that can be represented as

$$t_0 = r_{j\ell}(\lambda_k, \tilde{\lambda}_k, X^{\pi_n}_o, Z^{\pi_n}_o)(s_m)\alpha. \tag{3.22}$$

If $\alpha > \Delta_n\pi_n$, then by definition $Y^n_{j\ell m}(\mathcal{T}_{j\ell m} \vee T^o_{j\ell m}) = 0$ and that will be a contradiction. Hence $\alpha \leq \Delta_n\pi_n$ necessarily and $t_0 \leq T^o_{j\ell m}$. Also, from the (3.22), $t_0 \leq \mathcal{T}_{j\ell m}$ trivially. $\square$

There is another analogue to the lemma above;

Lemma 3.3. *If* $(X_c^{\pi_n}, Z_c^{\pi_n})(s_m) = (X_o^{\pi_n}, Z_o^{\pi_n})(s_m)$ *and*

$$\sum_k Y_{km} \left(\left(\sum_{i=1}^{3} \mathcal{T}_{ikm} \right) \vee T_{km}^c \right) = 1$$

then there is an unique k_0 *for which*

$$Y_{k_0 m} \left(\left(\sum_{i=1}^{3} \mathcal{T}_{ikm} \right) \wedge T_{k_0 m}^c \right) = 1$$

and $Y_{k_0 m}$ *jumps at some time* t_0 *before*

$$\left(\lambda_{k_0}(X_c^{\pi_n}(s_m)) \vee \tilde{\lambda}_{k_0}(Z_c^{\pi_n}(s_m)) \right) \Delta_m.$$

Proof. By the construction, and the assumption,

$$\sum_{i=1}^{3} \mathcal{T}_{ikm} = \left(\lambda_{k_0}(X_c^{\pi_n}(s_m)) \vee \tilde{\lambda}_{k_0}(Z_c^{\pi_n}(s_m)) \right) \Delta_m.$$

Also, neither $Z_c^{\pi_n}$ nor $X_c^{\pi_n}$ changes until the first firing of $Y_{k_0 m}$, so the claim follows. □

Based on the last two observations, we would also like to introduce the following lemma, which will be useful in proving the proposition 3.1.

Lemma 3.4. *Suppose that, for a given path of* $(X_o^{\pi_n}, Z_o^{\pi_n})(w)$, $(X_c^{\pi_n}, Z_c^{\pi_n})(w)$ *coupled in the way we described above,*

$$H_{m,n}(w) \stackrel{def}{=} \sum_{k=1}^{R} \max \left\{ \sum_{i=1}^{3} Y_{ikm}^n (\mathcal{T}_{ikm} \vee T_{ikm}^o), Y_{km}^n \left(\left(\sum_{i=1}^{3} \mathcal{T}_{ikm} \right) \vee T_{km}^c \right) \right\} \leq 1 \quad (3.23)$$

Then for all $m = 0, ..., N(n)$,

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_m, w) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m, w)$$

Proof. We have

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_0, w) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_0, w).$$

Trivially. We will omit w in the expressions from now on. Inductively arguing, assume that

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_m) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m). \tag{3.24}$$

We will show that

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1})$$

when (3.23) holds. If $H_{m,n} = 0$ for this m, then

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_o^{\pi_n}, Z_o^{\pi_n})(s_m) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1})$$

and there is nothing to do. Therefore we consider the case in which $H_{m,n} = 1$. More specifically, suppose that for some k_0,

$$\max\left\{\sum_{i=1}^{3} Y_{ik_0m}^n(\mathcal{T}_{ik_0m} \vee T_{ik_0m}^o), Y_{k_0m}^n\left(\left(\sum_{i=1}^{3}\mathcal{T}_{ik_0m}\right) \vee T_{k_0m}^c\right)\right\} = 1.$$

This means that

$$\max\left\{\sum_{i=1}^{3} Y_{ikm}^n(\mathcal{T}_{i\ell m} \vee T_{ikm}^o), Y_{km}^n\left(\left(\sum_{i=1}^{3}\mathcal{T}_{ikm}\right) \vee T_{km}^c\right)\right\} = 0$$

for all $k \neq k_0$ by the condition (3.23). WLOG we will also assume

$$\lambda_{k_0}(X_o^{\pi_n}(s_m)) > \tilde{\lambda}_{k_0}(Z_o^{\pi_n}(s_m)) \tag{3.25}$$

for this k_0, since the case otherwise works just the same. We will separately analyze the cases of $Y_{k_0m}^n\left(\left(\sum_{i=1}^{3}\mathcal{T}_{ik_0m}\right) \vee T_{k_0m}^c\right) = 1$ and $\sum_{i=1}^{3} Y_{ik_0m}^n(\mathcal{T}_{ik_0m} \vee T_{ik_0m}^o) = 1$, and show that

$$Y_{k_0m}^n\left(\left(\sum_{i=1}^{3}\mathcal{T}_{ik_0m}\right) \vee T_{k_0m}^c\right) = \sum_{i=1}^{3} Y_{ik_0m}^n(\mathcal{T}_{ik_0m} \vee T_{ik_0m}^o) = 1$$

with $(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1})$ either way.

First suppose that $Y_{k_0m}^n\left(\left(\sum_{i=1}^3 \mathcal{T}_{ik_0m}\right) \vee T_{k_0m}^c\right) = 1$. By lemma 3.3 and (3.24), $Y_{k_0m}^n(T_{k_0m}^c) = 1$ as well. We would like to make assessments about this t_0.

1. Consider the case of $t_0 \leq \mathcal{T}_{3k_0m} = \tilde{\lambda}_{k_0}(Z_o^{\pi_n}(s_m))\Delta_m(\pi_n)$. This in particular means that t_0 admits the representation

$$t_0 = \tilde{\lambda}_{k_0}(Z_o^{\pi_n}(s_m))\beta$$

for some $\beta \leq \Delta_m(\pi_n)$. It follows that

$$Y_{k_0m}^n\left(\int_{s_m}^{s_{m+1}} \tilde{\lambda}_{k_0}(Z_c^{\pi_n})ds\right) = 1,$$

and hence

$$(X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1}) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m) + (\zeta_{k_0}, \zeta_{k_0}).$$

By the coupling, $Y_{3k_0m}^n(\mathcal{T}_{3k_0m}) = 1$, so $\sum_{k=1}^R \sum_{i=1}^3 Y_{ikm}^n(\mathcal{T}_{ikm} \vee T_{ikm}^o) = 1$ is forced. By lemma 3.2, we must have $Y_{3k_0m}^n(T_{3k_0m}^o) = 1$ as well. We achieve

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_o^{\pi_n}, Z_o^{\pi_n})(s_m) + (\zeta_{k_0}, \zeta_{k_0}).$$

2. Consider the case of $\mathcal{T}_{3k_0m} < t_0 \leq T_{k_0m}^c$. Since $Y_{k_0m}^n(\mathcal{T}_{3k_0m}) = 0$,

$$\int_{s_m}^{s_{m+1}} \tilde{\lambda}_{k_0}(Z_c^{\pi_n}(s))ds = \lambda_{k_0}(Z_o^{\pi_n}(s_m))\Delta_m(\pi_n) = \mathcal{T}_{3k_0m} \tag{3.26}$$

necessarily. So

$$(X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1}) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m) + (\zeta_{k_0}, 0)$$

is guaranteed. Moreover, t_0 admits the representation $t_0 = \lambda_{k_0}(X_o^{\pi_n}(s_m))\alpha$ where

$$\Delta_m(\pi_n)\left(\frac{\tilde{\lambda}_{k_0}(Z_o^{\pi_n}(s_m))}{\lambda_{k_0}(X_o^{\pi_n}(s_m))}\right) \leq \alpha \leq \Delta_m(\pi_n).$$

Therefore $t_0 \leq (\mathcal{T}_{3k_0m} + \mathcal{T}_{1k_0m}) \wedge T^c_{k_0m}$ and

$$Y^n_{k_0m}(\mathcal{T}_{3k_0m} + \mathcal{T}_{1k_0m}) - Y^n_{k_0m}(\mathcal{T}_{3k_0m}) = 1.$$

By the coupling I have $Y^n_{1k_0m}(\mathcal{T}_{1k_0m}) = 1$.

With the assumption set forth in 3.4, $\sum_{k=1}^R \sum_{i=1}^3 Y^n_{ikm}(\mathcal{T}_{ikm} \vee T^o_{ikm}) = 1$ is forced.

By lemma 3.2, we must have $Y^n_{1k_0m}(T^o_{1k_0m}) = 1$ as well. We achieve

$$(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_o^{\pi_n}, Z_o^{\pi_n})(s_m) + (\zeta_{k_0}, 0).$$

as desired.

Next, suppose that $\sum_{i=1}^3 Y^n_{ik_0m}(\mathcal{T}_{ik_0m} \vee T^o_{ik_0m}) = 1$. This means that either one of $\{Y^n_{ik_0m}(\mathcal{T}_{ik_0m} \vee T^o_{ik_0m}), i = 1, 2, 3\}$ is 1. We can knock out $i = 2$ from the candidates, since (3.25) implies $Y_{2k_0m}(\mathcal{T}_{2k_0m} \vee T^o_{ik_0m}) = 0$.

1. Suppose that $Y^n_{3k_0m}(\mathcal{T}_{3k_0m} \vee T^o_{3k_0m}) = 1$. By lemma 3.2, $Y^n_{3k_0m}(T^o_{3k_0m}) = 1$ and $Y^n_{3k_0m}(\mathcal{T}_{3k_0m}) = 1$. So

   $$(X_o^{\pi_n}, Z_o^{\pi_n})(s_{m+1}) = (X_o^{\pi_n}, Z_o^{\pi_n})(s_m) + (\zeta_{k_0}, \zeta_{k_0}).$$

   By the coupling, $Y^n_{km}(\mathcal{T}_{3km}) = 1$. Y_{km} must have jumped at t_0 admitting the representation

   $$t_0 = \tilde{\lambda}_{k_0}(Z_o^{\pi_n}(s_m))\beta < \tilde{\lambda}_{k_0}(X_o^{\pi_n}(s_m))\beta$$

   for some $\beta \leq \Delta_m(\pi_n)$, so

   $$(X_c^{\pi_n}, Z_c^{\pi_n})(s_{m+1}) = (X_c^{\pi_n}, Z_c^{\pi_n})(s_m) + (\zeta_{k_0}, \zeta_{k_0})$$

as well.

