A general method for the computation of probabilities in systems of first order chemical reactions

Xueying Zhang, a Katrien De Cock, b Mónica F. Bugallo, c and Petar M. Djurić d

COSINE Laboratory, Department of Electrical & Computer Engineering, Stony Brook University, Stony Brook, New York 11794-2350

(Received 21 June 2004; accepted 9 December 2004; published online 7 March 2005)

We present a general method for the computation of molecular population distributions in a system of first-order chemical reactions. The method is based on the observation that the molecules in first-order reactions do not interact with each other. Therefore, the population distributions are a convolution of densities for one molecule. With this method one can study reactions involving any number of molecules. Such analysis is demonstrated on several examples, including an enzyme catalyst reaction and a first-order reaction chain. © 2005 American Institute of Physics.

[DOI: 10.1063/1.1855311]

I. INTRODUCTION

In small biological systems, it is often more appropriate to model the chemical reactions in a stochastic way rather than with the traditional differential equations for evolution of concentrations. The reasons are (a) the number of molecules involved in a biological system can be very small; 1 (b) there are many situations in which molecules are not homogeneously distributed; 2,3 (c) the change of molecular population levels is a discrete integer amount; and (d) the population change is not a deterministic process. 4,5

There are mainly two approaches for the stochastic study of the number of molecules in biochemical reactions: the first is based on the analysis of the master equation 6–8 and the second relies on Monte Carlo simulation methods. 9–11 Here, we adopt the first approach.

In 1967, McQuarrie summarized the stochastic study using the master equation approach. 7 For a reaction, it is assumed that in an infinitesimal time interval, the probability of having one reaction per unit reactant molecule combination is proportional to the length of the time interval. A probability difference function is first obtained based on the assumption, which leads to a differential-difference equation called the master equation of the reaction. The moment-generating function is then employed to transform the master equation into a partial differential equation. It can sometimes be solved to obtain the analytic solution. More often, the mean and variance of the number of molecules can only be obtained.

In 2000, Laurenzi introduced a different way of solving the master equation. 8 Instead of using the moment-generating function, he applied the Laplace transform. In this way, solving the partial differential equations is avoided, which is important for more complicated reactions. Instead, one needs to solve a set of linear equations. We will show how to obtain the solution of the master equation for any system of first-order reactions in yet another way.

In this paper we study systems of first-order reactions, i.e., combinations of (coupled) reactions of the type \( S_i \rightarrow S_j \). Because in such systems molecules do not chemically interact, the analysis is much simpler than when second-order reactions are involved. Although this situation might occur only rarely in practice, our analysis is also useful for systems where the first-order reactions are dominant and for systems where second-order reactions can be approximated by first-order reactions (see Sec. IV for an example).

The independence of the molecules in a first-order reaction system is exploited to derive the population distributions of the molecules in the system. Instead of solving the master equation for the complete system, where the number of states grows with the number of molecules, we first solve the master equation for only one molecule and use its solution to find the population distributions for all species.

The structure of the paper is as follows. In Sec. II we solve the master equation for one molecule in a first-order reaction system. The resulting probability distribution functions are used in Sec. III to obtain the population distributions when more molecules are introduced. In Sec. IV we illustrate the general results of Sec. III with specific examples. Finally, in Sec. V we give some concluding remarks.

II. ONE MOLECULE

In this section we study the master equation for one molecule in a system of first-order reactions. The solution will then be used to solve more general cases in Sec. III.

Assume that there are \( M \) molecule species, \( S_1,S_2,\ldots,S_M \) in the reaction system, and let the probability rate constant of the reaction \( S_i \rightarrow S_j \) be denoted by \( c_{ij} \). For a first-order reaction the specific probability rate constant is such that

\[ c_{ij} \Delta t (i \neq j) = \text{the probability for the first-order reaction} \]
$S_i \rightarrow S_j$ to happen per molecule in an infinitesimally small time interval $\Delta t$.

