

# A Different Look at the Chemical Master Equation

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## Abstract

The road back from CME to SSA. Explicitly reveal the approximations made when SSA and tau-leaping are used to sample the distribution produced by CME.

## 1 Introduction

Biological systems are frequently modeled as networks of interacting chemical kinetics. In systems formed by living cells, these reactions evolve stochastically and the stochastic effects typically become important when there are a small number of molecules of one or more species involved in a reaction [9]. The stochastic approach treats the time-evolution as a kind of randomness that is inherent to all biochemical systems.

Gillespie proposed the stochastic simulation algorithm (SSA) that is the stochastic process defined by the CME by using a Monte Carlo method [5]. Despite representing exact realizations of the CME, the amount of computational time of the SSA caused by executing every reaction is always an issue in real systems. This drawback motivates attempts to improve the computational efficiency with approximate algorithms.

One such approximate acceleration procedure is the “tau-leaping method” [6], in which some chosen time  $\tau$  that encompasses more than one reactions. Therefore, many reactions can be simulated at each step with a pre-selected time  $\tau$ . The tau-leaping method requires that the selected  $\tau$  must be small enough to satisfy the “leap condition”: The expected state change induced by the leap must be sufficiently small that propensity functions remain nearly constant during the time step  $\tau$ . The number of times that each reaction fires in time  $\tau$  can be approximated by a *Poisson random variable*.

While the tau-leaping method represents the efficiency for the one time scale systems, it gives unstable results with the larger stepsize solution especially for the stiff systems. Stiffness generally manifests when there are well-separated “fast” and “slow” time scales present, and the “fast modes” are stable. The implicit tau-leaping method improves the

numerical stability of the explicit tau-leaping method in the stiff systems [10]. With the improved step size selection strategies [6, 8], there exist several other tau-leaping attempts to accelerate the efficiency of the exact SSA through approximations [3, 2, 8, 11]. Algorithmic improvements to Gillespie’s SSA were proposed by Gibson and Bruck [4].

The paper is organized as follows. Section 2 describes the SSA with existing approximation algorithms.

## 2 Simulation of Stochastic Chemical Kinetics

Consider a chemical system in a constant volume container. The system is well-stirred and in thermal equilibrium at some constant temperature. There are  $N$  different chemical species  $S^1, \dots, S^N$ . Let  $X^i(t)$  denote the number of molecules of species  $S_i$  at time  $t$ . The state vector  $x(t) = [X^1(t), \dots, X^N(t)]$  defines the numbers of molecules of each species present at time  $t$ .

The chemical network consists of  $M$  reaction channels  $R_1, \dots, R_M$ . Each individual reaction destroys a number of molecules of reactant species, and produces a number of molecules of the products. Let  $\nu_j^i$  be the change in the number of  $S^i$  molecules caused by a single reaction  $R_j$ . The state change vector  $\nu_j = [\nu_j^1, \dots, \nu_j^N]$  describes the change in the entire state following  $R_j$ .

A propensity function  $a_j(x)$  is associated with each reaction channel  $R_j$ . The probability that one  $R_j$  reaction will occur in the next infinitesimal time interval  $[t, t + dt)$  is  $a_j(x(t)) \cdot dt$ .

The purpose of a stochastic chemical simulation is to trace the time evolution of the system state  $x(t)$  given that at the initial time  $\bar{t}$  the system is in the initial state  $x(\bar{t}) = \bar{x}$ .

### 2.1 Exact Stochastic Simulation Algorithm

The stochastic simulation algorithm (SSA) simulates every reaction event in succession. Let  $X(t) = x$ . Gillespie [5] shows that the probability that no reaction fires within the time interval  $[t, t + \tau)$  is

$$\mathcal{P}(\tau, \phi | x, t) = e^{-a_0(x)\tau}, \quad \text{where} \quad a_0(x) \equiv \sum_{j=1}^M a_j(x). \quad (1a)$$

