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Weighted next reaction method and parameter selection for efficient simulation of rare events in biochemical reaction systems

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Abstract

The weighted stochastic simulation algorithm (wSSA) recently developed by Kuwahara and Mura and the refined wSSA proposed by Gillespie et al. based on the importance sampling technique open the door for efficient estimation of the probability of rare events in biochemical reaction systems. In this paper, we first apply the importance sampling technique to the next reaction method (NRM) of the stochastic simulation algorithm and develop a weighted NRM (wNRM). We then develop a systematic method for selecting the values of importance sampling parameters, which can be applied to both the wSSA and the wNRM. Numerical results demonstrate that our parameter selection method can substantially improve the performance of the wSSA and the wNRM in terms of simulation efficiency and accuracy.

1 Introduction

Biochemical reaction systems in living cells exhibit significant stochastic fluctuations due to a small number of molecules involved in processes such as the transcription and translation of genes [1]. A number of exact [2-7] or approximate simulation algorithms [8-19] have been developed for simulating the stochastic dynamics of such systems. Recent research shows that some rare events occurring in biochemical reaction system with an extremely small probability within a specified limited time can have profound and sometimes devastating effects [20,21]. Hence, it is important that computational simulation and analysis of systems with critical rare events can efficiently capture such rare events. However, the existing exact simulation methods such as Gillespie's exact SSA [2,3] often require prohibitive computation to estimate the probability of a rare events, while the approximate methods may not be able to estimate such probability accurately.

The weighted stochastic simulation algorithm (wSSA) recently developed by Kuwahara and Mura [22] based on the importance sampling technique enables one to efficiently estimate the probability of a rare event.

However, the wSSA does not provide any method for selecting optimal values for importance sampling parameters. More recently, Gillespie et al. [23] analyzed the accuracy of the results yielded from the wSSA and proposed a refined wSSA that employed a try-and-test method for selecting optimal values for importance sampling parameters. It was shown that the refined wSSA could further improve the performance of wSSA. However, the try-and-test method requires some initial guessing for the sets of values from which the parameters can take. If the guessed values do not include the optimal value, then one cannot get appropriate values for the parameters. Moreover, if the number of parameters is greater than one, a very large set of values need to be guessed and tested, which may increase the likelihood of missing the optimal values and also increase computational overhead.

In this paper, we first apply the importance sampling technique to the next reaction method (NRM) of the SSA [4] and develop a weighted NRM (wNRM) as an alternative to the wSSA. We then develop a systematic method for selecting optimal values for importance sampling parameters that can be incorporated into both the wSSA and the wNRM. Our method does not need initial guess and thus can guarantee near optimal values for the parameters. Our numerical results in Section 5 demonstrate that the variance of the estimated

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probability of the rare event provided by the wSSA and wNRM with our parameter selection method can be more than one order magnitude lower than that provided by the wSSA or the refined wSSA for a given number of simulation runs. Moreover, the wSSA and wNRM with our parameter selection method require less simulation time than the refined wSSA for the same number of simulation runs. When this paper was under review, a method named doubly weighted SSA (dwSSA) was developed to automatically choose parameter values for the wSSA [24]. The dwSSA reduces the computational overhead required by the wSSA and the refined wSSA to select parameter values, but it produces similar variance for the estimated probability as the refined wSSA.

The remaining part of this paper is organized as follows. In Section 2, we first describe the system setup and then briefly review Gillespie's exact SSA [2,3], the wSSA [22] and the refined wSSA [23]. In Section 3, we develop the wNRM. In Section 4, we develop a systematic method for selecting optimal values for importance sampling parameters and incorporate the parameter selection procedure into both the wSSA and the NRM. In Section 5, we give some numerical examples that illustrate the advantages of our parameter selection method. Finally in Section 6, we draw several conclusions.

2 Weighted stochastic simulation algorithms

2.1 System Description

Suppose a chemical reaction system involves a well-stirred mixture of $N \geq 1$ molecular species $\{S_1, \dots, S_N\}$ that chemically interact through $M \geq 1$ reaction channels $\{R_1, \dots, R_M\}$. The dynamic state of this chemical system is described by the state vector $\mathbf{X}(t) = [X_1(t), \dots, X_N(t)]^T$, where $X_n(t)$, $n = 1, \dots, N$, is the number of S_n molecules at time t , and $[\cdot]^T$ denotes the transpose of the vector in the brackets. Following Gillespie [8], we define the dynamics of reaction R_m by a state-change vector $\mathbf{v}_m = [v_{1m}, \dots, v_{Nm}]^T$, where v_{nm} gives the changes in the S_n molecular population produced by one R_m reaction, and a propensity function $a_m(\mathbf{x})$ together with the fundamental premise of stochastic chemical kinetics:

$$a_m(\mathbf{x})dt \triangleq \text{the probability, given } \mathbf{X}(t) = \mathbf{x}, \text{ that one reaction } R_m \text{ will occur} \quad (1)$$

in the next infinitesimal time interval $[t, t + dt)$.

2.2 Gillespie's exact SSA

Based on the fundamental premise (1), Gillespie developed an exact SSA to simulate the occurrence of every reaction when the time evolves [3]. Specifically, Gillespie's SSA simulates the following event in each step:

$$E : \text{no reaction occurs in the time interval } [t, t + \tau], \text{ and a reaction } R_\mu \quad (2)$$

occurs in the infinitesimal time interval $(t + \tau, t + \tau + d\tau)$.

It has been shown by Gillespie [2,3] that τ and μ are two independent random variables and have the following probability density functions (PDF) and probability mass function (PMF), respectively,

$$p(\tau) = a_0(\mathbf{x}) \exp(-a_0(\mathbf{x})\tau), \quad \tau > 0, \quad (3)$$

and

$$p_\mu = a_\mu(\mathbf{x})/a_0(\mathbf{x}), \quad \mu = 1, \dots, M, \quad (4)$$

where $a_0(\mathbf{x}) = \sum_{m=1}^M a_m(\mathbf{x})$. Therefore, Gillespie's direct method (DM) for the SSA generates a realization of τ and μ according to PDF (3) and PMF (4), respectively, in each step of the simulation, and then updates the system state as $\mathbf{X}(t + \tau) = \mathbf{x} + \mathbf{v}_\mu$.

2.3 Weighted SSA

In order to estimate the probability of a rare event that occurs with an extremely low probability in a given time period, Gillespie's SSA may require huge computation. Recently, the wSSA [22] and the refined wSSA [23] were developed to estimate the probability of a rare event with substantial reduction of computation. Following Kuwahara and Mura [22], and Gillespie et al. [23], we define the rare event E_R as follows:

$$E_R \text{ is an event that starting at time } 0 \text{ in state } \mathbf{x}_0, \text{ the system will first reach} \quad (5)$$

any state in a specific set Ω at some time $\leq T$, and the probability of E_R is very small, i.e., $P(E_R) \ll 1$.

If we employ the SSA to estimate $P(E_R)$, we would have to make a large number n of simulation runs, with each starting at time 0 in state \mathbf{x}_0 and terminating either when some state $\mathbf{x} \in \Omega$ is first reached or when the system time reaches T . If k is the number of those n runs that terminate for the first reason, then $P(E_R)$ is estimated as $\hat{P}(E_R) = k/n$. Since $P(E_R) \ll 1$, n should be very large to get a reasonably accurate estimate of $P(E_R)$. The wSSA employs the importance sampling technique to reduce the number of runs needed to estimate $P(E_R)$.

Specifically, wSSA generates τ from its PDF (3) in the same way as used in Gillespie's DM method, but generates the reaction index μ from the following PMF:

$$q_\mu = b_\mu(\mathbf{x})/b_0(\mathbf{x}), \quad \mu = 1, \dots, M, \quad (6)$$

where $b_\mu(\mathbf{x}) = \gamma_\mu a_\mu(\mathbf{x})$, $\mu = 1, \dots, M$, $b_0(\mathbf{x}) = \sum_{\mu=1}^M b_\mu(\mathbf{x})$ and γ_μ , $\mu = 1, \dots, M$ are positive constants that need to be chosen carefully before simulations are run. Suppose a trajectory J generated in a simulation run contains h reactions and the i th reaction occurs at time t_i , then the wSSA changes the PDF of the

trajectory from $P_j = \prod_{i=1}^h a_{\mu_i}(\mathbf{x}_i) \exp(-a_0(\mathbf{x}_i)(t_i - t_{i-1}))$ to $Q_j = \prod_{i=1}^h b_{\mu_i}(\mathbf{x}_i)/b_0(\mathbf{x}_i) a_0(\mathbf{x}_i) \exp(-a_0(\mathbf{x}_i)(t_i - t_{i-1}))$, where $t_0 = 0$. By choosing appropriate γ_μ , $\mu = 1, \dots, M$, one can increase the probability of the trajectories that lead to the rare event. If k trajectories out of n simulation runs lead to the rare event, then the importance sampling technique tells us that an unbiased estimate of $P(E_R)$ is given by

$$\begin{aligned} \hat{P}(E_R) &= \frac{1}{n} \sum_{j=1}^k \frac{P_j^j}{Q_j^j} \\ &= \frac{1}{n} \sum_{j=1}^k \frac{\prod_{i=1}^h a_{\mu_i}^j(\mathbf{x}_i) / a_0^j(\mathbf{x}_i)}{\prod_{i=1}^h b_{\mu_i}^j(\mathbf{x}_i) / b_0^j(\mathbf{x}_i)} \\ &= \frac{1}{n} \sum_{j=1}^k \prod_{i=1}^h w_i^j \end{aligned} \quad (7)$$

where j and i are indices of the trajectories and reactions in a trajectory, respectively, $b_{\mu_i}^j(\mathbf{x}_i) = \gamma_\mu a_{\mu_i}^j(\mathbf{x}_i)$ and

$$w_i^j = \frac{p_{\mu_i}^j}{q_{\mu_i}^j} = \frac{a_{\mu_i}^j(\mathbf{x}_i) / a_0^j(\mathbf{x}_i)}{b_{\mu_i}^j(\mathbf{x}_i) / b_0^j(\mathbf{x}_i)}, \quad (8)$$

which can be obtained in each simulation step.

Kuwahara and Mura [22] did not provide any method for choosing γ_μ , although their numerical results with some pre-specified γ_μ for several reaction systems demonstrated that the wSSA could reduce computation substantially. Gillespie et al. [23] analyzed the variance of $\hat{P}(E_R)$ obtained from the wSSA and refined the wSSA by proposing a try-and-test method for choosing γ_μ . In the try-and-test method, several sets of values are pre-specified for γ_μ , $\mu = 1, \dots, M$. A relatively small number of simulation runs of the standard SSA are made for each set of the values to obtain an estimate of the variance of $\hat{P}(E_R)$, and then the set of values that yielded the smallest variance is chosen. Although the try-and-test method provides a way of choosing γ_μ , it requires some guessing to get several sets of pre-specified values for all γ_μ and also some computational overhead to estimate the variance of $\hat{P}(E_R)$ for each set of values. More recently, the dwSSA was developed in [24] to automatically choose parameter values for the wSSA by applying the cross-entropy method originally proposed in [25] for optimizing the importance sampling method.