The master equation describes the evolution of the molecules’ population distribution in the chemical system as a function of time. When there is only one molecule in a first-order reaction system, the master equation gives the time evolution of the probability that this molecule has become a certain chemical species. Let $p^{(i)}(t)$ be the probability that the molecule is in an $S_i$ molecule at time $t$. For example, in the simple system of reactions

$$S_1 \rightarrow S_2 \rightarrow S_3,
= c_{12} c_{23}
\begin{array}{c}
\text{reaction becomes}\\
\text{the differential equation describing the time evolution of } p^{(2)}
\text{is the following first-order linear differential equation:}
\end{array}
\frac{dp^{(2)}(t)}{dt} = c_{12} p^{(1)}(t) - (c_{21} + c_{23}) p^{(2)}(t).
\tag{2}
$$

We assume in the rest of this paper that the initial values for the probabilities are equal to zero: $p^{(i)}(0) = 0$, $i = 1, \ldots, M$. The injection of the molecule in the system is modeled by a source probability density function. For the given example, if the molecule begins as an $S_2$ molecule, the differential equation becomes

$$\frac{dp^{(2)}(t)}{dt} = c_{12} p^{(1)}(t) - (c_{21} + c_{23}) p^{(2)}(t) + f^{(2)}(t),
\tag{3}
$$

where $f^{(2)}(t)$ is the source’s probability density, i.e., $f^{(2)}(t) \Delta t$ is the probability that a molecule from the source is injected in state $S_2$ in the interval $[t, t+\Delta t]$. If the injection time is known precisely, e.g., $t = \tau$, the source’s probability density function is a delta function: $f^{(2)}(t) = \delta(t-\tau)$. Otherwise, the density function for the injection time of the molecule can have forms such as $ae^{-a(t-\tau)}u(t-\tau)$, $a\delta(t-\tau_1) + (1-a)\delta(t-\tau_2)$, and

$$\sum_{n=0}^{\infty} \frac{\lambda^n}{n!} \delta(t-n\tau).
\tag{5}
$$

In general, the system can be represented by a Markov chain with a transition matrix

$$C = \begin{pmatrix}
c_{11} & c_{12} & \cdots & c_{1M} \\
c_{21} & c_{22} & \cdots & c_{2M} \\
\vdots & \vdots & \ddots & \vdots \\
c_{M1} & c_{M2} & \cdots & c_{MM}
\end{pmatrix},
\text{where } c_{ii} = -\sum_{j=1, j \neq i}^{M} c_{ij}.
\tag{4}
$$

and the set of first-order linear differential equations has the following form:

$$\frac{dp^{(1)}(t)}{dt} = C^T \begin{pmatrix}
p^{(1)}(t) \\
p^{(2)}(t) \\
\vdots \\
p^{(M)}(t)
\end{pmatrix} + \begin{pmatrix}
f^{(1)}(t) \\
f^{(2)}(t) \\
\vdots \\
f^{(M)}(t)
\end{pmatrix},
\tag{5}
$$

where

$$\sum_{i=1}^{M} p^{(i)}(t) = 1,
\tag{6}
$$

and

$$\int_{t=0}^{\infty} f^{(i)}(t) dt = 1 \text{ if the molecule from source is injected into state } i,
\int_{t=0}^{\infty} f^{(i)}(t) dt = 0 \text{ otherwise.}
\tag{6}
$$

The equations can be solved by first applying the Laplace transform, followed by solving the resulting algebraic equation, and finally using the inverse Laplace transform. More specifically, after taking the Laplace transform, followed by solving the resulting algebraic equation, and finally taking the inverse Laplace transform, we obtain

$$sp = C^T p + f.
\tag{7}
$$

Let

$$L = (sI - C^T)^{-1}
\tag{8}
$$

and

$$G = L^{-1}(L),
\tag{9}
$$

where $L^{-1}$ is the inverse Laplace operator. If the elements of $G$ are denoted by $g_{ij}(t)$, and $f^{(m)}(s)$ is the nonzero element of $f$, the solutions $p^{(i)}(t)$ are given by

$$p^{(i)}(t) = g_{i0}(t) \otimes f^{(m)}(t),
\tag{10}
$$

where the symbol $\otimes$ denotes convolution. Finding the inverse Laplace transforms of the elements of $L$ may be tedious but it is straightforward.

