

Introducing Stochastic Simulation of Chemical Reactions Using the Gillespie Algorithm and MATLAB: REVISITED AND AUGMENTED

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In their contribution, Martínez-Urreaga and his collaborators^[1] have presented the stochastic simulation of a chemical reaction—specifically, a simple reversible chemical reaction whose rate law is of the first-order, or linear. Their work is indeed useful and informative: Randomly or stochastically behaving processes or systems are ubiquitous in the chemical or allied industries.^[2-9]

The current contribution involves two aspects and is intended to complement and augment the work of Martínez-Urreaga and his collaborators^[1] to enhance its usefulness. First, the reacting system (*i.e.*, the simple reversible chemical reaction) illustrated by them is modeled as a stochastic process, specifically a birth-death process—the most general subclass of Markovian processes.^[10, 11] The resultant model, in turn, gives rise to the master, or governing, equation^[11, 12] of the birth-death process whose solution renders it possible to obtain the analytical expressions for the process' means and higher moments about the means, *e.g.*, the variances, which are collectively a manifestation of the process' inherent fluctuations. Second, the master equation of the birth-death process is stochastically simulated via the Monte Carlo method.^[13] The method is implemented by the time-driven approach^[14, 15] in addition to the event-driven approach^[10, 15-23] adopted by

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Martínez-Urreaga and his collaborators^[1] on the basis of the Gillespie algorithm.^[10, 17, 18] The event-driven approach entails the determination of the probability distribution of a random waiting time or period of quiescence^[19, 20]; the simulation clock is advanced according to this random waiting time. Unlike the event-driven approach, the time-driven approach advances the simulation clock by a fixed time increment,^[14, 15] which can be estimated as a function of the intensities of transition embedded in the master equation of the process. The time-driven approach is especially useful when the probability distribution for the random waiting time in the event-driven approach is exceedingly complex to determine. The means and variances of the random variables characterizing the birth-death process have been computed in implementing the event-driven and time-driven approaches. For validation, the analytical solutions from the stochastic model as well as the numerical results from the Monte Carlo simulation are compared with each other. In addition, these results are validated by comparing the values of the means obtained from the solution of the deterministic model for the simple reversible chemical reaction as presented by Martínez-Urreaga and his collaborators.^[1]

The two approaches for stochastic simulation are further illustrated with the photoelectrochemical disinfection of bacteria whose rate of decaying is linear. The results from simulation are validated by comparing them with the available experimental data^[24] as well as with the analytical solutions derived from the corresponding stochastic model.

MODEL FORMULATION

The system under consideration comprises the populations of molecules of species A and B per unit volume that are being chemically transformed into one another according to the simple reversible reaction,



Clearly, the population of A decreases and that of B increases when one molecule of A transforms into one molecule of B with forward reaction-rate constant k_1 . Similarly, the population of B decreases and that of A increases when one molecule of B transforms into one molecule of A with reverse reaction-rate constant k_2 . The system constitutes, therefore, a special class of Markov processes, the birth-death process.^[11, 12] Thus, the numbers of molecules of A and B at time t , $N_A(t)$ and $N_B(t)$, respectively, can be taken as the random variables of the birth-death process of interest. A realization of $N_A(t)$ is denoted by n_A , and that of $N_B(t)$ by n_B . At any time t , the total number of molecules in the system remains constant; hence, the following relationship holds;

$$N_A(0) + N_B(0) = N_A(t) + N_B(t)$$

or

$$n_{A0} + n_{B0} = N_A(t) + N_B(t) \quad (2)$$

where $N_A(0)$ or n_{A0} is the number of molecules of A at the outset of the reaction, *i.e.*, at $t = 0$. Similarly, $N_B(0)$ or n_{B0} is the number of molecules of B at $t = 0$. These two quantities are constant, thereby indicating that only one of the random variables in Eq. (2) is independent. By denoting the total number of molecules at $t = 0$, *i.e.*, $(n_{A0} + n_{B0})$, as n_{T0} , Eq. (2) can be rewritten as

$$n_{T0} = N_A(t) + N_B(t) \quad (3)$$

If $N_A(t)$ is selected as the independent random variable, $N_B(t)$ can be expressed in terms of $N_A(t)$, from the above equation, as

$$N_B(t) = n_{T0} - N_A(t) \quad (4)$$

whose realization is naturally

$$n_B = n_{T0} - n_A \quad (5)$$

Consequently, the state space for the current system is all the possible numbers of molecules of A, *i.e.*, $\{n_{T0}, (n_{T0} - 1), \dots, 2, 1, 0\}$.

MASTER EQUATION

The derivation of the master equation of a stochastic process has been extensively elaborated in our previous contribution to this journal.^[25] For the birth-death process of interest, the probability balance around any arbitrary state n_A of the independent random variable, $N_A(t)$, gives rise to^[11, 12]

$$\begin{aligned} \frac{d}{dt} p(n_A; t) = & W_+(n_A - 1; t) p(n_A - 1; t) \\ & + W_-(n_A + 1; t) p(n_A + 1; t) \\ & - [W_+(n_A; t) + W_-(n_A; t)] p(n_A; t) \end{aligned} \quad (6)$$

This derivation is also detailed in Appendix A. The term, $p(n_A; t)$, in the above equation denotes the probability of n_A molecules being present at time t . On the basis of the first-order rate law, the intensity of birth, $W_+(n_A; t)$, and the intensity of death, $W_-(n_A; t)$, have been defined as^[1]

$$W_+(n_A; t) = \frac{dn_A}{dt} = k_2 n_B = k_2 (n_{T0} - n_A) \quad (7)$$

and

$$W_-(n_A; t) = -\frac{dn_A}{dt} = k_1 n_A, \quad (8)$$

respectively. It is worth noting that the intensities of birth and death can be defined on the basis of not only linear but also nonlinear rate laws, thereby giving rise to a variety of linear and non-linear stochastic models. In fact, the formulation of stochastic models for processes obeying nonlinear rate laws has been presented in some of our earlier contributions.^[26-28]

MEANS AND VARIANCES

The solution of the master equation, Eq. (6), renders it possible to obtain the mean and higher moments about the mean of the random variables, $N_A(t)$ and $N_B(t)$; see Appendix B.