3 Weighted NRM

The wSSA is based on the DM for the SSA, which needs to generate two random variables in each simulation step. However, the NRM of Gibson and Bruck [4]

requires only one random variable in each simulation step. In this section, we apply the importance sampling technique to the NRM and develop the wNRM.

The key to making the wSSA more efficient than the standard SSA is to change the probability of each reaction appropriately but without changing the distribution of the time τ between any two consecutive reactions. Since the NRM determines the reaction occurring in a simulation step by choosing the reaction that requires the smallest waiting time, it seems difficult to change the probability of each reaction without changing the distribution of τ . However, we notice that the PDF of τ in (3) only depends on $a_0(\mathbf{x})$ not individual $a_\mu(\mathbf{x})$. Hence, we can change the probability of each reaction by changing the corresponding propensity function but without changing the distribution of τ , so long as we keep the sum of the propensity functions equal to $a_0(\mathbf{x})$. To this end, we define

$$d_m(\mathbf{x}) = \frac{b_m(\mathbf{x})a_0(\mathbf{x})}{b_0(\mathbf{x})}, \quad m = 1, \dots, M, \quad (9)$$

where $b_m(\mathbf{x}) = \gamma_m a_m(\mathbf{x})$ is defined in the same way as in the wSSA. It is easy to verify that $d_0(\mathbf{x}) = \sum_{m=1}^M d_m(\mathbf{x}) = a_0(\mathbf{x})$. If we generate τ_m from an exponential distribution $p(\tau_m) = d_m(\mathbf{x}) \exp(-d_m(\mathbf{x})\tau_m)$, $\tau_m > 0$, as the waiting time of reaction channel m , and choose $\mu = \arg_m \min\{\tau_m, m = 1, \dots, M\}$ as the index of the channel that fires, then it can be easily shown that the PDF of $\tau = \min\{\tau_m, m = 1, \dots, M\}$ follows the exponential distribution in (3) and that the probability of reaction μ is $q_\mu = d_\mu(\mathbf{x})/d_0(\mathbf{x}) = b_\mu(\mathbf{x})/b_0(\mathbf{x})$. If we repeat this procedure in each simulation step, we would have modified the first reaction method (FRM) [3] for the standard SSA and got a weighted FRM (wFRM). Clearly, the wFRM is not efficient since it generates M random variables in each step. However, following Gibson and Bruck [4], we can convert the wFRM into a more efficient wNRM by reusing τ_m s.

In the FRM, we used τ_m to denote the putative waiting or relative time for the m th reaction channel to fire. Following Gibson and Bruck [4], we will use τ_m to denote the putative absolute time when the m th reaction channel will fire. Suppose that the μ th reaction channel fires at time t in the current step. After updating the state vector and propensity functions, we calculate new $d_m(\mathbf{x})$, $m = 1, \dots, M$, which we denote as $d_m^{\text{new}}(\mathbf{x})$. Then, we generate a random variable $\tilde{\tau}_\mu$ from an exponential distribution with parameter $d_\mu^{\text{new}}(\mathbf{x})$ and set $\tau_\mu = t + \tilde{\tau}_\mu$. For other channels with an index $m \neq \mu$, we update τ_m as follows:

$$\tau_m \leftarrow d_m(\mathbf{x}) / d_m^{\text{new}}(\mathbf{x}) (\tau_m - t) + t. \quad (10)$$

Following Gibson and Bruck [4], we can show that the new $\tau_m - t$, $m = 1, \dots, M$, are independent exponential random variables with parameters $d_m^{\text{new}}(\mathbf{x})$, $m = 1, \dots, M$, respectively. Therefore, in the next step, we can choose $\mu = \arg_m \min\{\tau_m, m = 1, \dots, M\}$ as the index of the channel that fires as done in NRM, update t as $t = \tau_\mu$ and then repeat the process just described. Clearly, the wNRM only needs to generate one random variable in each step. We can further improve the efficiency of the wNRM by using the dependency graph \mathcal{G} and the indexed priority queue \mathcal{P} defined by Gibson and Bruck [4]. The dependency graph \mathcal{G} tells precisely which propensity functions need to be updated after a reaction occurs. The indexed priority queue \mathcal{P} can be exploited to find the minimum τ_m and the reaction index in each step more efficiently than finding the reaction index from the PMF (4) directly as done in the DM. However, some computational overhead is needed to maintain the data structure of \mathcal{P} .

Essentially, our wNRM runs simulation in the same way as the NRM except that the wNM generates τ_m using a parameter $d_m(\mathbf{x})$ instead of $a_m(\mathbf{x})$. To estimate the probability of the rare event $\hat{P}(E_R)$, we calculate a weight $w_\mu = \frac{p_\mu}{q_\mu} = \frac{a_\mu(\mathbf{x})/a_0(\mathbf{x})}{d_\mu(\mathbf{x})/d_0(\mathbf{x})} = a_\mu(\mathbf{x})/d_\mu(\mathbf{x})$ in each step and get $\hat{P}(E_R)$ using (7). The wNRM is summarized in the following algorithm:

Algorithm 1 (wNRM)

1. $k_1 \leftarrow 0$, $k_2 \leftarrow 0$, set values for all γ_m ; generate a dependency graph \mathcal{G} .
2. **for** $i = 1$ to n , **do**
3. $t \leftarrow 0$, $\mathbf{x} \leftarrow \mathbf{x}_0$, $w \leftarrow 1$.
4. evaluate $a_m(\mathbf{x})$ and $b_m(\mathbf{x})$ for all m ; calculate all $d_m(\mathbf{x})$.
5. for each m , generate a unit-interval uniform random variable r_m ; $\tau_m = \ln(1/r_m)/d_m(\mathbf{x})$.
6. store τ_m in an indexed priority queue \mathcal{P} .
7. **while** $t \leq T$, **do**
8. **if** $\mathbf{x} \in \Omega$, **then**
9. $k_1 \leftarrow k_1 + w$, $k_2 \leftarrow k_2 + w^2$
10. break out the while loop
11. **end if**
12. find $\mu = \arg_m \min\{\tau_m, m = 1, \dots, M\}$ and $\tau = \min\{\tau_m, m = 1, \dots, M\}$ from \mathcal{P} .
13. $w \leftarrow w \times a_\mu(\mathbf{x})/d_\mu(\mathbf{x})$.
14. $\mathbf{x} \leftarrow \mathbf{x} + \mathbf{v}_\mu$, $t \leftarrow \tau$.
15. Find $a_m(\mathbf{x})$ need to be updated from \mathcal{G} ; evaluate these $a_m(\mathbf{x})$ and the corresponding $b_m(\mathbf{x})$; calculate all $d_m^{\text{new}}(\mathbf{x})$.
16. for all $m \neq \mu$, $\tau_m \leftarrow \frac{d_m(\mathbf{x})}{d_m^{\text{new}}(\mathbf{x})}(\tau_m - t) + t$; generate a unit-interval uniform random variable r_μ ; $\tau_\mu \leftarrow -\frac{\ln(r_\mu)}{d_\mu^{\text{new}}(\mathbf{x})} + t$; update \mathcal{P} .

17. $d_m(\mathbf{x}) \leftarrow d_m^{\text{new}}(\mathbf{x})$.
18. **end while**
19. **end for**
20. $\sigma^2 = k_2 - k_1^2$
21. calculate $\hat{P}(E_R) = k_1/n$, with a 68% uncertainty of $\pm\sigma/\sqrt{n}$.

Note that Gibson and Bruck [4] argued that the NRM is more efficient than the DM of Gillespie's SSA for the loosely coupled chemical reaction systems. On the other hand, Cao et al. [5] optimized the DM and argued that the optimized DM is more efficient for most practical reaction systems. Regardless of the debate about the efficiency, here we propose the wNRM as an alternative of the wSSA which is based on the DM. While our simulation results in Section 5 demonstrate that the wNRM is more efficient than the refined wSSA for the three reaction systems tested, the wSSA may be more efficient in simulating some other systems.

As in the wSSA, Algorithm 1 does not provide a method for selecting the values of parameters γ_m , $m = 1, \dots, M$. Although we could incorporate the try-and-test method in refined wSSA into Algorithm 1, we will develop a more systematic method for selecting parameters in the next section. This parameter selection method will be applicable to both the wSSA and the wNRM and can significantly improve the performance of both algorithms as will be demonstrated in Section 5.

4 Parameter selection for wSSA and wNRM

Let us denote the set of all possible state trajectories in the time interval $[0, T]$ as \mathcal{J} and the set of trajectories that first reach any state in Ω during $[0, T]$ as \mathcal{J}_E . Let the probability of a trajectory J be P_J . Then, we have $P(E_R) = \sum_{J \in \mathcal{J}_E} P_J = \sum_{J \in \mathcal{J}} P_J 1(J \in \mathcal{J}_E)$, where the indicator function $1(J \in \mathcal{J}_E) = 1$ if $J \in \mathcal{J}_E$ or 0 if $J \notin \mathcal{J}_E$. Importance sampling used in the wSSA and the wNRM arises from the factor that we can write $P(E_R)$ as

$$P(E_R) = \sum_{J \in \mathcal{J}} \frac{P_J 1(J \in \mathcal{J}_E)}{Q_J} Q_J, \quad (11)$$

where Q_J is the probability used in simulation to generate trajectory J , which is different from the true probability P_J if the original system evolves naturally. If we make n simulation runs with altered trajectory probabilities, (11) implies that we can estimate $P(E_R)$ as $\hat{P}(E_R) = \frac{1}{n} \sum_{J \in \mathcal{J}} \frac{P_J 1(J \in \mathcal{J}_E)}{Q_J}$ which is essentially (7). The variance of $\hat{P}(E_R)$ depends on Q_J s. Appropriate Q_J s yield small variance, thereby improving the accuracy of the estimate or equivalently reducing the number of runs for a given variance. The "rule of thumb" [23,26-28] for choosing good Q_J s is that Q_J should be roughly

proportional to $P_J 1(J \in \mathcal{J}_E)$. However, at least two difficulties arise if we apply the rule of thumb based on (11). First, the number of all possible trajectories is very large and we do not know the trajectories that lead to the rare event and their probabilities. Second, since we can only adjust the probability of each reaction in each step, it is not clear how this adjustment can affect the probability of a trajectory. To overcome these difficulties, we next use an alternative expression for $P(E_R)$ based on which we apply the importance sampling technique.

