A General Method for Numerically Simulating the Stochastic Time Evolution of Coupled Chemical Reactions

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An exact method is presented for numerically calculating, within the framework of the stochastic formulation of chemical kinetics, the time evolution of any spatially homogeneous mixture of molecular species which interreact through a specified set of coupled chemical reaction channels. The method is a compact, computer-oriented, Monte Carlo simulation procedure. It should be particularly useful for modeling the transient behavior of well-mixed gas-phase systems in which many molecular species participate in many highly coupled chemical reactions. For "ordinary" chemical systems in which fluctuations and correlations play no significant role, the method stands as an alternative to the traditional procedure of numerically solving the deterministic reaction rate equations. For nonlinear systems near chemical instabilities, where fluctuations and correlations may invalidate the deterministic equations, the method constitutes an efficient way of numerically examining the predictions of the stochastic master equation. Although fully equivalent to the spatially homogeneous master equation, the numerical simulation algorithm presented here is more directly based on a newly defined entity called "the reaction probability density function." The purpose of this article is to describe the mechanics of the simulation algorithm, and to establish in a rigorous, a priori manner its physical and mathematical validity; numerical applications to specific chemical systems will be presented in subsequent publications.

1. INTRODUCTION

The time evolution of a spatially homogeneous mixture of chemically reacting molecules is usually calculated by solving a set of coupled ordinary differential equations. If there are N chemically active molecular species present, there will be N differential equations in the set; each equation expresses the time-rate-of-change of the molecular concentration of one chemical species as a function of the molecular concentrations of all the species, in accordance with the stoichiometric forms and reaction constants of those chemical reactions which involve that particular species. This traditional method of analysis is based upon a *deterministic formulation* of chemical kinetics, in which the reaction constants are viewed as

403

reaction "rates," and the various species concentrations are represented by continuous, single-valued functions of time. Although this deterministic formulation is adequate in most cases, there are important situations, such as a nonlinear system in the neighborhood of a chemical instability, for which its underlying physical assumptions are unrealistic and its consequent predictions are unreliable.

An approach to the chemical kinetics of spatially homogeneous systems which is somewhat more broadly applicable than the deterministic formulation is the *stochastic formulation*. Here the reaction constants are viewed not as reaction "rates" but as reaction "probabilities per unit time," and the temporal behavior of a chemically reacting system takes the form of a Markovian random walk in the N-dimensional space of the molecular populations of the N species. In the stochastic formulation of chemical kinetics the time evolution is analytically described, not by a set of N coupled differential equations for the species concentrations, but rather by a single differential-difference equation for a grand probability function in which time and the N species populations all appear as independent variables. This differential-difference equation is customarily called the master equation, and the function which satisfies that equation measures the *probability* of finding various molecular populations at each instant of time.

From a *physical* point of view, the stochastic formulation of chemical kinetics is superior to the deterministic formulation: the stochastic approach is always valid whenever the deterministic approach is valid, and is sometimes valid when the deterministic approach is not. (Some may disagree with this assertion; we shall present arguments supporting it in Section 2). From a strictly *mathematical* point of view, though, the set of deterministic reaction rate equations for a given chemical system is invariably much easier to solve than the stochastic master equation for the same system. However, if the system involves more than a few molecular species and chemical reactions, it usually turns out that *neither* formulation of chemical kinetics is tractable by purely *analytical* methods, and one is forced to consider computer-oriented *numerical* methods. Considerable success in this vein has been realized within the deterministic formulation by applying finite-time-step techniques to the coupled differential reaction rate equations. Within the framework of the stochastic formulation, though, prospects for performing numerical calculations have until now been regarded as generally unpromising.

In this paper we present what appears to be an eminently feasible method for numerically calculating the stochastic time evolution of virtually any spatially homogeneous chemical system. This computational method does *not* try to numerically solve the master equation for a given system; instead, it is a systematic, computer-oriented procedure in which rigorously derived Monte Carlo techniques are employed to *numerically simulate* the very Markov process that the master equation describes analytically. The simulation algorithm is fully equivalent to

the master equation, even though the master equation itself is never explicitly used. The algorithm is simple, compact and efficient, yet is capable of handling systems involving many chemical species and many highly coupled and highly nonlinear chemical reactions. Except for its reliance upon some computer subroutine for generating "random" numbers uniformly in the unit interval, our computational procedure imposes no approximations on the stochastic formulation of chemical kinetics; in particular, it takes full account of the inherent statistical correlations and fluctuations that are neglected in the deterministic formulation of chemical kinetics. Furthermore, our computational procedure never has to approximate infinitesimal time increments dt by small but finite time steps Δt; it is of course the successive application of that particular approximation which often gives rise to computational inaccuracies and instabilities in the standard numerical methods for solving the deterministic reaction rate equations.

The general problem which we address here may be formulated as follows: We are given a volume V which contains molecules of N chemically active species S_i ($i = 1,..., N$), and possibly molecules of several inert species as well. Let

$$X_i \equiv \text{current number of molecules of chemical species}$$
$$S_i \text{ in } V, \qquad (i = 1, 2,..., N). \tag{1}$$

We are further given that these N chemical species S_i can participate in M chemical reactions R_μ ($\mu = 1,..., M$),[1] each characterized by a numerical *reaction parameter* c_μ which will be defined momentarily. For definiteness, we suppose that each reaction in the set $\{R_\mu\}$ is one of the following general types.

$$* \to \text{reaction products}, \tag{2a}$$

$$S_j \to \text{reaction products}, \tag{2b}$$

$$S_j + S_k \to \text{reaction products} \quad (j \neq k), \tag{2c}$$

$$2S_j \to \text{reaction products}, \tag{2d}$$

$$S_i + S_j + S_k \to \text{reaction products} \quad (i \neq j \neq k \neq i), \tag{2e}$$

$$S_j + 2S_k \to \text{reaction products} \quad (j \neq k), \tag{2f}$$

$$3S_j \to \text{reaction products}. \tag{2g}$$

Reaction type (2a) denotes a "spontaneous creation" or "external source" reaction, in which one or more members of $\{S_i\}$ appear as products but none as reactants. In types (2b)–(2g), the reaction products may contain none, one, or more than

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[1] We shall use Roman indices when referring to one of the N chemical species S_i, and Greek indices when referring to one of the M chemical reactions R_μ.

one of the chemical species in the set $\{S_i\}$. Note that each R_μ reaction is *uni-directional*, so any reversible reaction must be considered as two separate uni-directional reactions.

The *fundamental hypothesis* of the stochastic formulation of chemical kinetics (and the only "assumption" to be made by our computational method) is that the reaction parameter c_μ which characterizes reaction R_μ can be defined as follows.

$$c_\mu \, \delta t \equiv \text{average probability, to first order in } \delta t, \text{ that a} \qquad (3)$$
$$\text{particular combination of } R_\mu \text{ reactant molecules will}$$
$$\text{react accordingly in the next time interval } \delta t.$$

For example, if R_μ is of type (2c), then the probability that a particular S_j–S_k pair of molecules will react according to (2c) in the next time interval δt, averaged over all S_j–S_k pairs, is equal to $c_\mu \, \delta t + o(\delta t)$, where $o(\delta t)$ denotes unspecified terms which satisfy $o(\delta t)/\delta t \to 0$ as $\delta t \to 0$. In Section 2 we shall review the physical basis for (3), and we shall also examine the relationship between c_μ as defined in (3) and the more familiar "reaction rate constant" k_μ which is used in the deterministic formulation of chemical kinetics.

Our principle task is to develop a method for simulating the time evolution of the N quantities $\{X_i\}$, knowing only their initial values $\{X_i^{(0)}\}$, the forms of the M reactions $\{R_\mu\}$, and the values of the associated reaction parameters $\{c_\mu\}$. In Section 3 we develop the formal mathematical foundation for our simulation procedure. The operational steps of the algorithm itself are then outlined in Section 4, with the implementation of the crucial "Monte Carlo step" being discussed in detail in Section 5. A short resumé of the requisite Monte Carlo techniques is provided in the Appendix. In Section 6 we illustrate our general discussion by exhibiting a Fortran program which applies the simulation algorithm to a specific set of coupled chemical reactions; this example should also serve to convey a rough idea of what is required by the algorithm from the standpoint of a digital computer. We shall *not* undertake any actual numerical calculations here, though, since our concern in this paper is only to describe the simulation algorithm itself and to establish in an a priori manner that it is a rigorous consequence of the fundamental stochastic hypothesis (3). We conclude in Section 7 by giving a summary of our simulation algorithm, and making some preliminary observations about its advantages, limitations, and possible extensions.

2. RATIONALE FOR THE STOCHASTIC FORMULATION

The stochastic approach to chemical kinetics has been pursued over the past two decades by A. Rényi, A. Bartholomay, D. McQuarrie, and a number of others; for an extensive summary of this work, see the review article by McQuarrie [1].

The justification for using the stochastic approach, as opposed to the mathematically simpler deterministic approach, was that the former presumably took account of *fluctuations and correlations,* whereas the latter did not. It was subsequently demonstrated by Oppenheim *et al.* [2], and later proved conclusively by Kurtz [3], that the stochastic formulation reduces to the deterministic formulation in the thermodynamic limit (wherein the numbers of molecules of each species and the containing volume all approach infinity in such a way that the molecular concentrations approach finite values). This finding, coupled with the fact that the *deterministic* formulation can be derived from the Liouville equation (via the Boltzmann equation) in the *dilute* thermodynamic limit, shows that both formulations of chemical kinetics are legitimate in that special limit. But Oppenheim *et al.* [2] went further to suggest that, inasmuch as no one has yet succeeded in deriving the *stochastic* formulation from the Liouville equation, the stochastic formulation may be nothing more than an ad hoc transcription of the deterministic formulation, with no legitimate predictive value at all for fluctuations and correlations in finite chemical systems.

