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STOCHASTIC APPROACH TO CHEMICAL KINETICS

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CONTENTS

I. Introduction

In this article we shall present a summary of the various stochastic approaches and applications to chemical reaction kinetics, but before discussing these we first briefly introduce the basic ideas and definitions of classical or deterministic chemical kinetics. One of the basic questions to which chemists address themselves is the rate of chemical reactions, or in other words, how long it takes for a chemical reaction to attain completion, or equilibrium. Apparently the first significant quantitative investigation was made in 1850 by L. Wilhelmy [93]. He studied the inversion of sucrose (cane sugar) in aqueous solutions of acids, whose reaction is

$$\underset{}{H_2O} + \underset{\text{(sucrose)}}{C_{12}H_{22}O_{11}} \rightarrow \underset{\text{(glucose)}}{C_6H_{12}O_6} + \underset{\text{(fructose)}}{C_6H_{12}O_6}.$$

He found *empirically* that the rate of decrease of concentration of sucrose was simply proportional to the concentration remaining unconverted, i.e., if $S(t)$ is the concentration of sucrose, then

$$-\frac{dS}{dt} = kS. \tag{I-1}$$

The constant of proportionality is called the *rate constant* of the reaction. If S_0 is the initial concentration of sucrose, then

$$S(t) = S_0 e^{-kt}. \tag{I-2}$$

Since then an enormous number of reactions has been studied and the field of chemical kinetics is now one of the largest areas of chemical research. The importance of the field lies in the fact that it yields concise expressions for the time dependence of reactions, predicts yields, optimum economic conditions, and gives one much insight into the actual molecular processes involved. The detailed molecular picture of a reaction process is called the *mechanism* of the reaction.

In most cases, the rate, say the decrease of concentration of species 1, is found to depend upon the product of the concentrations of the other species present, so that

$$-\frac{dc_1}{dt} = kc_1^a c_2^b \cdots c_N^n. \tag{I-3}$$

The *order* of the reaction is defined as the sum of the exponents of the concentration terms on the right hand side of this expression. The inversion of sucrose, for example, is a first order reaction. It should be pointed out that it is not necessary for the order of a reaction to be an integer since it is determined simply

as the best fit of a rate equation to empirical data. Also it is important to realize that there is absolutely no connection between the stoichiometry of a chemical reaction and its order. For instance, of the two reactions

(a) $$2N_2O_5 \rightarrow 4NO_2 + O_2$$

and

(b) $$2NO_2 \rightarrow 2NO + O_2,$$

(a) is first order and (b) is the second order. This is because many reactions proceed through a number of steps or stages between initial reactants and final products and the *slow* ones determine the rate. Each of these individual steps is called an *elementary reaction.* We use the term *molecularity* to indicate the number of reactant molecules that enter into an elementary reaction. Unimolecular reactions are first order, bimolecular reactions are second order, etc., but the converse is not necessarily true. *Reaction order* applies to the empirical rate law; *molecularity* applies to the molecular mechanism of an elementary step.

What are the reasons for formulating classical chemical kinetics in a probabilistic or stochastic framework? A basic reason is that the process is in fact statistical in nature. An expression like Equation (I–2) considers the variable $S(t)$ to be a continuous real-valued function of time, and no deviations from this curve are considered. In general, however, the concentration or number of molecules in the system is an integer-valued random variable, and the process should be described by the probability density of this random variable. The mean of this distribution will then be the observed concentration and the variance will supply a measure of the inherent statistical fluctuations about the mean. For most simple reactions, however, the mean will be essentially the same as the deterministic solution and the fluctuations will be so small as to be of no importance. There is a great number of important exceptions to this which will be described below, but even if this were not so, it would still be of value to consider the statistical aspects of chemical kinetics in an effort to extend thermodynamics or statistical thermodynamics to time dependent systems, or in other words to predict rates from molecular properties. We shall discuss such an approach due to Montroll and Shuler [92] in a later section.

There are a number of reactions for which the deterministic approach is not adequate and stochastic models must in fact be used. The most obvious example are systems which contain a small number of reactant species, such as many reactions occurring in biological cells [8]. Another example is a process where a few activated molecules initiate an avalanche type reaction. Such a mechanism has recently been proposed for certain visual and blood clotting mechanisms [82], [84], [118]. Many reactions in the field of polymer chemistry have been formulated stochastically such as the distribution of chain lengths, the distribution of copolymeric composition [20], [21], [22], [37], [50], [51], [79], [86], [98],

[98], [99], [104], kinetics of reactant isolation [19], and the polymerization kinetics of biological macromolecules on templates [112], [127], [128]. Several of these will be discussed in Section (IV). Other examples are diffusion controlled chemical reactions [72], [97], [125], models of sterilization [36], chromatography [41], [42], [87], rearrangement of linear methylsilicone oils [102], [103], denaturation of polypeptides or proteins [90], [100], [109], relaxation of vibrational nonequilibrium distributions in shock waves [13], [16], [48], [62], [91], [106], [107], [110], theory of homogeneous and heterogeneous nucleation of vapours [4], [17], [23], [31], [45], [61], the theory of adsorption of gases onto solid surfaces [64], degradation of linear chain molecules [2], [3], [46], [63], [101], the separation of molecular compounds by countercurrent dialysis [71], the statistical processes of aggregation and polymerization [123], isotope exchange [68], and attempts to study irreversible thermodynamics through stochastic models [54]–[60], [67].

II. Historical Background

Although the mathematical techniques of stochastic processes have existed for some time [32], until ten years or so ago few applications of the theory to chemical kinetics had appeared. A great body of literature has existed in physics for many years, but in this article we shall try to concentrate specifically upon chemically oriented rate processes. We must, however, simply refer to the classic articles of Chandrasekhar [18], Uhlenbeck and Ornstein [116], Wang and Uhlenbeck [119], and the others that appear in Wax's monograph [121], for completeness.

The first application of stochastic ideas to chemical kinetics seems to be due to Kramers [77], [92], who treated a chemical reaction as a Brownian motion of particles, whose rate of passage over a potential barrier represents the rate of decomposition. This was an early attempt at trying to formulate macroscopic rate processes in terms of molecular parameters.

The next seems to be that of Delbrück [27] who studied a stochastic model of the so-called autocatalytic reaction $A \rightarrow B$. By autocatalytic, one means that the rate of disappearance of A is not only proportional to A, but also to B, so that the reaction tends to catalyze itself. Even though this appears to be a second order reaction, Delbrück assumed that the concentration of A is so large that it remains constant through the course of reaction and so the rate is simply given by

$$\frac{d\mathrm{B}}{dt} = k\mathrm{B},$$

which is a first order reaction. He showed that during the initial stages of reaction, the fluctuations in the number of reactant molecules was of the order of the square root of the number of reactant molecules.

It was not until 1953 that Singer [113] discussed the application of a stochastic method to the study of *irreproducible reactions*. He pointed out that a number

of chemical reactions, for instance, the oxidation of formic acid by potassium nitrate, the slow or explosive decomposition of some solids, and the initial stages of certain polymerization reactions have been reported to show large fluctuations or *irreproducibilities*. He concluded that in small systems, fluctuations in the number of reactant species could be responsible for irreproducible reactions, together of course with those due to the presence of impurities. Shortly thereafter Rényi [105] treated the bimolecular reaction of $A + B \rightarrow C$ and showed that the law of mass action, which is a basic axiom in the deterministic theory, is only approximately valid and does not hold for small systems. This work is outlined in Chapter 8 of Bharucha-Reid's monograph [14]. This was followed by a series of papers by Prékopa [102], [103], in which he used stochastic methods to study the rearrangement of linear methyl-silicone oils. During this time there was also a number of papers appearing in the biological or biostatistical literature dealing with population models and other applications, but since we are trying mainly to outline chemical applications, we simply refer to Chapter 4 of [14], which contains what seems to be a comprehensive review of biological applications and the reviews that have appeared in this journal by Gani [38] and Kimura [76]. In 1957 Bartholomay [7], [8] started a series of articles studying the Markovian basis of chemical kinetics, and then studied the unimolecular reaction $A \rightarrow B$ as a pure death process. Since then a large number of papers have appeared, and are continuing to appear at a larger rate now that chemists are becoming aware of the simple techniques of stochastic rate processes.

In 1960 Ishida [65] extended Bartholomay's method of treating unimolecular reactions to a more general stochastic process having a time dependent rate constant. Using this he studied the bimolecular process $2A \rightarrow B$ and a multidimensional stochastic model of the unimolecular decomposition theory of Kassel. Then McQuarrie [88] studied a number of simple first order reactions and also considered the effect of initial conditions on the expectation value and variance of product. This was followed by a study of two bimolecular processes, $2A \rightarrow B$ and $A + B \rightarrow C$, which were solved exactly by generating functions [89]. These seem to have been the first exact numerical results for bimolecular processes. Several approximate methods were also presented. During this time Bartholomay [11], [12], applied a stochastic model to the Michaelis-Menton reaction, one of importance in biochemistry. Shortly after, Ishida [66] also solved the above two bimolecular reactions exactly, and recently Darvey, Ninham, and Staff [25] solved a number of reversible bimolecular processes exactly for their equilibrium properties. This very nearly exhausts the simple elementary processes that have been studied.

Since 1960 or so, there have been a large number of papers on more complicated applications of stochastic ideas to chemical kinetics or related topics. These have been mentioned in the previous section.

In this article we shall review all the exact elementary reactions that have been

studied and then present a partial select review of some of the more complicated applications. The only other review of this type is Chapter 8 of [14], which covers essentially only the work of Rényi [105], Singer [113], and Bartholomay [7], [8], [9]. Chapter 4 of Bharucha-Reid's book contains an excellent discussion of biological stochastic models, and so little emphasis will be placed here on biological applications, except for a few recent articles.

In the next section we shall treat unimolecular and exactly solved bimolecular reactions, and some possible approximate methods. In the last section we shall present some selected more complex applications. It is hoped that the exactly solvable elementary reactions can serve as a basis for more complex reactions, cases on which to test badly needed approximate methods, and as a useful connection between rate processes and statistical mechanics. The experimentally useful results, however, are to be found in the more complex reactions which must in fact be treated stochastically.

III. Exactly Solvable Elementary Reactions

In this section we shall present a rather detailed discussion of the exactly solvable elementary reactions. By elementary we mean unimolecular and bimolecular reactions, and simple extensions of them. All of these can be thought of as various birth and death processes in one or several variables. Unimolecular reactions are represented by linear birth and death processes and bimolecular reactions are represented as quadratic birth and death processes. Bartholomay [7] has emphasized the connection between unimolecular reactions, linear birth and death processes, and the Q-matrix method of Doob. We shall simply assume the existence of differential-difference equations such as (III–1).

III.A. Unimolecular reactions

In this section we shall treat a variety of first order reactions. Such systems may be described by a finite or infinite set of states, $\{x\}$, each member of which corresponds to a specified number of some given type of molecule in the system. One then defines a set of transition probabilities of going from state x to state $x - j$, which in unimolecular reactions depend linearly upon x. The simplest example of this type of reaction is $A \rightarrow B$ which occurs particularly in radioactive decay processes. This process seems to have been first studied in a chemical context by Bartholomay [8].

a) *Reaction* $A \rightarrow B$ [8], [88]

Let the random variable $X(t)$ be the number of A molecules in the system at time t. The stochastic model is then completely defined by the following assumptions:

(1) The probability of transition $(x) \rightarrow (x - 1)$ in the interval $(t, t + \Delta t)$ is $kx\Delta t + o(\Delta t)$, where k is a constant and $o(\Delta t)$ means that $o(\Delta t)/\Delta t \rightarrow 0$ as $t \rightarrow 0$.

(2) The probability of a transition $(x) \to (x - j), j > 1$, in the interval $(t, t + \Delta t)$ is at least $o(\Delta t)$, since the time interval is considered to be small enough that only one molecule undergoes a transition.

(3) The reverse reaction occurs with probability zero.

A detailed balance gives

$$P_x(t + \Delta t) = k(x + 1)\Delta t P_{x+1}(t) + (1 - kx\Delta t) P_x(t) + o(\Delta t), \tag{III-1}$$

where $P_x(t) = \text{Prob}\{X(t) = x\}$. By the standard procedure of transposing $P_x(t)$ from the right-hand side, dividing by Δt, and then taking the limit $\Delta t \to 0$, one easily gets the differential-difference equation

$$\frac{dP_x}{dt} = k(x + 1) P_{x+1}(t) - kx P_x(t). \tag{III-2}$$

We assume that this procedure is valid. The validity of such transport equations has been discussed in some detail, e.g. by Van Hove [117]. By means of the generating function of $P_x(t)$, namely,

$$F(s, t) = \sum_{x=0}^{\infty} P_x(t) s^x \qquad |s| < 1, \tag{III-3}$$

Equation (III-2) may be transformed into a partial differential equation,

$$\frac{\partial F}{\partial t} = k(1 - s) \frac{\partial F}{\partial s}. \tag{III-4}$$

It should be mentioned here that even though the system we are considering has a finite number of states, the sum in Equation (III-3) runs from zero to infinity. This introduces no difficulty since we know physically that $P_x(t)$ must vanish for all time when $x \geqq x_0$, where x_0 is the total number of particles in the system, and so the sum is really finite. This same reasoning applies to later cases as well.

The solution of this, subject to the initial condition $F(s, 0) = s^{x_0}$, is

$$F(s, t) = [1 + (s - 1) e^{-kt}]^{x_0}. \tag{III-5}$$

By noting the easily proved relations

$$E\{X(t)\} = (\partial F/\partial s)_{s=1}$$

$$D^2\{X(t)\} = (\partial^2 F/\partial s^2)_{s=1} + (\partial F/\partial s)_{s=1} - (\partial F/\partial s)^2_{s=1}, \tag{III-6}$$

where $E\{X(t)\}$ is the expectation value or mean of $X(t)$, and $D^2\{X(t)\}$ is the variance, one obtains

$$\begin{aligned} E\{x(t)\} &= x_0 e^{-kt} \\ D^2\{X(t)\} &= x_0 e^{-kt}(1 - e^{-kt}). \end{aligned} \tag{III-7}$$

Note that the mean value of the stochastic representation is the deterministic result, showing that the two representations are "consistent in the mean". We shall see later that this is true only for unimolecular reactions. The stochastic model, however, also gives higher moments and so fluctuations can now be included in chemical kinetics. One sees that the stochastic approach is to chemical kinetics what statistical thermodynamics is to thermodynamics. An expansion of Equation (III–5) gives for $P_x(t)$,

$$P_x(t) = \binom{x_0}{x} e^{-xkt}(1 - e^{-kt})^{x_0 - x}$$

which is first due to Bartholomay [8].

b) *Reversible unimolecular reaction* $A \rightleftarrows B$

If we again let $X(t)$ be the concentration of A molecules at time t and let k_1 and k_2 be the forward and backward rate constants, respectively, then we obtain [88]

$$\text{(III–8)} \quad \frac{dP_x}{dt} = k_2(x_0 - x + 1)P_{x-1}(t) + k_1(x+1)P_{x+1}(t) - [k_1 x + k_2(x_0 - x)]P_x(t),$$

where x_0 is the total number of A and B molecules. The partial differential equation becomes

$$\text{(III–9)} \quad \frac{\partial F}{\partial t} = [k_1 + (k_2 - k_1)s - k_1 s^2]\frac{\partial F}{\partial s} + x_0 k_2(s-1)F.$$

If we assume that there are x_0 molecules of A at time zero, then the solution of Equation (III–9) is

$$\text{(III–10)} \quad F(s,t) = \left[\frac{\lambda e^{-kt}(s-1) + \lambda - s}{\lambda}\right]^{x_0},$$

where $\lambda = k_1/k_2$ and $k = k_1 + k_2$. Equations (III–6) give for the mean and variance:

$$\text{(III–11)} \quad E\{X(t)\} = [x_0/(k_1 + k_2)](k_1 e^{-kt} + k_2),$$

$$\text{(III–12)} \quad D^2\{X(t)\} = [x_0\omega/(1+\lambda)](1 - [\omega/(1+\lambda)]),$$

where $\omega = \lambda e^{-kt} + 1$. Such a reversible system at equilibrium ($t \to \infty$), can be studied by equilibrium statistical thermodynamics, which predicts that [53]

$$\text{(III–13)} \quad \overline{N_A^2} - (\overline{N}_A)^2 = \overline{N}_A\overline{N}_B/N = \overline{N_B^2} - (\overline{N}_B)^2,$$

where N_A and N_B are the numbers of A and B molecules, respectively, and $N = N_A + N_B$. Equations (III–11) and (III–12) show that this relationship is valid not only at equilibrium, but for all t. This is a surprising result and gives one hope that stochastic models of rate processes have a real connection with

time-dependent statistical thermodynamics. The exact connection, however, is not at all clear. For large λ, i.e., the forward rate constant much larger than the backward rate constant, Equation (III–12) reduces to Equation (III–7) whose maximum deviation is $x_0/4$, occurring at half-life of the reaction.

c) *Parallel first-order reactions*

$$A \xrightarrow{k_1} B$$

$$A \xrightarrow{k_2} C.$$

In a system such as this, one must consider a two-dimensional stochastic process. Let $X(t)$ be the number of A molecules at time t and $Y(t)$ be the number of B molecules. A detailed balance gives [88]

$$P_{x,y}(t+\Delta t) = k_1(x+1)\Delta t P_{x+1,y-1}(t) + k_2(x+1)\Delta t P_{x+1,y}(t) + (1 - k_1 x - k_2 x) P_{x,y}(t) + o(\Delta t).$$

The partial differential equation corresponding to this is

$$\frac{\partial F}{\partial t} = (k_1 r + k_2 - Ks)\frac{\partial F}{\partial s}, \tag{III–15}$$

where

$$F(r,s,t) = \sum_{x=0}^{\infty}\sum_{x=0}^{\infty} P_{x,y}(t)\, s^x r^y \tag{III–16}$$

and $K = k_1 + k_2$. If Equation (III–15) is solved with the initial condition $s^{x_0} r^{B_0}$, then

$$F(r,s,t) = ([k_1 r + k_2 - (k_1 r + k_2 - Ks)e^{-Kt}]/K)^{x_0} r^{B_0}. \tag{III–17}$$

The mean and variance of $X(t)$ and $Y(t)$ are

$$E\{X(t)\} = x_0 e^{-Kt} \tag{III–18}$$

$$D^2\{X(t)\} = x_0 e^{-Kt}(1 - e^{-Kt})$$

$$E\{Y(t)\} = B_0 + (k_1 x_0/k)(1 - e^{-Kt}) \tag{III–19}$$

$$D^2\{Y(t)\} = (k_1 x_0/K)(1 - e^{-Kt})(1 - [k_1(1 - e^{-Kt})/K]).$$

The means are in effect the deterministic result. The extension to n parallel reactions is obvious.

d) *More general initial conditions* [88]

We now discuss the reaction $A \rightarrow B$ again, but do not assume that initially there were exactly x_0 molecules of A in the system. Due to inaccuracies in weigh-

ing, etc., one always obtains a distribution about some initial concentration. In general this distribution would be Gaussian, but for large systems it can be more conveniently approximated by a binomial distribution:

$$\text{(III–20)} \qquad \text{Prob}\{X(0)=r\} = \binom{n}{r} p^r(1-p)^{n-r}, \qquad r = 0,1,2,\cdots n.$$

The mean m and variance σ^2 of Equation (III–20) are

$$\text{(III–21)} \qquad m = np, \qquad \sigma^2 = np(1-p).$$

We let $np = x_0$, and so $\sigma^2 = x_0(1-p)$. We shall consider x_0 to be fixed so that σ^2 can be varied by adjusting p. This can be done by simply adjusting n simultaneously so that the product $np = x_0$ is constant. In this way we can study the effect of varying p for fixed x_0, or physically, we can study the effect of various degrees of inaccuracy of the determination of the initial conditions. As p approaches unity, the initial conditions are more and more accurately determined. Equation (III–2) is now solved with the initial condition

$$\text{(III–22)} \qquad F(s,0) = [1+(s-1)p]^{x_0/p}$$

to give as its solution

$$\text{(III–23)} \qquad F(s,t) = [1+p(s-1)e^{-kt}]^{x_0/p} .$$

The mean and variance for this process are

$$\text{(III–24)} \qquad \begin{aligned} E\{X(t)\} &= x_0 e^{-kt}, \\ D^2\{X(t)\} &= x_0 e^{-kt}(1-pe^{-kt}). \end{aligned}$$

Note that the mean is dependent only upon the mean of the initial distribution and not upon its width. When $p = 1$, i.e., the mean and the variance of the initial distribution are x_0 and 0 respectively, then Equations (III–24) reduce to Equations (III–7). This was done to study the effect of an uncertainty in the initial conditions on the scatter in the rate data. This is seen in Figure 1 where Equation (III–24) is plotted against kt for various values of p. It thus seems possible to develop a scheme to determine rate constants even though the initial conditions have a known but sizeable spread.

e) *Triangular reaction*

Fredrickson [35] has considered first order stochastic triangular reactions between three chemical species. He points out that this system is of interest in irreversible thermodynamics and biology. He has applied it [36] specifically to the sterilization or the thermal killing of bacterial spores, the most resistant biological forms known. The triangular process is pictured in Figure 2. For first order reactions, transitions of a given molecule occur independently of

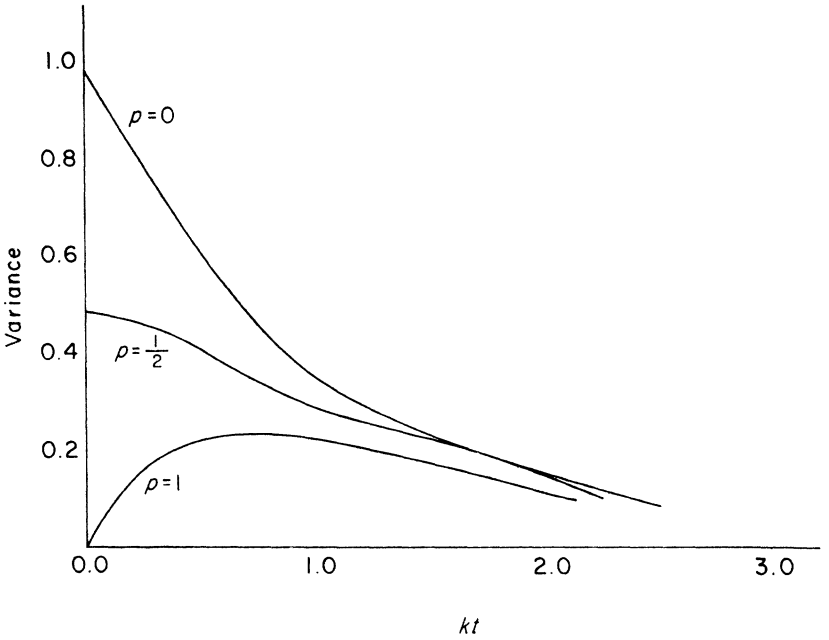


Figure 1
Variance against kt for the irreversible unimolecular case in which the initial conditions are described by a binomial distribution with mean x_0 and variance $x_0(1 - p)$

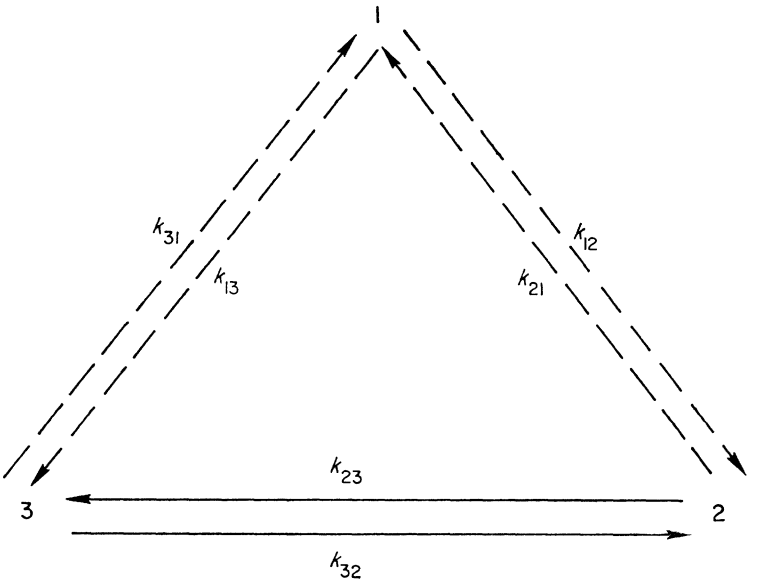


Figure 2
Schematic representation of the triangular unimolecular reaction

whatever transitions other molecules undergo. For instance, the probability that the nth molecule undergoes a transition $i \to j$ in time t to $t + \Delta t$ does not depend on what happens to the other $N - 1$ molecules in that time interval. Because of this hypothesis of independence, $P_{x_1x_2x_3}(t)$ must be given by the multinomial formula

$$P_{x_1x_2x_3}(t) = N! \prod_{j=1}^{3} \frac{[p_j(t)]^{x_j}}{x_j!}, \tag{III-25}$$

where N is the total number of molecules in the system (assumed to be closed), $p_i(t)$ is the probability that any one molecule is in state $i = 1, 2$, or 3, x_i is the number of molecules in state i. Since

$$\sum x_i = N \quad \text{and} \quad \sum p_i(t) = 1, \tag{III-26}$$

there are really only two independent random variables and so we have

$$P_{x_ix_j}(t) = \frac{N!}{x_i!\,x_j!(N - x_i - x_j)!}[p_i(t)]^{x_j}[p_j(t)]^{x_i}[1 - p_i(t) - p_j(t)]^{N-x_i-x_j}, \quad (i \neq j). \tag{III-27}$$

Note that the previous expressions for $P_x(t)$ in this section are of this binomial or multinomial distribution form. Equation (III–27) is of course not specified until the $p_i(t)$ are determined, but Fredrickson [35] shows that by means of the usual hypotheses, they are given by

$$\frac{d\boldsymbol{p}}{dt} = \boldsymbol{K}\boldsymbol{p} \tag{III-28}$$

where

$$\boldsymbol{K} = \begin{bmatrix} -(k_{12} + k_{13}) & k_{21} & k_{31} \\ k_{12} & -(k_{21} + k_{23}) & k_{32} \\ k_{13} & k_{23} & -(k_{31} + k_{32}) \end{bmatrix} \tag{III-29}$$

and

$$\boldsymbol{p}(0) = \boldsymbol{\phi}$$

where $\boldsymbol{\phi}$ is arbitrary.