Among these higher moments, the second moment about the mean, *i.e.*, the variance, is of utmost importance: It signifies the fluctuations, or scatterings, of the random variable about its mean.^[29]

Eq. (6) in conjunction with Eqs. (7) and (8) yields the expression for the mean of $N_A(t)$, $E[N_A(t)]$ or $\langle N_A(t) \rangle$, as

$$\langle N_A(t) \rangle = \frac{n_{T0}}{(k_1 + k_2)} \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1 + k_2) - k_2 \right] \exp[-(k_1 + k_2)t] + k_2 \right\} \quad (9)$$

Note that in the particular case where $n_{A0} = n_{T0}$, *i.e.*, where $n_{B0} = 0$, the above expression reduces to^[30,31]

$$\langle N_A(t) \rangle = \frac{n_{T0}}{(k_1 + k_2)} \{ k_1 \exp[-(k_1 + k_2)t] + k_2 \} \quad (10)$$

In addition, the mean of $N_B(t)$, $E[N_B(t)]$ or $\langle N_B(t) \rangle$, is, from Eqs. (4) and (9),

$$\langle N_B(t) \rangle = n_{T0} \left[1 - \frac{1}{(k_1 + k_2)} \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1 + k_2) - k_2 \right] \exp[-(k_1 + k_2)t] + k_2 \right\} \right] \quad (11)$$

Similarly, the expression for the variance of $N_A(t)$, $\text{Var}[N_A(t)]$ or $\sigma_A^2(t)$, is evaluated as

$$\sigma_A^2(t) = \frac{n_{T0}}{(k_1 + k_2)^2} \{ 1 - \exp[-(k_1 + k_2)t] \} \cdot \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 + k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\} \quad (12)$$

For the case, $n_{A0} = n_{T0}$, this equation becomes^[30]

$$\sigma_A^2(t) = \left(\frac{k_1}{k_1 + k_2} \right) \{ 1 - \exp[-(k_1 + k_2)t] \} \langle N_A(t) \rangle \quad (13)$$

where $\langle N_A(t) \rangle$ is given by Eq. (10). The standard deviation, $\sigma_A(t)$, is the square root of the variance, $\sigma_A^2(t)$; thus, from Eq. (12),

$$\sigma_A(t) = \frac{n_{T0}^{1/2}}{(k_1 + k_2)} \{ 1 - \exp[-(k_1 + k_2)t] \}^{1/2} \cdot \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 - k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\}^{1/2} \quad (14)$$

From Eqs. (4) and (12), the variance of $N_B(t)$, $\text{Var}[N_B(t)]$ or $\sigma_B^2(t)$, is

$$\sigma_B^2(t) = \frac{n_{T0}}{(k_1 + k_2)^2} \{ 1 - \exp[-(k_1 + k_2)t] \} \cdot \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 - k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\} = \sigma_A^2(t) \quad (15)$$

From this expression, $\sigma_B(t)$ is given by

$$\sigma_B(t) = \frac{n_{T0}^{1/2}}{(k_1 + k_2)} \{ 1 - \exp[-(k_1 + k_2)t] \}^{1/2} \cdot \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 - k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\}^{1/2} = \sigma_A(t) \quad (16)$$

Randomly or stochastically behaving processes or systems are ubiquitous in the chemical or allied industries.

***In general,
the stochastic
simulation of
chemical
kinetics can
focus on the
temporal
evolution of
the number
concentrations
of entities
comprising a
reacting system
or the spatial
interactions
among these
entities.***

The coefficient of variation, $CV(t)$, signifies the relative fluctuations of a random variable about its mean^[32]; it is computed as the ratio between the standard deviation, $\sigma(t)$, and the mean, $\langle N(t) \rangle$. From Eqs. (9) and (14), the coefficient of variation of $N_A(t)$, *i.e.*, $CV_A(t)$, is

$$CV_A(t) = \frac{\sigma_A(t)}{\langle N_A(t) \rangle} = \frac{n_{T0}^{1/2}}{(k_1 + k_2)} \left\{ 1 - \exp[-(k_1 + k_2)t] \right\}^{1/2} \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 - k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\}^{1/2} \\ = \frac{n_{T0}}{(k_1 + k_2)} \left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1 - k_2) + k_2 \right] \exp[-(k_1 + k_2)t] + k_2 \right\}$$

or

$$CV_A(t) = \frac{1}{n_{T0}^{1/2}} \left\{ 1 - \exp[-(k_1 + k_2)t] \right\}^{1/2} \frac{\left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1^2 - k_2^2) + k_2^2 \right] \exp[-(k_1 + k_2)t] + k_1 k_2 \right\}^{1/2}}{\left\{ \left[\left(\frac{n_{A0}}{n_{T0}} \right) (k_1 - k_2) - k_2 \right] \exp[-(k_1 + k_2)t] + k_2 \right\}} \quad (17)$$

By substituting the expression for $\langle N_A(t) \rangle$ as given by Eq. (9), the above equation can be rewritten as

$$CV_A(t) = \frac{1}{\langle N_A(t) \rangle} \left\{ \left[\left(\frac{k_2}{k_1 + k_2} \right) \exp[-(k_1 + k_2)t] + \left(\frac{k_1}{k_1 + k_2} \right) \right] \langle N_A(t) \rangle - \left(\frac{k_2}{k_1 + k_2} \right) n_{A0} \exp[-(k_1 + k_2)t] - \left(\frac{k_1}{k_1 + k_2} \right) n_{A0} \exp[-2(k_1 + k_2)t] \right\}^{1/2} \quad (18)$$

When $n_{A0} = n_{T0}$, this expression becomes

$$CV_A(t) = \left[\left(\frac{k_1}{k_1 + k_2} \right) \left\{ 1 - \exp[-(k_1 + k_2)t] \right\} \right]^{1/2} \frac{\langle N_A(t) \rangle^{1/2}}{\langle N_A(t) \rangle} \quad (19)$$

where $\langle N_A(t) \rangle$ is given by Eq. (10). In their contribution, Martínez-Urreaga and his collaborators^[1] indicate that the relative fluctuations of $N_A(t)$ about its mean $\langle N_A(t) \rangle$, *i.e.*, the coefficient of variation, $CV_A(t)$, are approximately of the order of $(\langle N_A(t) \rangle)^{1/2} / N_A(t)$, or $\langle N_A(t) \rangle^{-1/2}$ as revealed through Eqs. (18) and (19).