We shall present in this section a rather elementary argument which indicates that the physical basis of the stochastic formulation is considerably more substantial than this. Inasmuch as the legitimacy of the stochastic formulation hinges entirely on the assumption that each chemical reaction R_μ can be characterized in the manner of statement (3), the problem we address here is to determine under what conditions (3) has a legitimate physical basis.

To investigate this matter, let us see what is involved in calculating c_μ for the simple bimolecular reaction

$$R_\mu : \quad S_1 + S_2 \rightarrow 2S_3 \tag{4}$$
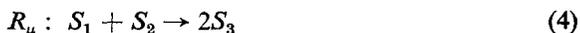
in the idealized case in which the S_i molecules are hard spheres with masses m_i and diameters d_i. In that case, a 1–2 *collision* will occur whenever the center-to-center distance between an S_1 molecule and an S_2 molecule decreases to $d_{12} \equiv (d_1 + d_2)/2$. Let v_{12} be the speed of an arbitrary S_1 molecule relative to an arbitrary S_2 molecule. Then, in the vanishingly small time interval δt, molecule 1 sweeps out relative to molecule 2 a "collision volume" $\delta V_{coll} = \pi d_{12}^2 \cdot v_{12}\, \delta t$, in the sense that if the center of 2 lies inside δV_{coll} then 1 and 2 will collide in time δt. The requirement that δt be vanishingly small is imposed for two reasons: first, this insures that δV_{coll} too will be vanishingly small, so that if the center of 2 *does* lie inside δV_{coll}, then there will be only a negligibly small probability that a 1–2 collision in the next δt interval will be *prevented* by an earlier collision of 1 or 2 with some other molecule; and secondly, the eventual application of the results of these calculations will require that we take the limit $\delta t \rightarrow 0$.

Now, in traditional textbook derivations of the deterministic reaction rate constant k_μ, the normal procedure at this point would be to require that the

system be *spatially homogeneous*, so that the distribution of the constituent mole-cules throughout the containing volume V may be regarded as "uniform", and to then consider "the number of S_2 molecules whose centers lie inside δV_{coll}." Unfortunately though, that quantity becomes *physically meaningless* in the inevitable limit $\delta V_{\text{coll}} \to 0$; for, in that limit δV_{coll} will obviously contain either 0 or 1 S_2 molecules, with the former possibility becoming more and more likely as the limiting process proceeds. It might be thought that this difficulty could be circumvented by considering instead the *average number* of S_2 molecules whose centers lie inside δV_{coll}. However, to deal with averages at this early stage of the calculation will lead to other conceptual difficulties later on; in the case of reaction (4), these difficulties arise essentially from the fact that the average number of S_1–S_2 molecular pairs is *not* exactly equal to the product of the average number of S_1 molecules times the average-number of S_2 molecules. Herein, of course, lies the source of the inexact nature of the deterministic reaction rate equations.

We can easily avoid all these difficulties, though, if we simply take the condition of "spatial homogeneity" to mean that the molecules are *randomly* distributed in a uniform sense throughout V (as would be the case, for example, in a well-mixed gas-phase system). We shall discuss later how this sort of spatial homogeneity might be physically insured. For now, through, we merely observe that this condition implies that the *probability* that the center of one S_2 molecule will lie inside δV_{coll} is given precisely by $\delta V_{\text{coll}}/V$. In this *stochastic* context, we may then proceed to utilize in a *logically consistent* manner the simple mathematical manipulations that are employed in conventional textbook treatments [4] of chemical kinetics: Thus, the *average probability* that a particular 1–2 molecular pair will *collide* in the next time interval δt is, to first order in δt,

$$\langle \delta V_{\text{coll}}/V \rangle = \pi d_{12}^2 \cdot \langle v_{12} \rangle \, \delta t/V, \qquad (5a)$$

where the brackets denote an average over the velocities of all S_1–S_2 molecular pairs. If we further assume that the S_1–S_2 mixture is in thermal (not chemical) equilibrium at absolute temperature T, so that not only are the positions of the molecules randomly distributed according to a uniform distribution inside V, but in addition the velocities of the molecules are randomly distributed according to Maxwell–Boltzmann distributions, then the average $\langle v_{12} \rangle$ is easily calculated, and the above expression becomes

$$\langle \delta V_{\text{coll}}/V \rangle = V^{-1} \pi d_{12}^2 (8kT/\pi m_{12})^{1/2} \, \delta t. \qquad (5b)$$

Here, k is Boltzmann's constant and m_{12} is the reduced mass $m_1 m_2/(m_1 + m_2)$. If every 1–2 collision leads to an R_μ reaction, then the above expression evidently corresponds exactly to the quantity $c_\mu \, \delta t$ defined in (3). However, it is more

reasonable to suppose that an R_μ reaction will occur in only those collisions in which the kinetic energy due to the relative motion along the line of centers at contact exceeds some prescribed value $u_\mu{}^*$, the "activation energy." If we repeat the above argument taking into account the collision geometry, and allowing only the "reactive collision" configurations, we will obtain the same result except for a diminuting factor of $\exp(-u_\mu{}^*/kT)$. Thus we conclude that, for the bimolecular hardsphere reaction R_μ in (4), if conditions of thermal equilibrium prevail for species S_1 and S_2, then the quantity defined in (3) indeed exists and the reaction parameter c_μ is given by

$$c_\mu = V^{-1}\pi d_{12}^2(8kT/\pi m_{12})^{1/2}\exp(-u_\mu{}^*/kT). \tag{6}$$

The key element in the foregoing analysis is the requirement that the reactant molecules always be randomly distributed uniformly throughout V; that is what set the stage for the introduction of the collision *probability* $\delta V_{\text{coll}}/V$. Unless some external stirring mechanism can be employed to fulfill this requirement, we must simply rely upon the natural motions of the molecules to keep the system well mixed. For this, it evidently suffices to require the system to be such that the non-reactive (elastic) molecular encounters, which serve to randomize and uniformize the positions of the molecules, occur much more frequently than the reactive (inelastic) molecular encounters, which change the population levels of the various molecular species. Clearly, this circumstance will allow a uniform redistribution of the molecules inside V prior to each reactive collision; in addition, this will also allow the continual restoration of the Maxwell–Boltzmann velocity distributions of the various species, which tend to be preferentially depleted on their high ends by the reactive collisions. Of course, the observation that nonreactive molecular encounters have an equilibrizing effect on molecular systems is certainly not new [4, 5], but the bearing of this fact on the issue of the legitimacy of the stochastic formulation of chemical kinetics does not seem to have been widely appreciated.

The condition that nonreactive molecular collisions occur much more frequently than reactive molecular collisions is thus a convenient criterion for applicability of the stochastic formulation of chemical kinetics. Whenever this condition is satisfied, it should be possible to characterize the occurrences of the reactions R_μ in the manner of (3). Of course, the actual calculation of c_μ will usually be much more involved than that sketched above for the simple hard-sphere bimolecular reaction (4); indeed, sometimes it will be easier to determine c_μ experimentally instead of theoretically. On the other hand, if reactive collisions occur more frequently than nonreactive collisions, then the stochastic formulation of chemical kinetics would probably not be strictly valid. Of course, we should not expect the usual deterministic formulation to be valid then either, inasmuch as it obviously presupposes uniform concentrations for all chemical species. In such cases we should probably have to resort to an approach closer to the Liouville equation,

i.e., a "molecular dynamics" approach in which the positions and velocities of all the molecules are accounted for explicitly before any averaging is performed.

Now let us examine the relationship between the reaction parameter c_μ, as defined in (3), and the more familiar reaction rate constant k_μ, which is used in the deterministic formulation of chemical kinetics. Referring again to the simple bimolecular reaction R_μ in (4), if there are $X_1(X_2)$ molecules of $S_1(S_2)$ inside V, then there will be X_1X_2 distinct combinations of reactant molecules inside V, and it follows from (3) and the addition theorem for probabilities that $X_1X_2 \cdot c_\mu \, dt$ gives the probability that an R_μ reaction will occur somewhere inside V in the next infinitesimal time interval dt. From this we may infer that $\langle X_1X_2c_\mu \rangle = \langle X_1X_2 \rangle \, c_\mu$ is the *average rate* at which R_μ reactions are occurring inside V, where $\langle \cdots \rangle$ now means an average taken over an ensemble of stochastically identical systems. The average reaction rate per unit volume would then be $\langle X_1X_2 \rangle \, c_\mu/V$, or in terms of the molecular concentrations $x_i \equiv X_i/V$, $\langle x_1x_2 \rangle \, Vc_\mu$. Now, the reaction rate constant k_μ is conventionally defined to be this average reaction rate per unit volume divided by the product of the average densities of the reactants; thus we obtain for R_μ in (4),

$$k_\mu = \langle x_1x_2 \rangle \, Vc_\mu/\langle x_1 \rangle \langle x_2 \rangle. \tag{7a}$$

However, in the deterministic formulation no distinction is made between the average of a product and the product of the averages; i.e., it is automatically assumed that $\langle x_ix_j \rangle = \langle x_i \rangle \langle x_j \rangle$. For $i \neq j$ this assumption nullifies the effects of *correlations*, and for $i = j$ it nullifies the effects of *fluctuations*. In any case, this assumption evidently simplifies the above expression for k_μ to

$$k_\mu \doteq Vc_\mu. \tag{7b}$$

And indeed, if we simply multiply (6) by V we get the well-known formula for the reaction rate constant for a hard-sphere bimolecular reaction [4].