The probability that the next reaction in the system will occur in the infinitesimal time interval  $[t + \tau, t + \tau + d\tau)$ , and will be an  $R_j$  reaction, is  $\mathcal{P}(\tau, R_j | x, t) d\tau$ . The corresponding reaction probability density function is

$$\mathcal{P}(\tau, R_j | x, t) = a_j(x) e^{-a_0(x)\tau}. \quad (1b)$$

The SSA algorithm uses a Monte Carlo approach to generate  $\tau$  and  $j$ . On each step of the SSA, two random numbers  $r_1$  and  $r_2$  are drawn from the uniform  $\mathcal{U}(0, 1)$  distribution. The next reaction occurs at time  $t + \tau$ , where

$$\tau = \frac{1}{a_0(\mathbf{x})} \ln \left( \frac{1}{r_1} \right).$$

The index of the next reaction  $R_j$  is given by the smallest integer  $j$  satisfying

$$\sum_{\ell=1}^j a_{\ell}(x) > r_2 a_0(x).$$

After  $\tau$  and  $j$  are obtained, the system states are updated by  $X(t + \tau) := x + \nu_j$ , and the time is updated by  $t := t + \tau$ . This simulation iteration proceeds until the time  $t$  reaches the final time.

It is clear from the stochastic nature of the system that a different simulation of the same cell over the same interval (using a different seed for the pseudo-random number generator) will involve a different number of reactions, and therefore will require a different compute time.

## 2.2 Tau-Leaping Method

The SSA is an exact stochastic method for chemical reactions, however, it is very slow for many real systems because the SSA simulates one reaction at a time. One approximate simulation approach is the tau-leaping method [6]. The basic idea is to simulate all reactions that occur during the time interval  $[t, t + \tau)$ . The interval length  $\tau$  is pre-selected, and must be small enough to satisfy the leap condition. The leap condition states that the expected state change induced by the leap is sufficiently small that the propensity functions remain nearly constant during the interval  $[t, t + \tau)$ .

Let  $X(t) = x$ , and let  $K_j(\tau; x, t)$  be the number of times the reaction channel  $R_j$  fires in the time interval  $[t, t + \tau)$ . After the leap the state is updated by

$$X(t + \tau) = x + \sum_{j=1}^M \nu_j K_j(\tau; x, t). \quad (2)$$

It has been shown [6] that if the leap condition is satisfied the channels  $j = 1, \dots, M$  fire independently of one another. The number of reactions in each channel is a Poisson random variable with mean and variance  $a_j(x)\tau$

$$K_j(\tau; x, t) \in \text{Poisson}(a_j(x)\tau), \quad j = 1, \dots, M.$$

A Poisson random variable counts the number of events that will occur during a time interval of length  $\tau$ , given that the probability of an event occurring in any future infinitesimal time  $dt$  has a constant value  $a_j(x) dt$ . The probability of having exactly  $k$  firings of the reaction channel  $R_j$  during the interval  $[t, t + \tau)$  is

$$\mathcal{P}(K_j(\tau; x, t) = k) = e^{-a_j(x)\tau} \frac{(a_j(x)\tau)^k}{k!}. \quad (3)$$

## 2.3 The Chemical Master Equation

Consider now the state space of the chemical system  $X(t) \in \mathbb{N}^N$ , and denote by  $\mathcal{P}(x, t) = \mathcal{P}(X(t) = x)$  the probability that the system state is  $x$  at time  $t$ . The *Chemical Master*

Equation (CME) [1, 7] describes the time evolution equation of the probability function of the system's state

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = \sum_{r=1}^M a_r(x - \nu_r) \mathcal{P}(x - \nu_r, t) - a_0(x) \mathcal{P}(x, t) \quad (4)$$

The solution of (4) gives complete information about the possible evolution of the system. However a complete solution is difficult to obtain due to the large dimension of the state space.

A less ambitious goal is to find the evolution probabilities around a given state. Consider that our system is in state  $\bar{x}$  at  $\bar{t}$ , i.e.,

$$\mathcal{P}(x, \bar{t}) = \begin{cases} 1 & \text{if } x = \bar{x}, \\ 0 & \text{otherwise.} \end{cases}$$

We are interested to find the evolution of probabilities over small evolution interval  $[\bar{t}, \bar{t} + \tau]$ . For a small leap length  $\tau$  the support of the probability function will remain near  $\bar{x}$ ,  $\mathcal{P}(x, \bar{t}) \neq 0$  only for  $x \approx \bar{x}$ . The propensities for all states  $x$  of nonzero probability are not much different than the propensity values at  $\bar{x}$ . This observation justifies the following approximation of the CME (4)

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = \sum_{r=1}^M a_r(\bar{x}) \mathcal{P}(x - \nu_r, t) - a_0(\bar{x}) \mathcal{P}(x, t) \quad (5)$$

where the arguments of all propensity functions have been changed from  $x$  or  $x - \nu_j$  to  $\bar{x}$ . Note that the approximate CME (5) maintains the sum of probabilities equal to one for any  $\bar{x}$ . This can be seen immediately by summing after  $x$ .