Let us denote the number of reactions occurring in the time interval $[0, t]$ as K_t and the maximum value of K_T as K_T^{\max} . Let E_K be the rare event occurring at the K th ($K \leq K_T^{\max}$) reaction at any $t \leq T$, and $P(E_K)$ be the probability of E_K in the original system that evolve naturally with the original probability rate constants. Then, we have

$$P(E_R) = \sum_{K=1}^{K_T^{\max}} P(E_K). \quad (12)$$

If $Q(E_K)$ is the probability of event E_K in the weighted system that evolves with adjusted probability rate constants, the rule of thumb for choosing good $Q(E_K)$ is that we should make $Q(E_K)$ approximately proportional to $P(E_K)$. However, it is still difficult to apply the rule of thumb, because it is difficult to control every $Q(E_K)$ simultaneously. Hence, we relax the rule of thumb and will maximize the $Q(E_K)$ corresponding to the maximum $P(E_K)$ or the one near maximum if the exact maximum $P(E_K)$ cannot be determined precisely. The rationale of this heuristic rule is based on the following argument. If $P(E_{K_E})$ is the maximum one among all $P(E_K)$, $K = 1, \dots, K_T^{\max}$, the sum of $P(E_{K_E})$ and its closely related terms, such as $P(E_{K_E-1})$, $P(E_{K_E+1})$, $P(E_{K_E-2})$ and $P(E_{K_E+2})$, very likely dominates the sum in the right-hand side of (12). Maximizing $Q(E_{K_E})$ not only proportionally increases $Q(E_{K_E})$, and its closely related terms, such as $Q(E_{K_E-1})$, $Q(E_{K_E+1})$, $Q(E_{K_E-2})$ and $Q(E_{K_E+2})$, but also significantly increases the probability of the occurrence of the rare event. Note that a similar heuristic rule relying on the event with maximum probability was proposed in [29] for estimating the probability of rare events in highly reliable Markovian systems.

Before proceeding with our derivations, we need to specify Ω . In the rest of the paper, we assume that Ω contains one single state \mathbf{X} defined as $X_i = X_i(0) + \eta$, where η is a constant and $i \in \{1, 2, \dots, N\}$. Let us denote the number of firings of the m th reaction channel in the trajectory leading to the rare event as K_m . Then, we have

$$\eta = \sum_{m=1}^M v_{im} K_m. \quad (13)$$

We first divide all reactions into three groups using the following general rule: G_1 group consists of reactions with $v_{im}\eta > 0$, G_2 group consists of reactions with $v_{im}\eta < 0$, and G_3 group consists of reactions with $v_{im} = 0$. The rationale for the partition rule is that the reactions in G_1 (G_2) group increase (decrease) the probability of the rare event and that the reactions in G_3 group do not affect $X_i(t)$ directly. We further refine the partition rule as follows. If a reaction R_m is in the G_1 group based on the general rule but $a_m(\mathbf{x}) = 0$ whenever one R_m reaction occurs, we move R_m into the G_3 group. Similarly, if a reaction R_m is in the G_2 group based on the general rule but $a_m(\mathbf{x}) = 0$ whenever one R_m reaction occurs, we move R_m into the G_3 group. For most cases, we only need the general partition rule. The refining rule described here is to deal with the situation where one or several $X_i(t)$ s always take values 1 or 0 as in the system considered in Section 5.3. More refining rules may be added following the rationale just described, after we see more real-world reaction systems.

We typically only need to consider elementary reactions including bimolecular and monomolecular reactions [30]. Hence, the possible values for all v_{im} are 0, ± 1 , ± 2 . For the simplicity of derivations, we now only consider the case where $v_{im} = 0, \pm 1$, i.e., we assume that the system does not have any bimolecular reactions with two identical reactant molecules or dimerization reactions. We will later generalize our method to the system with dimerization reactions. Let us define $K_{G_2} = \sum_{m \in G_2} K_m$, $K_{G_1} = \sum_{m \in G_1} K_m$ and $K_{G_3} = \sum_{m \in G_3} K_m$, then (13) becomes

$$\eta = K_{G_1} - K_{G_2}. \quad (14)$$

Let us denote \bar{K}_t as the expected value of K_t . Since the number of reactions occurring in any small time interval is approximately a Poisson random variable [8], K_t is the sum of a large number of independent Poisson random variables when t is relatively large. Then, by the central limit theorem, K_t can be approximated as a Gaussian random variable with mean \bar{K}_t . Indeed, in all chemical reaction systems [6,19,31] we tested so far, we observed that Kt follows a unimodal distribution with a peak at \bar{K}_t and its standard deviation is small relative to \bar{K}_t . Since the mean first passage time of the rare event is much larger than T [23], the rare event most likely occurs at a time near T . Based on these two observations, we argue that $P(E_{\bar{K}_T}) > P(E_K)$ for all $K < \bar{K}_T$. Therefore, we should have $K_E \geq \bar{K}_T$. When E_{K_E} occurs, we have

$$K_{G_1} + K_{G_2} + K_{G_3} = K_E. \quad (15)$$

Since both (14) and (15) need to be satisfied in order for the event E_{K_E} to occur and since $K_{G_1} \geq 0$, $K_{G_2} \geq 0$ and $K_{G_3} \geq 0$, we get the second requirement for K_E : $K_E \geq |\eta|$. Combining the two requirements on K_E , we obtain $K_E \geq \max\{\bar{K}_T, |\eta|\}$.

The probability $P(E_K)$ can be expressed as $P(E_K) = \int_0^T P(\mathbf{X}(t) \in \Omega, K_t = K) dt = \int_0^T P(\mathbf{X}(t) \in \Omega | K_t = K) P(K_t = K) dt$. Since $P(\mathbf{X}(t) \in \Omega | K_t = K)$ is determined by the constant K , it is independent of t . Hence, we have $P(E_K) = P(\mathbf{X}(t) \in \Omega | K_t = K) \int_0^T P(K_t = K) dt$. Due to the unimodal distribution of K_t we mentioned earlier, we have $\int_0^T P(K_t = K) dt \approx 1$ for those $K \ll \bar{K}_T$; $\int_0^T P(K_t = K) dt \approx 0.5$ for those K close to \bar{K}_T ; and $\int_0^T P(K_t = K) dt$ quickly decreases to zero when K increases beyond \bar{K}_T . In other words, $\int_0^T P(K_t = K) dt$ is approximately a constant for $K \leq \bar{K}_T$ and quickly decreases to zero when $K > \bar{K}_T$. Now let us consider event E_K with $K = |\eta|$ in the case $|\eta| > \bar{K}_T$. In this case, $P(\mathbf{X}(t) \in \Omega | K_t = K)$ is very small because this is an extreme case where $K_{G_2} = 0$ and $K_{G_3} = 0$ if $\eta > 0$ or $K_{G_1} = 0$ and $K_{G_3} = 0$ if $\eta < 0$. Therefore, we can increase $P(E_K)$ if we increase K , but we do not want to increase K too much because as we discussed $\int_0^T P(K_t = K) dt$ decreases quickly when K increases in the case $K > \bar{K}_T$. Consequently, we suggest that we choose $K_E = |\eta| + \sigma_{K_T}$, where σ_{K_T} is the standard deviation of K_T which can be estimated by making hundreds of runs of the standard SSA. In case $\bar{K}_T > |\eta|$, we choose $K_E = \bar{K}_T$ based on the same argument that $\int_0^T P(K_t = K_E) dt$ decreases quickly if we further increase K_E .

Applying the relaxed rule of thumb, we need to adjust probability rate constants in simulation to maximize $Q(E_{K_E}) = Q(\mathbf{X}(t) \in \Omega | K_t = K_E) \int_0^T Q(K_t = K_E) dt$. Since we do not change the distribution of τ , we do not change the distribution of K_T and thus $\int_0^T Q(K_t = K_E) dt$. Hence, maximizing $Q(E_K)$ is equivalent to maximizing $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$. Now we are in a position to summarize our strategy of applying the important sampling technique in simulation as follows: we will choose probability parameters to maximize $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$, where

$$K_E = \max\{\bar{K}_T, |\eta| + \sigma_{K_T}\}. \quad (16)$$

We next consider systems with only G_1 and G_2 reaction groups and then consider more general systems with all three reaction groups.

4.1 Systems with G_1 and G_2 reaction groups

Since we do not have G_3 group, (15) becomes

$$K_{G_1} + K_{G_2} = K_E. \quad (17)$$

Combining (14) and (17), we get $K_{G_1} = (K_E + \eta)/2$ and $K_{G_2} = (K_E - \eta)/2$ if the final state after the last reaction occurs is in Ω . The last reaction should be a reaction from G_1 group. Otherwise, the state already reached Ω before the last reaction occurs. Suppose that in simulation the total probability of the occurrence of reactions in G_1 group is a constant Q_{G_1} and then the total probability of the occurrence of reactions in G_2 group is $Q_{G_2} = 1 - Q_{G_1}$. Then, $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$ can be found from a binomial distribution as follows

$$Q(\mathbf{X}(t) \in \Omega | K_t = K_E) = \frac{(K_E - 1)!}{(K_{G_1} - 1)! K_{G_2}!} Q_{G_1}^{K_{G_1}} (1 - Q_{G_1})^{K_{G_2}}, \quad (18)$$

where $K_{G_1} = (K_E + \eta)/2$ and $K_{G_2} = (K_E - \eta)/2$ as determined earlier. Setting the derivative of $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$ with respect to Q_{G_1} to be zero, we get Q_{G_1} and Q_{G_2} that maximize $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$ as follows:

$$\begin{aligned} Q_{G_1} &= \frac{(K_E + \eta)}{2K_E} \\ Q_{G_2} &= \frac{(K_E - \eta)}{2K_E}. \end{aligned} \quad (19)$$

To ensure that reactions in G_1 (G_2) group occur with probability Q_{G_1} (Q_{G_2}) in each step of simulation, we adjust the probability of each reaction as follows

$$q_m = \begin{cases} \frac{Q_{G_1} a_m(\mathbf{x})}{a_{G_1}(\mathbf{x})}, & m \in G_1 \\ \frac{Q_{G_2} a_m(\mathbf{x})}{a_{G_2}(\mathbf{x})}, & m \in G_2, \end{cases} \quad (20)$$

where $a_{G_1}(\mathbf{x}) = \sum_{m \in G_1} a_m(\mathbf{x})$ and $a_{G_2}(\mathbf{x}) = \sum_{m \in G_2} a_m(\mathbf{x})$. It is easy to verify that $\sum_{m \in G_1} q_m = Q_{G_1}$ and $\sum_{m \in G_2} q_m = Q_{G_2}$. As defined in (8), the weight for estimating the probability of the rare event is $w_\mu = p_\mu / q_\mu$ if the μ th reaction channel fires.

