

An analytical solution of the stochastic master equation for reversible bimolecular reaction kinetics

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The kinetics of the binding reaction $A + B \rightleftharpoons C$ are solved exactly via the stochastic master equation, in which molecular populations are considered as time-dependent, integer-valued random variables. This transient solution extends previous work on the irreversible bimolecular reaction and the equilibrium state of the reversible bimolecular reaction. For small ensembles of reactants, comparisons are made between the results of the deterministic and stochastic approaches to the problem, and methods are presented to numerically evaluate the solution. © 2000 American Institute of Physics. [S0021-9606(00)51832-7]

I. INTRODUCTION

In recent years, nanoscopic processes such as receptor-mediated cell adhesion, receptor-mediated viral fusion, and chemistry-mediated nanoassembly have received increased attention. In the analyses of these small systems, the fundamentally probabilistic nature of chemical reaction cannot be neglected, and a deterministic treatment of chemical kinetics may not be satisfactory. Thus, one must turn to the stochastic approach to chemical kinetics, which addresses the dynamics of the probabilities of population states.

The stochastic approach to chemical kinetics was first employed by Delbrück¹ to describe the kinetic fluctuations in autocatalytic reaction. Subsequently, Bartholomay² and McQuarrie³ applied the theory to the unimolecular reactions $A \rightarrow B$ and $A \rightleftharpoons B$, respectively. The first application to the bimolecular reaction $A + B \rightarrow C$ was carried out by Rényi,⁴ and subsequently by McQuarrie⁵ and Ishida,⁶ both of whom additionally addressed the reaction $2A \rightarrow C$. However, the equations describing the stochastic processes of reversible bimolecular reactions such as $A + B \rightleftharpoons C$, $A + B \rightleftharpoons C + D$, or $2A \rightleftharpoons C + D$ have been solved only at their equilibrium states.⁷ This article outlines a method to exactly solve the stochastic master equation describing the reaction $A + B \rightleftharpoons C$ to determine the probability of a population state at any time during the course of the reaction.

II. THE REVERSIBLE BIMOLECULAR REACTION $A + B \rightleftharpoons C$

Consider a small, well-mixed, and closed volume v initially containing only A and B molecules at populations of α and β , respectively. Let $A(t)$, $B(t)$, and $C(t)$ be the integer-valued random variables giving the populations of A , B , and C molecules within v at time t . Furthermore, let $P(a, b, c, t)$ be the probability that $A(t)$, $B(t)$, and $C(t)$ have values of a , b , and c , respectively.

The form of $P(a, b, c, t)$ is determined by the *stochastic master equation*, which describes the means of transition to and from the state (a, b, c) during the stochastic process of chemical reaction. It may be defined via the following axioms:

- (1) The probability of a forward reaction event in the interval $(t, t + \Delta t)$ whereby $(a, b, c) \rightarrow (a - 1, b - 1, c + 1)$ is $k_1 ab \Delta t + O(\Delta t)$, where k_1 is the stochastic rate constant for the forward reaction.
- (2) The probability of a reverse reaction event in the interval $(t, t + \Delta t)$ whereby $(a, b, c) \rightarrow (a + 1, b + 1, c - 1)$ is $k_2 c \Delta t + O(\Delta t)$, where k_2 is the stochastic rate constant for the reverse reaction.

A rigorous microphysical demonstration of the validity of the preceding axioms has been carried out by Gillespie.⁸ A detailed balance yields

$$P(a, b, c, t + \Delta t) = k_1(a + 1)(b + 1)\Delta t P(a + 1, b + 1, c - 1, t) + k_2(c + 1)\Delta t P(a - 1, b - 1, c + 1, t) + (1 - k_1 ab \Delta t - k_2 c \Delta t)P(a, b, c, t) + O(\Delta t). \quad (1)$$

Rearranging this expression and letting $\Delta t \rightarrow 0$ yields the master equation as the following differential-difference equation:

$$\begin{aligned} \frac{dP(a, b, c, t)}{dt} = & k_1(a + 1)(b + 1)P(a + 1, b + 1, c - 1, t) \\ & - k_1 ab P(a, b, c, t) + k_2(c + 1)P(a - 1, b \\ & - 1, c + 1, t) - k_2 c P(a, b, c, t). \end{aligned} \quad (2)$$

While this expression involves three discrete variables, the problem at hand is actually univariate in nature. Considering the stoichiometry of the reaction, a , b , and c are related as follows:

$$\alpha - a = \beta - b = c. \quad (3)$$

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Hence, the probability density function $P(a,b,c,t)$ may be expressed as a function of just one species population. This article will address the solution of Eq. (2) in terms of the random variable $A(t)$, such that $P_a(t) = \text{Prob}(A(t)=a) = P(a, \beta - a + a, \alpha - a, t)$. This choice is wholly arbitrary, and the forthcoming analysis changes only superficially with the choice of $B(t)$ or $C(t)$ as the focal random variable.