This approach was apparently first suggested by Bartholomay [10] and amplified by Jachimowski and Russell [70] in a "set-theoretic approach" to reaction kinetics. Although strictly applicable only to first-order systems, it can be used to obtain approximate expressions for more complex reactions.

f) *Multicomponent case*

Since the stochastic models of first-order chemical reactions always lead to first order partial differential equations for the generating function, these models

can always be solved exactly. General first-order stochastic processes have been solved by Krieger and Gans [78] and by Gans [39]. Their motivation was a study of relaxation of multistate systems and not chemical kinetics *per se*, but the mathematical formulation is the same. They also showed that a system relaxing by a first-order process from one equilibrium state to another will maintain, at all times, a multinomial distribution. A stochastic model for the general system of first-order chemical reactions involving n chemical species was derived later by Darvey and Staff [26], from which again the multinomial distribution was shown to represent the probability time course of the components of the reaction. Their paper seems to be little different from that of Krieger and Gans, except perhaps for their viewpoint. They were able to show that the expected value for the number of molecules of any particular component of the general system of first-order reactions given by the stochastic model is consistent with the exact number of molecules predicted by the deterministic model obtained by using the principle of mass action, provided the probability parameters of the former model are interpreted as the rate constants of the latter model. This is clear, however, by simply multiplying their Equation (4):

$$\frac{dP_{x_1x_2\ldots x_n}(t)}{dt} = \sum_{\substack{i=1\\ i\neq j}}^{n}\sum_{j=1}^{n} k_{ij}(x_i+1)\,P_{x_1-x_i+1,x_j-1,\ldots,x_n}(t) - \sum_{\substack{i=1\\ i\neq j}}^{n}\sum_{j=1}^{n} k_{ij}x_iP_{x_1x_j\ldots x_n}(t) \tag{III-30}$$

by x_m, say, and summing over all the x's. If this is done, one finds, after some manipulation,

$$\frac{d\langle x_i\rangle}{dt} = \sum_{\substack{j=1\\ j\neq i}}^{n} k_{ji}\langle x_j\rangle - \sum_{\substack{j=1\\ j\neq i}}^{n} k_{ij}\langle x_i\rangle \qquad (i=1,2,\cdots,n), \tag{III-31}$$

which is the deterministic equivalent of the process described by Equation (III–30)

Another way of deriving equations for the moments is to use the technique of the cumulant generating function [88] which generates the cumulants or semi-invariants of the process. Let $K(u,t) = \ln F(e^u,t)$. The partial differential equation for $F(s,t)$ may then be transformed into one for $K(u,t)$. Since

$$K(u,t) = uE\{X(t)\} + \frac{u^2}{2!}D^2\{X(t)\} + \cdots, \tag{III-32}$$

both sides of the equation for $K(u,t)$ may be expanded in terms of the dummy variable u, and coefficients of like powers of u may be compared. This procedure produces a hierarchy of ordinary differential equations for the cumulants in which the equation for the nth cumulant is

$$\frac{d\chi_n}{dt} = f(\chi_n, \chi_{n-1}, \cdots, \chi_1), \tag{III-33}$$

where $f(\cdot)$ is a linear function. Unfortunately, this technique is applicable only to first-order processes, since the hierarchy does not uncouple in the case of processes of higher order. In particular, for a second-order process, Equation (III-33) becomes

$$\frac{d\chi_n}{dt} = f(\chi_{n+1}, \chi_n, \cdots, \chi_1). \tag{III-34}$$

A similar situation exists in the molecular distribution function theory of liquids [52] and one usually resorts to a superposition approximation. This amounts to assuming that, e.g., $\langle x^3 \rangle = \langle x \rangle \langle x^2 \rangle$ or something similar. Such an approximate treatment of other than first order reactions will be presented below.

g. *Unimolecular decomposition*

Ishida [65] has made an interesting application of these more general first order processes to what he calls "true" unimolecular gas reactions. These are reactions in which isolated molecules are excited either thermally or by radiation and are allowed to decay spontaneously. This necessarily requires low pressures in order to diminish the effect of collisions between molecules. Consider microscopically the multi-dimensional stochastic process for a reaction system, such that at time t the numbers of reactant molecules in the states of internal energies $\varepsilon_1, \varepsilon_2, \cdots, \varepsilon_i, \cdots$ are $x_1, x_2, \cdots, x_i, \cdots$, respectively, under the same conditions as in the previous section. Then if we denote the probability for this reaction system by $P_{x_1 x_2 \ldots}(t) = P(\{x_i\}, t)$, we have

$$\begin{aligned}\frac{d}{dt}P(\{x_i\}, t) = &- k_1^{(1)} x_1 P(\{x_i\}, t) + k_1^{(1)}(x_1 + 1) P_{x_1+1, x_2 \ldots}(t) \\ &- k_1^{(2)} x_2 P(\{x_i\}, t) + k_1^{(2)}(x_2 + 1) P_{x_1 x_2 + 1 \ldots}(t) - \cdots\end{aligned}$$

or

$$\begin{aligned}\frac{d}{dt}P(\{x_i\}, t) = &- \sum_i k_1^{(i)} x_i P(\{x_j\}_{j \neq i}, x_i, t) \\ &+ \sum_i k_1^{(i)}(x_i + 1) P(\{x_j\}_{j \neq i}, x_i + 1, t),\end{aligned} \tag{III-36}$$

where $P(\{x_j\}_{j \neq i}, x_i + 1, t) = P(x_1, x_2, \cdots, x_{i-1}, x_i + 1, x_{i+1}, \cdots, t)$ and the rate constant $k_1^{(i)}$, which is a function of energy ε_i, denotes the transition probability that a molecule in the internal state with an energy ε_i decomposes during unit time. Let the total number of reactant molecules at time t be $x = \sum x_i$ and the initial number of reactant molecules with the internal energy ε_i by x_i^0. If we multiply

both sides of Equation (III–36) by $\sum x_i$ and sum from 0 to x_0 ($i = 1, 2, \cdots$) with respect to each energy state, we obtain

$$\frac{d}{dt}\left\langle \sum_i x_i \right\rangle = -\left\langle k_1^{(1)} x_1 \sum_i x_i \right\rangle + \left\langle k_1^{(1)} x_1 \left(\sum_i x_i - 1 \right) \right\rangle$$

$$- \left\langle k_1^{(2)} x_2 \sum_i x_i \right\rangle + \left\langle k_1^{(2)} x_2 \left(\sum_i x_i - 1 \right) \right\rangle - \cdots$$

$$= -\left\langle \sum_i k_1^{(i)} x_i \right\rangle$$

that is,

$$\frac{d\langle x \rangle}{dt} = -\left\langle \sum_i k_1^{(i)} x_i \right\rangle . \tag{III–37}$$

Here if we set

$$\frac{\sum_i k_1^{(i)} x_i}{\sum_i x_i} = \bar{k}_1 , \tag{III–38}$$

Equation (III–37) becomes, according to $\sum_i k_1^{(i)} x_i = \bar{k}_1 x$,

$$\frac{d\langle x \rangle}{dt} = -\bar{k}_1 \langle x \rangle . \tag{III–39}$$

which formally agrees with Equation (III–39). The rate constant $\bar{k}_1$ denotes the "average" probability that one molecule undergoes a chemical transformation during unit time. On comparing Equation (III–39) with the conventional rate equation

$$\frac{dx}{dt} = -\bar{k}_1 x \tag{III–40}$$

it is seen that the application of the multi-dimensional stochastic model to the "true" unimolecular gas reaction presents us with an excellent method for calculating statistically the rate constant together with the number of reactant molecules. He then goes on to discuss $\bar{k}_1$ in terms of statistical thermodynamic quantities in relation to the well-known theories of unimolecular reaction kinetics. This is perhaps one of the most interesting applications of stochastic kinetics to strictly chemical processes. It is an example in which one sets up a detailed microscopic description of a chemical reaction and derives a macroscopic equation in which the parameters, the rate constant in this case, can be expressed in terms of molecular quantities in order to give more insight into the process. Ishida goes on to discuss the statistical mechanical significance of $\bar{k}_1$ in terms of the energy levels of the molecules. Herein lies the possible connection between

a stochastic description of chemical kinetics and statistical thermodynamics. We refer the reader to [65] for a detailed discussion of the statistical mechanical implications.

h) *Time dependent rate constant*

We have so far discussed stochastic models for processes in which the rate constant k_1 is independent of time, but Ishida [65] has extended this to the more general case in which the rate constant varies with time. Using $k(t)$ instead of k_1 in Equation (III–2), we have

$$\frac{dP_x(t)}{dt} = -k(t)xP_x(t) + k(t)(x+1)P_{x+1}(t). \tag{III–41}$$

The first-order partial differential equation for $F(s,t)$ is

$$\frac{\partial F}{\partial t} = k(t)(1-s)\frac{\partial F}{\partial s} \tag{III–42}$$

whose solution is

$$F(s,t) = f\left((1-s)\exp\left(-\int_0^t k(t)dt\right)\right), \tag{III–43}$$

where f is an arbitrary function to be determined by the initial condition. Using the initial condition that

$$F(s,0) = f(1-s) = s^{x_0}$$

we have

$$F(s,t) = \left\{\left(1-\exp\left(-\int_0^t k(t)dt\right)\right) + s\exp\left(-\int_0^t d(t)dt\right)\right\}^{x_0} \tag{III–44}$$

which satisfies the condition $F(1,t) = 1$, i.e., $\sum_{x=0}^{\infty} P_x(t) = 1$. Hence expanding the right hand side of Equation (III–44), we obtain the binomial distribution

$$P_x(t) = \binom{x_0}{x}\left\{\exp\left(-\int_0^t k(t)dt\right)\right\}^x\left\{1-\exp\left(-\int_0^t k(t)dt\right)\right\}^{x_0-x}. \tag{III–45}$$

The mean value for the number of reactant molecules at time t is given by

$$\langle x\rangle = x_0\exp\left(-\int_0^t k(t)dt\right). \tag{III–46}$$

Ishida has used this more general process as a basis for an approximate method for solving bimolecular processes. This will be described in Section (III–C).

This concludes our discussion of first order processes. In summary, any truly unimolecular process can be solved exactly since it leads to a first order partial differential equation for the generating function and these may be readily solved

by the method of characteristics. Usually however, one is only interested in the first few moments and these may be obtained either directly from the set of differential-difference equations or by means of the cumulant generating function. In all cases, the equations for the first moments are the same as the deterministic equations.

III. B. **Bimocular Reactions**

In this section we shall treat a number of rather simple bimolecular reactions. In the deterministic case we mean by bimolecular that the decay of some species A is proportional to A^2 for instance. This could, but not necessarily, describe the reaction $2A \rightarrow B$. Another example is the reaction $A + B \rightarrow C$, which could possibly, but again not necessarily, be described by

$$\frac{dC}{dt} = kAB.$$

We shall see that bimolecular reactions lead to second order partial differential equations for the generating function, a fact which makes bimolecular reactions much more difficult to treat than first order reactions.

Bimolecular reactions were first treated by Rényi [105] who considered the reaction $A + B \rightarrow C$. He solved the system of differential-difference equations by Laplace transforms and obtained a rather awkward expression for the molecular probability distribution. Since the generating function approach seems to yield more usable expressions, we shall concentrate on it. We shall discuss two processes $2A \rightarrow B$ and $A + B \rightarrow C$, which are the only two whose time dependence has been solved exactly [89], [66]. (See also Bailey [6].)

a) *The irreversible reaction* $2A \rightarrow B$

According to the deterministic theory of reaction kinetics, the rate of this irreversible bimolecular reaction is given by the differential equation

$$-\frac{dA}{dt} = kA^2. \tag{III-47}$$

From this, the number of reactant molecules in the system at time t is given by

$$A = \frac{A_0}{1 + A_0 kt}, \tag{III-48}$$

where A_0 is the initial concentration of A. It should be noted, however, that for small systems (with the concentration expressed as the number of molecules per constant volume of the reaction mixture) the rate, according to the law of mass action, is proportional to the concentrations of the reacting species, in other words, to the number of ways a pair of reactant molecules can be chosen from

the total of A molecules. Hence for the reaction $2A \rightarrow B$ the rate is proportional to $\frac{1}{2}A(A-1)$ or

$$-\frac{dA}{dt} = kA(A-1). \tag{III-49}$$

The number of reactant molecules at time t is given by

$$A = \frac{A_0}{A_0 + (1-A_0)e^{-kt}}. \tag{III-50}$$

However, the modified deterministic model expressed by Equation (III–50) still predicts a precise value for the number of reactant molecules at time t and neglects any fluctuations about this value.

Suppose that in Equation (III–48) we let $A(t) = A_0/n$, where n is some integer, say, and denote the time for this value of t by $t_{1/n}$. If $n = 2$, for instance, $t_{1/2}$ is called the half-life of the reaction. In general,

$$kt_{1/n} = \frac{(n-1)}{A_0}.$$

The time for this reaction to be 90% completed then is $90/A_0$ or $99/A_0$ for 99% completion. If A_0 then is of macroscopic order, kt for the reaction to proceed essentially to completion is quite small. These conditions make Equation (III–48) and (III–50) identical, as one should expect from their differential equations.

Just as in the unimolecular cases, the basis for the stochastic approach is to consider the reaction $2A \rightarrow B$ as being a pure death process with a continuous time parameter and transition probabilities for the elementary events which make up the reaction process. Letting the random variable $X(t)$ be the number of A molecules in the system at time t, the stochastic model is then completely defined by the following assumptions:

(1) The probability of the transition $(x+2) \rightarrow (x)$ in the interval $(t, t+\Delta t)$ is $\frac{1}{2}k(x+2)(x+1)\Delta t + o(\Delta t)$, where k is a constant and $o(\Delta t)/\Delta t \rightarrow 0$ as $\Delta t \rightarrow 0$.

(2) The probability of the transition $(x+j) \rightarrow (x)$, $j > 2$ in the interval $(t, t+\Delta t)$ is $o(\Delta t)$.

(3) The probability of the transition $(x-j) \rightarrow (x), j > 0$, in the interval $(t, t+\Delta t)$ is zero.

(4) The probability of the transition $(x) \rightarrow (x)$, in the interval $(t, t+\Delta t)$ is $\{1 - {}'kx(x-1)\Delta t\} + o(\Delta t)$.

In view of these assumptions the following relation is obtained [89]:

$$\begin{aligned} P_x(t+\Delta t) &= P_{x+2}(t)[\tfrac{1}{2}k(x+2)(x+1)\Delta t] \\ &+ P_x(t)[1 - \tfrac{1}{2}kx(x-1)\Delta t] + o(\Delta t), \end{aligned} \tag{III-51}$$

where $P_x(t) = \text{Prob}\{X(t) = x,\ x = 0, 2, 4, \cdots, x_0\}$, and x_0 is the initial number of A molecules. The differential-difference equation is

$$\frac{dP_x}{dt} = \tfrac{1}{2}k(x+2)(x+1)P_{x+2}(t) - \tfrac{1}{2}kx(x-1)P_x(t), \tag{III-52}$$

and the partial differential equation for the generating function is

$$\frac{\partial F}{\partial t} = \frac{k}{2}(1-s^2)\frac{\partial^2 F}{\partial s^2}. \tag{III-53}$$

Equation (III-53) may be solved by separation of variables to give

$$F(s,t) = \sum_{n=0}^{\infty} A_n C_n^{-\frac{1}{2}}(s)\, T_n(t), \tag{III-54}$$

where $C_n^{-\frac{1}{2}}(s)$ is a Gegenbauer polynomial [30], [122], i.e., a solution of

$$(1-s^2)[d^2C_n^{-\frac{1}{2}}(s)/ds^2] + n(n-1)C_n^{-\frac{1}{2}}(s) = 0 \tag{III-55}$$

and

$$T(t) = \exp\{-\tfrac{1}{2}kn(n-1)t\}. \tag{III-56}$$

The coefficients A_n can be determined most easily from the boundary condition,

$$\partial F/\partial s = x_0 s^{x_0-1} \text{ at } t = 0. \tag{III-57}$$

Using this boundary condition together with the relation [122],

$$-\frac{dC_n^{-\frac{1}{2}}}{ds} = -C_n^{\frac{1}{2}} = P_{n-1}(s),$$

where $P_n(s)$ is a Legendre polynomial, one can show that

$$\begin{aligned} A_n &= \frac{(1-2n)}{2}\int_{-1}^{1} x_0 s^{x_0-1} P_{n-1}(s)\, ds \\ &= \frac{1-2n}{2^n}\left\{\frac{\Gamma(x_0+1)\Gamma[(x_0-n+1)/2]}{\Gamma(x_0-n+1)\Gamma[(x_0+n+1)/2]}\right\} \qquad \text{(III-58)} \\ &\qquad n = 2, 4, \cdots, x_0. \end{aligned}$$

By using the relations,

$$\langle x\rangle = (\partial F/\partial s)_{s=1}, \quad \langle x(x-1)\rangle = (\partial^2 F/\partial s^2)_{s=1} \tag{III-59}$$

it can easily be shown that

$$\langle x\rangle = -1\sum_{n=2}^{x_0} A_n T_n(t), \tag{III-60}$$

$$\langle x(x-1)\rangle = -\sum_{n=2}^{x_0} \frac{n(n-1)}{2} A_n T_n(t), \tag{III-61}$$

where these sums are taken over the even integers only.

The coefficient of variation, CV(t), is used to measure the relative extent of fluctuations, i.e., fluctuations relative to the mean, and is

$$\mathrm{CV}(t) = \left\{\frac{\text{Variance}}{\langle x\rangle^2}\right\}^{\frac{1}{2}}. \tag{III-62}$$

The fraction of reactant molecules has been calculated at various times for $x_0 = 10$ and 50 from the deterministic, Equation (III–48), the modified deterministic, Equation (III–50) and stochastic expression, Equation (III–60). The results are shown in Figures 3 and 4. The coefficient of variation is plotted in

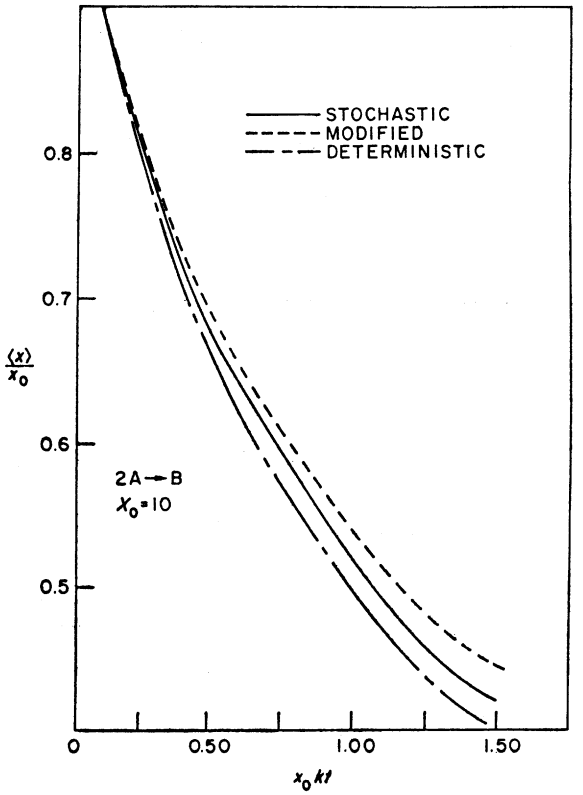


Figure 3
Mean against x_0kt for the irreversible bimolecular reaction $2A \rightarrow B$ ($x_0 = 10$)

Figure 5. The results indicate that the stochastic and deterministic means approach each other quite rapidly as the number of particles increases, though fluctuations

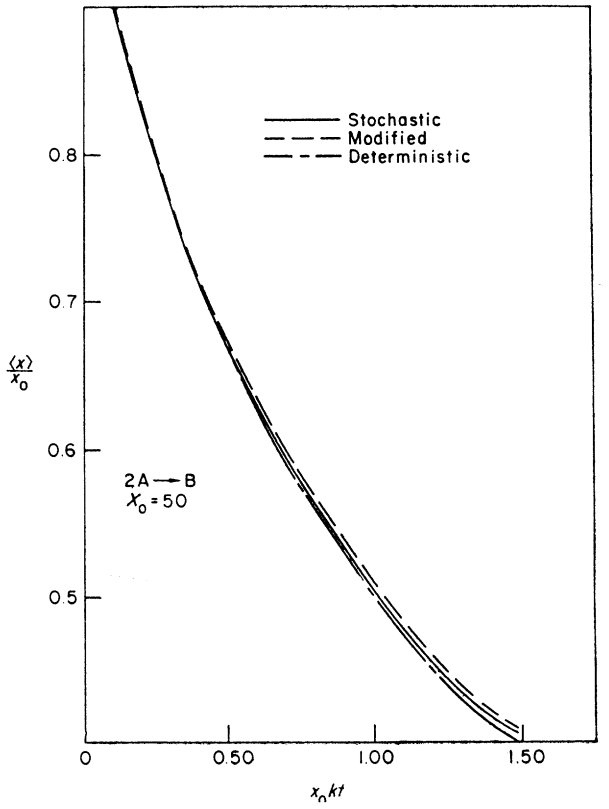


Figure 4
Mean against x_0kt for the irreversible bimolecular reaction $2A \rightarrow B$ ($x_0 = 50$)

about the mean still exist. Figure 5 shows that the relative fluctuations decrease as x_0 becomes large.

b) *The irreversible reaction* $A + B \rightarrow C$ [66], [89]

Let $X(t)$, the discrete, time-varying, random variable, be the number of A molecules at time t and $Y(t) = Z_0 + X(t)$, the number of B molecules where $Z_0 = Y(0) - X(0)$ and $Y(0) > X(0)$. The differential-difference equation for this bimolecular process is

$$\text{(III-63)} \qquad \frac{dP_x}{dt} = k(x+1)(Z_0 + x + 1)P_{x+1}(t) - kx(Z_0 + x)P_x(t)$$

and the corresponding partial differential equation is

$$\text{(III-64)} \qquad \frac{\partial F}{\partial t} = ks(1-s)\frac{\partial^2 F}{\partial s^2} + k(Z_0 + 1)(1-s)\frac{\partial F}{\partial s}.$$

Application of the method of separation of variables yields

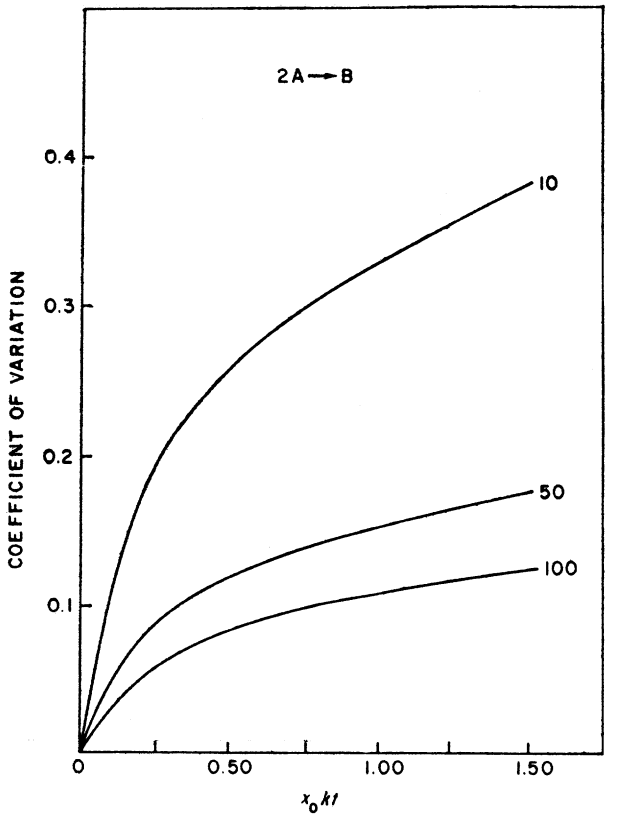


Figure 5
Coefficient of variation against x_0kt for the irreversible bimolecular reaction 2A → B for $x_0 = 10$, 50 and 100

$$F(s,t) = \sum_{n=0}^{\infty} A_n S_n(s)\, T_n(t), \tag{III-65}$$

where $S_n(s) = J_n(Z_0, Z_0 + 1, s)$ are Jacobi polynomials and solutions to the differential equation [96],

$$s(1-s)[d^2J_n(p,q,s)/ds^2] + [q - (p+1)s][dJ_n(p,q,s)/ds] + n(n+p)\,J_n(p,q,s) = 0 \tag{III-66}$$

and $T_n(t) = \exp\{-n(n+Z_0)kt\}$.

Using the boundary condition give by Equation (III-57) together with the relation,

$$\frac{dJ_n(p,q,s)}{ds} = [-n(n+p)/c]\,J_{n-1}(p+2, q+1, s) \tag{III-67}$$

and the orthogonality relation,

$$\text{(III-68)} \quad \int_0^1 s^{q-1}(1-s)^{p-q} J_n(p,q,s) J_m(p,q,s) ds = \frac{n!\{\Gamma(q)^2\Gamma(n+p-q+1)}{(2n+p)\Gamma(n+p)\Gamma(n+q)} \delta_{mn}$$

we obtain

$$\text{(III-69)} \quad A_n = \frac{(-)^n(2n+Z_0)\Gamma(n+Z_0)\Gamma(x_0+1)\Gamma(x_0+Z_0+1)}{\Gamma(n+1)\Gamma(Z_0+1)\Gamma(x_0-n+1)\Gamma(x_0+Z_0+n+1)},$$

where $n = 1, 2, 3, \cdots, x_0$.

