Fluctuations at chemical instabilities[a)]

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We consider the effects of fluctuations on chemical systems that have multiple steady states. The systems of interest have two stable steady states and one unstable steady state (a kinetic saddle point). As parameters vary, two or three of the steady states coalesce. We consider experiments beginning near the deterministic separatrix and formulate a stochastic first exit problem. The deterministic separatrix is surrounded by a band. We calculate the first exit probability $u(x)$ and mean exit time $\mathcal{T}(x)$ from this band, conditioned on initial position. Fluctuation formalisms connecting the Langevin equation and deterministic kinetic equations are discussed. We use the diffusion approximation so that $u(x)$ and $T(x)$ satisfy (backward) diffusion equations. Approximate solutions of the diffusion equations are constructed by an asymptotic method that involves various incomplete special functions. Two applications are discussed: (1) the spontaneous asymmetric synthesis model of F.C. Frank; (2) fluctuation effects on substrate inhibited reactions in open vessels.

I. FLUCTUATIONS AND SYSTEMS WITH MULTIPLE STEADY STATES

The classical method of describing the evolution of chemical reactions is by the use of a deterministic differential equation

$$\dot{x} = b(x), \quad x \epsilon R^n . \tag{1.1}$$

In Eq. (1.1), x is a macroscopic variable that represents concentrations of reactants or products. The macrovariable describes the average state of a large system and is obtained by averaging over many independent subunits. The form of $b(x)$ is determined by the reaction mechanism.

Steady states are characterized by $b(x) = 0$. If $b(x)$ is nonlinear, then the system may have multiple steady states. The eigenvalues of $B = (b^i, j)$ can be used to characterize the type of steady state. If all eigenvalues have nonzero real parts, the steady state is of normal type. Following Kubo *et al.*,[1] we distinguish two kinds of non-normal steady states: (1) the marginal type, in which the local dynamics are $\dot{x} \sim x^2$; (2) the critical type, in which the local dynamics are $\dot{x} \sim x^3$. A steady state is stable if all eigenvalues have negative real parts. A steady state is of marginal stability if some eigenvalues have zero real parts. The deterministic approach can be improved if statistical fluctuations are included. The concentrations, represented by a random variable $\tilde{x}(t)$, will fluctuate for two reasons.[2] First, due to experimental limitations, it is impossible to specify concentrations exactly. Second, even if the concentrations were known at some time t, the exact concentrations at a later time $t + \Delta t$ would not be known unless all of the microscopic variables were known at time t. The specification of all the microscopic variables is clearly impossible. With this viewpoint, Eq. (1.1) describes the average behavior of a large number of statistical variables. A more exact description of the system would specify the volume V of the reaction vessel and an integer valued random variable $\tilde{X}(t)$ that represents the number of molecules in V at time

t. The mean of $\tilde{x}(t) = \tilde{X}(t)/V$ will correspond to the deterministic concentration. The variance of $\tilde{x}(t)$ provides a measure of statistical fluctuations.[3]

In chemical systems, the intensity of fluctuations is proportional to $1/V$.[2,4] In macroscopic systems, V is large so that the fluctuations are of small intensity. When the fluctuations are of small intensity, Eq. (1.1) usually provides an adequate description of the evolution of the system. There are, however, exceptions, some of which have been studied. When reactions occur in relatively small volumes (e.g., biological cells) or involve small numbers of molecules, fluctuations can have a profound effect on the evolution of the system.[3,5] Initial fluctuations will be amplified in autocatalytic or chain reactions.[6]

Many authors have studied the effects of fluctuations on systems in the vicinity of the stable steady state.[7,8,9]

In this work, we investigate the effects of fluctuations on systems initially in a vicinity of a kinetic saddle point. A saddle point is kinetically unstable: Phase points close to the saddle move away as time increases. Hence, the saddle is a type of instability; it is an unstable steady state. There are a number of reasons for studying chemical systems in the vicinity of an unstable steady state. In the first place, one would like to verify that the unstable steady state exists.[10] Due to fluctuations, it is not possible to observe the unstable steady state. We will show that the unstable steady state has a certain probabilistic description. Second, in many reactions, the stable steady states represent ~0 or 100% completion of the reaction. The most significant kinetic information is obtained from rate data in a vicinity of the unstable steady state. Chang and Schmitz[10] point out that often it is desirable to start a chemical reactor near the unstable steady state, but that one stable steady state is preferred. In this case, one wishes to estimate the probability that the less desirable stable state is reached. The gating mechanisms of nerve membranes involve reactions with multiple steady states.[11] The study of fluctuations at the unstable steady state (threshold) may lead to information about conductivity mechanisms.[12,13]

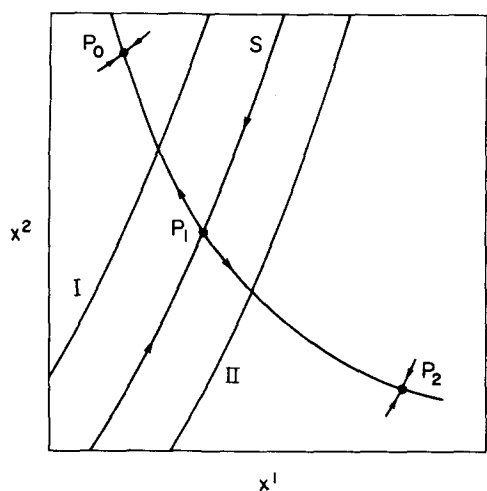In practice, it is very difficult to prepare a system in

FIG. 1. Formulation of the first exit problem in the (x^1, x^2) phase plane. The curve S is the deterministic separatrix and I and II are the first exit boundaries.

an unstable steady state. However, many systems exhibit behavior in which a stable steady state becomes unstable as a parameter is varied.[14-16] When a parameter α is less than a critical value α_c, the system has only one steady state P_1, which is stable. When α is increased so that $\alpha > \alpha_c$, P_1 becomes unstable and two stable steady states P_0 and P_2 are created. We call this the critical bifurcation. The mean-field ferromagnet exhibits such behavior. Many chemical systems also exhibit the critical bifurcation (Sec. V). A second type of bifurcation is possible as α increases. The steady state P_1 remains stable when $\alpha > \alpha_c$ and two new steady states Q_1, which is unstable, and Q_0, which is stable, appear. We call this the marginal bifurcation. The marginal bifurcation has not received adequate attention in the chemical literature. In Sec. V, we shall demonstrate that substrate inhibited reactions may exhibit the marginal bifurcation.

If P_1 is unstable when $\alpha > \alpha_c$, the system will always leave a neighborhood of P_1 and approach P_0 or P_2. Even if the system were initially at P_1, any minute fluctuation will cause it to leave the neighborhood of P_1. In the vicinity of an unstable steady state, fluctuations can never be ignored. According to the deterministic theory, the separatrix (Fig. 1) S divides the phase plane into two domains of attraction. All phase points initially on one side of S approach P_0; phase points on the other side approach P_2. Points initially on S approach the saddle point P_1.

When a more exact, stochastic description is used, the deterministic picture must be modified. No phase points will reach P_1 and remain there. Due to fluctuations, all phase points reach a vicinity of P_0 or P_2. More importantly, phase points which deterministically would approach P_0 might approach P_2 (and vice versa), namely, fluctuations may drive the system against the deterministic flow. Ideally, one would like to calculate the probability that a specified steady state is reached first. This problem is generally too difficult to solve. Instead, we surround the separatrix by a tube with boundaries I, II (Fig. 1). We will calculate the probability $u(x)$ that the process $\bar{x}(t)$ first exits from this tube through boundary
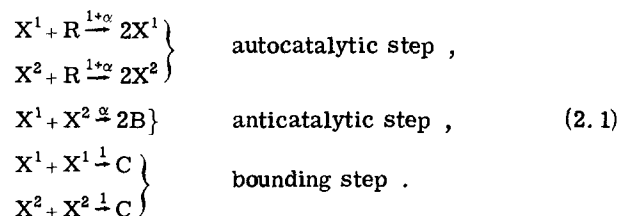
II, given that $\bar{x}(0) = x$. In the diffusion approximation, this probability satisfies a diffusion equation. We have constructed formal asymptotic solutions of the diffusion equation.[17] Our technique is a generalization of the ray or Hamilton–Jacobi method for diffusion equations.[18,19] We convert the second order boundary value problem for $u(x)$ to a first order problem for a function $\psi(x)$. The latter problem can be treated by the method of characteristics (of which Hamilton–Jacobi theory is a special case).

In Sec. II, we discuss a generalization of F.C. Frank's model of spontaneous asymmetric synthesis.[20] This model indicates the important role that fluctuations play for experiments starting near an unstable steady state. In Sec. III, we derive the stochastic kinetic equation (Langevin equation) and backward diffusion equation. There is presently controversy about the use of diffusion equations. Some of the aspects of the controversy are discussed when fluctuation formalisms connecting the Langevin equation with the deterministic kinetic equation are given. In Sec. IV, we summarize the asymptotic theory developed in Ref. 17. In Sec. V, we develop deterministic and stochastic models of substrate inhibited reactions. Our model is motivated by Degn's experiments on NADH oxidation.[14] Finally, in Sec. VI, we compare the theoretical predictions with Monte Carlo experiments.