4.2 Systems with G_1 , G_2 and G_3 reaction groups

Combining (14) and (15), we get $K_{G_1} = K_{G_2} + \eta$ and $K_{G_3} = K_E - \eta - 2K_{G_2}$. Since $K_{G_3} \geq 0$, we have $K_{G_2} \leq (K_E - \eta)/2$. Suppose that in simulation the total probabilities of the occurrence of reactions in G_1 , G_2 and G_3 are constants Q_{G_1} , Q_{G_2} and $Q_{G_3} = 1 - Q_{G_1} - Q_{G_2}$, respectively. Then, $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$ can be found from a multinomial distribution as follows

$$Q(\mathbf{X}(t) \in \Omega | K_t = K_E) = \sum_{K_{G_2}=0}^{(K_E-\eta)/2} \frac{(K_E - 1)!}{(K_{G_1} - 1)! K_{G_2}! (K_{G_3})!} Q_{G_1}^{K_{G_1}} Q_{G_2}^{K_{G_2}} Q_{G_3}^{K_{G_3}}, \quad (21)$$

where $K_{G_1} = K_{G_2} + \eta$ and $K_{G_3} = K_E - \eta - 2K_{G_2}$ as determined earlier. Since there are $(K_E - \eta)/2 + 1$ terms of the sum in (21), it is difficult to find Q_{G_1} , Q_{G_2} and Q_{G_3} that maximize $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$. So we will use

a different approach to find Q_{G_1} , Q_{G_2} and Q_{G_3} as described in the following.

Let \bar{K}_{G_1} , \bar{K}_{G_2} and \bar{K}_{G_3} be the average number of reactions of G_1 , G_2 and G_3 groups that occur in the time interval $[0, T]$ in the original system. Since we have $\bar{K}_{G_1} + \bar{K}_{G_2} + \bar{K}_{G_3} = \bar{K}_T$, we define $P_{G_1} = \bar{K}_{G_1}/\bar{K}_T$, $P_{G_2} = \bar{K}_{G_2}/\bar{K}_T$, and $P_{G_3} = \bar{K}_{G_3}/\bar{K}_T$. Then, we can approximate $P(X(t) \in \Omega | K_t = K_E)$ in the original system, which is the counter part of $Q(X(t) \in \Omega | K_t = K_E)$ in the weighted system, using the right-hand side of (21) but with Q_{G_i} , $i = 1, 2, 3$, replaced by P_{G_i} , $i = 1, 2, 3$, respectively. This gives

$$P(X(t) \in \Omega | K_t = K_E) \approx \sum_{K_{G_2}=0}^{(K_E-\eta)/2} \frac{(K_E-1)!}{(K_{G_1}-1)!K_{G_2}!(K_{G_3})!} P_{G_1}^{K_{G_1}} P_{G_2}^{K_{G_2}} P_{G_3}^{K_{G_3}}. \quad (22)$$

Suppose that the $(\kappa + 1)$ th term of the sum in (22) is the largest. We further relax the rule of thumb and maximize the $(\kappa + 1)$ th term of the sum in (21) to find Q_{G_1} , Q_{G_2} and Q_{G_3} .

It is not difficult to find the $(\kappa + 1)$ th term of the sum in (22). Let us denote the $(K_{G_2} + 1)$ th term of the sum in (22) as $f(K_{G_2})$. We can exhaustively search over all $K_{G_2} = 0, \dots, (K_E - \eta)/2$, $K_{G_2} = 0, \dots, (K_E - \eta)/2$ to find κ . However, this may require relatively large computation because the factorials involved in $f(K_{G_2})$. We can reduce computation by searching over $K_{G_2} = 1, \dots, (K_E - \eta)/2 - 1$, $K_{G_2} = 1, \dots, (K_E - \eta)/2 - 1$, which are given by

$$g(K_{G_2}) = \frac{(K_E - \eta - 2K_{G_2})(K_E - \eta - 2K_{G_2} - 1)P_{G_1}P_{G_2}}{(K_{G_2} + \eta)(K_{G_2} + 1)P_{G_3}^2}. \quad (23)$$

Specifically, we calculate all $g(K_{G_2})$ from (23). If $g(K_{G_2}) > 1$ but $g(K_{G_2} + 1) < 1$, then $f(K_{G_2})$ is a local maximum. After obtaining all local maximums, we can find the global maximum $f(\kappa)$ from the local maximums.

After we find κ , we set the partial derivatives of the $(\kappa + 1)$ th term of the sum in (21) with respect to Q_{G_1} and Q_{G_2} to be zero. This gives the following optimal Q_{G_1} , Q_{G_2} and Q_{G_3}

$$\begin{aligned} Q_{G_1} &= \frac{\kappa + \eta}{K_E} \\ Q_{G_2} &= \frac{\kappa}{K_E} \\ Q_{G_3} &= \frac{K_E - \eta - 2\kappa}{K_E}. \end{aligned} \quad (24)$$

Substituting Q_{G_1} and Q_{G_2} in (24) into (20), we get the probability q_m , $m \in G_1$ or G_2 that is used to generate the m th reaction in each step of simulation. For G_3 group, we get the probability of each reaction as follows

$$q_m = \frac{Q_{G_3} a_m(\mathbf{x})}{a_{G_3}(\mathbf{x})}, \quad m \in G_3, \quad (25)$$

where $a_{G_3}(\mathbf{x}) = \sum_{m \in G_3} a_m(\mathbf{x})$.

While we can use q_m in (25) to generate reactions in G_3 group, we next develop an optional method for fine-tuning q_m , $m \in G_3$, which can further reduce the variance of $\hat{P}(E_R)$. We divide G_3 group into three subgroups: G_{31} , G_{32} and G_{33} . Occurrence of reactions in G_{31} group increases the probability of occurrence of reactions in Q_{G_1} group or reduces the probability of the occurrence of the reactions in Q_{G_2} group, which in turn increases the probability of the rare event. Occurrence of reactions in G_{32} group reduces the probability of occurrence of reactions in Q_{G_1} group or increases the probability of the occurrence of reactions in Q_{G_2} group, which reduces the probability of the rare event. Occurrence of reactions in G_{33} group does not change the probability of occurrence of reactions in Q_{G_1} and Q_{G_2} groups, which does not change the probability of the rare event.

Let $\bar{K}_{G_{31}}$, $\bar{K}_{G_{32}}$ and $\bar{K}_{G_{33}}$ be the average number of reactions from G_{31} , G_{32} and G_{33} that occur in the time interval $[0, T]$ in the original system. we define $P_{G_{32}} = \bar{K}_{G_{32}}/\bar{K}_T$, $P_{G_{33}} = \bar{K}_{G_{33}}/\bar{K}_T$ and $P_{G_{31}} = \bar{K}_{G_{31}}/K_E$. Our goal is to make Q_{31} to be greater than $P_{G_{31}}$ and Q_{32} to be less than $P_{G_{32}}$ to increase the probability of the rare event. However, this may not be feasible when $Q_{G_3} < P_{G_3}$. Hence, we can fine-tune $Q_{G_{31}}$, $Q_{G_{32}}$ and $Q_{G_{33}}$ only when $Q_{G_3} \geq P_{G_3}$ and propose the following formula to determine Q_{31} , Q_{32} and Q_{33} :

$$\begin{aligned} Q_{G_{31}} &= P_{G_{31}} + Q_{G_3} \alpha - P_{G_3} \beta \\ Q_{G_{32}} &= P_{G_{32}} + Q_{G_3} (1 - \alpha) - P_{G_3} (1 - \beta) \\ Q_{G_{33}} &= P_{G_{33}} \end{aligned} \quad (26)$$

where $\alpha, \beta \in (0, 1)$ are two pre-specified constants. It is not difficult to verify from (26) that $Q_{G_{31}} + Q_{G_{32}} + Q_{G_{33}} = Q_{G_3}$. To ensure that $P_{G_{31}} \leq Q_{G_{31}} < Q_{G_3} - Q_{G_{33}}$ and $0 < Q_{G_{32}} \leq P_{G_{32}}$, we choose α and β satisfying $0 \leq \beta < 1$ and $1 - \frac{P_{G_{32}}}{Q_{G_3}} (1 - \beta) \leq \alpha < \min\{1, 1 + \frac{P_{G_{32}}}{Q_{G_3}} - \frac{P_{G_{31}}}{Q_{G_3}} (1 - \beta)\}$.

Finally, we obtain q_m for $m \in G_3$ as follows

$$q_m = \begin{cases} \frac{Q_{G_{31}} a_m(\mathbf{x})}{a_{G_{31}}(\mathbf{x})}, & m \in G_{31} \\ \frac{Q_{G_{32}} a_m(\mathbf{x})}{a_{G_{32}}(\mathbf{x})}, & m \in G_{32} \\ \frac{Q_{G_{33}} a_m(\mathbf{x})}{a_{G_{33}}(\mathbf{x})}, & m \in G_{33}, \end{cases} \quad (27)$$

where $a_{G_{3i}}(\mathbf{x}) = \sum_{m \in G_{3i}} a_m(\mathbf{x})$, $i = 1, 2, 3$.

4.3 Systems with dimerization reactions

So far we assumed that the system did not have any dimerization reactions, i.e. the system consisted of reactions with $|v_{im}| = 0$ or 1. We now generalize our methods developed earlier to the system with dimerization reactions. If there are dimerization reactions in G_1 and G_2 groups, we further divide G_1 group into G_{11} and G_{12} subgroups and G_2 group into G_{21} and G_{22} subgroups. The G_{11} group contains reactions with $v_{im}\text{sign}(\eta) = 1$, where $\text{sign}(\eta) = 1$ when $\eta > 0$ and $\text{sign}(\eta) = -1$ when $\eta < 0$. The G_{12} group contains reactions with $v_{im}\text{sign}(\eta) = 2$. The G_{21} group contains reactions with $v_{im}\text{sign}(\eta) = -1$, while the G_{22} group contains reactions with $v_{im}\text{sign}(\eta) = -2$.

Let us define $K_{G_{11}} = \sum_{m \in G_{11}} K_m$, $K_{G_{12}} = \sum_{m \in G_{12}} K_m$, $K_{G_{21}} = \sum_{m \in G_{21}} K_m$ and $K_{G_{22}} = \sum_{m \in G_{22}} K_m$. Clearly, we have $K_{G_1} = K_{G_{11}} + K_{G_{12}}$ and $K_{G_2} = K_{G_{21}} + K_{G_{22}}$. Then, (13) becomes

$$K_{G_{11}} + 2K_{G_{12}} - K_{G_{21}} - 2K_{G_{22}} = \eta. \quad (28)$$

Let us consider systems with G_1 and G_2 groups but without G_3 group. Although we still have $K_{G_1} + K_{G_2} = K_E$ or equivalently $K_{G_{11}} + K_{G_{12}} + K_{G_{21}} + K_{G_{22}} = K_E$, we cannot obtain four unknowns $K_{G_{11}}$, $K_{G_{12}}$, $K_{G_{21}}$ and $K_{G_{22}}$ from only two equations.