By dividing throughout by k_1 and defining a dimensionless time $\tau = k_1 t$ and dimensionless dissociation constant $K = k_2/k_1$, Eq. (2) may be simplified to the following equations:

$$\begin{aligned} \frac{dP_0(\tau)}{d\tau} &= (\beta - \alpha + 1)P_1(\tau) - K\alpha P_0(\tau), \\ \frac{dP_a(\tau)}{d\tau} &= (a+1)(\beta - \alpha + a + 1)P_{a+1}(\tau) - a(\beta - \alpha + a) \\ &\quad \times P_a(\tau) + K(\alpha - a + 1)P_{a-1}(\tau) \\ &\quad - K(\alpha - a)P_a(\tau), \\ \frac{dP_\alpha(\tau)}{d\tau} &= -\alpha\beta P_\alpha(\tau) + KP_{\alpha-1}(\tau). \end{aligned} \quad (4)$$

Equation (4) implicitly assumes that $A(t)$ may be equal to zero, which is only possible if the species A is the limiting reagent. If not, the first of these equations will have a slightly different form. For the purposes of simplifying the analysis, let $\beta \geq \alpha$.

In Eq. (4), the equations describing the rates of change of the probabilities of the fully occupied ($A(\tau) = \alpha$) and depleted ($A(\tau) = 0$) states have been explicitly written to emphasize that $P_{\alpha+1}(\tau) = P_{-1}(\tau) = 0$. In so closing the system,

these equations are tantamount to transport equations with no net sources or sinks. Consequently, the sum of all probabilities $P_a(\tau)$ is a conserved quantity. That is, given the initial condition,

$$P_a(0) = \begin{cases} 1 & a = \alpha \\ 0 & \text{otherwise} \end{cases}, \quad (5)$$

the following constraint is implied at all times:

$$\sum_{a=0}^{\alpha} P_a(\tau) = 1. \quad (6)$$

Laplace transformation of these equations yields a linear system of algebraic equations. Let the Laplace transform of $P_a(\tau)$ be defined as

$$V_a(p) = \int_0^{\infty} \exp(-p\tau) P_a(\tau) dt. \quad (7)$$

Subsequently, Eq. (4) may be rewritten as

$$p\mathbf{V} = \mathbf{M}\mathbf{V} + \hat{\mathbf{P}}, \quad (8)$$

where \mathbf{V} and $\hat{\mathbf{P}}$ are defined as the $(\alpha + 1)$ -dimensional column vectors

$$\mathbf{V} = \begin{pmatrix} V_0(p) \\ V_1(p) \\ \vdots \\ V_\alpha(p) \end{pmatrix}, \quad \hat{\mathbf{P}} = \begin{pmatrix} P_0(t=0) \\ P_1(t=0) \\ \vdots \\ P_\alpha(t=0) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ \vdots \\ 1 \end{pmatrix}, \quad (9)$$

and \mathbf{M} is the $(\alpha + 1) \times (\alpha + 1)$ matrix defined as

$$\mathbf{M} = \begin{bmatrix} -u_0 & h_1 & 0 & 0 & \cdot & \cdot & \cdot & 0 \\ u_0 & -(h_1 + u_1) & h_2 & 0 & \cdot & \cdot & \cdot & 0 \\ 0 & u_1 & -(h_2 + u_2) & h_3 & \cdot & \cdot & \cdot & 0 \\ 0 & 0 & u_2 & -(h_3 + u_3) & \cdot & \cdot & \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & 0 \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & h_\alpha \\ 0 & 0 & 0 & 0 & 0 & 0 & u_{\alpha-1} & -(h_\alpha + u_\alpha) \end{bmatrix}. \quad (10)$$

Here the following definitions have been invoked:

$$h_a = a(\beta - \alpha + a), \quad (11)$$

$$u_a = K(\alpha - a). \quad (12)$$

Lastly, the implicit normalization condition in Laplace space becomes

$$p \sum_{a=0}^{\alpha} V_a(p) = 1. \quad (13)$$

Solving Eq. (8) for \mathbf{V} , one obtains the following relation for the Laplace-transformed probability distribution

$$\mathbf{V} = [p\mathbf{I} - \mathbf{M}]^{-1} \hat{\mathbf{P}}, \quad (14)$$

with the inverse matrix defined in terms of the adjoint and determinant of $[p\mathbf{I} - \mathbf{M}]$ as

$$[p\mathbf{I} - \mathbf{M}]^{-1} = \frac{\text{adj}(p\mathbf{I} - \mathbf{M})}{\det(p\mathbf{I} - \mathbf{M})}. \quad (15)$$

Since the only nonzero element of \hat{P} is its last, only the last column of $[p\mathbf{I}-\mathbf{M}]^{-1}$ is needed to specify \mathbf{V} . Therefore, determination of the cofactors of the last row of $[p\mathbf{I}-\mathbf{M}]$ is sufficient to solve Eq. (14). It can be shown that the cofactor of the last $(\alpha+1)$ row and j th column is given by

$$C_{\alpha+1,j} = (-1)^{\alpha+1+j} D_{j-1}(p) \prod_{i=j}^{\alpha} -h_i, \quad (16)$$

where here, $D_j(p)$ is the determinant of the submatrix of $[p\mathbf{I}-\mathbf{M}]$ composed of its first j rows and columns.

