NRM. In Sec. V, we introduce the ODM and present some numerical results which illustrate its efficiency.

II. BACKGROUND

In this section we briefly review the three formulations of SSA: Direct, first reaction, and next reaction, and describe the Heat Shock Response (HSR) model that will be used in some of the numerical experiments.

A. Stochastic simulation algorithm

Suppose the system involves N molecular species $\{S_1,\ldots,S_N\}$, represented by the state vector $X(t)=[X_1(t),\ldots,X_N(t)]$, where $X_i(t)$ is the number of molecules of species S_i at time t. M reaction channels $\{R_1,\ldots,R_M\}$ are involved in the system. Assume the system is well stirred and in thermal equilibrium. The dynamics of reaction channel R_j is characterized by the *propensity function* a_j and by the *state change vector* $\nu_j=(\nu_{1j},\ldots,\nu_{Nj})$: $a_j(x)dt$ gives the probability that, given $X(t)=x$, one R_j reaction will occur in the next infinitesimal time interval $[t,t+dt)$, and ν_{ij} gives the change in the population of S_i induced by one R_j reaction.

The dynamics of the system obeys the CME (Refs. 4 and 5),

$$\frac{\partial P(x,t|x_0,t_0)}{\partial t}=\sum_{j=1}^{M}\left[a_j(x-\nu_j)P(x-\nu_j,t|x_0,t_0)-a_j(x)P(x,t|x_0,t_0)\right], \tag{1}$$

where the function $P(x,t|x_0,t_0)$ denotes the probability that $X(t)$ will be x, given that $X(t_0)=x_0$. The CME is hard to solve both theoretically and numerically except for very simple systems. In practice, simulation methods are used. The SSA (Refs. 4 and 5) is a well-known stochastic simulation method which is rigorously equivalent to the CME. Starting from the initial states, the SSA simulates the trajectory by repeatedly answering the following two questions and updating the states:

(1) When (time τ) will the next reaction fire?
(2) Which (reaction channel index μ) reaction will fire next?

The distributions of τ and μ are formulated to answer the two questions. Let

$$a_0(X)=\sum_{j=1}^{M}a_j(X). \tag{2}$$

The time τ, given $X(t)=x$, that the reaction will fire at $t+\tau$, is the exponentially distributed random variable with mean $[1/a_0(x)]$,

$$p(\tau=s)=a_0(x)\exp[-a_0(x)s], \tag{3}$$

and the index μ of that firing reaction is the integer random variable with probability

$$P(\mu=j)=\frac{a_j(x)}{a_0(x)}. \tag{4}$$

In each step, the SSA generates random numbers and calculates τ and μ according to the probability distributions (3) and (4). Three different but stochastically equivalent formulations for SSA are proposed as follows.

B. Direct method

On each step, the direct method generates two random numbers r_1 and r_2 in $U(0,1)$ [the set of uniformly distributed random numbers in the interval (0,1)]. The time for the next reaction to occur is given by $t+\tau$, where τ is given by

$$\tau=\frac{1}{a_0(x)}\ln\left(\frac{1}{r_1}\right). \tag{5}$$

The index μ of the occurring reaction is given by the smallest integer satisfying

$$\sum_{j'=1}^{\mu}a_{j'}(t)>r_2a_0(t). \tag{6}$$

The system states are updated by $X(t+\tau)=X(t)+\nu_\mu$. Then the simulation proceeds to the next occurring time.

Algorithm direct method

(1) Initialization (set the initial numbers of molecules. Set $t=0$).
(2) Calculate the propensity functions a_i $(i=1,\ldots,M)$ and a_0 from Eq. (2).
(3) Generate two random numbers r_1 and r_2 in $U(0,1)$.
(4) Calculate τ according to Eq. (5).
(5) Search for μ as the smallest integer satisfying Eq. (6).
(6) Update the states of the species to reflect execution of reaction μ. Set $t\leftarrow t+\tau$.
(7) Go to step 2.

C. First reaction method

The first reaction method generates a τ_k for each reaction channel R_k according to

$$\tau_k=\frac{1}{a_k(x)}\ln\left(\frac{1}{r_k}\right)\quad(k=1,\ldots,M), \tag{7}$$

where $r_1,\ldots,r_M$ are M statistically independent samplings of $U(0,1)$. Then τ and μ are chosen as

$$\tau=\min\{\tau_1,\ldots,\tau_M\}, \tag{8}$$

and

$$\mu=\text{the index of }\min\{\tau_1,\ldots,\tau_M\}. \tag{9}$$

Algorithm first reaction method

(1) Initialization (set the initial numbers of molecules. Set $t=0$).
(2) Calculate the propensity functions a_i $(i=1,\ldots,M)$.
(3) Generate M independent random numbers from $U(0,1)$.
(4) Generate the time τ_i $(i=1,\ldots,M)$ according to Eq. (7).
(5) Find τ and μ according to Eqs. (8) and (9).
(6) Update the states of the species to reflect execution of reaction μ. Set $t\leftarrow t+\tau$.
(7) Go to step 2.