Suppose that $\bar{K}_{G_{11}}$, $\bar{K}_{G_{12}}$, $\bar{K}_{G_{21}}$ and $\bar{K}_{G_{22}}$ are average number of reactions from G_{11} , G_{12} , G_{21} and G_{22} groups that occur in the time interval $[0, T]$ in the original system. We notice from (20) that we do not change the ratio of the probabilities of two reactions in the same group, i.e., $q_{m_1}/q_{m_2} = p_{m_1}/p_{m_2}$ if m_1 and m_2 are in the same G_1 or G_2 group. Therefore, we would expect that $K_{G_{12}}/K_{G_{11}} \approx \bar{K}_{G_{12}}/\bar{K}_{G_{11}}$ and $K_{G_{22}}/K_{G_{21}} \approx \bar{K}_{G_{22}}/\bar{K}_{G_{21}}$. Using these two relationships, we can write (28) as

$$\lambda_1 K_{G_1} - \lambda_2 K_{G_2} = \eta \quad (29)$$

$$\text{where } \lambda_1 = \frac{(\bar{K}_{G_{11}} + 2\bar{K}_{G_{12}})}{(\bar{K}_{G_{11}} + \bar{K}_{G_{12}})} \text{ and } \lambda_2 = \frac{(\bar{K}_{G_{21}} + 2\bar{K}_{G_{22}})}{(\bar{K}_{G_{21}} + \bar{K}_{G_{22}})}$$

From (17) and (29), we obtain $K_{G_1} = (\lambda_1 K_E + \eta)/(\lambda_1 + \lambda_2)$ and $K_{G_2} = (\lambda_2 K_E - \eta)/(\lambda_1 + \lambda_2)$. Substituting K_{G_1} and K_{G_2} into (18) and maximizing $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$, we obtain

$$\begin{aligned} Q_{G_1} &= \frac{\lambda_1 K_E + \eta}{(\lambda_1 + \lambda_2) K_E} \\ Q_{G_2} &= \frac{\lambda_2 K_E - \eta}{(\lambda_1 + \lambda_2) K_E}. \end{aligned} \quad (30)$$

We then substitute Q_{G_1} and Q_{G_2} into (20) to get q_m .

Now let us consider the systems with G_1 , G_2 and G_3 reactions. From (29), we have $K_{G_1} = (\lambda_2 K_{G_2} + \eta)/\lambda_1$, and from (15) and (29), we obtain

$K_{G_2} \leq (\lambda_1 K_E - \eta)/(\lambda_1 + \lambda_2)$. Since $K_{G_3} \geq 0$, we have $K_{G_2} \leq (\lambda_1 K_E - \eta)/(\lambda_1 + \lambda_2)$. Following the derivations in Section 4.2, we can get q_m for any reaction. More specifically, substituting K_{G_1} , K_{G_3} and the upper limit of K_{G_2} into (21), we obtain $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$. We can also get $P(\mathbf{X}(t) \in \Omega | K_t = K_E)$ similar to (22) by replacing Q_{G_i} in $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$ with P_{G_i} . Then, we determine the maximum term of the sum in $P(\mathbf{X}(t) \in \Omega | K_t = K_E)$ and denote the value of K_{G_2} corresponding to the maximum term as $\kappa + 1$. We find Q_{G_1} , Q_{G_2} and Q_{G_3} by maximizing the $(\kappa + 1)$ th term of the sum in $Q(\mathbf{X}(t) \in \Omega | K_t = K_E)$. Finally, we substitute Q_{G_1} and Q_{G_2} into (20) to get q_m , $m \in G_1$ or G_2 . For the reactions in G_3 group, we can either substitute Q_{G_3} into (25) to obtain q_m , or if we want to fine-tune q_m , we use (26) and (27) to get q_m .

4.4 wSSA and wNRM with parameter selection

The key to determining probability of each reaction q_m is to find the total probability of each group, Q_{G_1} , Q_{G_2} , $Q_{G_{31}}$, $Q_{G_{32}}$ and $Q_{G_{33}}$. This requires the average number of reactions of each group occurring during the interval $[0, T]$ in the original system, \bar{K}_T , $\bar{K}_{G_{11}}$, $\bar{K}_{G_{12}}$, $\bar{K}_{G_{21}}$, $\bar{K}_{G_{22}}$, $\bar{K}_{G_{31}}$, $\bar{K}_{G_{32}}$, $\bar{K}_{G_{33}}$. If the system is relatively simple, we may get these numbers analytically. If we cannot obtain them analytically, we can estimate them by running Gillespie's exact SSA. Since the number of runs needed to estimate these numbers is much smaller than the number of runs needed to estimate the probability of the rare event, the computational overhead is negligible.

We then summarize the wSSA incorporating the parameter selection method in the following algorithm. We will not include the procedure for fine-tuning the probability rate constants of reactions in the G_3 group, but will describe how to add this optional procedure to the algorithm. We will also describe how to modify Algorithm 1 to incorporate the parameter selection procedure into the wNRM.

Algorithm 2 (wSSA with parameter selection)

1. run Gillespie's exact SSA 10^3 - 10^4 times to get estimates of \bar{K}_T , $\bar{K}_{G_{11}}$, $\bar{K}_{G_{12}}$, $\bar{K}_{G_{21}}$, $\bar{K}_{G_{22}}$, and σ_{K_T} ; determine K_E from (16).
2. if the system has only G_1 and G_2 reactions, calculate Q_{G_1} and Q_{G_2} from (19) if there is no dimerization reaction or from (30) if there are dimerization reaction(s), if the system has G_1 , G_2 and G_3 reactions, calculate Q_{G_1} , Q_{G_2} and Q_{G_3} from (24).
3. $k_1 \leftarrow 0$, $k_2 \leftarrow 0$.
4. **for** $i = 1$ to n , **do**
5. $t \leftarrow 0$, $\mathbf{x} \leftarrow \mathbf{x}_0$, $w \leftarrow 1$.
6. **while** $t \leq T$, **do**
7. **if** $\mathbf{x} \in \Omega$, **then**

8. $k_1 \leftarrow k_1 + w, k_2 \leftarrow k_2 + w^2$
9. *break out the while loop*
10. **end if**
11. *evaluate all $a_m(\mathbf{x})$; calculate $a_0(\mathbf{x})$.*
12. *generate two unit-interval uniform random variables r_1 and r_2 .*
13. $\tau \leftarrow \ln(1/r_1)/a_0(\mathbf{x})$
14. *calculate all q_m from (20) and (25).*
15. $\mu \leftarrow$ *smallest integer satisfying*
 $\sum_{m=1}^{\mu} q_m > r_2 q_0$.
16. $w \leftarrow w \times (a_{\mu}(\mathbf{x})/a_0(\mathbf{x})) / (q_{\mu}(\mathbf{x})/q_0(\mathbf{x}))$.
17. $\mathbf{x} \leftarrow \mathbf{x} + \mathbf{v}_{\mu}, t \leftarrow t + \tau$.
18. **end while**
19. **end for**
20. $\sigma^2 = k_2 - k_1^2$
21. *estimate $\hat{P}(E_R) = k_1/n$, with a 68% uncertainty of $\pm\sigma/\sqrt{n}$.*

If $Q_{G_3} \geq P_{G_3}$ and we want to fine-tune the probability rate constants of the reactions in the G_3 group, we modify Algorithm 2 as follows. In step 1, we also estimate $\bar{K}_{G_{32}}, \bar{K}_{G_{32}}$ and $\bar{K}_{G_{33}}$ and choose the value of α and β in (26). In step 2, we also calculate $Q_{G_{31}}, Q_{G_{32}}$ and $Q_{G_{33}}$ from (26). In step 14, we calculate q_m for G_3 reactions from (27) instead of (25). Comparing with the refined wSSA [23], the wSSA with our parameter selection procedure does not need to make some guessing about the parameters for adjusting the probability of each reaction q_m , but directly calculate q_m using a systematically developed method. This has two main advantages. First, our method will always adjust q_m appropriately to reduce the variance of $\hat{P}(E_R)$, whereas the refined wSSA may not adjust q_m as well as our method, especially if the initial guessed values are far away from the optimal values. Second, as we mentioned earlier, the computational overhead of our method is negligible, whereas the refined wSSA requires non-negligible computational overhead for determining parameters. Indeed, as we will show in Section 5, the variance of $\hat{P}(E_R)$ provided by the wSSA with our parameter selection method can be more than one order of magnitude lower than that provided by the refined wSSA for given number of n . Moreover, the wSSA with our parameter selection method is faster than the refined wSSA, since it requires less computational overhead to adjust q_m .

We can also incorporate our parameter selection method without the fine-tuning procedure into the wNRM as follows. We replace the first step of Algorithm 1 with the first three steps of Algorithm 2. We then modify the fourth step of Algorithm 1 as follows: evaluate all $a_m(\mathbf{x})$, calculate all q_m from (20) and (25), and calculate all $d_m(\mathbf{x})$ as $d_m(\mathbf{x}) = q_m a_0(\mathbf{x})$. Finally, we change the fifth step of Algorithm 1 to the following:

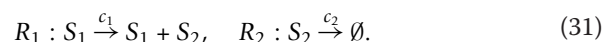
find $a_m(\mathbf{x})$ need to be updated from \mathcal{G} and evaluate these $a_m(\mathbf{x})$; calculate all q_m from (20) and (25), and calculate all $d_m^{\text{new}}(\mathbf{x})$ as $d_m^{\text{new}}(\mathbf{x}) = q_m a_0(\mathbf{x})$. We can also fine-tune the probability rate constants of G_3 reactions in the wNRM in the same way as described in the previous paragraph for the wSSA. Note that since our parameter selection method employs a systematic method for partitioning reactions into three groups as discussed earlier, our method can be applied to any real chemical reaction systems.

5 Numerical examples

In this section, we present simulation results for several chemical reaction systems to demonstrate the accuracy and efficiency of the wSSA and wNRM with our parameter selection method, which we refer to as wSSAs and wNRMs, respectively, in the rest of the paper. All simulations were run in Matlab on a PC with an Intel dual Core 2.67-GHz CPU and 3G-byte memory running Windows XP.

5.1 Single species production-degradation model

This simple system was originally used by Kuwahara and Mura [22] and then Gillespie et al. [23] to test the wSSA and the refined wSSA. It includes the following two chemical reactions:



In reaction R_1 , species S_1 synthesizes species S_2 with a probability rate constant c_1 , while in reaction R_2 , species S_2 is degraded with a probability rate constant c_2 . We used the same initial state and probability rate constants as used in [22,23]: $X_1(0) = 1, X_2(0) = 40, c_1 = 1$ and $c_2 = 0.025$.