Employing the preceding equations, $V_a(p)$ may be expressed as a function of determinants of submatrices of $[p\mathbf{I}-\mathbf{M}]$.

$$V_a(p) = \frac{C_{\alpha+1,\alpha+1}(p)}{\det(p\mathbf{I}-\mathbf{M})} \quad (17)$$

$$= \frac{(-1)^{\alpha+a+2} D_a(p) \prod_{i=a+1}^{\alpha} -h_i}{D_{\alpha+1}(p)}. \quad (17')$$

The numerator of Eq. (17') may be simplified considerably:

$$\begin{aligned} & (-1)^{\alpha+a+2} D_a(p) \prod_{i=a+1}^{\alpha} -h_i \\ &= (-1)^{\alpha+a} D_a(p) \prod_{i=a+1}^{\alpha} -(i)(\beta-\alpha+i) \end{aligned} \quad (18)$$

$$= D_a(p) \prod_{i=a+1}^{\alpha} (i) \prod_{i=a+1}^{\alpha} (\beta-\alpha+i). \quad (18')$$

Subsequently, each of the finite product terms in Eq. (18') may be expressed as ratios of gamma functions, permitting Eq. (17) to be written as

$$V_a(p) = \frac{\alpha! \beta!}{(\beta-\alpha+a)! a!} \frac{D_a(p)}{D_{\alpha+1}(p)} \quad (19)$$

$$= \frac{1}{(\beta-\alpha+1)_a a!} \frac{\alpha! \beta!}{(\beta-\alpha)!} \frac{D_a(p)}{D_{\alpha+1}(p)}. \quad (19')$$

Equation (19) is the exact solution of Eq. (4) in Laplace space. Because $D_a(p)$ is the characteristic polynomial of an $a \times a$ matrix, it is an a th order polynomial of p possessing a highest order coefficient of unity. Moreover, since $a \in [0, \alpha]$, the order of the polynomial $D_a(p)$ is always less than $D_{\alpha+1}(p)$. Hence, Eq. (19) is proper for all a . The polynomials $D_a(p)$ may be generated recursively using the formula

$$D_a - (p + u_{a-1} + h_{a-1}) D_{a-1} + u_{a-2} h_{a-1} D_{a-2} = 0, \quad (20)$$

where $D_0 = 1$ and $D_1 = p + u_0$ are the initial conditions (Appendix A).

Having constructed the polynomials, the probability distribution $P_a(\tau)$ may be inverted from $V_a(p)$ using the residue theorem⁹

$$P_a(\tau) = \sum_{j=0}^{\alpha} \lim_{p \rightarrow \lambda_j} ((p - \lambda_j) \exp(p\tau) V_a(p)), \quad (21)$$

where $\{\lambda_j\}$ are the roots of $D_{\alpha+1}(p)$. As $D_{\alpha+1}(p) = \det(p\mathbf{I} - \mathbf{M})$, these roots are exactly equal to the eigenvalues of \mathbf{M} . Making use of Eq. (21), the exact solution of Eq. (4) is

$$\begin{aligned} P_a(\tau) &= \frac{1}{(\beta-\alpha+1)_a a!} \frac{\alpha! \beta!}{(\beta-\alpha)!} \\ &\times \sum_{j=0}^{\alpha} \frac{D_a(\lambda_j)}{\partial_p D_{\alpha+1}(\lambda_j)} \exp(\lambda_j \tau), \end{aligned} \quad (22)$$

where

$$\partial_p D_{\alpha+1}(\lambda_j) = \left(\frac{\partial D_{\alpha+1}(p)}{\partial p} \right)_{p=\lambda_j}.$$

Construction of $D_a(\lambda_j)$ and $\partial_p D_{\alpha+1}(\lambda_j)$ for evaluation is outlined in Appendix B.

III. EQUILIBRIUM SOLUTION OF THE REVERSIBLE BIMOLECULAR REACTION $A + B \rightleftharpoons C$

The equilibrium probabilities $P_a(\infty)$ follow analytically from Eq. (19). These may be determined using the initial- and final-value theorems for Laplace transforms, that is,¹⁰

$$\lim_{p \rightarrow \infty} p V_a(p) = P_a(0), \quad (23)$$

$$\lim_{p \rightarrow 0} p V_a(p) = P_a(\infty). \quad (24)$$

For any $a < \alpha$, the order of $D_{\alpha+1}(p)$ is higher than that of $p D_a(p)$, but when $a = \alpha$, the orders of both polynomials (as well as the highest order coefficients) are equal. Therefore, Eq. (23) reproduces the original initial conditions denoted by \hat{P} . Furthermore, in order for $P_a(\infty)$ to be nonzero for all a , $D_{\alpha+1}(p)$ must have a root of zero.