II. SPONTANEOUS ASYMMETRIC SYNTHESIS

In this section, we present a generalization of the model of Frank.[20] This model exhibits multiple steady states and the critical bifurcation. It provides a simple illustration of the effects of fluctuations at chemical instabilities.

Let x^1 and x^2 denote the concentration of two enantiomers. Following Frank,[20] we assume that each enantiomer is the catalyst for its own production and anticatalyst for the other. The reaction scheme that we consider is

$$\left. \begin{array}{l} X^1 + R \xrightarrow{1+\alpha} 2X^1 \\ X^2 + R \xrightarrow{1+\alpha} 2X^2 \end{array} \right\} \quad \text{autocatalytic step ,}$$

$$X^1 + X^2 \xrightarrow{2} 2B \} \quad \text{anticatalytic step ,} \qquad (2.1)$$

$$\left. \begin{array}{l} X^1 + X^1 \xrightarrow{1} C \\ X^2 + X^2 \xrightarrow{1} C \end{array} \right\} \quad \text{bounding step .}$$

The last two reactions are added to insure that all concentrations remain bounded. We set $R = 1$. The kinetic equations are

$$\dot{x}^1 = (1+\alpha)x^1 - \alpha x^1 x^2 - (x^1)^2 , \qquad (2.2)$$

$$\dot{x}^2 = (1+\alpha)x^2 - \alpha x^1 x^2 - (x^2)^2 . \qquad (2.3)$$

When $\alpha < 1$, the only steady state is the racemic state (1, 1), which is stable [Fig. 2(a)]. When $\alpha > 1$, the racemic state (1, 1) is unstable. Two stable steady states appear on the x^1 and x^2 axes. When $\alpha > 1$, if a sample is initially in the racemic state, any small fluctuation will cause the sample to "spontaneously" evolve towards one of the two resolved states [Fig. 2(b)].

The effects of fluctuations will be most noticeable near the deterministic separatrix S: $x^1 = x^2$. Far from the separatrix, if the intensity of the fluctuations is small, it is unlikely that fluctuations will greatly influence the
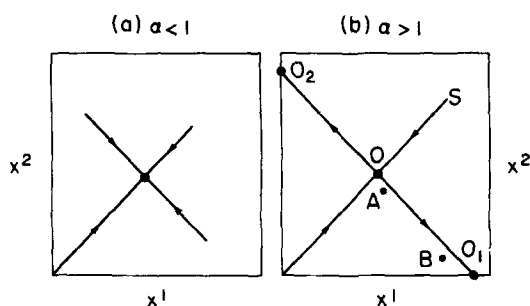
FIG. 2. Phase portrait of the model considered in Sec. II: (a) the case $\alpha < 1$—the racemic steady state $(1,1)$ is a stable node; (b) the case $\alpha > 1$—the racemic steady state $(1,1)$ is unstable (a saddle point) and the two resolved states are stable.

outcome of an experiment. For example, an experiment starting at point A in Fig. 2(b) is more likely to approach O_1 than an experiment starting at O. The result of an experiment starting at point B will probably not be affected by fluctuations of small intensity.

The fluctuations can be modeled by treating the reactions (2.1) as a birth and death process or by other formalisms (Sec. III). The theory given in Sec. IV can be used to treat the above model when fluctuations are included.

III. STOCHASTIC KINETIC EQUATIONS, FLUCTUATION FORMALISMS, BACKWARD EQUATION, AND FIRST EXIT PROBLEM

A. Stochastic kinetic equations

The macrovariable $x(t)$ represents the average concentrations of reactants at time t and evolves according to the kinetic equation

$$\dot{x}^i = b^i(x), \quad x^i(0) = x^i_0, \quad i = 1, 2 \ . \tag{3.1}$$

According to the statistical theory of chemical kinetics, $x(t)$ is the mean value of a random variable $\tilde{x}(t)$ which will satisfy a stochastic kinetic equation. It is not yet possible to derive the stochastic kinetic equation from basic principles. Ideally, one would start with the Liouville equation and reduce it to a stochastic kinetic equation. This reduction has been performed only on the simplest system.[21] Instead, we shall use a Langevin method[8] and add a stochastic term to the right hand side of Eq. (3.1). The source of the stochastic term is the random motion of the solvent and solute molecules which occurs on a time scale τ small compared to the macroscopic time scale t on which measurements are made.

The increments in τ and t are related by a parameter α:

$$\Delta \tau = \Delta t \ \alpha^2 \ , \tag{3.2}$$

where α^2 will characterize the fast time scale. The random process generated by the microscopic motions is assumed to be a mixing process $\tilde{Y}(\tau)$. In most of the physical literature,[22,23] it is assumed that

$$E[\tilde{Y}^k(s)\tilde{Y}^l(0)] = \delta^{kl}(s) \ , \tag{3.3}$$

where $\delta^{kl}(s) = 0$ unless $k = l$ and $s = 0$. We shall not make

this assumption and define

$$\gamma^{kl} = \int_0^\infty E[\tilde{Y}^k(s)\tilde{Y}^l(0)] ds \ . \tag{3.4}$$

In the case that Eq. (3.3) holds, $\tilde{Y}(\tau)$ is the "white noise" process. We assume that the stochastic variable $\tilde{x}(t; \alpha)$ satisfies

$$\frac{d\tilde{x}^i(t; \alpha)}{dt} = b^i(\tilde{x}) + \sqrt{\epsilon} \ \frac{\sigma^i_j(\tilde{x})}{\alpha} \ \tilde{Y}^j(t/\alpha^2), \quad i = 1, \ldots, n. \tag{3.5}$$

Langevin was the first to use a kinetic equation of the form (3.5).[8] Such equations often have been used in the last 50 years by most physical scientists working in this field. The use of Eq. (3.5) represents an approximate, somewhat *ad hoc*, way of treating stochastic effects in macroscopic systems. Equation (3.5) is the stochastic kinetic equation that will be used in the rest of this work.

The functions $b^i(x)$ appearing in Eq. (3.5) are the same functions appearing in the macroscopic equation (3.1). They determine the average or macroscopic evolution of $x(t)$. For example, for the model of spontaneous asymmetric synthesis,

$$b^1(x) = (1 + \alpha)x^1 - \alpha x^1 x^2 - (x^1)^2 \tag{3.6a}$$

$$b^2(x) = (1 + \alpha)x^2 - \alpha x^1 x^2 - (x^2)^2 \ . \tag{3.6b}$$

The functions $\sigma^i_j(\tilde{x})$ characterize the second moments of the stochastic variable $\tilde{x}(t; \alpha)$. It is assumed that $\tilde{Y}(t/\alpha^2)$ is a zero mean process. Then, from Eq. (3.5), one obtains

$$E\left\{ \left[\frac{d\tilde{x}^i(t; \alpha)}{dt} - b^i(\tilde{x}) \right] \left[\frac{d\tilde{x}^j(t; \alpha)}{dt} - b^j(\tilde{x}) \right] |\tilde{x}(t; \alpha) = x \right\}$$

$$= \frac{\epsilon \sigma^i_k(x)}{\alpha} \ \frac{\sigma^j_l(x)}{\alpha} \ E\{\tilde{Y}^k(t/\alpha^2)\tilde{Y}^l(t/\alpha^2)\} \ . \tag{3.7}$$

If the $\sigma^i_j(x)$ were known, then the second moments of $d\tilde{x}/dt$ could be calculated from Eq. (3.7). In reality, the $\sigma^i_j(x)$ are not known and a fluctuation formalism is needed in order to calculate the second moment of $d\tilde{x}/dt$. The fluctuation formalism will also provide a connection between the Langevin equation (3.5) and the deterministic kinetic equation (3.1).

B. Fluctuation formalisms

There is controversy presently about the connection between Eqs. (3.5) and (3.1) when $b(x)$ is nonlinear. If Eq. (3.5) is averaged unconditionally, one obtains

$$\frac{dx^i}{dt} \equiv E\left\{\frac{d\tilde{x}^i}{dt}\right\} = E\{b^i(\tilde{x})\} \ . \tag{3.8}$$

It is usually claimed that since, in general, $E[b^i(\tilde{x})] \neq b^i(x)$, Eq. (3.5) is not an appropriate extension of Eq. (3.1).

However, there is an implicit conditioning in Eq. (3.1) which was ignored when Eq. (3.8) was derived. To see this, reconsider Eq. (3.1) written as

$$x^i(t + dt) - x^i(t) = b^i(x)dt \ , \tag{3.9}$$

by which we mean that, conditioned on $x(t) = x$, the increment in x^i is given by Eq. (3.9). The confusion about Eq. (3.5) arises by ignoring the conditioning in Eq. (3.1).