This method is illustrated in details by example 1. As already mentioned, the technique of using the Laplace transform for solving the master equation was introduced by Laurenzi in Ref. 8. The difference between his and our approach is that Laurenzi was solving the many-molecule master equation, while here we only solve the one-molecule master equation.

In the deterministic framework, the concentrations of the species are found by solving the same differential equations...
where $S_i$ into the system with the same probability density $n_i$. Molecules in state $m$ at time $t$ is not. Thus, $N_0(t)$ is sample. In Sec. III B, the molecules can originate from different sources.

### III. MORE MOLECULES

In this section we treat the case when several molecules are injected into the system. First, in Sec. III A, we assume that all molecules are inserted by the same source, so that they all start as the same chemical species. In Sec. III B, the purpose for employing the Gaussian approximation is to save computation time when the number of molecules is very large, as well as to make the analysis more tractable. Numerical examples of the comparison between analytic distributions and their Gaussian approximations can be found in Ref. 12.

The purpose for employing the Gaussian approximation is to save computation time when the number of molecules is very large, as well as to make the analysis more tractable. Numerical examples of the comparison between analytic distributions and their Gaussian approximations can be found in Ref. 12.

The same purpose can be achieved if the binomial distribution (11) is approximated by a Poisson distribution. Conditions for the validity of such approximation are stricter. First, the number of molecules should be large. Second, the probability for a single molecule in state $i$ should be small [e.g., $p^i(t) < 0.1$]. Finally, the product of $x$ and $p^i(t)$ should be a sizable number. Under such conditions, the variance of the binomial distribution roughly equals the mean. Then (11) can be approximated by the Poisson distribution with parameter $\lambda_i = xp^i(t)$, or

$$P^i_n(t) \approx \frac{\lambda_i^n}{n!} e^{-\lambda_i}.$$  

### B. More sources

If there are several sources which are independent from each other, the probability mass function for state $S_i$ is the convolution of binomial distributions. Suppose there are $J$ independent sources. Denote the number of molecules at state $S_i (i = 1, \ldots, M)$ at time $t$ by $N_0(t)$, and denote the number of molecules at state $S_i$ that are injected from source $j$ by $N_j(t) (j = 1, \ldots, J)$. Then, $N_0(t) = \sum_{j=1}^{J} N_j(t)$. Since $N_j(t)$ are independent random variables, the probability mass function of the random variable $N_0(t)$ is the convolution of the probability mass functions of the random variables $N_j(t)$.

For example, let $x$ $S_k$ molecules be injected by the source functions $f_{i,j}^k(t)$ and $y$ $S_i$ molecules by $f_{i,j}^k(t)$. Each of the $x$ $S_k$ molecules gives rise to the state probabilities $p_{i,j}^k(t)$, whereas a molecule introduced by $f_{i,j}^k(t)$ to $p_{i,j}^k(t)$ ($i = 1, \ldots, M$). Then, the number of molecules at state $S_i$ that are injected from source $k$ is $K_i^k(t)$, which has a binomial distribution $\binom{n}{p_{i,j}^k(t)}(1-p_{i,j}^k(t))^{x-n}$. Similarly, the number of molecules at state $S_i$ that are injected from source $l$ is $K_i^l(t)$, which has a binomial distribution $\binom{n}{p_{i,j}^l(t)}(1-p_{i,j}^l(t))^{y-n}$. The probability mass function of $N_0(t)$, the total number of molecules at state $S_i$, is equal to the convolution of two binomial distributions, i.e.,

$$P^i_n(t) = \binom{x}{n} (p_{i,j}^k(t))^{x-n} \binom{y}{n} (p_{i,j}^l(t))^{y-n},$$  

where the convolution is along the $n$ axis, that is

$$y_1(n) \otimes y_2(n) = \sum_{m=0}^{\infty} y_1(m)y_2(n-m).$$

The mean $\mu_i(t)$ and variance $\sigma_i^2(t)$ of $N_0(t)$ are

$$\mu_i(t) = xp_{i,j}^k(t) + yp_{i,j}^l(t),$$

$$\sigma_i^2(t) = xp_{i,j}^k(t)(1-p_{i,j}^k(t)) + yp_{i,j}^l(t)(1-p_{i,j}^l(t)),$$

respectively.