### 3 SSA as a Markov Process

Next, we assume that the probabilities change only slightly during the short time interval  $[\bar{t}, \bar{t} + \tau]$  under consideration. We further approximate the equation (5) by holding the probabilities  $\mathcal{P}(x - \nu_r, t)$  at their  $\bar{t}$  value  $\mathcal{P}(x - \nu_r, \bar{t})$ . The resulting approximate CME reads:

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = \sum_{r=1}^M a_r(\bar{x}) \mathcal{P}(x - \nu_r, \bar{t}) - a_0(\bar{x}) \mathcal{P}(x, t). \quad (6)$$

Rearranging the terms in (6)

$$\frac{\partial}{\partial t} (e^{a_0(\bar{x})t} \mathcal{P}(x, t)) = e^{a_0(\bar{x})t} \sum_{r=1}^M a_r(\bar{x}) \mathcal{P}(x - \nu_r, \bar{t}),$$

integrating analytically on  $[\bar{t}, \bar{t} + \tau]$

$$\begin{aligned} e^{a_0(\bar{x})(\bar{t}+\tau)} \mathcal{P}(x, \bar{t} + \tau) &= e^{a_0(\bar{x})\bar{t}} \mathcal{P}(x, \bar{t}) \\ &+ \frac{e^{a_0(\bar{x})(\bar{t}+\tau)} - e^{a_0(\bar{x})\bar{t}}}{a_0(\bar{x})} \sum_{r=1}^M a_r(\bar{x}) \mathcal{P}(x - \nu_r, \bar{t}), \end{aligned}$$

and multiplying with  $\exp(-a_0(\bar{x})(\bar{t} + \tau))$  leads to the following solution:

$$\mathcal{P}(x, \bar{t} + \tau) = e^{-a_0(\bar{x})\tau} \mathcal{P}(x, \bar{t}) + \frac{1 - e^{-a_0(\bar{x})\tau}}{a_0(\bar{x})} \sum_{r=1}^M a_r(\bar{x}) \mathcal{P}(x - \nu_r, \bar{t}) . \quad (7)$$

We now assess the transition probabilities during the interval  $[\bar{t}, \bar{t} + \tau]$  as described by the approximate CME solution (7).

1. If  $x = \bar{x}$  then  $\mathcal{P}(x, \bar{t}) = 1$ ,  $\mathcal{P}(x - \nu_r, \bar{t}) = 0$  for  $r = 1, \dots, M$ , and

$$\mathcal{P}(\bar{x}, \bar{t} + \tau) = e^{-a_0(\bar{x})\tau} . \quad (8a)$$

2. If  $x = \bar{x} + \nu_r$  for some  $r$  then  $\mathcal{P}(x, \bar{t}) = 0$ ,  $\mathcal{P}(x - \nu_r, \bar{t}) = 1$ , and  $\mathcal{P}(x - \nu_\ell, \bar{t}) = 0$  for  $\ell \neq r$ . We have that

$$\mathcal{P}(\bar{x} + \nu_r, \bar{t} + \tau) = \frac{1 - e^{-a_0(\bar{x})\tau}}{a_0(\bar{x})} a_r(\bar{x}) , \quad r = 1, \dots, M . \quad (8b)$$

3. For all other values of  $x$  it holds that  $\mathcal{P}(x, \bar{t}) = \mathcal{P}(x - \nu_r, \bar{t}) = 0$  and therefore

$$\mathcal{P}(x, \bar{t} + \tau) = 0 . \quad (8c)$$

The probabilities (8) account for a single reaction in the interval  $[\bar{t}, \bar{t} + \tau]$ , and therefore they correspond to the SSA scenario.

The probability (8a) that the system remains in the state  $\bar{x}$  is equal to the SSA probability (1a) that no reaction occurs during the interval  $[\bar{t}, \bar{t} + \tau]$ .

