

## LETTERS TO THE EDITOR

The Letters to the Editor section is divided into three categories entitled Notes, Comments, and Errata. Letters to the Editor are limited to one and three-fourths journal pages as described in the Announcement in the 1 July 2004 issue.

## COMMENTS

## Comment on "Stiffness in stochastic chemically reacting systems: The implicit tau-leaping method" [J. Chem. Phys. 119, 12784 (2003)]

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In the Appendix of the paper by Rathinam *et al.*,<sup>1</sup> the authors correctly derive expressions for the expected value and variance of the number of  $S_1$  molecules in the first order reversible reaction  $S_1 \xrightleftharpoons[c_2]{c_1} S_2$ . We show that the same expressions can be obtained by using the generating function in solving the master equation. In addition, our approach allows for the computation of the probabilities for the number of  $S_1$  molecules at a certain time  $t$  when the reaction parameters, i.e., the initial number of molecules  $X_1(0)$  and  $X_2(0)$  of  $S_1$  and  $S_2$ , respectively, and the reaction rates  $c_1$  and  $c_2$ , are given.

The master equation is a differential-difference equation that describes the evolution of the probability  $p_x(t)$ , i.e., the probability that the number of  $S_1$  molecules at time  $t$  is equal to  $x$ . The master equation for the first order reversible reaction is<sup>2</sup>

$$\frac{dp_x(t)}{dt} = c_1(x+1)p_{x+1}(t) + c_2(x_T - x + 1)p_{x-1}(t) - [c_1x + c_2(x_T - x)]p_x(t), \quad (1)$$

where  $x_T$  is equal to the total number of  $S_1$  and  $S_2$  molecules:  $x_T = X_1(t) + X_2(t)$ . One way of solving the master equation is to transform it into a partial differential equation by use of the generating function, which is defined as

$$F(s, t) = \sum_{x=0}^{x_T} p_x(t) s^x, \quad |s| < 1. \quad (2)$$

Multiplying the left- and right-hand sides of Eq. (1) by  $s^x$  and summing over  $x=0$  to  $x=x_T$ , we obtain

$$\frac{\partial F}{\partial t} = [c_1 + (c_2 - c_1)s - c_2s^2] \frac{\partial F}{\partial s} + x_T c_2 (s - 1) F. \quad (3)$$

The solution of this partial differential equation with initial condition

$$F(s, 0) = \sum_{x=0}^{x_T} p_x(0) s^x = s^{X_1(0)},$$

and boundary condition

$$F(1, t) = \sum_{x=0}^{x_T} p_x(t) = 1,$$

is equal to

$$F(s, t) = \left( \frac{-\lambda(1-s)e^{-ct} + \lambda + s}{(1-s)e^{-ct} + \lambda + s} \right)^{X_1(0)} \times \left( \frac{(1-s)e^{-ct} + \lambda + s}{1 + \lambda} \right)^{x_T}, \quad (4)$$

where  $c = c_1 + c_2$  and  $\lambda = c_1/c_2$ .

As mentioned by Rathinam *et al.*,<sup>1</sup> for the case  $X_1(0) = 0$  or  $X_2(0) = 0$  one can find an analytic solution for the distribution function. For example, let  $X_2(0) = 0$  and hence  $X_1(0) = x_T$ , then  $F(s, t)$  reduces to<sup>3</sup>

$$F(s, t) = \left( \frac{\lambda e^{-ct}(s-1) + \lambda + s}{1 + \lambda} \right)^{x_T}. \quad (5)$$

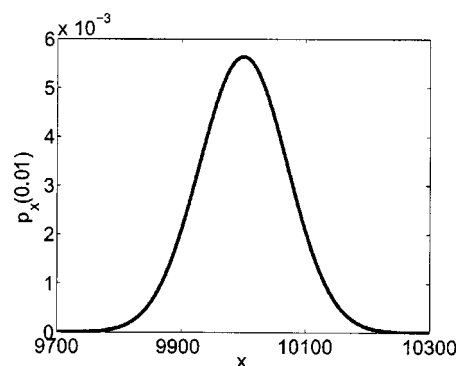


FIG. 1. The distribution function for the number of  $S_1$  molecules in the first order reversible reaction after  $t = 0.01$  s. The initial values are  $X_1(0) = X_2(0) = 10^4$  and the rate parameters are equal to  $c_1 = c_2 = 10^5$ .

An expansion of Eq. (5) around  $s=0$  gives the analytic expression for the probabilities,

$$p_x(t) = \binom{x_T}{x} \left(\frac{c_1}{c}\right)^{x_T} \left(e^{-ct} + \frac{1}{\lambda}\right)^x (1 - e^{-ct})^{x_T-x},$$

for  $t \geq 0$  and  $x=0,1,\dots,x_T$ .

