

Conditioned averages in chemical kinetics

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It is argued that the molecular population functions which satisfy the deterministic reaction-rate equations, and the first moments of the solution to the stochastic master equation, can be generally regarded as differently conditioned averages of the same random variables. Although these two kinds of averages usually differ only on the microscopic scale, it is pointed out they can differ macroscopically for chemical oscillators. However, this is not a sign of any inconsistency in the theory because it is fully explained by the different conditionings employed. Both kinds of averages are seen to play legitimate, useful roles in describing the dynamics of a stochastically evolving chemical system.

I. INTRODUCTION

Our purpose in this paper is to clarify the connection between two kinds of dynamical variables in the theory of chemical kinetics. We begin by giving a brief summary of the "stochastic formulation" of chemical kinetics, so that we can expose our basic assumptions and establish a consistent notation.

Consider a well-stirred chemical system containing N molecular species S_i ($i = 1, \dots, N$) which interreact through M chemical reaction channels R_μ ($\mu = 1, \dots, M$). The current "state" of the system is specified by the N -dimensional vector $\mathbf{x} = (x_1, x_2, \dots, x_N)$, where x_i is defined to be the current total number of S_i molecules in the system (a nonnegative integer). Each reaction channel R_μ is fully characterized by two quantities: First there is a point function $a_\mu(\mathbf{x})$, defined by

$a_\mu(\mathbf{x}) dt \equiv$ probability that, given the system is in state \mathbf{x} at time t , an R_μ reaction will occur in the next infinitesimal time interval $(t, t + dt)$. (1)

Generally, $a_\mu(\mathbf{x})$ is equal to the product of a "reaction constant" c_μ times the total number of distinct R_μ molecular reactant combinations available when the state is \mathbf{x} .¹ Second, there is an N -dimensional vector $\nu_\mu = (\nu_{\mu 1}, \nu_{\mu 2}, \dots, \nu_{\mu N})$, where

$\nu_{\mu i} \equiv$ net change in x_i caused by an R_μ reaction. (2)

Typically, $\nu_{\mu i}$ is one of the integers $-2, -1, 0, 1$, or 2 . Reaction R_μ thus induces the "state transition" $\mathbf{x} \rightarrow \mathbf{x}' = \mathbf{x} + \nu_\mu$.

Assuming that the system starts at time $t = 0$ in a given state $\mathbf{x} = \mathbf{x}_0 = (x_{01}, x_{02}, \dots, x_{0N})$, then Eqs. (1) and (2) imply that for $t > 0$ the system executes a continuous-time Markovian random walk over the discrete integer lattice space of \mathbf{x} . The usual way of mathematically analyzing this temporal behavior is through the probability function

$P(\mathbf{x}; t | \mathbf{x}_0) \equiv$ probability that the system will be in state \mathbf{x} at time t , given that it was in state \mathbf{x}_0 at time 0. (3a)

If the total number of S_i molecules in the system at time t is represented by the random function of time $X_i(t)$,

and if $\mathbf{X}(t) = [X_1(t), \dots, X_N(t)]$, then Eq. (3a) can also be written²

$$P(\mathbf{x}; t | \mathbf{x}_0) \equiv \text{prob}\{\mathbf{X}(t) = \mathbf{x} | \mathbf{X}(0) = \mathbf{x}_0\}. \quad (3b)$$

A time-evolution equation for P is obtained by using Eq. (1) and the laws of probability theory to write $P(\mathbf{x}; t + dt | \mathbf{x}_0)$ as the sum of the probabilities of the $M + 1$ ways³ of arriving in state \mathbf{x} at time $t + dt$ from time t :

$$P(\mathbf{x}; t + dt | \mathbf{x}_0) = \sum_{\mu=1}^M P(\mathbf{x} - \nu_\mu; t | \mathbf{x}_0) \cdot a_\mu(\mathbf{x} - \nu_\mu) dt + P(\mathbf{x}; t | \mathbf{x}_0) \cdot \left[1 - \sum_{\mu=1}^M a_\mu(\mathbf{x}) dt \right].$$

This leads to the "master equation"

$$\frac{\partial}{\partial t} P(\mathbf{x}; t | \mathbf{x}_0) = \sum_{\mu=1}^M [a_\mu(\mathbf{x} - \nu_\mu) P(\mathbf{x} - \nu_\mu; t | \mathbf{x}_0) - a_\mu(\mathbf{x}) P(\mathbf{x}; t | \mathbf{x}_0)]. \quad (4)$$

The "average" of any function $f(\mathbf{x}) = f(x_1, \dots, x_N)$ at time t is customarily defined by

$$\begin{aligned} \langle f(\mathbf{x}) \rangle_t &\equiv \sum_{\mathbf{x}_1=0}^{\infty} \sum_{\mathbf{x}_2=0}^{\infty} \cdots \sum_{\mathbf{x}_N=0}^{\infty} f(\mathbf{x}) P(\mathbf{x}; t | \mathbf{x}_0) \\ &\equiv \sum_{\mathbf{x}} f(\mathbf{x}) P(\mathbf{x}; t | \mathbf{x}_0). \end{aligned} \quad (5)$$