In this section, two probabilistic formalisms for the connection between Eqs. (3.5) and (3.1) are given. They both have the property that the deterministic kinetic equation is obtained as an appropriate *conditional* average of the stochastic equations.

In order to help illustrate the idea, the following model set of reactions is considered:

(a) $Y^1 \to B$,

(b) $2Y^1 + A \to 3Y^1$,

(c) $Y^1 + Y^2 \to 2B$,   (3.10)

(d) $Y^2 \to B$,

(e) $2Y^2 + A \to 3Y^2$.
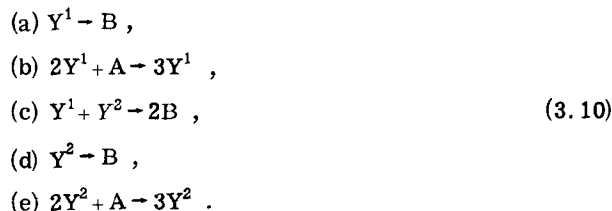
All rate constants are set equal to 1. In the general case, of course, one has a set of m reactions of the form

$$\sum_{i=1}^{n} \nu_k^i X^i \to \sum_{i=1}^{n} \eta_k^i X^i, \quad k = 1, 2, \ldots, m. \quad (3.11)$$

In Eq. (3.11), $X = (X^1, \ldots, X^n)$ is a vector representing the reacting species, and $\nu_k = (\nu_k^i, \ldots, \nu_k^n)$ and $\eta_k = (\eta_k^1, \ldots, \eta_k^n)$ are vectors representing generalized stochimetric coefficients in the kth elementary reaction.

The mass action kinetic equations corresponding to Eqs. (3.10) are

$$dy^1/dt = a(y^1)^2 - (y^1 + y^1 y^2) , \quad (3.12a)$$

$$dy^2/dt = a(y^2)^2 - (y^2 + y^1 y^2) . \quad (3.12b)$$

In Eqs. (3.12), y^1 and y^2 are taken as number concentrations of y^1 and y^2, respectively, and $a = [A]$ is assumed to be a constant.

In the general case, the kinetic equation will take the form

$$dx^i/dt = b^{i+}(x) - b^{i-}(x) , \quad (3.13)$$

where $b^{i+}(x)$, $b^{i-}(x) > 0$ and are determined by the stochiometry (3.11).

The fluctuation formalisms can now be discussed.

1. Reinterpretation of the kinetic equation

The fluctuation formalism given in this section is based solely on the kinetic equation (3.12) or (3.13). The information provided by the reaction mechanism is not used.

Let $\tilde{y}(t)$ [corresponding to Eqs. (3.12)] and $\tilde{x}(t)$ [corresponding to Eq. (3.13)] be random variables representing the number of Y or X at time t. First consider the model problem. Let $d\tilde{y} = \tilde{y}(t + dt) - \tilde{y}(t)$. In order to obtain a stochastic kinetic equation that will yield the deterministic equation as a conditional average, we postulate that

$$\Pr\{d\tilde{y}^1 = 1 \,|\, \tilde{y}(t) = y\} = a(y^1)^2 dt + o(dt) , \quad (3.14a)$$

$$\Pr\{d\tilde{y}^1 = -1 \,|\, \tilde{y}(t) = y\} = (y^1 + y^1 y^2) \, dt + o(dt) , \quad (3.14b)$$

$$\Pr\{d\tilde{y}^2 = 1 \,|\, \tilde{y}(t) = y\} = a(y^2)^2 dt + o(dt) , \quad (3.14c)$$

$$\Pr\{d\tilde{y}^2 = -1 \,|\, \tilde{y}(t) = y\} = (y^2 + y^1 y^2) \, dt + o(dt) , \quad (3.14d)$$

$$\Pr\{\text{all other transitions}\} = o(dt) . \quad (3.14e)$$

From the transition probabilities (3.14), one obtains

$$E\{d\tilde{y}^1 \,|\, \tilde{y}(t) = y\} = [a(y^1)^2 - (y^1 + y^1 y^2)] dt + o(dt) \quad (3.15a)$$

$$E\{d\tilde{y}^2 \,|\, \tilde{y}(t) = y\} = [a(y^2)^2 - (y^2 + y^1 y^2)] dt + o(dt) . \quad (3.15b)$$

Dividing by dt and taking the limit $dt \to 0$ in Eq. (3.15) gives Eq. (3.12). If molar concentrations rather than number concentrations were used, then the transition of one molecule is replaced by $1/NV$ moles/liter, where N is Avogadro's number and V is the volume of the system. In this case, $E(d\tilde{y}) = 0(1/NV)$ and $E[(d\tilde{y})^2] = 0[(1/NV)^2]$, and a rescaling of the time variable is needed to obtain the mass action kinetic equation.

In the general case, the kinetic equation is given by Eq. (3.13). One postulates that

$$\Pr\{d\tilde{x}^i = 1 \,|\, \tilde{x}(t) = x\} = b^{i+}(x) dt + o(dt) , \quad (3.16a)$$

$$\Pr\{d\tilde{x}^i = -1 \,|\, \tilde{x}(t) = x\} = b^{i-}(x) dt + o(dt) , \quad (3.16b)$$

$$\Pr\{\text{all other transitions}\} = o(dt) . \quad (3.16c)$$

The postulates (3.16) are based on the assumption that the reaction mechanism is not known, but that the kinetic equation (3.13) is known.

From these transition probabilities, one obtains that

$$E\{d\tilde{x}^i \,|\, \tilde{x}(t) = \tilde{x}\} = [b^{i+}(x) - b^{i-}(x)] dt + o(dt). \quad (3.17)$$

Dividing by dt and taking the limit $dt \to 0$ in Eq. (3.17) yields the kinetic equation (3.13).

Now, consider covariance terms. If only the kinetic equation is given, we postulate that fluctuations in each species are independent. For the model system (3.14), one finds

$$E\{(d\tilde{y}^1)^2 \,|\, \tilde{y}(t) = y\} = 1^2 a(y^1)^2 dt$$
$$+ o(dt) + (-1)^2 (y^1 + y^1 y^2) \, dt + o(dt)$$
$$= [y^1 + a(y^1)^2 + y^1 y^2] dt + o(dt) \quad (3.18)$$

and similarly for $E\{(d\tilde{y}^2)^2 \,|\, \tilde{y}(t) = y\}$. Assuming that fluctuations in each species are independent events, one obtains, for example,

$$\Pr\{d\tilde{y}^1 = 1, \, d\tilde{y}^2 = 1 \,|\, \tilde{y}(t) = y\}$$
$$\Pr\{d\tilde{y}^1 = 1 \,|\, \tilde{y}(t) = y\} \Pr\{d\tilde{y}^2 = 1 \,|\, \tilde{y}(t) = y\} = o(dt) . \quad (3.19)$$

Hence, $E\{d\tilde{y}^1 d\tilde{y}^2 \,|\, \tilde{y}(t) = y\} = o(dt)$. Thus, the covariance matrix

$$(a^{ij}) = \lim_{dt \to 0} \frac{1}{dt} E\{d\tilde{y}^i d\tilde{y}^j \,|\, \tilde{y}(t) = y\} \quad (3.20)$$

is diagonal:

$$a^{ij} = \begin{bmatrix} y^1 + a(y^1)^2 + y^1 y^2 & 0 \\ 0 & y^2 + a(y^2)^2 + y^1 y^2 \end{bmatrix} . \quad (3.21)$$

In the general case, corresponding to Eq. (3.16), one finds that

$$a^{ij} = \lim_{dt \to 0} \frac{1}{dt} E\{d\tilde{x}^i d\tilde{x}^j \,|\, \tilde{x}(t) = x\} = \text{diag}[b^{i+}(x) + b^{i-}(x)] . \quad (3.22)$$

2. Use of the reaction mechanism

In a chemical system, in addition to the kinetic equation, the reaction mechanism provides information. Consider the model system (3.10). Taking the reactions in the order shown in Eq. (3.10), we assume that the joint transition probabilities for changes in $\bar{y}^1$ and $\bar{y}^2$ are

(a) $\Pr\{d\bar{y}^1 = -1, \ d\bar{y}^2 = 0 \,|\, \bar{y}(t) = y\} = y^1 dt + o(dt)$,

(b) $\Pr\{d\bar{y}^1 = 1, \ d\bar{y}^2 = 0 \,|\, \bar{y}(t) = y\} = a(y^1)^2 dt + o(dt)$,

(c) $\Pr\{d\bar{y}^1 = -1, \ d\bar{y}^2 = -1 \,|\, \bar{y}(t) = y\} = y^1 y^2 dt + o(dt)$,

(d) $\Pr\{d\bar{y}^1 = 0, \ d\bar{y}^2 = -1 \,|\, \bar{y}(t) = y\} = y^2 dt + o(dt)$,