If R_μ had been an S_1–S_1 reaction instead of an S_1–S_2 reaction, then the number of distinct reactable pairs would have been $X_1(X_1 - 1)/2 \simeq X_1^2/2$, and we would have obtained $k_\mu \doteq Vc_\mu/2$ instead. For monomolecular reactions k_μ and c_μ will be equal; for trimolecular reactions we will get a factor of V^2 instead of V.

In summary, we see that the *mathematical* relationship between c_μ and k_μ is always rather simple, but from a *physical* standpoint c_μ appears to be on much firmer ground. We also see that the stochastic formulation of chemical kinetics for spatially homogeneous systems does indeed take proper account of correlations and fluctuations which are ignored in the deterministic formulation. The works of Oppenheim *et al.* [2] and Kurtz [3] have proved that the effects of these correlations and fluctuations vanish in the thermodynamic limit. Just how large the system must be before the thermodynamic limit can be considered "reached" will vary with the situation. Experience indicates that, for most systems, the

constituent molecules need number only in the hundreds or thousands in order for the deterministic approach to be adequate; thus, for most systems the differences between the deterministic and stochastic formulations are purely academic, and one is free to use whichever formulation turns out to be more convenient or efficient. However, near chemical instabilities in certain nonlinear systems, fluctuations and correlations can produce dramatic effects, even for macroscopic numbers of molecules [6, 7, 8]; for these systems the stochastic formulation would be the more appropriate choice.

3. The Reaction Probability Density Function

The *usual* stochastic approach [1] to the coupled chemical reactions problem outlined in Section 1 focuses upon the grand probability function

$$\mathscr{P}(X_1, X_2, ..., X_N; t) \equiv \text{the probability that there will be } X_1 \text{ molecules}$$
$$\text{of } S_1, \text{ and } X_2 \text{ molecules of } S_2, ..., \text{ and } X_N \qquad (8)$$
$$\text{molecules of } S_N, \text{ in } V \text{ at time } t,$$

and its moments

$$X_i^{(k)}(t) \equiv \sum_{X_1=0}^{\infty} \cdots \sum_{X_N=0}^{\infty} X_i^{k} \mathscr{P}(X_1, ..., X_N; t) \qquad (i = 1, ..., N; k = 1, 2, ...). \quad (9)$$

Physically, $X_i^{(k)}(t)$ is "the average (number)^k of S_i molecules in V at time t." By "average" here we mean an average taken over many repeated realizations or runs from time 0 to time t of the stochastic process described by (3), with each run starting in the same initial state $\{X_i^{(0)}\}$.[2] The number X_i of S_i molecules found at time t will vary from run to run; however, the average of the kth power of the values found for X_i in these runs will approach $X_i^{(k)}(t)$ in the limit of infinitely many runs. Particularly useful are the $k = 1$ and $k = 2$ averages; this is because the quantities

$$X_i^{(1)}(t) \qquad (10a)$$

and

$$\Delta_i(t) \equiv \{X_i^{(2)}(t) - [X_i^{(1)}(t)]^2\}^{1/2} \qquad (10b)$$

measure, respectively, the average number of S_i molecules in V at time t, and the magnitude of the root-mean-square fluctuations about this average.

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[2] These runs can be performed simultaneously instead of sequentially if we use an "ensemble" of many identical systems.

In other words, we may "reasonably expect" to find between

$$[X_i^{(1)}(t) - \Delta_i(t)] \quad \text{and} \quad [X_i^{(1)}(t) + \Delta_i(t)]$$

molecules of S_i in V at time t.

The so-called master equation is just the time evolution equation for the function $\mathcal{P}(X_1, ..., X_N; t)$, and it can be rigorously derived from (3) by using simple probability calculus. However, more often than not the master equation turns out to be virtually intractable, both analytically and numerically. Attempts to use the master equation to construct tractable time-evolution equations for the moments $X_i^{(k)}(t)$ are likewise usually fruitless; this is because the equation for the kth moment typically involves one or more higher order moments, so that the set of moment equations is infinitely open-ended.

Our computational method avoids these "traditional" difficulties by starting off from the fundamental stochastic hypothesis (3) in a different way. More specifically, the principle theoretical construct upon which our numerical procedure is based is not the grand probability function $\mathcal{P}$ in (8), nor any of its derived quantities, but rather an entity which we shall call the *reaction probability density function*, $P(\tau, \mu)$. This quantity is defined by

$$P(\tau, \mu)\, d\tau \equiv \text{probability at time } t \text{ that the } next$$
$$\text{reaction in } V \text{ will occur in the differential} \tag{11}$$
$$\text{time interval } (t + \tau, t + \tau + d\tau), and \text{ will be an } R_\mu \text{ reaction.}$$

In the terminology of probability theory, $P(\tau, \mu)$ is a joint probability density function on the space of the continuous variable τ ($0 \leqslant \tau < \infty$) and the discrete variable μ ($\mu = 1, 2, ..., M$). To the author's knowledge, this quantity has not been considered in detail before by workers in chemical kinetics, or at least it has not been utilized in the systematic way we shall propose here. In this section we shall derive from the basic postulate (3) an exact analytical expression for $P(\tau, \mu)$; in the following sections we shall use $P(\tau, \mu)$ to construct a rigorous algorithm for simulating the temporal development of our chemical system.

To derive a formula for $P(\tau, \mu)$, we begin by defining the M state variables $h_1, h_2, ..., h_M$ by

$$h_\mu \equiv \text{number of distinct molecular reactant combinations for}$$
$$\text{reaction } R_\mu \text{ found to be present in } V \text{ at time } t. \tag{12}$$

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[3] It is tacitly assumed in (3) that the probability for more than one reaction to occur in δt is $o(\delta t)$. Since we are eventually going to take the limit $\delta t \to 0$, it is permissible here to simply regard as *impossible* the occurrence of more than one reaction in δt.

With (3) and the addition theorem for mutually exclusive probabilities,[3] we therefor have

$$h_\mu c_\mu \, \delta t = \text{probability, to first order in } \delta t, \text{ that an } R_\mu \text{ reaction will occur in } V \text{ in the next time interval } \delta t. \tag{13}$$

In general, h_μ will be a function of the current X_i values of the reactant species in R_μ. For the specific reaction types in (2), (12) implies[4]

$$h_\mu = 1, \qquad\qquad\qquad \text{for type (2a) reactions;} \tag{14a}$$
$$h_\mu = X_j, \qquad\qquad\qquad \text{for type (2b) reactions;} \tag{14b}$$
$$h_\mu = X_j X_k, \qquad\qquad\quad \text{for type (2c) reactions;} \tag{14c}$$
$$h_\mu = X_j(X_j - 1)/2, \qquad \text{for type (2d) reactions;} \tag{14d}$$
$$h_\mu = X_i X_j X_k, \qquad\qquad \text{for type (2e) reactions;} \tag{14e}$$
$$h_\mu = X_j X_k(X_k - 1)/2, \quad \text{for type (2f) reactions;} \tag{14f}$$
$$h_\mu = X_j(X_j - 1)(X_j - 2)/6, \quad \text{for type (2g) reactions.} \tag{14g}$$

We shall calculate the probability in (11) as the product of $P_0(\tau)$, the probability at time t that *no* reaction will occur in the time interval $(t, t + \tau)$, times $h_\mu c_\mu \, d\tau$, the subsequent probability that an R_μ reaction will occur in the next differential time interval $(t + \tau, t + \tau + d\tau)$:

$$P(\tau, \mu) \, d\tau = P_0(\tau) \cdot h_\mu c_\mu \, d\tau. \tag{15}$$

Note that we need not worry about more than one reaction occurring in $(t + \tau, t + \tau + d\tau)$, since the probability for this is $o(d\tau)$.

To calculate $P_0(\tau)$, the probability that no reaction occurs in $(t, t + \tau)$, imagine the interval $(t, t + \tau)$ to be divided into K subintervals of equal length $\epsilon = \tau/K$. The probability that *none* of the reactions $R_1, \ldots, R_M$ occurs in the first ϵ subinterval $(t, t + \epsilon)$ is, by (13) and the multiplication theorem for probabilities,

$$\prod_{\nu=1}^{M} [1 - h_\nu c_\nu \epsilon + o(\epsilon)] = 1 - \sum_{\nu=1}^{M} h_\nu c_\nu \epsilon + o(\epsilon).$$

This is also the *subsequent* probability that no reaction occurs in $(t + \epsilon, t + 2\epsilon)$, and *then* in $(t + 2\epsilon, t + 3\epsilon)$, and so on. Since there are K such ϵ subintervals between t and $t + \tau$, then $P_0(\tau)$ can be written

$$P_0(\tau) = \left[1 - \sum_\nu h_\nu c_\nu \epsilon + o(\epsilon)\right]^K$$
$$= \left[1 - \sum_\nu h_\nu c_\nu \tau/K + o(K^{-1})\right]^K.$$

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[4] We let (14a) *define* h_μ for reaction type (2a), since definition (12) is ambiguous for that type. Equation (13) is then valid for *all* reaction types.

This is true for any $K > 1$, and in particular it is true in the limit of infinitely large K. Therefore,

$$P_0(\tau) = \lim_{K \to \infty} \left[1 - \left(\left(\sum_\nu h_\nu c_\nu \tau + o(K^{-1})/K^{-1} \right) \middle/ K \right) \right]^K,$$

or, using the standard limit formula for the exponential function,

$$P_0(\tau) = \exp \left[- \sum_{\nu=1}^M h_\nu c_\nu \tau \right]. \tag{16}$$

We should note in passing that it would be incorrect to derive (16) by simply multiplying M individual probabilities $\exp(-h_\nu c_\nu \tau)$, corresponding to the non-occurrence of each reaction R_ν in $(t, t + \tau)$; the reason we cannot do this is that $\exp(-h_\nu c_\nu \tau)$ is the probability that R_ν will not occur in $(t, t + \tau)$ *only* in the *absence* of all other reaction channels which involve the R_ν reactants.