Multiplying Eq. (4) by $f(\mathbf{x})$ and then summing over \mathbf{x} leads to

$$\frac{d}{dt} \langle f(\mathbf{x}) \rangle_t = \sum_{\mu=1}^M \langle [f(\mathbf{x} + \nu_\mu) - f(\mathbf{x})] a_\mu(\mathbf{x}) \rangle_t. \quad (6)$$

In particular, putting $f(\mathbf{x}) = x_i$ in Eq. (6) yields a set of time-evolution equations for the first moments of P :

$$\frac{d}{dt} \langle x_i \rangle_t = \sum_{\mu=1}^M \nu_{\mu i} \langle a_\mu(x_1, \dots, x_N) \rangle_t, \quad i = 1, \dots, N. \quad (7)$$

If all the functions $a_\mu(x_1, \dots, x_N)$ were constant or linear in their arguments, then we could put $\langle a_\mu(x_1, \dots, x_N) \rangle_t = a_\mu(\langle x_1 \rangle_t, \dots, \langle x_N \rangle_t)$, and Eq. (7) would constitute a complete, closed set of equations for the $\langle x_i \rangle_t$. However, this will not be the case if any $a_\mu(x_1, \dots, x_N)$ is nonlinear in any of its arguments, because the right side of Eq. (7) will then involve higher order moments, such as $\langle x_i x_j \rangle_t$. Of course, we can al-

ways use Eq. (6) to generate new equations giving the time derivatives of these higher order moments, but the right sides of these new equations will then introduce still higher order moments. Thus, in the general case, Eq. (7) must be regarded as merely the first of an infinite, open-ended hierarchy of moment equations.

The traditional "macroscopic" or "deterministic" approach to chemical kinetics avoids the open-endedness problem by treating the evolution of the system as a continuous-state deterministic process instead of a discrete-state stochastic process. More precisely, $a_\mu(\mathbf{x})dt$ in Eq. (1) is regarded as the number of R_μ reactions that will occur in $(t, t+dt)$, given the state \mathbf{x} at time t . This in turn implies the existence of N continuous, non-random molecular population functions $\bar{x}_1(t), \dots, \bar{x}_N(t)$ satisfying

$$\bar{x}_i(t+dt) = \bar{x}_i(t) + \sum_{\mu=1}^M \nu_{\mu i} a_\mu(\bar{x}_1(t), \dots, \bar{x}_N(t)) dt,$$

since the μ th term in the sum on the right is (in this interpretation) the change in the S_i molecular population in $(t, t+dt)$ due to R_μ reactions. This leads to the deterministic "reaction-rate equations"

$$\frac{d}{dt} \bar{x}_i(t) = \sum_{\mu=1}^M \nu_{\mu i} a_\mu(\bar{x}_1(t), \dots, \bar{x}_N(t)), \quad i=1, \dots, N. \quad (8)$$

We are concerned here with the connection between the N functions $\langle x_i \rangle_t$ and the N functions $\bar{x}_i(t)$. The former are defined by the prescription (5), and satisfy the open set of differential Eq. (7); the latter constitute the solution of the closed set of differential Eq. (8), but otherwise seem to be physically undefined in a strictly stochastic context. If we neglect the correlating effects of microscopic fluctuations and approximate

$$\langle a_\mu(x_1, \dots, x_N) \rangle_t \approx a_\mu(\langle x_1 \rangle_t, \dots, \langle x_N \rangle_t), \quad (9a)$$

then Eq. (7) would be approximately the same as Eq. (8), and we could conclude that

$$\langle x_i \rangle_t \approx \bar{x}_i(t). \quad (9b)$$

In fact, it has been argued that Eq. (9b) becomes a strict equality in the thermodynamic limit for not-too-dense systems.⁵

All these considerations seem to suggest that $\bar{x}_i(t)$ is a "somewhat illegitimate but usually adequate stand-in" for $\langle x_i \rangle_t$: More specifically, it would appear that even though (i) $\bar{x}_i(t)$ lacks the formal stochastic credentials of $\langle x_i \rangle_t$, we need not be overly concerned since (ii) $\langle x_i \rangle_t$ always differs only negligibly from $\bar{x}_i(t)$ for macroscopic chemical systems. However, the purpose of this paper is to point out that neither (i) nor (ii) is strictly correct: In Sec. II we shall argue that $\bar{x}_i(t)$ can in fact be defined and legitimately invoked in a strictly stochastic context. And, in Sec. III we shall demonstrate that for some macroscopic systems (chemical oscillators, for example) $\langle x_i \rangle_t$ can differ quite dramatically from $\bar{x}_i(t)$.