2. Suppose that $Y^n_{1k_0m}(\mathcal{T}_{1k_0m} \vee T^o_{1k_0m}) = 1$. By lemma 3.2, $Y^n_{1k_0m}(T^o_{1k_0m}) = 1$ and $Y^n_{1k_0m}(\mathcal{T}_{1k_0m}) = 1$. It also follows that $Y^n_{1k_0m}$ jumps at t_0 admitting the representation

$$t_0 = (\lambda_{k_0}(X^{\pi_n}_o(s_m)) - \lambda_{k_0}(Z^{\pi_n}_o(s_m)))\beta$$

for some $\beta \leq \Delta_m(\pi_n)$, and

$$(X^{\pi_n}_o, Z^{\pi_n}_o)(s_{m+1}) = (X^{\pi_n}_o, Z^{\pi_n}_o)(s_m) + (\zeta_{k_0}, 0).$$

By the coupling $Y^n_{k_0m}(\mathcal{T}_{1k_0m} + \mathcal{T}_{3k_0m}) - Y^n_{k_0m}(\mathcal{T}_{3k_0m}) = 1$, so $Y^n_{k_0m}(\mathcal{T}_{3k_0m}) = 0$. Since $Y^n_{k_0m}(\mathcal{T}_{3k_0m}) = 0$, (3.26) holds again. Also, the coupling dictates $Y^n_{k_0m}$ to make the first jump at $t_0 + \mathcal{T}_{3k_0m}$. Since $(t_0 + \mathcal{T}_{3k_0m})/\lambda_{k_0}(X_{s_m}) < \Delta_m(\pi_n)$, we are sure that $t_0 < T^c_{k_0m}$. Altogether, we have

$$\int_{s_m}^{s_{m+1}} \tilde{\lambda}_{k_0}(Z^{\pi_n}_c(s))ds \leq t_0 \leq T^c_{k_0m}$$

and therefore

$$(X^{\pi_n}_c, Z^{\pi_n}_c)(s_{m+1}) = (X^{\pi_n}_c, Z^{\pi_n}_c)(s_m) + (\zeta_{k_0}, 0).$$

□

It is not so difficult to see that, when λ_k and $\tilde{\lambda}_k$ are uniformly bounded for all k, we can make the condition in lemma 3.4 happen with probability greater than $1 - \epsilon$ for any ϵ by setting $mesh(\pi_n)$ small enough. We do not have such an uniform bound on λ. Also, we have to note that we don't necessarily have $(X^{\pi_n}_c, Z^{\pi_n}_c)(t) = (X^{\pi_n}_o, Z^{\pi_n}_o)(t)$ for all $t \in [s_m, s_{m+1}]$ even if the condition for the lemma 3.4 holds. If $t \in [s_m, s_{m+1}]$,

however, we can have $(X_c^{\pi_n}, Z_c^{\pi_n})(t) = (X_o^{\pi_n}, Z_o^{\pi_n})(t)$ with an additional condition; that neither $(X_c^{\pi_n}, Z_c^{\pi_n})$ nor $(X_o^{\pi_n}, Z_o^{\pi_n})$ jump at all in $[s_m, s_{m+1}]$ containing t . Put K_0^n to be

$$K_0^n = \{m \in \{0, ..., N(n) - 1\} \ ; \ \{t_j\}_{j=1}^K \cap [s_m, s_{m+1}) \neq \emptyset\},$$

and let us return to the proof of the proposition 3.1.

Proof. **(of 3.1)** As we remarked earlier, it suffices to show (3.14). Let $\epsilon > 0$. We will show that, for large enough n,

$$P(\max_{i=0,...,K} |(X_o^{\pi_n}(t_i), Z_o^{\pi_n}(t_i)) - (X_c^{\pi_n}(t_i), Z_c^{\pi_n}(t_i))| > 0) < \epsilon.$$

We will resort to a variation of localization argument and take advantage of the fact that X and Z are both nonexplosive. Let $M > 0$, and let $H_{m,n}$ be as defined in lemma 3.4. We will define the event on which 3.4 holds. Define

$$A_n(\mathbf{t}) = \{\omega : H_{m,n}(\omega) \leq 1 \text{ if } m \notin K_0^n \text{ and } H_{m,n}(\omega) = 0 \text{ if } m \in K_0^n\}\,. \tag{3.27}$$

$$\begin{aligned} B_{M,n} =\{\omega : \max\{&\sup_{s\leq T} \lambda_k(X_o^{\pi_n}(s)), \sup_{s\leq T} \lambda_k(Z_o^{\pi_n}(s)), \\ &\sup_{s\leq T} \lambda_k(Z_c^{\pi_n}(s)), \sup_{s\leq T} \lambda_k(X_c^{\pi_n}(s)\} \leq M\} \end{aligned} \tag{3.28}$$

I would like to remind ourselves that the number of fires in each path is finite, and hence that *sup* is achieved everywhere it appears above. As we saw, $A_n(\mathbf{t}) \subset \{(X_o^{\pi_n}, Z_o^{\pi_n})(\mathbf{t}) = (X_c^{\pi_n}, Z_c^{\pi_n})(\mathbf{t})\}$. Therefore

$$\begin{aligned} P((X_o^{\pi_n}, Z_o^{\pi_n})(\mathbf{t}) \neq (X_c^{\pi_n}, Z_c^{\pi_n})(\mathbf{t})) &\leq P(A_n^C(\mathbf{t})) \\ &= P(A_n^C(\mathbf{t}) \cap B_{M,n}) + P(A_n(\mathbf{t}) \cap B_{M,n}^C) \end{aligned} \tag{3.29}$$

For the second piece above, we note that

$$B_{M,n}^C \subset \{\sup_{s\leq T} \lambda_k(X_o^{\pi_n}(s)) > M\} \cup \{\sup_{s\leq T} \tilde{\lambda}_k(Z_o^{\pi_n}(s)) > M\} \cup \{\sup_{s\leq T} \lambda_k(X_c^{\pi_n}(s)) > M\} \cup \{\sup_{s\leq T} \tilde{\lambda}_k(Z_c^{\pi_n}(s)) > M\} \tag{3.30}$$

Now, recall that the marginal distribution of $X_c^{\pi_n}$ and $X_o^{\pi_n}$ are the same as the marginal distribution of X, and that the same goes for $Z_c^{\pi_n}$ and $Z_o^{\pi_n}$ compared with Z. Therefore, for all n we have

$$P(B_{M,n}^C) \leq 2 * \left[P(\sup_{s\leq T}\{\lambda_k(X_s)\} > M) + P(\sup_{s\leq T}\{\tilde{\lambda}_k(Z_s)\} > M) \right]. \tag{3.31}$$

By the monotone convergence theorem and the fact that the processes are all non explosive, the RHS of (3.31) will tend to 0 as $M \to \infty$. Therefore we can take M large enough so that the second piece of (3.29) is smaller than $\epsilon/2$. Let us fix this M, and look at the first piece.

Let us consider the localized version of H. In particular, let

$$H_{m,n}^M(w) \equiv \sum_{k=1}^{R} \max\left\{ \sum_{i=1}^{3} Y_{ikm}^n(M\Delta_m(\pi_n)), Y_{km}^n(3M\Delta_m(\pi_n)) \right\}$$

Then it is clear that, for any $q > 0$,

$$(\{H_{m,n} > q\} \cap B_{M,n}) \subset \left(\{H_{m,n}^M > q\} \cap B_{M,n}\right) \subset \{H_{m,n}^M > q\}$$

Therefore we can say

$$\begin{aligned} &P(A_n^C(\mathbf{t}) \cap B_{M,n}) \\ &\leq P(H_{m,n}^M > 1 \text{ for some } m \notin K_0^n \ \ \textbf{OR} \ \ H_{m,n}^M > 0 \text{ for some } m \in K_0^n) \\ &\leq \sum_{m\notin K_0^n} P(H_{m,n}^M > 1) + \sum_{m\in K_0^n} P(H_{m,n}^M > 0) \end{aligned} \tag{3.32}$$

Also, for any $p > 0$,

$$\begin{aligned} P(Poi(p) > 1) =& 1 - exp(-p)(1+p) \\ \leq& 1 - (1-p)(1+p) \\ =& p^2 \end{aligned} \tag{3.33}$$

and

$$P(Poi(p) > 0) = 1 - exp(-p) \leq p \tag{3.34}$$

We note that

$$P(\{H^M_{m,n} > q\}) \leq P(Poi(6RM\Delta_m(\pi_n)) > q)$$

Now , if $mesh(\pi_n) = \delta_n$, then $P(A^C_n(\mathbf{t}) \cap B_M)$ is at most

$$\begin{aligned} P(A^C_n(\mathbf{t}) \cap B_M) \leq& \sum_{m \notin K^n_0} (6RM\Delta_m(\pi_n))^2 + \sum_{m \in K^n_0} (6RM\Delta_m(\pi_n)) \\ \leq& (6RM)^2\delta_n \sum_{m \notin K^n_0} \frac{\Delta_m(\pi_n)}{\delta_n}\Delta_m(\pi_n) + 6RM|K^n_0|\delta_n \\ \leq& (6RM)^2\delta_n T + 6RM|K^n_0|\delta_n \end{aligned} \tag{3.35}$$

In the third inequality, I used the fact that $\frac{\Delta_m(\pi_n)}{\delta_n} < 1$, by the definition of mesh. We can take n large enough so that (3.35) is less than $\epsilon/2$. For such n,

$$P((X^{\pi_n}_o, Z^{\pi_n}_o)(\mathbf{t}) \neq (X^{\pi_n}_c, Z^{\pi_n}_c)(\mathbf{t})) < \epsilon,$$

as required. □

It is to be hoped that the proposition 3.1 implies the weak convergence of $(X^{\pi_n}_c, Z^{\pi_n}_c)$ to (X_o, Z_o) in Skorohod's sense. However, in order to achieve the result we require $\{(X^{\pi_n}_c, Z^{\pi_n}_c\}$ to be precompact in Skorohod topology. The following is a result available in [32].

Theorem 3.5. *Suppose that $\{X_n\}$ is a series of processes with in the Skorohod space of all càdlàg functions$D_E[0,\infty)$. Then the law of $\{X_n\}$ is precompact if and only if the following two conditions hold:*

1. *For each η, t there is a compact set $\Gamma_{eta,t}$ on E such that*

$$\inf P(X_n(t) \in \Gamma_{\eta,t}) < \eta$$

2. *For each $\eta > 0$ and $T > 0$ there exists $\delta > 0$ such that*

$$\sup_n P(w'(X_n, \delta, T) \geq \eta) < \eta$$

where

$$w'(X, \delta, T) \stackrel{def}{=} \inf_{\pi} \max_{a,b \in [t_i, t_{i-1}]} |X(a) - X(b)|$$

with π ranging over all partition of $[0, T]$ with $t_i - t_{i-1} > \delta$.