The first moment and the second factorial moment are

$$\text{(III-70)} \quad \langle x \rangle = \sum_{n=1}^{x_0} \frac{(2n+Z_0)\Gamma(x_0+1)\Gamma(x_0+Z_0+1)T_n(t)}{\Gamma(x_0-n+1)\Gamma(x_0+Z_0+n+1)},$$

$$\text{(III-71)} \quad \langle x(x-1) \rangle = \sum_{n=2}^{x_0} \frac{(n-1)(n+Z_0+1)(2n+Z_0)\Gamma(x_0+1)\Gamma(x_0+Z_0+1)}{\Gamma(x_0-n+1)\Gamma(x_0-Z_0+n+1)} T_n(t).$$

For the bimolecular reaction $A + B \rightarrow C$, if it is assumed that Z_0 is very large, that is $Y(0) \gg X(0)$, it can be easily shown that the bimolecular process changes to a "pseudo first-order" process. When Z_0 is sufficiently large, only the first term in the expansion of (III-70) is needed,

$$\text{(III-72)} \quad x_0[(Z_0+2)/(x_0+Z_0+1)]\exp\{-(Z_0+1)kt\}.$$

For large Z_0 this reduces to

$$\text{(III-73)} \quad x_0 \exp\{-(Z_0+1)kt\} = x_0 \exp\{-k't\}$$

or

$$\langle x \rangle = x_0 \exp\{-k't\}.$$

In a similar manner, Equation (III-71) becomes

$$\text{(III-74)} \quad \langle x(x-1) \rangle = x_0(x_0-1)\exp\{-2k't\}.$$

The variance is

$$\text{(III-75)} \quad D^2\{X(t)\} = x_0 e^{-k't}(1-e^{-k't}),$$

which is identical with the variance found by Bartholomay [8] and McQuarrie [88] for the unimolecular reaction $A \rightarrow B$.

The mean and the coefficient of variation for this process look much like those in Figures (3), (4), and (5) ([89]).

This same pair of reactions was also studied by Ishida [66] who used a Laplace transform technique. Although superficially quite different results were obtained, they are in fact identical to those presented above.

Reversible bimolecular reactions such as $A + B \rightleftarrows C + D$ can be solved exactly by the method of separation of variables and the ordinary differential equations in the variable s are Lamé equations. This makes the evaluation of the

Fourier-type coefficients very difficult since derivative formulas such as Equation (III–67) and orthogonality conditions do not seem to exist or at least are not easily used. In addition to this, even if such formulae did exist, it seems unlikely that numerical results could be easily obtained. It does turn out, however, that these reversible bimolecular processes can be solved exactly and conveniently in the equilibrium limit, and this was done by Darvey, Ninham, and Staff [25].

c) *Equilibrium solutions* [25]

Consider the reversible bimolecular reaction

$$\text{(I)} \qquad \mathrm{A} + \mathrm{B} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{C} + \mathrm{D}$$

and let $A(t)$, $B(t)$, $C(t)$, and $D(t)$ be random variables which represent the numbers of molecules of species A, B, C, and D present at time t. We let a, b, c, and d be the (integer) values which these random variables can achieve. The possible states of the system at time t which could lead to the state specified by a, b, c, d at time $t + \Delta t$ involving not more than one molecular transformation in the time interval Δt are $\{a+1,\ b+1,\ c-1,\ d-1\}$, $\{a-1,\ b-1,\ c+1,\ d+1\}$, and $\{a,\ b,\ c,\ d\}$. Denoting by $P(a,b,c,d;t)$ the probability that, at time t,

$$A(t) = a, \qquad B(t) = b, \qquad C(t) = c, \qquad D(t) = d,$$

we have

$$\begin{aligned} P(a,b,c,d;t+\Delta t) &= k_1(a+1)(b+1)\Delta t\, P(a+1,b+1,c-1,d-1;t) \\ &+ k_2(c+1)(d+1)\Delta t P(a-1,b-1,c+1,d+1;t) \\ &+ [1-(k_1ab+k_2cd)\Delta t]\,P(a,b,c,d;t)+o(\Delta t). \end{aligned} \tag{III–76}$$

However, since the system is conservative, the four random variables are related through the initial concentrations which are taken to be

$$A(0) = \alpha, \qquad B(0) = \beta, \qquad C(0) = \gamma, \qquad D(0) = \delta.$$

Clearly,

$$\alpha - a = \beta - b = c - \gamma = d - \delta, \tag{III–57}$$

so that the probability time course of the reaction can be described by a single random variable. We choose this to be $A(t)$, the number of molecules of species A present at time t. Equation (III–76) then becomes

$$\begin{aligned} P_a(t+\Delta t) &= k_1(a+1)(\beta-\alpha+a+1)\Delta t\, P_{a+1}(t) \\ &+ k_2(\gamma+\alpha-a+1)(\delta+\alpha-a+1)\,\Delta t\, P_{a-1}(t) \\ &+ [1-k_1a(\beta-\alpha+a)\Delta t-k_2(\gamma+\alpha-a)(\delta+\alpha-a)]P_a(t)+o(\Delta t), \end{aligned} \tag{III–78}$$

where $P_a(t)$ replaces $P(a,b,c,d;t)$.

We then solve the corresponding differential-difference equation subject to the initial condition

(III–79) $$P_a(0) = \delta_{\alpha a}.$$

The equations which describe other reactions with second-order steps can be written down in a similar way. For example,

(II) $$\mathrm{A} + \mathrm{B} \underset{k_2}{\overset{k_a}{\rightleftarrows}} \mathrm{C},$$

(III–80) $$[dP_a(t)/dt] = k_1[(a+1)(\beta-\alpha+a+1)P_{a+1}(t) - a(\beta-\alpha+a)P_a(t)] + k_2[(\gamma+\alpha-a+1)P_{a-1}(t) - (\gamma+\alpha-a)P_a(t)].$$

(III) $$2\mathrm{A} \underset{k_c}{\overset{k_a}{\rightleftarrows}} \mathrm{C} + \mathrm{D},$$

(III–81) $$[dP_a(t)/dt] = k_1[(a+2)(a+1)P_{a+2}(t) - a(a-1)P_a(t)]/2 + k_2[2\gamma+\alpha-a+2)(2\delta+\alpha-a+2)P_{a-2}(t) - (2\gamma+\alpha-a)(2\delta+\alpha-a)P_a(t)]/4.$$

(IV) $$2\mathrm{A} \underset{k_c}{\overset{k_a}{\rightleftarrows}} \mathrm{C},$$

(III–82) $$[dP_a(t)/dt] = k_1[(a+2)(a+1)P_{a+2}(t) - a(a-1)P_a(t)]/2 + k_2[(2\gamma+\alpha-a+2)P_{a-2}(t) - (2\gamma+\alpha-a)P_a(t)]/2.$$

These three equations are also subject to the initial condition given by Equation (III–79). If the left-hand sides of these equations are set equal to zero and then the right-hand sides transformed by means of generating functions, one gets

(I) $$\mathrm{A} + \mathrm{B} \underset{k_2}{\overset{k_1}{\rightleftarrows}} \mathrm{C} + \mathrm{D};$$

(III–83) $$s(1-Ks)(d^2S/ds^2) + [\beta-\alpha+1+K(2\alpha+\gamma+\delta-1)s](dS/ds) - K(\alpha-\gamma)(\alpha+\delta)S = 0.$$

(II) $$\mathrm{A} + \mathrm{B} \rightleftarrows \mathrm{C};$$

(III–84) $$s(d^2S/ds^2) + (\beta-\alpha+1+Ks)(dS/ds) - K(\alpha+\gamma)S = 0.$$

(III) $$2\mathrm{A} \rightleftarrows \mathrm{C} + \mathrm{D};$$

(III–85) $$(2 - Ks_2)(d^2S/ds^2) + K(2\alpha + 2\gamma + 2\delta - 1)s(dS/ds) - K(\alpha + 2\gamma)(\alpha + 2\delta)S = 0.$$

(IV) $$2A \rightleftarrows C;$$

(III–86) $$d^2S/ds^2 + Ks(dS/ds) - K(\alpha + 2\gamma)S = 0,$$

where $K = k_1/k_2$ and the S's are related to the equilibrium generating functions by

$$F(s, \infty) = g_0 S(s),$$

where g_0 is a constant given by requiring that $F(1, \infty) = 1$.

The equilibrium generating functions for the above four processes (I), (II), (III), (IV), are given respectively by

(III–87) $$F(s, \infty) = \frac{{}_2F_1(-\alpha - \gamma, -\alpha - \delta, \beta - \alpha + 1; Ks)}{{}_2F_1(-\alpha - \gamma, -\alpha - \delta, \beta - \alpha + 1; K)}, \beta \geqq \alpha,$$

(III–88) $$F(s, \infty) = \frac{{}_1F_1(-\alpha - \gamma, \beta - \alpha + 1; -Ks)}{{}_1F_1(-\alpha - \gamma; \beta - \alpha + 1; -K)}, \beta \geqq \alpha,$$

(III–89) $$F(s, \infty) = \begin{cases} \dfrac{{}_2F_1(-\frac{1}{2}\alpha - \gamma, -\frac{1}{2}\alpha - \delta; \frac{1}{2}; \frac{1}{2}Ks^2)}{{}_2F_1(-\frac{1}{2}\alpha - \gamma, -\frac{1}{2}\alpha - \delta; \frac{1}{2}; \frac{1}{2}K)}, & \alpha \text{ even} \\ \dfrac{{}_2F_1[-\frac{1}{2}(\alpha-1) - \gamma, -\frac{1}{2}(\alpha-1) - \delta; \frac{3}{2}; \frac{1}{2}(Ks^2)]}{{}_2F_1[-\frac{1}{2}(\alpha-1) - \gamma, -\frac{1}{2}(\alpha-1) - \delta; \frac{3}{2}; \frac{1}{2}K]}, & \alpha \text{ odd} \end{cases}$$

(III–90) $$F(s, \infty) = \begin{cases} \dfrac{{}_1F_1[-\frac{1}{2}\alpha - \gamma; \frac{1}{2}; -\frac{1}{2}(Ks^2)]}{{}_1F_1(-\frac{1}{2}\alpha - \gamma; \frac{1}{2}; -\frac{1}{2}K)}, & \alpha \text{ even} \\ \dfrac{{}_1F_1[-\frac{1}{2}(\alpha - 1) - \gamma; \frac{3}{2}; -\frac{1}{2}(Ks^2)]}{{}_1F_1[-\frac{1}{2}(\alpha - 1) - \gamma; \frac{3}{2}; -\frac{1}{2}K]}, & \alpha \text{ odd,} \end{cases}$$

where the F_2's and ${}_1F_1$'s are the usual hypergeometric functions. The deterministic and stochastic means are given in Table 1.

Darvey *et al.* [25] have shown how the variances for these processes can be written in terms of the difference between the stochastic mean values and the deterministic solutions. If we write this difference as

(III–91) $$\Delta = [\mu_a(\infty) - a_\infty]/a_\infty$$

where $\mu_a(\infty)$ is the stochastic mean and a_∞ is the deterministic solution, then, for (I), (II), (III), (IV) respectively,

(III–92) $$\sigma_a^2(\infty) = -a_\infty^2\Delta^2 - a_\infty\{[\beta - \alpha + K(2\alpha + \gamma + \delta)/(1 - K)] + 2a_\infty\}\Delta;$$

(III–93) $$\sigma_a^2(\infty) = -a_\infty^2\Delta^2 - a_\infty(\beta - \alpha + K + 2a_\infty)\Delta;$$

TABLE I

Expected values and deterministic solutions for various reversible bimolecular reactions

Reaction	Stochastic mean, $\mu_a(\infty)$	Deterministic solution, a_∞
$A + B \rightleftarrows C + D$	$K\frac{(\alpha+\gamma)(\alpha+\delta)}{(\beta-\alpha+1)}\frac{{}_2F_1(-\alpha-+1,-\alpha-\delta+1;\beta-\alpha+2;K)}{{}_2F_1(-\alpha-\gamma,-\alpha-\delta;\beta-\alpha+1;K)}$, $\beta \geqq \alpha$	$K = \frac{\alpha_\infty(\beta-\alpha+a_\infty)}{(\gamma+\alpha-a_\infty)(\delta+\alpha-a_\infty)}$
$A + B \rightleftarrows C$	$K\frac{(\alpha+\gamma)}{(\beta-\alpha+1)}\frac{{}_1F_1(-\alpha-\gamma+1;\beta-\alpha+2;-K)}{{}_1F_1(-\alpha-\gamma;\beta-\alpha+1;-K)}$, $\beta \geqq \alpha$	$K = \frac{a_\infty(\beta-\alpha+a_\infty)}{(\gamma+\alpha-a_\infty)}$
$2A \rightleftarrows C + D$	$\frac{1}{2}K(\alpha-2\gamma)(\alpha-2\delta)\frac{{}_2F_1(-\frac{1}{2}\alpha-\gamma+1,-\frac{1}{2}\alpha-\delta+1;\frac{3}{2};\frac{1}{2}K)}{{}_2F_1(-\frac{1}{2}\alpha-\gamma,-\frac{1}{2}\alpha-\delta,\frac{1}{2};\frac{1}{2}K)}$, α even $\frac{1}{8}K(\alpha-1+2\gamma)(\alpha-1+2\delta)\frac{{}_2F_1[-\frac{1}{2}(\alpha-1)-\gamma+1),-\frac{1}{2}(\alpha-1)-\delta+1;\frac{5}{2};\frac{1}{2}K]}{{}_2F_1[-\frac{1}{2}(\alpha-1)-\gamma,-\frac{1}{2}(\alpha-1)-\delta;\frac{3}{2};\frac{1}{2}K]}$, α odd	$K = \frac{2a_\infty(a_\infty-1)}{(2\gamma+\alpha-a_\infty)(2\delta+\alpha-a_\infty)}$
$2A \rightleftarrows C$	$K(\alpha-2\gamma)\frac{{}_1F_1(-\frac{1}{2}\alpha-\gamma+1;\frac{3}{2};-\frac{1}{2}K)}{{}_1F_1(-\frac{1}{2}\alpha-\gamma;\frac{1}{2};-\frac{1}{2}K)}$, α even $\frac{1}{2}K(\alpha-1+2\gamma)\frac{{}_1F_1[-\frac{1}{2}(\alpha-1)-\gamma+1;\frac{5}{2};-\frac{1}{2}K]}{{}_1F_1[-\frac{1}{2}(\alpha-1)-\gamma;\frac{3}{2};-\frac{1}{2}K]}$, α odd	$K = \frac{a_\infty(a_\infty-1)}{(2\gamma+\alpha-a_\infty)}$

$$\text{(III–94)} \quad \sigma_a^2(\infty) = -a_\infty^2\Delta^2 + 2a_\infty\{[1 - K(\alpha + \gamma + \delta)/(2 - K)] - a_\infty\}\Delta;$$

$$\text{(III–95)} \quad \sigma_a^2(\infty) = -a_\infty^2\Delta^2 + a_\infty(1 - K - 2a_\infty)\Delta.$$

These four equations explicitly point out that if the variance of bimolecular processes is zero or negligible, the deterministic results and the stochastic means are equal. This was shown very elegantly by Rényi [105] in his consideration of the irreversible bimolecular reaction $A + B \to C$. If the concentrations of A, B, and C are given by the random variables $X_1(t)$, $X_2(t)$, and $X_3(t)$ respectively, then it is easy to show that

$$\text{(III–96)} \quad \frac{dE\{X_3(t)\}}{dt} = kE\{X_1(t)\}E\{X_2(t)\} + kD^2\{X_3(t)\},$$

where E and D^2 are the mean and variance. By simple manipulation he showed that Equation (III–96) can be put in the form

$$\text{(III–97)} \quad \frac{dE\{X_3(t)\}}{dt} = kE\{X_1(t)X_2(t)\},$$

which is to be compared to the deterministic equation

$$\text{(III–98)} \quad \frac{d\mathrm{C}}{dt} = k\mathrm{AB}.$$

Equation (III–97) is immediately "derivable" from Equation (III–98) by simply "taking the average" of both sides of Equation (III–98). The deterministic approach always assumes that $E\{\mathrm{AB}\}$ can be replaced by $E\{\mathrm{A}\}E\{\mathrm{B}\}$ and, as Equation (III–96) shows, this amounts to setting $D^2\{C(t)\} = 0$, and this is true only for a delta function type density function, i.e. one in which all central moments vanish. By a similar heuristic argument, it can be seen that the deterministic solution and the stochastic mean values are always the same for unimolecular processes. This was pointed out (but never really proved in general) by McQuarrie ([88]).

This concludes a discussion of exactly solvable second-order processes. As one can see, only a very few second order cases can be solved exactly for their time dependence. The more complicated reversible reactions such as $2\mathrm{A} \rightleftarrows \mathrm{C}$ seem to lead to very complicated generating functions in terms of Lamé functions and the like. This shows that even for reasonably simple second and third order reactions, approximate techniques are needed. This is not only true in chemical kinetics, but in other applications as well, for example, population or genetic models. The actual models in these fields are beyond the scope of this review, but the mathematical problems are very similar. See [14] for a discussion of many of these models. In the next section we shall present the various approximations which have been used in the hope that better and more sophisticated ones can

be developed, or perhaps that they already exist, being unknown to those working in chemical applications of stochastic processes.

III.C. Approximate methods

Although the stochastic approach is applicable to all types of reaction systems, in most realistic cases the system of equations which defines the stochastic model cannot be solved exactly, and approximate methods must be used. Since the quantities of main interest in the stochastic approach are usually only the first moment $\langle x \rangle$ and the second moment $\langle x^2 \rangle$, much effort can be saved by applying methods which produce these lower moments without having to solve for the probability density function or generating function.

Two approximations have been used by McQuarrie, *et al.* [89]. A set of equations involving the time derivatives of the moment of the concentration can be generated from the differential-difference equation for the process under consideration by multiplying the differential-difference equation by x^n and summing over the variable x. This technique is equivalent to the use of the cumulant generating function which generates the cumulants of the process.

Consider again the irreversible bimolecular reaction $2A \rightarrow B$. Multiplication of Equation (III–52) by x and x^2, respectively, followed by summation over x, gives

$$\frac{d\langle x \rangle}{dt} = -k\langle x^2 \rangle + k\langle x \rangle \tag{III–99}$$

$$\frac{d\langle x^2 \rangle}{dt} = -2k\langle x^3 \rangle + 4k\langle x^2 \rangle - 2k\langle x \rangle . \tag{III–100}$$

In all second-order cases the set of equations obtained in this manner cannot be solved unless some relation between the higher and lower moments is assumed. Two approximate methods of determining the first and second moments have been formulated and are given below.

(1) An assumption frequently made is that it is permissible to express the higher moments as a product of the lower moments, e.g., $\langle x^3 \rangle = \langle x^2 \rangle \langle x \rangle$. The resulting equations are nonlinear and, in most cases, cannot be solved simultaneously unless a further approximation is made.

Equations (III–99) and (III–100) offer an example where results are readily obtained, however. Putting $\langle x^2 \rangle = \langle x \rangle^2$ into Equation (III–99) yields the solution,

$$\langle x \rangle = \frac{k_0}{x_0 + (1 - x_0)\exp\{-kt\}} \tag{III–101}$$

which is the same as Equation (III–50). The assumption that $\langle x^2 \rangle = \langle x \rangle^2$ is equivalent to reducing the stochastic model to the deterministic model, i.e.,

TABLE II

Fraction of reactant and coefficient of variation for the exact and approximate methods. $2A \rightarrow B$. s refers to the exact solutions and 1 and 2 refer to approximations 1 and 2 respectively.

x_0kt	$\langle x_s\rangle/x_0$	$\langle x_1\rangle/x_0$	$\langle x_2\rangle/x_0$	CV_s	CV_1	CV_2
			$x_0 = 10$			
0.25	0.815	0.818	0.802	0.196	0.213	0.214
0.50	0.686	0.695	0.684	0.258	0.304	0.306
0.75	0.593	0.606	0.592	0.300	0.375	0.377
1.00	0.521	0.539	0.513	0.332	0.435	0.444
1.50	0.421	0.444	0.411	0.382	0.542	0.548
			$x_0 = 50$			
0.25	0.803	0.803	0.801	0.091	0.099	0.101
0.50	0.670	0.671	0.670	0.119	0.141	0.141
0.75	0.576	0.577	0.575	0.137	0.172	0.172
1.00	0.504	0.508	0.502	0.152	0.199	0.200
1.50	0.404	0.408	0.401	0.176	0.244	0.246
			$x_0 = 100$			
0.25	0.801	0.801	0.801	0.059	0.070	0.070
0.50	0.669	0.670	0.668	0.082	0.100	0.100
0.75	0.574	0.574	0.573	0.097	0.122	0.122
1.00	0.502	0.503	0.501	0.109	0.141	0.141
1.50	0.402	0.402	0.401	0.125	0.173	0.173

TABLE III

Fraction of reactant and coefficient of variation for the exact and approximate methods. $A + B \rightarrow C$. $A_0 = B_0$. s refers to the exact solutions and 1 and 2 refer to approximations 1 and 2 respectively.

x_0kt	$\langle x_s\rangle/x_0$	$\langle x_1\rangle/x_0$	$\langle x_2\rangle/x_0$	CV_s	$CV_1 = CV_2$
		$x_0 = 10$			
0.25	0.798	0.800	0.799	0.121	0.158
0.50	0.662	0.667	0.661	0.192	0.226
0.75	0.565	0.572	0.562	0.226	0.278
1.00	0.491	0.500	0.487	0.250	0.324
1.50	0.389	0.400	0.382	0.293	0.390
		$x_0 = 50$			
0.25	0.799	0.800	0.799	0.056	0.071
0.50	0.664	0.667	0.664	0.091	0.105
0.75	0.567	0.572	0.567	0.101	0.122
1.00	0.498	0.500	0.497	0.105	0.144
1.50	0.398	0.400	0.396	0.125	0.174
		$x_0 = 100$			
0.25	0.800	0.800	0.800	0.037	0.050
0.50	0.666	0.667	0.667	0.057	0.071
0.75	0.571	0.572	0.571	0.070	0.086
1.00	0.499	0.500	0.498	0.076	0.100
1.50	0.399	0.400	0.398	0.088	0.122

setting the variance equal to zero. Putting $\langle x^3 \rangle = \langle x^2 \rangle \langle x \rangle$, and using Equation (III–101) for the first moment, a solution of Equation (III–100) can be obtained. These assumptions give

$$\langle x^2 \rangle = \langle x \rangle^2 \{\tfrac{2}{3}[(x_0 - 1)/x_0](e^{2kt} - e^{-kt}) + 1\}, \tag{III–102}$$

or

$$D^2\{X(t)\} = \tfrac{2}{3}[(x_0 - 1)/x_0](e^{2kt} - e^{-kt}). \tag{III–103}$$

The coefficient of variation derived from this is shown in Tables II and III for the reactions $2A \rightarrow B$ and $A + B \rightarrow C$, respectively. If the moment equations are truncated beyond the third or if Equation (III–101) is not used in Equation (III–100), the algebra becomes severe. Consequently, so far as I know, this type of approximation has not been exploited to its full potential in chemical kinetics although it seems to have much promise.

(2) The second method formulated for determining the first and second moments is somewhat empirical. The coefficient of variation for unimolecular and bimolecular processes (see Figure 5) suggests that $[CV]^2$ increases exponentially with time. Hence, if it is assumed that

$$[CV]^2 = \exp\{pt\} - 1 \tag{III–104}$$

where p is constant, then

$$\langle x^2 \rangle = \langle x \rangle^2 \exp\{pt\} \tag{III–105}$$

since $[CV]^2 = (\langle x^2 \rangle - \langle x \rangle^2)/\langle x \rangle^2$.

Substituting Equation (III–105) into Equation (III–99) and solving for the first moment gives

$$\langle x \rangle = \frac{x_0(p + k)}{x_0 k \exp\{pt\} - (px_0 - p - k)\exp\{-kt\}}. \tag{III–106}$$

The constant p can be determined from the equation involving the time derivative of the second moment if it is assumed that $\langle x^n \rangle = x_0^n$ at time $t = 0$. Differentiating (III–105) with respect to t gives

$$\begin{aligned} d\langle x^2 \rangle &= p\langle x \rangle^2 e^{pt} + 2\langle x \rangle e^{pt} d\langle x \rangle/dt \\ &= p\langle x \rangle^2 e^{pt} - 2k\langle x \rangle \langle x^2 \rangle e^{pt} + 2k\langle x \rangle^2 e^{pt}. \end{aligned} \tag{III–107}$$

By equating (III–100) and (III–107), setting $t = 0$, it can be shown that

$$p = 2[(x_0 - 1)/x_0]k.$$

Therefore,

$$\langle x^2 \rangle = \langle x \rangle^2 \exp\{2[(x_0 - 1)/x_0]kt\}. \tag{III–108}$$

For large x_0, that is, as $x_0 \to \infty$,

$$\langle x^2 \rangle \to \langle x \rangle^2$$

since $(x_0 - 1)/x_0 \to 1$ and $kt \approx O(1/x_0) \to 0$.

Consider the reaction $A + B \to C$, for the case $A_0 = B_0$. Multiplication of Equations (III–63) by x and x^2, respectively, and summation over x yields

(III–109) $$d\langle x \rangle/dt = -k\langle x^2 \rangle, \quad d\langle x^2 \rangle/dt = -2k\langle x^3 \rangle + k\langle x^2 \rangle.$$

When the higher moments are expressed in terms of the lower moments (Approximate Method 1), these equations have the solutions

$$\langle x \rangle = x_0/(1 + x_0 kt), \qquad \langle x^2 \rangle = \langle x \rangle^2 \exp\{kt\}.$$

When (III–105) is substituted in (III–109) (Approximate Method 2), the first and second moments are

(III–110) $$\langle x \rangle = \frac{x_0}{1 + x_0[\exp\{kt\} - 1]},$$

(III–111) $$\langle x^2 \rangle = \langle x \rangle^2 \exp\{kt\}.$$

The mean and the coefficient of variation have been calculated from the approximate methods for the bimolecular reactions $2A \to B$ and $A + B \to C$. The results are given in Tables II and III together with the exact solutions. The subscripts s, 1 and 2, refer to the results obtained from the exact equations, and those obtained from Approximate Methods 1 and 2. Jachimowski *et al.* [69] have applied the second approximate method to the Michaelis-Menten scheme for enzyme-substrate reactions in biochemistry.