II. $\langle x_i \rangle_t$ AND $\bar{x}_i(t)$ AS DIFFERENTLY CONDITIONED AVERAGES OF $X_i(t)$

The interpretation of the quantity

$$\langle x_i \rangle_t \equiv \sum_{\mathbf{x}} x_i P(\mathbf{x}; t | \mathbf{x}_0) \quad (10)$$

as "the average number of S_i molecules in the system at time t " is not quite complete: It is that average "conditioned on the system being in state \mathbf{x}_0 at time 0." This same conditioning clearly applies to all averages of the kind (5). We could make this more explicit by invoking the random functions of time $X_i(t)$ [see Eq. (3b)] and writing

$$\langle x_i \rangle_t = \langle X_i(t) | \mathbf{X}(0) = \mathbf{x}_0 \rangle, \quad (11)$$

which we read as "the average value of $X_i(t)$, given that $\mathbf{X}(0) = \mathbf{x}_0$." [Notice that the right hand side of Eq. (11) is not a redefinition of $\langle x_i \rangle_t$, but merely a more descriptive notation for that quantity.] Henceforth, we shall refer to $\langle x_i \rangle_t$ as the *initially conditioned average* of $X_i(t)$.

We shall now argue that $\bar{x}_i(t)$ too may be regarded as a kind of conditioned average of the random function $X_i(t)$. To this end, we first introduce a new random function of time $dX_i(t)$ defined by

$$dX_i(t) \equiv X_i(t+dt) - X_i(t). \quad (12)$$

Evidently, $dX_i(t)$ is the change in the number of S_i molecules in the infinitesimal time interval $[t, t+dt]$. Now, in that time interval, either no reactions will occur or else some one of the R_μ reactions will occur,³ so $dX_i(t)$ can assume only one of the integer values $0, \nu_{1i}, \nu_{2i}, \dots, \nu_{Mi}$. If the system is in state \mathbf{x} at time t , then according to Eq. (1) the probability that $dX_i(t)$ will assume the value $\nu_{\mu i}$ as a result of an R_μ reaction is just $a_\mu(\mathbf{x})dt$. In particular, if we take $\mathbf{x} = [\bar{x}_1(t), \dots, \bar{x}_N(t)] \equiv \bar{\mathbf{x}}(t)$, then

$$\text{prob}\{dX_i(t) = \nu_{\mu i} \text{ (via } R_\mu) | \mathbf{X}(t) = \bar{\mathbf{x}}(t)\} = a_\mu(\bar{\mathbf{x}}(t)) dt.$$

It follows that the *average* of the random variable $dX_i(t)$, given that $\mathbf{X}(t) = \bar{\mathbf{x}}(t)$, is

$$\langle dX_i(t) | \mathbf{X}(t) = \bar{\mathbf{x}}(t) \rangle = \sum_{\mu=1}^M \nu_{\mu i} a_\mu(\bar{\mathbf{x}}(t)) dt. \quad (13)$$

Comparing Eq. (13) with Eq. (8), we have the result⁶

$$\bar{x}_i(t+dt) - \bar{x}_i(t) = \langle dX_i(t) | \mathbf{X}(t) = \bar{\mathbf{x}}(t) \rangle. \quad (14)$$

Equation (14) says that the change in the sure function \bar{x}_i in the infinitesimal time interval $[t, t+dt]$ is equal to the *average* of the random change function $dX_i(t)$, provided that $\mathbf{X}(t) = \bar{\mathbf{x}}(t)$. We thus conclude that the function $\bar{x}_i(t)$ may be regarded as the "average number of S_i molecules at time t , conditioned on the premise that in every infinitesimal interval $[t', t'+dt']$ between times 0 and t the random change $d\mathbf{X}(t')$ in the system state vector is equal to its mean $\langle d\mathbf{X}(t') \rangle$." We propose to call $x_i(t)$ the *continuously conditioned average* of $X_i(t)$.

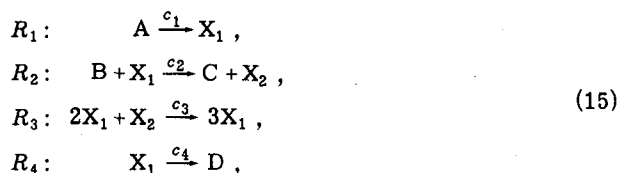
We are thus led to the view that $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ are *differently conditioned averages of the random function* $X_i(t)$. The initially conditioned average $\langle x_i \rangle_t$ is conditioned by the single requirement that the random state vector coincide with \mathbf{x}_0 at time 0. The continuously conditioned average $\bar{x}_i(t)$ is conditioned both by that requirement and by the further requirement that the random change in the state vector in each infinitesimal time interval between 0 and t always be equal to its mean. The fact that $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ are averages of the same physical quantity is certainly intuitively reasonable;

however, since these two averages are *conditioned differently*, they are *not* required to be equal to each other. Indeed, in the next section we shall call attention to a case in which $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ behave quite differently, yet both are "correct" given their specific conditionings.

In principle, the initially conditioned average $\langle x_i \rangle_t$ can be calculated from straightforward observations on real evolving systems: We take a large number N of replicas of the system under consideration, start them all out at time 0 in state x_0 , and then note the number of S_i molecules that each replica has at the chosen instant t . The average of those numbers will be equal to $\langle x_i \rangle_t$, at least to within a relative statistical uncertainty that goes to zero as $N \rightarrow \infty$. However, the continuously conditioned average $\bar{x}_i(t)$ *cannot* be calculated by an analogous experimental recipe, because the continuous conditioning procedure, although well defined mathematically, cannot be implemented on real systems. The reason for this is that the condition $dX_j(t') = \langle dX_j(t') \rangle$ requires that $dX_j(t')$ be equal to an *infinitesimal* [see Eq. (13)], whereas for any *real* system $dX_j(t')$ will always be equal to one of the *integers* $0, \nu_{1j}, \nu_{2j}, \dots, \nu_{Mj}$. It is important to emphasize, though, that this does *not* imply any inconsistency in the continuously conditioned average, because there is no hard rule that conditionings must be physically implementable. Indeed, the history of chemical kinetics demonstrates that a great deal of useful, descriptive information about a chemical system can be learned from the continuously conditioned averages—i.e., from the solution of the deterministic reaction-rate equations (8). This is true not only in the "usual" case in which $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ are numerically almost indistinguishable,⁵ but also, as we shall see next, even in those exceptional cases in which $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ differ substantially from each other.