Unfortunately the conditions in the theorem 3.5 do not hold in general for our $\{(X_c^{\pi_n}, Z_c^{\pi_n})\}$. Consider, for example, the following simple linear growth system

$$0 \rightarrow A \tag{1}$$

and the corresponding $(X_o, Z_o), (X_c^{\pi_n}, Z_c^{\pi_n})$ with

$$\lambda_1(x) = \theta x, \qquad \tilde{\lambda}_1(x) = (\theta + \epsilon)x$$

and the initial condition

$$X_o(0) = Z_o(0) = X_c^{\pi^n}(0) = Z_c^{\pi^n}(0) > 0.$$

Then for any $\beta > 0$ there is a finite probability $\alpha > 0$ that in the interval $[0, \beta]$, X_o and Z_o makes the "first jump" simultaneously. By the argument we made in the proof

above, for any $\epsilon > 0$ and $\sigma > 0$ there exists some M such that if $n > M$, then for probability greater then $\alpha - \epsilon$, both $X_c^{\pi_n}$ and $Z_c^{\pi_n}$ make the first jumps in this interval at times τ_x and τ_z respectively with $0 < \tau_x - \tau_z < \sigma$. Note that $\tau_x - \tau_z = 0$ happens with probability 0 in our situation. This in particular means that for any σ,

$$\sup_n P(w'((X_c^{\pi_n}, Z_c^{\pi_n}), \sigma, t_0) \geq 1) \geq \alpha$$

And $\{(X_c^{\pi_n}, Z_c^{\pi_n})\}$ fails to have precompact laws.

3.3.2 Weak convergence in product Skorohod topology

We can achieve the convergence of $(X_c^{\pi_n}, Z_c^{\pi_n})$ in a weaker topology. In this subsection, we would like to prove the following.

Proposition 3.6. *Let X and Z be non explosive jump processes in a Skorohod space of càd làg functions $D_{\mathbb{R}^d}[0,\infty)$ as given in (1.4) with intensities $\lambda_k(x,s) = \lambda_k(x(s))$, $\tilde{\lambda}_k(x,s) = \tilde{\lambda}_k(x(s))$, respectively. Consider then the product topology on*

$$\mathcal{D} := D_{\mathbb{R}^d}[0,\infty) \times D_{\mathbb{R}^d}[0,\infty).$$

Also, let $\pi_n = \{s_j^n\}$ be a sequence of partitions of $[0,\infty)$ such that

$$mesh(\pi^n) = \max_{j<\infty}(s_j^n - s_{j-1}^n) \to 0.$$

Then for all $f : \mathcal{D} \to \mathbb{R}$ that are bounded and continuous,

$$E[f(X_c^{\pi_n}, Z_c^{\pi_n})] \to E[f(X_o, Z_o)].$$

I would note that the function f is allowed to be a path dependent statistic. We need some preparations. The following is another critical result in [32] regarding the Skorohod topology.

Theorem 3.7. *For each $t \geq 0$ and polish space E, define $\pi_t : D_E[0,\infty) \to E$ by $\pi_t(x) = x(t)$. Then the Borel σ-algebra $\mathcal{W}$ of $D_E[0,\infty)$ is given by*

$$\mathcal{W} = \sigma(\pi_t, t \in D).$$

where D is any dense subset of $[0,\infty)$.

Using the result above, we can obtain the generators for $\mathcal{D}$.

Corollary 3.1. *The Borel σ-algebra of $\mathcal{D}$ is given by*

$$\sigma(\pi_t \times \pi_s, s, t \in D).$$

where $(\pi_t \times \pi_s)(x,z) = (x(t), z(s))$.

Next, I would like to make a corollary to the proposition 3.1.

Corollary 3.2. *Let $s = \{s_0 < s_1 < s_2 < \cdots < s_{m_1}\}$, $t = \{t_0 < t_1 < t_2 < \cdots < t_{m_2}\}$ and*

$$f_i : \mathbb{R}^d \to \mathbb{R} \quad i = 0, ..., m_1 \qquad g_j : \mathbb{R}^d \to \mathbb{R} \quad j = 0, ..., m_2$$

be bounded and continuous functions on $\mathbb{R}^d$, and assume the conditions set forth in the proposition 3.1. Then

$$E\left[\prod_{i=0}^{m_1} f_i((X_c^{\pi_n}(s_i)) \prod_{j=0}^{m_2} g_j(Z_c^{\pi_n}(t_j)))\right] \to E\left[\prod_{i=0}^{m_1} f_i((X_o(s_i)) \prod_{j=0}^{m_2} g_j(Z_o(t_j)))\right]$$

Proof. A standard Portmanteau argument works. Recall again that

$$E\left[\prod_{i=0}^{m_1} f_i((X_o^{\pi_n}(s_i))\prod_{j=0}^{m_2} g_j(Z_o^{\pi_n}(t_j)))\right] = E\left[\prod_{i=0}^{m_1} f_i((X_o(s_i))\prod_{j=0}^{m_2} g_j(Z_o(t_j)))\right].$$

Let $max\{g, f\} < M$. On the coupled space,

$$\begin{aligned} E\Bigg[\prod_{i=0}^{m_1} f_i((X_c^{\pi_n}(s_i))\prod_{j=0}^{m_2} g_j(Z_c^{\pi_n}(t_j))) - \prod_{i=0}^{m_1} f_i((X_o^{\pi_n}(s_i))\prod_{j=0}^{m_2} g_j(Z_o^{\pi_n}(t_j)))\Bigg] \\ \leq 2M^{m_1+m_2} P(\max_{\tau\in\{s_i\}\cup\{t_j\}} |(X_o^{\pi_n}(\tau), Z_o^{\pi_n}(\tau)) - (X_c^{\pi_n}(\tau), Z_c^{\pi_n}(\tau))| \neq 0) \\ \to 0. \end{aligned} \tag{3.36}$$

□

We now put everything together in order to prove 3.6.

Proof. We would like to show that $(X_c^{\pi_n}, Z_c^{\pi_n})$ satisfies the conditions in theorem 3.5 with respect to the space $\mathcal{D}$. To show that $(X_c^{\pi_n}, Z_c^{\pi_n})$ is precompact, we need to show that, for any $\epsilon > 0$, there exists a compact set C^ϵ such that

$$\inf_n P((X_c^{\pi_n}, Z_c^{\pi_n}) \in C^\epsilon) > 1 - \epsilon.$$

Marginally, $X \sim X_c^{\pi_n}$ and $Z \sim Z_c^{\pi_n}$. If $P(X \in A^\epsilon) > 1 - \epsilon/2$ and $P(Z \in B^\epsilon) > 1 - \epsilon/2$ for compact $A^\epsilon, B^\epsilon \subset D[0, \infty)$, then $P((X, Z) \in A^\epsilon \times B^\epsilon) > 1 - \epsilon$ with $A^\epsilon \times B^\epsilon$ compact in the product topology. Therefore it suffices to show that X and Z both separately satisfy the conditions in theorem 3.5. Since X is a nonexplosive pure jump process, it clearly passes the first condition. Also, recall that X is constructed with R channels of

Poisson processes. Hence for any $T > 0$ and $M > 0$,

$$\begin{aligned} P(w'(X,\delta,T) > 0) &\leq P(w'(X,\delta,T) > 0 : \sup_{k=1,..,R,p<T} \lambda_k(X(p)) \leq M) \\ &\quad + P(\sup_{k=1,..,R,p<T} \lambda_k(X(p)) > M) \qquad (3.37) \\ &= P(w'(Y(MR\cdot),\delta,T) > 0) + P(\sup_{k=1,..,R,p<T} \lambda_k(X(p)) > M) \end{aligned}$$

where $Y(MR\cdot)$ is a rate MR poisson process. Since X is non explosive, we may take M large enough to control the second piece, and for this M we can choose δ small enough to control the first piece. That is, $\lim_{\delta\to 0} P(w'(X,\delta,T) > 0) = 0$. This tells us that X also passes the second condition. The same procedure works for Z. Now we know that $\{(X_c^{\pi_n}, Z_c^{\pi_n})\}$ is precompact in the product topology. Together with Corollary 3.2, we are done since

$$E\left[\prod_{i=0}^{m_1} f_i(X_o(s_i)) \prod_{j=0}^{m_2} g_j(Z_o(t_j))\right] \quad ; \quad \{s_i\},\{t_j\} \subset [0,\infty), f_i, g_i \in \overline{C}(\mathbb{R}^d) \qquad (3.38)$$

characterizes the law of (X_o, Z_o). To see how (3.38) characterizes the law of (X_o, Z_o), suppose that for some other process (X^*, Z^*),

$$E\left[\prod_{i=0}^{m_1} f_i(X_o(s_i)) \prod_{j=0}^{m_2} g_j(Z_o(t_j))\right] = E\left[\prod_{i=0}^{m_1} f_i(X_o^*(s_i)) \prod_{j=0}^{m_2} g_j(Z_o^*(t_j))\right]$$
$$\forall \ \{s_i\},\{t_j\} \subset [0,\infty), f_i, g_i \in \overline{C}(\mathbb{R}^d).$$

Note that we can approximate the indicator functions of open sets $\{A_i\}$, $\{B_j\}$ of $\mathbb{R}^d$ with increasing sequence of functions f_i^n, g_i^n, respectively. By the monotone convergence theorem, we have

$$E\left[\prod_{i=0}^{m_1} 1_{A_i}(X_o(s_i)) \prod_{j=0}^{m_2} 1_{B_j}(Z_o(t_j))\right] = E\left[\prod_{i=0}^{m_1} 1_{A_i}(X_o^*(s_i)) \prod_{j=0}^{m_2} 1_{B_j}(Z_o^*(t_j))\right]$$

for any open sets $\{A_i\}$, $\{B_j\}$ in $\mathbb{R}^d$. Now we apply a version of monotone class theorem:

Theorem 3.8. *Let H be a linear space of bounded functions on Ω that contains constants, and let $\mathcal{L}$ be a collection of subsets of Ω such that if $A, B \in \mathcal{L}$ then $A \cap B \in \mathcal{L}$, Suppose $\chi_A \in H$ for any $A \in \mathcal{L}$. Also suppose that $\{f_n\} \subset H$, $f_1 \leq f_2 \leq \cdots$ and $\sup_n f_n \leq c$ for some constant c imply that $f \equiv bp\lim_{n\to\infty} f_n \in H$ [1]. Then H contains all bounded $\sigma(\mathcal{L})$ measurable functions.*

For us, we put H to be the set of all Borel measurable functions $f : D_E[0,\infty) \times D_E[0,\infty) \to \mathbb{R}$ for which

$$E[f(X, Z)] = E[f(X^*, Z^*)]. \tag{3.39}$$

Next,

$$\mathcal{L} = \{\text{Any finite intersections of } (\pi_t \times \pi_s)^{-1}(A); t \in [0,\infty), A \in \mathcal{B}(\mathbb{R}^d \times \mathbb{R}^d)\}$$

The corollary 3.2 shows that $\chi_U \subset H$ for any $U \in \mathcal{L}$. Moreover, the last condition on H is guaranteed by the monotone convergence theorem. This shows that any $\sigma(\mathcal{L})$ measurable function is in H. By the corollary 3.1, this implies that (3.39) holds for any function f that is borel measurable on $D_E[0,\infty) \times D_E[0,\infty)$. □

There is still much work to be done in the development of new couplings and the relationship among existing couplings. While the split coupling performs well in many situations, there has never been any result on what particular statistics it optimizes. This study, however, revealed at least one source of the advantage of the split coupling. Recall that the local CRP (3.9) was created in the hope of "resetting" the Poisson channels at very small intervals to prevent a fast decoupling. This study shows that the

[1] *This stands for bounded pointwise convergence, which means* $\sup_n \|f_n\|_\infty < \infty$ *and* $\lim_{n\to\infty} f_n(x) = f(x)$ *for each* $x \in \Omega$.

split coupling is, in essence, continuously "resetting" the rate of each Poisson channels.