Ishida, [65], has introduced another approximation which he has applied to the reaction $2A \to B$. This method treats a bimolecular process as a unimolecular process, but with a time dependent rate constant which is obtained from the deterministic case. The deterministic rate of the bimolecular reaction $2A \to B$ is expressed in the form

(III–112) $$\frac{d(2n)}{dt} = k(2n)^2,$$

where $2n$ denotes the number of reactant molecules at time t and k the rate constant. Solving Equation (III–112) under the initial condition that $2n = 2n_0$ at $t = 0$, we obtain

(III–113) $$2n = \frac{2n_0}{1 + k(2n_0)t}$$

or if we set $2n = N$, this becomes

(III–114) $$N = \frac{N_0}{1 + kN_0t}.$$

From Equation (III–113) the probability that any one of n reactant molecules undergoes a chemical transformation during the time interval $(t, t + \Delta t)$ is given by

(III–115) $$\frac{|\Delta n|}{n} = \frac{kN_0}{1 + kN_0t}\Delta t + o(\Delta t).$$

If we set $kN_0/(1 + kN_0t) = k(t)$, then we have according to Equation (III–41)

(III–116) $$\frac{dP_n}{dt} = -\frac{kN_0}{1 + kN_0t}nP_n(t) + \frac{kN_0}{1 + kN_0t}(n + 1)P_{n+1}(t).$$

Multiplying both sides of Equation (III–116) by n and summing over all values of n, we obtain the differential equation describing the mean value for the number of reactant molecules

(III–117) $$\frac{d\langle n\rangle}{dt} = -\frac{kN_0}{1 + kN_0t}\langle n\rangle$$

or

(III–118) $$\frac{d\langle N\rangle}{dt} = -\frac{kN_0}{1 + kN_0t}\langle N\rangle,$$

whose solution is given by

(III–119) $$\langle N\rangle = \frac{N_0}{1 + kN_0t}$$

for the initial condition that $N = N_0$ at $t = 0$. It should be noted that Equation (III–119) agrees "in the mean" with the result derived by the deterministic theory. If we multiply both sides of Equation (III–116) by n^2 and sum over all values of n, we obtain as the differential equation for the second moment $\langle n^2\rangle$

(III–120) $$\frac{d\langle n^2\rangle}{dt} = -2\frac{kN_0}{1 + kN_0t}\langle n^2\rangle + \frac{kN_0}{1 + kN_0t}\langle n\rangle$$

which is transformed into the form, writing $2n = N$ and using Equation (III–119),

(III–121) $$\frac{d\langle N^2\rangle}{dt} + 2\frac{kN_0}{1 + kN_0t}\langle N^2\rangle = 2k\left(\frac{N_0}{1 + kN_0t}\right)^2.$$

Solving this under the initial condition that $N = N_0$ at $t = 0$, we obtain

(III–122) $$\begin{aligned}\langle N^2\rangle &= \left(\frac{N_0}{1 + k_2N_0t}\right)^2(1 + 2k_2t)\\ &= \langle N\rangle^2(1 + 2k_2t).\end{aligned}$$

The variance $\sigma^2(t) = \langle N^2 \rangle - \langle N \rangle^2$ is then

$$\sigma^2(t) = 2k_2 t \langle N \rangle^2, \tag{III–123}$$

and consequently the coefficient of variation $\delta(t) = \sigma(t)/\langle N \rangle$ is

$$\delta(t) = (2kt)^{\frac{1}{2}}. \tag{III–124}$$

This approximation of Ishida's can also be obtained by assuming that the coefficient of variation varies as $(kt)^{\frac{1}{2}}$ instead of $(e^{pt} - 1)^{\frac{1}{2}}$. Note that all three of the above approximations yield essentially the same expression for $\langle x^2 \rangle$ for small kt. We have shown for the deterministic case that $1/n$ of the reaction is over when $kt = (n-1)/x_0$ and so for all but the smallest values of x_0, kt is indeed small for most of the course of the reaction. For extremely small x_0, Ishida should use Equation (III–49) instead of Equation (III–112), as he points out in a footnote. If this is done, one obtains

$$\langle x^2 \rangle = \langle x \rangle^2 e^{2kt},$$

which reduces to Equation (III–122) if only linear terms in kt are retained. Thi is to be compared with Equation (III–108). The only difference is a factor $(x_0 - 1)/x_0$ in the exponential.

Unfortunately these seem to be the only approximations that have been used in the stochastic approach to chemical kinetics. The first has the appeal that it can perhaps be improved by truncating the hierarchy of moment equations at higher order, but one soon gets into difficult algebra. The rate of convergence of such a procedure is not at all clear. The second seems to have some potential, but its drawback is that it is not clear that the coefficient of variation has this behaviour for all reactions. It possibly does not. The most appealing is Ishida's which seems to be relatively easy to apply if one can solve for the deterministic mean and then integrate the $k(t)$ derived from it. Substitution of this into Equation (III–45) then yields the generating function.

Except for the second approximation which has been applied to one biochemical reaction [69], these have not been applied to any complex systems. This area is one that needs much development, not only in chemically oriented problems, but also in problems in the field of genetics, epidemics, and population studies.

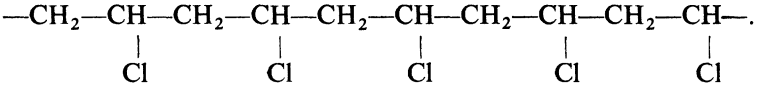
This concludes our discussion of elementary type reactions. Again we note that there are unfortunately few real applications of these to chemical or physical systems. On the other hand such simple models or slight extensions of them have found use in other fields. (See [14], Chapter 4). In the next section we shall discuss a selected group of more complicated processes which do in fact have direct application to physical or chemical systems.

IV. Selected Applications

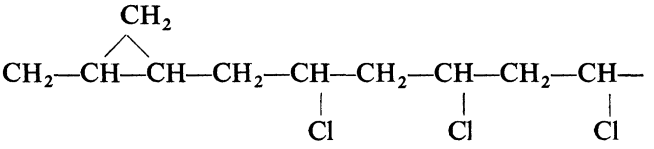
In this final section we shall outline some of the many chemical kinetic situations to which probability models have been applied. The selection is by no means exhaustive, but is chosen simply on the basis on the author's familiarity and bias.

IV.A. **Kinetics of reactant isolation** [19]

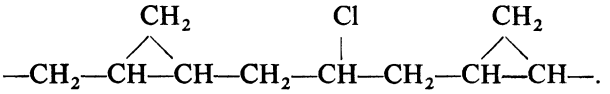
There are examples of systems in which species firmly attached to sites can react with one another. The reaction is usually confined to groups occupying adjacent sites. A classic example of such a system is the polymer, polyvinyl chloride, whose structure is [34]



The addition of zinc to a solution of polyvinyl chloride will extract chlorines in a pair-wise manner to give, for example, for one zinc atom,



The next zinc atom might give



Now the lone chlorine atom has found itself isolated, since the zinc only extracts two adjacent chlorines. Such a result is called reactant isolation, and one wishes to predict the chlorine concentration left in the polymer as a function of time. It was shown by Flory in 1939 [33] that the fraction of chlorines unreacted should approach e^{-2}, and this was used in fact by Marvel *et al.* [85] to determine the structure of polyvinyl chloride. Other examples are the condensation of the polymer of methyl vinyl ketone [33] and the vulcanization of natural rubber [81]. The vulcanization studies supply another example where a molecular structure was determined by a kinetic scheme. The complete time dependence of the process was recently derived by Cohen and Reiss [19] using a novel method of multiplets, which will now be outlined.

Consider a chain of N sites between which bonds are formed. A single un-

bonded site is referred to as a "singlet", a run of two sites as a "doublet", etc. In general, a run of n sites is termed an "n-tuplet". It should be noted that an "n-tuplet" may contain two distinct "$(n-1)$-tuplets", three distinct "$(n-2)$-tuplets", etc. This is illustrated in Figure 6.

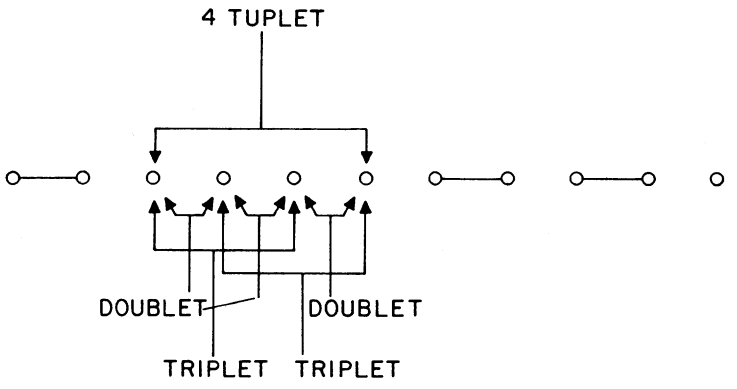


Figure 6
An illustration of n-tuplets

Consider an ensemble of M identical chains of N sites. Denote the number of n-tuplets in the jth chain at time t by $C_n^{(j)}(t)$. Let $k(t)dt$ be the probability that a bond forms between two unreacted neighbours in the time interval $(t, t+dt)$, the same for all pairs of neighbours. In most cases k may be assumed to be independent of time, but it is no more difficult to consider it as depending on time. The rate of change of $C_n^{(j)}(t)$ with time is

$$-\frac{dC_n^{(j)}(t)}{dt} = k(t)\{(n-1)C_n^{(j)} + 2C_{n+1}^{(j)}\}. \tag{IV-1}$$

The minus sign appears because the reaction is irreversible and n-tuplets can only be destroyed, never created. The first term on the right corresponds to the destruction of n-tuplets by the formation of a bond within the n-tuplet itself. Since there are $(n-1)$ possible bonds within an n-tuplet, the rate of destruction is proportional to $k(t)(n-1)C_n^{(j)}$. The second term on the right corresponds to the destruction of n-tuplets by the formation of a bond between either of its terminal sites and a site not belonging to an n-tuplet.

The mean number of n-tuplets averaged over the M identical chains is

$$\bar{C}_n(t) = M^{-1}\sum_{j=1}^{m} C_n^{(j)}(t). \tag{IV-2}$$

Summing (IV-1) over j and dividing by M yields

$$-\frac{d\bar{C}_n}{dt} = k(t)\{(n-1)\bar{C}_n + 2\bar{C}_{n+1}\}. \tag{IV-3}$$

Initially there are $N-n+1$ n-tuplets so that the initial conditions are

$$\bar{C}_n(0) = N-n+1. \tag{IV-4}$$

By introducing the variable

$$z = \int_0^t k(t)dt, \tag{IV-5}$$

Equation (IV-3) becomes

$$-\frac{d\bar{C}_n}{dz} = (n-1)\bar{C}_n + 2\bar{C}_{n+1} \tag{IV-6}$$

whose solution, subject to Equation (IV-4) is,

$$\bar{C}_n = \exp[-(n-1)z \sum_{s=0}^{N-n} (N-n-s+1)\frac{[2e^{-z}-2]}{s!}. \tag{IV-7}$$

The fraction of n-tuplets which survive, or the probability of survival of an n-tuplet, is

$$\begin{aligned} P_n(z) &= \frac{\bar{C}_n}{N-n+1} \\ &= \exp[-(n-1)z] \sum_{s=0}^{N-n} \left(1 - \frac{s}{N-n+1}\right) \frac{[2e^{-z}-2]^s}{s!}. \end{aligned} \tag{IV-8}$$

In the case of an infinitely long chain ($N \to \infty$), we have for all finite n,

$$P_n(z) = \exp[-(n-1)z]\exp\{-2[1-\exp(-z)]\}. \tag{IV-9}$$

At infinite time ($z \to \infty$), $P_1(\infty)$ is

$$P_1(\infty) = e^{-2}, \tag{IV-10}$$

which is the result obtained by Flory [33].

If this problem were formulated in terms of the more obvious quantity, "runs", Equation (IV-6) would involve summations on the right hand side and would be much more difficult to solve. The "multiplet" idea has also been used to advantage in solving a formulation of the kinetics of polypeptide denaturation, which will be discussed later. Cohen and Reiss also considered a system in the form of a ring, end effects in a linear chain, the effect of diluents, and the generating function for particle survival, but these will not be given here. To the best of my knowledge, however, the reversible process has not been solved.

IV.B. **Reaction kinetics of a long chain molecule**

Consider a long chain molecule again, each segment of which carries a reactive substitutent or group. In many cases the reactivity of each substituent depends upon the states of its two nearest neighbours. For example, the reactivity might be greater if one or both neighbors have reacted than if neither has. We wish to formulate a model for this process which produces the average fraction of reacted groups at time t. Examples of such processes are hydrolysis rates of methylmethacrylate [28], and *p*-nitrophenyl methacrylate [94], [95]; pyrolysis of poly(*t*-butyl acrylate) [108]; and polypeptide denaturation [83], [109]. In 1963 there were several advances in this area, [1], [5], [73], [74], [80], and some confusion or disagreement arose, but the problem was finally settled. The problem was later formulated in terms of multiplets in a study of polypeptide denaturation [90] and this will be outlined now.

Consider the schematic model of a polypeptide α-helix, shown in Figure 7. Apparently the hydrogen on a nitrogen atom (amide hydrogen) bonds to the oxygen

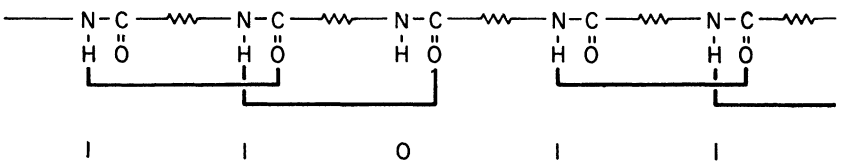


Figure 7
A schematic representation of a partially bonded polypeptide chain

on a carbon atom (carboxyl oxygen) three sites down the chain. This forces the polypeptide molecule to assume a rather rigid helical structure (α-helix) [115], [120]. For simplicity we shall assume, however, that a given hydrogen atom bonds to its nearest neighbour carbonyl oxygen. Statistical mechanical studies on this system [40], [126] indicate that this is a satisfactory simplification. We can then represent a partially hydrogen bonded polypeptide molecule by a sequence of zeros and ones, a zero standing for an unbonded hydrogen atom and a one standing for a bonded hydrogen atom. The section illustrated in Figure 7 can then be described by 11011. We consider only an irreversible renaturation process, meaning that a completely unbonded chain becomes a completely helical chain. Due to steric factors (which can be understood with the aid of a model), it is relatively difficult for an unbonded segment between two unbonded segments to become bonded; it is less difficult if one of its nearest neighbors is bonded, and very easy if both of its nearest neighbor hydrogen atoms are bonded. We shall denote the rate constants for these elementary steps by k_1, k_2, and k_3 so that

$$10001 \xrightarrow{k_1} 10101,$$

(IV–II)
$$10011 \xrightarrow{k_2} 11011,$$

$$11011 \xrightarrow{k_3} 11111;$$

k_2 and k_3 are perhaps similar in magnitude, and k_1 probably differs from either of these by an order of magnitude of σ^{-1} or $\sigma^{-\frac{1}{2}}$, where σ is the nucleation parameter ($\sim 10^{-3}$) of Gibbs and DiMarzio [40] and Zimm and Bragg [126].

We are interested in determining the decay with time of the number or fraction of segments unbonded, say. We now introduce the idea of a j-tuplet again. (See Figure 6.) We denote the number of j-clusters by B_j and the number of j-tuplets by P_j. Since there are j 1-tuplets in a j-cluster, $j-1$ 2-tuplets (doublets) in a j-cluster, etc., one finds for the relation between the P_j and B_j,

$$\begin{aligned} P_1 &= B_1 + 2B_2 + 3B_3 + \cdots + NB_N \\ P_2 &= B_2 + 2B_3 + 3B_4 + \cdots + (N-1)B_N \\ P_3 &= B_3 + 2B_4 + 3B_5 + \cdots + (N-2)B_N \\ &\cdots\cdots\cdots \\ P_N &= B_N \end{aligned} \tag{IV–22}$$

or

$$P_j = \sum_{i=0}^{N-j} (i+1)B_{j+i}. \tag{IV–13}$$

These equations may be inverted by inspection to give

$$B_j = P_j - 2P_{j+1} + P_{j+2}, \qquad 1 \leqq j \leqq N \tag{IV–14}$$

if we set P_n, $n > N$, identically zero.

It is now most convenient to proceed by deriving a set of equations for the rate of change of the number of j-tuplets, dP_j/dt, in terms of the number of j-clusters, B_j, and then transform this into a set of equations for the dP_j/dt in terms of the P_j. Figure 6 serves as a reference for the derivation of the first few equations. Clearly,

$$\begin{aligned} dP_1/dt &= -k_3B_1 - 2k_2B_2 - 2k_2B_3 - k_1B_3 - 2k_2B_4 - 2k_1B_4 + \cdots \\ &= -k_1P_3 - 2k_2(P_2 - P_3) - k_3(P_1 - 2P_2 + P_3), \end{aligned} \tag{IV–15}$$

and

$$\begin{aligned} dP_2/dt &= -2k_2B_2 - 2k_2B_3 - 2k_1B_3 - 2k_2B_4 - 4k_1B_4 + \cdots \\ &= -2k_2(P_2 - P_3) - 2k_1P_3. \end{aligned} \tag{IV–16}$$

The terms on the right-hand side of the first of Equations (IV–15) and (IV–16) are arrived at in the following manner: $2k_2B_2$ since each of the two zeros in a 2-cluster can transform with a rate constant k_2; $2k_2B_3$ since each of the two end zeros in a 3-cluster can transform with a rate constant k_2; $2k_1B_3$ because the one middle zero in a 3-cluster eliminates two 2-tuplets when it transforms; $2k_2B_4$ because of the two end zeros in a 4-cluster; $4k_1B_4$ since each of the two middle zeros of a 4-cluster eliminates two doublets upon transforming. Proceeding in a like manner,

$$\text{(IV–17)} \qquad \begin{aligned} dP_3/dt &= -2k_2B_3 - k_1B_3 - 2k_2B_4 - 4k_1B_4 - 2k_2B_5 - 7k_1B_5 + \cdots \\ &= -2k_2(P_3 - P_4) - k_1(P_3 + 2P_4). \end{aligned}$$

The general pattern may not be apparent at this stage, but if several more equations are written out the general term may be seen to be

$$\text{(IV–18)} \qquad dP_j/dt = -2k_2(P_j - P_{j+1}) - k_1[(j-2)P_j + 2P_{j+1}], \quad j \geqq 2.$$

We place no upper bound on j since we assume that the chain is long enough to neglect an end effect, which manifests itself in separate equations for dP_N/dt and dP_{N-1}/dt.

We are now faced with the problem of solving this system of equations. Assume that

$$\text{(IV–19)} \qquad P_j(t) = e^{-jk_1t}\psi(t)$$

where $\psi(t)$ is to be determined. We substitute this into Equation (IV–18) to obtain

$$\text{(IV–20)} \qquad \frac{d\psi}{dt} = 2(k_1 - k_2)(1 - e^{-k_1t})\psi(t),$$

which gives

$$\text{(IV–21)} \qquad P_j(t) = e^{-jk_1t}\exp\{2(k_1 - k_2)[t - (1 - e^{-k_1t})/k_1]\},$$

where we have used the initial condition $P_j(0) = 1$ for all finite j. The value 1 results from normalization, i.e., by dividing every $P_j(t)$ by $N - j$. What we require is an expression for $P_1(t)$, which is the total number of zeros, or the number of unbonded hydrogen atoms, as a function of time. This is obtained by substituting $P_2(t)$ and $P_3(t)$ from Equations (IV–21) into Equation (IV–15) and solving the resultant first-order linear differential equation. Equation (IV–15) becomes

$$\text{(IV–22)} \qquad \frac{dP_1}{dt} + k_3P_1 = 2(k_3 - k_2)P_2 + (2k_2 - k_1 - k_3)P_3$$

and

$$P_1(t) = e^{-k_3 t}\left[2(k_3 - k_2)e^{2(k_2-k_1)/k_1}\int e^{(k_3-2k_2)t}\exp\left\{\frac{2(k_1-k_2)}{k_1}e^{-k_1 t}\right\}dt\right.$$

(IV-23)

$$\left. + (2k_2 - k_1 - k_3)e^{2(k_2-k_1)/k_1}\int e^{(k_3-k_1-2k_2)t}\exp\left\{\frac{2(k_1-k_2)}{k_1}e^{-k_1 t}\right\}dt + k\right],$$

where k is an integration constant. Each of the integrals in Equation (IV-23) is of the form

$$\int e^{-at}\exp\{be^{-ct}\}\,dt. \tag{IV-24}$$

This may be converted to a well-known function, namely, the incomplete gamma function [30], by setting $u = -be^{-ct}$,

$$\int e^{-at}\exp\{be^{-ct}\}dt = \frac{1}{(-b)^{a/c}c}\int_{be^{-ct}}^{-b} u^{a/c}e^{-u}dt \tag{IV-25}$$

$$= \frac{1}{c(-b)^{a/c}}[\gamma(a/c, -b) - \gamma(a/c, -be^{-ct})],$$

where $\gamma(a,x)$ is the incomplete gamma function,

$$\gamma(a,x) = \int_0^x u^{a-1}e^{-u}du. \tag{IV-26}$$

With these substitutions, Equation (IV-23) becomes

$$P_1(t) = e^{-k_3 t}\left[1 - \frac{2(k_3-k_1)\exp\{2(k_2-k_1)/k_1\}}{k_1\left[2\left(\frac{k_2}{k_2}-1\right)\right]^{2(k_2-k_3)/k_1}}\right.$$

$$\times\left\{\gamma\left[\frac{2k_2-k_3}{k_1}, 2\left(\frac{k_2}{k_1}-1\right)e^{-k_1 t}\right] - \gamma\left[\frac{2k_2-k_3}{k_1}, 2\left(\frac{k_2}{k_1}-1\right)\right]\right\}$$

$$- \frac{(2k_2-k_1-k_3)\exp\{2(k_2-k_1)/k_1\}}{k_1\left[2\left(\frac{k_2}{k_1}-1\right)\right]^{2(k_2+k_1-k_3)/k_1}} \tag{IV-27}$$

$$\times\left\{\gamma\left[\frac{2k_2+k_1-k_3}{k_1}, 2\left(\frac{k_2}{k_1}-1\right)e^{-k_1 t}\right]\right.$$

$$\left.\left. - \gamma\left[\frac{2k_2+k_1-k_3}{k_1}, 2\left(\frac{k_2}{k_1}-1\right)\right]\right\}\right].$$

Equation (IV–27) can be simplified by first letting $k_2 = k_3$, letting $k_2/k_1 = x$, and measuring time in units of k_1, i.e., letting $k_1 t = \tau$; k_2 and k_3 should be of similar magnitude, and equating them has very little effect on the results. Then

$$\text{(IV–28)}\quad P_1(\tau) = e^{-x\tau}\left(1 + \frac{e^{2(x-1)}}{2[2(x-1)]^x}\{\gamma[1+x, 2(x-1)] - \gamma[1+x, 2(x-1)e^{-\tau}\right).$$

Equation (IV–28) is plotted in Figure 8 for various values of x.

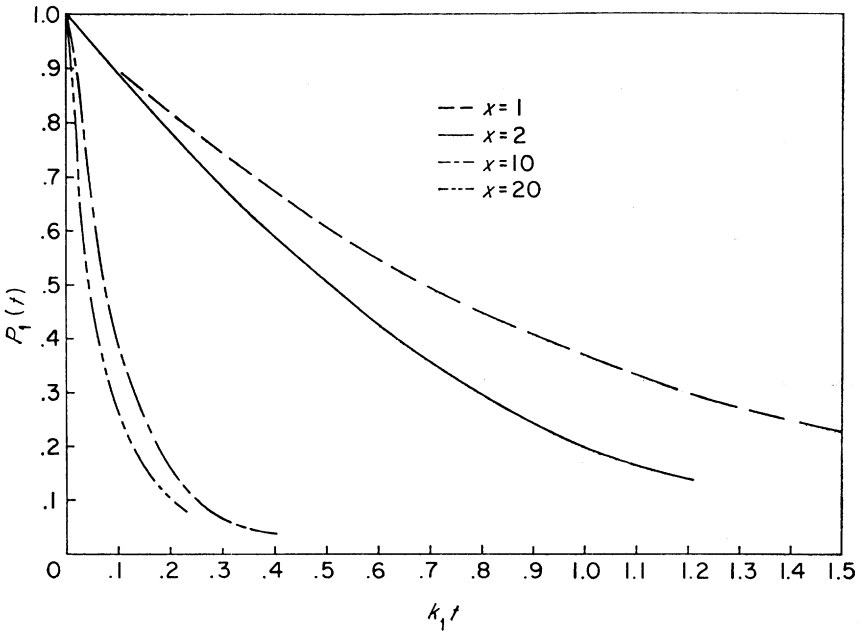


Figure 8
Fraction of unbonded polypeptide segments against $k_1 t$
for various ratios of elementary rate constants

It may be noted that the initial slope of $P_1(t)$ against $k_1 t$ is always -1; that is, the process starts off behaving as if it had a single relaxation time k_1. Likewise, the end of the reaction exhibits a single relaxation time k_3. The physical meaning of this is that in all initial processes, an unbonded segment with unbonded neighbors reacts to form a bond; whereas in all final steps, an unbonded segment neighbored by bonded segments reacts. Even though we only consider the polypeptide kinetics here, the general result is immediately applicable to the cases studied by Keller *et al.* We also point out related work by Pipkin and Gibbs [100] and Gō [43], [44].

A very important extension of this, namely, the reversible case, has not, I believe, been solved.

IV. C. **Copolymerization statistics**

The last polymeric-type example we wish to discuss is a derivation of the degree of polymerization distribution (degree of polymerization is the number of monomer units in a polymer), the overall composition, and the compositional distribution for copolymers containing any number of different monomers [37], [115]. An initial system of two different kinds of monomers, say, will produce polymer chains of various lengths and various compositions. A number of papers have dealt with the degree of polymerization and compositional statistics of this process [20], [21], [22], [37], [50], [51], [79], [86], [98], [99], [104], and simply as a representative example, we present the work of Frensdorf and Pariser [37]. This should suffice to introduce the types of problems that have been considered.