As we mentioned before, when the number of molecules is large, the binomial distribution can be well approximated by a Gaussian distribution with the same mean and variance. One property of Gaussian distributions is that the convolution of two Gaussian distributions yields a Gaussian distribution. Therefore, the convolution result in (13) can be approximated by a Gaussian distribution with mean (14) and variance (15). The Poisson distribution has the same prop-
obtain the well-known result for $f$. Taking the Laplace transform leads to $S_m$. The matrix $L$ for $S_1 \rightarrow S_2$, where only molecules $S_1$ are injected into the system with probability density function $f^{(1)}(t) = \delta(t)$. The first step is to rewrite (5) with $M = 2$, $c_{12} = c$, $c_{21} = 0$, and $f^{(2)}(t) = 0$
\[
\begin{pmatrix}
\frac{dp^{(1)}(t)}{dt} \\
\frac{dp^{(2)}(t)}{dt}
\end{pmatrix} = \begin{pmatrix}
-c & c \\
0 & 0
\end{pmatrix} \begin{pmatrix}
p^{(1)}(t) \\
p^{(2)}(t)
\end{pmatrix} + \begin{pmatrix}
\delta(t) \\
0
\end{pmatrix}.
\]
Taking the Laplace transform leads to $S^{(1)}(s) = \begin{pmatrix} -c & c \\ 0 & 0 \end{pmatrix} S^{(1)}(s) + \begin{pmatrix} 1 \\ 0 \end{pmatrix}$.
The matrix $L$ from (8) is given by $L = \begin{pmatrix} 0 & 1 \\ \frac{1}{s + c} & \frac{1}{s} \end{pmatrix}$.
After taking the inverse Laplace transform of $L$, we obtain $G = \begin{pmatrix} e^{-ct} & 0 \\ 1 - e^{-ct} & u(t) \end{pmatrix}$, where $u(t)$ is the unit step function. The final solution is $p^{(1)}(t) = e^{-ct}u(t)$, $p^{(2)}(t) = (1 - e^{-ct})u(t)$.
In the rest of the paper we will drop the use of $u(t)$, and so we point out that the given solutions for $p(t)$ are valid only for $t \geq 0$. When $f^{(1)}(t)$ is some other density function $p^{(1)}(t) = \int_0^\infty f^{(1)}(\tau)e^{-c(t-\tau)}d\tau$, $p^{(2)}(t) = \int_0^\infty f^{(1)}(\tau)(1 - e^{-c(t-\tau)})d\tau$.

Note that if an $S_2$ molecule is injected into the system with $f^{(2)}(t)$, $p^{(1)}(t) = 0$ and $p^{(2)}(t) = f^{(2)}(t)$.

By substituting the probabilities of (19) and (20) in (13), we obtain the distribution for the $S_1$ molecules.
\[
P^{(1)}(t) = \begin{pmatrix}
x \\ n
\end{pmatrix} \left( \frac{1}{c_1 + c_2} (c_2 + c_1 e^{-(c_1 + c_2)t}) \right)^n \times \left( 1 - \frac{1}{c_1 + c_2} (c_2 + c_1 e^{-(c_1 + c_2)t}) \right)^{x-n}.
\]
\[
P^{(2)}(t) = \begin{pmatrix}
x \\ n
\end{pmatrix} \left( \frac{1}{c_2 + c_1} (1 - e^{-(c_2 + c_1)t}) \right)^n.
\]

And similarly for the $S_2$ molecules.

Note that when only $S_1$ or only $S_2$ molecules are present at $t = 0$, the distribution reduces to the first and second convolution factor in (21), respectively. The population distribution for this special case has already been given by McQuarrie.