Equation (8b) gives the probability of the transition  $\bar{x} \rightarrow \bar{x} + \nu_r$  during the interval  $[\bar{t}, \bar{t} + \tau]$ . Integrating the SSA reaction probability density function (1b) over  $[\bar{t}, \bar{t} + \tau]$  gives the probability that one reaction  $R_r$  happens during this interval

$$\int_{\bar{t}}^{\bar{t}+\tau} \mathcal{P}(t, r | \bar{x}, \bar{t}) dt = a_r(\bar{x}) \int_{\bar{t}}^{\bar{t}+\tau} e^{-a_0(\bar{x})(t-\bar{t})} dt = \frac{1 - e^{-a_0(\bar{x})\tau}}{a_0(\bar{x})} a_r(\bar{x}) ,$$

and is exactly the transition probability (8b).

**Comment.** The inverse route of determining the SSA transition probabilities from the CME does not explicitly account for the time  $\tau$  to the next reaction. The CME allows for the possibility that the next reaction happens after  $[\bar{t}, \bar{t} + \tau)$  by including a nonzero probability (8a) of the state not changing.

**Comment.** It is tempting to conclude that, since the exact SSA algorithm samples (5), it provides an order one numerical approximation of the CME (4). However this cannot be claimed since one cannot take the limit  $\tau \rightarrow 0$  (the individual reactions happen at discrete times).

**Comment.** An alternative reasoning to derive a continuous counterpart of the exact simulation algorithm (1) is as follows. Consider a time interval  $[\bar{t}, \bar{t} + \tau]$  short enough such that at most one reaction can take place. The probability that exactly one reaction  $R_r$  happens during  $[\bar{t}, \bar{t} + \tau]$  is the product of probabilities of the following independent events:

- no reaction happens during  $[\bar{t}, t)$ ,
- reaction  $R_r$  fires during the infinitesimal interval  $[t, t + dt)$ , and
- no reaction fires during  $[t + dt, \bar{t} + \tau]$ .

Recalling the transition probabilities (8), the probability that exactly one  $R_r$  fires during  $[\bar{t}, \bar{t} + \tau]$  is

$$\begin{aligned}
\mathcal{P}(\bar{x} + \nu_r, \bar{t} + \tau) &= \int_{\bar{t}}^{\bar{t} + \tau} e^{-a_0(\bar{x})(t - \bar{t})} a_r(\bar{x}) e^{-a_0(\bar{x} + \nu_r)(\bar{t} + \tau - t)} dt \\
&= a_r(\bar{x}) \int_0^\tau e^{-a_0(\bar{x})\theta} e^{-a_0(\bar{x} + \nu_r)(\tau - \theta)} d\theta \\
&= a_r(\bar{x}) e^{-a_0(\bar{x})\tau} \int_0^\tau e^{(a_0(\bar{x}) - a_0(\bar{x} + \nu_r))(\tau - \theta)} d\theta \\
&= a_r(\bar{x}) e^{-a_0(\bar{x})\tau} \int_0^\tau e^{(a_0(\bar{x}) - a_0(\bar{x} + \nu_r))\zeta} d\zeta \\
&= a_r(\bar{x}) e^{-a_0(\bar{x})\tau} \frac{1 - e^{(a_0(\bar{x}) - a_0(\bar{x} + \nu_r))\tau}}{a_0(\bar{x} + \nu_r) - a_0(\bar{x})} \\
&= a_r(\bar{x}) \frac{e^{-a_0(\bar{x})\tau} - e^{-a_0(\bar{x} + \nu_r)\tau}}{a_0(\bar{x} + \nu_r) - a_0(\bar{x})}.
\end{aligned}$$

**Comment.** The same probabilities (8a)–(8b) are obtained if the approximations  $a_r(x - \nu_r) \approx a_r(\bar{x})$  for all  $r$  are not used in (5), i.e., if one starts with the following CME approximation:

$$\frac{\partial \mathcal{P}(x, t)}{\partial t} = \sum_{r=1}^M a_r(x - \nu_r) \mathcal{P}(x - \nu_r, t) - a_0(\bar{x}) \mathcal{P}(x, t). \quad (9)$$

**Comment.** If the approximation  $a_0(x) \approx a_0(\bar{x})$  is not used in (5) the resulting transition probabilities are:

$$\mathcal{P}(\bar{x}, \bar{t} + \tau) = e^{-a_0(\bar{x})\tau}, \quad \mathcal{P}(\bar{x} + \nu_r, \bar{t} + \tau) = \frac{1 - e^{-a_0(\bar{x} + \nu_r)\tau}}{a_0(\bar{x} + \nu_r)} a_r(\bar{x}).$$