The equilibrium distribution may be computed without knowledge of the full Taylor series of $D_a(p)$. Consider the last terms of the first few polynomials $D_a(p)$ generated by Eq. 20:

$$\begin{aligned} D_0 &= 1, \\ D_1 &= p + u_0, \\ D_2 &= p^2 + (u_0 + u_1 + h_1)p + u_1 u_0, \\ D_3 &= p^3 + (u_0 + u_1 + u_2 + h_1 + h_2)p^2 + (u_0 u_1 + u_1 u_2 \\ &\quad + u_2 u_0 + u_0 h_2 + u_2 h_1 + h_1 h_2)p + u_2 u_1 u_0. \end{aligned} \quad (25)$$

It may be proven that the p^0 coefficient of any $D_a(p)$ is always an incremental product of u_i ,

$$D_a(0) = \prod_{i=0}^{a-1} u_i = K^a \frac{\alpha!}{\Gamma(\alpha - a + 1)} = (-K)^a (-\alpha)_a. \quad (26)$$

Equation (26) demonstrates that $D_a(0)$ is nonzero for all $a \in [0, \alpha]$, and confirms that $D_{\alpha+1}(0) = 0$. Combining this result with Eqs. (19) and (24) gives the following solution for the equilibrium probability distribution:

$$P_a(\infty) = \lim_{p \rightarrow 0} \left\{ p \frac{1}{(\beta - \alpha + 1)_a a!} \frac{\alpha! \beta!}{(\beta - \alpha)!} \frac{D_a(p)}{D_{\alpha+1}(p)} \right\} \quad (27)$$

$$= \frac{(-\alpha)_a (-K)^a}{(\beta - \alpha + 1)_a a!} \left\{ \frac{\alpha! \beta!}{(\beta - \alpha)!} \lim_{p \rightarrow 0} \left(\frac{1}{\partial_p D_{\alpha+1}(p)} \right) \right\}. \quad (27')$$

Then, making use of the normalization condition for $P_a(\tau)$ [Eq. (6)], one may simplify the bracketed term to give

$$\left\{ \frac{\alpha! \beta!}{(\beta - \alpha)!} \lim_{p \rightarrow 0} \left(\frac{1}{\partial_p D_{\alpha+1}(p)} \right) \right\} = \frac{1}{{}_1F_1(-\alpha; \beta - \alpha + 1; -K)}. \quad (28)$$

Thus, the equilibrium probabilities $P_a(\infty)$ are given by the following equation:

$$P_a(\infty) = \frac{(-\alpha)_a (-K)^a}{(\beta - \alpha + 1)_a a!} \cdot \frac{1}{{}_1F_1(-\alpha; \beta - \alpha + 1; -K)}. \quad (29)$$

This equation was implicitly discovered by Darvey *et al.*,⁷ who solved the steady-state version of Eq. (4) [that is, when $dP_a(\tau)/d\tau=0$] by the method of generating functions.

IV. THE IRREVERSIBLE BIMOLECULAR REACTION $A+B \rightarrow C$

The method of solution just discussed also works neatly for the irreversible bimolecular reaction process ($K=0$). In this case, \mathbf{M} is upper-diagonal and its eigenvalues follow directly as

$$\lambda_j = -h_j = -j(\beta - \alpha + j). \quad (30)$$

Subsequently, $D_a(p)$ is exactly equal to the product of the first $(a-1)$ diagonal elements of $[p\mathbf{I} - \mathbf{M}]$, or

$$D_a(p) = \prod_{j=0}^{a-1} (p + j(\beta - \alpha + j)) \quad a \in [0, \alpha + 1]. \quad (31)$$

Consequently, for irreversible reaction, Eq. (19) becomes

$$V_a(p) = \frac{\alpha! \beta!}{(\beta - \alpha + a)! a!} \frac{1}{\prod_{j=a}^{\alpha} (p + j(\beta - \alpha + j))}. \quad (32)$$

Here, application of Eq. (21) gives the probability distribution as

$$P_a(\tau) = \frac{\alpha! \beta!}{(\beta - \alpha + a)! a!} \times \sum_{j=a}^{\alpha} \frac{\exp(-j(\beta - \alpha + j)\tau)}{\prod_{i=a, i \neq j}^{\alpha} (i(\beta - \alpha + i) - j(\beta - \alpha + j))}. \quad (33)$$

The product in the denominator may be simplified (Appendix C) to give the following equation for $P_a(\tau)$:

$$P_a(\tau) = \frac{\alpha! \beta!}{(\beta - \alpha + a)! a!} \sum_{j=a}^{\alpha} (-1)^{j-a} \times \frac{(\beta - \alpha + 2j)(\beta - \alpha + a + j - 1)!}{(\alpha - j)!(j - a)!(\beta + j)!} \times \exp(-j(\beta - \alpha + j)\tau). \quad (34)$$

This equation is mathematically identical to those of Rényi,⁴ McQuarrie,⁵ and Ishida⁶ for the reaction $A + B \rightarrow C$, albeit in a different form.

V. RELATIONSHIP BETWEEN STOCHASTIC AND DETERMINISTIC MODELS

Theoretically, the expectation value of $P_a(\tau)$ should approach the deterministic population of A molecules as α and β become large. The common deterministic approach models the reaction $A + B \rightleftharpoons C$ using the law of mass action, where the population of A molecules is defined by the following nonlinear differential equation:

$$\frac{dA(t)}{dt} = -k_1 A(t) B(t) + k_2 C(t). \quad (35)$$

The solution of this *de facto* univariate equation, subject to the initial conditions and stoichiometric constraints before discussed, is

$$A(\tau) = \alpha - \frac{\exp(-\gamma_1 \tau) - \exp(-\gamma_2 \tau)}{\frac{1}{\gamma_1} \exp(-\gamma_1 \tau) - \frac{1}{\gamma_2} \exp(-\gamma_2 \tau)}, \quad (36)$$

where

$$\gamma_{1,2} = \frac{1}{2} ((\alpha + \beta + K) \pm \sqrt{(\alpha + \beta + K)^2 - 4\alpha\beta}), \quad (37)$$

and α , β , K , and τ are defined as before.