Inserting (16) into (15), we arrive at the following exact expression for the reaction probability density function defined in (11):

$$P(\tau, \mu) = h_\mu c_\mu \exp \left[- \sum_{\nu=1}^M h_\nu c_\nu \tau \right]. \tag{17}$$

To be precise, this formula gives $P(\tau, \mu)$ for $0 \leqslant \tau < \infty$ and $1 \leqslant \mu \leqslant M$, with τ real and μ integer; for all other values of τ and μ, $P(\tau, \mu)$ is zero. A schematic plot of $P(\tau, \mu)$ is shown in Fig. 1. The domain of definition of $P(\tau, \mu)$ consists of the M lines in the $\tau\mu$-plane extending from the first M integer points on the μ-axis in the positive τ direction. The area shown shaded in Fig. 1 is evidently equal to
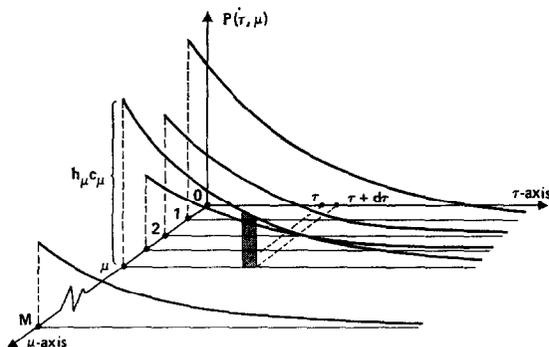
FIG. 1.   Schematic plot of the reaction probability density function $P(\tau, \mu)$ as given in (17). The shaded area is by definition equal to the probability in (11), and the sum of the areas under all M curves is by (18) equal to unity.

the probability in (11). We note that this probability density function is properly normalized over its domain of definition, since

$$\int_0^\infty d\tau \sum_{\mu=1}^M P(\tau, \mu) = \sum_{\mu=1}^M h_\mu c_\mu \int_0^\infty d\tau \exp\left[-\sum_{\nu=1}^M h_\nu c_\nu \tau\right] = 1. \tag{18}$$

We also observe that $P(\tau, \mu)$ depends, through the quantity in the exponential, on the reaction parameters for *all* reactions (not just R_μ) and on the current numbers of molecules of *all* reacting species (not just the R_μ reactants).

4. THE SIMULATION ALGORITHM

The basic idea of our computational procedure is to use Monte Carlo techniques to simulate the stochastic process described by $P(\tau, \mu)$ in (17). Assuming that we have access to a fast digital computer, our simulation algorithm is straightforward, and may be outlined as follows:

Step 0 (initialization). Set the time variable $t = 0$. Specify and store initial values for the N variables X_1, X_2,..., X_N, where X_i is the current number of molecules of chemical species S_i. Specify and store the values of the M reaction parameters c_1, c_2,..., c_M for the M chemical reactions $\{R_\mu\}$. Using (14), calculate and store the M quantities $h_1 c_1$, $h_2 c_2$,..., $h_M c_M$ which collectively determine the reaction probability density function $P(\tau, \mu)$ in (17). Finally, specify and store a series of "sampling times" $t_1 < t_2 < \cdots$, and also a "stopping time" t_{stop}.

Step 1. By employing suitable Monte Carlo techniques, generate one random pair (τ, μ) according to the joint probability density function $P(\tau, \mu)$ in (17). Explicit methods for doing this are presented in Section 5.

Step 2. Using the numbers τ and μ generated in Step 1, advance t by τ, and change the $\{X_i\}$ values of those species involved in reaction R_μ to reflect the occurrence of one R_μ reaction. Then, recalculate the $h_\nu c_\nu$ quantities for those reactions R_ν whose reactant X_i-values have just been changed. (For example, suppose R_μ is the reaction $S_1 + S_2 \rightarrow 2S_3$. Then after replacing t by $t + \tau$, we would replace X_1, X_2 and X_3 by $X_1 - 1$, $X_2 - 1$ and $X_3 + 2$, respectively; we would then recalculate $h_\nu c_\nu$ in accordance with (14) for every reaction R_ν in which either S_1 or S_2 or S_3 appears as a *reactant*.)

Step 3. If t has just been advanced through one of the sampling times t_i, read out the current molecular population values X_1, X_2,..., X_N. If $t > t_{\text{stop}}$, or if no more reactants remain (all $h_\mu = 0$), terminate the calculation; otherwise, return to Step 1.

The computer storage space required for the above procedure is evidently quite minimal: The principle quantities which must be carried in computer memory are the $N + 2M$ quantities $\{X_i\}$, $\{c_\mu\}$ and $\{h_\mu c_\mu\}$, and it is difficult to imagine any system of M coupled chemical reactions involving N molecular species for which the required memory storage space would exceed a few hundred word locations. On the other hand, the speed of the computer is quite critical: Since each individual molecular reaction is simulated in turn, the speed with which the central arithmetic unit can execute Steps 1, 2 and 3 will impose an upper limit on how many molecular reactions can be effected. This in turn limits both the number of reactant molecules the system can contain and the length of time over which the evolution of the system can be followed. Indeed, the maximum number of reactant molecules and the maximum evolution time will be roughly inversely proportional to each other, and their product will be roughly proportional to the speed of the computer. Fortunately, Steps 2 and 3 are simple to execute, and, except for the few read-outs in Step 3, the computer never needs to go outside of its central memory core. As we shall see in the next section, the same is also true of Step 1. Therefore, in spite of the excruciating meticulousness of our simulation procedure, modern high speed computers should render it practical in many nontrivial situations.

By carrying out the above procedure from time 0 to time t, we evidently obtain only *one possible* realization of the stochastic process defined in (3). In order to get a statistically complete picture of the temporal evolution of the system, we must actually carry out *several independent* realizations or "runs," each starting with the same initial set of molecules and proceeding to the same time t. If we make K runs in all, and record the quantities

$$X_i(k, t) \equiv \text{ the number of } S_i \text{ molecules found in run } k \text{ at time } t,$$
$$(k = 1,..., K) \quad (19)$$

then we may assert that the *average* or *expected* number of S_i molecules at time t is [cf. (9) and (10a)]

$$X_i^{(1)}(t) \simeq (1/K) \sum_{k=1}^{K} X_i(k, t), \quad (20)$$

and the root-mean-square magnitude of the $\pm$ fluctuations which may reasonably be expected to occur about this average is [cf. (9) and (10b)]

$$\Delta_i(t) \simeq \left\{ (1/K) \sum_{k=1}^{K} [X_i(k, t)]^2 - \left[(1/K) \sum_{k=1}^{K} X_i(k, t) \right]^2 \right\}^{1/2}. \quad (21)$$

The $\simeq$ signs in (20) and (21) become $=$ signs in the limit $K \to \infty$. However, the fact that we obviously cannot pass to this limit of infinitely many runs is not a practical source of difficulty. On the one hand, if $\Delta_i(t) \ll X_i^{(1)}(t)$, then the results

$X_i(k, t)$ will not vary much with k; in that case the estimate of $X_i^{(1)}(t)$ would be accurate even for $K = 1$. On the other hand, if $\Delta_i(t) \gtrsim X_i^{(1)}(t)$, then a highly accurate estimate of $X_i^{(1)}(t)$ is not really necessary; of more practical significance and utility in this case would be the *approximate range* over which the numbers $X_i(k, t)$ are scattered for several runs k. In practice, somewhere between $K = 3$ and $K = 10$ runs should provide a statistically adequate picture of the state of the chemical system at time t.

5. IMPLEMENTING THE MONTE CARLO STEP

The description of our simulation algorithm given in the preceding section is complete, except for the details of how to carry out Step 1. In this section we shall present two different procedures, which we shall call respectively the *direct method* and the *first-reaction method*, for implementing this crucial "Monte Carlo step." As we shall see, both of these methods are rigorous and exact, but if the number of reactions M exceeds 3 then the direct method should be a bit more efficient.

The term Monte Carlo is currently applied to a large and diverse collection of computational procedures. A standard reference work on this many-faceted subject is the book of Hammersley and Handscomb [9]. However, for a nonspecialist's introduction to the general theory and methods of generating random points according to a prescribed probability density function (which is the task before us here), the reader is referred to [10, Chap. 2]. Relevant portions of that reference are summarized in our text and Appendix.

Most large digital computer facilities have available a short routine which will generate on call a random number (or more properly, a "pseudorandom" number) from the uniform distribution in the unit interval [11, 12]. We shall denote such a random number by r. By definition, the probability that a generated value r will fall inside any given subinterval of the unit interval is equal to the length of that subinterval, and is independent of its location:

$$\text{For} \quad 0 \leqslant \alpha < \beta \leqslant 1, \quad \text{Prob}\{\alpha \leqslant r \leqslant \beta\} = \beta - \alpha. \quad (22)$$

We shall take it for granted here that we have ready access to some such "uniform random number generator." Our object now is to develop methods for using the output values r of a uniform random number generator to generate a random pair (τ, μ) according to the probability density function $P(\tau, \mu)$ in (17).