As a polymer chain grows from a solution containing monomers, the monomer units attach themselves to the active end of the chain (assuming, as usual, that there is only one). We shall assume that only the terminal units affect the rate of addition of the next monomer unit. We say that the growing chain is in a state i if its terminal unit is an i monomer and that it undergoes a transition to state j upon addition of a j monomer. We let the transition probability for this process be P_{ij}; P_{ij} can be related to the corresponding rate constants by

$$P_{ij} = k_{ij}M_j/(k_{iT} + \sum_j k_{ij}M_j), \tag{IV-29}$$

where k_{iT} is the rate constant for termination of chains in state i, k_{ij} is the rate constant for adding a j monomer to a chain ending in an i monomer, and M_j is the concentration of the j monomer. We write all these transition probabilities in a matrix $\boldsymbol{Q}$

$$\boldsymbol{Q} \equiv \begin{array}{c|cccccc} & I & T & 1 & 2 & \cdots \\ \hline I & 0 & 0 & I_1 & I_2 & \cdots \\ T & 0 & 1 & 0 & 0 & \cdots \\ 1 & 0 & T_1 & P_{11} & P_{12} & \cdots \\ 2 & 0 & T_2 & P_{21} & P_{22} & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \cdots \\ \vdots & \vdots & \vdots & \vdots & \vdots & \cdots \end{array} \tag{IV-30}$$

where T_i is the probability of termination of a chain ending in the ith monomer, and I_i is the probability of reaction of the initiating species with the ith monomer. For a system of m different monomers, $\boldsymbol{Q}$ is a square stochastic matrix of order $m+2$.

Determination of the DP distribution* requires finding $P_{IT}^{(n)}$, the IT element of $\boldsymbol{Q}^n$. The matrix element $P_{IT}^{(n)}$ represents the probability of going from state I to state T in exactly n steps. Since $n+1$ steps are required to add n monomer units and because $P_{IT}^{(n+1)}$ includes all sequences of n or fewer monomer units, the desired distribution is

$$F(n) = P_{IT}^{(n+1)} - P_{IT}^{(n)}, \tag{IV-31}$$

where $F(n)$ is the mole fraction of n-mers in the copolymer.

Employing the standard expansion of $\boldsymbol{Q}$, one writes

$$\boldsymbol{Q}^n = \sum_i \lambda_i^n \boldsymbol{A}_i, \tag{IV-32}$$

where the λ_i are the $m+2$ eigenvalues of $\boldsymbol{Q}$, and

$$\boldsymbol{A}_i \equiv |q_i\rangle\langle q_i|. \tag{IV-33}$$

Here, $|q_i\rangle$ and $\langle q_i|$ are the column and row eigenvectors of $\boldsymbol{Q}$, respectively, and are defined by

$$\boldsymbol{Q}\,|q_i\rangle = \lambda_i |q_i\rangle \tag{IV-34}$$

$$\langle q_i|\boldsymbol{Q} = \lambda_i \langle q_i| \tag{IV-35}$$

and

$$\langle q_i|q_i\rangle = 1. \tag{IV-36}$$

A root of unity and one of zero can be factored out of the secular determinant and the problem is reduced to solving the submatrix $\boldsymbol{P}$, given by

$$\boldsymbol{P} \equiv \begin{bmatrix} P_{11} & P_{12} & P_{13} & \cdot & \cdot & \cdot & \cdot \\ P_{21} & P_{22} & P_{23} & \cdot & \cdot & \cdot & \cdot \\ P_{31} & P_{32} & P_{33} & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \end{bmatrix} \tag{IV-37}$$

and finding its normalized eigenvectors, $|p_i\rangle$ and $\langle p_i|$.

The required element $A_{IT}^{(i)}$ of $\boldsymbol{A}_i$ is given by

$$A_{IT}^{(i)} = -[1/\lambda_i(1-\lambda_i)]\langle i|p_i\rangle\langle p_i|t\rangle, \tag{IV-38}$$

where $\langle i|$ is the row vector with elements $I_1, I_2, \cdots, I_m$ and $|t\rangle$ the column vector with elements $T_1, T_2, \cdots, T_m$. Since

$$T_j = 1 - \sum_i P_{ji} \tag{IV-39}$$

it can be shown that

* DP — degree of polymerization.

$$\langle \boldsymbol{p}_i | \boldsymbol{t} \rangle = (1 - \lambda_i) \langle \boldsymbol{p}_i | \boldsymbol{1} \rangle \tag{IV–40}$$

where $|\boldsymbol{1}\rangle$ is the unit column vector of order m.

It follows from Equations (IV–31), (IV–32), (IV–38), and (IV–40) that

$$F(n) = \sum_i (1 - \lambda_i) \lambda_i^{n-1} \langle \boldsymbol{i} | \boldsymbol{p}_i \rangle \langle \boldsymbol{p}_i | \boldsymbol{1} \rangle, \tag{IV–41}$$

where the summation is over the m roots of $\boldsymbol{P}$.

Equation (IV–41) shows that the DP for a copolymer of m different monomers is a combination of m binomial distributions. The mean of DP, $\bar{N}_n$, is easily obtained from Equation (IV–41):

$$\bar{N}_n = \sum_{n=1}^{\infty} nF(n) = \sum_i (1 - \lambda_i)^{-1} \langle \boldsymbol{i} | \boldsymbol{p}_i \rangle \langle \boldsymbol{p}_i | \boldsymbol{1} \rangle . \tag{IV–42}$$

Higher moments of the distribution can be obtained in an analogous fashion.

To construct the generating function for the distribution of monomer 1, one proceeds in a fashion analogous to that used above for deriving the DP distribution. To this end a matrix $\boldsymbol{Q}_s$ is defined, which is obtained from $\boldsymbol{Q}$ [Equation (IV–30)] by multiplying the column labeled 1 by the dummy variable s. Then the element $P_{IT}^{(n)}$ of $\boldsymbol{Q}_s^n$ is made up of terms which each represent the probability of going from state I to state T by a specific path multiplied by a power of s equal to the number of times state 1 has been crossed. The desired generating function for the distribution of monomer 1 in molecules of n monomer units is then given by an expression analogous to Equation (IV–41). The generating function for any other monomer is obtained in the same way, except that the elements of the appropriate column of $\boldsymbol{Q}$ are multiplied by s.

The treatment is carried out like that leading from Equation (IV–31) to Equation (IV–41). The generating function is then given by

$$G(s, n) = [F(n)]^{-1} \sum_i \lambda_{s,i}^{n-1} \langle \boldsymbol{i}_s | \boldsymbol{p}_{s,i} \rangle \langle \boldsymbol{p}_{s,i} | \boldsymbol{t} \rangle \tag{IV–43}$$

where the $|\boldsymbol{p}_{s,i}\rangle$ and $\langle \boldsymbol{p}_{s,i}|$ are the eigenvectors corresponding to the roots $\lambda_{s,i}$ of the matrix $\boldsymbol{P}_s$,

$$\boldsymbol{P}_s \equiv \begin{bmatrix} sP_{11} & P_{12} & P_{13} & \cdot & \cdot & \cdot \\ sP_{21} & P_{22} & P_{22} & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \end{bmatrix}, \tag{IV–44}$$

$|\boldsymbol{t}\rangle$ is the column vector with elements $T_1, T_2, \cdots, T_m$, $\langle \boldsymbol{i}_s|$ the row vector with elements $sI_1, I_2, I_3, \cdots, I_m$, and $[F(n)]^{-1}$ is the normalizing factor, chosen so that $G(1, n) = 1$.

The compositional distribution described by $G(s, n)$ enumerates how many copolymer molecules of DP = n contain a given number of units of monomer 1.

A problem of interest is how many molecules of the whole copolymer contain a specific mole fraction of monomer 1. This is not a discrete integral distribution and, hence, not readily expressed as a generating function. However, its moments can be obtained by suitably summing the moments of $G(s,n)$ over all values of n by means of the DP distribution given in the previous section.

A mathematical approach analogous to this one can obviously also be used in calculating bond-type distributions, for example, by applying the generating index s to matrix elements P_{ij} and P_{ji} bonds between units of monomers i and j.

Many papers have appeared on this subject but Hijmans [50] seems to have the most complete discussion of this type of problem and various extensions of it. By using a generalization of Cauchy's theorem and the method of steepest descents he is able to express the results in compact form. He has shown that the distribution function for the fraction of molecules with a given composition is a product of an exponential distribution in the total number of monomers and a multidimensional Gaussian distribution in a set of variables which characterizes the relative deviation of the composition from its average. He and others have also considered the effect of the penultimate monomer on the various distributions.

Recently Lauritzen *et al.* [79] have treated the even more general case in which the addition of monomer is reversible. Only nearest-neighbor interactions are assumed and the rate constants α^{ij} for addition of species j to a chain ending in species i, and β^{ij}, for the removal of species j from a chain ending in i, are assumed known and independent of chain length, except for those referring to the first step of the chain, which are distinct. The full kinetic equations for the growth of such chains are formulated and a solution obtained for steady-state conditions. It is shown that when the matrix of α^{ij}/β^{ij} is indecomposable and primitive, a solution of the equations which is independent of chain length always exists for sufficiently long chains, and computational methods for obtaining this solution for a relatively large number of components (of the order of 10) are presented. In addition, the relationship of α^{ij}/β^{ij} to the energetics of the system is derived.

One problem in all these papers is that the transition probabilities are assumed to be constants. However, Equation (IV–29) shows that they do in fact depend upon the M_j, and as the chains grow the M_j, and hence the P_j change. Several experimental conditions allow this to be overcome, but in general, it seems that the P_{ij} should depend upon n. So far as I know, this effect is untouched.

IV.D. **Random walk model of unimolecular decomposition**

In this section we treat an application of stochastic techniques to a microscopic treatment of unimolecular reactions due to Montroll and Shuler [92]. Theirs is a discrete random walk extension of a Brownian motion model used by Kramers

in 1940 [77]. Consider an ensemble of reactant molecules with quantized energy levels to be immersed in a large excess of chemically inert gas which acts as a constant temperature heat bath throughout the reaction. The reactant molecules are initially in a Maxwell-Boltzmann distribution, say, appropriate to a temperature T_0 such that $T_0 < T$, where T is the temperature. By collision with the heat bath molecules, the reactants are excited in a step-wise process onto their higher energy levels until they reach level $N+1$ where they decompose and are irreversibly removed from the reaction system. The collisional transition probabilities per unit time W_{mn} which govern the rate of transition of reactant molecules between levels with energies E_n and E_m are functions of the quantum numbers n and m and can, in principle, be calculated in terms of the interaction of the reactant molecules with the heat bath.

This corresponds to a one-dimensional random walk with an absorbing barrier, with the transition probabilities given by quantum mechanics. The time dependent distribution of the reactant molecules among the energy levels $n = 0, 1, \cdots, N$ is then given by the fraction of walkers in state n. The rate of activation is inversely proportional to the mean first passage time to the $(N+1)$th level. In general the quantum mechanical transition probabilities are quite difficult to obtain, but if the reactant molecules can be treated as simple harmonic oscillators (in a quantum mechanical sense), and if only weak interactions exist between the oscillators and heat bath molecules, an explicit calculation of the collisional transition probabilities can be carried out. This was done first by Landau and Teller [49]. If the transition probability per collision, P_{10}, for the transition $0 \rightarrow 1$ can be determined, then Landau and Teller showed that

$$P_{mn} = [(m+1)\delta_{n-1,m} + m\delta_{n+1,m}]P_{10} = P_{nm}. \tag{IV-45}$$

P_{mn} is the probability per collision of a transition from state n to state m. Note that only transitions between neighboring levels are allowed. From the simple kinetic theory of gases, the transition probabilities per unit time, W_{mn}, are given by

$$\begin{aligned} W_{n+1,n} &= ZN^*e^{-\theta}P_{n,n+1} \\ W_{n-1,n} &= N^*P_{n,n-1}. \end{aligned} \tag{IV-46}$$

The quantity Z is the number of collisions per unit time suffered by the oscillator when the gas density is one molecule per unit volume, N is the total concentration of heat bath molecules, and $\theta = h\nu/kT$, where h is Planck's constant, k the Boltzmann constant, T the absolute temperature, and ν the fundamental vibrational frequency of the oscillators.

The potential energy curve of the dissociating harmonic oscillators is taken to be that of a truncated harmonic oscillator with a finite number of equally spaced energy levels such that level N is the last bound level. The dissociation

or activation energy for the reaction is then $E_{N+1} = h\nu(N + 1)$. This potential energy curve is shown in Figure 9.

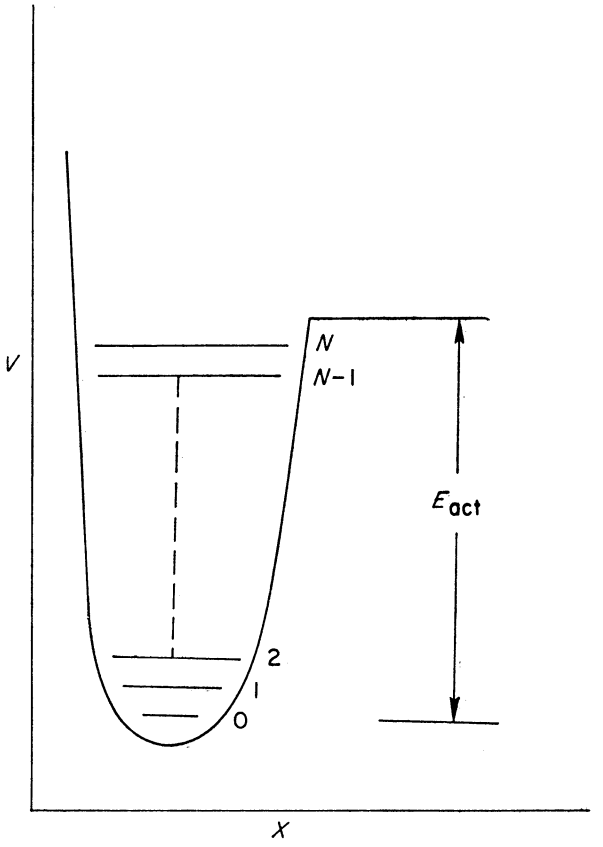


Figure 9
Potential energy diagram of the truncated harmonic oscillator model

Let $F(t)$ be the fraction of molecules which have not yet reached $(N + 1)$ in the time interval $(0, t)$. Then if $x_n(t)$ is the fraction of molecules in level n,

$$F(t) = \sum_{n=0}^{N} x_n(t). \tag{IV-47}$$

Since particles are not conserved, this is a dishonest process. The fraction of molecules which dissociates in an infinitesimal time interval $(t, t + \delta t)$ is

$$-[F(t + \delta t) - F(t)] = -(dF/dt)\delta t. \tag{IV-48}$$

If $P(t)$ is the distribution of first passage times for transitions past level N, the number of molecules which pass N in the interval $(t, t + \delta t)$ is $P(t)\delta t$. Then

$$P(t) = -\frac{dF}{dt} = -\frac{d}{dt}\sum_{n=0}^{N} x_n(t). \tag{IV-49}$$

The mean first passage time is

$$t = \int_0^\infty tP(t)\,dt = -\int_0^\infty t\frac{d}{dt}\sum_{n=0}^{N} x_n(t)\,dt \tag{IV-50}$$

$$= \int_0^\infty \sum_{n=0}^{N} x_n(t)\,dt. \tag{IV-51}$$

The differential-difference transport equations which determine the $x_n(t)$ are

$$\frac{dx_0}{dt} = -W_{10}x_0 + W_{01}x_1, \tag{IV-52}$$

$$\frac{dx_j}{dt} = W_{j,j-1}x_{j-1} - (W_{j-1\ j} + W_{j+1,j})x_j + W_{j.j+1}x_{j+1} \tag{IV-53}$$

$$j = 1,2,\cdots,N-1,$$

$$\frac{dx_N}{dt} = W_{N,N-1}x_{N-1} - (W_{N-1,N} + W_{N+1,N})x_N. \tag{IV-54}$$

The distribution of first passage times $P(t)$ can be found by summing these equations to give

$$P(t) = -\frac{d}{dt}\sum_{n=0}^{N} x_n(t) = W_{N+1,N}x_N(t), \tag{IV-55}$$

and the mean first passage time is

$$\bar{t} = W_{N+1,N}\int_0^\infty t\,x_N(t)\,dt. \tag{IV-56}$$

The model can be generalized to the case in which transitions may occur to other than nearest neighbor levels. This would be necessary in models more sophisticated than the truncated harmonic oscillator where other than nearest neighbor transitions were allowed.

Let us write Equations (IV-52), (IV-53), (IV-54) in the form

$$\frac{dX(t)}{dt} = AX(t) \tag{IV-57}$$

where $X(t)$ is a vector with components $x_0(t), x_1(t), \cdots, x_N(t)$. The solution is

$$X(t) = e^{At}X(0). \tag{IV-58}$$

Now express the exponential matrix as a linear combination of the characteristic matrices of A, the $f_j(A)$'s which satisfy the relations

$$Af_j(A) = \lambda_j f_j(A) \qquad j = 0,1,2,\cdots,N$$

(IV-59) $$f_k(A)f_j(A) = \delta_{kj}f_j(A)$$

$$\sum_{j=0}^{N} f_j(A) = I,$$

where I is the identity matrix and the λ_j's are the eigenvalues of A, Since the first of these equations implies that $G(A)f_j(A) = G(\lambda_j)f_j(A)$, then

(IV-60) $$e^{At}I = e^{At}\sum_{j=0}^{N} f_j(A)$$

(IV-61) $$= \sum_{j=0}^{N} e^{At}f_j(t) = \sum_{j=0}^{N} e^{\lambda_j t}f_j(A)$$

and

(IV-62) $$\int_0^\infty X(t)\,dt = \sum_{j=0}^{N}\left\{\int_0^\infty e^{\lambda_j t}dt\right\}f_j(A)X(0)$$

(IV-63) $$= -\sum_{j=0}^{N}\lambda_j^{-1}f_j(A)X(0) = -\sum_{j=0}^{N}A^{-1}f_j(A)X(0)$$

(IV-64) $$= -A^{-1}X(0)$$

(IV-65) $$= \frac{(-)^{N+1}}{\det A}\{a_N I + a_{n-1}A + \cdots + A^N\}X(0).$$

In the last line we have made use of the Cayley-Hamilton theorem and the a_j's are the coefficients in the secular equation of A. In particular

(IV-66) $$a_N = (-)^N \sum_i \lambda_0\lambda_1\cdots\lambda_{i-1}\lambda_{i+1}\cdots\lambda_N$$

(IV-67) $$= (-)^N \det A \sum_{i=0}^{N}\lambda_i^{-1} = (-)^N \det A \,\mathrm{tr}\,A^{-1}.$$

Let $\langle i|A^m|j\rangle$ be the elements in the ith row and jth column of the matrix A^m. Then the mean first passage time from an initial jth state is

(IV-68) $$\bar{t} = \int_0^\infty \sum_{n=0}^{N} x_n(t)\,dt = -\sum_{i=0}^{N}\langle i|A^{-1}|j\rangle$$

(IV-69) $$= \frac{(-)^{N+1}}{\det A}\sum_{l=0}^{N} a_l \sum_{i=0}^{N}\langle i|A^{N-l}|j\rangle.$$

When all the molecules are initially in the ground state and when det A is a continuant, Montroll and Shuler [92] show that Equation (IV-69) reduces to

$$\bar{t} = -\mathrm{tr}A^{-1}$$

We now explicitly consider the model of the unimolecular decomposition, that of a truncated harmonic oscillator. Using the Landau-Teller quantum mechanical transition probabilities, we write

$$\frac{dx_n}{dt} = \kappa\{ne^{-\theta}x_{n-1} - [n + (n+1)e^{-\theta}]x_n + (n+1)x_{n+1}\} \qquad n = 0, 1, 2, \cdots, N-1, \tag{IV-70}$$

$$\frac{dx_N}{dt} = \kappa\{Ne^{-\theta}x_{N-1} - [N + (N+1)e^{-\theta}]x_N\}, \tag{IV-71}$$

where $\kappa = P_{10}$ of Equation (IV-45) and depends only on the coupling betwen molecules and heat bath. These equations can be symmetrized by introducing $y_n = x_n \exp(\frac{1}{2}n\theta)$ which gives

$$\frac{dY}{dt} = BY \tag{IV-72}$$

where B is now a symmetric matrix. Using the symmetric and continuant properties of B, Montroll and Shuler show that

$$\kappa t = -\kappa \operatorname{tr} B^{-1} \tag{IV-73}$$

$$= \sum_{j=1}^{N+1} e^{j\theta}\left\{\frac{1}{j} + \frac{1}{j+1} + \cdots + \frac{1}{N+1}\right\}. \tag{IV-74}$$

As $N \to \infty$,

$$\kappa t = \frac{e^{(N+1)\theta}}{(N+1)(e^{-\theta}-1)^2}\left\{1 + \frac{e^{-\theta}}{N(1-e^{-\theta})} + o(N^{-2})\right\}. \tag{IV-75}$$

The standard theories of chemical kinetics are equilibrium theories in which a Maxwell-Boltzman distribution of reactants is postulated to persist during a reaction [124]. The equilibrium theory first passage time is the $N \to \infty$ limit in Equation (IV-75). Corrections to it then are to be expected when the second term in Equation (IV-75) is no longer negligible, i.e., when N is not much greater than $e^{-\theta}(1-e^{-\theta})^{-1}$. The mean first passage time and rate of activation deviate from their equilibrium value by more than 10 percent when

$$N(1 - e^{-\theta}) < 10e^{-\theta}, \tag{IV-76}$$

or roughly when $E_{activation}/kT < 10$. This result is in agreement with other statistical mechanical estimates of this effect.

Montroll and Shuler were also able to solve Equations (IV-70) and (IV-71) for $x_n(t)$. They found that

$$x_n(t) = \sum_{j=0}^{N} a_j I_n(\mu_j) \exp\{\mu_j(e^{-\theta} - 1)t\kappa\}, \tag{IV-77}$$

where the $l_n(z)$ are Gottlieb polynomials [47] and the μ_j are the zeros of $l_{N+1}(z)$. By means of the orthogonality relations of the Gottlieb polynomials, the a_j are found to be given by

$$a_j = \sum_{n=0}^{N} x_n(0)\, l_n(\mu_j)\, e^{n\theta} \Big/ \sum_{n=0}^{N} l_n^2(\mu_j)\, e^{n\theta}. \tag{IV-78}$$

When all the molecules are initially in state m,

$$x_n(t) = \sum_{j=0}^{N} \left\{ \frac{l_m(\mu_j) l_n(\mu_j) e^{m\theta}}{\sum_{s=0}^{N} l_s^2(\mu_j) e^{s\theta}} \right\} \exp\{\mu_j(e^{-\theta} - 1)\, t\kappa\}. \tag{IV-79}$$

When $x_n(0)$ is a Boltzmann distribution with an initial temperature such that the population of levels greater than N is completely negligible,

$$x_n(t) = \sum_{j=0}^{N} \left\{ l_n(\mu_j) \left[\frac{1 - e^{-(\theta_0 - \theta)}}{1 - e^{-\theta_0}} \right]^{\mu j} \Big/ \sum_{m=0}^{N} l_m^2(\mu_j) e^{m\theta} \right\} \exp\{-\mu_j(1 - e^{-\theta}) t\kappa\}. \tag{IV-80}$$

Using Equation (IV-55) for $P(t)$, mean first passage times may then be calculated and compared to either the equilibrium result ($N \to \infty$) to test the range of validity of this assumption or to experiment. The agreement with experiment is not very good [13], [111] but then again the model outlined here is only a first step. The obvious refinement is the use of a more realistic model for the oscillators and a calculation of transition probabilities for strong interactions. Kim [75] has studied an anharmonic oscillator model, but no numerical results have appeared. He did consider in some detail, however, the conditions under which the macroscopic rate law

$$-\frac{dc}{dt} = kc \tag{IV-81}$$

is valid.

IV. E. **Kinetics of biological macromolecules**

In this section we summarize some recent work [112], [127], [128] concerning the kinetics of DNA replication and demonstrate how even such complex phenomena can be given a useful treatment by means of relatively simple stochastic methods. The DNA molecule plays a central role in genetic reproduction and consists of two long linear strands intertwined in the form of a double helix [115]. Each strand is made up of four complex bases whose arrangement contains the genetic information required for the transformation of proteins used in the cell. The two strands are held together by hydrogen bonds which must be broken in order for the helix to unwind; this in turn is necessary for the DNA molecule to self-replicate. The new (or daughter) DNA molecules are made by

copying the old (or parent) chains using the latter as a template. It is now commonly agreed, on the basis of considerable experimental work [15], that for *in vivo* systems this template replication has a "Y" configuration as shown in Figure 10. This implies a simultaneous (enzymatic) unwinding of the parent helix and the formation of the daughter helices. It appears likely that the continued replication of the daughter helices plays a role in the further opening of the parent helix and, conversely, if the unwinding rate is not sufficiently large relative to the polymerization rate along the template then replication can be repressed by lack of accessible template sites. The model we shall describe provides a basis for studying this competitive process.

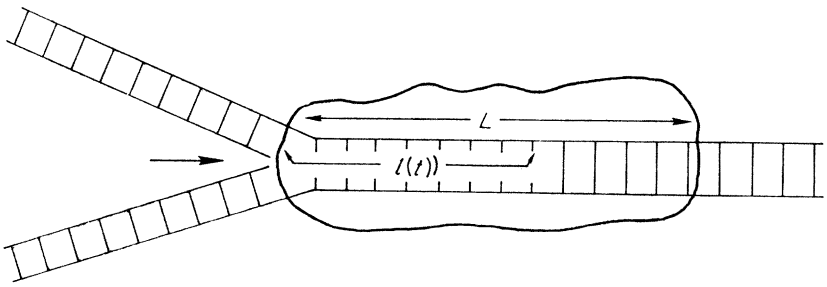


Figure 10
The "Y" model for a replicating double helix with an enzyme activated region of length L base pairs, and instantaneous number of accessible template sites $l(t)$

In order to focus our attention on this question and to formulate a simple kinetic model for DNA replication, it is sufficient to ignore the specific sequence structure of the molecule and consider the parent and daughter helices to be homopolymeric. The well-known fact that the sequence of four bases in each daughter is an exact complementary copy of the parent is not an essential feature in studying the coupled unwinding and replication mechanisms.

The role of the enzymes in these processes must be treated phenomenologically, since explicit details of enzymatic reactions are not known as yet. Fortunately this can be done quite naturally by means of stochastic methods. Indeed one of the great virtues of this approach to biological (as well as other) problems is its ability to summarize quite readily complex (and perhaps not well-understood) details of the process.