The expectation value of $P_a(\tau)$ is calculated using the standard formula

$$\mu_A = \sum_{i=0}^{\alpha} a P_a(\tau). \quad (38)$$

The deterministic and stochastic approaches are compared in Figs. 1 and 2. In agreement with the results of Rényi, the law of mass action does not hold exactly for small numbers of reactants, but is remarkably close to the expectation of $P_a(\tau)$. Even for a very small system with $\alpha = 10$, the difference in the means is negligible.

More significant, however, is the potential for deviation from mass-action kinetics, represented by the standard deviation (σ_A) in Fig. 3. The standard deviation is defined as the square root of the variance, defined by

$$\sigma_A^2 = \sum_{i=0}^{\alpha} (a - \mu_A)^2 P_a(\tau). \quad (39)$$

Figure 3 shows how the transient behavior of σ_A varies with K . As $K \rightarrow 0$, the process becomes irreversible, starting with only reactant and concluding only with product. Thus, the variance is exactly zero at both the very beginning and very

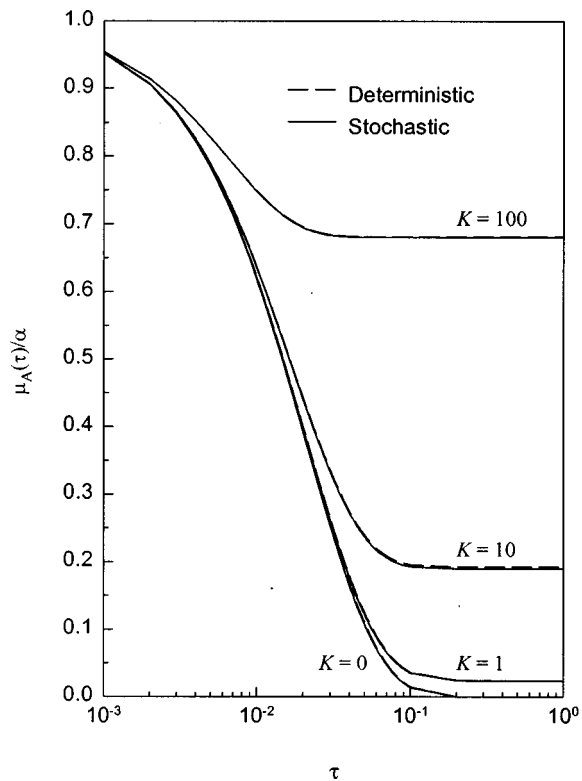


FIG. 1. Conversion of limiting reactant for a system with initial reactant populations $A(0) = \alpha = 10$, $B(0) = \beta = 50$. $K = k_2/k_1$ is the dimensionless dissociation constant.

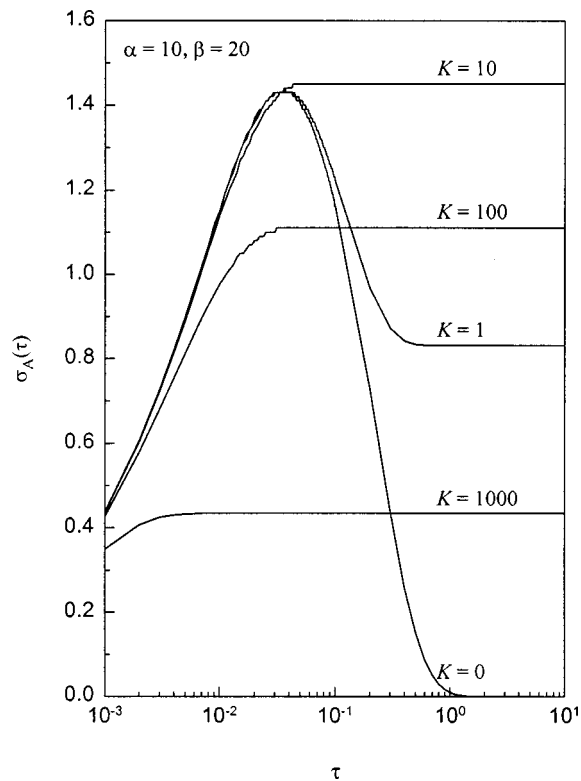


FIG. 3. Time dependence of the standard deviation σ_A of the limiting reactant population for initial reactant populations $\alpha = 10$, $\beta = 20$.