A. The "Direct" Method

The first method we shall discuss is based on the fact that any two-variable probability density function can be written as the product of two one-variable

probability density functions, a procedure known as "conditioning." We shall condition $P(\tau, \mu)$ in the form

$$P(\tau, \mu) = P_1(\tau) \cdot P_2(\mu \mid \tau). \tag{23}$$

Here, $P_1(\tau) \, d\tau$ is the probability that the next reaction will occur between times $t + \tau$ and $t + \tau + d\tau$, irrespective of which reaction it might be; and $P_2(\mu \mid \tau)$ is the probability that the next reaction will be an R_μ reaction, given that the next reaction occurs at time $t + \tau$.

By the addition theorem for probabilities, $P_1(\tau) \, d\tau$ is obtained by summing $P(\tau, \mu) \, d\tau$ over all μ-values; thus,

$$P_1(\tau) = \sum_{\mu=1}^{M} P(\tau, \mu).$$

Substituting this into (23) and solving for $P_2(\mu \mid \tau)$ gives

$$P_2(\mu \mid \tau) = P(\tau, \mu) \bigg/ \sum_{\nu=1}^{M} P(\tau, \nu).$$

These two equations evidently express the two one-variable density functions in (23) in terms of the given two-variable density function $P(\tau, \mu)$. Substituting $P(\tau, \mu)$ from (17) yields at once

$$P_1(\tau) = a \exp(-a\tau) \qquad (0 \leqslant \tau < \infty), \tag{24a}$$

$$P_2(\mu \mid \tau) = a_\mu/a \qquad (\mu = 1, 2,..., M), \tag{24b}$$

where we have for convenience abbreviated

$$a_\mu \equiv h_\mu c_\mu \qquad (\mu = 1, 2,..., M) \tag{25}$$

and

$$a \equiv \sum_{\mu=1}^{M} a_\mu \equiv \sum_{\mu=1}^{M} h_\mu c_\mu . \tag{26}$$

We observe in passing that, in this particular case, $P_2(\mu \mid \tau)$ is independent of τ. We also note that, as we should expect, both of these one-variable density functions are properly normalized over their respective domains of definition:

$$\int_0^\infty P_1(\tau) \, d\tau = \int_0^\infty a \exp(-a\tau) \, d\tau = 1; \qquad \sum_{\mu=1}^{M} P_2(\mu \mid \tau) = \sum_{\mu=1}^{M} a_\mu/a = 1.$$

The idea of the "direct method" is to first generate a random value τ according to $P_1(\tau)$ in (24a), and then generate a random integer μ according to $P_2(\mu \mid \tau)$ in (24b). The resulting random pair (τ, μ) will be distributed according to $P(\tau, \mu)$.[5]

[5] For a formal proof and a more general discussion of this procedure, see [10, pp. 23–35].

As we show in the Appendix (cf. (A4)), a random value τ may be generated according to $P_1(\tau)$ in (24a) by simply drawing a random number r_1 from the uniform distribution in the unit interval and taking

$$\tau = (1/a)\ln(1/r_1). \tag{27a}$$

Then, as we also show in the Appendix (cf. (A7)), a random integer μ may be generated according to $P_2(\mu \mid \tau)$ in (24b) by drawing another random number r_2 from the uniform distribution in the unit interval and taking μ to be that integer for which

$$\sum_{\nu=1}^{\mu-1} a_\nu < r_2 a \leqslant \sum_{\nu=1}^{\mu} a_\nu\ ; \tag{27b}$$

i.e., the successive values a_1, a_2,... are cumulatively added (in a computer do-loop) until their sum is observed to equal or exceed $r_2 a$, whereupon μ is then set equal to the index of the last a_ν term added.

In summary, the "direct" method for generating a random pair (τ, μ) according to $P(\tau, \mu)$ is to draw two random numbers r_1 and r_2 from our uniform random number generator, and then calculate τ and μ from (27a) and (27b), respectively. To carry out this procedure in the most efficient manner, we should store not only the M quantities $\{a_\mu\} \equiv \{h_\mu c_\mu\}$ but also their sum a. Then, in the course of updating the $\{a_\mu\}$ values after each reaction, we may also update a by simply subtracting each old a_μ-value and adding the corresponding new one.

Given a fast, reliable uniform random number generator, the above procedure can be easily programmed and rapidly executed. The direct method is therefore a simple, fast, rigorous procedure for implementing Step 1 of our simulation algorithm.

B. The "First-reaction" Method

We now present an alternate method for implementing Step 1 of our simulation algorithm. Although this method is usually not quite as efficient as the direct method, it is worth discussing here because of the added insight it provides into our stochastic simulation approach.

Using the notation $a_\nu \equiv h_\nu c_\nu$ adopted in Section 5A, it is a simple matter to show from (13) that

$$P_\nu(\tau)\,d\tau = \exp(-a_\nu\tau) \cdot a_\nu\,d\tau \tag{28}$$

would be the probability at time t for an R_ν reaction to occur in the time interval $(t + \tau, t + \tau + d\tau)$, *were it not for the fact* that the number of R_ν reactant com-

binations might be altered between times t and $t + \tau$ by the occurrence of other reactions. This being the case, let us generate a "tentative reaction time" τ_ν for reaction R_ν according to the probability density function P_ν in (28), and in fact do the same for *all* reactions $\{R_\nu\}$. Thus, in accordance with (A4), we put

$$\tau_\nu = (1/a_\nu) \ln(1/r_\nu) \qquad (\nu = 1, 2,..., M), \tag{29a}$$

where r_ν is a random number from the uniform distribution in the unit interval. From these M *tentative* reactions, we choose as the *actual next* reaction the one which occurs *first*; i.e., we take

$$\tau = \text{smallest } \tau_\nu \text{ for all } \nu = 1, 2,..., M;$$
$$\mu = \nu \text{ for which } \tau_\nu \text{ is smallest.} \tag{29b}$$

We shall now prove that this method of generating a random pair (τ, μ), which we shall call the "first-reaction method," is in fact a completely correct way of implementing Step 1 of our simulation algorithm. Our proof will consist of showing that the probability density function for the random pair (τ, μ) generated according to this procedure coincides with the function $P(\tau, \mu)$ in (17).

Let $\tilde{P}(\tau, \mu) \, d\tau$ be the probability that the procedure described above will result in the next reaction being an R_μ reaction *and* occurring in the time interval $(t + \tau, t + \tau + d\tau)$. From (29b) we may evidently write this probability as

$$\tilde{P}(\tau, \mu) \, d\tau = \text{Prob}\{\tau < \tau_\mu < \tau + d\tau\} \times \text{Prob}\{\tau_\nu > \tau, \text{ all } \nu \neq \mu\}. \tag{30}$$

From (28) we see that the first factor here is just

$$\text{Prob}(\tau < \tau_\mu < \tau + d\tau) = \exp(-a_\mu\tau) \cdot a_\mu \, d\tau. \tag{31a}$$

For the second factor in (30), we have from (29a) that

$$\text{Prob}\{\tau_\nu > \tau, \text{ all } \nu \neq \mu\} = \text{Prob}\{(1/a_\nu) \ln(1/r_\nu) > \tau, \text{ all } \nu \neq \mu\}$$

$$= \text{Prob}\{r_\nu < \exp(-a_\nu\tau), \text{ all } \nu \neq \mu\}$$

$$= \prod_{\substack{\nu=1 \\ \nu \neq \mu}}^{M} \text{Prob}\{r_\nu < \exp(-a_\nu\tau)\},$$

where the last step follows from the fact that the random numbers r_ν in (29a) are independent of one another. Now, r_ν is a random number from the uniform distribution in the unit interval, so the probability that it will be less than a given number

between 0 and 1 is just equal to that given number (cf. (22) for $\alpha = 0$). Thus we obtain

$$\text{Prob}\{\tau_\nu > \tau, \text{ all } \nu \neq \mu\} = \prod_{\substack{\nu=1 \\ \nu \neq \mu}}^{M} \exp(-a_\nu \tau). \tag{31b}$$

Now inserting (31a) and (31b) into (30), we get

$$\tilde{P}(\tau, \mu)\, d\tau = a_\mu\, d\tau \cdot \prod_{\nu=1}^{M} \exp(-a_\nu \tau)$$

$$= a_\mu \exp\left[-\sum_{\nu=1}^{M} a_\nu \tau\right] d\tau,$$

or, with (17) and the definition $a_\nu \equiv h_\nu c_\nu$,

$$\tilde{P}(\tau, \mu)\, d\tau = P(\tau, \mu)\, d\tau. \tag{32}$$

Thus, the first-reaction method, as defined through (29a) and (29b), is indeed a legitimate way to implement Step 1 of our simulation algorithm.

It is tempting to try to extend this method by letting the "second next" reaction be the one for which τ_ν has the second smallest value. However, that would *not* be legitimate, because the prospects for that second reaction will usually be altered by the changes in the molecular population caused by the first reaction, and these altered prospects are not taken into account by the proposed simple extension of the first-reaction method. For example, using the second earliest reaction would in principle allow the second reaction to involve molecules already destroyed in the first reaction, yet would not allow the second reaction to involve molecules created in the first reaction.

The first-reaction method is of course just as rigorous and exact as the direct method. It is probably easier to code for a computer than the direct method, and in many respects it is intuitively quite appealing. However, the first-reaction method evidently requires M separate random numbers from the uniform random number generator in order to effect each molecular reaction, whereas the direct method always requires only 2; hence, for $M \geqslant 3$ the first-reaction method will be wasteful of random numbers. This is an important consideration, because all pseudorandom number generators have a limited output capacity, and even the direct method is going to tax the random number generator quite heavily. In addition, the first-reaction method will be slower for large M, since the computer needs more time to calculate M logarithms (cf. (29a)) than to add M terms (cf. (27b)). Therefore, for $M \geqslant 3$ the direct method is probably the method of choice for implementing Step 1 of our simulation algorithm.