The sum of probabilities in this case is not preserved exactly:

$$e^{-a_0(\bar{x})\tau} + \sum_{r=1}^M \frac{1 - e^{-a_0(\bar{x} + \nu_r)\tau}}{a_0(\bar{x} + \nu_r)} a_r(\bar{x}) = 1 + \mathcal{O}(\tau).$$

## 4 Tau-Leaping as a Markov Process

Assume the system at time  $\bar{t}$  is in the state  $\bar{x}$ . In the tau-leap method the number of times a reaction  $R_r$  fires in  $[\bar{t}, \bar{t} + \tau]$  is a random variable  $K_r$  which is Poisson distributed (3) with parameter  $a_r(\bar{x})\tau$ . The probability that one reaction  $R_j$  fires exactly  $k_j$  times, i.e.,  $\mathcal{P}(K_j = k_j)$ , is given by equation (3).

Assuming that each reaction channel fires independently, the probability that each reaction  $R_r$  fires exactly  $k_r$  times,  $r = 1, \dots, M$ , is the product of  $M$  Poisson probabilities:

$$\mathcal{P}(K_1 = k_1, \dots, K_M = k_M) = \prod_{r=1}^M e^{-a_r(\bar{x})\tau} \cdot \frac{(a_r(\bar{x})\tau)^{k_r}}{k_r!} = e^{-a_0(\bar{x})\tau} \cdot \prod_{r=1}^M \frac{(a_r(\bar{x})\tau)^{k_r}}{k_r!}. \quad (10)$$

The effect of  $(k_1, \dots, k_M)$  reactions is the following change in the state vector:

$$X(\bar{t} + \tau) = \bar{x} + \sum_{r=1}^M k_r \nu_r. \quad (11)$$

Consider the set of all possible firing sequences  $k = (k_1, \dots, k_M)$  that produce the same state change

$$\mathcal{K}(\Delta x) = \left\{ (k_1, \dots, k_M) \in \mathbb{R}^M : k_1 \geq 0, \dots, k_M \geq 0, \sum_{r=1}^M k_r \nu_r = \Delta x \right\}.$$

The probability to transition from the state  $\bar{x}$  at  $\bar{t}$  to a state  $x$  at  $\bar{t} + \tau$ ,  $\mathcal{P}(X(\bar{t} + \tau) = x)$ , is the sum of the probabilities of all possible firing sequences that, through (11), lead to the state change  $\Delta x = x - \bar{x}$ . Using (10) we have that

$$\mathcal{P}(x, \bar{t} + \tau) = e^{-a_0(\bar{x})\tau} \cdot \sum_{k \in \mathcal{K}(x - \bar{x})} \prod_{r=1}^M \frac{(a_r(\bar{x})\tau)^{k_r}}{k_r!}.$$

Let  $Q^i$  be the total possible number of molecules of species  $i$ ,  $i = 1, \dots, N$ . The number of molecules of species  $i$ ,  $x^i$ , can take values between zero and the total number,  $0 \leq x^i \leq Q^i$ . The total number of all possible states in which the chemical system can be found is

$$Q = \prod_{i=1}^N (Q^i + 1).$$

Consider an ordering of the  $Q$  possible states in a one-dimensional vector. Denote by  $\mathcal{I}(x)$  the one-dimensional index of the state  $x$ . A reaction  $R_r$  changes the state vector; the corresponding change in the state index is:

$$\mathcal{I}(x) - \mathcal{I}(x - \nu_r) = d_r, \quad r = 1, \dots, M.$$

Note that  $d_r$  depends on  $\nu_r$  and on the total number of molecules of each species but it does not depend on  $x$ . For example consider the case of a column-wise ordering (first increase the

numbers of molecules of species one, then increase the molecules of species two, and so on). Then:

$$\begin{aligned}\mathcal{I}([x]) &= (Q^{N-1} + 1) \cdots (Q^1 + 1) \cdot x^N + \dots \\ &\quad + (Q^2 + 1)(Q^1 + 1) \cdot x^3 + (Q^1 + 1) \cdot x^2 + x^1 + 1, \\ \mathcal{I}([x - \nu_r]) &= (Q^{N-1} + 1) \cdots (Q^1 + 1) \cdot (x^N - \nu_r^N) + \dots \\ &\quad + (Q^2 + 1)(Q^1 + 1) \cdot (x^3 - \nu_r^3) + (Q^1 + 1) \cdot (x^2 - \nu_r^2) + x^1 - \nu_r^1 + 1,\end{aligned}$$

and therefore the shifts corresponding to each reaction are

$$d_r = (Q^{N-1} + 1) \cdots (Q^1 + 1) \cdot \nu_r^N + \dots + (Q^2 + 1)(Q^1 + 1) \cdot \nu_r^3 + (Q^1 + 1) \cdot \nu_r^2 + \nu_r^1. \quad (12)$$

Note also that  $d_r$  can be positive or negative.