STOCHASTIC SIMULATION

The master equation of the birth-death process, Eq. (3), is stochastically simulated by means of the Monte Carlo method. The stochastic simulation of chemical kinetics by this method has been known for many years.^[17, 18, 21, 33-36] A number of the works devoted to it, however, fail to deal with the crux of any stochastic simulation, which is its capability to estimate not only the mean but also higher moments about the mean, especially the vari-

ance.^[25] According to Haseltine and Rawlings,^[37] “... stochastic simulation of chemical kinetics has received an increased amount of attention from the modeling community. . . .” In general, the stochastic simulation of chemical kinetics can focus on the temporal evolution of the number concentrations of entities comprising a reacting system or the spatial interactions among these entities. The former can be accomplished by resorting to the classical formulation of the Monte Carlo method,^[13] and the latter can be carried out by means of Kinetic Monte Carlo (KMC) methods, which take into account the spatial distribution of the entities at the atomic or molecular scale.^[38, 39] In this work, the Monte Carlo method is deployed for stochastically simulating the temporal evolution of the numbers of molecules of A and B for the simple reversible reaction; thus, the simulation of spatial interactions among these molecules is not considered. The two basic procedures to implement the method, one resorting to the event-driven approach^[10, 15-23] and the other resorting to the time-driven approach,^[14, 15] are described in detail; these two approaches differ in the manner of updating the simulation clock of the process’s temporal evolution.

Event-Driven Approach

The event-driven approach advances the simulation clock by a random waiting time, τ , which has an exponential distribution.^[10, 19] No event takes place during the time interval, $(t, t + \tau)$, and only one event occurs at the end of this time interval at which the state of the system is specified by the probability of transition corresponding to each event. The Gillespie algorithm^[10, 17, 18] comprises a series of steps to perform the Monte Carlo simulation of Markov processes by the event-driven approach. This algorithm has been recently extended^[35] to accelerate the computing speed of the original formulation.^[17, 18] Herein, Gillespie’s original algorithm, as presented by Martínez-Urreaga and his collaborators,^[1] has been revised and augmented to include the evaluation of the means, variances, and standard deviations of the birth-death process of interest as described below.

Step 1. Define the total number of molecules per unit volume, n_{T0} , the total number of simulations, or trajectories, Z_f , and the length of each simulation, t_f . Initialize the simulation counter as $Z \leftarrow 1$.

Step 2. Initialize clock time t , data-recording time θ ,^[31] the realizations of $N_A(t)$ and $N_B(t)$ at time t and simulation Z , *i.e.*, $n_{A,Z}(t)$ and $n_{B,Z}(t)$, respectively, and the realizations of $N_A(\theta)$ and $N_B(\theta)$ at time θ and simulation Z , *i.e.*, $n_{A,Z}(\theta)$ and $n_{B,Z}(\theta)$, respectively, as follows:

$$\begin{aligned}\theta &\leftarrow t_0 \\ n_{A,Z}(t_0) &\leftarrow n_{A0} \\ n_{B,Z}(t_0) &\leftarrow [n_{T0} - n_{A,Z}(t_0)] \\ n_{A,Z}(\theta_0) &\leftarrow n_{A,Z}(t_0) \\ n_{B,Z}(\theta_0) &\leftarrow n_{B,Z}(t_0)\end{aligned}$$

Step 3. Sample a realization u from the uniform random variable, U , on interval $(0, 1)$. Estimate τ according to the following expression^[10];

$$\tau = \frac{1}{-\{W_+[n_{A,Z}(t); t] + W_-[n_{A,Z}(t); t]\}} \ln(1-u) \quad (20)$$

where $W_+[n_{A,Z}(t); t] = k_2[n_{T0} - n_{A,Z}(t)]$ and $W_-[n_{A,Z}(t); t] = k_1 n_{A,Z}(t)$ are the intensities of birth and death, Eqs. (7) and (8), respectively; see Appendices C and D.

Step 4. Advance clock time as $t \leftarrow (t + \tau)$.

Step 5. If $(\theta < t)$, then continue to the next step; otherwise, continue to Step 8.

Step 6. Compute the sample means, variances, and standard deviations at time θ as follows:

a. Record the value of realizations at θ :

$$\begin{aligned}n_{A,Z}(\theta) &\leftarrow n_{A,Z}(t - \tau) \\ n_{B,Z}(\theta) &\leftarrow n_{B,Z}(t - \tau)\end{aligned}$$

b. Store the sum of realizations at θ :

$$\begin{aligned}\Xi_{A,Z}(\theta) &\leftarrow \sum_{Z=1}^Z n_{A,Z}(\theta) \\ \Xi_{B,Z}(\theta) &\leftarrow \sum_{Z=1}^Z n_{B,Z}(\theta)\end{aligned}$$

c. Store the sum of squares of realizations at θ :

$$\begin{aligned}\Phi_{A,Z}(\theta) &\leftarrow \sum_{Z=1}^Z n_{A,Z}^2(\theta) \\ \Phi_{B,Z}(\theta) &\leftarrow \sum_{Z=1}^Z n_{B,Z}^2(\theta)\end{aligned}$$

d. Store the square of sum of realizations at θ :

$$\begin{aligned}\Psi_{A,Z}(\theta) &\leftarrow \left[\sum_{Z=1}^Z n_{A,Z}(\theta) \right]^2 = [\Xi_{A,Z}(\theta)]^2 \\ \Psi_{B,Z}(\theta) &\leftarrow \left[\sum_{Z=1}^Z n_{B,Z}(\theta) \right]^2 = [\Xi_{B,Z}(\theta)]^2\end{aligned}$$

e. Compute the sample means at θ ^[13, 19, 20]:

$$m_{A,Z}(\theta) \leftarrow \frac{1}{Z} \sum_{Z=1}^Z n_{A,Z}(\theta) = \frac{1}{Z} \Xi_{A,Z}(\theta) \quad (21)$$

$$m_{B,Z}(\theta) \leftarrow \frac{1}{Z} \sum_{Z=1}^Z n_{B,Z}(\theta) = \frac{1}{Z} \Xi_{B,Z}(\theta) \quad (22)$$

f. If $1 < Z \leq Z_f$, then compute the sample variances and standard deviations at θ ^[13, 19, 20]:

$$s_{A,Z}^2(\theta) \leftarrow \frac{1}{(Z-1)} \left\{ \sum_{Z=1}^Z n_{A,Z}^2(\theta) - \frac{1}{Z} \left[\sum_{Z=1}^Z n_{A,Z}(\theta) \right]^2 \right\} = \frac{1}{(Z-1)} \left\{ \Phi_{A,Z}(\theta) - \frac{1}{Z} \Psi_{A,Z}(\theta) \right\} \quad (23)$$

$$s_{B,Z}^2(\theta) \leftarrow \frac{1}{(Z-1)} \left\{ \sum_{Z=1}^Z n_{B,Z}^2(\theta) - \frac{1}{Z} \left[\sum_{Z=1}^Z n_{B,Z}(\theta) \right]^2 \right\} = \frac{1}{(Z-1)} \left\{ \Phi_{B,Z}(\theta) - \frac{1}{Z} \Psi_{B,Z}(\theta) \right\} \quad (24)$$

$$s_{A,Z}(\theta) \leftarrow [s_{A,Z}^2(\theta)]^{1/2} \quad (25)$$

$$s_{B,Z}(\theta) \leftarrow [s_{B,Z}^2(\theta)]^{1/2} \quad (26)$$

Step 7. Advance θ by a conveniently small $\Delta\theta$ as $\theta \leftarrow (\theta + \Delta\theta)$. If $(\theta \leq t_f)$, then return to Step 5; otherwise, continue to Step 10.

Step 8. Determine the state of the system at the end of time interval $(t, t + \tau)$. To accomplish this, sample a realization u' from the uniform random variable, U , on interval $(0, 1)$ and compute the probability of transition corresponding to the birth event, $w_+[n_{A,Z}(t); t]$, as follows:

$$w_+[n_{A,Z}(t); t] = \frac{W_+[n_{A,Z}(t); t]}{W_+[n_{A,Z}(t); t] + W_-[n_{A,Z}(t); t]} \quad (27)$$

If $\{0 < u' < w_+[n_{A,Z}(t); t]\}$, then a birth event occurs, *i.e.*, the population of molecules of A increases by one; thus,

$$\begin{aligned} n_{A,Z}(t) &\leftarrow [n_{A,Z}(t - \tau) + 1] \\ n_{B,Z}(t) &\leftarrow [n_{T0} - n_{A,Z}(t)] \\ n_{A,Z}(\theta) &\leftarrow n_{A,Z}(t) \\ n_{B,Z}(\theta) &\leftarrow n_{B,Z}(t) \end{aligned}$$

Otherwise, a death event occurs, *i.e.*, the population of molecules of A decreases by one; thus,

$$\begin{aligned} n_{A,Z}(t) &\leftarrow [n_{A,Z}(t - \tau) - 1] \\ n_{B,Z}(t) &\leftarrow [n_{T0} - n_{A,Z}(t)] \\ n_{A,Z}(\theta) &\leftarrow n_{A,Z}(t) \\ n_{B,Z}(\theta) &\leftarrow n_{B,Z}(t) \end{aligned}$$

Step 9. Repeat Steps 3 through 8 until t_f is reached.

Step 10. Update simulation counter as $Z \leftarrow (Z + 1)$.

Step 11. Repeat Steps 2 through 10 until Z_f is reached.

Given in Appendix E is the computer code in MATLAB for performing Monte Carlo simulation on the basis of the Gillespie algorithm via the event-driven approach as presented above.

Time-Driven Approach

As briefly indicated at the outset of this contribution, the time-driven

approach^[14, 15] differs from the event-driven approach: It advances the simulation clock by a fixed time increment of Δt , which is sufficiently small so that at most one or no event occurs during time interval $(t, t + \Delta t)$. At the end of this interval, the state of the process is determined by the probability of transition corresponding to each event. The series of steps for implementing Monte Carlo simulation of Markov processes in general and the birth-death process of interest in particular by the time-driven approach is given below.

Step 1. Define the total number of molecules per unit volume, n_{T0} , the total number of simulations, or trajectories, Z_f , and the length of each simulation, t_f . Initialize the simulation counter as $Z \leftarrow 1$. Compute time increment Δt as follows:

$$\Delta t = \frac{1}{[W_+^M(n_A; t) + W_-^M(n_A; t)]} \quad (28)$$

where $W_+^M(n_A; t)$ and $W_-^M(n_A; t)$ are the maximum possible values of the intensities of birth and death, respectively.

Step 2. Initialize time t and the realizations of $N_A(t)$ and $N_B(t)$ at time t and simulation Z , *i.e.*, $n_{A,Z}(t)$ and $n_{B,Z}(t)$, respectively, as follows:

$$\begin{aligned} t &\leftarrow t_0 \\ n_{A,Z}(t_0) &\leftarrow n_{A0} \\ n_{B,Z}(t_0) &\leftarrow [n_{T0} - n_{A,Z}(t_0)] \end{aligned}$$

Step 3. Compute the sample means, variances, and standard deviations at time t as follows:

a. Record the values of realizations at t :

$$\begin{aligned} n_{A,Z}(t) &\leftarrow n_{A,Z} \\ n_{B,Z}(t) &\leftarrow n_{B,Z} \end{aligned}$$

b. Store the sum of realizations at t :

$$\begin{aligned} \Xi_{A,Z}(t) &\leftarrow \sum_{Z=1}^Z n_{A,Z}(t) \\ \Xi_{B,Z}(t) &\leftarrow \sum_{Z=1}^Z n_{B,Z}(t) \end{aligned}$$

c. Store the sum of squares of realizations at t :

$$\begin{aligned} \Phi_{A,Z}(t) &\leftarrow \sum_{Z=1}^Z n_{A,Z}^2(t) \\ \Phi_{B,Z}(t) &\leftarrow \sum_{Z=1}^Z n_{B,Z}^2(t) \end{aligned}$$

d. Store the square of sum of realizations at t:

$$\Psi_{A,Z}(t) \leftarrow \left[\sum_{Z=1}^Z n_{A,Z}(t) \right]^2 = [\Xi_{A,Z}(t)]^2$$

$$\Psi_{B,Z}(t) \leftarrow \left[\sum_{Z=1}^Z n_{B,Z}(t) \right]^2 = [\Xi_{B,Z}(t)]^2$$

e. Compute the sample means at t:

$$m_{A,Z}(t) \leftarrow \sum_{Z=1}^Z n_{A,Z}(t) = \frac{1}{Z} \Xi_{A,Z}(t) \quad (29)$$