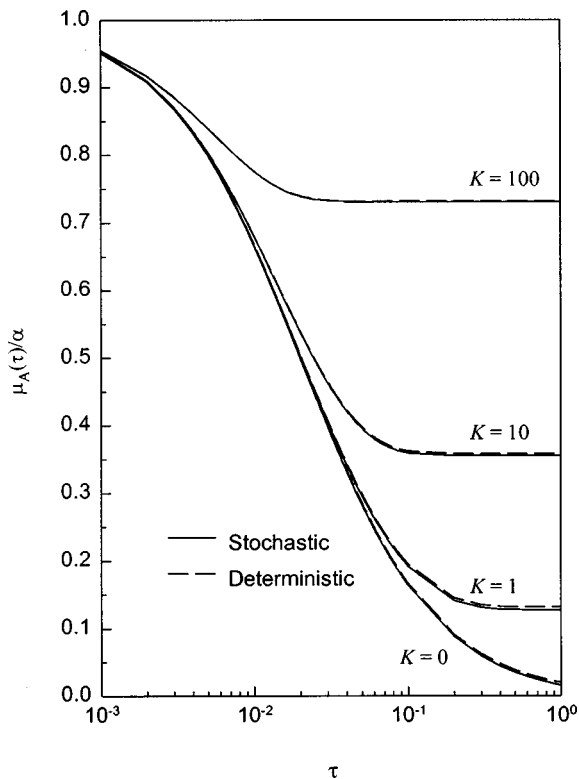


FIG. 2. Conversion of limiting reactant for initial reactant populations $A(0) = \alpha = 50$, $B(0) = \beta = 50$.

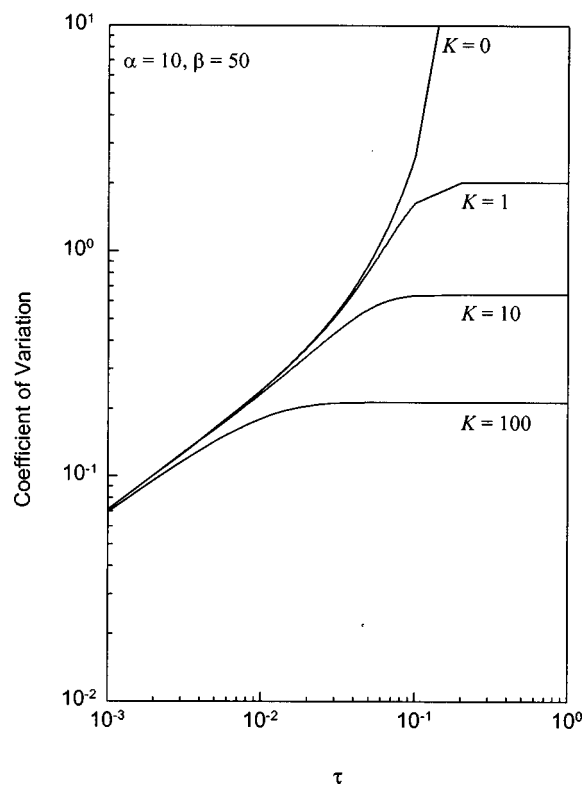


FIG. 4. Time dependence of the coefficient of variation for initial reactant populations of $\alpha = 10$, $\beta = 50$ at various dissociation constants K . The coefficient of variation is the ratio of the standard deviation and the average of the limiting reactant population distribution.

end of the reaction process. However, initially the variance becomes very large as the population states become occupied. Likewise, for small K , a peak is observed, followed by a monotonic decrease to the equilibrium solution. However, for large K , the reverse reaction brings the system to equilibrium fast enough to curtail the peak.

Another statistic of note is the coefficient of variation—the ratio of the standard deviation and the mean. The coefficient of variation gives a measure of the relative deviation. Its dynamics are given as a function of K and initial limiting reagent population α in Figs. 4 and 5. Because the dynamics of the mean are embedded in the coefficient of variation, the coefficient of variation is a monotonically increasing function of time. Subsequently, its decrease with increasing α and K is more apparent.

The ranges of K used in the figures are not arbitrary. Because the stochastic rate constants $k_1[\text{s}^{-1}]$ and $k_2[\text{s}^{-1}]$ are related to the deterministic rate constants $k_f[\text{mol}\cdot\text{L}^{-1}\cdot\text{s}^{-1}]$ and $k_r[\text{s}^{-1}]$ by the relations¹¹

$$k_1 = \frac{k_f}{N_A v} \quad \text{and} \quad k_2 = k_r, \quad (40)$$

the nondimensional K is given by

$$K = N_A K_D v, \quad (41)$$

where N_A is Avogadro's number, $K_D (=k_r/k_f)$ is the standard equilibrium constant for dissociation, and v is the system volume. Subsequently, owing to the ranges of measurable K_D and the immensity of N_A , K will typically exceed unity unless reaction is irreversible. Due to swift reverse-reaction, no reaction takes place for very large K .

VI. DISCUSSION

The value of the stochastic approach is not so much its capacity to predict the average population or concentration of reactive species in small systems, but to explore the quantal-dynamics of the reaction process and their ramifications. As Figs. 2–5 show, a description of the reaction dynamics using mass action kinetics may be up to 20% off in small systems. These situations arise commonly in biology for signaling in intracellular contact areas or proteolytic digestion in the interiors of liposomes. Thus, the stochastic approach serves as a means of evaluating the limitations of the deterministic approach as well as placing it on a more rigorous mathematical basis.