III. AN EXAMPLE OF MACROSCOPIC INEQUALITY BETWEEN $\langle x_i \rangle_t$ AND $\bar{x}_i(t)$: CHEMICAL OSCILLATORS

The Brusselator⁷ is the two-component, four-reaction system



in which the molecular populations a and b of species A and B are assumed to remain essentially constant. The functions a_μ and vectors ν_μ for this system are

$$\begin{aligned} a_1(x_1, x_2) &= c_1 a, & \nu_1 &= (1, 0), \\ a_2(x_1, x_2) &= c_2 b x_1, & \nu_2 &= (-1, 1), \\ a_3(x_1, x_2) &= c_3 x_2 x_1 (x_1 - 1)/2, & \nu_3 &= (1, -1), \\ a_4(x_1, x_2) &= c_4 x_1, & \nu_4 &= (-1, 0). \end{aligned}$$

It follows from Eq. (8) that the continuously conditioned averages $\bar{x}_1(t)$ and $\bar{x}_2(t)$ satisfy the *closed* set of differential equations⁸

$$\frac{d\bar{x}_1}{dt} = c_1 a - c_2 b \bar{x}_1 + \frac{c_3}{2} \bar{x}_1 (\bar{x}_1 - 1) \bar{x}_2 - c_4 \bar{x}_1, \quad (16a)$$

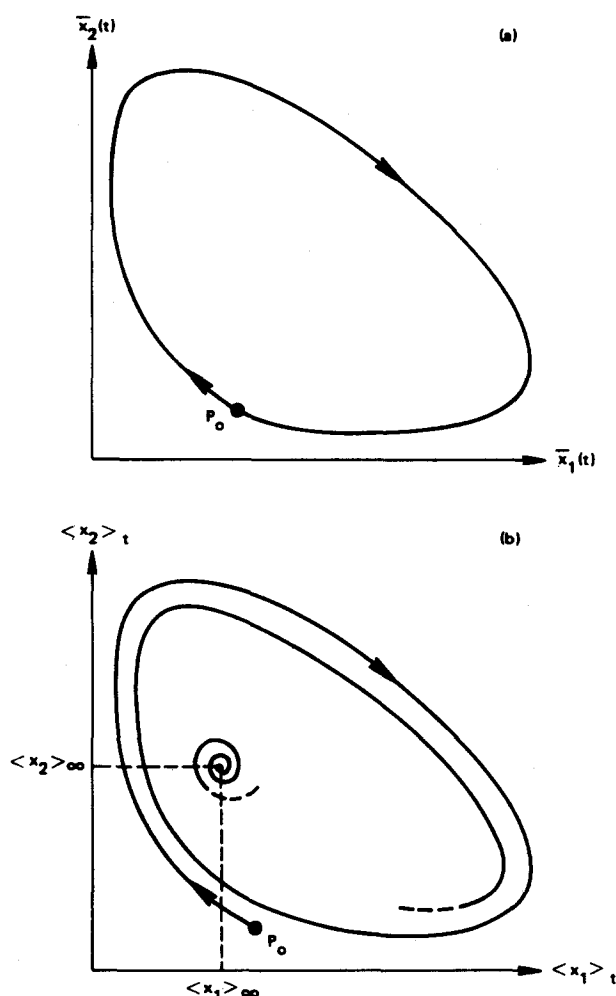


FIG. 1. Schematic plots of (a) the trajectory of the point $(\bar{x}_1(t), \bar{x}_2(t))$, and (b) the trajectory of the point $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$, for the Brusselator system (15) in its oscillating regime.

$$\frac{d\bar{x}_2}{dt} = c_2 b \bar{x}_1 - \frac{c_3}{2} \bar{x}_1 (\bar{x}_1 - 1) \bar{x}_2. \quad (16b)$$

Also, it follows from Eq. (7) that the initially conditioned averages $\langle x_1 \rangle_t$ and $\langle x_2 \rangle_t$ satisfy the *open* set of differential equations

$$\frac{d\langle x_1 \rangle}{dt} = c_1 a - c_2 b \langle x_1 \rangle + \frac{c_3}{2} \langle x_1 (x_1 - 1) x_2 \rangle - c_4 \langle x_1 \rangle, \quad (17a)$$

$$\frac{d\langle x_2 \rangle}{dt} = c_2 b \langle x_1 \rangle - \frac{c_3}{2} \langle x_1 (x_1 - 1) x_2 \rangle. \quad (17b)$$