Following this ordering the probabilities of all possible system states can be arranged similarly in a one-dimensional vector

$$P_{\mathcal{I}(x)}(t) = \mathcal{P}(x, t), \quad 1 \leq \mathcal{I}(x) \leq T.$$

Consider the diagonal matrix  $A_0 \in \mathbb{R}^{Q \times Q}$ :

$$(A_0)_{i,j} = \begin{cases} -a_0(\bar{x}) & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases},$$

and the diagonal Toeplitz matrices  $A_1, \dots, A_M \in \mathbb{R}^{Q \times Q}$ :

$$(A_r)_{i,j} = \begin{cases} a_r(\bar{x}) & \text{if } i - j = d_r \\ 0 & \text{if } i - j \neq d_r \end{cases}, \quad r = 1, \dots, M.$$

The approximate CME equation (5) can be written in matrix-vector notation as follows:

$$P' = \sum_{r=0}^R A_r \cdot P, \quad \bar{t} \leq t \leq \bar{t} + \tau; \quad P(\bar{t}) = \delta_{\mathcal{I}(\bar{x})}, \quad (13)$$

where  $\delta_j \in \mathbb{R}^Q$  is a vector whose  $j^{\text{th}}$  entry equals one, and all the other entries are equal to zero. The solution of the linear ODE (13) is given by the matrix exponential, and can be approximated as follows:

$$P(\bar{t} + \tau) = \exp\left(\tau \sum_{r=0}^R A_r\right) \cdot P(\bar{t}).$$

The exponential of the sum can be approximated, to first order in  $\tau$ , by the product of individual matrix exponentials. This leads to the approximate solution

$$P(\bar{t} + \tau) \approx \exp(\tau A_0) \cdot \exp(\tau A_1) \cdots \exp(\tau A_R) \cdot P(\bar{t}).$$

The exponentials of diagonal Toeplitz matrices can be evaluated analytically. We have that:

$$(e^{\tau A_0})_{i,j} = \begin{cases} e^{-a_0(\bar{x})\tau} & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases}$$



and

$$(e^{\tau A_r})_{i,j} = \begin{cases} \frac{(a_r(\bar{x}) \tau)^k}{k!} & \text{if } i - j = k \cdot d_r \text{ for } k = 0, 1, \dots, \theta_r(i), \\ 0 & \text{otherwise,} \end{cases} \quad r = 1, \dots, M.$$

This matrix has multiple diagonals, spaced  $d_r$  positions apart from each other. The diagonal index is  $kd_r$  with  $k \geq 0$ . The diagonals intersected by the row  $i$  are characterized by

$$k \geq 0 \quad \& \quad 1 \leq j = i - k \cdot d_r \leq Q \quad \Leftrightarrow \quad i - Q \leq k \cdot d_r \leq i - 1$$

i.e.,

$$0 \leq k \leq \theta_r(i), \quad \theta_r(i) = \begin{cases} \left\lfloor \frac{i-1}{d_r} \right\rfloor & \text{for } d_r > 0, \\ \left\lfloor \frac{Q-i}{|d_r|} \right\rfloor & \text{for } d_r < 0. \end{cases}$$

The action of the matrix exponential on a vector is computed as follows:

$$w_i = (\exp(\tau A_r) \cdot v)_i = \sum_{k_r=0}^{\theta_r(i)} \frac{(a_r(\bar{x}) \tau)^{k_r}}{k_r!} \cdot v_{i-k_r \cdot d_r},$$

and

$$\begin{aligned} (\exp(\tau A_p) \cdot w)_i &= \sum_{k_p=0}^{\theta_p(i)} \frac{(a_p(\bar{x}) \tau)^{k_p}}{k_p!} \cdot w_{i-k_p \cdot d_p} \\ &= \sum_{k_p=0}^{\theta_p(i)} \frac{(a_p(\bar{x}) \tau)^{k_p}}{k_p!} \sum_{k_r=0}^{\theta_r(i-k_p \cdot d_p)} \frac{(a_r(\bar{x}) \tau)^{k_r}}{k_r!} \cdot v_{i-k_p \cdot d_p - k_r \cdot d_r}. \end{aligned}$$