It is observed that the system is at equilibrium, since $a_1(\mathbf{x}_0) = c_1 \times X_1(0) = c_2 \times X_2(0) = a_2(\mathbf{x}_0)$. It can be shown [22] that $X_2(t)$ is a Poisson random variable with mean equal to 40. References [22,23] sought to estimate $P(E_R) = P_{t \leq 100}(X_2 \rightarrow \theta | \mathbf{x}_0)$, the probability of $X_2(t) = \theta$ for $t \leq 100$ and several values of θ between 65 and 80. Since θ is about four to six standard deviations above the mean value 40, $P_{t \leq 100}(X_2 \rightarrow \theta | \mathbf{x}_0)$ is very small.

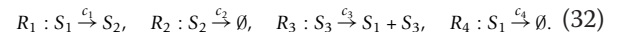
Kuwahara and Mura [22] employed the wSSA to estimate $P(E_R)$ and used $b_1(\mathbf{x}) = \delta a_1(\mathbf{x})$ and $b_2(\mathbf{x}) = 1/\delta a_2(\mathbf{x})$ with $\delta = 1.2$ for four different values of θ : 65, 70, 75 and 80. Gillespie et al. [23] applied the refined wSSA to estimate $P(E_R)$ and used the same way to determine $b_1(\mathbf{x})$ and $b_2(\mathbf{x})$ but found that $\delta = 1.2$ is near optimal for $\theta = 65$ and that $\delta = 1.3$ is near optimal for $\theta = 80$. We repeated the simulation of Gillespie et al. [23] for $\theta = 65, 70, 75$ and 80 with $\delta = 1.2, 1.25, 1.25$ and 1.3, respectively. We then applied the wSSAs and the wNRMs to estimate $P(E_R)$ for $\theta =$

65, 70, 75 and 80. This system has only two types of reaction: R_1 is a G_1 reaction and R_2 is a G_2 reaction. Since the system is at equilibrium with $a_0(\mathbf{x}_0) = 2$, \bar{K}_T with $T = 100$ is estimated to be 200, and thus $K_E = \bar{K}_T = 200$. Using (19), we get $q_1 = Q_{G_1} = (K_E + \theta - 40)/(2K_E)$ and $q_2 = 1 - q_1$.

Table 1 gives the estimated probability $\hat{P}(E_R)$ and the sample variance σ^2 for the wNRMps, the wSSAps and the refined wSSA, obtained from 10^7 simulation runs with $\theta = 65, 70, 75$ and 80 . It is seen that $\hat{P}(E_R)$ is almost identical for all three methods. However, the wNRMps and the wSSAps provide variance almost two order of magnitude lower than the refined wSSA for $\theta = 80$, or less than or almost one order of magnitude lower than the refined wSSA for $\theta = 75, 70$ and 65 . Moreover, the wNRMps and the wSSAps need about 60 and 70% CPU time of the refined wSSA, respectively. Note that the CPU time for the refined wSSA in Table 1 does not include the time needed for searching for the optimal value of δ for each θ . The less CPU time used by the wNRMps is expected since it only requires to generate one random variable in each step, whereas the wSSAps and the refined wSSA need to generate two random variables. It is also reasonable that the wSSAps requires less CPU time than the refined wSSA, because the wSSAps needs less computation to calculate the probability of each reaction in each step. Figure 1 compares the standard deviation (σ/\sqrt{n}) of $\hat{P}(E_R)$ for the wSSAps and the refined wSSA with different number of runs, n . Since the wNRMps provides almost the same standard deviation as the wSSAps, we do not plot it in the figure. It is seen that the wSSAps consistently yields much smaller standard deviation than the refined wSSA for all values of n . It was shown in [24] that the dwSSA yielded similar variance comparing to the refined wSSA. Therefore, our parameter selection method also substantially outperforms the dwSSA in this example.

5.2 A reaction system with G_1, G_2 and G_3 reactions

The previous system only contains a G_1 reaction and a G_2 reaction. We used the following system with G_1, G_2 and G_3 reactions to test the wNRMps and the wSSAps:



In this system, a monomer S_1 converts to S_2 with a probability rate constant c_1 , while S_2 is degraded with a probability rate constant c_2 . Meanwhile, another species S_3 synthesizes S_1 with a probability rate constant c_3 and S_1 degrades with a probability rate constant c_4 . In our simulations, we used the following values for the probability rate constants and the initial state:

$$c_1 = 0.1, \quad c_2 = 0.1, \quad c_3 = 8, \quad c_4 = 0.1, \quad (33)$$

and

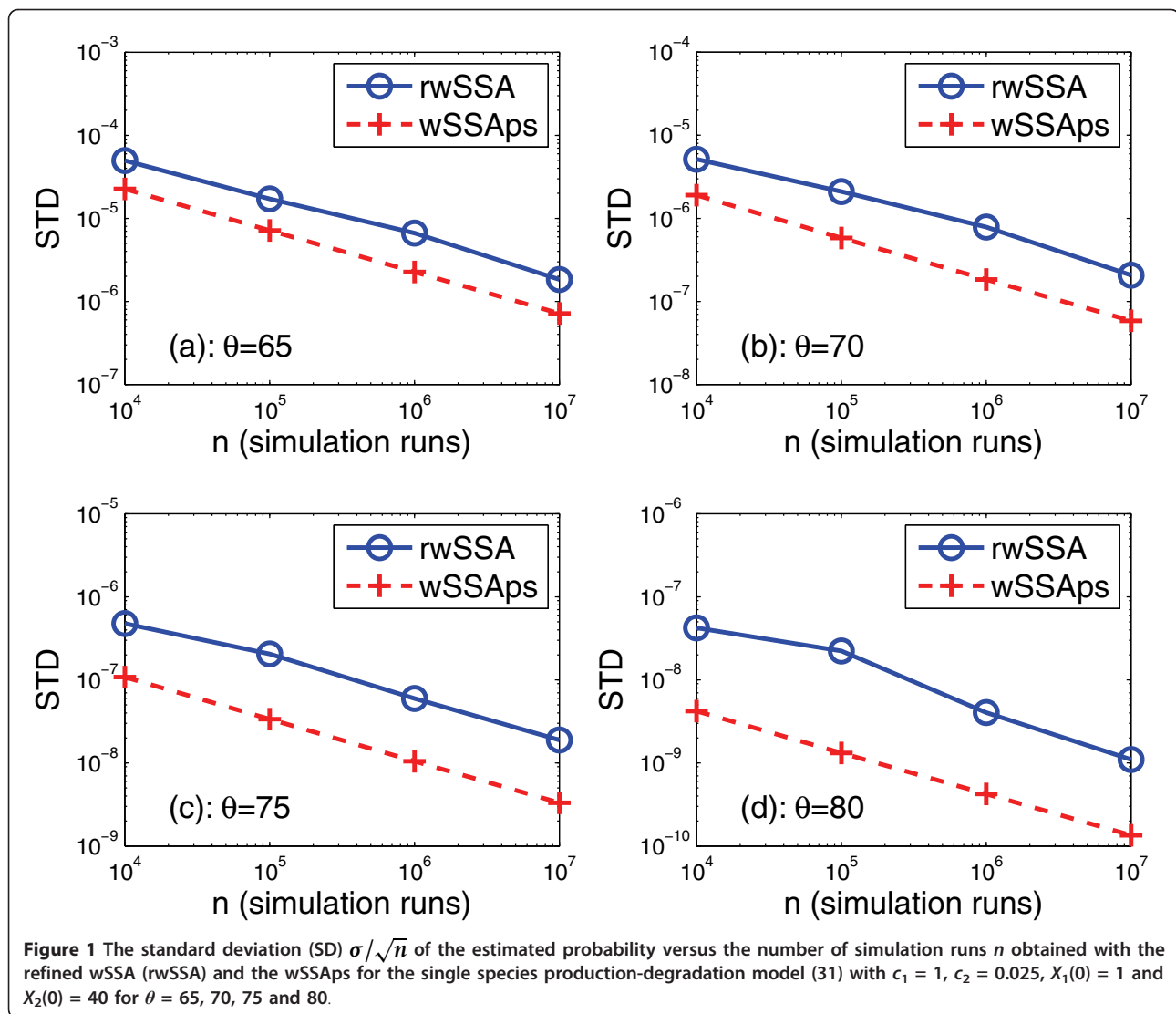
$$X_1(0) = 40, \quad X_2(0) = 40, \quad X_3(0) = 1. \quad (34)$$

This system is at equilibrium and the mean value of $X_2(t)$ is 40. We are interested in $P(E_R) = P_{t \leq 10}(X_2 \rightarrow \theta | \mathbf{x}(0))$, the probability of $X_2(t) = \theta$ for $t \leq 10$. We chose $\theta = 65$ and 68 in our simulations. To apply the wSSAps and the wNRMps to estimate $P(E_R)$, we divide the system into three groups. The G_1 group contains reaction R_1 ; the G_2 group includes reaction R_2 ; the G_3 group consists of reactions R_3 and R_4 . When fine-tuning the parameters, we further divided G_3 into a G_{31} group which contains reaction R_3 and a G_{32} group which contains reaction R_4 . Since the system is at equilibrium and we have $a_0(\mathbf{x}_0) = 20$, $a_1(\mathbf{x}_0) = 4$, $a_2(\mathbf{x}_0) = 4$, $a_3(\mathbf{x}_0) = 8$ and $a_4(\mathbf{x}_0) = 4$, we get $\bar{K}_T = 200$, $\bar{K}_1 = 40$, $\bar{K}_2 = 40$, $\bar{K}_3 = 80$ and $\bar{K}_4 = 40$. Therefore, we get $K_E = \bar{K}_T = 200$ and the following probabilities: $P_{G_1} = 0.2$, $P_{G_2} = 0.2$ and $P_{G_3} = 0.6$.