6. AN EXAMPLE

To describe our simulation algorithm in more concrete terms, let us consider a spatially homogeneous system composed of four chemical species, W, X, Y and Z, subject to the following set of six coupled chemical reactions:

$$X \underset{c_2}{\overset{c_1}{\rightleftharpoons}} Y, \tag{33a}$$

$$2X \underset{c_4}{\overset{c_3}{\rightleftharpoons}} Z, \tag{33b}$$

$$W + X \underset{c_6}{\overset{c_5}{\rightleftharpoons}} 2X. \tag{33c}$$

We suppose that the values of the six reaction parameters $c_1, ..., c_6$ are given, as are also the initial numbers of molecules, W_0, X_0, Y_0, Z_0, of the respective chemical species inside the containing volume V. We shall not undertake here any actual numerical calculations of the behavior of the system for specific values of these input parameters; however, we shall describe in some detail a Fortran program which employs our stochastic simulation algorithm to effect such calculations. Before we do this, though, let us see how this problem looks from the viewpoints of, first, the deterministic reaction rate equations, and second, the stochastic master equation.

In the deterministic approach we would regard the c_μ's as reaction "rates," and we would represent the numbers of W, X, Y, and Z molecules in V at time t by continuous functions, say $W(t)$, $X(t)$, $Y(t)$ and $Z(t)$. We would then try to obtain these four functions by solving the following set of coupled ordinary differential equations, subject to the initial condition $W(0) = W_0$, $X(0) = X_0$, $Y(0) = Y_0$, $Z(0) = Z_0$:

$$dW/dt = -c_5 WX + \tfrac{1}{2}c_6 X^2, \tag{34a}$$

$$dX/dt = -c_1 X + c_2 Y - c_3 X^2 + 2c_4 Z + c_5 WX - \tfrac{1}{2}c_6 X^2, \tag{34b}$$

$$dY/dt = c_1 X - c_2 Y, \tag{34c}$$

$$dZ/dt = \tfrac{1}{2}c_3 X^2 - c_4 Z. \tag{34d}$$

These equations are perhaps more familiar when expressed in terms of the concentrations $w \equiv W/V$, $x \equiv X/V$, etc., and the reaction rate constants k_μ as discussed in Section 2; e.g., the first equation is evidently equivalent to $dw/dt = -k_5 wx + k_6 x^2$, where $k_5 \equiv Vc_5$ and $k_6 \equiv Vc_6/2$. Either way, though, the set of equations does not appear to be solvable in closed form by purely analytical methods, so we would probably attempt a numerical solution by using a finite-

time-step algorithm on a digital computer. However, the nonlinear character of the set of reactions in (33) may give rise to "multiple steady states" for certain ranges of the input parameters [6, 7, 8]; when these occur, the chemical behavior of the system cannot be reliably predicted within the framework of the deterministic formulation.

The usual stochastic approach begins by focusing attention on the probability function $\mathscr{P}(W, X, Y, Z; t)$, which is defined to be the probability of finding W of the W-type molecules and X of the X-type molecules, etc., inside V at time t. By applying the standard rules of probability theory, it is a straightforward matter to deduce from (3) the master equation

$$\partial \mathscr{P}(W, X, Y, Z; t)/\partial t$$
$$= c_1[(X + 1) \mathscr{P}(W, X + 1, Y - 1, Z; t) - X\mathscr{P}(W, X, Y, Z; t)]$$
$$+ c_2[(Y + 1) \mathscr{P}(W, X - 1, Y + 1, Z; t) - Y\mathscr{P}(W, X, Y, Z; t)]$$
$$+ c_3[\tfrac{1}{2}(X + 2)(X + 1) \mathscr{P}(W, X + 2, Y, Z - 1; t)$$
$$\quad - \tfrac{1}{2}X(X - 1) \mathscr{P}(W, X, Y, Z; t)]$$
$$+ c_4[(Z + 1) \mathscr{P}(W, X - 2, Y, Z + 1; t) - Z\mathscr{P}(W, X, Y, Z; t)]$$
$$+ c_5[(W + 1)(X - 1) \mathscr{P}(W + 1, X - 1, Y, Z; t) - WX\mathscr{P}(W, X, Y, Z; t)]$$
$$+ c_6[\tfrac{1}{2}(X + 1) X\mathscr{P}(W - 1, X + 1, Y, Z; t)$$
$$\quad - \tfrac{1}{2}X(X - 1) \mathscr{P}(W, X, Y, Z; t)]. \tag{35}$$

In principle, this time-evolution equation can be solved subject to the given initial condition $\mathscr{P}(W, X, Y, Z; 0) = \delta_{W,W_0}\delta_{X,X_0}\delta_{Y,Y_0}\delta_{Z,Z_0}$ to obtain $\mathscr{P}(W, X, Y, Z; t)$ uniquely for all $t > 0$. In practice, however, this equation is virtually intractable. Notice that even a computer solution by a finite-time-step procedure is out of the question here, because of the astronomical amount of computer memory that would be required just to store the current values of the function $\mathscr{P}$ on the 4-dimensional integer lattice space of the variables W, X, Y and Z.

We can, however, numerically analyze this problem within the framework of the stochastic formulation by using our simulation algorithm. Below is a Fortran program (minus format statements) which will cause a digital computer to simulate the time evolution of the given chemical system from time t_1 to time t_2, printing out the numbers of $W, X, Y,$ and Z molecules found inside V at successive time intervals of t_{int} :

```
C PRØGRAM TØ SIMULATE REACTIØNS (33).
  DIMENSIØN C(6), A(6)
1 READ((C(MU), MU = 1, 6), T, W, X, Y, Z, T2, TINT)
  TPRINT = T
```

```
10  A(1) = C(1) * X
    A(2) = C(2) * Y
    A(3) = C(3) * X * (X − 1.)/2.
    A(4) = C(4) * Z
    A(5) = C(5) * W * X
    A(6) = C(6) * X * (X − 1.)/2.
    A0 = A(1) + A(2) + A(3) + A(4) + A(5) + A(6)
20  CALL URN(R1, R2)
21  T = T + ALØG(1./R1)/A0
22  IF (T .LT. TPRINT) GØ TØ 25
23  PRINT(TPRINT, W, X, Y, Z)
    TPRINT = TPRINT + TINT
    GØ TØ 22
25  R2A0 = R2 * A0
    SUM = 0.
26  DØ 29 NU = 1, 6
    MU = NU
    SUM = SUM + A(NU)
    IF (SUM .GE. R2A0) GØ TØ 30
29  CØNTINUE
30  GØ TØ (31, 32, 33, 34, 35, 36), MU
31  X = X − 1.
    Y = Y + 1.
    GØ TØ 40
32  X = X + 1.
    Y = Y − 1.
    GØ TØ 40
33  X = X − 2.
    Z = Z + 1.
    GØ TØ 40
34  X = X + 2.
    Z = Z − 1.
    GØ TØ 40
35  X = X + 1.
    W = W − 1.
    GØ TØ 40
36  X = X − 1.
    W = W + 1.
40  IF (T .LT. T2) GØ TØ 10
    STØP
    END
```

The fact that this short, simple computer program, which requires only 27 memory locations for its variables, can exactly simulate the process described by the complicated master equation (35) illustrates a prime virtue of our simulation algorithm. Let us now describe the workings of this program in detail.

The system's time is denoted by the variable T, and the numbers of species molecules inside V at time T are denoted by the respective variables W, X, Y and Z. In statement 1 the values of the externally specified parameters are read in as follows: the six reaction parameters c_1 ,..., c_6 are read into C(1),..., C(6); the initial time t_1 is read into T; the numbers of molecules at the initial time t_1 are read into W, X, Y, and Z; the stopping time t_2 is read into T2; and the time interval t_{int} between computer printouts is read into TINT. The magnitudes of these externally specified parameters are largely arbitrary; they will affect the total running time of the program, but not its memory storage requirements. Following statement 1 the variable TPRINT is initialized; this variable simply keeps track of the times at which computer printouts of the molecular population are to be made.

The main computational sequence is entered at statement 10. Here we proceed to evaluate for the current molecular population the quantities a_1 ,..., a_6 (denoted by A(1),..., A(6)) according to (25) and (14), and also the quantity a (denoted by A0) according to (26). Next, in statement 20 we call subroutine URN, which returns two independent random numbers R1 and R2 from the uniform distribution in the unit interval.[6] R1 and R2 correspond to the random numbers r_1 and r_2 in the "direct method" generating formulas (27a) and (27b). In statement 21 we increase the current value of T by the amount τ as given in (27a); this brings the system clock up to the occurrence time of the "next" reaction. In statement 22 we check to see if T has just been advanced beyond the next printout time; if it has, we print out the molecular populations at that print-out time before proceeding. (The program is arranged so that the *initial* molecular population will always be printed out.) The determination of just which reaction R_μ occurs at time T is accomplished by the seven statements beginning at statement 25. Here, according to the prescription of (27b), the values a_1 , a_2 , etc., are successively added together until their sum is observed to equal or exceed r_2a (denoted by R2A0), whereupon the reaction index μ (denoted by MU) is set equal to the index of the last a_ν term added. Statement 30 then branches to the specific statements which effect the occurrence of one R_μ reaction by appropriately altering the molecular population. For example,

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[6] See Refs. [9, 11] and (especially) [12] for ways of constructing subroutine URN for specific digital computers. The *name* URN is suggested for two reasons. First, as an accronym for "Uniform Random Number Generator," it emphasizes the sometimes unappreciated fact that "uniformness" and "randomness" are not logical concomitants, and that one can also legitimately have a set of random numbers distributed according to a nonuniform or biased distribution. Second, the urn is the container traditionally used by classically refined statisticians to "hold" random numbers for subsequent "drawings"—precisely its function in our program.

if MU $= 4$ we branch to statement 34, which increases the number of X molecules by 2 and decreases the number of Z molecules by 1, in accordance with the inverse of reaction (33b). Then, if T has not reached the stopping time T2, we return to statement 10 to recalculate A(1),..., A(6) and A0 for the new molecular population, in preparation for the simulation of the next molecular reaction. (We have not bothered here to program around unnecessary recalculations of the A(NU) quantities; e.g., if MU $= 4$ on the last reaction then Y will not have been changed and A(2) need not be recalculated. For a larger system it would undoubtedly pay to avoid such redundancies.) The program repeatedly cycles from statement 10 to statement 40, simulating each successive molecular reaction in turn until T has finally been advanced to time T2, whereupon the program terminates.