The model of Zimmerman and Simha can be described as follows. Each double-stranded (homopolymeric) parent template molecule is presumed to have length N. At any time t a given base pair at site position j along the template (say measured from the left end in Fig. 10, $j = 1, 2, \cdots, N$) either still possesses an intact hydrogen bond, or this bond has been broken providing a free template site, or the site possesses incorporated monomer in a newly replicated daughter helix. To avoid unessential details we assume both daughter helices are simul-

taneously replicated in an identical manner, so that it is sufficient to consider either one. Following current understanding of DNA replication it is assumed that replication occurs only in one direction from one end of the template with a single growing center for each daughter. Zimmerman and Simha have developed a kinetics for multicenter growth along a simple linear template [127] but such complications are not required for the present application. It is supposed that monomer reaches the template at each position j with equal probability by means of a first order diffusion process with effective rate constant k_{diff} and is deposited if the site is empty. Further, if this site is adjacent to the growing chain ends, incorporation with daughter helices will occur, characterized by a first order process with rate constant k. One can also allow for unincorporated monomer desorption but this simply causes the expected shift (slowing) of the time scale and for simplicity will be omitted here. Experimental evidence indicates that depolymerization of dimers and higher order species need not be considered.

Replication occurs by means of single monomer addition to each of the two growing chains at the junction of the "Y", which therefore moves (see Figure 10) to the right during the process. The parent helix, under the influence of the enzyme unwinds ahead of these growing chains leaving a region of expected length $l(t)$ in which the base pair hydrogen bonds have been broken. The enzyme is incorporated phenomenologically in the model by supposing that it has an effective region of action along the template encompassing a fixed number of sites L. This region begins at all times at the junction of the Y and extends through the unbound portion of the parent helix into the bound portion as shown schematically in Figure 10. Unwinding of the parent helix can take place only within this region, where it occurs for a given base pair with effective rate constant k_0. Since the enzyme is pushed along by the replicating daughters, the latter drive the unwinding process by continuously permitting new portions of the bound helix to react with the enzyme. This is the essential feature of the model that couples the unwinding and replication mechanisms. When in this region of enzyme activity a hydrogen bond is broken at a location less than or equal to some critical number c of template sites from the end of the bound part of the parent helix, it is supposed that all base pairs between it and this end open instantaneously. All these template sites are then available to receive the diffusing monomer and thus participate in the replication of the daughter helixes. A base pair which opens at a distance greater than c positions from the unbound end causes no further breaking of hydrogen bonds and is, therefore, isolated from the replicating chains. The model assumes an ensemble of equal-length parent helices each one of which is activated initially by an enzyme according to the first order rate process $h(t) = k_e \exp(-k_e(t))$. For certain technical reasons, and without loss of generality, it is supposed that the initiation mechanism results in the formation of a dimer.

The kinetics of the replicating daughters can be described in terms of a set

of elementary probabilities $\lambda_j(t)$, $j = 2, 3, \cdots, N$ which give the likelihood for any given replicating molecule that each of the two growing daughter helices has reached the jth template site at time t. In order to write down differential equations for the $\lambda_j(t)$ it is convenient to introduce a function $\psi(t)$ which gives the probability of transition from daughter helices of length j to those of length $j + 1$ in the time interval $[t, t + dt]$. As the notation indicates, $\psi(t)$ turns out to be independent of j, which greatly simplifies the treatment of the system of equations for the $\lambda_j(t)$. These are

$$\begin{aligned} \frac{d\lambda_2(t)}{dt} &= -\psi(t)\lambda_2(t), \\ \frac{d\lambda_{j+1}(t)}{dt} &= \psi(t)(\lambda_j(t) - \lambda_{j+1}(t)), \quad 2 \leqq j \leqq N-2, \\ \frac{d\lambda_N(t)}{dt} &= \psi(t)\lambda_{N-1}(t). \end{aligned} \tag{IV-82}$$

This familiar set of equations leads to a Poissonian type of distribution for the λ_j

$$\begin{aligned} \lambda_j(t) &= h(t) * e^{-w(t)} \frac{w(t)^{j-2}}{(j-2)!}, \quad 2 \leqq j \leqq N-1, \\ \lambda_N(t) &= h(t) * e^{-w(t)} \sum_{i=N-2}^{\infty} \frac{w(t)^i}{i!}, \end{aligned} \tag{IV-83}$$

where $h(t)$ is the enzyme arrival distribution defined earlier, $*$ is the convolution operator and

$$w(t) = \int_0^t \psi(t)\, dt. \tag{IV-84}$$

The probability that no growth has occurred for a given template is just $\lambda_0(t) = 1 - \int_0^t h(t)\, dt$. One can then compute the conversion (C), number average degree of polymerization (P_n) and weight average degree of polymerization (P_w) in the usual fashion from the moments

$$\sum_{j=2}^{N} j\lambda_j, \qquad \sum_{j=2}^{N} j^2\lambda_j,$$

so that

$$C = \frac{\sum_{j=2}^{N} j\lambda_j}{N}, \quad P_n = \frac{\sum_{j=2}^{N} j\lambda_j}{\sum_{j=2}^{N} \lambda_j}, \quad P_w = \frac{\sum_{j=2}^{N} j^2\lambda_j}{P_n}. \tag{IV-85}$$

The interesting problem then is the determination of the transition probability $\psi(t)$.

Clearly there are three independent events which must take place in order for each of the daughter helices to increase their length by one base pair:

(1) An empty template site immediately adjacent to the growing chains must be available,

(2) There must be a monomer unit present in this site through diffusion,

(3) The polymerization, that is incorporation, of this unit in the growing chain must take place.

The probability for the first of these events can be written in the form $1 - \phi_0(t)$, where $\phi_0(t)$ is the probability that at time t there are no unbound base pairs available. Since a first order diffusion process has been assumed, the probability denoted by $p(t)$ that a monomer unit has diffused to any position along the template is simply $p(t) = 1 - \exp(-k_{\text{diff}}t)$. The probability that the adjacent monomer will be incorporated in the interval $[t, t + dt]$ is just $k_{\text{pol}}\,dt$, so that we have finally for the transition probability in this interval

$$\psi(t)dt = k_{\text{pol}}p(t)(1 - \phi_0(t))dt. \tag{IV-86}$$

If the unwinding rate k_0 is large compared with k_{pol} then clearly ϕ_0 will be very small and $\psi(t)$ reduces to $k_{\text{pol}}p(t)$ which leads immediately to a simple explicit solution of the problem. In the contrary case one must find $\phi_0(t)$ which it turns out requires a complete description of the kinetics of the unwinding process. For this purpose one introduces the quantities $\phi_k(t)$, $k = 0, 1, \cdots, L$, (ϕ_0 having already been defined) which give the probability that there are k successive pairs of unbound template sites at time t. The index k is defined relative to the moving enzyme and replicating system; for example, $k = 0$ always refers to the position just ahead of the growing daughter helices. Using the $\phi_k(t)$ one can immediately obtain the function $l(t)$ (see Figure 10) which gives the expected length of the region of unbound base pairs as

$$l(t) = \sum_{k=1}^{L} k\phi_k(t). \tag{IV-87}$$

To describe the fluctuations of the length of the region it is necessary to calculate the second moment $\sum_{k=1}^{L} k^2\phi_k(t)$. To correspond to the assumption that the initiation of polymerization is by means of a dimer, it is assumed that $\phi_2(0) = 1$ and $\phi_k(0) = 0$ for all other k. Thus, from Equation (IV-87), $l(0) = 2$. The differential equations for the ϕ_k are considerably more complicated than those for the λ_j, but they are formulated in the same way by consideration of the mechanisms which affect the length of the region of unbound base pairs. For example, for the values of k satisfying $c + 1 \leqq k \leqq L - c$, one finds

$$\frac{d\phi_k(t)}{dt} = k_0 \sum_{p=1}^{c} \phi_{k-p}(t) - (ck_0 + k_{\text{pol}}\,p(t))\,\phi_k(t) + k_{\text{pol}}p(t)\,\phi_{k+1}(t). \tag{IV-88}$$

Each of the terms on the right in Equation (IV–88) can be understood physically as follows. The first sum represents the c ways that k unbound base pairs can be obtained from $k-1$, $k-2, \cdots, k-c$ unbound pairs at the previous instant of time. The second term represents ways of losing a region of k unbound base pairs through further unwinding (which can occur in c independent ways corresponding to the c pairs ahead of the k unbound pair) or through "using up" one of the unbound template sites by polymerization. The transition probability for this is $k_{\text{pol}}p(t)$ and not $k_{\text{pol}}p(t)(1-\phi_0(t))$, since for the values of k being considered ($c+1 \leqq k \leqq L-c$) we can be assured of at least two empty template sites (c being always $\geqq 1$). The last term represents a positive contribution to the formation of a region of length k from one of length $k+1$ through polymerization. Similar differential equations can be written for other regions of the index k. In each case the equation is linear (see (IV–88) for example) but with variable coefficients, and a closed solution is possible only in special cases (see [128]).

One such situation is when $c=1$ and t is taken large enough for $p(t)$ to be replaced by its asymptotic value k_{pol}. The system of equations for the ϕ_k in this case is similar to others which arise in a variety of stochastic models (see [24]). In fact the problem then is formally equivalent to a single-server queuing problem [114] where the function $l(t)$ gives the length of the "queue" and the polymerization process is "served" by unwinding the parent helix.

In the general case for any c and variable coefficients a general numerical solution is quite readily obtained [128] permitting a complete evaluation of the effect of all parameters on the kinetics. It turns out that the critical rate parameter is the dimensionless ratio $\kappa \equiv k_{\text{pol}}/k_0$ and this together with the quantity c provide the most interesting variables to explore in the numerical calculations. We shall give a few typical results from [128] here for the case when $k_e/k_{\text{diff}} = 0.5$, $k_{\text{pol}}/k_{\text{diff}} = 100$ and $L = 15$.

In Figure 11 is plotted the dispersion ratio P_w/P_n for the DNA polymerization process as a function of the percent conversion. Considering first the four curves for $c=1$ and various κ values one observes that the distribution is narrowest for the larger κ, that is when the rate of the polymerization process is large compared to that of the unwinding process. In this case these two processes are highly coupled and the replication is hindered by a relatively slow unwinding of the the parent helix. Figure 11 shows that greater homogeneity is obtained through the action of the unwinding mechanism as a regulation for the replication. Looking now at the curve for $c=2$, $\kappa = 10.0$ we see that increasing c quite naturally provides more available template sites and therefore broadens the distribution for a fixed value of κ.

The time dependent competition between the unwinding and replicating mechanisms in this model can most conveniently be described in terms of the function $l(t)$ defined by Equation (IV–87). When values of $l(t)$ are large the replication proceeds unhindered; when $l(t) < 1$ replication is at least temporarily halted.

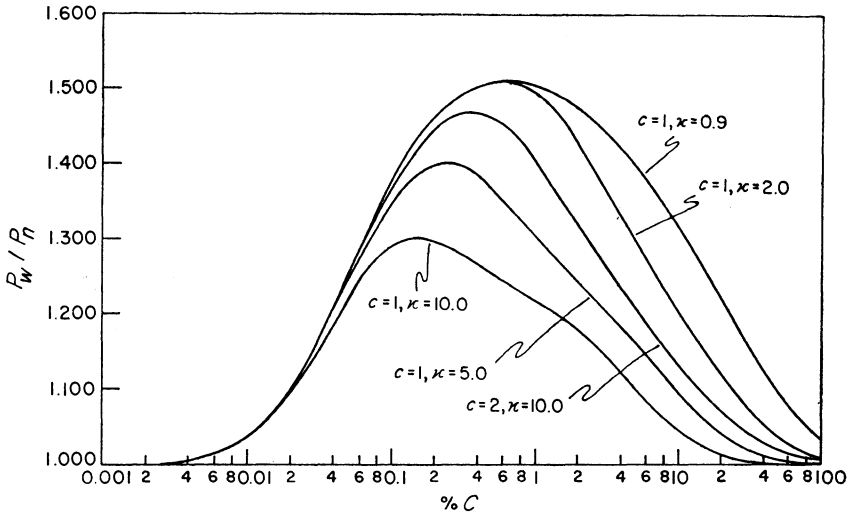


Figure 11
Ratio of weight to number average degree of polymerization against C for $L = 15$ and various κ and c values

The dependence of $l(t)$ on the conversion for $c = 1$ and various κ values is shown in Figure 12. In each case there is an increase in l from its initial value to a maxi-

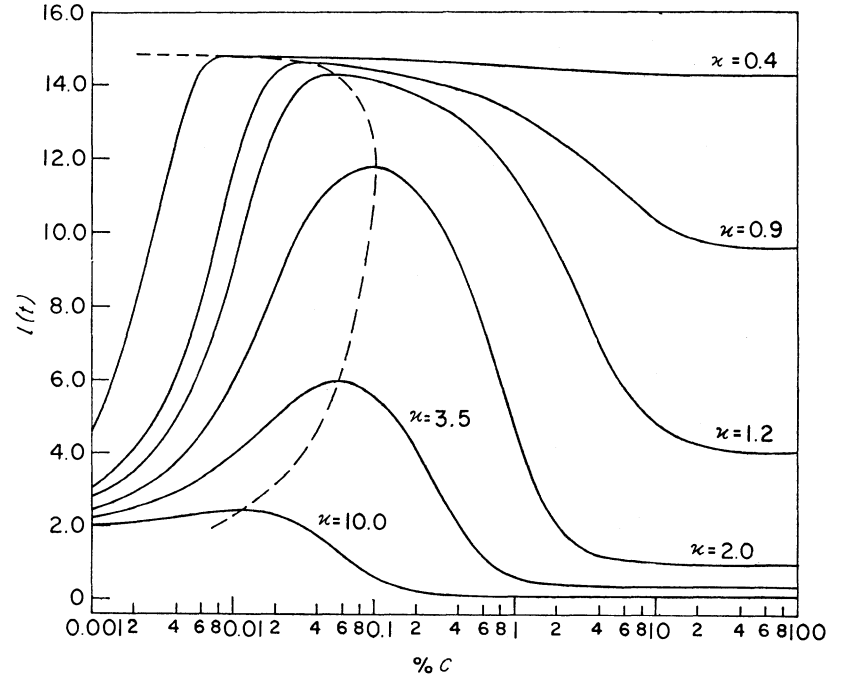


Figure 12
Expected number of template sites available for replication against C for $L = 15$, $c = 1$ and various κ

mum whose magnitude and location depend upon κ (see the dotted line in Figure 12. After reaching its maximum, l declines, the more rapidly the larger the κ, and this effect depends critically on κ particularly in the region about $\kappa = 1.0$ (when k_{pol} and k_0 are essentially the same). Thus for the larger κ (say, $\kappa > 2$) there is a brief moment during the early stages of replication where the open template region is large, but then the relatively rapid polymerization process "catches up" with the slow unwinding and the length of the open region sharply diminishes. For small κ the maximum l achieved is essentially the length of the effective region of the enzyme L (which equals 15 in this case). For $\kappa = 0.4$ this maximum is maintained throughout the replication, and hence the unwinding and polymerization processes are effectively uncoupled. As κ increases the maximum achieved is reduced to about 12 for $\kappa = 2.0$ and finally to 2.4 for $\kappa = 10.0$. The condition $\kappa = 2.0$ is critical for the unwinding as can be observed from Figure 12, both in regard to the rapid decline of l from its maximum and the asymptotic value of unity. For all larger κ, l falls below one and the polymerization is on the average inhibited during virtually the entire replication process.

The dependence of the function l on c is depicted in Figures 13a and 13b for $\kappa = 2.0$ and 10.0, respectively. In the former the effect of increasing c is almost completely present already for $c = 2$ when the situation is strikingly different from $c = 1$. Thus for $\kappa = 2.0$ a value of $c = 2$ is more than sufficient to uncouple the polymerization and unwinding mechanisms. For $\kappa = 10.0$ however (Figure 13b), the effect of increasing c is more gradual, and the polymerization is substantially hindered when $c < 4$. In this case the critical asymptotic value of unity occurs between $c = 2$ and $c = 3$. It is interesting to note in this connection that for typical DNA systems experimental evidence suggests that c is on the order of 5. Zimmerman and Simha have also found that the parameter L has little effect on the results as long as it is larger than some small minimal value, say between 5 and 10. This would seem to support the current belief that the number of active enzyme sites on the template is quite small.

In summary, calculations using this model clearly indicate how the unwinding of the DNA parent can sensitively influence the replication of daughter helices. This may well be the major means for the enzymatic control of DNA replication and thus protein synthesis in the cell.

IV.F. **Miscellaneous applications**

In this last section we wish to describe very briefly several additional applications. For one reason or another (mostly space) it was decided not to devote a whole section to each one, but they are interesting and important enough not to be omitted.

a) *Theory of nonrandom degradation of linear chain molecules*

There have been a large number of papers published (see [115] for earlier references) on the theory of degradation or depolymerization of long chain mole-

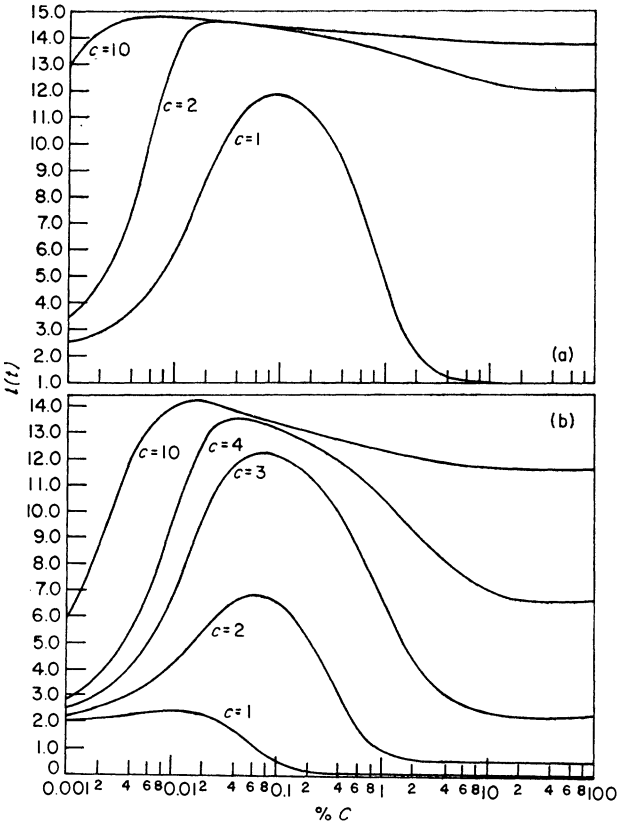


Figure 13
Expected number of template sites available for replication against C for $L = 15$ and various c: (a) $\kappa = 2.0$, (b) $\kappa = 10.0$

cules. Under the action of heat, light, ultrasonics, or suitable chemical reagents, polymer molecules will degrade or break up. An important problem in polymer chemistry is to study the kinetics of the process and the final distribution of sizes. Early work assumed that all the initial polymer molecules had the same degree of polymerization and that the reactivity of every bond in a molecule is the same. It can be argued that the first restriction is not too important, but for chemical reasons the second assumption can be quite unsatisfactory. Over the years these conditions have been relaxed, and we refer to Amemiya [2], [3] for the solutions to the rate equations for this process in which the initial distribution of lengths is arbitrary and the rupture of a bond is non-random. The results however are long and formal, and to my knowledge have not been studied numerically or compared to experiment.

b) *Multiple zone reactions*

In certain physical systems reactions may proceed in a number of small isolated zones, but the experimental observation is the overall chemical change. An ex-

ample is the creation by irradiation of free radicals in polymers, which are trapped in the solid state at temperatures so low that reaction is impossible. By then heating the solid to a higher temperature the free radicals acquire sufficient energy to overcome the diffusional barriers for reaction and recombination begins. The physical picture is equivalent to having a number of bottles containing reaction mixtures of varying, small, initial concentrations and in which all the reactions start at the same time. If the reaction in each bottle is bimolecular, say, will the observed rate of decrease of the *total* number of reactant molecules be second-order? This type of problem is discussed by Dole and Inokuti [29], who found that if the initial concentrations in the reaction zones are random, the overall observed reaction rate is second-order. In other cases, they found, a transition from overall second-order to overall first-order as the reaction proceeded.

c) *Nucleation theory*

A vapor, when compressed to the point where its pressure exceeds its vapor pressure at that temperature, will condense to form liquid droplets, so that the final stable pressure is just the equilibrium vapor pressure. This condensation usually and readily takes place on dust particles, the walls, or ions formed by extraneous cosmic radiation or the like. Under extremely clean and ion-free conditions, however, it is possible to avoid condensation and achieve a metastable state in which the actual pressure of the vapor is greater than its equilibrium vapor pressure at that temperature Such a state is possible since the dust or ion nuclei on which the vapor molecules readily condense and grow are absent, and vapor molecules must form clusters of themselves to act as nuclei. Such a process is called homogeneous nucleation. Homogeneous nucleation theory has been formulated as a birth and death process in which the states of the system correspond to specified numbers of molecules in a cluster. The transition probabilities for this process are not linear or quadratic, but fractional powers. This seems to complicate matters enormously and most treatments assume a steady-state condition. Recently, however, several papers have appeared which explicitly treat the non-steady state behavior. We refer mainly to Courtney [23] who has solved a 100 or so difference-differential birth and death equations numerically on a computer. He was then able to study the effect of the steady-state assumption on classical homogeneous nucleation theory [31], [61]. We also refer to Andres and Boudart [4] who calculated the mean time to attain steady-state by a method similar to that of Montroll and Shuler [92] given in Section IV.D. We lastly point out the work of Goodrich [45] who treated nucleation formally as a birth and death process and was able to calculate lag times. This work constitutes perhaps the most complete treatment of nucleation from a stochastic standpoint and is of great interest. In view of the complex nature of the rate equations here, this is an example of a system in which approximate techniques can be quite useful.

d) *Statistical thermodynamics*

It was mentioned in the introduction that one of the reasons for formulating stochastic models for various processes was to seek an understanding of non-equilibrium or irreversible thermodynamics. In a series of papers by Hill [54]–[60], entitled "Studies in irreversible thermodynamics", he has formulated a stochastic model for a simple statistical mechanical system (lattice gas) immersed in a heat bath. Rate equations are derived and solved for the means and variances of the stochastic variables, and these are used to study the validity of the usual force-flux equations and the reciprocal relations of irreversible thermodynamics. He has also found certain restrictions concerning the relative rates of attainment of equilibrium with the surroundings and with internal processes. Statistical mechanics is used to provide the equilibrium properties of the model system and the connection between chemical potentials and kinetic parameters. He then extends the lattice model to one that can exchange molecules with two heat baths and applies it to membrane transport phenomena, of great interest in biology. By means of the exactly solvable model, Hill is able to study the thermodynamics of membrane transport. In one of the papers in this series [54] he introduces the idea of a diagrammatic representation of steady state fluxes for unimolecular systems. Work of a similar nature has been published by Ishida [67] who tries to formulate stochastically the nonequilibrium thermodynamics of chemical reactions. He shows that the relation between entropy and fluctuation is obtainable from such stochastic considerations.

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Note added in proof:

During the time since this review was written (April 1967) several additional papers have appeared, to which we refer by simply listing them below. Professor Prékopa kindly drew attention to the second and third references.

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Stochastic Simulation of Chemical Kinetics

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tau-leaping, master equation, Langevin equation, stiff systems

Abstract

Stochastic chemical kinetics describes the time evolution of a well-stirred chemically reacting system in a way that takes into account the fact that molecules come in whole numbers and exhibit some degree of randomness in their dynamical behavior. Researchers are increasingly using this approach to chemical kinetics in the analysis of cellular systems in biology, where the small molecular populations of only a few reactant species can lead to deviations from the predictions of the deterministic differential equations of classical chemical kinetics. After reviewing the supporting theory of stochastic chemical kinetics, I discuss some recent advances in methods for using that theory to make numerical simulations. These include improvements to the exact stochastic simulation algorithm (SSA) and the approximate explicit tau-leaping procedure, as well as the development of two approximate strategies for simulating systems that are dynamically stiff: implicit tau-leaping and the slow-scale SSA.

1. INTRODUCTION

Reaction-rate equation (RRE): the set of coupled, first-order, ordinary differential equations traditionally used to describe the time evolution of a well-stirred chemical system

The most accurate way to depict the time evolution of a system of chemically reacting molecules is to do a molecular dynamics simulation, meticulously tracking the positions and velocities of all the molecules, and changing the populations of the species appropriately whenever a chemical reaction occurs. Chemical reactions in this approach are viewed as distinct, essentially instantaneous physical events, and they are generally of two elemental types: unimolecular, occurring as a result of processes internal to a single molecule, and bimolecular, occurring as a result of a collision between two molecules. (Trimolecular and higher order reactions are approximate representations of sequences of two or more elemental reactions.)

From a classical mechanics viewpoint, one might suppose that such a system is deterministic, in that a given initial state always leads to the same state at some specified later time. There are three reasons why this is not so: First, even if the system evolved deterministically with respect to the positions, velocities, and molecular populations of the species, it would not evolve deterministically with respect to the species populations alone. Second, quantum indeterminacy unavoidably enters; e.g., in a unimolecular reaction we can never know exactly when a molecule will transform itself into a different isomeric form. Third, chemical systems are usually not mechanically isolated; rather, they are in contact with a heat bath, whose essentially random perturbations keep the system in thermal equilibrium at some temperature.

In view of the fact that molecular populations in a chemically reacting system are integer variables that evolve stochastically, it is remarkable that chemical kinetics has traditionally been analyzed using a mathematical formalism in which continuous (real) variables evolve deterministically: Traditional chemical kinetics holds that in a well-stirred, thermally equilibrated chemical system, the number of molecules X_i of each chemical species S_i ($i = 1, \ldots, N$) evolves in time according to a set of coupled ordinary differential equations (ODEs) of the form

$$\frac{dX_i}{dt} = f_i(X_1, \ldots, X_N) \quad (i = 1, \ldots, N) \tag{1}$$

where the functions f_i are inferred from the specifics of the various reactions. This set of equations is called the reaction-rate equation (RRE). It is usually expressed in terms of the concentration variables $Z_i \equiv X_i/\Omega$, where Ω is the system volume, but that scalar transformation is not important here. Even more remarkable is that for systems of test-tube size or larger, the RRE seems to work quite well. But if the system is small enough that the molecular populations of at least some of the reactant species are not too many orders of magnitude larger than one, discreteness and stochasticity may play important roles. Whenever that happens, and it often does in cellular systems in biology (1–7), Equation 1 does not accurately describe the system's true behavior.