$$m_{B,Z}(t) \leftarrow \sum_{Z=1}^Z n_{B,Z}(t) = \frac{1}{Z} \Xi_{B,Z}(t) \quad (30)$$

f. If $1 < Z \leq Z_f$, then compute sample the variances and standard deviations at t:

$$s_{A,Z}^2(t) \leftarrow \frac{1}{(Z-1)} \left\{ \sum_{Z=1}^Z n_{A,Z}^2(t) - \frac{1}{Z} \left[\sum_{Z=1}^Z n_{A,Z}(t) \right]^2 \right\} = \frac{1}{(Z-1)} \left\{ \Phi_{A,Z}(t) - \frac{1}{Z} \Psi_{A,Z}(t) \right\} \quad (31)$$

$$s_{B,Z}^2(t) \leftarrow \frac{1}{(Z-1)} \left\{ \sum_{Z=1}^Z n_{B,Z}^2(t) - \frac{1}{Z} \left[\sum_{Z=1}^Z n_{B,Z}(t) \right]^2 \right\} = \frac{1}{(Z-1)} \left\{ \Phi_{B,Z}(t) - \frac{1}{Z} \Psi_{B,Z}(t) \right\} \quad (32)$$

$$s_{A,Z}(t) \leftarrow [s_{A,Z}^2(t)]^{1/2} \quad (33)$$

$$s_{B,Z}(t) \leftarrow [s_{B,Z}^2(t)]^{1/2} \quad (34)$$

Step 4. Advance time as $t \leftarrow (t + \Delta t)$.

Step 5. Estimate the probabilities of transition corresponding to the birth and death events as $\{W_+[n_{A,Z}(t);t]\Delta t$ and $\{W_+[n_{A,Z}(t);t]+W_-[n_{A,Z}(t);t]\Delta t$, respectively.

Step 6. Determine the state of the system at the end of time interval $(t, t + \Delta t)$. To accomplish this, sample a realization u from the uniform random variable U on interval $(0, 1)$ and compare it with the probabilities of transition for the birth and death events. If $u < [W_+(n_A;t)]\Delta t$, then a birth event occurs; thus,

$$n_{A,Z}(t) \leftarrow [n_{A,Z}(t - \Delta t) + 1]$$

$$n_{B,Z}(t) \leftarrow [n_{T0} - n_{A,Z}(t)]$$

If $u < [W_+(n_A;t) + W_-(n_A;t)]\Delta t$, then a death event occurs; thus,

$$n_{A,Z}(t) \leftarrow [n_{A,Z}(t - \Delta t) - 1]$$

$$n_{B,Z}(t) \leftarrow [n_{T0} - n_{A,Z}(t)]$$

Otherwise, no event occurs; thus,

$$n_{A,Z}(t) \leftarrow n_{A,Z}(t - \Delta t)$$

$$n_{B,Z}(t) \leftarrow [n_{T0} - n_{A,Z}(t)]$$

Step 7. Repeat Steps 3 through 6 until t_f is reached.

Step 8. Update the simulation counter as $Z \leftarrow (Z + 1)$.

Step 9. Repeat Steps 2 through 8 until Z_f is reached.

Given in Appendix F is the computer code in MATLAB for performing Monte Carlo simulation via the time-driven approach as presented above.

RESULTS AND DISCUSSION

The means, variances, and standard deviations of the random variables, $N_A(t)$ and $N_B(t)$, characterizing the simple reversible reaction have been computed with the values for k_1 and k_2 , and the two sets of values for n_{A0} and n_{B0} , given by Martínez-Urreaga and his collaborators.^[1] Thus, k_1 is $4 \cdot 10^{-3} \text{ s}^{-1}$ and k_2 is $1 \cdot 10^{-3} \text{ s}^{-1}$; the first set of values for n_{A0} and n_{B0} comprises 175 molecules of A and 25 molecules of B, and the second set comprises 3,500 molecules of A and 500 molecules of B.

The means, $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$, have been computed from the stochastic model according to their corresponding analytical expressions, Eqs. (9) and (11); the results are illustrated for the first set of n_{A0} and n_{B0} in Figure 1 (next page) and for the second set of n_{A0} and n_{B0} in Figure G-1 in Appendix G. In these figures, the numbers of molecules of A and B obtained from the solution of the deterministic model as presented by Martínez-Urreaga and his collaborators^[1] are superimposed for comparison. Clearly, the values of $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$ obtained from the stochastic model are in excellent accord with the corresponding deterministic values, thereby verifying that the mean component of the stochastic model for the birth-death process is equivalent to the deterministic model.

The standard deviations, $\sigma_A(t)$ and $\sigma_B(t)$, signify the variability attributable to the internal or characteristic noises of the process as predicted by the stochastic model. The values of $\sigma_A(t)$ and $\sigma_B(t)$ have been computed from Eqs. (14) and (16), respectively; they are plotted in Figures 1 and G-1 as the standard deviation envelopes, $[\langle N_A(t) \rangle \pm \sigma_A(t)]$ for $N_A(t)$ and $[\langle N_B(t) \rangle \pm \sigma_B(t)]$ for $N_B(t)$,

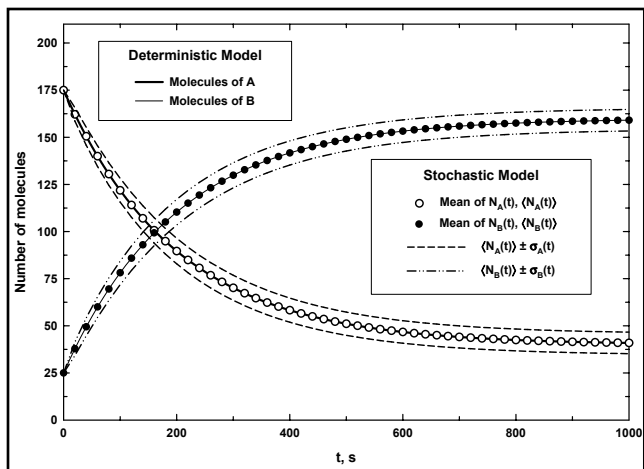


Figure 1. Temporal evolution of the numbers of molecules of A and B per unit volume with $n_{A0} = 175$ and $n_{B0} = 25$: The solutions from the stochastic model are compared with those from the deterministic model.

respectively. Note that the variability or dispersion of the process is more pronounced in Figure 1 than in Figure G-1: As indicated by Martínez-Urreaga and his collaborators^[1] and earlier in the current contribution, the relative extent of fluctuations of a random variable $N(t)$ about its mean $\langle N(t) \rangle$ is approximately of the order $(\langle N(t) \rangle)^{1/2} / \langle N(t) \rangle$, or $\langle N(t) \rangle^{-1/2}$, *i.e.*, it is inversely proportional to the square root of the population size. In other words, the smaller the population size, the greater the extent of variability or dispersion of the process about its mean and vice versa.