Generalizing this equation leads to

$$\begin{aligned} (\exp(\tau A_1) \cdots \exp(\tau A_M) \cdot v)_i &= \sum_{k_1=0}^{\theta_1(i)} \frac{(a_1(\bar{x}) \tau)^{k_1}}{k_1!} \sum_{k_2=0}^{\theta_2(i-k_1 \cdot d_1)} \frac{(a_2(\bar{x}) \tau)^{k_2}}{k_2!} \cdots \\ &\quad \cdots \sum_{k_M=0}^{\theta_M(i-\sum_{r=1}^{M-1} k_r \cdot d_r)} \frac{(a_M(\bar{x}) \tau)^{k_M}}{k_M!} \cdot v_{i-\sum_{r=1}^M k_r \cdot d_r} \end{aligned}$$

Starting with a delta initial condition at  $j = \mathcal{I}(\bar{x})$ , the probability of a state  $x$  with  $i = \mathcal{I}(x)$  is

$$\begin{aligned} (\exp(\tau A_1) \cdots \exp(\tau A_M) \cdot v)_{i=j+\sum_{r=1}^M k_r \cdot d_r} &= \sum_{k_1=0}^{\theta_1(j+\sum_{r=1}^M k_r \cdot d_r)} \frac{(a_1(\bar{x}) \tau)^{k_1}}{k_1!} \sum_{k_2=0}^{\theta_2(j+\sum_{r=2}^M k_r \cdot d_r)} \frac{(a_2(\bar{x}) \tau)^{k_2}}{k_2!} \cdots \\ &\quad \cdots \sum_{k_M=0}^{\theta_M(j+k_M \cdot d_M)} \frac{(a_M(\bar{x}) \tau)^{k_M}}{k_M!} \cdot \delta_j \end{aligned}$$

Using the index notation, the probability given by the tau leaping method is

$$\mathcal{K}(i-j) = \left\{ (k_1, \dots, k_M) \in \mathbb{R}^M : k_1 \geq 0, \dots, k_M \geq 0, \sum_{r=1}^M k_r d_r = i-j \right\}.$$

$$P_i(\bar{t} + \tau) = e^{-a_0(\bar{x})\tau} \sum_{\sum_{r=1}^M k_r d_r = i-j} \prod_{r=1}^M \frac{(a_r(\bar{x})\tau)^{k_r}}{k_r!}.$$

## 5 Example

Consider the following system of extended Lotka reactions [5]



with  $N = 2$  and  $M = 4$ . The propensity functions are

$$a_1(x) = c_1 Y x^1 \quad (15a)$$

$$a_2(x) = c_2 x^1 x^2 \quad (15b)$$

$$a_3(x) = c_3 x^2 \quad (15c)$$

$$a_4(x) = c_4 x^1 \quad (15d)$$

and the stoichiometric array is

$$\nu = (\nu_j^i)_{1 \leq i \leq 2, 1 \leq j \leq 4} = \begin{bmatrix} 1 & -1 & 0 & -1 \\ 0 & 1 & -1 & 0 \end{bmatrix}.$$

With  $Y = \text{const}$  and  $c_4 = c_1 Y$  we have that  $x^1(t) + x^2(t) + Z(t) = \text{const}$  (since the sum of the corresponding time derivatives is zero). The system starts with no  $Z$  molecules,  $Z(\bar{t}) = 0$ . Consequently the maximum numbers of molecules for the species of interest are

$$0 \leq x^1(t), x^2(t) \leq x^1(t) + x^2(t) + Z(t) = x^1(\bar{t}) + x^2(\bar{t}) = Q^1 = Q^2.$$

According to (16) the shifts corresponding to each reaction are

$$\begin{aligned} d_1 &= (Q^1 + 1) \times \nu_1^2 + \nu_1^1 = 1 \\ d_2 &= (Q^1 + 1) \times \nu_2^2 + \nu_2^1 = Q^1 \\ d_3 &= (Q^1 + 1) \times \nu_3^2 + \nu_3^1 = -1 - Q^1 \\ d_4 &= (Q^1 + 1) \times \nu_4^2 + \nu_4^1 = -1 \end{aligned}$$