Stochastic chemical kinetics attempts to describe the time evolution of a well-stirred chemically reacting system in a way that takes honest account of the system's discreteness and stochasticity. In this chapter I briefly review the theoretical foundations of stochastic chemical kinetics and then describe some recent advances in numerical-simulation strategies that are supported by this theory.

2. STOCHASTIC CHEMICAL KINETICS: THE CHEMICAL MASTER EQUATION AND THE STOCHASTIC SIMULATION ALGORITHM

State-change vector: the change in the vector of the species' molecular populations induced by a single occurrence of a particular reaction

Propensity function: the function whose product with dt gives the probability that a particular reaction will occur in the next infinitesimal time dt

Let us consider a well-stirred system of molecules of N chemical species $\{S_1, \ldots, S_N\}$, which interact through M chemical reactions $\{R_1, \ldots, R_M\}$. We assume that the system is confined to a constant volume Ω and is in thermal (but not chemical) equilibrium at some constant temperature. We let $X_i(t)$ denote the number of molecules of species S_i in the system at time t. Our goal is to estimate the state vector $\mathbf{X}(t) \equiv (X_1(t), \ldots, X_N(t))$, given that the system was in state $\mathbf{X}(t_0) = \mathbf{x}_0$ at some initial time t_0.

The justification for the tacit assumption that we can describe the system's state by specifying only the molecular populations, ignoring the positions and velocities of the individual molecules, lies in the conditions responsible for the system being well stirred. The fundamental assumption being made is that the overwhelming majority of molecular collisions that take place in the system are elastic (nonreactive), and further that the net effect of these elastic collisions is twofold: First, the positions of the molecules become uniformly randomized throughout Ω; second, the velocities of the molecules become thermally randomized to the Maxwell-Boltzmann distribution. To the extent that this happens, we can ignore the nonreactive molecular collisions, the simulation of which would occupy most of the computation time in a molecular dynamics simulation, and concern ourselves only with events that change the populations of the chemical species. This simplifies the problem enormously.

The changes in the species populations are of course a consequence of the chemical reactions. Each reaction channel R_j is characterized mathematically by two quantities. The first is its state-change vector $\boldsymbol{\nu}_j \equiv (\nu_{1j}, \ldots, \nu_{Nj})$, where ν_{ij} is the change in the S_i molecular population caused by one R_j reaction, so if the system is in state $\mathbf{x}$ and one R_j reaction occurs, the system immediately jumps to state $\mathbf{x} + \boldsymbol{\nu}_j$. The other characterizing quantity for R_j is its propensity function a_j, which is defined so that

$$a_j(\mathbf{x})\, dt \triangleq \text{the probability, given } \mathbf{X}(t) = \mathbf{x}, \text{ that one } R_j \text{ reaction will occur somewhere inside } \Omega \text{ in the next infinitesimal time interval } [t, t + dt). \quad (2)$$

Definition 2 can be regarded as the fundamental premise of stochastic chemical kinetics because everything else in the theory follows from it via the laws of probability. The physical rationale for Definition 2 for unimolecular and bimolecular reactions can be briefly summarized as follows.

If R_j is the unimolecular reaction $S_1 \rightarrow$ product(s), the underlying physics, which is usually quantum mechanical, dictates the existence of some constant c_j, such that $c_j dt$ gives the probability that any particular S_1 molecule will so react in the next infinitesimal time dt. It then follows from the laws of probability that if there are currently x_1 S_1 molecules in the system, the probability that some one of them will undergo the R_j reaction in the next dt is $x_1 \cdot c_j dt$. Thus the propensity function in Equation 2 is $a_j(\mathbf{x}) = c_j x_1$.

If R_j is a bimolecular reaction of the form $S_1 + S_2 \rightarrow$ product(s), kinetic theory arguments and the well-stirred condition together imply the existence of a constant c_j,

Chemical master equation (CME): the equation that determines the probability that each species will have a specified molecular population at a given future time

such that $c_j dt$ gives the probability that a randomly chosen pair of S_1 and S_2 molecules will react according to R_j in the next infinitesimal time dt (8–11). The probability that some one of the $x_1 x_2$ S_1-S_2 pairs inside Ω will react according to R_j in the next dt is therefore $x_1 x_2 \cdot c_j dt$, and that implies that the propensity function in Equation 2 is $a_j(\mathbf{x}) = c_j x_1 x_2$. If instead the bimolecular reaction had been $S_1 + S_1 \rightarrow$ product(s), we would have reckoned the number of distinct S_1 molecular pairs as $\frac{1}{2}x_1(x_1 - 1)$, and so obtained for the propensity function $a_j(\mathbf{x}) = c_j \frac{1}{2} x_1(x_1 - 1)$.

Evaluating c_j completely from first principles is a challenging task, requiring specific assumptions to be made about how the reaction R_j physically occurs. Unimolecular c_j's and bimolecular c_j's are quite different from each other. For example, whereas a unimolecular c_j is independent of the system volume Ω, a bimolecular c_j is inversely proportional to Ω, reflecting the fact that two reactant molecules will have a harder time finding each other inside a larger volume. It turns out that for a unimolecular reaction, c_j is numerically equal to the reaction-rate constant k_j of conventional deterministic chemical kinetics, whereas for a bimolecular reaction, c_j is equal to k_j/Ω if the reactants are different species, or $2k_j/\Omega$ if they are the same species (8–11). However, these results should not be taken to imply that the mathematical forms of the propensity functions are just heuristic extrapolations of the reaction rates of deterministic chemical kinetics. The propensity functions are grounded in molecular physics, and the formulas of deterministic chemical kinetics are approximate consequences of the formulas of stochastic chemical kinetics, not the other way around.

Although the probabilistic nature of Equation 2 precludes making an exact prediction of $\mathbf{X}(t)$, we might hope to infer the probability

$$P(\mathbf{x}, t \mid \mathbf{x}_0, t_0) \stackrel{\Delta}{=} \text{Prob}\{\mathbf{X}(t) = \mathbf{x}, \text{ given } \mathbf{X}(t_0) = \mathbf{x}_0\}. \tag{3}$$

It is not difficult to derive a time-evolution equation for $P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$ by applying the laws of probability to the fundamental premise (Equation 2). The result is the chemical master equation (CME) (10–12):

$$\frac{\partial P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)}{\partial t} = \sum_{j=1}^{M} [a_j(\mathbf{x} - \boldsymbol{\nu}_j) P(\mathbf{x} - \boldsymbol{\nu}_j, t \mid \mathbf{x}_0, t_0) - a_j(\mathbf{x}) P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)]. \tag{4}$$

In principle, the CME completely determines the function $P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$. But a close inspection reveals that the CME is actually a set of coupled ODEs, with one equation for every possible combination of reactant molecules. It is therefore not surprising that the CME can be solved analytically for only a few simple cases, and even numerical solutions are prohibitively difficult in other cases.

It is also difficult to infer anything about the behavior of averages such as $\langle h(\mathbf{X}(t)) \rangle \equiv \sum_{\mathbf{x}} h(\mathbf{x}) P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$ if any of the reaction channels are bimolecular. For example, if we multiply the CME (Equation 4) through by $\mathbf{x}$ and then sum over all $\mathbf{x}$, we get

$$\frac{d\langle \mathbf{X}(t) \rangle}{dt} = \sum_{j=1}^{M} \boldsymbol{\nu}_j \langle a_j(\mathbf{X}(t)) \rangle. \tag{5}$$

If all the reactions were unimolecular, the propensity functions would all be linear in the state variables, and we would have $\langle a_j(\mathbf{X}(t)) \rangle = a_j(\langle \mathbf{X}(t) \rangle)$, so Equation 5 would

reduce to a closed ODE for the first moment $\langle \mathbf{X}(t) \rangle$. But if any reaction is bimolecular, the right-hand side of Equation 5 will contain at least one quadratic moment of the form $\langle X_i(t) X_{i'}(t) \rangle$, and Equation 5 would then be merely the first of an infinite, open-ended set of equations for all the moments.

In the hypothetical case in which there are no fluctuations—i.e., if $\mathbf{X}(t)$ were a deterministic or sure process—we would have $\langle h(\mathbf{X}(t)) \rangle = h(\mathbf{X}(t))$ for all functions h, and Equation 5 would then reduce to

$$\frac{d\mathbf{X}(t)}{dt} = \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\mathbf{X}(\mathbf{t})). \tag{6}$$

This is precisely the RRE (Equation 1), with the functions $f_i(\mathbf{X}) \equiv \sum_j \nu_{ij} a_j(\mathbf{X})$ now explicitly rendered. As a set of coupled ODEs, Equation 6 characterizes $\mathbf{X}(t)$ as a continuous, deterministic process. But while this shows that the RRE would be valid if all fluctuations could be ignored, it does not provide any justification for doing that. Below I discuss how, and under what conditions, the discrete, stochastic CME description approximately gives rise to the continuous, deterministic RRE description.

Because the CME (Equation 4) can rarely be solved for the probability density function of $\mathbf{X}(t)$, perhaps we should look for a way to construct numerical realizations of $\mathbf{X}(t)$, i.e., simulated trajectories of $\mathbf{X}(t)$ versus t. This is not the same as solving the CME numerically, as that would give us the probability density function of $\mathbf{X}(t)$ instead of a random sample of $\mathbf{X}(t)$. The key to generating simulated trajectories of $\mathbf{X}(t)$ is not the function $P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$, but rather a new probability function $p(\tau, j \mid \mathbf{x}, t)$, which is defined as follows:

$$p(\tau, j \mid \mathbf{x}, t)\, d\tau \;\triangleq\; \text{the probability, given } \mathbf{X}(t) = \mathbf{x}, \text{ that the next reaction in the system will occur in the infinitesimal time interval } [t + \tau, t + \tau + d\tau), \text{ and will be an } R_j \text{ reaction.} \tag{7}$$

Formally, this function is the joint probability density function of the two random variables time to the next reaction (τ) and index of the next reaction (j), given that the system is currently in state $\mathbf{x}$. It is not difficult to derive an exact formula for $p(\tau, j \mid \mathbf{x}, t)$ by applying the laws of probability to the fundamental premise (Equation 2). The result is (8–11)

$$p(\tau, j \mid \mathbf{x}, t) = a_j(\mathbf{x}) \; \exp(-a_0(\mathbf{x})\, \tau), \tag{8}$$

where

$$a_0(\mathbf{x}) \triangleq \sum_{j'=1}^{M} a_{j'}(\mathbf{x}). \tag{9}$$

Equation 8 is the mathematical basis for the stochastic simulation approach. It implies that τ is an exponential random variable with mean (and standard deviation) $1/a_0(\mathbf{x})$, while j is a statistically independent integer random variable with point probabilities $a_j(\mathbf{x})/a_0(\mathbf{x})$. There are several exact Monte Carlo procedures for generating samples of τ and j according to these distributions. Perhaps the simplest is the so-called direct method, which follows by applying the standard inversion generating method of Monte Carlo theory (11): We draw two random numbers r_1 and r_2 from the uniform

distribution in the unit interval, and take

$$\tau \;=\; \frac{1}{a_0(\mathbf{x})}\ln\left(\frac{1}{r_1}\right), \tag{10a}$$

$$j \;=\; \text{the smallest integer satisfying } \sum_{j'=1}^{j} a_{j'(\mathbf{x})} > r_2\, a_0(\mathbf{x}). \tag{10b}$$

Stochastic simulation algorithm (SSA): a Monte Carlo procedure for numerically generating time trajectories of the molecular populations in exact accordance with the CME

With this generating method (or any mathematically equivalent one), we have the following stochastic simulation algorithm (SSA) for constructing an exact numerical realization of the process $\mathbf{X}(t)$ (8, 9):

0. Initialize the time $t = t_0$ and the system's state $\mathbf{x} = \mathbf{x}_0$.
1. With the system in state $\mathbf{x}$ at time t, evaluate all the $a_j(\mathbf{x})$ and their sum $a_0(\mathbf{x})$.
2. Generate values for τ and j using Equations 10a,b (or their equivalent).
3. Effect the next reaction by replacing $t \leftarrow t + \tau$ and $\mathbf{x} \leftarrow \mathbf{x} + \boldsymbol{\nu}_j$.
4. Record $(\mathbf{x}, t)$ as desired. Return to Step 1, or else end the simulation.

The $\mathbf{X}(t)$ trajectory produced by the SSA may be thought of as a stochastic version of the trajectory that would be obtained by solving the RRE (Equation 6). But note that the time step τ in the SSA is exact and not a finite approximation to some infinitesimal dt, as is the time step in a typical ODE solver. If it is found that every SSA-generated trajectory is practically indistinguishable from the RRE trajectory, then we may conclude that microscale randomness is ignorable. But if the SSA trajectories are found to deviate significantly from the RRE trajectory, or from each other, then we must conclude that microscale randomness is not ignorable, and the deterministic RRE does not provide an accurate description of the system's true behavior.

Because the SSA and the CME are each derived without approximation from the fundamental premise (Equation 2), they are logically equivalent to each other. But even when the CME is intractable, the SSA is easy to implement; indeed, as a numerical procedure, the SSA is simpler than most procedures that are used to numerically solve the RRE (Equation 6). The catch is that the SSA is often very slow, essentially because it insists on simulating every individual reaction event. The mathematical reason for this slowness can be traced to the factor $1/a_0(\mathbf{x})$ in Equation 10a, which will be small if any reactant population is large.

To illustrate the foregoing ideas, consider the simple reaction

$$S \xrightarrow{c} \emptyset. \tag{11}$$

The propensity function for this reaction is $a(x) = c\,x$, and the state-change vector is $\nu = -1$. The RRE (Equation 6) reads $dX/dt = -c\,X$, and the solution to this ODE for the initial condition $X(0) = x_0$ is

$$X(t) = x_0 \mathrm{e}^{-ct} (\text{RREsolution}). \tag{12}$$

The CME (Equation 4) reads

$$\frac{\partial}{dt} P(x, t \mid x_0, 0) = a(x+1)P(x+1, t \mid x_0, 0) - a(x)P(x, t \mid x_0, 0).$$

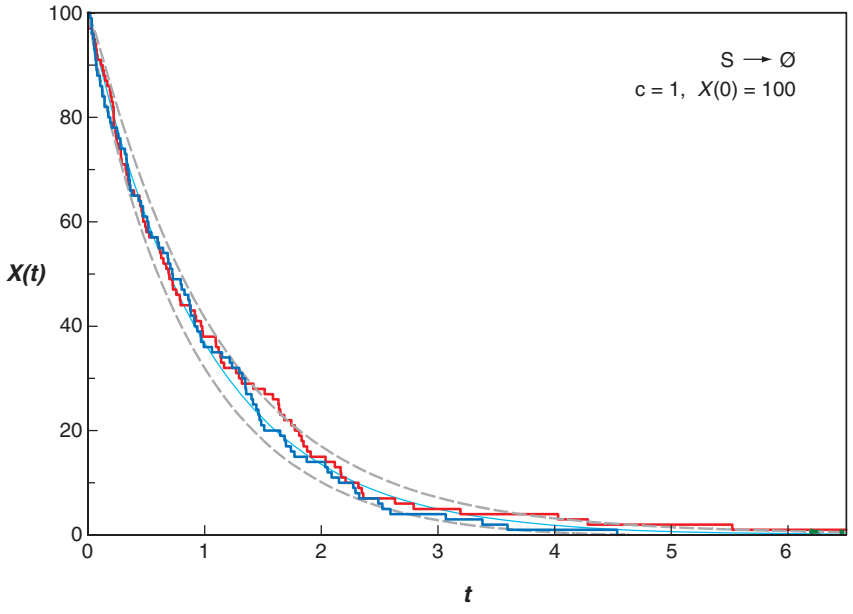

Figure 1

Simulating the simple isomerization reaction (Equation 11). The thin light blue line shows the solution (Equation 12) of the reaction-rate equation (RRE). The two dashed gray lines show the one-standard-deviation envelope $\langle X(t)\rangle \pm \mathrm{sdev}\{X(t)\}$ of Equations 14a,b as predicted by the solution of the chemical master equation (CME) (Equation 13). The red and blue jagged curves show the trajectories produced by two separate runs of the stochastic simulation algorithm (SSA).

Because $P(x_0 + 1, t \mid x_0, 0) \equiv 0$, we can solve this equation exactly by successively putting $x = x_0, x_0 - 1, \ldots, 0$. The result is

$$P(x, t \mid x_0, 0) = \frac{x_0!}{x!(x_0 - x)!} \mathrm{e}^{-cxt}(1 - \mathrm{e}^{-ct})^{x_0 - x} \quad (x = 0, \ldots, x_0), \tag{13}$$

which we recognize as the probability density function for the binomial random variable with mean and standard deviation

$$\langle X(t)\rangle = x_0 \mathrm{e}^{-ct}, \tag{14a}$$

$$\mathrm{sdev}\{X(t)\} = \sqrt{x_0 \mathrm{e}^{-ct}(1 - \mathrm{e}^{-ct})}. \tag{14b}$$

Note that $\langle X(t)\rangle$ is identical to the solution (Equation 12) of the RRE; this will always be so if all the propensity functions are linear in the populations, but not otherwise. The SSA for this reaction is simple: In state x at time t, we draw a unit-interval uniform random number r, increase t by $\tau = (1/ax)\ln(1/r)$, decrease x by 1, and then repeat. **Figure 1** shows numerical results for $c = 1$ and $x_0 = 100$.

3. ELABORATIONS ON AND IMPROVEMENTS TO THE STOCHASTIC SIMULATION ALGORITHM

The version of the SSA described above is the one originally presented in References 8 and 9. A number of earlier works applied similar if not equivalent procedures to specific model systems (13–19) but paid little attention to developing the supporting theory. In this section I focus on some later elaborations on and improvements to the SSA.

One elaboration of the SSA already noted in Reference 8 is an alternative to the direct method (Equation 10) for generating values of τ and j. Called the first-reaction method, it begins by drawing M random numbers $r_1, \ldots, r_M$ from the unit-interval uniform distribution and computing

$$\tau_{j'} = \frac{1}{a_{j'}(\mathbf{x})} \ln\left(\frac{1}{r_{j'}}\right) \quad (j' = 1, \ldots, M); \tag{15a}$$

then it takes

$$\left.\begin{array}{l} \tau = \text{the smallest of the } \{\tau_{j'}\} \\ j = \text{the index of the smallest } \{\tau_{j'}\} \end{array}\right\}. \tag{15b}$$

Heuristically, $\tau_1, \ldots, \tau_M$ are putative times to the next firings of the respective reaction channels; however, we accept only the earliest of those and discard the rest. It can be proved (8) that this procedure, like the direct method, generates values for τ and j in exact accord with the joint density function (Equation 8). However, if the system has many reaction channels, this method will be computationally less efficient than the direct method.

A generalization of the direct and first-reaction methods that includes both as special cases is L. Lok's (unpublished manuscript) first-family method. The M reactions are partitioned into L families $\{F_1, \ldots, F_L\}$ and then relabeled so that the M_l reactions in family F_l are $\{R_1^l, \ldots, R_{M_l}^l\}$. Each family F_l is then viewed as a pseudoreaction with propensity function $a_0^l(\mathbf{x}) \equiv \sum_{j=1}^{M_l} a_j^l(\mathbf{x})$. To generate the time τ to the next reaction event and the index pair (l, j) that identifies that reaction, we draw $L + 1$ random numbers $r_1, \ldots, r_{L+1}$ from the uniform distribution in the unit interval. We use the first L of these to compute

$$\tau_{l'} = \frac{1}{a_0^{l'}(\mathbf{x})} \ln\left(\frac{1}{r_{l'}}\right) \quad (l' = 1, \ldots, L); \tag{16a}$$

then we take

$$\left.\begin{array}{l} \tau = \text{the smallest of the } \{\tau_{l'}\} \\ l = \text{the index of the smallest } \{\tau_{l'}\} \end{array}\right\}, \tag{16b}$$

and finally

$$j = \text{the smallest integer satisfying } \sum_{j'=1}^{j} a_{j'}^l(\mathbf{x}) > r_{L+1}\, a_0^l(\mathbf{x}). \tag{16c}$$

Heuristically, Equations 16a,b generate the time step τ to, and the index l of, the next firing family, and Equation 16c then decides which reaction in F_l actually fires. It can be proved (L. Lok, unpublished manuscript) that this procedure generates values for τ and $j = (l, j)$ in exact accord with the joint density function (Equation 8). It reduces to the direct method if all the reactions are taken to be members of one family, and it reduces to the first-reaction method if each reaction is taken to be a family unto itself. For intermediate partitionings, the method may afford bookkeeping advantages when M is large.

A reformulation of the SSA that, for large N and M, significantly increases its speed as compared with the direct method is Gibson & Bruck's (20) next-reaction method.

Essentially a heavily revised version of the first-reaction method, the next-reaction method saves the putative next firing times of all reaction channels in an indexed binary tree priority queue, which is constructed so that the firing time of each parent node is always earlier than the firing times of its two daughter nodes. The time and index of the next occurring reaction are therefore always available at the top node of the queue. The indexing scheme and the binary-tree structure of the queue facilitate updating the queue as a result of changes caused by occurring reactions. With added effort, we can even make the next-reaction method consume only one uniform random number per additional reaction event, in contrast to the two required by the direct method. Although the next-reaction method can be significantly faster than the direct method, it is much more challenging to code. For more details, see References 20 and 21.

Lok & Brent (22) have developed a stochastic simulation software package called Moleculizer that uses a slightly simplified version of the next-reaction method, but with a unique twist: Reaction channels and species are introduced only when they are needed, and removed when they are not needed. The target application for Moleculizer is the simulation of the pheromone-response mechanism in yeast, a chemical system that entails a potentially enormous number of species and reaction channels. Lok showed that, at least when using the SSA, it is not necessary to introduce all the reactions and species at the beginning of a simulation, and for the yeast system in particular, a just-in-time introduction of the reactions and species makes feasible an otherwise infeasible simulation. Lok also observes that this just-in-time strategy cannot be used with the RRE, which is noteworthy because the RRE too becomes unwieldy when enormous numbers of species and reaction channels are involved; thus we have yet another reason for using stochastic simulation instead of deterministic simulation on biological systems. For further discussion of these points, see Reference 22.

Cao et al. (21) recently introduced a modified direct method that often makes the direct method competitive in speed with the next-reaction method. These authors observed that if the reaction channels are indexed so that reactions R_j with larger propensity functions are assigned lower index values j, then the average number of terms summed in the computation (Equation 10b) is minimized. The consequent gain in speed can be significant for systems with many reactions and a wide range of propensity function values, a common circumstance in biological models. The modified direct method starts off with a relatively short prerun using the direct method in which the average sizes of the propensity functions are assessed. Then it reindexes the reactions accordingly and resumes the simulation, at a usually much-greater speed. See Reference 21 for details.

McCollum et al. (23) have recently proposed a further improvement on the direct method in what they call the sorting direct method. Similar to the modified direct method, the sorting direct method seeks to index the reaction channels in order of decreasing values of their propensity functions so as to optimize the search in Equation 10b. But the sorting method does this dynamically, and without the need for a prerun, by using a simple bubble-up tactic: Whenever a reaction channel fires, the index of the firing channel is interchanged with the index of the next lower indexed channel

(if there is one). Doing this repeatedly tends to establish the desired index ordering. This tactic not only eliminates the prerun of the modified direct method, but it also accommodates any changes in the relative sizes of the propensity functions that might develop as the simulation proceeds.

H. Li & L.R. Petzold (unpublished manuscript) have recently proposed the logarithmic direct method, another novel twist on the direct method. Its strategy is to collect and store the partial sums of the propensity functions during the computation of the full sum a_0 in Equation 9. The value of j in Equation 10b can then be found rapidly by conducting a binary search over those partial sums. Although the logarithmic direct method (24) may not always result in as great a speed gain as the sorting direct method (23) or the optimized direct method (21), it can avoid a potential accuracy problem that may afflict those other two methods. Arranging the reaction indices in order of decreasing size of the propensity functions does make the linear search Equation 10b go faster, but it also makes that search potentially less accurate; e.g., if we were carrying k decimals in the sum on the left side of Equation 10b and the highest-indexed propensity function happened to be k orders of magnitude smaller than a_M, then numerical truncation results in R_M never firing at all. For maximal numerical accuracy in executing Equation 10b, reactions with smaller propensity functions should be assigned lower index values—just the opposite of what the modified and sorting direct methods do. The logarithmic direct method is not susceptible to this problem because it does not depend on any ordering scheme for the reaction indices; indeed, with the logarithmic direct method, the ordering could deliberately be arranged to achieve maximum accuracy. It might also be possible to overcome the inaccuracy problem by using Lok's first-family method, grouping reactions with very small propensities together into a family F_1 and all the other reactions into a family F_2: Most of the time the selection in Equation 16b falls to family F_2, but on those rare occasions when it falls to F_1, the subsequent search in Equation 16c is accomplished without involving the larger-valued propensity functions, so no truncation errors arise.

Improvements to the SSA along the lines described above are certainly beneficial, but any procedure that simulates every reaction event one at a time, no matter how efficiently it does that, will simply be too slow for many practical applications. This prompts us to look for ways to sacrifice some of the exactness of the SSA in return for greater simulation speed. One way of doing that is to use an approximate simulation strategy called tau-leaping.