We are not aware of analytic expressions for the terms in the Taylor expansion of  $F(s,t)$  when neither  $X_1(0)$  nor  $X_2(0)$  is equal to 0. However, what can be computed is the expected value of the number of  $S_1$  molecules at time  $t$  and its variance,<sup>1</sup> and, in addition, the probabilities  $p_x(t)$  when  $X_1(0)$ ,  $X_2(0)$ ,  $c_1$ , and  $c_2$  are given.

The expected value of  $S_1$  molecules at time  $t$  and its variance can be found from  $F(s,t)$  as follows:

$$E(X_1(t)) = \left(\frac{\partial F}{\partial s}\right)_{s=1} = \frac{(1 - e^{-ct})x_T}{\lambda + 1} + X_1(0)e^{-ct}, \quad (6)$$

$$\begin{aligned} \text{Var}(X_1(t)) &= \left(\frac{\partial^2 F}{\partial s^2}\right)_{s=1} + \left(\frac{\partial F}{\partial s}\right)_{s=1} - \left(\frac{\partial F}{\partial s}\right)_{s=1}^2 \\ &= \frac{1}{(1+\lambda)^2} (1 - e^{-ct}) \{x_T \lambda + e^{-ct} \\ &\quad \times [X_1(0)(\lambda^2 - 1) + x_T]\}. \end{aligned} \quad (7)$$

By manipulating the expressions in Eqs. (6) and (7) one can obtain the results of Rathinam *et al.*,<sup>1</sup> i.e., Eqs. (A11) and (A13) in their paper, respectively.

The advantage of our approach is in that, even for the general case where neither  $X_1(0)$  nor  $X_2(0)$  is equal to 0, we can obtain numerical values for the probabilities  $p_x(t)$ . Indeed, when  $X_1(0)$ ,  $X_2(0)$ ,  $c_1$ , and  $c_2$  are given, the probability  $p_x(t)$  is computed as the coefficient of the term of order  $x$  in the Taylor series of  $F(s,t)$  about  $s=0$ . In Example 2 of their paper, Rathinam *et al.*<sup>1</sup> simulate 10 000 trajectories of SSA (Gillespie's<sup>4</sup> Stochastic Simulation Algorithm) in order to get a good estimate of the distribution. On the other hand, with our approach, we can determine the desired distribution exactly.

The probabilities  $p_x(t)$  ( $x=0,\dots,x_T$ ) can also be computed by following the method described by Laurenzi,<sup>5</sup> which is based on the Laplace transform of the master equation.

In this way, solving the partial differential equation (3) is avoided, which is important for more complicated reactions. Instead, one has to solve the set of linear equations  $(sI - M)V(s) = P$ , where  $I \in \mathbb{R}^{(x_T+1) \times (x_T+1)}$  is the identity matrix, the elements of  $M \in \mathbb{R}^{(x_T+1) \times (x_T+1)}$  in row  $i$  and column  $j$  are defined as

$$M(i,j) = \begin{cases} -u_{i-1} - c_1(i-1) & \text{if } i=j \\ c_1 i & \text{if } i=j-1 \\ u_{j-1} & \text{if } i=j+1 \\ 0 & \text{otherwise,} \end{cases}$$

with  $u_i = c_2(x_T - i)$ , the vector  $P \in \mathbb{R}^{x_T+1}$  is equal to  $(0 \cdots 0 \ 1 \ 0 \cdots 0)^T$  with the element 1 in row  $X_1(0)+1$  and  $V(s) \in \mathbb{R}^{x_T+1}$ . The  $i$ th element of  $V(s)$  is then equal to the Laplace transform of  $p_{i-1}(t)$ . Consequently, the time dependent probabilities are obtained by taking the inverse Laplace transform of the elements of  $V(s)$ .

Finally, we note that the computation of the probabilities from any analytically derived expression for large values of  $x_T$  may be a numerically challenging task.

*Example.* Assume that<sup>6</sup>  $X_1(0)=10^4$ ,  $X_2(0)=10^4$ ,  $c_1=10^5$ , and  $c_2=10^5$ . The coefficients  $p_x(t)$  in the Taylor series of  $F(s,t)$  in Eq. (4) around  $s=0$  for  $x=9700, 9701, \dots, 10300$  and  $t=0.01$  s were computed in MAPLE. They are shown in Fig. 1.

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<sup>1</sup>M. Rathinam, L. R. Petzold, Y. Cao, and D. T. Gillespie, J. Chem. Phys. **119**, 12784 (2003).

<sup>2</sup>D. A. McQuarrie, J. Appl. Probab. **4**, 413 (1967).

<sup>3</sup>The expression for  $F(s,t)$  given by McQuarrie (Ref. 2) contains a few errors.

<sup>4</sup>D. T. Gillespie, J. Comput. Phys. **22**, 403 (1976).

<sup>5</sup>I. J. Laurenzi, J. Chem. Phys. **113**, 3315 (2000).

<sup>6</sup>Note that Rathinam *et al.* (Ref. 1) consider in their Example 2 the reversible reaction between  $S_1$  and  $S_3$  (not  $S_2$ ), and hence  $X_3(0)=10^4$  [while  $X_2(0)=100$ ].