Also, the performance of the couplings have been tested only for the MLMC and for the sensitivity analysis. While the split coupling does well in reducing the variance of

$$g(X, Z) = X - Z,$$

it might not do so well for other functions of g. For future work, we shall investigate and explore more systematic ways construct the couplings to reduce the variance for many different types of g.

Chapter 4

Law of large numbers limit of a discrete stochastic system with random delay time

4.1 Introduction

One of the most familiar biological process that involves delay is transcription. We can simplify the whole process and write this reaction as

$$D \to D + M,$$

where D and M represent DNA and mRNA, respectively. Let $X_M(t)$ and $X_D(t)$ be the population of the mRNA molecules and that of the DNA molecules in the system at time t, respectively. If we model the process with a continuous time Markov chain as done in the introduction (1.6) under mass action kinetics (1.7), we would obtain

$$X_M(t) = X_M(0) + Y\left(\int_0^t X_D(s)ds\right) \tag{4.1}$$

with Y being an unit rate Poisson process. We claim that there is a technical fallacy in this choice of the model. The model above is biologically unrealistic in that it implies that each transcription is processed instantly, while the real transcription process requires

nontrivial time for its completion. In [20], Schwanhausser reports that the speed of transcription can be as slow as two mRNA molecules per hour. More particularly, $X_M(t)$ in (4.1) is an overestimate of the actual number of $mRNA$ molecules present in the system at time t. Instead, the real meaning of X_M in (4.1) is the number of the transcription processes that have initiated before time t. We are therefore in the position to consider the concept of "Delay." Further, when we make the problem slightly more realistic and include T, the transcriptase, into the process, we have to consider the possible failure of the transcription by the premature detachment of the transcriptase from the DNA molecule. Such an instance is mentioned, for example, by Ribeiro [64]. We can write this system as

$$D + T \to D^* \tag{4.2}$$

$$D^* \to M + D + T \tag{4.3}$$

$$D^* \to D + T \tag{4.4}$$

where D^* is a DNA-transcriptase complex. Aside from the example we presented above, modeling dynamical systems with delay has a wide range of applications. In epidemiology the transmission of the disease can be delayed by incubation period, and in ecology the population growth is modulated by gestation period.

Before we proceed further, we would like to simplify the problem and articulate more about the modeling of a delay itself. In the previous example, the fact that the products of (4.2) affect the rate of the delayed reaction (4.4) complicates the problem, as the entire system ceases to be Markovian once we allow the delayed reaction to feed into

itself. For example, consider the reaction

$$A \to B. \tag{4.5}$$

There are two intuitive ways to include "Delay" into (4.5). Upon the initiation of the reaction, we may choose A to be immediately consumed, and B to emerge after some holding time τ. That is, if t^* is the time of the reaction (4.5), then

$$X_A(t^*) = X_A(t^*-) - 1, \quad X_B(t^*-) = X_B(t^*).$$

This modeling choice is often termed *immediate consumption*. We may also choose A to remain in the system for some holding time τ, and B to emerge instantly afterward. That is, $X(t^*-) = X(t^*)$. This modeling choice is termed *delayed consumption*. Barbuti et al [63] argue explicitly that immediate consumption of reactants is not appropriate for some biological systems. They describe the system of cell mitosis, in which the model can overestimate the final cell numbers if it allows the premitotic phase to initiate without any chance of cancellation. In this chapter, we will consider a delayed consumption which is subject to a cancellation with a fixed certain probability. We will set up the problem on the single molecule level using the random time change representation in (1.6), and demonstrate a technique in taking its law of large numbers limit ODE.

4.2 Kurtz's classical scaling and Law of Large Numbers

There have been multiple efforts made in analyzing systems with delay. Barbuti et al. [63] created a simulation algorithm for a system with delayed consumption. Schlict [65]

computed the expectation of the output quantity from a continuous time production that has a generally distributed delay time. In [36] and [37] , Garcia and Kurtz developed a scheme based on the theory of Poisson random measure that allowed the computation of the law of large numbers (LLN) limit of the M/G queueing process and the S.I.R model. While the LLN limit of the M/G model is not explicitly stated in neither [36] nor [37], it is easy to extend their techniques to the case of M/G. In this chapter, we will show a different computation of the LLN for an analogue of M/G model in the setting of CRN. The following theorem from Kurtz [52] will be the key to our work:

Theorem 4.1. *Let $\zeta_k \in \mathbb{R}^S, k = 1, ..., R$, and let $\lambda_k : \mathbb{R}^s \to \mathbb{R}^+$ be a continuous function. If Y_k are independent unit rate Poisson process, then let X^N and x respectively be the solutions of the systems*

$$X^N(t) = x(0) + \frac{1}{N} Y_k \left(\int_0^t N\lambda_k(X^N(s))ds \right) \zeta_k.$$

and

$$x(t) = x(0) + \sum_k \left(\int_0^t \lambda_k(x(s))ds \right) \zeta_k.$$

If

$$F(\cdot) \equiv \sum_{k=1}^{R} \lambda_k(\cdot) \cdot \zeta_k$$

is Lipshitz, then for any fixed t,

$$\lim_{N\to\infty} \sup_{s<t} |X_N(s) - x(s)| = 0 \qquad \textit{almost surely.}$$

The theorem (4.1) provides us with the LLN limit for the Continuous Time Markov Chain models of the population dynamics of chemical reaction networks under "the

classical scaling". Under the classical scaling, all the species exists in same scale N, and the reaction rates scales linearly in N. We would like to use this machinery to compute the LLN limit for the specific type of systems with interruptible delay.

As a starting example, let us consider the following standard, non delayed kinetic networks

$$A \xrightarrow{r_1} B \tag{1}$$

$$\emptyset \xrightarrow{r_2} A \tag{2}$$

$$A \xrightarrow{r_3} \emptyset. \tag{3}$$

As usual, let us first model the system as (1.6). The populations of species A and B at time t are given by the solutions of the system

$$X_A(t) = X_A(0) - Y_1\left(\int_0^t r_1 X_A(s)ds\right) + Y_2\left(r_2 t\right) - Y_3\left(\int_0^t r_3 X_A(s)ds\right) \tag{4.6}$$

$$X_B(t) = X_B(0) + Y_1\left(\int_0^t r_1 X_A(s)ds\right) - Y_c\left(\int_0^t r_1 X_A(s)ds\right). \tag{4.7}$$

where $Y_\cdot$ are independent unit Poisson process. We would like to introduce a delay into the reaction (1). In particular, we will require each incidence of (1) to spend a fixed duration of length τ before its completion. This means that (1) does not consume the species A immediately, and that (1) can be interrupted by (3) before producing the species B. In other words, the reaction (1) is subject to premature termination. Thus, at all time t , the population of A can be decomposed into two groups; (I) the ones who have initiated the reaction (1), and (II) the ones who have not. We will distinguish the ones belonging to (I) by identifying them as the intermediate species A^*, and calling the rest by A. We can therefore say that there is an auxiliary reaction

$$A \xrightarrow{r_1} A^*$$

occurring at rate $r_1 X_A$, in which A is immediately consumed. A^* then transforms to B with a fixed holding time of length τ. In terms of chemistry, A^* can be considered as activated complex. Let us denote this non-Markovian reaction by

$$A^* \underset{\tau}{\to} B,$$

and rewrite the system with new labels.

$$A \xrightarrow{r_1} A^* \tag{1a}$$

$$A^* \underset{\tau}{\to} B \tag{1b}$$

$$\emptyset \xrightarrow{r_2} A \tag{2}$$

$$A \xrightarrow{r_3} \emptyset \tag{3}$$

$$A^* \xrightarrow{r_3^*} \emptyset \tag{3*}$$

The population dynamics of A is strictly Markovian. More concretely, X_A is a solution of

$$X_A(t) = X_A(0) - Y_a\left(\int_0^t r_1 X_A(s)ds\right) + Y_2\left(r_2 t\right) - Y_3\left(r_3 \int_0^t X_A(s)ds\right), \tag{4.8}$$

where $Y_\cdot$ are independent unit Poisson processes. X_{A^*} and X_B, on the other hand, are non-Markovian and require more care. First let

$$R_0(t) = Y_a\left(\int_0^t r_1 X_A(s)ds\right),$$

be the counting process giving the total number of times the reaction $(1a)$ has occurred by time t. This process counts the total number of A^* particles that have entered the system by time t. $R_0(t)$ contains both $X_{A^*}(t)$, the number of A^* particles that are

currently in the system, and those that already have exited the system. We will further decompose X_{A^*} into two groups; (I) those that will complete the reaction $(1b)$ before the interruption by (3^*), and (II) those that will fail to do so. In the model above, each particle of A^* is given a lifetime of length η, a positive random variable with distribution $expo(r_3^*)$. We will denote the first group and the second group respectively by A_1^* and A_2^*. Let us also denote the lifetime of the ith particle of A_1^* by η_i. Therefore those belonging

	A_1^*	A_2^*
Lifetime	τ	η
Delayed Product	B	$\emptyset$

to the first group are the ones with $\eta_i > \tau$ or equivalently the ones that live long enough to complete $(1b)$. Based on the logic we built so far, we can say that $X_B(t)$ is equal to the number of A^* that have entered the system before $t-\tau$ and satisfies $\eta > \tau$. Also, the A^* particles in the system at time t are those that are yet to be removed from the system via (3^*) nor $(1b)$. If T_i is a ith jump time of $R_0(t)$, then

$$X_{A^*}(t) = \sum_{i=R_0(t-\tau)+1}^{R_0(t)} 1((t-T_i) < \eta_i) = \int_0^t 1((t-s) < \eta_{R_0(s-)}) dR_0(s)$$

On the other hand, a particle of A^* that has entered the system after $t-\tau$ does not contribute to $X_B(t)$, since it requires the duration of length τ to produce B. Hence

$$X_B(t) = \sum_{i=1}^{R_0(t-\tau)} 1(\tau < \eta_i) = \int_0^{t-\tau} 1(\tau < \eta_{R_0(s-)}) dR_0(s)$$

We would like to know the limit of $X_{A^*}(t)$ and $X_B(t)$ in the scaling of (4.1) above.