By running the program several times with the same input parameters, but different initializations of subroutine URN, we may obtain means and variances in the manner of (20) and (21). Alternatively, we may simply wish to follow the temporal behavior of the system to see if and how a steady state is approached, and if and how transitions between multiple steady states occur. Notice that any of the six reactions can be blocked out simply by setting its reaction parameter to zero. It is also easy to artificially hold the number of molecules of any species constant; e.g., if we wished to keep the number of Y molecules constant, reflecting perhaps a very large population of Y molecules which is not appreciably affected by the reactions, then we would simply remove the two statements following statements 31 and 32, respectively. Clearly, a wide variety of interesting dynamical features of the set of coupled chemical reactions in (33) can be investigated with this stochastic simulation program.

7. SUMMARY AND DISCUSSION

In this paper we have presented a relatively simple procedure for calculating the time evolution of any spatially homogeneous chemical system in which the dynamics of the chemical reactions R_μ can be characterized in the manner of (3). Equation (3) is the fundamental postulate of the stochastic master equation approach to chemical kinetics, in which the dynamics of the chemical system is regarded as a Markov process in the space of the species population numbers. In Section 2 we argued that this stochastic approach ought to be valid whenever *nonreactive* molecular collisions occur much more frequently than *reactive* molecular collisions. We also discussed in Section 2 the relationship between the reaction parameter c_μ, defined in (3), and the more familiar reaction rate constant k_μ, which forms the basis of the deterministic approach to chemical kinetics. We concluded that *algebraically* the relationship between c_μ and k_μ is quite simple, but *conceptually* c_μ appears to be on somewhat firmer ground than k_μ.

The computational procedure presented here is a systematic, computer-oriented, Monte Carlo algorithm, which directly simulates the Markov process defined by (3). However, the simulation algorithm is based, not on the master equation, but on the "reaction probability density function" $P(\tau, \mu)$ defined in (11). Given a specified population of molecules at time 0, the simulation algorithm is executed as follows: First, the function $P(\tau, \mu)$ for the current molecular population is determined in accordance with (17); second, using either of the two Monte Carlo methods (27) or (29), a pair of random numbers (τ, μ) is generated according to this density function; and third, the time variable is advanced by τ, and the molecular population is adjusted to reflect the occurrence of one molecular reaction R_μ. By repeatedly cycling through these three steps, we may work our way from time 0 to any specified time $t > 0$, and thereby obtain one stochastically unbiased state of the chemical system at time t. By examining the outcomes of several such runs, each of which starts from the same initial state and proceeds to the same time t, we may deduce both the *mean* state and time t and also the approximate magnitude of the random *fluctuations* that may reasonably be expected to occur about this mean state. This computational procedure was described more concretely in Section 6, where we presented a Fortran program implementing the simulation algorithm for a sample set of coupled chemical reactions.

Our derivation of the mathematical form of $P(\tau, \mu)$ from the fundamental hypothesis (3) does not involve any additional assumptions or approximations (see Section 3). Furthermore, our methods for generating random τ and μ values commensurate with $P(\tau, \mu)$ are likewise completely rigorous (see Section 5 and the Appendix). Consequently, our numerical simulation algorithm may be regarded as *exact*. By contrast, the commonly used numerical algorithms which solve the deterministic reaction rate equations must be considered as *approximate* for two reasons: first, the reaction rate equations themselves are approximate, relative to (3), because they ignore effects due to correlations and fluctuations; and second, virtually all numerical methods for solving sets of coupled differential equations entail approximating infinitesimal time increments dt by finite time steps Δt.

It turns out that, for most macroscopic chemical systems, the neglect of correlations and fluctuations is a legitimate approximation [2, 3]. For these cases the deterministic and stochastic approaches are essentially equivalent, and one is free to use whichever approach turns out to be more convenient or efficient. If an *analytical* solution is required, then the deterministic approach will always be much easier than the stochastic approach. However, if one is forced to settle for a *numerical* solution, then the choice between the two approaches should be considerably more even. In particular, it may (or may not) turn out that our stochastic simulation algorithm offers a convenient way around the so-called "stiffness" difficulty that occurs with the coupled differential reaction rate equations when the reaction rates range over many orders of magnitude.

For spatially homogeneous systems that are driven to conditions of chemical instability, correlations and fluctuations will give rise to transitions between non-equilibrium steady states, and the usual deterministic approach is incapable of accurately describing the time behavior. Among the pioneering investigations into this interesting area of chemical kinetics are the recent works of McNeil and Walls [6], Nitzan *et al.* [7], and Matheson *et al.* [8], all of whom have made use of spatially homogeneous master equations to study chemical instabilities in certain simple systems. Our stochastic simulation algorithm is directly applicable to these studies, and it should be especially useful for extending them to more complex systems involving many chemical species and many highly coupled chemical reaction channels.

The principle source of computational inaccuracy in our simulation algorithm is the limited "randomness" of the particular unit-interval uniform random number generator that is used. It is known, for example, that so-called simple multiplicative congruential generators exhibit nonrandom pairwise correlations between successively generated values. Since our procedure normally uses successive random numbers in pairs to calculate the τ and μ values for each reaction, it would probably be more prudent to use a "compound" multiplicative congruential generator, which randomly mixes two or more of the simple ones [12]. The "resolution" of the generator, or the number of decimal digits to which the generator can be regarded as being effectively random, is an important consideration. For example, an n-digit generator may have trouble reliably sampling any reaction R_μ which has a relative probability a_μ/a less than 10^{-n}. Another important property of a uniform random number generator is its "period," or how many values it will put out before it starts repeating itself. The period can obviously never be greater than the word size of the computer, but in most cases the period will be considerably less than this. It is not necessarily fatal if the generator cycles several times during the course of a long run, but too many cycles can obviously lead to spurious results. This writer frankly regards the construction of computer codes to generate uniform random numbers as a gray (if not black) art, which is best entrusted to experts in the field [12]. Fortunately, the present state of this art is quite good, and will probably improve with time.

The computer storage space required by our simulation algorithm is quite small. This is an important consideration, since charges at most large computer facilities are based not only on how long a job runs but also on how much memory storage is used. However, since our algorithm simulates the occurrence of each individual molecular reaction, it places a considerable premium on the *speed* of the computer. In general, *the required computation time will be directly proportional to the number of individual molecular reactions that actually take place in the system.* This must be kept in mind when specifying the initial molecular population and the containing volume V. Another point to bear in mind in this connection is that our algorithm,

like Nature, deals only with whole numbers of molecules; thus, for example, if species S_i is to be present only in several parts per million relative to species S_j, then the initial number of S_j molecules should be larger than 10^6.

It was brought to the author's attention by one of the referees that the simulation algorithm presented here is similar to a computational scheme used earlier by Bunker et al. [13]. In terms of present notation, Bunker et al. use the same μ-selection rule as in (27b), but they replace the τ-selection rule in (27a) by simply $\tau = 1/a$. Since $1/a$ is precisely the mean value of the τ-distribution described by $P_1(\tau)$ in (24a), this substitution is not unreasonable, and we may expect that in many situations the consequent loss of fidelity will be slight enough to justify avoiding the computational effort of generating a random number r_1 and taking the logarithm of its reciprocal; in fact, if one is interested *only* in finding the *steady states* of a system, one may simply *dispense* with the τ-selection process altogether. (Of course, the use of the mean τ-step instead of the properly randomized τ-step will *not* eliminate the need to carry out several independent runs when averages are desired.) In their paper, Bunker et al. characterize their computational procedure as a "hybrid method, intermediate between differential equation solution and Monte Carlo," which it clearly is; however, they derive their method in a heuristic way within the context of the deterministic reaction rate formalism. By contrast, the computational procedure presented here is an "exact method," which has been derived in a mathematically rigorous way from very fundamental physical considerations. This analysis has made it quite clear that the underlying dynamics of a chemically reacting system in thermal equilibrium is stochastic rather than deterministic, and consequently the stochastic approach (as exemplified *analytically* by the spatially homogeneous master equation and *numerically* by our stochastic simulation algorithm) provides an intrinsically better description of the system's behavior than does the deterministic set of coupled reaction rate equations. In particular, no apologies need be made for the fluctuations that occur in a (correctly done) Monte Carlo simulation, since these fluctuations are *really present*, and can in some cases give rise to macroscopically observable effects; and in those cases in which fluctuations turn out to be unimportant, that fact too will emerge quite naturally from the calculations themselves. In a sense, then, our work here has placed the hybrid method of Bunker et al. in the context of a more rigorous framework, thus providing an a priori means of assessing its validity. Clearly, though, the procedure of Bunker et al. is intrinsically more legitimate than any computational scheme which is based on the deterministic reaction rate equations—a point that was not obvious from their original work [13].