It is well known that, for a certain range of values of the reaction parameters $c_1 a$, $c_2 b$, c_3 , and c_4 , the solution functions $\bar{x}_1(t)$ and $\bar{x}_2(t)$ of the deterministic reaction-rate equations (16) are oscillatory in time. More specifically, starting from almost any point in the first quadrant of the $\bar{x}_1 \bar{x}_2$ plane, the point $(\bar{x}_1(t), \bar{x}_2(t))$ will asymptotically approach a closed, stable, *limit cycle trajectory*, whose location, size, and cycle period T are determined by the specific values of the reaction parameters. In particular, if $(\bar{x}_1(0), \bar{x}_2(0))$ coincides with any point P_0 lying on the limit cycle trajectory, as shown schematically in Fig. 1(a), then $(\bar{x}_1(t), \bar{x}_2(t))$ will again coincide with P_0 at times $t = T, 2T, 3T, \dots$

The appearance of the higher order moments $\langle x_1 x_2 \rangle_t$ and $\langle x_1^2 x_2 \rangle_t$ in the time-evolution equations (17) for $\langle x_1 \rangle_t$ and $\langle x_2 \rangle_t$ renders those equations open, and hence insoluble by known techniques. However, it is tempting to suppose that, at least for macroscopic systems, $\langle x_1(x_1 - 1)x_2 \rangle_t$ will be well approximated by $\langle x_1 \rangle_t(\langle x_1 \rangle_t - 1)\langle x_2 \rangle_t$, and hence that the functions $\langle x_1 \rangle_t$ and $\langle x_2 \rangle_t$ will behave in approximately the same way as the functions $\bar{x}_1(t)$ and $\bar{x}_2(t)$. In particular, we might expect that the point $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ will describe a limit cycle trajectory which differs only microscopically from that described by $\bar{x}_1(t)$ and $\bar{x}_2(t)$. However, we shall now argue that the point $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ will in fact trace out an *inwardly spiraling curve*, asymptotically approaching some fixed point $(\langle x_1 \rangle_\infty, \langle x_2 \rangle_\infty)$, as shown schematically in Fig. 1(b).

The foregoing conclusion is implied, although never explicitly stated, in recent independent analyses by van Kampen,⁹ White,¹⁰ Feistel and Ebeling,¹¹ and Schraner, Grossmann, and Richter.¹³ A mathematically rigorous analysis is quite difficult, but an easy, heuristic way to understand what is going on here is to examine a typical *numerical simulation* of the Brusselator in its oscillating regime. Such a simulation was recently carried out by one of the authors¹² using a Monte Carlo procedure that is rigorously equivalent to the stochastic premises of Sec. I.¹ The results of that simulation are reproduced in Fig. 2.

The "curves" in Fig. 2 show that a typical Brusselator system, evolving in the stochastic manner prescribed in Sec. I, indeed exhibits the expected limit cycle behavior. Allowing for the effects of intrinsic microscopic fluctuations, the limit cycle trajectory, as estimated from Fig. 2(c), and the cycle period, as estimated from Fig. 2(a) or 2(b), are quite consistent with the solutions $\bar{x}_1(t)$ and $\bar{x}_2(t)$ of the corresponding reaction-rate equations (16). We note in passing that the fluctuations in the limit cycle path along its outside diagonal leg in Fig. 2(c), and the concomitant amplitude fluctuations in Figs. 2(a) and 2(b), are unusually large—about an order of magnitude larger than the " \sqrt{n} fluctuation rule" would predict; we believe this effect to be genuine, and not an artifact of the simulation.¹⁴

It is apparent from Fig. 2(c) that random fluctuations cause only temporary excursions away from the limit cycle path: When the system point strays off of that path, the position-dependent "forces" $a_u(X_1, X_2)$ tend to move the system point back onto the path. The system thus has *positive stability* with respect to fluctuations *transverse* to the limit cycle path. However, the system has only *neutral stability* with respect to fluctuations *along* the limit cycle path.⁹ To see that this is so, imagine that at some instant t the system point (X_1, X_2) coincides with the deterministically orbiting point (\bar{x}_1, \bar{x}_2) , but that at some later instant t' the inherent randomness in the motion of (X_1, X_2) has resulted in (X_1, X_2) being where (\bar{x}_1, \bar{x}_2) was at the slightly earlier instant $t' - \tau$ ($\tau > 0$). Owing to the past-forgetting nature of Markov processes, the system point at time t' has no way of knowing that it is "behind schedule" by τ , so it will make no attempt to "catch up." The fact that it has suffered a negative phase shift ($= -2\pi\tau/T$) relative to the deter-