(e) $\Pr\{d\bar{y}^1 = 0, \ d\bar{y}^2 = 1 \,|\, \bar{y}(t) = y\} = a(y^2)^2 dt + o(dt)$. (3.23)

We assume that the probability of all other transitions is $o(dt)$. Upon summing, the transition probabilities in Eq. (3.23) yield those in Eq. (3.14). However, the probabilities in Eq. (3.23) provide information about *joint* transitions. This information is obtained because the reaction mechanism was used to construct Eq. (3.23). In particular, when (a^{ij}) is calculated using Eq. (3.23), we find that

$$a^{ij} = \lim_{dt \to 0} \frac{1}{dt} \, E\{d\bar{y}^i d\bar{y}^j \,|\, \bar{y}(t) = y\}$$

$$= \begin{bmatrix} a(y^1)^2 + y^1 y^2 + y^1 & y^1 y^2 \\ y^1 y^2 & a(y^2)^2 + y^2 + y^1 y^2 \end{bmatrix} . \quad (3.24)$$

Hence, the covariance matrix has nonzero off-diagonal terms. This result would be obtained if Keizer's fluctuation–dissipation postulates were used.[2]

In the general case, the reaction mechanism is used to construct joint transition probabilities for each of the m reactions:

$$\Pr\{d\bar{x}^1 = r_k^1, \ d\bar{x}^2 = r_k^2, \ldots, \ d\bar{x}^n = r_k^n \,|\, \bar{x}(t) = x\}$$
$$= \lambda^k(x) dt + o(dt), \quad k = 1, 2 \ldots, m. \quad (3.25)$$

The coefficients r_k^i correspond to the net change in the ith species in the kth reaction. From Eq. (3.11), we find that

$$r_k^i = \eta_k^i - \nu_k^i . \quad (3.26)$$

Then,

$$E\{d\bar{x}^i \,|\, \bar{x}(t) = x\} = r_k^i \lambda^k(x) dt + o(dt) . \quad (3.27)$$

In Eq. (3.27), the repeated index k is summed from 1 to m. Equation (3.27) will correspond to the deterministic kinetic equation.

Finally, the covariance term is

$$E\{d\bar{x}^i d\bar{x}^j \,|\, \bar{x}(t) = x\} = \lambda^k(x) \, r_k^i r_k^j dt + o(dt) . \quad (3.28)$$

Whenever joint transitions are possible (e.g., when species are coupled in a reaction), the covariance (a^{ij}) will contain off-diagonal terms. The procedure given here yields results equivalent to Keizer's fluctuation–dissipation postulates (see Ref. 2).

3. Treatment of systematic terms

The procedures outlined in Secs. III.B.1 and III.B.2 are based on statistical pictures of the chemical reaction.

When systematic terms are present, an ambiguity may arise. In order to illustrate the source of the ambiguity, an additional reaction is added to Reactions (3.10):

(f) $C \to Y^2$.

The Y^1 kinetic equation remains the same, but the kinetic equation for Y^2 becomes (where $c = [C]$).

$$dy^2/dt = a(y^2)^2 - y^1 y^2 - y^2 + c . \quad (3.29)$$

The ambiguity arises in the treatment of the constant term in a fluctuation formalism. Two options are possible.

Option 1: fluctuating systematic term. The systematic term has molecular origins itself and thus will also fluctuate. Hence, Eq. (3.14c) is modified to

$$\Pr\{d\bar{y}^2 = 1 \,|\, \bar{y}(t) = y\} = [a(y^2)^2 + c] dt + o(dt) , \quad (3.30)$$

or an additional transition is added to Eqs. (3.23):

(e) $\Pr\{d\bar{y}^2 = 1, \ d\bar{y}^1 = 0 \,|\, \bar{y}(t) = y\}$

$$= [a(y^2)^2 + c] dt + o(dt) . \quad (3.31)$$

Regardless of the choice of formalism, when the covariance term is calculated, we find that

$$E\{(d\bar{y}^2)^2 \,|\, \bar{y}(t) = y\} = [a(y^2)^2 + c + y^2 + y^1 y^2] dt + o(dt). \quad (3.32)$$

All other terms remain the same. Thus, the systematic term appears in the covariance.

Option 2: fluctuations about the systematic part. In this case, Eq. (3.29) is rewritten as a kinetic equation for deviations from the systematic part

$$dy^2/dt - c = a(y^2)^2 - y^1 y^2 - y^2 . \quad (3.33)$$

The transition probabilities (3.14c) and (3.14d) are replaced by

$$\Pr\{d\bar{y}^2 - c\,dt = 1 \,|\, \bar{y}(t) = y\} = a(y^2)^2 dt + o(dt), \quad (3.34a)$$

$$\Pr\{d\bar{y}^2 - c\,dt = -1 \,|\, \bar{y}(t) = y\} = (y^1 + y^1 y^2) dt + o(dt). \quad (3.34b)$$

The kinetic equation (3.29) is obtained as an appropriate conditional average using Eqs. (3.34a) and (3.34b). Since $E\{d\bar{y}\} = o(dt)$, we find that

$$E\{(d\bar{y}^2 - c\,dt)^2 \,|\, \bar{y}(t) = y\} = E\{(d\bar{y})^2 \,|\, \bar{y}(t) = y\} + o(dt). \quad (3.35)$$

Thus, the systematic term will not appear in the covariance calculation.

It is not clear which option in the treatment of the systematic term should be used.

C. Backward equations and the first exit problems

The above approach is a backward conditioning, rather than the usual forward or Fokker–Planck approach. Hence, we are led to the use of backward diffusion equations rather than the Fokker–Planck equation.

We assume that $\bar{x}(0; \alpha) = x_0$ remains a deterministic initial condition.

As $\alpha \to 0$, $\bar{x}(t; \alpha)$ converges to a diffusion process $\bar{x}(t)$. Let

$$u(t, x) = E\{u_0[\bar{x}(t)] \,|\, x(0) = x\} . \quad (3.36)$$

Then, $u(t, x)$ satisfies the backward equation

$$u_t = \tfrac{1}{2}\epsilon a^{ij} u_{ij} + b^i u_i + \epsilon c^i u_i \ , \tag{3.37}$$

where

$$a^{ij}(x) = \sigma_k^i(x)\sigma_l^j(x)(\gamma^{kl} + \gamma^{lk}) \ , \tag{3.38a}$$

$$c^i(x) = \gamma^{kl}\,\sigma_k^j\,\frac{\partial}{\partial x^j}(\sigma_l^i) \ . \tag{3.38b}$$

If $\bar{Y}(\tau)$ were white noise, the resulting diffusion equation would be

$$u_t = \tfrac{1}{2}\epsilon a^{ij} u_{ij} + b^i u_i \ . \tag{3.39}$$

If a^{ij} is independent of x, then Eqs. (3.37) and (3.39) are identical. Elsewhere,[17] we present a numerical comparison of solutions of Eqs. (3.37) and (3.39). Our results indicate that Eq. (3.39) is an excellent approximation to Eq. (3.37) if the boundaries are nonsingular.

Presently, much controversy surrounds the use of another diffusion equation, the Fokker–Planck equation.[4] The controversy involves the derivation of the Fokker–Planck equation. We point out that Eq. (3.37) is obtained rigorously from Eq. (3.5), but that the Fokker–Planck equation cannot be obtained rigorously by any method. Rather, the Fokker–Planck equation should be viewed as the formal adjoint of Eq. (3.37).[25,26] Our use of the backward equation is justified, in so far as the kinetic equation (3.5) is valid.

Equation (3.5) is not the usual "white noise" stochastic kinetic equation, since the process $\bar{Y}(s)$ has a correlation function that is not a delta function. The usual white noise equation is of the form

$$d\tilde{x}^i = b^i(\tilde{x})dt + \sqrt{\epsilon a^{ij}}\ d\tilde{W}_j \ . \tag{3.40}$$

It is possible to interpret Eq. (3.5) along the lines of Eq. (3.40),[27,28] using Stratonovich's approach to stochastic differential equations.[28] We consider a sequence of processes $\bar{Y}^n(\tau)$ which converge to $\tilde{W}(\tau)$ as $n \to \infty$. If the stochastic variable in the resulting Eq. (3.5) is $\tilde{x}^n(t)$, then as $n \to \infty$, $\tilde{x}^n \to \tilde{x}$, where $\tilde{x}$ satisfies[27]

$$d\tilde{x}^i = \left[b^i(\tilde{x}) + \frac{1}{4}\epsilon\frac{\partial}{\partial x^j}\,a^{ij} \right]dt + \sqrt{\epsilon a^{ij}}\ d\tilde{W}_j \ . \tag{3.41}$$

In particular, for the mean macroscopic motion, we obtain

$$\frac{dx^i}{dt} = b^i(x) + \frac{1}{4}\epsilon\frac{\partial}{\partial x^j}\,a^{ij} \tag{3.42}$$

and not Eq. (3.1). A special case of Eq. (3.42) was first discovered by Polder.[29] For large systems, ϵ is small and Eqs. (3.42) and (3.1) have the same qualitative behavior. Some details may change, but the overall picture remains unchanged. Since macroscopic equations are only meant to be approximate, this approach seems valid. It is interesting to note that the use of a white noise equation forces a "renormalization" of the mean motion.