The sample means, $m_{A,Z}(\theta)$ and $m_{B,Z}(\theta)$, have been computed through the Monte Carlo method on the basis of the event-driven approach by averaging the realizations of $N_A(t)$ and $N_B(t)$ from Z successive simulations. The results are illustrated for $Z = 2$ in Figure 2 and $Z = 50$ in Figure 3 for the first set of n_{A0} and n_{B0} ; the values of $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$ computed from the stochastic model as well as the numbers of molecules of A and B obtained from the solution of the deterministic model are superimposed in both figures for comparison. Clearly, $m_{A,Z}(\theta)$ and $m_{B,Z}(\theta)$ approach $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$, respectively, as the number of simulations, Z , varies from 2 to 50. The results are in line with the Weak Law of Large Numbers (WLLN), stating that the sample mean approaches the population mean as the size of the sample becomes large.^[29] In stochastically simulating the birth-death process, the size of the samples, *i.e.*, the numbers of realizations of $N_A(t)$ and $N_B(t)$, increases as the number of simulations, Z , increases. Similarly, $m_{A,Z}(\theta)$ and $m_{B,Z}(\theta)$ are essentially identical to $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$, respectively, when they are computed by averaging 50 simulations, *i.e.*, $Z = 50$, for the second set of n_{A0} and n_{B0} ; see Figure G-2 in Appendix G. The sample standard deviation envelopes, $[m_{A,Z}(\theta) \pm s_{A,Z}(\theta)]$ for $N_A(t)$ and $[m_{B,Z}(\theta) \pm s_{B,Z}(\theta)]$ for $N_B(t)$, are also plotted in Figures 2 and 3 as well as in Figure G-2 in Appendix G; they are essentially identical to $[\langle N_A(t) \rangle \pm \sigma_A(t)]$

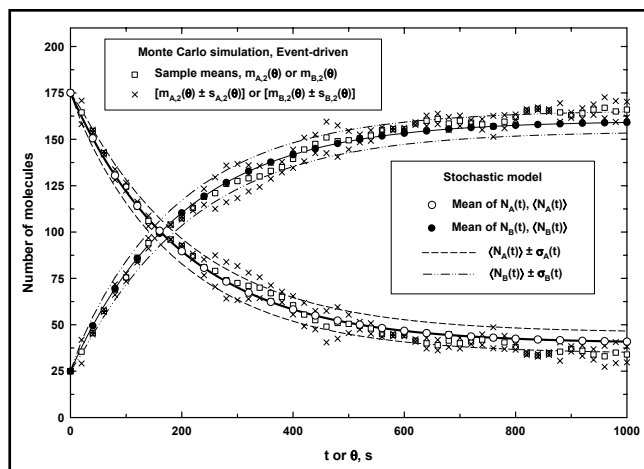


Figure 2. Temporal evolution of the means and standard deviation envelopes of the numbers of molecules of A and B per unit volume with $n_{A0} = 175$ and $n_{B0} = 25$: The average of two Monte Carlo simulations via the event-driven approach is compared with the analytical solutions resulting from the stochastic model; the solution of the deterministic model is represented by the solid lines.

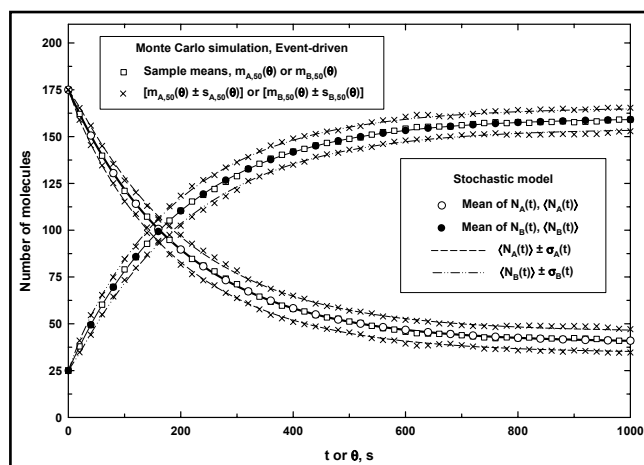


Figure 3. Temporal evolution of the means and standard deviation envelopes of the numbers of molecules of A and B per unit volume with $n_{A0} = 175$ and $n_{B0} = 25$: The average of 50 Monte Carlo simulations via the event-driven approach is compared with the analytical solutions resulting from the stochastic model; the solution of the deterministic model is represented by the solid lines.

and $[\langle N_B(t) \rangle \pm \sigma_B(t)]$, respectively, for $Z = 50$.

Figures G-3 and G-4 in Appendix G exhibit $m_{A,Z}(t)$ and $m_{B,Z}(t)$ as well as $[m_{A,Z}(t) \pm s_{A,Z}(t)]$ and $[m_{B,Z}(t) \pm s_{B,Z}(t)]$, which have been computed through the Monte Carlo method by resorting to the time-driven approach. For the first set of n_{A0} and n_{B0} , the results with $Z = 2$ are presented in Figure G-3, and those with $Z = 50$ are presented in Figure G-4; they are compared with the solutions of the deterministic and stochastic models. Note that $m_{A,Z}(t)$ and $m_{B,Z}(t)$ in Figure G-4

are equivalent to $\langle N_A(t) \rangle$ and $\langle N_B(t) \rangle$, respectively, for $Z = 50$; this is also the case for the second set of n_{A0} and n_{B0} as illustrated in Figure G-5 in Appendix G.

Table 1 lists the computational times, required by the Monte Carlo method via the event-driven and time-driven approaches, for estimating the sample means, variances, and standard deviations of the random variables, $N_A(t)$ and $N_B(t)$, characterizing the simple reversible reaction. To perform the Monte Carlo simulations by resorting to these approaches, the MATLAB codes given in Appendices E and F were implemented on a PC (Pentium IV 3.0 GHz with 512 MB RAM; Windows XP). Clearly, the time required by the event-driven approach was shorter than that required by the time-driven approach.