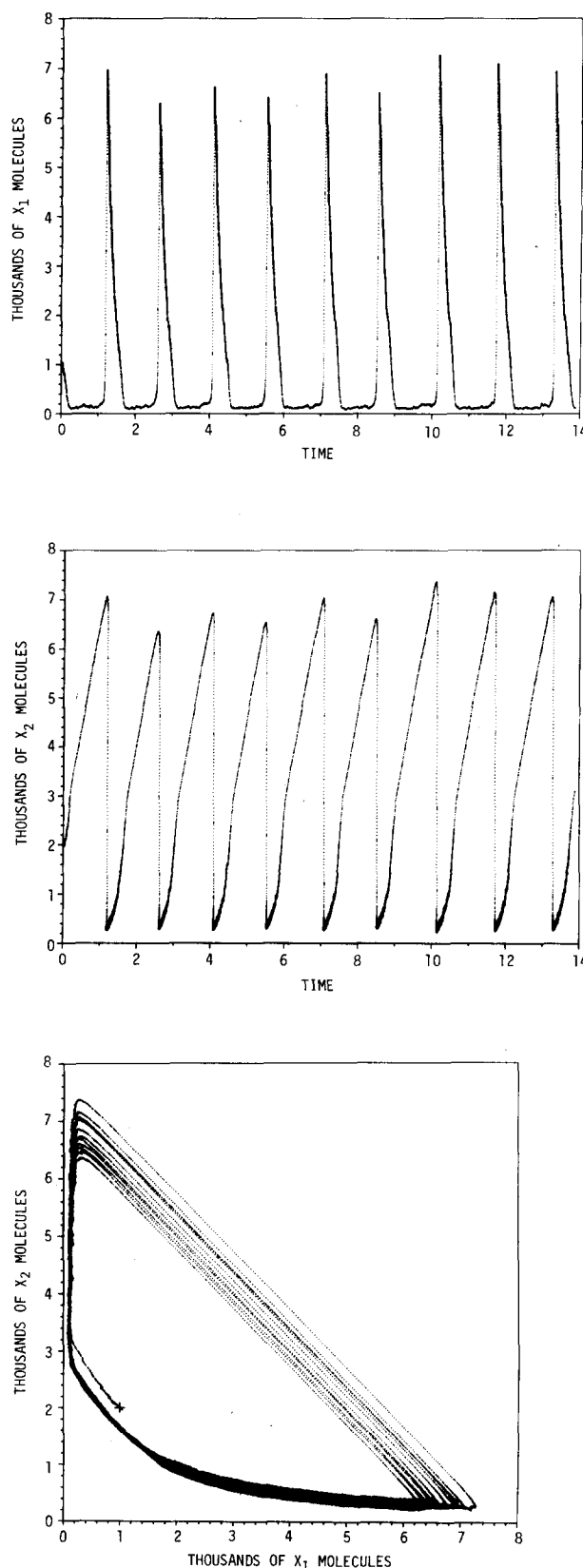


FIG. 2. Results of a 2×10^6 reaction stochastic simulation of the Brusselator system (15), with $c_1 a = 5 \times 10^3$, $c_2 b = 50$, $c_3 = 5 \times 10^{-6}$, and $c_4 = 5$ (reproduced from Ref. 12). (a) shows $[t, X_1(t)]$ plotted every hundredth reaction; (b) shows $[t, X_2(t)]$ plotted every hundredth reaction; (c) shows $[X_1(t), X_2(t)]$ plotted every fiftieth reaction. The direction of motion in (c) is clockwise. The unit of time is determined by the units assigned to the reaction constants.

ministically orbiting point (\bar{x}_1, \bar{x}_2) is now in the past, and can therefore have no bearing on either the size or the sign of the *next* fluctuation-induced phase shift. Evidently, the *phase* of (X_1, X_2) executes, relative to the phase of (\bar{x}_1, \bar{x}_2) , a random walk that is very reminiscent of Einstein's classical model of one-dimensional diffusion.

To see what these observations tell us about the time behavior of the probability function $P(\mathbf{x}; t | \mathbf{x}_0)$ for the Brusselator, we make use of the fact that $P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02})$ may be regarded as the normalized density of representative points in the $x_1 x_2$ plane of an ensemble of many identical Brusselator systems, all in the state $(\mathbf{x}_{01}, \mathbf{x}_{02})$ at time 0. Thus, at $t=0$, $P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02})$ is a unit spike at the point $(\mathbf{x}_{01}, \mathbf{x}_{02})$, which we shall take to lie on the continuously conditioned limit cycle trajectory. As t increases from 0, this unit spike starts moving along the limit cycle trajectory in much the same way as the continuously conditioned point (\bar{x}_1, \bar{x}_2) would. However, the spike also starts to *spread out* as the individual ensemble members experience the effects of random microscopic fluctuations. The observations of the preceding paragraph imply that the spreading *transverse* to the limit cycle trajectory will be reasonably well confined, but that the spreading *along* the limit cycle trajectory will increase with each revolution as the systems in the ensemble gradually lose phase coherence with each other. Eventually, some system points will start "lapping" others, and the function $P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02})$ relaxes from an orbiting peak to an orbiting ripple of slowly diminishing amplitude on top of a slowly growing background. Ultimately, there will be no phase coherence at all among the ensemble members, and no orbiting behavior can be observed in the surface described by $P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02})$: *Even though all the representative points of the ensemble members continue to oscillate in much the same way as the continuously conditioned point (\bar{x}_1, \bar{x}_2) , the local density of those representative points in the $x_1 x_2$ plane will no longer change with time.* $P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02})$ thus becomes, in the limit $t \rightarrow \infty$, a time-independent crater-shaped function, which is clearly also independent of the initial point $(\mathbf{x}_{01}, \mathbf{x}_{02})$:

$$\lim_{t \rightarrow \infty} P(\mathbf{x}_1, \mathbf{x}_2; t | \mathbf{x}_{01}, \mathbf{x}_{02}) = P_\infty(\mathbf{x}_1, \mathbf{x}_2). \quad (18)$$

We may expect that the larger our Brusselator system is (in the thermodynamic limit sense), the slower will the limit in Eq. (18) be approached; however, for any finite Brusselator system, no matter how large, the sensible time dependence of P will inevitably disappear after some finite duration.