The fundamental equation derived above is Eq. (3.37). A time independent version can be derived as follows: We surround the separatrix by a band with boundaries I, II. Let $\bar{T}(x)$ be min$\{t: \ \tilde{x}(t)\in$I or $\tilde{x}(t)\in$II $|\tilde{x}(0) = x\}$. Let $u(x) = \mathrm{Pr}\{\tilde{x}[\bar{T}(x)]\in$II$\}$. Then, $u(x)$ satisfies[26]

$$0 = \tfrac{1}{2}\epsilon a^{ij} u_{ij} + b^i u_i + \epsilon c^i u_i \ . \tag{3.43}$$

The boundary conditions for Eq. (3.43) are $u(x) = 0$ if $x\in$I, and $u(x) = 1$ if $x\in$II. The function $u(x)$ is the probability that the process $\tilde{x}(t)$ first exits from the band around the separatrix through boundary II.

We distinguish three cases of increasing complexity:

(1) The first is the normal case, in which the separatrix tube contains only the unstable steady state.

(2) The second is the marginal case, in which the separatrix tube contains the unstable steady state and one stable steady state. As one parameter varies, the two steady states coalesce and annihilate each other (the marginal bifurcation). After the bifurcation, only one stable steady state remains. This steady state is not in the separatrix tube, so that the deterministic flow is always across the tube in the same direction.

The first exit problem as formulated is of little interest. A more interesting question involves the expected time to reach boundary II, given that $\tilde{x}(0) = x$, $T(x)$. Let $d(x)$ denote the distance from the point x to II. Let

$$T(x) = \int_0^{\infty} t u_t(t, x)dt \ , \tag{3.44}$$

where $u(t, x)$ satisfies Eq. (3.37) with boundary conditions $u(t, x) = 1$ on II, $u_i \to 0$ as $d \to \infty$, and $u(0, x) = 0$ unless $x\in$II. Then, $u(t, x)$ is the probability that $\tilde{x}(t)$ has reached II by time t, given that $\tilde{x}(0) = x$.

$T(x)$ satisfies[30]

$$\tfrac{1}{2}\epsilon a^{ij} T_{ij} + b^i T_i + \epsilon c^i T_i = - u(x) \ , \tag{3.45}$$

where $u(x)$ is the probability of eventually reaching II, given that $\tilde{x}(0) = x$. $T(x)$ satisfies the boundary condition $T(x) = 0$ if x is on II, and a growth condition.[30]

(3) The third is the critical case, in which the separatrix tube contains the unstable steady state and both stable steady states. As two parameters vary, the three steady states move together and coalesce (the critical bifurcation). The remaining steady state is assumed to be stable.

The above classification scheme generalizes the work of Kubo et al.[1] to systems with more than one space dimension.

IV. AN ASYMPTOTIC TECHNIQUE

Equations (3.43) and (3.45) are singularly perturbed elliptic equations. They are further complicated by the vanishing of $b(x)$ at one or more points in the domain of interest. In Ref. 17, a general theory for such problems is developed. Here, we highlight the theory. Only the leading terms in the expansions are studied, since they are the most crucial. Further details can be found in Ref. 17.

A. Canonical integrals

We consider the canonical one-dimensional version of Eq. (3.43):

$$0 = \tfrac{1}{2}\epsilon a(x) u_{xx} + b(x)u_x \qquad (4.1)$$

$$u(r_0) = 0, \quad u(r_1) = 1 \ . \qquad (4.2)$$

In Eq. (4.1), we assume that $a(x)$ is always positive. The solution of Eq. (4.1) satisfying the boundary conditions (4.2) is

$$u(x) = k \int_{r_0}^x \exp\left[-\int^y \frac{2b(S)}{\epsilon a(S)}\, dS \right] dy \ , \qquad (4.3)$$

where k is a normalizing constant. We shall analyze Eq. (4.3) by using Laplace's method.[31] The basic idea behind Laplace's method is as follows: For small ϵ, the main contribution to Eq. (4.3) comes from the values of y which minimize the argument of the exponential function. If

$$\Phi(y) = \int^y \frac{2b(S)}{a(S)}\, dS \ ,$$

then $\Phi'(y) = 2b(y)/a(y)$, so that the main contribution to Eq. (4.3) comes from the vicinity of the deterministic steady states, i.e., solutions of $b(y) = 0$. One then does a Taylor expansion of $\Phi(y)$ about the point where $b(y) = 0$ and $b'(y) > 0$. Further details and exact estimates are in Ref. 31.

In the *marginal case*, b depends on one paramater η and for $\eta > 0$ the equation $b(x, \eta) = 0$ has two solutions $x_0(\eta)$, $x_1(\eta)$ place's method yields

$$u(x) = k \int_{r_0}^x \left[\exp - \frac{b'(x_0)}{\epsilon a(x_0)} \, (S - x_0)^2 \right] dS + 0(\sqrt{\epsilon}). \qquad (4.4)$$

A change of variables converts Eq. (4.4) to

$$u(x) = kE[\psi(x)/\sqrt{\epsilon}\,] + 0(\sqrt{\epsilon}) \ , \qquad (4.5)$$

where $\psi(x)$ is a regular function and $E(z)$ is the error integral

$$E(z) = \int_{z_0}^z e^{-s^2/2}\, dS \ . \qquad (4.6)$$

The $0(\sqrt{\epsilon})$ term in Eq. (4.5) involves $E'[\psi(x)]$, the derivative of the error integral.[17]

In the *marginal case*, b depends on one parameter η and for $\eta > 0$ the equation $b(x, \eta) = 0$ has two solutions $x_0(\eta)$, $x_1(\eta)$ $\in (r_0, r_1)$. When $\eta \to 0$, the two solutions coalesce and annihilate each other. We assume that (for $\eta > 0$) $b'(x_0, \eta) > 0$, $b'(x_1, \eta) < 0$ so that x_0 is the unstable steady state. Since $b'(x_0, 0) = 0$ at the marginal type steady state, the analysis leading to the error function is not appropriate. Another term in the Taylor expansion of $\Phi(y)$ is needed. In this case, we find that[17]

$$u(x) = kA[\psi(x)/\epsilon^{1/3}, \alpha/\epsilon^{2/3}] + 0(\epsilon^{2/3}) \ , \qquad (4.7)$$

where $A(z, \beta)$ is the incomplete Airy integral

$$A(z, \beta) = \int_{z_0}^z \exp\left(-\frac{1}{3} S^3 + \beta S\right) dS \ . \qquad (4.8)$$

The parameter α in Eq. (4.7) is determined by a regularity condition.[17]

In the *critical case*, $b = b(x, \eta, \delta)$ depends upon two parameters and the critical type steady state is characterized by the vanishing of $b(x_0, 0, 0)$, $b'(x_0, 0, 0)$, and $b''(x_0, 0, 0)$ with a nonvanishing third derivative. Again, an additional term in the Taylor expansion of $\Phi(y)$ is needed. It can be shown[17] that $u(x)$ can be expressed in terms of the incomplete Pearcey integral

$$P(z, \alpha, \beta) = \int_{z_0}^z \exp\left(\frac{1}{4} S^4 - \frac{\alpha S^2}{2} - \beta S\right) dS \ . \qquad (4.9)$$

The parameters α and β can be expressed in terms of the deterministic parameters η and δ.

A similar analysis holds for a canonical version of Eq. (3.45).

We return now to the partial differential equation (3.43). The above analysis indicates that a possible solution of Eq. (3.43) is given by

$$u(x) = g(x, \epsilon)S[\psi(x), \delta, \epsilon] + h(x, \epsilon)S'[\psi(x), \delta, \epsilon] \ . \qquad (4.10)$$

In Eq. (4.10), $g(x, \epsilon)$ and $h(x, \epsilon)$ are power series in ϵ and $S[\psi(x), \delta, \epsilon]$ is the error integral in the normal case, the incomplete Airy integral in the marginal case, and the incomplete Pearcey integral in the critical case. The functions $\psi(x)$, $g(x, \epsilon)$, $h(x, \epsilon)$, and parameters δ are to be determined. In Secs. IV. B–IV. D, we summarize the results of the complete analysis given in Ref. 17.