To be more precise, if

$$X_A^N(t) = X_A^N(0) - \frac{1}{N}\left\{ Y_a\left(N\int_0^t r_1 X_A^N(s)ds\right) + Y_3\left(Nr_3 t\right) - Y_4\left(Nr_4\int_0^t X_A(s)ds\right)\right\}$$
$$R_0^N(t) = Y_a\left(\int_0^t r_1 N X_A^N(s)ds\right), \tag{4.9}$$

then we can define X_B^N and $X_{A^*}^N$ analogously as

$$X_{A^*}^N(t) = \frac{1}{N}\sum_{i=R_0^N(t-\tau)+1}^{R_0^N(t)} 1((t-T_i)<\eta_i), \qquad X_B^N(t) = \frac{1}{N}\sum_{i=1}^{R_0^N(t-\tau)} 1(\tau<\eta_i)$$

What will happen to X_B^N and $X_{A^*}^N$ as $N\to\infty$? As promised, we will use theorem (4.1) to answer this question.

4.3 A system with general delay time

We would like to further generalize our problem.

Proposition 4.2. *Consider a CRN with species $\{C_i\}_{i=1}^S$ for which its scaled population dynamics is given by $\mathbf{X}^N(\cdot)$. Suppose that there is, in addition, a non Markovian reaction*

$$A^* \to B \tag{β}$$

which satisfy the following properties:

1. *A^* is produced by the counting process*

$$R_0^N(t) \equiv Y_\beta\left(\int_0^t N\lambda_\beta(\mathbf{X}^N(s))ds\right).$$

2. *The reaction (β) is subject to a premature cancellation with probability $(1-p)$. Conditional on the cancellation, the A^* particle remains in the system for the duration τ_2, a positive random variable with cumulative law F_2.*

3. *Conditional on the successful completion of* (β)*, the* A^* *particle remains in the system for the duration* $\tau_1 \sim F_1$*.*

Let ξ_i *be the Bernnouli random variable that is* 1 *if the* i*th* A^* *succeeds in producing* B*, so that*

$$\tau = \xi\tau_1 + (1-\xi)\tau_2$$

is the lifetime of any A^* *particle. Let* τ_{ij} *be the* j*th realization of* τ_i*. Consider the solutions of*

$$X^N_{A^*}(t) = \frac{1}{N}\int_0^t 1(t-s < \tau_{R^N_0(s-)})dR^N_0(s)$$
$$X^N_B(t) = \frac{1}{N}\int_0^t \xi_{R^N_0(s-)}1(t-s > \tau_{1,R^N_0(s-)})dR^N_0(s).$$

If $x : \mathbb{R}^t \to \mathbb{R}^S$ *is the solution of the corresponding ODE system for which*

$$\lim_{N\to\infty}\sup_{s\le T}|X^N_{C_i}(s) - x_{C_i}(s)| = 0, \qquad i = 1, ..., S$$

almost surely, then

$$\lim_{N\to\infty}\sup_{s\le T}|X^N_B(s) - x_B(s)| = 0, \qquad \lim_{N\to\infty}\sup_{s\le T}|X^N_{A^*}(s) - x_{A^*}(s)| \quad \textit{almost surely}$$

where

$$x_B(t) = \int_0^t \lambda_\beta(x(s))pF_1(t-s)ds \tag{4.10}$$

and

$$x_{A^*}(t) = \int_0^t \lambda_\beta(x(s))\left\{p(1-F_1(t-s)) + (1-p)(1-F_2(t-s))\right\}ds. \tag{4.11}$$

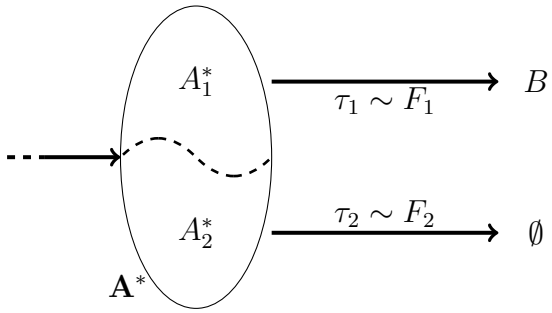

Figure 3: Pictorial image of proposition (4.2). $A^* \to B$ with delaytime τ_1 happens with probability p, and $A^* \to \emptyset$ with delaytime τ_2 happens with probability $1-p$. It is equivalent to M/G queue with two servers with respective holding times τ_1 and τ_2, in which the customers choose the first server by a fixed probability p.

Remark 4.3. *For an A^* particle that entered the system at time s, $t-s < \tau$ implies that the particle is still in the system at time t. Also, if $\xi 1(t-s > \tau_1) = 1$, then this means that the corresponding A^* particle has already produced B and has exited the system by time t.*

Remark 4.4. *Note that the case of* (4.5) *we described in the beginning of this section is a special case of the proposition above with τ_1 fixed,*

$$\xi \sim Ber(p), \qquad p = \exp(-r_2\tau_1)$$

and

$$\begin{aligned} F_1(x) &= 1_{x\geq\tau_1} \\ F_2(x) &= \frac{1-\exp(-r_2x)}{1-p}1_{x<\tau_1} + 1_{x\geq\tau_1}. \end{aligned} \tag{4.12}$$

Under the condition (4.12),

$$\begin{aligned} pF_1(t-s) &= p1_{(t-s)\geq\tau_1} \\ &= p1_{s\leq t-\tau_1} \end{aligned} \tag{4.13}$$

and

$$\begin{aligned}
&p(-F_1(t-s))1_{s<t} + (1-p)(1-F_2(t-s))1_{s<t} \\
&= p1_{t-s<\tau_1, s<t} + (1-p)\left(1 - \left(\frac{1-\exp(-r_2(t-s))}{1-p}1_{t-s<\tau_1} + 1_{t-s\geq\tau_1}\right)1_{s<t}\right) \\
&= \left(p + (1-p)\frac{\exp(-r_2(t-s)) - p}{1-p}\right)1_{t-s<\tau_1, s<t} \\
&= \exp(-r_2(t-s))1_{t-\tau_1<s<t}.
\end{aligned} \tag{4.14}$$

So

$$x_B = \int_0^{t-\tau_1} r_1 x_A(s)\exp(-r_2\tau_1)\ ds$$
$$x_{A^*} = \int_{t-\tau_1}^{t} r_1 x_A(s)\exp(-r_2(t-s))ds.$$

Remark 4.5. *It is worthwhile to note that when $p = 1$ and $F_1(t)$ is absolutely continuous with respect to t, the limit in proposition 4.2 is the same (via Leibnitz' rule) as the approximation of $E[X_B(t)]$ that Schlicht suggests:*

$$\frac{d}{dt}x_B(t) \cong \int_0^t \lambda_\beta(x_B(t-s))F_1(ds)$$

which in fact is an equality when λ is linear [65]. Schlict also considers a case in which multiple complexes create B with different delay time. We can in fact easily adopt our result to the same situation by modifying the proof slightly. We will omit the modified result, however, to avoid notational overflow.

As for the strategy of the proof of proposition 4.2, we will use the framework of "thinning" introduced in the introduction. Let us prelude the proof with a lemma concerning this concept.

Lemma 4.6. *Let $M_i : i \in \mathbb{Z}^+$ be a sequence of iid random variables with bounded moments. Also, let R_0^N be a positive, nonexplosive pure jump process with the following properties:*

1. *$R_0^N(s) - R_0^N(s-) \in \{1, 0\}$ for all s.*

2. *For every T, there exists a continuous, non decreasing deterministic process $x(\cdot) \geq 0$ such that*

$$\lim_{N\to\infty} \sup_{s\leq T} \left| \frac{R_0^N(s)}{N} - x(s) \right| = 0$$

   almost surely.

3. *For each s, $\lim_{N\to\infty} R_0^N(s) = \infty$.*

Then for any $T < \infty$,

$$\sup_{t\leq T} \left| \frac{1}{N} \int_0^t M_{R_0^N(s-)} dR_0^N(s) - \int_0^t E[M] dx(s) \right| \to 0. \tag{4.15}$$

almost surely.

Proof. First, I will show that

$$\left| \frac{1}{N} \int_0^t M_{R_0^N(s-)} dR_0^N(s) - \int_0^t E[M] dx(s) \right| \to 0$$

for a fixed t. To see this, just simply note that

$$\frac{1}{N} \int_0^t M_{R_0^N(s-)} dR_0^N(s) = \frac{1}{N} \sum_{i=0}^{R_0^N(t-)} M_i \tag{4.16}$$

$$= \frac{R_0^N(t-)}{N} \frac{1}{R_0^N(t-)} \sum_{i=0}^{R_0^N(t-)} M_i \tag{4.17}$$

By the continuity of x and the law of large numbers, the above expression clearly converges to $E[M]x(t)$.

We want to extend the argument above to the original claim in the proposition 4.3. For simplicity, put

$$Q_R^N(t) \stackrel{def}{=} \frac{1}{N}\int_0^t M_{R_0^N(s-)} dR_0^N(s), \qquad Q_x(t) \stackrel{def}{=} \int_0^t E[M]x(s)ds.$$

Let $0 = t_0 < t_1 < \cdots < t_m = T$ be a partition of $[0,T]$ for which

$$\max_{i=0,\ldots,m-1} \sup_{s,u\in[t_i,t_{i+1}]} |Q_x(s) - Q_x(u)| < \epsilon/3$$

We know that there exists $N_*(\cdot)$ which is finite almost surely such that if $N > N_*$, then

$$\max_{i=0,\ldots,m} \left|Q_R^N(t_i) - Q_x(t_i)\right| < \epsilon/3.$$

Fix this N, and $w \in \Omega$ for which $N_*(w) < \infty$. If $s \in [t_i, t_{i+1}]$, then since Q_N^R is increasing,

$$Q_x(t_i) - \epsilon/3 < Q_N^R(t_i) < Q_N^R(s) < Q_N^R(t_{i+1}) < Q_x(t_{i+1}) + \epsilon/3$$

And trivially $Q_x(s) \in (Q_x(t_i) - \epsilon/3, Q_x(t_{i+1}) + \epsilon/3)$ as well. Since

$$(Q_x(t_{i+1}) + \epsilon/3) - Q_x(t_i) - \epsilon/3 < \epsilon,$$

$$|Q_R^N(s) - Q_x(s)| < \epsilon.$$

Since s is arbitrary,

$$\sup_{t\le T} |Q_R^N(s) - Q_x(s)| < \epsilon$$

as desired. □

With the lemma above at our disposal, we would like to prove the result in proposition 4.2.