From Fig. 2, we can infer that the "crater" described by $P_\infty(\mathbf{x}_1, \mathbf{x}_2)$ will be fairly high and narrow along the hyperbolic portion of the limit cycle, but low and broad over the diagonal leg (where each system point evidently spends only a very small fraction of its time).¹³ However, of more direct interest to us than the specific shape of $P_\infty(\mathbf{x}_1, \mathbf{x}_2)$ is what the *existence* of this limiting function implies about $\langle x_i \rangle_t$ and $\langle x_i \rangle_\infty$: Combining Eq. (10) with Eq. (18), we have the result that

$$\lim_{t \rightarrow \infty} \langle x_i \rangle_t = \sum_{x_1=0}^{\infty} \sum_{x_2=0}^{\infty} x_i P_\infty(\mathbf{x}_1, \mathbf{x}_2) \equiv \langle x_i \rangle_\infty, \quad i=1, 2, \quad (19)$$

where $\langle x_i \rangle_\infty$ is evidently independent of both t and $(\mathbf{x}_{01}, \mathbf{x}_{02})$. We thus conclude that, although the point $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ indeed starts out on the initially conditioned limit cycle path, it gradually spirals inward to some fixed point $(\langle x_1 \rangle_\infty, \langle x_2 \rangle_\infty)$, as shown schematically in Fig. 1(b). As with Eq. (18), the rate of approach to the limit point will probably be a decreasing function of the thermodynamic largeness of the system; however, for any finite Brusselator system, no matter how large, the spiraling will inevitably occur, and the limit point will be effectively reached within some finite length of time. It should be clear from the generality of our arguments that such behavior is not peculiar to the Brusselator alone, but will be exhibited by virtually any stable chemical oscillator.

As stated previously, we are not the first to note that Eq. (18) holds for chemical oscillator systems.^{9,11,13} However, the consequent implication of the difference, schematized in Fig. 1, between $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ does not seem to have been widely appreciated. Our point here is not only that this difference does exist, but that it is quite understandable, and not indicative of any "discrepancy," if we view $\langle x_i \rangle_t$ and $\bar{x}_i(t)$ as the initially conditioned and continuously conditioned averages of the random function $X_i(t)$. Clearly, *both* of these averages are useful in describing the temporal behavior of the Brusselator; however, it is obviously important that their specific conditionings be kept in mind.

We shall conclude by showing how the simulation results in Fig. 2 can be used to quantitatively estimate both the coordinates of the limit point in Fig. 1(b) and also the approximate number of revolutions executed by $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ in reaching that limit point.

As we have seen, the overriding long-term effect in a stochastically evolving Brusselator is the loss of phase coherence between $(X_1(t), X_2(t))$ and $(X_1(0), X_2(0))$. Thus, the problem of predicting the location of the point $(X_1(t), X_2(t))$ for any sufficiently large t is *approximately* the same as the problem of predicting the location of the deterministically evolving point $(\bar{x}_1(t), \bar{x}_2(t))$ at some *random* instant $t = t_{\text{ran}}$. Since the average of a series of very many measurements of $\bar{x}_i(t)$ at different random times will be equal to the integral mean of $\bar{x}_i(t)$ over one complete cycle T , then

$$\langle x_i \rangle_\infty \approx T^{-1} \int_0^T \bar{x}_i(\tau) d\tau, \quad i=1, 2, \quad (20)$$

where $(\bar{x}_1(0), \bar{x}_2(0))$ is a point on the limit cycle trajectory.

To within the accuracy of Eq. (20) we may approximate the time curves of $\bar{x}_1(t)$ and $\bar{x}_2(t)$ with the time curves shown in Figs. 2(a) and 2(b), respectively. These latter curves were integrated graphically over the nine complete cycles shown, and the results were divided by the time required to execute those cycles. We found that

$$\langle x_1 \rangle_\infty \approx 1070, \quad \langle x_2 \rangle_\infty \approx 3670. \quad (21)$$

Notice that the limit point $(\langle x_1 \rangle_\infty, \langle x_2 \rangle_\infty)$ does *not* coincide with the point (1000, 2000) which nulls the right-hand sides of Eqs. (16) for the parameter values used in Fig. 2.