$$A = \begin{bmatrix} a_0^{(1)} & a_4^{(2)} & 0 & 0 & a_3^{(5)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_1^{(1)} & a_0^{(2)} & a_4^{(3)} & 0 & 0 & a_3^{(6)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_1^{(2)} & a_0^{(3)} & a_4^{(4)} & 0 & 0 & a_3^{(7)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ a_2^{(1)} & 0 & a_1^{(3)} & a_0^{(4)} & a_4^{(5)} & 0 & 0 & a_3^{(8)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & a_2^{(2)} & 0 & a_1^{(4)} & a_0^{(5)} & a_4^{(6)} & 0 & 0 & a_3^{(9)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & a_2^{(3)} & 0 & a_1^{(5)} & a_0^{(6)} & a_4^{(7)} & 0 & 0 & a_3^{(10)} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & a_2^{(4)} & 0 & a_1^{(6)} & a_0^{(7)} & a_4^{(8)} & 0 & 0 & a_3^{(11)} & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & a_2^{(5)} & 0 & a_1^{(7)} & a_0^{(8)} & a_4^{(9)} & 0 & 0 & a_3^{(12)} & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & a_2^{(6)} & 0 & a_1^{(8)} & a_0^{(9)} & a_4^{(10)} & 0 & 0 & a_3^{(13)} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(7)} & 0 & a_1^{(9)} & a_0^{(10)} & a_4^{(11)} & 0 & 0 & a_3^{(14)} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(8)} & 0 & a_1^{(10)} & a_0^{(11)} & a_4^{(12)} & 0 & 0 & a_3^{(15)} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(9)} & 0 & a_1^{(11)} & a_0^{(12)} & a_4^{(13)} & 0 & 0 & a_3^{(16)} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(10)} & 0 & a_1^{(12)} & a_0^{(13)} & a_4^{(14)} & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(11)} & 0 & a_1^{(13)} & a_0^{(14)} & a_4^{(15)} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(12)} & 0 & a_1^{(14)} & a_0^{(15)} & a_4^{(16)} \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & a_2^{(13)} & 0 & a_1^{(15)} & a_0^{(16)} \end{bmatrix}$$

## 6 Exponential ROW

Let  $W \approx A$ .

An EXP-ROW method reads

$$\begin{aligned} k_i &= \phi(\gamma h W) \left( f(u_i) + h W \sum_{j=1}^{i-1} \gamma_{i,j} k_j \right) \\ &= \phi(\gamma h W) \left( A u_i + h W \sum_{j=1}^{i-1} \gamma_{i,j} k_j \right) \\ &= h^{-1} \gamma^{-1} (\exp(\gamma h W) - I) \left( W^{-1} A u_i + h \sum_{j=1}^{i-1} \gamma_{i,j} k_j \right) \\ u_i &= y_0 + h \sum_{j=1}^{i-1} \alpha_{i,j} k_j \\ y_1 &= y_0 + h \sum_{i=1}^s b_i k_i. \end{aligned}$$

Conditions up to order 2 are.

$$\begin{aligned}\sum_i b_i &= 1 \\ \sum_j b_j \sum_k \alpha_{j,k} &= 1/2 \\ \sum_j b_j \sum_k \gamma_{j,k} &= -\gamma/2.\end{aligned}$$

A method of order 4 is:

$$\begin{aligned}k_1 &= \phi\left(\frac{1}{3}hW\right)f(y_0); \\ k_2 &= \phi\left(\frac{2}{3}hW\right)f(y_0); \\ k_3 &= \phi(hW)f(y_0); \\ w_4 &= -7/300k_1 + 97/150k_2 - 37/300k_3; \\ u_4 &= y_0 + hw_4; \\ d_4 &= f(u_4) - f(y_0) - hWw_4; \\ k_4 &= \phi\left(\frac{1}{3}hW\right)d_4; \\ k_5 &= \phi\left(\frac{2}{3}hW\right)d_4; \\ k_6 &= \phi(hW)d_4; \\ w_7 &= 59/300k_1 - 7/75k_2 + 269/300k_3 + \frac{2}{3}(k_4 + k_5 + k_6); \\ u_7 &= y_0 + hw_7; \\ d_7 &= f(u_7) - f(y_0) - hWw_7; \\ k_7 &= \phi\left(\frac{1}{3}hW\right)d_7; \\ y_1 &= y_0 + h(k_3 + k_4 - 4/3k_5 + k_6 + 1/6k_7)\end{aligned}$$

## 7 Conclusions

In this paper we explain the approximations made by SSA and tau-leaping when used to sample the distribution from the CME.

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