Proof. **of Prop 4.2.**

Let $\{\xi_i; i \in \mathbb{Z}_{\geq 0}\}$ be a sequence of Bernoulli random variables with parameter p, and let $\{U_{ij}; i \in \mathbb{Z}_{\geq 0}, j = 1, 2\}$ be a sequence of uniform random variables over the interval $[0, 1]$ such that $F_j^{-1}(U_{ij}) = \tau_{i1}$. We would like to split $X^N_{A^*}$, as follows. Let A_1^* be a category of A^* particle that successfully complete the reaction (β), and the 'species' A_2^* be the category that exits the system before the completion of (β). Then

$$R^N_{01}(t) = \int_0^t \xi_{R_0^N(s)} dR_0^N(s) R_{02}^N(t) \qquad = \int_0^t (1 - \xi_{R_0^N(s-)}) dR_0^N(s) \tag{4.18}$$

are counting processes that count the production of A_1^* and A_2^*, respectively. We can therefore write

$$R_0^N = R_{01}^N + R_{02}^N,$$

and define

$$X^N_{A_1^*}(t) \stackrel{def}{=} \frac{1}{N} \int_0^t 1(t - s > F_1^{-1}(U_{R^N_{01}(s-),1})) dR^N_{01}(s) \tag{4.19}$$

$$X^N_{A_2^*}(t) \stackrel{def}{=} \frac{1}{N} \int_0^t 1(t - s > F_2^{-1}(U_{R^N_{02}(s-),2})) dR^N_{02}(s) \tag{4.20}$$

This way we can also simplify X_B^N as

$$X_B^N = \frac{R^N_{01}(t)}{N} - X^N_{A_1^*}(t) \tag{4.21}$$

Since we know the limit of the first term of (4.21), it suffices to obtain the limit of (4.19) and (4.20). By themselves, further analysis is yet difficult. We will approach the problem by approximating (4.19) and (4.20). We will approximate (4.19) first. The approximation of (4.20) works in the exactly same way. Let

$$\pi = \{0 = p_0 < p_1 < p_2 < \cdots < p_n = 1\}$$

be a partition of $[0,1]$. Put $\Delta p_i = p_i - p_{i-1}$,

$$mesh(\pi) = \max_{i \le n} \{\Delta p_i\}.$$

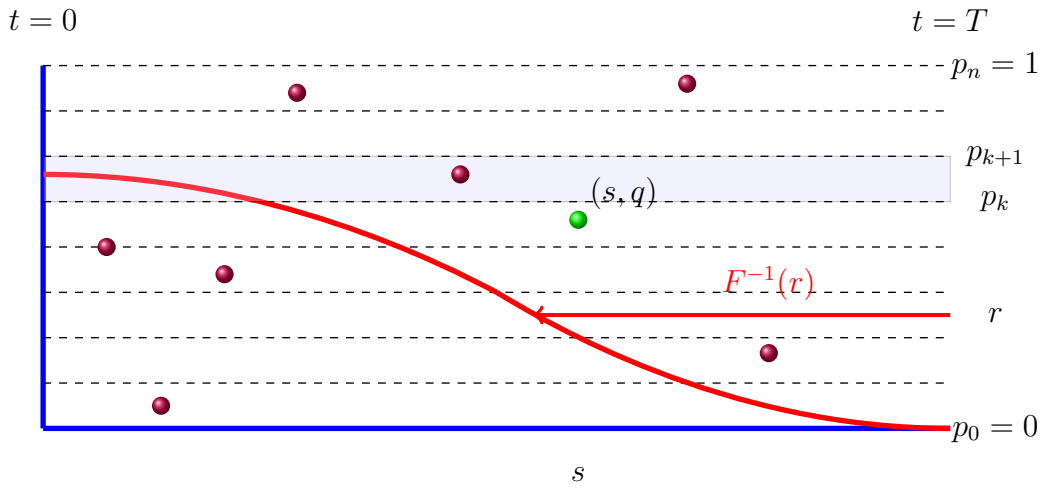

Figure 4: A Pictorial image of the setup in the in proof. Vertical axis measures the U (uniform random variable) value, and the horizontal axis measures the t (time) value. Lifetime of a particle born in the shaded region is $\nu \in [F^{-1}(p_k), F^{-1}(p_{k+1})]$. A particle with $(U,t) = (s,q)$ enters the system at time s, and will stay in the system for a duration of $F^{-1}(q)$. Particles above the curve are in the system by time T, and particles below are not.

We would like to note that

$$\left\{ w; \begin{array}{c} U(w) \in [p_{i-1}, p_i) \\ t - s < F_1^{-1}(U(w)) \end{array} \right\} \subset \left\{ w; \begin{array}{c} U(w) \in [p_{i-1}, p_i) \\ s > t - F_1^{-1}(p_i) \end{array} \right\} \tag{4.22}$$

$$\left\{ w; \begin{array}{c} U(w) \in [p_{i-1}, p_i) \\ s > t - F_1^{-1}(p_{i-1}) \end{array} \right\} \subset \left\{ w; \begin{array}{c} U(w) \in [p_{i-1}, p_i) \\ t - s < F_1^{-1}(U(w)) \end{array} \right\} \tag{4.23}$$

Based on (4.22) and (4.23), we can claim that

$$\begin{aligned} X^N_{A_1^* up}(t) &= \frac{1}{N} \sum_{i=1}^{n} \int_{(t - F_1^{-1}(p_i)) \wedge 0}^{t} 1(U_{R_0^N(s-),1} \in [p_{i-1}, p_i)) dR_{01}^N(s) \\ X^N_{A_1^* low}(t) &= \frac{1}{N} \sum_{i=1}^{n} \int_{(t - F_1^{-1}(p_{i-1})) \wedge 0}^{t} 1(U_{R_0^N(s-),1} \in [p_{i-1}, p_i)) dR_{01}^N(s) \end{aligned} \tag{4.24}$$

are respectively upper and lower bound for $X^N_{A_1^*}(t)$. Then by lemma 4.3 and theorem 4.1,

$$\lim_{N\to\infty}\sup_{s\le t}|X^N_{A_1^* up}(s)-x_{A_1^* up}(s)|=0 \qquad \lim_{N\to\infty}\sup_{s\le t}|X^N_{A_1^* low}(s)-x_{A_1^* low}(s)|=0$$

where

$$\begin{aligned} x_{A_1^* up}(t) &= \sum_{i=1}^{n}\int_{(t-F_1^{-1}(p_i))\wedge 0}^{t} p\lambda_\beta(x(s))\Delta p_i\ ds \\ x_{A_1^* low}(t) &= \sum_{i=1}^{n}\int_{(t-F_1^{-1}(p_{i-1}))\wedge 0}^{t} p\lambda_\beta(x(s))\Delta p_i\ ds \end{aligned} \tag{4.25}$$

We will rearrange these integrals. Let $F_1^{-1}(1)=\tau_1^{max}$. After tedious reindexing,

$$\begin{aligned} x_{A^*_{1,up}}(t) &= \sum_{i=1}^{n}\left(\int_{(t-F_1^{-1}(p_i))\wedge 0}^{t} p\lambda_\beta(x(s))\Delta p_i\ ds\right) \\ &= \sum_{\ell=1}^{n}\int_{(t-F_1^{-1}(p_\ell))\wedge 0}^{(t-F_1^{-1}(p_{\ell-1}))\wedge 0} p\lambda_\beta(x(s))(p-p_{\ell-1,1})ds \\ &\ge \int_{(t-\tau_1^{max})\wedge 0}^{t} p\lambda_\beta(x(s))p(1-F_1(t-s))p\ ds \\ &= \int_0^t p\lambda_\beta(x(s))(1-F_1(t-s))ds \end{aligned} \tag{4.26}$$

The last equality is from that $F_1(s)=1$ for $s>\tau_1^{max}$. The inequality comes from the fact that when

$$s\in[(t-F_1^{-1}(p_\ell))\wedge 0,(t-F_1^{-1}(p_{\ell-1}))\wedge 0]$$

then

$$1-p_{\ell-1}\ge 1-F_1(t-s)\ge 1-p_\ell. \tag{4.27}$$

Likewise,

$$x_{A^*_{1,low}}(t)=\sum_{i=1}^{n}\left(\int_{(t-F_1^{-1}(p_{i-1}))\wedge 0}^{t} p\lambda_\beta(x(s))\Delta p_i ds\right) \tag{4.28}$$

and

$$\begin{aligned}
&= \sum_{\ell=1}^{n-1} \int_{(t-F_1^{-1}(p_\ell))\wedge 0}^{(t-F_1^{-1}(p_{\ell-1}))\wedge 0} \lambda_\beta(x(s))p(1-p_\ell)ds \\
&\leq \int_{(t-F_1^{-1}(p_{n-1}))\wedge 0}^{t} \lambda_\beta(x(s))p(1-F_1(t-s))ds \\
&\leq \int_{(t-\tau_1^{max})\wedge 0}^{t} \lambda_\beta(x(s))p(1-F_1(t-s))ds \\
&= \int_0^t \lambda_\beta(x(s))p(1-F_1(t-s))ds
\end{aligned} \tag{4.29}$$

Note that

$$\begin{aligned}
x_{A^*_{1,up}}(t) - x_{A^*_{1,low}}(t) &= \sum_{\ell=1}^{n-1} \int_{(t-F_1^{-1}(p_\ell))\wedge 0}^{(t-F_1^{-1}(p_{\ell-1}))\wedge 0} p\lambda_\beta(x(s))\Delta p_\ell ds \\
&\qquad + \int_{(t-F_1^{-1}(p_n))\wedge 0}^{(t-F_1^{-1}(p_{n-1}))\wedge 0} p\lambda_\beta(x(s))(1-p_{n-1})ds \\
&= \sum_{\ell=1}^{n} \int_{(t-F_1^{-1}(p_\ell))\wedge 0}^{(t-F_1^{-1}(p_{\ell-1}))\wedge 0} p\lambda_\beta(x(s))\Delta p_\ell ds \\
&\leq mesh(\pi) \int_{t-\tau_1^{max}}^{t} p\lambda_\beta(x(s))ds \\
&\leq mesh(\pi) \int_0^t p\lambda_\beta(x(s))ds \\
\Rightarrow \sup_{r\leq t} |x_{A^*_{1,up}}(r) - x_{A^*_{1,low}}(r)| &\leq mesh(\pi) \int_0^t p\lambda_\beta(x(s))ds
\end{aligned} \tag{4.30}$$

Taking mesh π to 0, we see that

$$\lim_{N\to\infty} \sup_{s\leq t} |X^N_{A^*_1}(s) - x_{A^*_1}(s)| = 0$$

where

$$x_{A^*_1}(t) = \int_0^t \lambda_\beta(x(s))p(1-F_1(t-s))ds \tag{4.31}$$

Likewise arguing,

$$\lim_{N\to\infty} \sup_{s\leq t} |X^N_{A^*_2}(s) - x_{A^*_2}(s)| = 0$$

where

$$x_{A_2^*}(t) = \int_0^t \lambda_\beta(x(s))(1-p)(1-F_2(t-s))ds. \tag{4.32}$$

It is now clear that

$$x_{A^*} = x_{A_1^*} + x_{A_2^*} \quad \text{and} \quad x_B(t) = \int_0^t \lambda_\beta(x(s))p\ ds - x_{A_1^*}(t)$$

satisfy the desired property. □

The proposition 4.2 supports Schlict's result [65]. Nevertheless, we would also like to remind the reader that the ODE system does not agree with the system of the expectation of the corresponding stochastic system unless the CRN consists only of monomer reactions. In this light, the law of large numbers problem discussed in this chapter is completely different from that of [65]. Also, that equation (4.2) is entirely different from a delayed ODE (under the assumption of immediate consumption) provides more evidence that the stochasticity shall not be ignored even in large scale chemical reaction networks.