If $\theta = 65$, we have $\eta = 25$. Using (23), we obtained $\kappa = 29$. Substituting κ into (24), we got $Q_{G_1} = 0.27$, $Q_{G_2} = 0.145$ and $Q_{G_3} = 0.585$. We then chose $\alpha = 0.85$ and $\beta = 0.80$ and calculated $Q_{G_{31}}$ and $Q_{G_{32}}$ from (26) as

Table 1 Estimated probability of the rare event $\hat{P}(E_R)$ and the sample variance σ^2 as well as the CPU time (in s) with 10^7 runs of the wNRMps, the wSSAps and the refined wSSA for the single species production-degradation model (31): (a) $\theta = 65$ and 70 and (b) $\theta = 75$ and 80

(a)	$\theta = 65$			$\theta = 70$		
	$\hat{P}(E_R)$	σ^2	Time	$\hat{P}(E_R)$	σ^2	Time
wNRMps	2.29×10^{-3}	5.09×10^{-6}	14472	1.68×10^{-4}	3.40×10^{-8}	16140
wSSAps	2.29×10^{-3}	5.10×10^{-6}	16737	1.68×10^{-4}	3.40×10^{-8}	18555
Refined wSSA	2.29×10^{-3}	3.39×10^{-5}	24340	1.68×10^{-4}	4.29×10^{-7}	25492
(b)	$\theta = 75$			$\theta = 80$		
	$\hat{P}(E_R)$	σ^2	Time	$\hat{P}(E_R)$	σ^2	Time
wNRMps	8.42×10^{-6}	1.10×10^{-10}	15640	2.99×10^{-7}	1.82×10^{-13}	16260
wSSAps	8.42×10^{-6}	1.10×10^{-10}	18582	2.99×10^{-7}	1.82×10^{-13}	18960
Refined wSSA	8.43×10^{-6}	3.58×10^{-9}	26314	2.99×10^{-7}	1.29×10^{-11}	26987

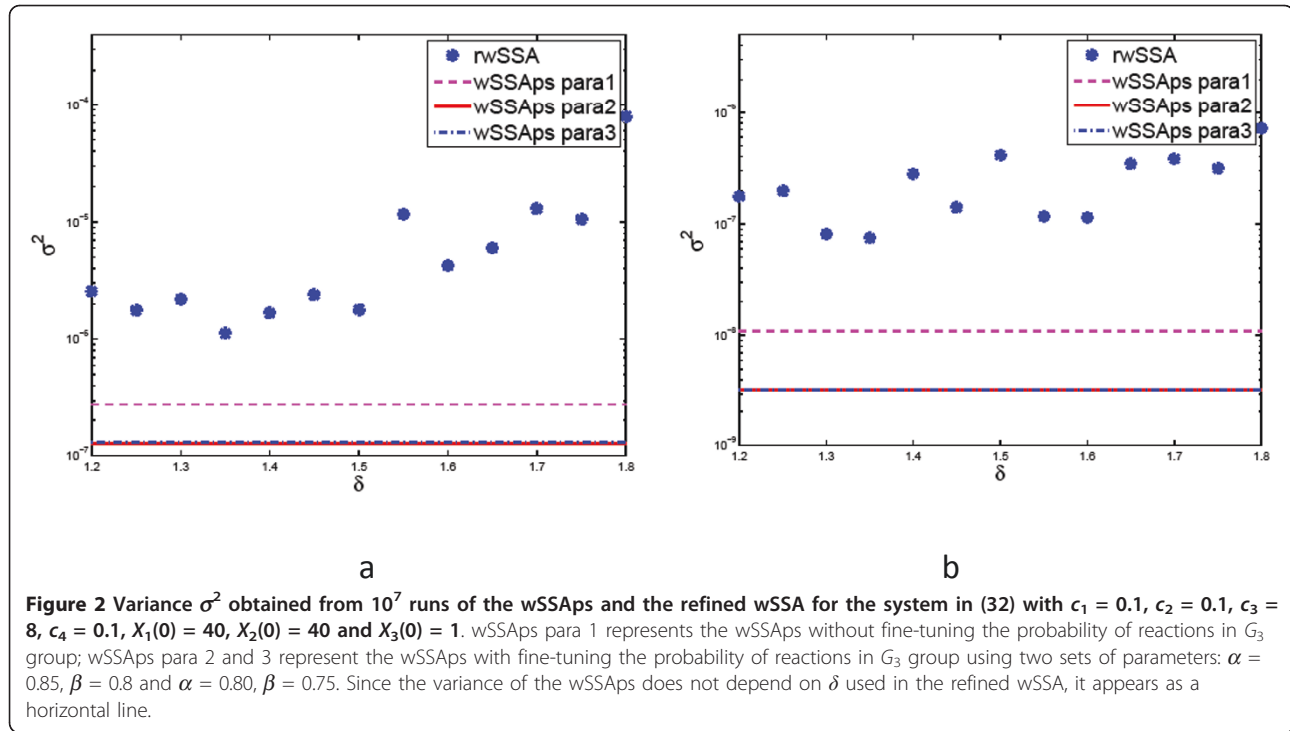


$\hat{P}(E_R)$ and $Q_{G_{32}} = 0.1678$. Similarly, if $\theta = 68$, we got $\kappa = 26$, which resulted in $Q_{G_1} = 0.27$ and $Q_{G_2} = 0.13$. Again, selecting $\alpha = 0.85$ and $\beta = 0.80$, we got $Q_{G_{31}} = 0.430$ and $Q_{G_{32}} = 0.170$. To test whether the wNRMps and the wSSAps are sensitive to parameters α and β , we also used another set of parameters $\alpha = 0.80$ and $\beta = 0.75$.

In order to compare the performance of the wNRMps and the wSSAps with that of the refined wSSA, we also ran simulations with the refined wSSA. In the refined wSSA, we chose the following parameters $\gamma_1 = \delta$, $\gamma_2 = 1/\delta$ and $\gamma_m = 1$, $m = 3, 4$ to adjust propensity functions. Since the optimal value of α is unknown, we ran the refined wSSA for $\delta = 1.2, 1.25, 1.3, 1.35, 1.40, 1.45, 1.50, 1.55, 1.60, 1.65, 1.70, 1.75$ and 1.80 to determine the best δ . Figure 2 shows the variance of $\hat{P}(E_R)$ obtained from the simulations with the refined wSSA and the

wSSAps. Since the wNRMps yielded almost the same variance as the wSSAps, we only plotted the variance obtained from the wSSAps. It is seen that the wSSAps provides variance more than one order of magnitude lower than that provided by refined wSSA with the best δ . It is also observed that the wSSAps is not very sensitive to the parameters α and β , since the variance obtained with two different sets of values for α and β is almost the same.

Table 2 lists $\hat{P}(E_R)$ and its variance obtained from $n = 10^7$ runs of the refined wSSA, the wNRMps and the wSSAps. We first ran the wNRMps and the wSSAps without fine-tuning the probability of reactions in G_3 group and calculated q_m using (25). We then ran the wNRMps and the wSSAps with fine-tuning the probability of reactions in G_3 group and used two sets of parameters ($\alpha = 0.85, \beta = 0.80$; $\alpha = 0.80, \beta = 0.75$) and (26)



to calculate q_m for the reactions in G_3 group. We also made 10^{11} runs of the exact SSA to estimate $\hat{P}(E_R)$. It is seen that the wNRMps, the wSSAps and the refined wSSA all yield the same $\hat{P}(E_R)$ as the exact SSA. However, the wNRMps and the wSSAps with fine-tuning the

probabilities of G_3 reactions offer variance more than one order of magnitude lower than that provided by the refined wSSA. Without fine-tuning the probabilities of G_3 reactions, the wNRMps and the wSSAps provided a little bit larger variance but still almost one order of magnitude lower than that provided by the refined wSSA. Table 2 also shows that the wNRMps and the wSSAps needed only 60-70% CPU time needed by the refined wSSA. Again, the CPU time of the refined wSSA in Table 2 does not include the time needed for searching for the optimal value of δ for each θ . If we include this time, the CPU time of the refined wSSA will be almost doubled.

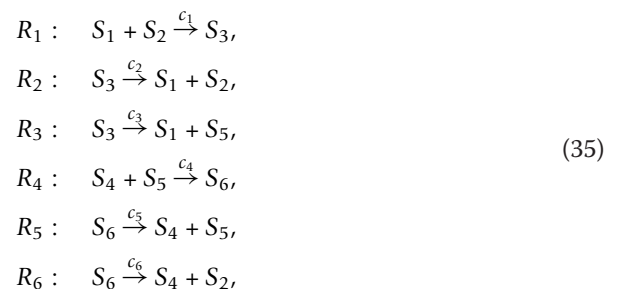
Table 2 Estimated probability of the rare event $\hat{P}(E_R)$ and the sample variance σ^2 as well as the CPU TIME (in s) with 10^7 runs of the wNRMps, the wSSAps and the refined wSSA for the system given in (32): (a) $\theta = 65$ and (b) $\theta = 68$

(a)	$\hat{P}(E_R)$	σ^2	Time
wNRMps without G_3 fine-tuning	1.14×10^{-4}	2.77×10^{-7}	13381
wSSAps without G_3 fine-tuning	1.14×10^{-4}	2.74×10^{-7}	17484
wNRMps with $\alpha = 0.85, \beta = 0.80$	1.14×10^{-4}	1.27×10^{-7}	13504
wSSAps with $\alpha = 0.85, \beta = 0.80$	1.14×10^{-4}	1.28×10^{-7}	16649
wNRMps with $\alpha = 0.80, \beta = 0.75$	1.14×10^{-4}	1.29×10^{-7}	13540
wSSAps with $\alpha = 0.80, \beta = 0.75$	1.14×10^{-4}	1.29×10^{-7}	17243
Refined wSSA	1.14×10^{-4}	1.54×10^{-6}	24499
(b)	$\hat{P}(E_R)$	σ^2	Time
wNRMps without G_3 fine-tuning	1.49×10^{-5}	1.14×10^{-8}	14087
wSSAps without G_3 fine-tuning	1.49×10^{-5}	1.09×10^{-8}	17285
wNRMps with $\alpha = 0.85, \beta = 0.80$	1.49×10^{-5}	3.28×10^{-9}	13920
wSSAps with $\alpha = 0.85, \beta = 0.80$	1.49×10^{-5}	3.29×10^{-9}	17862
wNRMps with $\alpha = 0.80, \beta = 0.75$	1.49×10^{-5}	3.32×10^{-9}	14018
wSSAps with $\alpha = 0.80, \beta = 0.75$	1.49×10^{-5}	3.30×10^{-9}	17858
Refined wSSA	1.49×10^{-5}	7.93×10^{-8}	24739

The probability of the rare event estimated from 10^{11} runs of exact SSA method is 1.14×10^{-4} for $\theta = 65$ and 1.49×10^{-5} for $\theta = 68$

5.3 Enzymatic futile cycle model

The enzymatic futile cycle model used in [22,23] consists of two instances of the elementary single-substrate enzymatic reaction described by the following six reactions:



This system essentially consists of a forward-reverse pair of enzyme-substrate reactions, with the conversion of S_2 into S_5 catalyzed by S_1 in the first three reactions and the conversion of S_5 into S_2 catalyzed by S_4 in the last three reactions. We used the same probability rate constants and initial state as used in [22,23]:

$$c_1 = 1, c_2 = 1, c_3 = 0.1, c_4 = 1, c_5 = 1, c_6 = 0.1, \quad (36)$$

and

$$X_1(0) = 1, X_2(0) = 50, X_3(0) = 0, X_4(0) = 1, X_5(0) = 50, X_6(0) = 0. \quad (37)$$

With the above rate constants and initial state, $X_2(t)$ and $X_2(5)$ tend to equilibrate about their initial value 50. References [22,23] sought to estimate $P(E_R) = P_{t \leq 100}(X_5 \rightarrow \theta | \mathbf{x}(0))$, the probability that $X_5(t) = \theta$ for $t \leq 100$ and several values of θ between 25 and 40. We repeated simulations with the refined wSSA in [23] for $\theta = 25$ and 40. The refined wSSA employed the following parameters $\gamma_3 = \delta$, $\gamma_6 = 1/\delta$ and $\gamma_m = 1$, $m = 1, 2, 4, 5$, and we used the best value of δ determined in [23]: $\delta = 0.35$ for $\theta = 25$ and $\delta = 0.60$ for $\theta = 40$.