B. Normal case

In the normal case, we find that

$$u(x) = g^0 E[\psi(x)/\sqrt{\epsilon}\,] + 0(\sqrt{\epsilon}) \ , \qquad (4.11)$$

where $E(z)$ is the error integral satisfying

$$E''(z) = -zE'(z), \quad z_0 \leq z \leq z_1 \ . \qquad (4.12)$$

The function $\psi(x)$ must satisfy

$$b^i \psi_i - \tfrac{1}{2} a^{ij} \psi_i \psi_j \psi = 0 \ , \qquad (4.13)$$

with initial data $\psi = 0$ on S. Equation (4.13) is obtained by evaluating derivatives of $u(x)$ [using Eq. (4.12) to replace $E''(\psi/\sqrt{\epsilon})$ by $-(\psi/\sqrt{\epsilon})E'(\psi/\sqrt{\epsilon})$], substituting into Eq. (3.43), and collecting terms according to powers of ϵ. Equation (4.13) arises as the coefficient of the $\epsilon^{-1/2}$ term. It is possible to derive an equation for the normal derivative of ψ, ψ_n, on the deterministic separatrix. We find[17]

$$\frac{d\psi_n}{dt} + \hat{b}\psi_n - \frac{\hat{a}}{2} \psi_n^3 = 0 \ , \qquad (4.14)$$

where

$$\hat{b}(t) = [(b^2)^2 b_{,1}^1 - b^1 b^2(b_{,1}^2 + b_{,2}^1) + (b^1)^2 b_{,2}^2]/[(b^1)^2 + (b^2)^2] \ , \qquad (4.15)$$

$$\frac{\hat{a}}{2} = \{a^{11}[(b^2)^4 + (b^1)^2(b^2)^2] - 2a^{12}[(b^1)^3 b^2 + b^1(b^2)^3]$$
$$+ a^{22}[(b^1)^2(b^2)^2 + (b^1)^4]\}/[(b^1)^2 + (b^2)^2]^2 \ . \qquad (4.16)$$

Equation (4.14) is obtained by differentiating Eq. (4.13) with respect to x^k and switching to tangential and normal coordinates. Since $dx^i/dt = b^i$,

$$b^i \frac{\partial}{\partial x^i} = \frac{d}{dt} \ , \qquad (4.17)$$

where t measures "time" along S. At the saddle point, Eq. (4.14) becomes

$$\psi_n(\infty) = \sqrt{2\hat{b}(\infty)/\hat{a}(\infty)} \ . \qquad (4.18)$$

Thus, we can calculate $\psi_n(t)$ on the separatrix. In the vicinity of the separatrix, $\psi(x)$ can be determined by a Taylor expansion.

The function g^0 is a constant. For simplicity, we assume that $\psi = \psi_{\mathrm{I}}$ on boundary I and $\psi = \psi_{\mathrm{II}}$ on boundary II. Then, we set $z_0 = \psi_{\mathrm{I}}$ and

$$g^0 \equiv 1/E(\psi_{\mathrm{II}}/\sqrt{\epsilon}) \ . \tag{4.19}$$

If ψ is not constant on the boundaries, then u differs from 0 on I by exponentially small terms and from 1 on II by exponentially small terms.[17] Other terms are treated in an analogous fashion.

C. Marginal case

Here, we find that

$$u(x) = g^0 A[\psi(x)/\epsilon^{1/3}, \alpha_0/\epsilon^{2/3}] + O(\epsilon^{2/3}) \ , \tag{4.20}$$

where $A(z, \beta)$ is the incomplete Airy integral

$$\frac{d^2 A(z, \beta)}{dz^2} = -(z^2 - \beta) \frac{dA}{dz}(z, \beta) \ . \tag{4.21}$$

In this case, the parameter α_0 and functions $\psi(x)$ and g^0 must be determined. Instead of Eq. (4.13), we obtain

$$b^i \psi_i - \frac{a^{ij}}{2} \psi_i \psi_j (\psi^2 - \alpha_0) = 0 \ , \tag{4.22}$$

with data $\psi = \sqrt{\alpha_0}$ on S.

In the marginal case, $b(x)$ vanishes at two points in the separatrix tube (see Fig. 4) Q_0 and Q_1. We set

$$\psi(Q_0) = -\sqrt{\alpha_0}, \quad \psi(Q_1) = \sqrt{\alpha_0} \ ; \tag{4.23}$$

the parameter α_0 is determined as follows: Associated with Eq. (4.22) is a set of ordinary differential equations known as the ray or characteristic equations[18]

$$dx^i/ds = b^i - a^{ij} p_j (\psi^2 - \alpha_0) \ , \tag{4.24}$$

$$\frac{d\psi}{ds} = p_i \frac{dx^i}{ds} \ , \tag{4.25}$$

$$\frac{dp_k}{ds} = -b^i_{,k} \psi_i + \frac{a^{ij}}{2} p_i p_j (\psi^2 - \alpha_0) + a^{ij} p_i p_j p_k \psi \ , \tag{4.26}$$

where $\psi_i \equiv p_i$ is treated as an independent variable. Solving Eq. (4.22) and integrating Eqs. (4.24)–(4.26) are equivalent. Thus, ψ can be calculated by solving Eqs. (4.24)–(4.26).

The parameter α_0 is determined by an iterative procedure. Let $\alpha_0^{(0)}$ be the first guess for α_0. We start the integration of Eqs. (4.24)–(4.26) just away from Q_0, where $\alpha_0 = -\sqrt{\alpha_0^{(0)}}$, and follow rays that hit the separatrix. When a ray hits the separatrix, if $\psi \neq \sqrt{\alpha_0^{(0)}}$, then $\alpha_0^{(0)}$ must be replaced by a better estimate $\alpha_0^{(1)}$. The procedure can be repeated until α_0 is known to any desired accuracy.

The function $\psi(x)$ and constant g^0 are calculated as in the normal case. At the bifurcation value $\eta = 0$, Q_0 and Q_1 coalesce. Thus, $\alpha_0 = 0$ when $\eta = 0$. It can be shown that all constructions remain regular at the bifurcation value.[17]

At the bifurcation, we are more interested in $T(x)$ than

$u(x)$, since $u \approx 1$ for all x in the tube. By arguments similar to the above, we can show that

$$T(x) = g^0 B(\psi/\epsilon^{1/3}, \alpha_0/\epsilon^{2/3}, 1/\epsilon^{1/3}, 0) + k^0(x) + O(\epsilon^{2/3}) \ , \tag{4.27}$$

where $B(z, \alpha, \gamma_1, \gamma_2)$ satisfies an inhomogeneous version of Eq. (4.21):

$$\frac{d^2 B}{dz^2} = -(z^2 - \alpha) \frac{dB}{dz} - \gamma_1 + \gamma_2 z \ , \quad z_0 \leq z \ . \tag{4.28}$$

The expression (4.27) for $T(x)$ is substituted into Eq. (3.45) and terms are collected according to powers of ϵ. We obtain equations for ψ and the parameter α_0 is determined as described above. The value of g^0 is determined from the equation that k^0 must satisfy, i.e.,

$$b^i k_i^0 - \frac{a^{ij}}{2} \psi_i \psi_j g^0 = -1 \ . \tag{4.29}$$

At the point where $b(x)$ vanishes, we obtain

$$g^0 = 2/a^{ij} \psi_i \psi_j \ . \tag{4.30}$$

We set $k^0(x) \equiv 0$ if $x \in \mathrm{II}$ and can determine $k^0(x)$ by solving Eq. (4.29) by the method of characteristics.[40]

D. Critical case

Here, we find that

$$u(x) = g^0 P[\psi(x)/\epsilon^{1/4}, \alpha_0/\epsilon^{1/2}, \beta_0/\epsilon^{3/4}] + O(\epsilon^{3/4}) \ , \tag{4.31}$$

where $P(z, \alpha, \beta)$ is the incomplete Pearcey integral

$$d^2 P/dz^2 = (z^3 - \alpha z - \beta)(dP/dz) \ . \tag{4.32}$$

The arguments of the previous two sections are repeated, except that now $b(x)$ vanishes at three points in the separatrix tube and two parameters must be determined.

Details of all these calculations are given in Ref. 17.

V. FLUCTUATION EFFECTS ON SUBSTRATE INHIBITED REACTIONS

A. Multiple steady states in enzyme reactions

The experiments of Degn[14] conclusively demonstrated that multiple stable steady states actually can be observed. In his experiments, Degn was concerned with observing the multiple steady states and not with fluctuation effects. It is clear, however, that his techniques could be used to study fluctuation effects at the unstable steady state. In this section, we study fluctuation effects on a substrate inhibited reaction. Our choice of model was motivated by Degn's experiments, but is not meant to correspond to the experiments exactly.
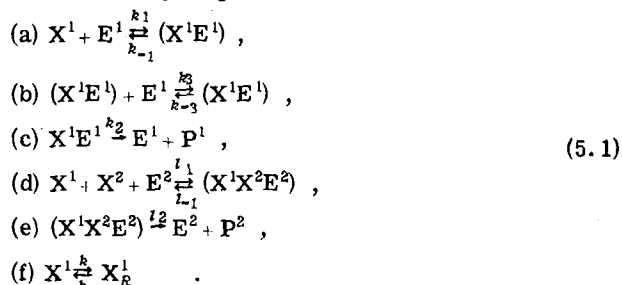
In this section, we develop a model of Degn's experiments. The model has the following features:

(1) A reaction vessel of volume V can exchange substrate "1" with an external reservoir of volume V'.