The work of Garcia on the S.I.R model [36] captures the very essence of the proof we presented in this chapter. Garcia used the Glivenko-Cantelli convergence of the Poisson random measure to analyze the S.I.R model with randomly distributed infectious period. In the language of Garcia and Kurtz, what we did is equivalent to taking a Glivenko-Cantelli convergence of a Poisson random measure on $[0,1] \times \mathbb{R}_{\geq 0}$ with mean measure $F_1 \times m$, where m is the Lebesgue measure. Put this way, the technique we presented in this chapter cannot be considered new.

Also, at this point, the technique in this chapter is yet not applicable to the analysis of the transcription example in the beginning, since it is difficult to analyze the asymptotic

behavior of X_{D^*}. The only Markov component of the system in the example is the counting process of (4.2), which is given by

$$X^N_{D^*_{tot}}(t) = \frac{1}{N} Y\left(\int_0^t N X^N_D(s) X^N_T(s) ds\right) \tag{4.33}$$

Note that when X^N_D is non-Markovian, it is difficult to show the convergence of $X^N_{D^*_{tot}}$ to an absolutely continuous solution by directly appealing to (4.1). We believe that we can use Garcia and Kurtz' method of Glivenko-Cantelli convergence to analyze more complex CRNs with delay, and this is an avenue for future work.

Chapter 5

Miscellaneous results and conclusion

In this final chapter we will provide three miscellaneous results. In the first section, we will discuss a condition which guarantees the non-explosivity of a class of stochastically modeled chemical reaction networks. The deficiency of a network is a property of the topology of a CRN and we will show that a deficiency zero CRN with a strongly connected reaction graph (which admits a product form stationary distribution [6]) does not blow up in finite time. In the second section, we will discuss MLMC [38] in further detail, and introduce a package for the automatic generation of MLMC code. Lastly, we will discuss a way to utilize MLMC for sensitivity analysis, which leads to the most efficient unbiased estimator for sensitivities available today.

5.1 Finite blowup time for mass action kinetics

In this subsection, we will discuss a condition under which a stochastically modeled CRN with certain topological properties does not explode in finite time. The importance of this subject is apparent in our construction of the stochastic model (1.8). As mentioned in the introduction, if we know the process is non-explosive, then we can construct the well defined process forward in time with any exact simulation method like Gillespie's method, and we can write out the likelihood of a path up to any bounded time. We will

base our non-explosivity condition on the following three aspects of the graph topology of CRN. Throughout the text, let us suppose a CRN $(\mathcal{S}, \mathcal{C}, \mathcal{R})$ with R number of reactions, d number of species, complexes $\{\nu_j\} \subset \mathbb{R}^d$, and reaction rate constants $\{r_k : k = 1, ..., R\} \subset \mathbb{R}_{\geq 0}$.

Definition 5.1. *A CRN is weakly reversible if the corresponding reaction graph is strongly connected.*

Definition 5.2. *The deficiency of a CRN is $\delta = |\mathcal{C}| - \ell - s$, where $|\mathcal{C}|$ is the number of complexes(vertices), ℓ is the number of linkage classes(the connected components), and s is the number of species(the dimension of the state space).*

Definition 5.3. *For $x, c \in \mathbb{R}^d_{\geq 0}$, let us denote $c^x \stackrel{def}{=} \prod_{i=1}^d c_i^{x_i}$, where we interpret $0^0 = 1$. A state $c \in \mathbb{R}^d_{\geq 0}$ of a CRN is complex balanced if for each vertex ν,*

$$\sum_{\nu_k \to \nu} r_k c^{\nu_k} = \sum_{\nu \to \nu_j} r_j c^{\nu_j}.$$

where summations are over all reactions that produces ν and over all reactions that ν produces, respectively. It has been shown by [6] that, weakly reversible, deficiency zero CRN admitting a complex balanced state has a product-form stationary distribution. However, the existence of a stationary distribution usually does not guarantee non-explosivity. For example, consider the following example of a random walk on $\mathbb{Z}_{\geq 0}$ with transition rates

$$q_{x,x+1} = \lambda 2^x, \qquad q_{x,x-1} = \mu 2^x$$

where $1 < \frac{\lambda}{\mu} < 2$. This process is transient, and it is easily observed that

$$\pi(x) = \frac{1}{2^x} \left(\frac{\lambda}{\mu} \right)^x$$

is a stationary distribution of the process. However, the process with invariant distribution is non-explosive if and only if the process is positive recurrent. So the process is explosive. We will show that a weakly reversible chemical reaction network admitting a complex balanced state is non-explosive. We will base our argument on [6] and Reuter's theorem, which we will state below:

Theorem 5.1. *(Reuter's theorem [15]) Let Q be the infinitesimal generator of the Markov process over the state space S. The process explodes if and only if there exists an uniformly bounded, nonzero $z \in \mathbb{R}^{|S|}$ such that*

$$\sum_{y \in S} q_{xy} z_y = z_x$$

for all $x \in S$.

Theorem 5.2. *(Anderson, Craciun and Kurtz [6]) Consider an deficiency zero CRN. Suppose that the intensity function for the kth reaction from the complex ν_k at the state $x \in \mathcal{S} = \mathbb{Z}^d$ is given by*

$$\lambda_k(x) = r_k \frac{\theta(x)}{\theta(x - \nu_k)} \prod_{\ell=1}^{d} 1_{x_\ell > \nu_{k\ell}}$$

where

$$\theta(x) = \prod_{i=1}^{d} \prod_{j=1}^{x_i} \theta_i(j)$$

and each θ_i is any positive valued function that vanishes outside the positive quadrant. Suppose further that the associated mass-action based deterministic system has an equilibrium state c. Then the stationary distribution of the stochastic model (1.6) *of CRN is given by*

$$\pi(x) = M \frac{1}{\theta(x)} \prod_{i=1}^{d} c_i^{x_i}.$$

where M is a normalizing constant, so long as $\pi(x)$ is summable.

It should be noted, as commented in [6], that the process admits this stationary distribution only if $\pi(x)$ is summable. For instance, for Michealis-Menten kinetics, one might chose parameters so that the product-form stationary distribution as given by the theorem above does not exist. For a more formalized condition for the appropriate parameters for the kinetics, we refer the reader to [6]. Now, with the following lemma, we can connect the above two theorems to make the desired conclusion about non-explosivity of this class of CRNs.

Lemma 5.3. *Consider a Markov process on a state space S with generator Q and a stationary distribution π. If*

$$\sum_y \sum_x \pi(x) q_{xy}$$

is absolutely summable, then the process does not explode.

Proof. Suppose that the network does explode, but

$$\sum_y \sum_x \pi(x) q_{xy}$$

is absolutely summable. By Reuter's theorem, there exists a uniformly bounded, nonzero vector $z \in \mathbb{Z}_{\geq 0}^{|S|}$ such that, for all x in the state space $\mathcal{S}$,

$$\sum_y q_{xy} z_y = z_x.$$

Without loss of generality, let

$$\|z\| < 1.$$

Then

$$\sum_y \sum_x |\pi(x) q_{xy} z_y| \leq \sum_y \sum_x \pi(x) |q_{xy}|$$

Hence by assumption, $\sum_y \sum_x \pi(x) q_{xy} z_y$ is absolutely summable. Thus by Fubini's theorem,

$$\sum_y \sum_x \pi(x) q_{xy} z_y = \sum_x \sum_y \pi(x) q_{xy} z_y$$

and in particular,

$$\sum_y \sum_x \pi(x) q_{xy} z_y = \sum_y z_y \sum_x \pi(x) q_{xy} = 0.$$

On the other hand,

$$\sum_x \sum_y \pi(x) q_{xy} z_y = \sum_x \pi(x) \sum_y q_{xy} z_y = \sum_x \pi_x z_x$$

and we can conclude that $\sum_x \pi_x z_x = 0$. Because $\pi(x) \geq 0$, we must have $z = 0$ necessarily. This is a contradiction. □

We therefore have the following corollary.

Corollary 5.1. *If a CRN is weakly reversible, deficiency zero system admitting a complex balanced equilibrium under the ODE deterministic model, it is not explosive as long as the kinetics model is "appropriate" as set forth in [6] and* $\frac{\theta(x)}{\theta(x-\nu_k)}$ *is bounded.*

Proof. Every q_{xy} in the generator corresponds to a $\lambda_k(x)$ in the theorem (5.2). Now simply note that

$$\lambda_k(x)\pi(x) = \frac{M r_k}{\theta(x-\nu_k)} \prod c_i^{x_i}.$$

Since $\frac{\theta(x)}{\theta(x-\nu_k)}$ is bounded, $\lambda_k(x)\pi(x) < K\pi(x)$ for some constant K, and $\sum \lambda_k(x)\pi(x)$ is absolutely summable. We can apply the lemma 5.3. □

The CRN with mass action kinetics satisfies the condition set forth in the corollary. Indeed, it sounds plausible that we should be able to remove the "deficiency zero" condition in the corollary above. This is a possible avenue for next research.

5.2 Implementation of MLMC

While the MLMC scheme we introduced in (3.1.2) is fast and unbiased, there are some technical issues to be confronted in its implementation. The most important unresolved issue of all is the number of levels to be used for the algorithm. In [8], Anderson implemented the MLMC for the system of translation and dimerization

$$\begin{aligned} G &\overset{25}{\to} G + M, \\ M &\overset{1000}{\to} M + P, \\ P + P &\overset{0.001}{\to} D, \\ M &\overset{0.1}{\to} \emptyset, \\ P &\overset{1}{\to} \emptyset. \end{aligned} \tag{5.1}$$

with different number of levels.

Nothing can be inferred about the number of sample paths to be allocated at each level without actually simulating the paths and estimating the variance. To counter this problem we conduct pre-computations to obtain heuristic information about the variance of each level. More precisely, we take the following steps:

1. Prompt the user for the number of levels, stepsizes h_k, and the desired size of variance σ.

2. Precompute the empirical variance $\hat{\sigma}_k$ at each level, and estimate the computational cost at each level.

3. Minimize the CPU time under the restraint

$$\sigma \geq \sum \frac{\hat{\sigma}_k}{n_k} \tag{5.2}$$

by controlling n_k, which is the number of paths to be allocated for the level k. Note that $\frac{\hat{\sigma}_k}{n_k}$ is an estimator for the variance of the average of n_k samples of the coupled pair at the level k.