Figures 2 and 3 in conjunction with Figures G-2 through G-5 in Appendix G reveal a fundamental distinction between the variations attributable to the inherent or internal noises of a random process and those attributable to the numerical method to stochastically simulate it. The former can only be quantified in terms of higher moments about the means of the random variables characterizing the process, especially, the variances or standard deviations. The latter arise from the generation of samples on the basis of random numbers; these variations tend to vanish as the number of random samples increases, i.e., as the number of simulation runs becomes large.

The efficacy of the two approaches for stochastic simulation via the Monte Carlo method, i.e., the event-driven and time-driven approaches, are further illustrated with an example of photoelectrochemical disinfection of bacteria whose rate of decaying is assumed to be of the first-order, or linear. In contrast to a chemical reaction involving molecules that are discrete and microscopic in size; the disinfection of bacteria deals with microorganisms which are also discrete but mesoscopic in size. In general, the inherent fluctuations of a system comprising mesoscopic entities are appreciably more pronounced than those of a system comprising microscopic entities, especially, when the number concentrations of such entities are minute.

Naturally, the system of interest is the population of bacteria per unit volume. Catalyzed photoelectrochemically, these bacteria die one at a time; moreover, the bacteria have ceased to grow and do not reproduce throughout the deactivation. This system constitutes a special instance of the birth-death processes in which the intensity of birth is absent; hence, it is termed the pure-death process.^[10, 11, 25]

In modeling the photoelectrochemical disinfection of bacteria as a pure-death process, the number of live bacteria at time t , $N_C(t)$, is taken as the random variable of the process; a realization of $N_C(t)$ is denoted by n_C . All the possible numbers of bacteria are the states of the process, and the collection of these numbers, $\{n_{C0}, (n_{C0} - 1), \dots, 2, 1, 0\}$, constitutes the state space, where n_{C0} is the initial number of bacteria, i.e., $N_C(0)$ or n_C at $t = 0$. For the pure-death process, the probability balance around any arbitrary state n_C of the independent random variable, $N_C(t)$, leads to^[11]

$$\frac{d}{dt} p(n_C; t) = W_-(n_C + 1; t)p(n_C + 1; t) - W_-(n_C; t)p(n_C; t) \quad (35)$$

which is the master equation of the process^[11, 25]; see Appendix A. On the basis of the first-order rate law, the intensity of death, $W_-(n_C; t)$, in the above expression is

$$W_-(n_C; t) = -\frac{dn_C}{dt} = k_3 n_C \quad (36)$$

where k_3 is the first-order rate constant. For the pure-death process, the expressions of the mean, $E[N_C(t)]$ or $\langle N_C(t) \rangle$, and the variance, $\text{Var}[N_C(t)]$ or $\sigma_C^2(t)$, are obtained from Eqs. (35) and (36) as^[25, 40]

$$\langle N_C(t) \rangle = n_{C0} \exp(-k_3 t) \quad (37)$$

and

$$\sigma_C^2(t) = n_{C0} \exp(-k_3 t) [1 - \exp(-k_3 t)], \quad (38)$$

respectively; see Appendix B. Obviously, $\sigma_C^2(t)$ can be related to $\langle N_C(t) \rangle$ as

$$\sigma_C^2(t) = [1 - \exp(-k_3 t)] \langle N_C(t) \rangle \quad (39)$$

The standard deviation, $\sigma_C(t)$, is, from Eq. (38),

$$\sigma_C(t) = n_{C0}^{1/2} \{ \exp(-k_3 t) [1 - \exp(-k_3 t)] \}^{1/2} \quad (40)$$

TABLE 1 Computational Times for Estimating the Sample Means, Variances, and Standard Deviations of the Random Variables, $N_A(t)$ and $N_B(t)$, Characterizing the Simple Reversible Reaction by the Monte Carlo Method via the Event-Driven and Time-Driven Approaches				
Initial values	Event-driven approach*		Time-driven approach§	
	Z = 2	Z = 50	Z = 2	Z = 50
$n_{A0} = 175$ $n_{B0} = 25$	< 1 s	< 1 s	1 s	1 s
$n_{A0} = 3,500$ $n_{B0} = 500$	1 s	9 s	5 s	17 s
Notes:				
* In the event-driven approach, the sample means, variances, and standard deviations have been recorded every two seconds, i.e., $\Delta\theta = 2$ s.				
§ In the time-driven approach, the fixed time increment, Δt , has been computed according to Eq. 28 in the text with $W_+^M(n_A; t) = k_1 n_{A0} = k_2 (n_{A0} + n_{B0})$ and $W_-^M(n_A; t) = k_3 n_{A0}$. Thus, $\Delta t = 1.111$ s with $n_{A0} = 175$ and $n_{B0} = 25$, and $\Delta t = 0.056$ s with $n_{A0} = 3,500$ and $n_{B0} = 500$.				

or, from Eq. (39),

$$\sigma_c(t) = [1 - \exp(-k_3 t)]^{1/2} \langle N_c(t) \rangle^{1/2} \quad (41)$$

From Eqs. (37) and (40), the coefficient of variation, $CV_c(t)$, is computed as

$$CV_c(t) = \frac{1}{n_{CO}^{1/2}} \left[\frac{1 - \exp(-k_3 t)}{\exp(-k_3 t)} \right]^{1/2}, \quad (42)$$

which can be rewritten as

$$CV_c(t) = [1 - \exp(-k_3 t)]^{1/2} \frac{\langle N_c(t) \rangle^{1/2}}{\langle N_c(t) \rangle} \quad (43)$$

Note that for the pure-death process the relative fluctuations of $N_c(t)$ about its mean $\langle N_c(t) \rangle$, as given by $CV_c(t)$, are approximately of the order of $(\langle N_c(t) \rangle)^{1/2} / \langle N_c(t) \rangle$, or $\langle N_c(t) \rangle^{-1/2}$, as indicated by Martínez-Urreaga and his collaborators.^[11]