Also note that deriving the mean and variance for the number of $S_1$ and $S_2$ molecules is straightforward, as explained in Sec. III B, and leads to the same results as reported in Refs. 14 and 15.

C. Example 3: A combination of the first-order irreversible and first-order reversible reaction

Consider the reaction system...
and obtain

\[ S_1 \rightarrow S_2 \rightarrow S_3, \]  

(22)

and assume there are \( x \) \( S_1 \) molecules and \( y \) \( S_2 \) molecules at \( t = 0 \). Again, we first solve (5) with \( f^{(1)}(t) = \delta(t) \), \( f^{(2)}(t) = \delta(t) = 0 \) to find the probabilities due to one \( S_1 \) molecule and obtain

\[
p_1^{(1)}(t) = \frac{\sqrt{m} - c_1 + c_2 + c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t}\]

\[+ \frac{\sqrt{m} + c_1 - c_2 - c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t},\]

\[
p_1^{(2)}(t) = \frac{c_1}{\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t} - \frac{c_1}{\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t},\]  

(23)

Next, we solve (5) with \( f^{(1)}(t) = f^{(3)}(t) = 0 \), \( f^{(2)} = \delta(t) \) to find the probabilities due to one \( S_2 \) molecule and find that

\[
p_2^{(1)}(t) = \frac{c_2}{\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t} - \frac{c_2}{\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t},\]

\[
p_2^{(2)}(t) = \frac{\sqrt{m} + c_1 - c_2 - c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t}\]

\[+ \frac{\sqrt{m} - c_1 + c_2 + c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t},\]

\[
p_2^{(3)}(t) = 1 - \frac{\sqrt{m} + c_1 - c_2 - c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t}\]

\[+ \frac{\sqrt{m} - c_1 + c_2 + c_3}{2\sqrt{m}} e^{-(1/2)(\sqrt{m} + c_1 + c_2 + c_3)t}.\]  

(24)

The substitution of the probabilities in (13) by the probabilities in (23) and (24) yields the population distribution for the \( S_1 \), \( S_2 \), and \( S_3 \) molecules.

**D. Example 4: A first-order reaction chain**

Consider a first-order reaction chain in its general form

\[ S_1 \rightarrow S_2 \rightarrow \cdots \rightarrow S_i \rightarrow \cdots \rightarrow S_N. \]  

(25)

Assume that \( c_i \neq c_j \) when \( i \neq j \) \((i=1, \ldots, N \text{ and } j=1, \ldots, N)\) and that \( x \) molecules enter the system in state \( S_1 \) at time \( t = 0 \). The input probability distribution of state \( S_1 \) is \( f^{(1)}(t) \)
\( \delta(t) \). Then, using the method introduced in the previous sections, the state probabilities for one molecule are equal to

\[
p^{(i)}(t) = \begin{cases} 
\frac{1}{c_i} \sum_{j=1}^{i} M_j^{(1)} e^{-c_j t}, & c_i > 0 \\
1 - \sum_{j=1}^{i-1} M_j^{(1)} e^{-c_j t}, & c_i = 0, i \geqslant 2, \\
1, & c_i = 0, i = 1
\end{cases}
\]

where

\[
M_p^{(k,m)} = \begin{cases} 
\prod_{j=k+p}^{m} \frac{c_j}{c_j - c_p}, & m > k \\
1, & m = k.
\end{cases}
\]

The probability that \( n \) of the \( x \) molecules are in state \( S_i \) at time \( t \) is given by

\[
P_n^{(i)}(t) = \left( \frac{x}{n} \right) (p^{(i)}(t))^n (1 - p^{(i)}(t))^{x-n}.
\]

If there are \( c_i \)'s equal to \( c_j \)'s, a closed-form solution is also possible.