(2) Substrate 1 is converted into product by a substrate inhibited enzyme. The concentration of substrate 1 in the reservoir is $\tilde{x}_r^1$, or $\bar{X}_r^1$ molecules. An example of this re-

action is the oxidation (x^1 being [O_2]) of NADH catalyzed by horse radish peroxidase.

(3) Substrate "2" is continually fed into the reaction vessel, at rate α, and reacts with substrate 1. The reaction is catalyzed by an enzyme that obeys the usual Michaelis–Menten mechanism.[30] An example of this reaction is the oxidation of glucose catalyzed by glucose idase.

The elementary steps involved in these reactions are

(a) $X^1 + E^1 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (X^1 E^1)$,

(b) $(X^1 E^1) + E^1 \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} (X^1 E^1)$,

(c) $X^1 E^1 \overset{k_2}{\rightleftharpoons} E^1 + P^1$,   (5.1)

(d) $X^1 + X^2 + E^2 \underset{l_{-1}}{\overset{l_1}{\rightleftharpoons}} (X^1 X^2 E^2)$,

(e) $(X^1 X^2 E^2) \overset{l_2}{\rightleftharpoons} E^2 + P^2$,

(f) $X^1 \underset{k}{\overset{k}{\rightleftharpoons}} X_R^1$.

In order to derive the kinetic equations for the concentrations of X^1 and X^2, we use the Michaelis–Menten assumption.[33] Nondimensional concentration variables are:

$$x^i(t) = \frac{[\text{concentration of species } i \text{ at time } t]}{[\text{concentration of species } i \text{ at 0}]} \quad . \quad (5.2)$$

Then, the kinetic equations for x^1 and x^2 are[14,32]

$$\dot{x}^1 = \frac{-x^1(k_2/k_1 x^{10})}{\frac{k_2}{k_1 x^{10}} + \frac{k_{-1}}{k_1 x^{10}} + x^1 + \frac{k_3 x^{10}(x^1)^2}{k_{-3}}}$$

$$+ k(x_r^1 - x^1)\frac{-x^2 x^1(l_2/x^{10}x^{20}l_1)}{\frac{(l_{-1}+l_2)}{x^{10}x^{20}l_1} + x^2 x^1} \quad , \quad (5.3)$$

$$\dot{x}^2 = \alpha - \frac{x^2 x^1(l_2/x^{10}x^{20}l_1)}{\frac{(l_{-1}+l_2)}{x^{10}x^{20}l_1} + x^2 x^1} \quad . \quad (5.4)$$

In the above equations, x^{i0} is the initial concentration of species i. We choose the following values of the parameters: $\alpha = 0.09$, $x^{10} = x^{20} = 10^{-7} M$, $k_1 = 1.2 \times 10^7$ liter/M sec, $k_{-1} = 0.12$ sec^{-1}, $k_2 = 1.68$ sec^{-1}, $k_3 = 1.3 \times 10^6 M^{-2}$ sec^{-1}, $k_{-3} = 0.01$ sec^{-1}, $l_{-1} = 0$ sec^{-1}, and $l_2/l_1 x^{10} x^{20} = 0.1$. The values of x^{i0} and k_i roughly correspond to Chance's[35] experimental data. The l_i were chosen as "reasonable" estimates, since no data were available. With these choices, we obtain

$$\dot{x}^1 = \frac{-1.4x^1}{1.5 + x^1 + 13(x^1)^2} + k(x_r^1 - x^1) - \frac{x^1 x^2}{1 + 10x^1 x^2} \quad , \quad (5.5)$$

$$\dot{x}^2 = 0.09 - \frac{x^1 x^2}{1 + 10x^1 x^2} \quad . \quad (5.6)$$

We assume that $\epsilon = 0.01$ and the "volume" $V = 1/\epsilon$. Equations (5.5) and (5.6) are model equations that exhibit the marginal and critical bifurcations. They are not meant to simulate a particular set of experiments. Since the rate constants of enzyme preparations vary widely, this appears to be a reasonable approach. We will refer to (x^1, x^2) as concentration variables. We will treat V as a nondimensional quantity and treat $X^i = Vx^i$ as a variable corresponding to the number of "molecules."

B. Stochastic model of the enzyme reaction

In the stochastic model, the natural random variables are the *numbers* of molecules of species 1 and 2 in the reaction vessel at time t; denote these by $\tilde{X}^1(t)$ and $\tilde{X}^2(t)$, respectively. The fluctuating concentrations are then given by $\tilde{x}^i(t) = \tilde{X}^i(t)/V$. From the reaction mechanism (5.1), one could construct transition probabilities in the five dimensional space [X^1, X^2, E^1, E^2, $(X^1 E^1)$]. In order to derive the equivalent of the kinetic equations (5.5) and (5.6), the Michaelis–Menten assumption must be applied to the transition probabilities; E^1, E^2, and $(X^1 E^1)$ will be replaced by their steady state values. Once this replacement is performed, the transition probabilities are given in terms of X^1 and X^2 only. By using the Michaelis–Menten assumption, we are treating the enzyme concentrations as parameters rather than variables. Thus, one assumes that fluctuations in enzyme level can be ignored in comparison to fluctuations in substrate level. This assumption is consistent with the work of Heyde and Heyde,[36] who found that the steady state fluctuations in enzyme concentration were 10^6 to 10^8 times smaller than fluctuations in substrate concentration.

When the above procedure is used, the following transition probabilities are obtained for $d\tilde{X}^i = \tilde{X}^i(t+dt) - \tilde{X}^i(t)$:

$$\Pr\{d\tilde{X}^1 = 1, d\tilde{X}^2 = 0 \,|\, \vec{X}(t) = X\} = \frac{kX_R}{V'} dt + o(dt) \quad , \quad (5.7)$$

$$\Pr\{d\tilde{X}^1 = -1, d\tilde{X}^2 = 0 \,|\, \vec{X}(t) = X\}$$

$$= \left[\frac{1.4X^1}{1.5V + X^1 + 13(X^1)^2} + \frac{kX^1}{V}\right]dt + o(dt) \quad , \quad (5.8)$$

$$\Pr\{d\tilde{X}^1 = -1, d\tilde{X}^2 = -1 \,|\, \vec{X}(t) = X\} = \frac{X^1 X^2}{V^2 + 10X^1 X^2} dt + o(dt) \quad (5.9)$$

$$\Pr\{d\tilde{X}^1 = 0, d\tilde{X}^2 = 1 \,|\, \vec{X}(t) = X\} = 0.09Vdt + o(dt) \quad . \quad (5.10)$$

In deriving Eqs. (5.7)–(5.10), we have used the first option described in Sec. III.B.3 for the treatment of systematic terms.

The work of Gillespie[37] could, in principle, be used to replace some of the macroscopic parameters by combinations of microscopic parameters. It is not clear that much would be gained for a complicated system such as the one considered here. However, Gillespie points out that the stochastic approach should be valid if the number of reactive collisions is a small fraction of the total number of collisions. This should be the case for the problems considered here.

Since the stochastic kinetic equation (3.5) was not derived from first principles, a prescription must be given for the calculation of $\epsilon(a^{ij})$ in Eq. (3.37). In order to give the prescription, two steps are followed. First, Eq. (3.5) is reinterpreted as a white noise equation. Second, the fluctuation formalism discussed in Sec. III.B is applied.

Instead of the kinetic equation (3.5), consider the kinetic equation [also see Eq. (3.40)–(3.42)]

$$d\tilde{x}^i = b^i(\tilde{x})dt + \sqrt{\epsilon a^{ij}}\, dW_j \quad . \quad (5.11)$$

In Eq. (5.11), $W(t)$ is the Wiener process or Brownian motion. The functions b^i and ϵa^{ij} have the simple interpretation[26]:

$$b^i = \lim_{\Delta t \to 0} \frac{1}{\Delta t} E\{[\tilde{x}^i(t + \Delta t) - \tilde{x}^i(t)] | \tilde{x}^k(t) = x^k, k = 1, \cdots, n\},$$
(5.12)

$$\epsilon a^{ij} = \lim_{\Delta t \to 0} \frac{1}{\Delta t} E\{[\tilde{x}^i(t + \Delta t) - \tilde{x}^i(t)][\tilde{x}^j(t + \Delta t) - \tilde{x}^j(t)] | \tilde{x}^k(t)$$

$$= x^k, k = 1, \cdots, n\} .$$
(5.13)

Equations (5.12) and (5.13) are the Ito interpretation of Eq. (5.11). In Sec. III.B, fluctuation formalisms that can be used to calculate the expectations in Eqs. (5.12) and (5.13) were discussed.