The temporal mean of the model, Eq. (37), has been regressed on the experimental data for the photoelectrochemical disinfection of *E.coli*^[24] near the termination period of the process. By identifying 140 cells per milliliter as the initial population of bacteria, n_{CO} , the nonlinear regression by means of the adaptive random search procedure^[41,42] has resulted in 0.091 min^{-1} for the value of k_3 . With these values of n_{CO} and k_3 , $\langle N_c(t) \rangle$ and $\sigma_c(t)$ have been computed from Eqs. (37) and (40), respectively. Figure 4 illustrates the resultant values of $\langle N_c(t) \rangle$ and $[\langle N_c(t) \rangle \pm \sigma_c(t)]$ in conjunction with the experimental data.^[24] In addition, the sample means, $m_{CZ}(\theta)$ and $m_{CZ}(t)$, and standard deviation envelopes, $[m_{CZ}(\theta) \pm s_{CZ}(\theta)]$ and $[m_{CZ}(t) \pm s_{CZ}(t)]$, have been computed via the Monte Carlo method by resorting to both the event-driven and time-driven approaches, respectively. The results from averaging 50 simulations, *i.e.*, $Z = 50$, are presented in Figure 4 for comparison. Note that the results from Monte Carlo simulation closely approximate the analytical results from the stochastic model. As expected, the deviations or fluctuations of the experimental data^[24] are substantially more pronounced than those predicted by the stochastic model: The overall deviations of the experimental data include those attributable not only to the internal noises of the process but also to the external noises arising from inevitable manipulation errors and instrumental limitations that can never be totally suppressed.

CONCLUDING REMARKS

The contribution of Martínez-Urreaga and his collaborators^[11] on the stochastic simulation of chemical reactions, specifically, a simple reversible chemical reaction, has been complemented and augmented in two aspects. First, a stochastic model for a simple reversible chemical reaction has been derived based on the first-order, *i.e.*, linear, rate law as a birth-death process. The master equation arising from the model has rendered it possible to analytically obtain the ex-

pected means and variances of the process. Second, the master equation of the process has been stochastically simulated through the Monte Carlo method via the time-driven approach in addition to the event-driven approach on the basis of the Gillespie algorithm. The process's means and variances from numerical simulation are in accord with the solutions of the deterministic and stochastic models. To further reveal their efficacy, the two approaches for stochastic simulation by the Monte Carlo method are illustrated with the photoelectrochemical disinfection of bacteria obeying the first-order rate law. The mean computed from stochastic simulation are in line with the available experimental data as well as with the analytical results derived from the corresponding stochastic model. As expected, the fluctuations of the data about their mean are large when compared with those computed from the stochastic simulation.

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NOMENCLATURE

$E[N_A(t)]$	mean, expected value, or the first moment of the random variable, $N_A(t)$
$E[N_B(t)]$	mean of the random variable, $N_B(t)$
$E[N_C(t)]$	mean of the random variable, $N_C(t)$

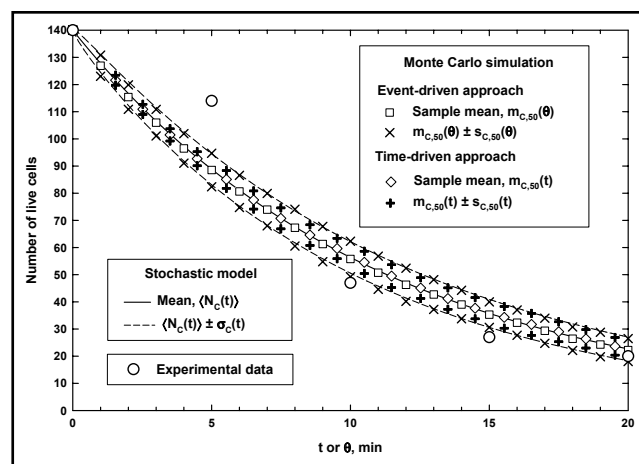


Figure 4. Temporal evolution of the mean and standard deviation envelope near the tail-end of photoelectrochemical disinfection of a population of *E. coli* per unit volume: The average of 50 Monte Carlo simulations by resorting to the event-driven and time-driven approaches is compared with the analytical solutions resulting from the stochastic model; the initial population of bacteria, n_{CO} , is 140 cells per milliliter.

k_1	forward reaction-rate constant, s^{-1}
k_2	reverse reaction-rate constant, s^{-1}
k_3	first-order rate constant, min^{-1}
$N_A(t)$	random variable representing the number of molecules of A at time t
$N_B(t)$	random variable representing the number of molecules of B at time t
$N_C(t)$	random variable representing the number of live bacteria at time t
n_A	realization of the random variable, $N_A(t)$
n_B	realization of $N_B(t)$
n_C	realization of $N_C(t)$
n_{A0}	number of molecules of A at $t = 0$, $N_A(0)$
n_{B0}	number of molecules of B at $t = 0$, $N_B(0)$
n_{T0}	total number of molecules at any arbitrary t, ($n_{A0} + n_{B0}$)
n_{C0}	number of live cells at $t = 0$, $N_C(0)$
$\langle N_A(t) \rangle$	$E[N_A(t)]$
$\langle N_B(t) \rangle$	$E[N_B(t)]$
$\langle N_C(t) \rangle$	$E[N_C(t)]$
$p(n_A; t)$	probability of n_A molecules being present at time t
$p(n_C; t)$	probability of n_C live bacteria being present at time t
t	time
U	uniform random variable on interval (0,1)
u	realization of U
$\text{Var}[N_A(t)]$	variance of the random variable, $N_A(t)$
$\text{Var}[N_B(t)]$	variance of $N_B(t)$
$\text{Var}[N_C(t)]$	variance of $N_C(t)$
$W_+(n_A; t)$	intensity of birth for the birth-death process in state n_A at time t
$W_-(n_A; t)$	intensity of death for the birth-death process in state n_A at time t
$W_-(n_C; t)$	intensity of death for the pure-death process in state n_C at time t

Greek Letters

θ	data-recording time in the event-driven approach
$\sigma_A^2(t)$	$\text{Var}[N_A(t)]$
$\sigma_B^2(t)$	$\text{Var}[N_B(t)]$
$\sigma_C^2(t)$	$\text{Var}[N_C(t)]$
$\sigma_A(t)$	standard deviation of the random variable, $N_A(t)$
$\sigma_B(t)$	standard deviation of $N_B(t)$
$\sigma_C(t)$	standard deviation of $N_C(t)$
τ	random waiting time in the event-driven approach

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APPENDICES

Seven appendices (Appendices A through G) can be viewed or downloaded from the corresponding author's Web site at <http://www.che.ksu.edu/faculty/fan/Fan_Research.htm>, or can be obtained as hard copies by writing to fan@ksu.edu. □