**E. Example 5: A numerical example for the first-order reaction chain**

Consider the first-order reaction chain

\[
S_1 \rightarrow S_2 \rightarrow S_3 \rightarrow S_4 \rightarrow S_5 \rightarrow S_6 \rightarrow S_7.
\]

Suppose there are 1000 \( S_i \) molecules at time \( t = 0 \). The values of the reaction parameters \( c_1, \ldots, c_6 \) are 4.3, 16.6, 1.2, 2.8, 11.4, 11.9, respectively, with unit \( s^{-1} \). We used two methods to obtain the probability mass of \( S_7 \) at time \( t = 1.5 \) s

- (1) by direct calculation (DC) using (26), and
- (2) by running 500 realizations of the SSA (stochastic simulation algorithm), which is a Monte Carlo method for numerically computing the time evolution of a chemical system.

The resulting probability mass functions are shown in Figs. 1 and 2. From Fig. 2 it is clear that the 500 SSA realizations are not enough for an accurate evaluation of the probability distribution, even though the computation time it took is much longer than the direct calculation using (26). Obviously, methods based on analytic solutions are better than those based on Monte Carlo simulations. However, in cases of more complex reactions where neither analytic solutions nor good approximations of population distributions exist, the SSA is the method of choice.

We have shown in Sec. III A that when \( x \rightarrow \infty \) and \( p^{(i)}(t) \rightarrow 0 \) [e.g., \( p^{(i)}(t) < 0.1 \)], the binomial distribution (11) can be approximated by the Poisson distribution with mean \( \lambda = x p^{(i)}(t) \). The purpose of the approximation is to make the analysis more tractable. In many situations, however, the condition \( p^{(i)}(t) \rightarrow 0 \) is not valid. Using the reaction chain (25) and reaction parameter \( c_1, \ldots, c_6 \) of this example, the probabilities of a single molecule to be in state \( S_i \) (i...
F. Example 6: An enzyme–substrate reaction

Let us consider an enzyme reaction where a soluble substrate with an A–B structure reacts with immobilized enzyme molecules located on the surface of cells [see Fig. 4(a)]. The formulation of this chemical reaction is given by

\[ AB + R \rightarrow ARB \rightarrow AR + B, \]

where \( AB \) is the substrate molecule, \( R \) is the enzyme molecule, and \( ARB \) is the enzyme–substrate complex, known as the intermediate product. This reaction is illustrated in Fig. 4(b). The superscript of \( c_1^{(2)} \) emphasizes that this specific probability rate constant is for a second-order reaction.

Several simplifications can be applied. First, \( AR \) can be eliminated because the number of \( AR \) molecules has the same probability distribution as the number of \( B \) molecules. Such elimination obviously has no effect on the accuracy of the obtained results. Furthermore, if the number of \( AB \) molecules is \( X_{AB} \), the product of \( X_{AB} \) and the reaction parameter \( c_1 \) represents the probability rate for an \( R \) molecule to transfer into state \( ARB \). If \( c_1 = c_1^{(2)} X_{AB} \), the reaction (28) can be simplified as

\[ c_1 \rightarrow c_3 \quad R \rightarrow ARB \rightarrow B. \]

This equation has the same structure as Eq. (22). The only difference is that the value of \( c_1 \) varies with time.

A property for many enzyme reactions is that the number of substrate molecules is sufficiently large, and that the number of substrate molecules consumed during the course of the reaction is negligible in comparison to the total number of substrate molecules. Therefore, we can assume that \( X_{AB} \) is approximately equal to its initial value, and \( c_1 \) can be seen as constant. Thus, after simplification and approximation, the results in (23) can be used here.

As an example, we have calculated the mean and variance of the population of molecule species \( R, ARB, \) and \( B \) with the following initial values: \( X_R(0) = 10^4 \), \( X_{ARB}(0) = 4.8176 \times 10^{10} \), and reaction parameters \( c_2 = 1 \) \( s^{-1} \), \( c_3 = 100 \) \( s^{-1} \), and \( c_1^{(2)} = 4.1930 \times 10^{-16} \) \( s^{-1} \). The volume in which the reactions are observed is equal to 0.01 l.

The obtained results are shown in Figs. 5–8. The expected population of molecule species are given in Figs. 5 and 6 (zoomed plot). The variance is shown in Figs. 7 and 8.