We created a package that produces a Matlab code that implements the MLMC simulation for any CRN. The figure (5) summarizes the runtime of the MLMC for the approximation of $X_D(1)$ in the example 5.1 with the initial condition $X_G(0) = 1$ and $X_M(0) = X_P(0) = X_D(0) = 0$.

stepsize and # levels	$\hat{X}_D$	CPU time (sec)	# random numbers generated
$h = 3^\ell$, $\ell = 3 \sim 6$	3,714.4 $\pm$ 1.0	3,503.3	1.694×10^9
$h = 3^\ell$, $\ell = 2 \sim 5$	3,714.3 $\pm$ 1.0	2,300.1	9.797×10^8
$h = 3^\ell$, $\ell = 3 \sim 5$	3,713.6 $\pm$ 1.0	4,132.6	1.591×10^9
$h = 3^\ell$, $\ell = 2 \sim 3$	3,714.6 $\pm$ 1.0	9,714.8	1.635×10^9

Figure 5: Runtime with different number of levels

There are many issues in terms of implementation. For example, notice that the number of levels and the range of ℓ greatly affects the runtime and the number of random variables generated. Also, the number of precomputations to be done to solve the linear program (5.2) is chosen arbitrary. These are all avenues for future research towards a better implementation of MLMC.

5.3 Sensitivity analysis using Girsanov transformation and MLMC

In this section, we will discuss a way to apply the MLMC for sensitivity analysis using the Girsanov transformation. Amongst all the known methods for sensitivity analysis, the Girsanov method is the only method that computes an unbiased estimator for sensitivity analysis. The method was originally introduced by Plyasunov and Arkin [13]. However, for long simulated paths, the computational cost of the method was high in comparison to finite difference methods [4] [19] due to high variance of the estimator. In this section we aim to skirt the problem by applying the Girsanov method in combination with the MLMC, which in essence is a variance reduction method.

Let $(\mathcal{C}, \mathcal{S}, \mathcal{R})$ be a CRN with R reactions, d species, and reaction vectors ζ_k. Also suppose that $\{\lambda_k^\theta : J[0,\infty)^d \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0}; \theta \in \mathbb{R}_{\geq 0} \quad k = 1, ..., R\}$ is a family of positive continuous functions that are differentiable with respect to θ, and that the process X_θ as defined in (1.8) under a probability measure P with reaction intensities $Z_k = \lambda_k^\theta$ is non-explosive. If f is a continuous function, we would like to compute $\frac{d}{d\theta}E[f(X_\theta(t))]$. In order to apply MLMC to this problem, we need a sequence of processes that approximate X_θ, and also couple the consecutive pairs of the approximate processes tightly. If V_i are the approximating processes, we will compute the target as

$$\frac{d}{d\theta}E^P[f(X_\theta(t))] = \left(\sum_{i=0}^{M-1} \frac{d}{d\theta}E^P[f(V_{i+1}(t)) - f(V_i(t))]\right) + \frac{d}{d\theta}E^P[f(V_0(t))]$$

where $V_M \stackrel{def}{=} X$.

For now, let us denote $V \stackrel{def}{=} V_1$, and focus on the first level. The rest of the levels

works in exactly same way. Suppose that the counting processes for V have the intensity

$$\{\tilde{\lambda}_k^\theta : J[0,\infty)^d \times \mathbb{R}_{\geq 0} \to \mathbb{R}_{\geq 0} : \theta \in \mathbb{R}_{\geq 0} \quad k = 1, ..., R\}.$$

We couple X and V using the split coupling(3.4) with $\lambda_k = \lambda_k^\theta$ and $\tilde{\lambda}_k = \tilde{\lambda}_k^\theta$.

More precisely, consider the process $W_\theta = (X_\theta, V_\theta)$ in $\mathbb{R}^{2d}_{\geq 0}$ and define elements in $\mathbb{R}^{2d}$ given by

$$\zeta_{1k} = [\zeta_k, O], \qquad \zeta_{2k} = [O, \zeta_k] \qquad \zeta_{3k} = [\zeta_k, \zeta_k]$$

Then with the notation

$$r_{ik}(\lambda^\theta, \tilde{\lambda}^\theta, X_\theta, Z_\theta, s) = g_{ik}^\theta(W_\theta, s),$$

the process W_θ with the split coupling is given by

$$W_\theta(t) = W_\theta(0) + \sum_{k=1}^{R} \sum_{i=1}^{3} Y_{ik} \left(\int_0^t g_{ik}^\theta(W_\theta, s) ds \right) \zeta_{ik}. \tag{5.3}$$

Next, let $q(W(t)) \stackrel{def}{=} f(X(t)) - f(V(t))$. Recall from the introduction that we may write

$$E^P[q(W(t))] = E^Q[q(W(t))L(\theta, t)]$$

where Q is the measure under which the counting processes Y_{ik} are independent unit rate Poisson processes, and $L(t)dQ = dP$ with L as given in (1.11). Under the Leibnitz condition, we can commute the expectation with the derivative, and $\frac{d}{d\theta} E^P[q(W(t))]$ can be computed as

$$\begin{aligned}\frac{d}{d\theta}E^Q[q(W(t))L(\theta,t)] &= E^Q[q(W(t))\frac{d}{d\theta}L(\theta,t)] \\ &= E^Q[q(W(t))\frac{\frac{d}{d\theta}L(\theta,t)}{L(\theta,t)}L(\theta,t)] \\ &= E^Q[q(W(t))\left(\frac{d}{d\theta}\log(L(\theta,t))\right)L(\theta,t)] \\ &= E^P[q(W(t))\frac{d}{d\theta}\log(L(\theta,t))]\end{aligned} \tag{5.4}$$

We remind ourselves that the Leibnitz condition requires the followings:

1. $E^P[q(W_\theta(t))]$ exists
2. $\frac{d}{d\theta}\log(L(\theta,w,t))$ exists for almost sure w and t.
3. There exists a random variable $|q(W_\theta)\frac{d}{d\theta}\log(L(\theta,w,t))| < G$ with P-finite expectation.

The Leibnitz won't be true in general for our case, since for $\lambda, \tilde{\lambda} \in C^\infty$,$\lambda(x) \wedge \tilde{\lambda}(x)$ is not necessarily in C^∞ with respect to θ.

Now, if $w \in J[0,\infty)^{2d}$, let $N(w,t)-1$ be the total number of jumps of w in the interval $[0,t)$. Then the likelihood $L(\theta,w,t)$ of a path w up to time t can be simplified to

$$\begin{aligned}L(\theta,w,t) &= exp\left(-\int_0^t \sum_{k,i} g_{ik}^\theta(w,s)ds\right)\prod_{j=0}^{N(w,t)-1} g_{win_j}^\theta(W,s_{j-1}) \\ \log L(\theta,w,t) &= -\int_0^t \sum_{k,i} g_{ik}^\theta(w,s)ds + \sum_{j=0}^{N(w,t)-1} \log g_{win_j}^\theta(w,s_{j-1})\end{aligned} \tag{5.5}$$

where win_j is the index of the jth reaction of w and s_j is the time of the jth reaction with a convention that $s_0 = 0, \quad s_{N(w,t)} = t$.

We can therefore write

$$\frac{d}{d\theta}\log(L(\theta, W_\theta, t)) = \sum_{i,k} -\frac{d}{d\theta}\int_0^t g_{ik}^\theta(W_\theta, s) + \sum_j \frac{\frac{d}{d\theta}g_{win_j}(W_\theta, j)}{g_{win_j}(W_\theta, s_j)} \tag{5.6}$$

5.3.1 A special case

If λ and $\tilde{\lambda}$ are both proportional to θ, then by simple computation we see

$$\frac{d}{d\theta}\log(L(\theta, w, t)) = \frac{1}{\theta}\sum_{i\in\{1,2,3\}, k\in J(\theta)} \tilde{Y}_{ik}\left(\int_0^t g_{ik}^\theta(W_\theta, s)ds\right)(w) \tag{5.7}$$

where $\tilde{Y}$ is a compensated unit Poisson process and $J(k)$ is the set of reactions for which the rate λ depends on θ. To be more general, if

$$\lambda_{\cdot k}^\theta(x, s) = \eta_{\cdot k}(\theta)\gamma_k(x, s) \tag{5.8}$$

and η is differentiable with respect to θ, then

$$\frac{d}{d\theta}\log(L(\theta, w, t)) = \sum_{i\in\{1,2,3\}, k\in J(\theta)} \frac{\frac{d}{d\theta}\eta_{ik}(\theta)}{\eta_{ik}(\theta)}\tilde{Y}_{ik}\left(\int_0^t g_{ik}^\theta(w_\theta, s)ds\right)(w). \tag{5.9}$$

Note that when (5.8) holds, then we do not need to worry about the second part of the Leibnitz condition condition.

We can in fact do even better. Note if A and B are random variables, the variance of $A - \alpha B$ is minimized with $\alpha = \frac{Cov(A,B)}{Var(B)}$. We may take advantage of the fact that $M(t) \stackrel{def}{=} \frac{d}{d\theta}\log(L(t, w))$ is a martingale, and correct the coarsest term by $-\alpha M(t)$. In the next section, we will show a computational result comparing the direct Girsanov method and the MLMC Girsanov method.

5.3.2 Numerical Example

We consider an example of central dogma with the following parameters;

$$G \stackrel{2}{\to} G + M, \quad M \stackrel{10}{\to} M + P, \quad M \stackrel{\theta}{\to} \emptyset, \quad P \stackrel{1}{\to} \emptyset$$

where G, M ,P respectively represent DNA particle, mRNA particle, and peptide particle. Under mass action kinetics model, the rates of reactions λ_k in this CRN are linear. Also, by using the intensity property in the introduction,

$$E\left[Y\left(\int_0^t Z(s)ds\right)\right] = E\left[\int_0^t Z(s)ds\right]$$

and we can solve $E[X_M(t)]$ and $E[X_P(t)]$ as a solution of an ODE system. Solving the system we get

$$EX_P(30,\theta) \cong 79.94\Big|_{\theta=1/4} \qquad J(\theta) = \frac{d}{d\theta}EX_P(30,\theta) \cong -318.07\Big|_{\theta=1/4}.$$

We measured the CPU time required to estimate the value $J(\theta)$ with variance less than 10 using the MLMC-Girsanov method. We summarized the result in the figure 6. Note the significant gain in runtime.

stepsize and # levels	$\hat{J(\theta)}$ (95% interval)	CPU time	# random numbers generated
$h = 3^\ell$, $\ell = 1 \sim 2$	-315.69 $\pm$ 6.06	136.70 sec	2.7 $\times 10^8$
$h = 3^\ell$, $\ell = 1 \sim 3$	-317.87$\pm$ 5.94	248.85 sec	2.9 $\times 10^8$
$h = 4^\ell$, $\ell = 1 \sim 4$	-319.62 $\pm$ 5.74	332.30 sec	4.6 $\times 10^8$
Direct Girsanov	-321.89 $\pm$ 6.16	5394.6 sec	2.8 $\times 10^{10}$

Figure 6: Comparison of the Girsanov-MLMC method and the direct Girsanov method, both with $+\alpha M(t)$ correction

In terms of runtime, the common finite difference method (CFD) in combination with split coupling [4] eclipses our result above. However, the estimator from the CFD method is biased, whereas that of the Girsanov method is unbiased. This example provides still another motivation to further study the MLMC method.

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