Finally, we make note of three possible variations or extensions of the computational procedure offered here. First, we observe that the expressions for h_μ in (14) for the various reaction types listed in (2) follow from the definition given in (12). However, if one has legitimate physical reasons for assuming that h_μ for

any reaction has a *different* form than required by (14), involving perhaps fractional powers of the numbers of reactant molecules, it is obviously a simple matter to alter h_μ accordingly in our computational procedure. Indeed, it will be observed that h_μ and c_μ are used in our simulation algorithm only in the combination $h_\mu c_\mu \equiv a_\mu$. It follows that our simulation algorithm requires *only* that the probability on the right side of (13) be expressible as $a_\mu \, \delta t$, where a_μ can be *any specified function* of the current molecular population, the physical properties of the molecules, and the thermal environment of the system.

Second, we note that if the temperature dependencies of the reaction parameters $\{c_\mu\}$ are known, as for example in (6), then our simulation algorithm can be extended to accommodate a *time-varying temperature*. However, any change in the temperature must be slow enough that the entire system may always be regarded as having a single temperature, and also slow enough that the temperature change between successive molecular reactions be negligibly small. The temperature change may either be externally caused, such as the diurnal temperature changes induced in an atmospheric chemical system; or, it may be caused by the heat absorbed or released in the chemical reactions themselves, a phenomenon that is especially easy to account for in our one-reaction-at-a-time approach. In either case, by monitoring the net heat flow into or out of the system, the system temperature may be constantly adjusted on the basis of an assumed system heat capacity. The resulting temperature changes may be taken into account by periodically updating the reaction parameters $\{c_\mu\}$, and the associated quantities $\{a_\mu\}$ and a, as necessary.

Finally, we describe a modification of our simulation algorithm which, although rather awkward, might allow one to deal in an *approximate* way with *spatial inhomogeneities*. The basic idea is to divide the volume V into a number of subvolumes V_l $(l = 1, 2,..., L)$ in such a way that spatial homogeneity may be assumed *within* each subvolume. Each subvolume V_l would then be characterized by its own (uniformly distributed) molecular population $\{X_{l,i}\}$, and also a set of reaction parameters $\{c_{l,i}\}$ appropriate to the (uniform) temperature T_l inside V_l. The diffusive transfer of one molecule of species S_i from the subvolume V_l to a contiguous subvolume $V_{l'}$ could be simulated by the simultaneous occurrence of the type (2b) reaction $S_i \to 0$ in V_l and the type (2a) reaction $* \to S_i$ in $V_{l'}$:

$$X_{l,i} \to X_{l,i} - 1,$$
$$X_{l',i} \to X_{l',i} + 1. \tag{36a}$$

The probability coefficient $a_\mu \equiv h_\mu c_\mu$ for this "species-i diffusive transfer reaction" might conceivably have the form

$$a_\mu = D_i A_{ll'}[(X_{l,i}/V_l) - (X_{l',i}/V_{l'})]/d_{ll'}, \quad \text{if} \quad X_{l,i}/V_l > X_{l',i}/V_{l'},$$
$$= 0, \qquad\qquad\qquad\qquad\qquad \text{otherwise,} \tag{36b}$$

where $d_{ll'}$ is the center-to-center distance between subvolumes V_l and $V_{l'}$, $A_{ll'}$ is the interfacing area between these two subvolumes, and D_i is an appropriately scaled molecular diffusivity for chemical species S_i. The transfer of thermal energy between contiguous subvolumes might perhaps be effected by the methods outlined in the preceding paragraph. The dynamics of the system as a whole would be governed by a suitably generalized form of the reaction probability density function. One likely candidate for this would be the function defined by

$$P(\tau, \mu, l) \, d\tau \equiv \text{probability at time } t \text{ that the } next \text{ reaction in } V \text{ will}$$
$$\text{occur in the time interval } (t + \tau, t + \tau + d\tau), \text{ and} \quad (37)$$
$$\text{will be an } R_\mu \text{ reaction inside the subvolume } V_l.$$

The simulation would then proceed by applying our Monte Carlo methods to generate random triplets (τ, μ, l) according to this three-variable probability density function. For extensive, complicated systems this approach would probably be impractical because of the large number of subvolumes required and the resulting plethora of reaction channels, particularly those channels controlling diffusive transfers between contiguous subvolumes. However, this approach might be quite feasible for a system confined to a tubular volume in which the gradients are small and entirely along the tube axis; in that case each subvolume would have only two neighbors. For the present, though, attempts to extend our simulation algorithm to spatially inhomogeneous systems seem rather premature, and probably should await a more precise determination of the domain of feasibility of the algorithm for spatially homogeneous systems.

APPENDIX: THE INVERSION GENERATING METHOD

Equations (27a), (27b), and (29a) are applications of a general Monte Carlo technique called the "inversion method," whereby one uses random numbers from the uniform distribution in the unit interval (see (22)) to construct random numbers distributed according to *any prescribed* probability density function. In this Appendix we review this well-known generating technique for both continuous-single-variable and discrete-single-variable probability density functions. The application of the inversion method to multivariable probability density functions is discussed in [10, Chap. 2].

Suppose we wish to generate a random real number x according to the probability density function $P(x)$. By definition, $P(x') \, dx'$ is to be the probability that x will lie between x' and $x' + dx'$. Consider the function

$$F(x) \equiv \int_{-\infty}^{x} P(x') \, dx'. \quad (A1)$$

Evidently, $F(x_0)$ is the probability that x will be less than x_0. The function $F(x)$ defined by (A1) is called the probability *distribution* function, and is to be clearly distinguished from the probability *density* function $P(x)$. Notice that

$$F(-\infty) = 0 \quad \text{and} \quad F(+\infty) = 1; \qquad (A2)$$

the second equality is the "normalization condition," which expresses the fact that every random x has got to be someplace. Notice also that, since $P(x)$ is everywhere nonnegative, then (A1) implies that $F(x)$ rises from 0 at $x = -\infty$ to 1 at $x = +\infty$ in a nondecreasing way.

The inversion method for generating a random value x according to a given density function $P(x)$ is simply to draw a random number r from the uniform distribution in the unit interval, and take for x that value which satisfies $F(x) = r$; in other words, take

$$x = F^{-1}(r), \qquad (A3)$$

where F^{-1} is the inverse of the distribution function corresponding to the given density function P. (Note that the range and monotonicity of $F(x)$ insure the existence of $F^{-1}(r)$ in $0 \leqslant r \leqslant 1$.)

To prove that this procedure is correct, let us calculate the probability that the x-value so generated will lie between x' and $x' + dx'$. By construction, this probability is the same as the probability that r will lie between $F(x')$ and $F(x' + dx')$. Since r is a random number from the uniform distribution in the unit interval, then by (22) this probability is just

$$F(x' + dx') - F(x') = F'(x')\, dx' = P(x')\, dx',$$

where the second equality follows from (A1). We conclude, then, that the probability density function for the random number x generated according to (A3) is indeed $P(x)$.

For example, suppose we wish to generate a random number x according to the probability density function

$$\begin{aligned} P(x) &= A \exp(-Ax), \quad &\text{for} \quad 0 \leqslant x < \infty, \\ &= 0, \quad &\text{otherwise,} \end{aligned} \qquad (A4a)$$

where A is a positive constant. Using (A1), we easily calculate the corresponding probability distribution function to be $F(x) = 1 - \exp(-Ax)$. Then putting $F(x) = r$ and inverting (and for simplicity replacing the random variable $1 - r$ by the statistically equivalent random variable r), we obtain

$$x = (1/A) \ln(1/r) \qquad (A4b)$$

as the rule for generating a random number x according to the probability density function $P(x)$ in (A4a). This is the formula used in (27a) and (29a).

In the discrete case, the problem is to generate a random integer i according to the probability density function $P(i)$, where $P(i')$ is now the probability that i will *equal i'*. The corresponding distribution function $F(i)$ is defined by

$$F(i) \equiv \sum_{i'=-\infty}^{i} P(i'), \tag{A5}$$

and $F(i_0)$ is evidently the probability that i will be less than *or equal to i_0*.

The inversion method for generating i according to $P(i)$ is to draw a random number r from the uniform distribution in the unit interval and take for i that value which satisfies

$$F(i-1) < r \leqslant F(i). \tag{A6}$$

To prove that this procedure is correct, let us calculate the probability that the resulting integer i will equal i'. This probability is just the probability that r will lie between $F(i'-1)$ and $F(i')$, and by (22) this probability is

$$F(i') - F(i'-1) = \sum_{i''=-\infty}^{i'} P(i'') - \sum_{i''=-\infty}^{i'-1} P(i'') = P(i').$$

This proves that $P(i)$ is indeed the probability density function for the random number i generated according to the rule (A6).

For example, suppose we wish to generate a random integer i according to the density function

$$P(i) = a_i \bigg/ \sum_{j=1}^{M} a_j, \qquad \text{for} \quad i = 1, 2, ..., M, \tag{A7a}$$
$$= 0, \qquad\qquad\quad \text{otherwise},$$

where the a_i's are nonnegative numbers. Then applying (A6) we see that we must choose i to be that integer for which

$$\sum_{i'=1}^{i-1} P(i') < r \leqslant \sum_{i'=1}^{i} P(i')$$

or

$$\sum_{i'=1}^{i-1} a_{i'} < r \sum_{j=1}^{M} a_j \leqslant \sum_{i'=1}^{i} a_{i'}. \tag{A7b}$$

This is the generating formula used in (27b).

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