Another advantage of the stochastic approach is its capacity to give the probabilities of population states in time. While highly-efficient stochastic reaction kinetics algorithms exist for the simulation of coupled reactions of arbitrary molecularity,¹¹ only by solution of the master equation can one exactly obtain the probability distribution $P_a(t)$. Such distributions may have application in intercellular binding, for example, permitting one to compute the probability that adhesive receptors will bind adjacent cells as a function of their contact time. Other possible applications also include probabilistic analysis of receptor-mediated viral fusion or in-

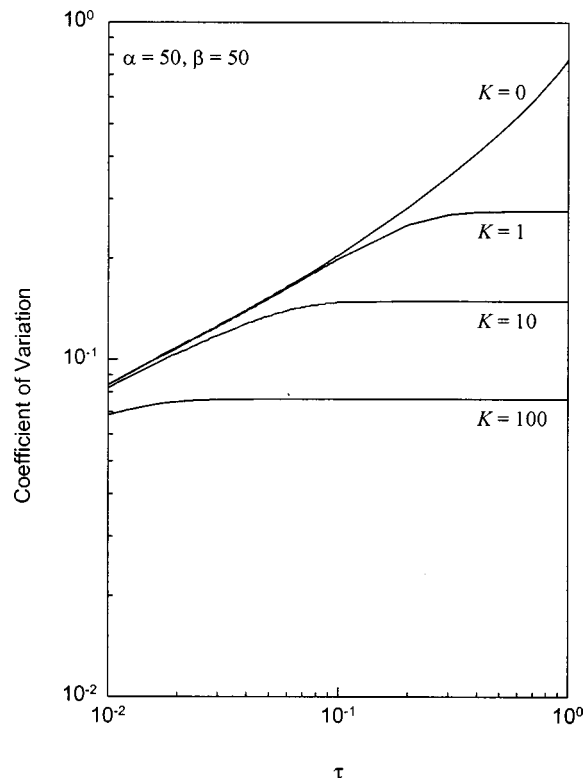


FIG. 5. Time dependence of the coefficient of variation for initial reactant populations of $\alpha = 50$, $\beta = 50$ at various dissociation constants K .

tracellular trafficking of molecules, where the formation of only a few complexes may have significant consequences on subsequent events.

Lastly, the methods of solution of the master equation given here may have application in the analysis of other reaction systems. The method of Laplace transforms is well suited to solving this type of system, since t is defined on $[0, \infty)$. Furthermore, as opposed to the generating-function method, which creates intractable partial-differential equations, the matrix method discussed here permits analytical solution in terms of computationally manageable functions and recurrences, and may permit solution of master equations for other bimolecular reaction systems such as $2A \rightleftharpoons C$, $A + B \rightleftharpoons C + D$, or $2A \rightleftharpoons C + D$.

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APPENDIX A

The polynomials $D_a(p)$ represent the determinants of the submatrices of $[p\mathbf{I} - \mathbf{M}]$ composed of the first a rows and columns. Their recursion relation follows directly from a study of the determinant D_m of an $m \times m$ tridiagonal matrix \mathbf{X} . Performing row-operations on the determinant to convert it to upper-triangular form,

$$\begin{aligned}
 D_m = \det(X) &= \begin{vmatrix} a_1 & b_1 & 0 & 0 & 0 & 0 \\ c_1 & a_2 & b_2 & 0 & 0 & 0 \\ 0 & c_2 & a_3 & b_3 & 0 & 0 \\ 0 & 0 & c_3 & \cdot & \cdot & 0 \\ 0 & 0 & 0 & \cdot & \cdot & b_{m-1} \\ 0 & 0 & 0 & 0 & c_{m-1} & a_m \end{vmatrix} \\
 &= \begin{vmatrix} a_1 & b_1 & 0 & 0 & 0 & 0 \\ 0 & a_2 - \frac{b_1 c_1}{a_1} & b_2 & 0 & 0 & 0 \\ 0 & c_2 & a_3 & b_3 & 0 & 0 \\ 0 & 0 & c_3 & \cdot & \cdot & 0 \\ 0 & 0 & 0 & \cdot & \cdot & b_{m-1} \\ 0 & 0 & 0 & 0 & c_{m-1} & a_m \end{vmatrix} \\
 &= \frac{1}{a_1} \begin{vmatrix} a_1 & b_1 & 0 & 0 & 0 & 0 \\ 0 & a_2 a_1 - b_1 c_1 & b_2 a_1 & 0 & 0 & 0 \\ 0 & c_2 & a_3 & b_3 & 0 & 0 \\ 0 & 0 & c_3 & \cdot & \cdot & 0 \\ 0 & 0 & 0 & \cdot & \cdot & b_{m-1} \\ 0 & 0 & 0 & 0 & c_{m-1} & a_m \end{vmatrix} \\
 &= \frac{1}{a_1} \begin{vmatrix} a_1 & b_1 & 0 & 0 & 0 & 0 \\ 0 & a_2 a_1 - b_1 c_1 & b_2 a_1 & 0 & 0 & 0 \\ 0 & 0 & a_3 - \frac{c_2 b_2 a_1}{a_2 a_1 - b_1 c_1} & b_3 & 0 & 0 \\ 0 & 0 & c_3 & \cdot & \cdot & 0 \\ 0 & 0 & 0 & \cdot & \cdot & b_{m-1} \\ 0 & 0 & 0 & 0 & c_{m-1} & a_m \end{vmatrix} \\
 &= \frac{1}{a_1} \frac{1}{a_2 a_1 - b_1 c_1} \begin{vmatrix} a_1 & b_1 & 0 & 0 & 0 & 0 \\ 0 & a_2 a_1 - b_1 c_1 & b_2 a_1 & 0 & 0 & 0 \\ 0 & 0 & a_3 (a_2 a_1 - b_1 c_1) - c_2 b_2 a_1 & b_3 (a_2 a_1 - b_1 c_1) & 0 & 0 \\ 0 & 0 & c_3 & \cdot & \cdot & 0 \\ 0 & 0 & 0 & \cdot & \cdot & b_{m-1} \\ 0 & 0 & 0 & 0 & c_{m-1} & a_m \end{vmatrix},
 \end{aligned}
 \tag{A1}$$