Tau-leaping: an approximate way of accelerating the SSA in which each time step τ advances the system through possibly many reaction events

Leap condition: an accuracy-assuring restriction on tau-leaping that requires τ to be small enough that no propensity function changes by a significant amount

4. TAU-LEAPING: THE BRIDGE TO THE REACTION-RATE EQUATION

With the system in state $\mathbf{x}$ at time t, let us suppose there exists a $\tau > 0$ that satisfies the following leap condition: During $[t, t + \tau)$, no propensity function is likely to change its value by a significant amount. With $a_j(\mathbf{x})$ remaining essentially constant during $[t, t + \tau)$, it then follows from the fundamental premise (Equation 2) that the number of times reaction channel R_j fires in $[t, t + \tau)$ is a Poisson random variable with mean (and variance) $a_j(\mathbf{x})\,\tau$. Therefore, to the degree that the leap condition is

satisfied, we can approximately leap the system ahead by a time τ by taking (25, 26)

$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{P}_j(a_j(\mathbf{x})\tau)\boldsymbol{\nu}_j, \tag{17}$$

Chemical Langevin equation (CLE): a differential equation driven by zero-mean Gaussian noise that describes tau-leaping when the reactant populations are sufficiently large

where $\mathbf{x} = \mathbf{X}(t)$, and $\mathcal{P}_j(m_j)$ is a statistically independent Poisson random variable with mean (and variance) m_j.

Equation 17 is the basic tau-leaping formula. In the next section below I discuss how we can use it to perform faster stochastic simulations. But for now, let us suppose that τ is not only small enough to satisfy the leap condition, but also large enough that the expected number of firings of each reaction channel R_j during τ is $\gg 1$:

$$a_j(\mathbf{x})\,\tau \gg 1 \text{ for all } j = 1, \ldots, M. \tag{18}$$

Then, denoting the normal (Gaussian) random variable with mean m and variance σ^2 by $\mathcal{N}(m, \sigma^2)$, and invoking the mathematical fact that a Poisson random variable with a mean and variance that is $\gg 1$ can be approximated as a normal random variable with that same mean and variance, we can further approximate Equation 17 as

$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \mathcal{N}_j(a_j(\mathbf{x})\tau, a_j(\mathbf{x})\tau)\,\boldsymbol{\nu}_j = \mathbf{x} + \sum_{j=1}^{M} \left[a_j(\mathbf{x})\tau + \sqrt{a_j(\mathbf{x})\tau}\,\mathcal{N}_j(0,1)\right]\boldsymbol{\nu}_j.$$

The last step here invokes the well-known property of the normal random variable that $\mathcal{N}(m, \sigma^2) = m + \sigma\mathcal{N}(0, 1)$. Collecting terms gives us what is known as the chemical Langevin equation (CLE) or Langevin leaping formula (25),

$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} \boldsymbol{\nu}_j a_j(\mathbf{x})\tau + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\mathbf{x})}\,\mathcal{N}_j(0,1)\sqrt{\tau}, \tag{19}$$

where $\mathbf{x} = \mathbf{X}(t)$, and each $\mathcal{N}_j(0, 1)$ is a statistically independent normal random variable with mean 0 and variance 1. Again, this equation is valid only to the extent that during τ, no propensity function changes its value significantly, yet every reaction channel fires many more times than once. It is usually possible to find a τ that satisfies these opposing conditions if all the reactant populations are sufficiently large.

In the theory of continuous Markov processes, it can be shown that the CLE (Equation 19) can also be written in the white-noise form (25, 27)

$$\frac{d\mathbf{X}(t)}{dt} \doteq \sum_{j=1}^{M} \boldsymbol{\nu}_j\, a_j(\mathbf{X}(t)) + \sum_{j=1}^{M} \boldsymbol{\nu}_j \sqrt{a_j(\mathbf{X}(t))}\,\Gamma_j(t)\,. \tag{20}$$

Here the $\Gamma_j(t)$ are statistically independent Gaussian white-noise processes, satisfying $\langle \Gamma_j(t)\,\Gamma_{j'}(t')\rangle = \delta_{jj'}\,\delta(t-t')$, where the first delta function is Kronecker's and the second is Dirac's. Equation 20 is just another way of writing Equation 19; the two equations are mathematically equivalent. Equations of the form of Equation 20, with the right side the sum of a deterministic drift term and a stochastic diffusion term proportional to Gaussian white noise, are known as Langevin equations or stochastic differential equations. In most occurrences of Langevin equations in science and engineering applications, the form of the stochastic diffusion term is postulated ad hoc; here, however, it has been derived. Continuous Markov process theory also implies that

Thermodynamic limit: the infinite-population, infinite-volume, finite-concentration limit in which the stochastic CLE reduces (usually) to the deterministic RRE

the probability density function $P(\mathbf{x}, t \mid \mathbf{x}_0, t_0)$ of the random variable $\mathbf{X}(t)$ in the CLE Equations 19 and 20 obeys a well-defined partial differential equation called the chemical Fokker-Planck equation (CFPE). References 25, 27, and 28 give a derivation and discussion of the CFPE.

The thermodynamic limit is defined as the limit in which the species populations X_i and the system volume Ω all approach infinity, but in such a way that the species concentrations X_i/Ω stay constant. As this limit is approached, all propensity functions grow in direct proportion to the size of the system. This is obvious for a unimolecular propensity function of the form $c_j x_i$; for a bimolecular propensity function of the form $c_j x_i x_{i'}$, this follows because c_j is inversely proportional to Ω. Therefore, as the thermodynamic limit is approached, the term on the left side of the CLE (Equation 20) and the first term on the right side both grow like the system size, whereas the second term on the right grows more slowly as the square root of the system size. In the full thermodynamic limit, the last term becomes negligibly small compared with the other terms, and the CLE (Equation 20) reduces to the RRE (Equation 6). Thus we have derived the RRE from the fundamental stochastic premise (Equation 2). The approximations made in this derivation are schematized in **Figure 2**, which summarizes the theoretical structure of stochastic chemical kinetics (29).

5. THE EXPLICIT TAU-LEAPING SIMULATION ALGORITHM

The basic tau-leaping formula (Equation 17) suggests an obvious strategy for approximately doing stochastic simulations: In the current state $\mathbf{x}$, we first choose a value for τ that satisfies the leap condition. Next, we generate for each j a sample k_j of the Poisson random variable with mean $a_j(\mathbf{x})\,\tau$, by using, for example, the numerical procedure described in Reference 30. (Because the Poisson random numbers $k_1, \ldots, k_M$ are statistically independent, they could be generated simultaneously on M parallel processors, which would result in a substantial gain in computational speed.) Finally, we update the state from $\mathbf{x}$ to $\mathbf{x} + \sum_j k_j \boldsymbol{\nu}_j$. If the values generated for the k_j are sufficiently large, this approximate procedure will be faster than the exact SSA. But several practical issues need to be resolved to effectively implement this strategy: First, how can we estimate in advance the largest value of τ that satisfies the leap condition? Second, how can we ensure that the generated k_j-values do not cause some R_j to fire so many times that the population of some reactant is driven negative? Finally, how can we arrange it so that tau-leaping segues efficiently to the SSA?

The method originally suggested in Reference 26 for estimating the largest value of τ that satisfies the leap condition has undergone two successive refinements (31, 32). The latest τ-selection procedure (32) is not only more accurate than the earlier procedures, but also faster, especially if M is large. It computes the largest value of τ for which the estimated fractional change $\Delta_\tau a_j/a_j$ in each propensity function during τ is bounded by a user-specified accuracy-control parameter ε ($0 < \varepsilon \ll 1$). However, it does this in an indirect way: It chooses τ so that the estimated fractional change $\Delta_\tau x_i/x_i$ in each reactant population is bounded by an amount $\varepsilon_i = \varepsilon_i(\varepsilon, x_i)$ (except that no x_i is required to change by an amount less than one), where the functions

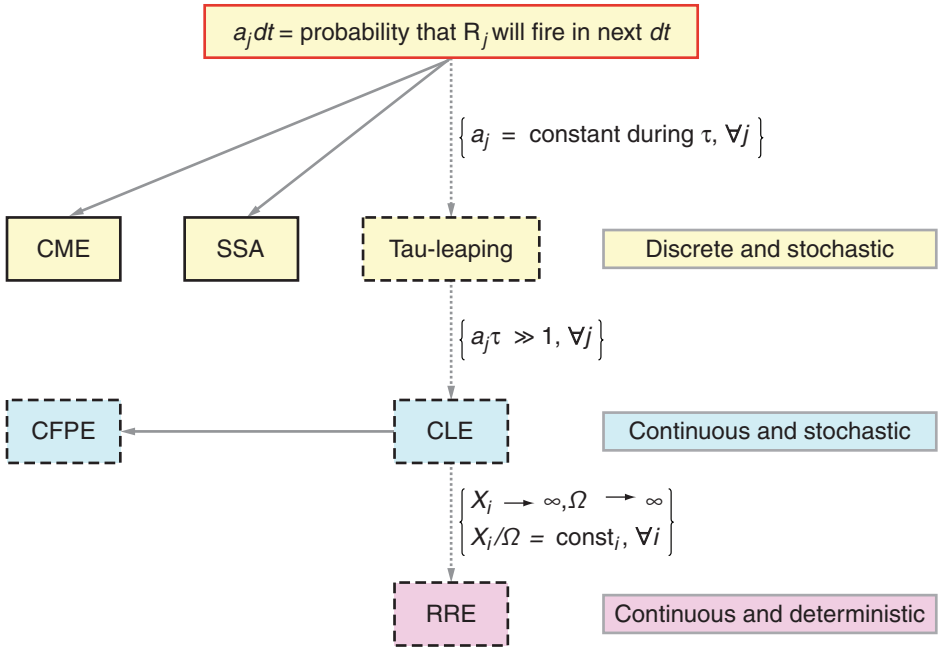

Figure 2

Logical structure of stochastic chemical kinetics. Everything follows from the fundamental premise at the top via the laws of probability theory. Inference routes that are exact are shown by solid arrows. Inference routes that are approximate are shown by dotted arrows, with the condition justifying the approximation indicated in braces immediately to the right. Solid-outlined boxes are exact results: the chemical master equation (CME) and the stochastic simulation algorithm (SSA). Dashed-outlined boxes are approximate results: the tau-leaping formula, the chemical Langevin equation (CLE), the chemical Fokker-Planck equation (CFPE), and the reaction-rate equation (RRE). The condition justifying the arguments leading from the fundamental premise to tau-leaping is called the leap condition, and the condition justifying the arguments leading from the CLE to the RRE is called the thermodynamic limit.

ε_i have been chosen so that $\Delta_\tau a_j/a_j$ for every j is then bounded by the stipulated amount ε. As is shown in Reference 32, the algebraic forms of the functions $\varepsilon_i(\varepsilon, x_i)$ that accomplish this are quite simple, and they can easily be inferred by inspection at the outset of the simulation. Enforcing the bound

$$|\Delta_\tau x_i| \leq \max\{\varepsilon_i x_i, 1\} \tag{21}$$

is accomplished by first noting from the basic tau-leaping formula (Equation 17) that

$$\Delta_\tau x_i \doteq \sum\nolimits_j \mathcal{P}_j(a_j\tau)\nu_{ij}.$$

Because the statistically independent Poisson random variables $\mathcal{P}_j(a_j\tau)$ have means and variances $a_j\tau$, the means and variances of $\Delta_\tau x_i$ are

$$\langle \Delta_\tau x_i \rangle \doteq \sum\nolimits_j \nu_{ij}(a_j\tau), \quad \text{var}\{\Delta_\tau x_i\} \doteq \sum\nolimits_j \nu_{ij}^2(a_j\tau). \tag{22}$$

Condition 21 is deemed to be adequately fulfilled if it is satisfied by both $\langle \Delta_\tau x_i \rangle$ and $\sqrt{\text{var}\{\Delta_\tau x_i\}}$. The resulting set of inequalities yields an efficient, explicit formula for the largest permissible value of τ (32).

As for keeping the generated random numbers k_j from driving the R_j reactant populations negative, several strategies have been proposed. Tian & Burrage (33)—and, independently, Chatterjee et al. (34)—proposed approximating the unbounded Poisson random numbers k_j with bounded binomial random numbers. But it turns out that it is usually not the unboundedness of the Poisson k_j's that produces negative populations, but rather the lack of coordination in tau-leaping between different reaction channels that separately decrease the population of a common species. Cao et al. (35) have proposed a different approach that resolves this difficulty and also establishes a smooth connection with the SSA. In their approach, we first identify as critical all those reactions with nonzero propensities that are currently within n_c firings of exhausting one of its reactants, n_c being a user-specified integer. All other reactions are called noncritical. The noncritical reactions are handled by the regular Poisson tau-leaping method, and a maximum leap time τ' is computed for them using the procedure described in the preceding paragraph. For the critical reactions, we use the direct method formulas Equations 10a,b to estimate the time τ'' to, and index j_c of, the next critical reaction. The actual time step τ is then taken to be the smaller of τ' and τ''; if the former, no critical reaction fires, and if the latter, only one critical reaction (R_{j_c}) fires. Because the total number of critical reactions firing during τ is never greater than one, it is impossible for any critical reaction to drive any population negative.

If n_c is taken so large that every reaction becomes critical, the foregoing procedure reduces to the exact SSA. This is fortunate because although tau-leaping theoretically becomes exact (and hence equivalent to the SSA) as $\tau \to 0$, it also becomes grossly inefficient in that limit. This is because when τ is small, the Poisson random numbers $k_j = \mathcal{P}_j(a_j\tau)$ usually all are zero, resulting in a small tau-leap with no reactions firing. It is not efficient to do tau-leaping when τ is less than a few multiples of $1/a_0(\mathbf{x})$, the expected next time step in the SSA. But by using a reasonable value for n_c (e.g., between 5 and 50), along with a reasonable value of ε (e.g., between 0.01 and 0.06), large leaps are taken whenever possible, and a gradual transition to the SSA occurs automatically as needed for accuracy. Finally, if we write the code for generating a Poisson random number with mean (and variance) m so that when $m \gg 1$, it generates instead a normal random number with mean and variance m, then a smooth transition from tau-leaping to the more computationally efficient Langevin leaping will occur automatically.

Reference 32 gives a more detailed description of the current explicit tau-leaping procedure. Tests indicate that for many systems in which the molecular populations of at least some of the reactant species are large, it produces significantly faster simulations than the SSA with only a slight loss of accuracy.

6. SIMULATING STIFF SYSTEMS

A system of ODEs is said to be stiff if is characterized by well-separated fast and slow dynamical modes, the fastest of which is stable. The solution space of a stiff ODE has a slow manifold, on which the state point moves slowly, and off which the state point

moves rapidly toward the slow manifold. Researchers have devoted much effort over the years to understanding and overcoming the computational problems posed by stiff ODEs (36) because such equations arise in many practical contexts. Stiff RREs in particular are quite commonplace.

Stiffness is just as computationally troublesome in the stochastic context. When the SSA simulates a stiff system, it moves along as usual, one reaction at a time, oblivious to the stiffness. But because the great majority of the reactions are the usually uninteresting fast ones, the simulation proceeds slowly from a practical point of view. The explicit tau-leaping algorithm also performs as advertised on stiff systems. But because the τ-selection procedure that keeps the algorithm accurate restricts τ to the timescale of the system's fastest mode, then even those leaps seem frustratingly small. I conclude by describing two recently developed strategies for simulating stiff chemical systems: the implicit tau-leaping algorithm and the slow-scale SSA (ssSSA).

Slow-scale SSA (ssSSA): an approximation to the SSA for systems with fast and slow reactions in which only the latter are explicitly simulated

6.1. The Implicit Tau-Leaping Algorithm

A well-known strategy for numerically solving a stiff ODE $dx/dt = f(x)$ is to replace the explicit updating formula $x_{t+\Delta t} = x_t + f(x_t)\Delta t$ with an implicit formula, such as $x_{t+\Delta t} = x_t + f(x_{t+\Delta t})\Delta t$ (36). The latter equation of course has to be solved to obtain $x_{t+\Delta t}$ at each time step. But even when that can only be done numerically (Newton iteration is usually used), the extra effort is usually more than compensated by the ability to use much-larger values of Δt for the same degree of accuracy.

The tau-leaping formula (Equation 17), where $\mathbf{x} = \mathbf{X}(t)$, is obviously an explicit updating formula. To make it implicit by replacing $\mathbf{x}$ in the argument of the Poisson random variable with $\mathbf{X}(t+\tau)$, however, raises some serious questions in the context of Markov process theory, where updates are supposed to be past-forgetting; moreover, even if that replacement could be justified theoretically, there appears to be no way to solve the resulting equation for $\mathbf{X}(t+\tau)$. Rathinam et al. (37) have proposed a partial implicitization, in the following implicit tau-leaping formula:

$$\mathbf{X}(t+\tau) \doteq \mathbf{x} + \sum_{j=1}^{M} [\mathcal{P}_j(a_j(\mathbf{x})\tau) - a_j(\mathbf{x})\tau + a_j(\mathbf{X}(t+\tau))\tau]\boldsymbol{\nu}_j. \qquad (23)$$

In this formula, the mean of the Poisson random variable $\mathcal{P}_j(a_j(\mathbf{x})\tau)$ is subtracted out and replaced by its value at the later time $t+\tau$, but the variance has been left unchanged. The advantage of this formula is that, once the Poisson random numbers have been generated using the current state $\mathbf{x}$, the equation can then be solved for $\mathbf{X}(t+\tau)$ using the same (deterministic) numerical techniques developed for implicit ODE solvers (36). Noninteger values for the components of $\mathbf{X}(t+\tau)$ can be avoided by rounding the quantity in brackets in Equation 23 to the nearest nonnegative integer and then recomputing $\mathbf{X}(t+\tau)$ directly from Equation 23 (37).

Tests of this implicit tau-leaping strategy show that it produces significantly faster simulations than the explicit tau-leaping formula (Equation 17) for stiff systems, but with one major qualification: Formula 23 excessively damps the fluctuations in the fast components of $\mathbf{X}(t)$. Rapid fluctuations of the state point transverse to the slow manifold naturally occur in a stochastically evolving system, as can be seen in

simulations made with the exact SSA. But Equation 23 suppresses these fluctuations. However, we can restore the properly fluctuating fast variables whenever desired by taking a succession of much shorter explicit tau-leaps or SSA steps, a tactic called downshifting. For more details, see Reference 37.

Cao & Petzold (38) subsequently proposed a trapezoidal implicit tau-leaping formula, which has the same form as Equation 23 except that a factor of $1/2$ appears in front of each of the last two terms in the brackets. Tests suggest that the trapezoidal formula often gives more accurate results than Equation 23 for a given value of τ.

6.2. The Slow-Scale Stochastic Simulation Algorithm

A different approach to stochastically simulating stiff chemical systems is one that was inspired by the well-known Michaelis-Menten approximation in deterministic chemical kinetics (39). Several different ways of realizing this approach have been proposed (40–48), but all are rooted in the same basic idea of eliminating the fast entities through a kind of quasi-steady-state approximation (41). Arguably the clearest articulation of this approach, at least as regards its theoretical justification within stochastic chemical kinetics, is the ssSSA of References 42 and 45.

The ssSSA proceeds in a series of steps, the first of which is to make a provisional partitioning of the reaction channels $R = \{R_1, \ldots, R_M\}$ into fast and slow subsets, R^{f} and R^{s}. Assigned to R^{f} are those reactions whose propensity functions tend to have the largest values. All the other reactions are assigned to R^{s}. If it is not obvious how to make this partitioning, then it may be that the system is not really stiff, and therefore not a candidate for the ssSSA. In any case, this provisional partitioning of the reactions will later be subjected to an acceptance test.

The second step is to partition the species $S = \{S_1, \ldots, S_N\}$ into fast and slow subsets, S^{f} and S^{f}, according to the following rule: Any species whose population gets changed by a fast reaction is classified as a fast species; all other species (if there are any) are classified as slow. This rule induces a partitioning of the process $\mathbf{X}(t)$ into a fast process $\mathbf{X}^{\mathrm{f}}(t)$ and a slow process $\mathbf{X}^{\mathrm{s}}(t)$. Note the subtle but important asymmetry that a fast species can get changed by a slow reaction, but a slow species cannot get changed by a fast reaction.

The third step defines the virtual fast process $\hat{\mathbf{X}}^{\mathrm{f}}(t)$ as the fast species populations evolving under only the fast reactions R^{f}; i.e., $\hat{\mathbf{X}}^{\mathrm{f}}(t)$ is $\mathbf{X}^{\mathrm{f}}(t)$ with all the slow reactions switched off. The virtual fast process $\hat{\mathbf{X}}^{\mathrm{f}}(t)$ is a Markov process, whereas the real fast process $\mathbf{X}^{\mathrm{f}}(t)$ is generally non-Markovian, and hence practically intractable.

Next we require that two stochastic stiffness conditions be satisfied: First, $\hat{\mathbf{X}}^{\mathrm{f}}(t)$ must be stable, in that it approaches as $t \to \infty$ a well-defined time-independent random variable $\hat{\mathbf{X}}^{\mathrm{f}}(\infty)$. This is the counterpart to the deterministic stiffness requirement that the fastest dynamical mode be stable. Second, the approach $\hat{\mathbf{X}}^{\mathrm{f}}(t) \to \hat{\mathbf{X}}^{\mathrm{f}}(\infty)$ must be effectively accomplished in a time that is small compared with the expected time to the next slow reaction. This is a more precise specification of the degree of separation that must exist between the timescales of the fast and slow reactions. If we find these two stiffness conditions are satisfied, then our original classification of the fast

reactions is deemed acceptable; otherwise we must try another set of fast reactions, or else we must conclude that the system is not really stiff, and the ssSSA cannot be applied.

With the stochastic stiffness conditions satisfied, we now invoke the slow-scale approximation—a result that can be mathematically derived from the fundamental premise (Equation 2) (42). The slow-scale approximation states, in essence, that we can ignore the fast reactions and simulate the system one slow reaction at a time, provided we replace the propensity function of each slow reaction by its average with respect to the asymptotic virtual fast process $\hat{\mathbf{X}}^{\mathrm{f}}(\infty)$. More precisely, if $\hat{P}(\mathbf{y}^{\mathrm{f}}, \infty \mid \mathbf{x}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}})$ is the probability that $\hat{\mathbf{X}}^{\mathrm{f}}(\infty) = \mathbf{y}^{\mathrm{f}}$ given that $\mathbf{X}(t) = (\mathbf{x}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}})$, then the propensity function $a_j^{\mathrm{s}}(\mathbf{x}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}})$ of each slow reaction R_j^{s} at time t can be approximated on the timescale of the slow reactions by

$$\bar{a}_j^{\mathrm{s}}(\mathbf{x}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}}) \equiv \sum_{\mathbf{y}^{\mathrm{f}}} \hat{P}(\mathbf{y}^{\mathrm{f}}, \infty \mid \mathbf{x}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}})\, a_j^{\mathrm{s}}(\mathbf{y}^{\mathrm{f}}, \mathbf{x}^{\mathrm{s}}). \tag{24}$$

The ssSSA thus proceeds by simulating, in the manner of the SSA, the slow reactions using the propensity functions (Equation 24) and ignoring the fast reactions. We can exhibit the populations of the fast species whenever desired by Monte Carlo sampling the probability function $\hat{P}$.

The approaches of References 43, 44, 47 and 48 differ from the ssSSA approach described above in the way the averages (Equation 24) are computed and the way in which the fast-species populations are generated. All rely on making relatively short SSA runs of the virtual fast process between the slow reactions.

Although the ssSSA can be challenging to implement, it has been successfully applied to a number of simple stiff systems (42), as well as the prototypical Michaelis-Menten system (45) that is so ubiquitous in enzymatic reactions. These applications showed increases in simulation speed over the exact SSA of two to three orders of magnitude with no perceptible loss of simulation accuracy.

7. OUTLOOK

The robustness and efficiency of both the SSA and the explicit tau-leaping algorithm have been considerably improved in the past few years, and those procedures seem to be nearing maturity. However, there is still room for improvement on the stiffness problem. Such improvement may come in the form of refinements to the implicit tau-leaping procedure and the ssSSA, and a clarification of the theoretical connection between those two approaches for dealing with stiff systems. Also needed are robust, adaptive strategies for deciding during a simulation when to use which simulation method. There is also a need for a better understanding of several foundational issues, such as how the reaction constants c_j are to be derived in the context of diffusional kinetics, and what are the effects of the molecular-crowding conditions usually present in living cells. Finally, the problem of how best to simulate systems that are not well stirred, a problem that is not addressed in this review, holds a great many challenges.

SUMMARY POINTS

1. The SSA is a procedure for numerically simulating well-stirred chemically reacting systems by stepping in time to successive molecular reaction events in exact accord with the premises of the CME.
2. The ability of the SSA to take proper account of the discrete, stochastic nature of chemical reactions makes it better suited to cellular chemical kinetics than the traditional RRE because in cellular systems the small numbers of molecules of some key reactants can amplify the effects of discreteness and randomness.
3. Because the SSA simulates every successive molecular reaction event that occurs in the system, it is often too slow for practical simulation of realistic cellular systems.
4. An approximate speedup to the SSA is provided by tau-leaping, in which time is advanced by a preselected amount τ and the numbers of firings of the individual reaction channels are approximated by Poisson random numbers.
5. If the expected number of firings of each reaction channel during a tau-leap is much greater than one, the Poisson random numbers are well approximated by normal random numbers, and the result is equivalent to a Langevin-type equation called the CLE.
6. In the thermodynamic (macroscopic) limit, the noise terms in the CLE become negligibly small and the CLE reduces to the conventional RRE, thereby establishing deterministic chemical kinetics in the context of stochastic chemical kinetics.
7. For stiff systems—which evolve on both fast and slow timescales with the fastest modes being stable—accuracy in tau-leaping requires τ to be small on the fastest timescale, which makes even tau-leaping seem too slow.
8. Two acceleration procedures for stiff systems are implicit tau-leaping, which mirrors the implicit Euler method in ODE theory, and the ssSSA, in which the fast reactions are skipped over and only the slow reactions are directly simulated using specially modified propensity functions.

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1. Earliest application of the SSA to a real biological system demonstrating that stochasticity can play a critically important role.

7. Demonstrates the surprising ability of external noise to cause a monostable system to become bistable.

8. Introduced the SSA.

10. Clarified the physical and mathematical foundations of the CME and the SSA.

12. Introduced the CME.

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25. Gave a conceptually transparent derivation of the CLE from the CME that clarified its form and the approximations involved.

26. Introduced tau-leaping and a variation called k-leaping.

27. A tutorial on Langevin equations, Fokker-Planck equations, Gaussian white noise, Brownian motion, and related subjects.

32. Describes the latest, most efficient version of explicit tau-leaping.

42. Introduced the ssSSA.

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