In this system, we always have $X_2(t) + X_5(t) = 100$. So when the rare event occurs at time t , we have $X_5(t) = \theta$ and $X_2(t) = 100 - \theta$. The rare event is therefore defined as $X_5 = 50 + \eta$ with $\eta = \theta - 50$ or equivalently $X_2 = 50 - \eta$. According to the partition rule defined in Section 4, R_3 is a G_2 reaction; R_6 is a G_1 reaction; R_1, R_2, R_4 and R_5 are G_3 reactions.

We ran Gillespie's SSA 10^3 times and got an estimate of \bar{K}_T as $\bar{K}_T = 432$, and thus $K_E = \bar{K}_T = 432$. When $\theta = 40$, we have $\eta = -10$. Using (23) and $K_E = 432$, we obtained $\kappa = 6$. Substituting κ into (24), we got $Q_{G_2} = 6/432$, $Q_{G_2} = 6/432$ and $Q_{G_3} = 410/432$. In this example, there always have certain reactions whose propensity functions are zero, since we always have $X_1(t) + X_3(t) = 1$ and $X_4(t) + X_6(t) = 1$. Due to this special property, we calculate the probability of each reaction as follows. The system has only 4 states in terms of $X_3(t)$ and $X_6(t)$: $X_3(t)X_6(t) = 11, 01, 10$ or 00 . From the 10^3 runs of Gillespie's exact SSA, we estimated the probability of reactions occurring in reach state as $P_{11} \approx 1/2$, $P_{01} = P_{10} \approx 1/4$ and $P_{00} \approx 0$. Note that reaction R_6 only occurs in states 11 and 01 and we denote its probability in these two states used in the wSSAs as q_6^{11} and q_6^{01} and its natural probability as p_6^{11} and p_6^{01} . The probability p_6^{11} can be calculated as $p_6^{11} = 1/22$ and p_6^{01} can be approximated as $p_6^{01} = 1/511$ assuming $X_2(t) = 50$ since the system is in equilibrium. Then, using the relationships: $Q_{G_1} = q_6^{11}P_{11} + q_6^{01}P_{01}$ and $q_6^{11}/q_6^{01} = p_6^{11}/p_6^{01}$, we get $q_6^{11} = 0.0725$ and $q_6^{01} = 0.0031$. Reaction R_3 only occurs in states 11 and 10 and its probability can be obtained similarly as $q_3^{11} = 0.0272$ and $q_3^{10} = 0.0012$. In a state s (s

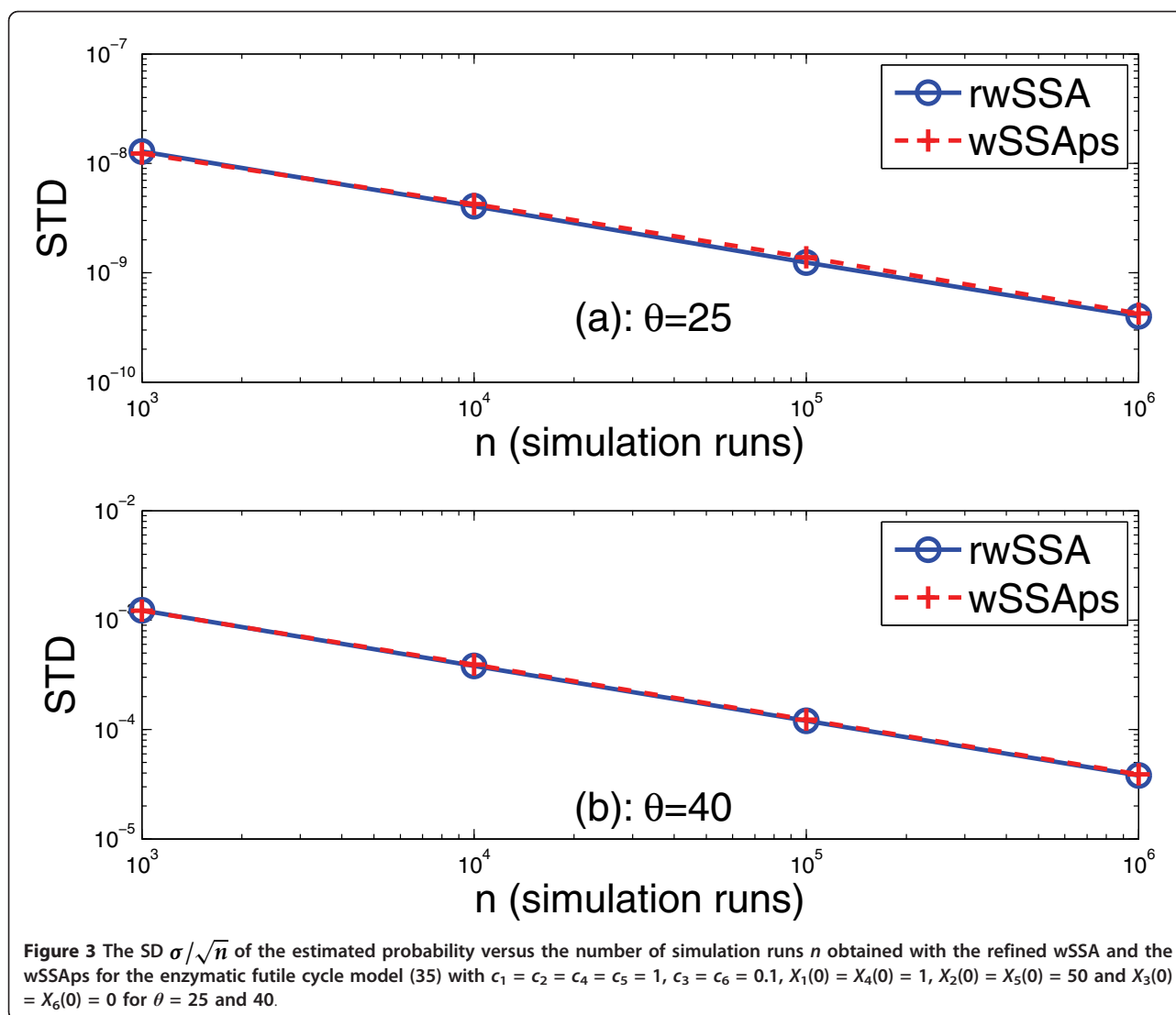
$= 11, 01, 10$ or 00), we calculate $Q_{G_3} = 1 - q_6^s - q_3^s$ and then calculated q_m^s , $m = 1, 2, 4$ and 5 , from (25). Surprisingly, q_6^{11} , q_6^{01} , q_3^{11} and q_3^{10} we calculated are very close to the values used in the refined wSSA which were obtained by making 10^5 runs of the refined wSSA for each of seven guessed values of γ . In contrast, we do not need to guess the values of parameters but calculate them analytically, and all the information needed in our calculation was obtained from 10^3 of Gillespie's exact SSA, which incurs negligible computational overhead.

When $\theta = 25$, we have $\eta = -25$. Using (23) and $\bar{K}_T = 432$, we obtained $\kappa = 3$. Substituting κ into (24), we got $Q_{G_1} = 28/432$, $Q_{G_2} = 3/432$ and $Q_{G_3} = 401/432$. Similar to the previous calculation, we got $q_6^{11} = 0.1269$, $q_3^{11} = 0.0136$, $q_3^{10} = 0.0136$ and $q_3^{10} = 0.0006$ and then calculated the probabilities of other reactions from (25). Again q_6^{11} , q_6^{01} , q_3^{11} and q_3^{10} we obtained are very close to the values used in the refined wSSA.

Table 3 lists the simulation results obtained from 10^6 runs of the wNRMps, the wSSAs and the refined wSSA for $\theta = 40$ and 25. It is seen that the estimated probability $\hat{P}(E_R)$ and variance σ^2 are almost identical for all three methods, which is expected because the probability of each reaction in three methods is almost the same. This implies that all three methods may have used near optimal values for the importance sampling parameters. However, in the previous two systems, the parameters used by the refined wSSA are far away from their optimal values, because the wSSAs and the wNRMps provided much lower variance than the refined wSSA. It is also seen from Table 3 that the wSSAs used almost the same CPU time as that used by the refined wSSA and that the wNRMps used about 80% of the CPU time of the refined wSSA. Again, the CPU time of the refined wSSA does not include the time needed to find the optimal value of δ . Figure 3 depicts the standard deviation of the estimated probability versus the number of simulation runs n for the

Table 3 Estimated probability of the rare event $\hat{P}(E_R)$ and the sample variance σ^2 as well as the CPU TIME (in s) with 10^6 runs of the wNRMps, the wSSAs and the refined wSSA for the enzyme futile cycle model (35): (a) $\theta = 25$ and (b) $\theta = 40$

(a)	$\hat{P}(E_R)$	σ^2	Time
wNRMps	1.74×10^{-7}	1.81×10^{-13}	4183.2
wSSAs	1.74×10^{-7}	1.80×10^{-13}	5316.9
Refined wSSA	1.74×10^{-7}	1.61×10^{-13}	5337.2
(b)	$\hat{P}(E_R)$	σ^2	Time
wNRMps	4.21×10^{-2}	1.51×10^{-3}	3589.4
wSSAs	4.21×10^{-2}	1.51×10^{-3}	4388.3
Refined wSSA	4.21×10^{-2}	1.51×10^{-3}	4406.6



wSSAps and the refined wSSA. Since the wNRMs provides almost the same standard deviation as the wSSAps, we did not plot it in the figure. It is again seen that the wSSAps and the refined wSSA yield almost the same standard deviation for all values of n in this case. It was demonstrated in [24] that the dwSSA yielded comparable variance as the refined wSSA. Therefore, our parameter selection method offers similar performance to the dwSSA in this example.

6 Conclusion

The wSSA and the refined wSSA are innovative variation of Gillespie's standard SSA. They provide an efficient way for estimating the probability of rare events that occur in chemical reaction systems with an extremely low probability in a given time period. The wSSA was developed based on the directed method of the

SSA. In this paper, we developed an alternative wNRM for estimating the probability of the rare event. We also devised a systematic method for selecting the values of importance sampling parameters, which is absent in the wSSA and the refined wSSA.

This parameter selection method was then incorporated into the wSSA and the wNRM. Numerical examples demonstrated that comparing with the refined wSSA and the dwSSA, the wSSA and the wNRM with our parameter selection procedure could substantially reduce the variance of the estimated probability of the rare event and speed up simulation.

Abbreviations

NRM: next reaction method; wNRM: weighted NRM; wSSA: weighted stochastic simulation algorithm.

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Competing interests

The author declares that they have no competing interests.

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