a trend yields the following recursion relation:

$$D_n = a_n D_{n-1} - c_{n-1} b_{n-1} D_{n-2}. \tag{A2}$$

Here, $D_n (n \in [0, m])$ is the determinant of an $n \times n$ tridiagonal matrix with elements $\{a_{ij}\}$, $\{b_i\}$, and $\{c_i\}$, and D_{n-j} are the determinants of its submatrices resulting from the removal of the last j columns and rows. To define the difference equation, the initial conditions $D_0 = 1$, and $D_1 = a_1$ are required.

The coefficients of the tridiagonal matrix $[pI - M]$ may be related to those of X by the following equations:

$$a_n = p + u_{n-1} + h_{n-1}, \tag{A3}$$

$$b_n = -h_n, \tag{A4}$$

$$c_n = -u_{n-1}. \tag{A5}$$

Making these substitutions renders D_n a function of p and yields Eq. (20).

APPENDIX B

As the recursion relation for $D_a(p)$ [Eq. (20)] is a second-order difference equation with nonconstant coefficients, obtaining its analytical solution is exceedingly difficult. Consequently, when evaluating Eq. (22) for $P_a(\tau)$, one must construct the polynomials $D_a(p)$ using the recursion relation, and find the roots of $D_{\alpha+1}(p)$ numerically.

Let us define the polynomials $D_a(p)$ and $\partial_p D_a(p)$ as follows:

$$D_a(p) = \sum_{i=0}^a \Theta_{a,i} p^i, \quad (\text{B1})$$

$$\partial_p D_a(p) = \sum_{i=0}^a i \Theta_{a,i} p^{i-1}. \quad (\text{B2})$$

The coefficients $\Theta_{a,i}$ may be constructed using the recursion relation for the polynomials. By taking the $(a+i)$ th derivative of Eq. (20) and setting p to zero, the following equation results, relating the $\Theta_{a,a-i}$ coefficient to higher order coefficients of other polynomials:

$$\Theta_{a,a-i} - \Theta_{a-1,a-1-i} - (u_{a-1} + h_{a-1}) \Theta_{a-1,a-i} + u_{a-2} h_{a-1} \Theta_{a-2,a-i} = 0. \quad (\text{B3})$$

Noting the initial conditions of Eq. (20), the initial conditions for this bivariate recurrence are $\Theta_{0,0} = \Theta_{1,1} = 1$ and $\Theta_{1,0} = u_0$. Subsequently, Eq. (B3) may be used to compute the coefficients of the polynomials $D_a(p)$ and $\partial_p D_a(p)$ in Eq. (22).

Once the polynomials have been generated, the roots of $D_{\alpha+1}(p)$ may be calculated by any number of root-finding algorithms. However, due to the fact that \mathbf{M} is tridiagonal and can be large in practice, the roots $\{\lambda_j\}$ of $D_{\alpha+1}(p)$ are more easily and better calculated as its eigenvalues. To this end the QR algorithm for real Hessenberg matrices is recommended,¹² which rapidly converges on the eigenvalues owing to the sparseness of \mathbf{M} .

APPENDIX C

To simplify the expression

$$x = \frac{1}{\prod_{i=a, i \neq j}^{\alpha} (i(\beta - \alpha + i) - j(\beta - \alpha + j))}, \quad (\text{C1})$$

first note that the argument of the product may be factored as follows:

$$x = \frac{1}{\prod_{i=a, j \neq i}^{\alpha} (i-j)(i+j+\beta-\alpha)} \quad (\text{C2})$$

$$= \frac{1}{\prod_{i=a}^{j-1} (i-j)(i+j+\beta-\alpha) \prod_{i=j+1}^{\alpha} (i-j)(i+j+\beta-\alpha)}. \quad (\text{C2}')$$

Subsequently, the two product terms may be evaluated, giving

$$\prod_{i=a}^{j-1} (i-j) = (-1)^{j-a} (j-a)!, \quad (\text{C3})$$

$$\prod_{i=a}^{j-1} (i+j+\beta-\alpha) = \frac{(2j+\beta-\alpha-1)!}{(j+a+\beta-\alpha-1)!}, \quad (\text{C4})$$

$$\prod_{i=j+1}^{\alpha} (i-j) = (\alpha-j)!, \quad (\text{C5})$$

$$\prod_{i=j+1}^{\alpha} (i+j+\beta-\alpha) = \frac{(\beta+j)!}{(\beta-\alpha+2j)!}. \quad (\text{C6})$$

Combining the preceding results yields the surprisingly simple equation

$$x = (-1)^{j-a} (\beta - \alpha + 2j) \frac{(j+a+\beta-\alpha-1)!}{(j-a)! (\alpha-j)! (\beta+j)!}. \quad (\text{C7})$$

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