To estimate the number of cycles required for $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ to effectively reach its limit point in Fig. 1(b)—or, equivalently, the number of cycles required for total loss of phase coherence—we proceed as follows: Let T_i be the time required for the i th oscillation of the Brusselator, and let

$$T_j^{(n)} = \sum_{i=1}^n T_i$$

denote the time required for n oscillations. Assuming that the numbers T_1, T_2, T_3, \dots can be regarded as independent elements of a fixed set of random numbers $\{T_i\}$, then $T_j^{(n)}$ can be regarded as an element of a fixed set of random numbers $\{T_j^{(n)}\}$ whose mean $T^{(n)}$ and variance σ_n^2 are related to the mean T and variance σ^2 of the set $\{T_i\}$ according to

$$T^{(n)} = nT, \quad (22a)$$

$$\sigma_n^2 = n\sigma^2. \quad (22b)$$

The last relation shows how the statistical uncertainty σ_n in the time required for n cycles increases with n .^{10,11} Initially, the individual Brusselators in our ensemble are all in phase with each other; they will be effectively out of phase when the uncertainty in the time required for n cycles has become comparable to the time required for a single cycle. Thus, using Eq. (22b), the critical number of oscillations n_c required for loss of phase coherence satisfies $(n_c\sigma^2)^{1/2} = T$. Solving for n_c gives¹¹

$$n_c = (T/\sigma)^2. \quad (23)$$

It follows that the approximate time t_c required for loss of phase coherence is $t_c = n_c T = T^3/\sigma^2$.

We measured the eight time intervals between the nine vertical rise lines in Fig. 2(a). The values obtained ranged from 1.42 to 1.61 time units and their mean and standard deviation were calculated to be $T \approx 1.51$ and $\sigma \approx 0.07$, respectively. Substituting these values into Eq. (22), we conclude that

$$n_c \approx 465. \quad (24)$$

Thus, the point $(\langle x_1 \rangle_t, \langle x_2 \rangle_t)$ for the Brusselator system simulated in Fig. 2 should effectively arrive at its limit point (1070, 3670) [see Eq. (21)] after about 465 oscillations, or, equivalently, in about 700 time units.

Open-ended hierarchies of equations such as Eq. (17) arise in many areas of physics. Because of their intractability, such equations are usually analyzed by

making some kind of "closure approximation," the simplest being that which would reduce Eq. (17) to Eq. (16). It is therefore noteworthy that the rather detailed picture of the time behavior of $\langle x_1 \rangle_t$ and $\langle x_2 \rangle_t$ developed here was *not* obtained by making any artificial closure assumptions.

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- ¹D. T. Gillespie, J. Comput. Phys. **22**, 403 (1976); J. Stat. Phys. **16**, 311 (1977).
- ²The right side of Eq. (3b) is read "the probability that $X(t) = \mathbf{x}$, given that $X(0) = \mathbf{x}_0$."
- ³It is implicitly assumed in Eq. (1) that the probability for more than one reaction to occur in the system in any infinitesimal time interval dt is of order > 1 in dt , and hence is effectively zero.
- ⁴D. A. McQuarrie, J. Appl. Probl. **4**, 413 (1967).
- ⁵I. Oppenheim, K. E. Shuler, and G. H. Weiss, J. Chem. Phys. **50**, 460 (1969); T. G. Kurtz, J. Chem. Phys. **57**, 2976 (1972).
- ⁶M. Mangel, J. Chem. Phys. **69**, 3697 (1978).
- ⁷I. Prigogine and R. Lefever, J. Chem. Phys. **48**, 1695 (1968).
- ⁸If one makes the macroscopically legitimate replacement $\bar{x}_1(\bar{x}_1 - 1) \rightarrow \bar{x}_1^2$ and then uses the density variables $\xi_1 = \bar{x}_1/V$, $\xi_2 = \bar{x}_2/V$, $\alpha = a/V$, and $\beta = b/V$, where V is the total system volume, then Eqs. (16) take the more customary form

$$d\xi_1/dt = k_1\alpha - k_2\beta\xi_1 + k_3\xi_1^2\xi_2 - k_4\xi_1,$$

$$d\xi_2/dt = k_2\beta\xi_1 - k_3\xi_1^2\xi_2,$$
 where $k_1 = c_1$, $k_2 = Vc_2$, $k_3 = V^2c_3/2$, and $k_4 = c_4$. For most purposes, including ours here, the distinction between these equations and Eq. (16) is unimportant.
- ⁹N. G. van Kampen, in *Advances in Chemical Physics*, edited by I. Prigogine and S. Rice (Wiley, New York, 1976), Vol. **34**, p. 293.
- ¹⁰B. White, SIAM J. Appl. Math. **32**, 666 (1977).
- ¹¹R. Feistel and W. Ebeling, Physica **114**, 93A (1978).
- ¹²D. T. Gillespie, J. Phys. Chem. **81**, 2340 (1977).
- ¹³R. Schraner, S. Grossmann, and P. H. Richter, Z. Phys. **B 35**, 363 (1979).
- ¹⁴This effect has been observed in three separate stochastic simulation studies of the Brusselator: Ref. 12 (see Secs. IVC and IVD); J. S. Turner, J. Phys. Chem. **81**, 2379 (1977) (see Sec. VC.2); and Ref. 13 [see Figs. 3(b) and 3(d)]. Since different random number generators were used in these three studies, it seems unlikely that this effect can be attributed to correlations in the pseudorandom numbers. Furthermore, Turner reports *experimental* observation of strikingly similar behavior in the Belousov-Zhabotinski reaction.