Using the fluctuation formalism described in Sec. III. B.1 yields the following covariance matrix:

$$\epsilon a(x) = \frac{1}{(100)^2} \begin{bmatrix} (\lambda_1 + \mu_1)x^1 & 0 \\ & \\ 0 & (\lambda_2 + \mu_2)x^2 \end{bmatrix},$$
(5.14)

where

$$\lambda_1 x^1 = k x_r^1 ,$$
(5.15)

$$\mu_1 x^1 = \frac{1.4x^1}{1.5 + x^1 + 13(x^1)^2} + kx^1 + \frac{x^1 x^2}{1 + 10x^1 x^2} ,$$
(5.16)

$$\lambda_2 x^2 = 0.09 ,$$
(5.17)

$$\mu_2 x^2 = \frac{x^1 x^2}{1 + 10x^1 x^2} .$$
(5.18)

If the fluctuation formalism described in Sec. III.B.2 were used, the covariance (5.16) would have off-diagonal terms. There will be little difference in the behavior of solutions of the diffusion equation when the covariance matrix with off-diagonal terms is used. When the transition probabilities are used to calculate the infinitesimal drift $b^i(x)$, we find

$$b^1(x) = \frac{1}{100} (\lambda_1 - \mu_1)x^1 ,$$
(5.19)

$$b^2(x) = \frac{1}{100} (\lambda_2 - \mu_2)x^2 .$$
(5.20)

A rescaling of the time yields $\dot{x}^i = b^i(x)$, so that the mean stochastic motion and the law of mass action agree.

The covariance (5.14) and drift (5.19) and (5.20) were used in all of the calculations reported in this paper.

In summary, the diffusion equation corresponding to Eq. (3.5) is

$$u_t^{st} = \tfrac{1}{2}\epsilon a^{ij} u_{ij} + (b^i + \epsilon c^i)u_i,$$
(5.21)

where $c^i = \tfrac{1}{4} a_{,j}^{ij}$. The backward equation corresponding to Eq. (5.11) is

$$u_t^{wn} = \tfrac{1}{2}\epsilon a^{ij} u_{ij} + b^i u_i ,$$
(5.22)

with $\epsilon a(x)$ given by Eq. (5.14) and $b(x)$ by Eqs. (5.19) and (5.20). We shall use Eq. (5.22) to approximate (5.21). Elsewhere,[17] one dimensional versions of Eqs. (5.21) and (5.22) are compared. The results indicate that, for the

problems of interest here, the choice of stochastic calculus is not important. Thus, Eqs. (5.11) and (5.22) are useful approximations to Eqs. (3.5) and (5.21), respectively.

VI. COMPARISON OF THE THEORY WITH MONTE CARLO EXPERIMENTS

No exact solution of the two dimensional backward equations (5.21) or (5.22), with b^i given by Eqs. (5.19) and (5.20) and ϵa^{ij} given by Eq. (5.14), could be found. Thus, the asymptotic results will be compared with Monte Carlo experiments. The Monte Carlo experiments were performed in one of two ways. In the first technique, the transition probabilities (5.7)–(5.10) were used to construct a birth and death process. In the second technique, the Ito equation[38,39]

$$d\tilde{x} = b(\tilde{x})\,dt + \sqrt{\epsilon a(\tilde{x})}\,d\tilde{W}$$
(6.1)

was used directly to calculate increments in $\tilde{x}$. In Eq. (6.1), $\tilde{W}(t)$ is Brownian motion, i.e., $E(d\tilde{W}) = 0$, $E(d\tilde{W}^2) = dt$, and increments of $d\tilde{W}$ are normally distributed. The two techniques lead to equivalent first exit probabilities.

A. The normal case

When $k = 0.038$ and $k x_r^1 = 0.2225$ in Eq. (5.5), the corresponding deterministic system is the normal type. The first exit probability was calculated using the theory of Sec. IV. The integration of the equation for ψ_n used a fourth order Runge–Kutta routine. In Fig. 3, the deterministic phase protrait and the $u = 0.3$ contour of first exit probability are plotted. In Table I, the probability calculated using the theory is compared with the probability observed in Monte Carlo simulations.

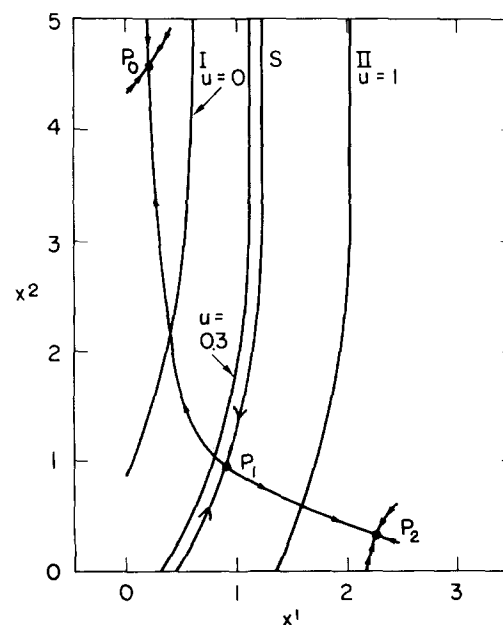The function $\psi(x)$ was calculated in a vicinity of S by a

FIG. 3. First exit boundaries and phase portrait of the substrate inhibited system considered in Sec. V, in the normal case.

TABLE I. Comparison of the theory with Monte Carlo experiments in the normal case.

Test point	Theory	Experiment (# trials)
(0.878, 1.025)	0.50	0.51 (2000)
(0.49, 0.058)	0.50	0.49 (1700)
(0.75, 0.75)	0.40	0.39 (1750)
(0.54, 0.55)	0.22	0.23 (1500)
(0.40, 1.24)	0.03	0.02 (2000)
(0.65, 1.125)	0.17	0.15 (2000)
(0.475, 1.20)	0.05	0.04 (2000)
(0.73, 0.72)	0.41	0.39 (1700)

Taylor expansion. The contours were calculated by using the leading part of the expansion of $u(x)$.

B. The marginal case

When $k = 0.0533$ and $kx_r^1 = 0.24898$ and the boundaries I and II are as shown in Fig. 4, the theory of the marginal case will apply.

The parameter α_0 in the Airy integral was calculated by the method of characteristics. A double precision Runge–Kutta routine was used. When a ray hit the separatrix, $\psi_t = b^i \psi_i = 0$. The intersection of the ray and the separatrix was noted by calculating ψ_t along the ray. Similar results were obtained when a routine with error control was used (UBC DDIFSY). The method of false position was used to calculate iterates of α. The value of ψ on boundary I was calculated by a Taylor expansion about the node Q_0, where $\psi = -\sqrt{\alpha_0}$.

In Table II, we compare the theory with Monte Carlo experiments for a number of test points. Also shown are some theoretical results in which the Error integral was used. Using the leading part of the asymptotic expansion, contours of first exit probability could be calculated. The 0.30 contour is shown in Fig. 4. The theory using
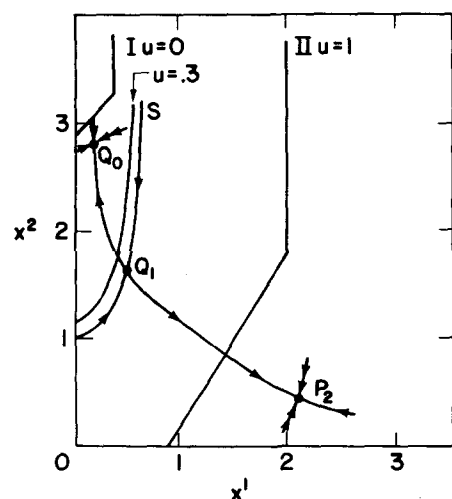

FIG. 4. First exit boundaries and phase portrait of the substrate inhibited system considered in Sec. V, in the marginal case.
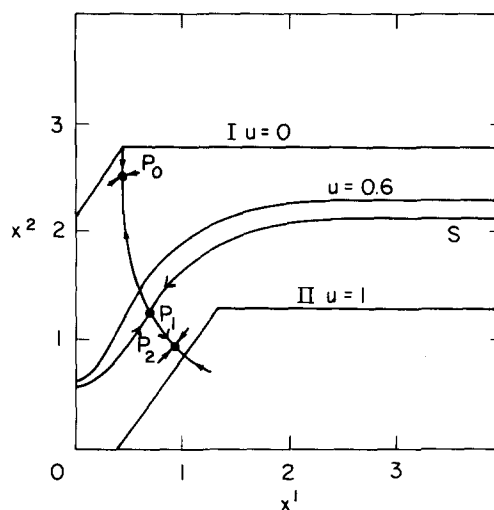

FIG. 5. First exit boundaries and phase portrait of the substrate inhibited system considered in Sec. V, in the critical case.

the error integral did not yield satisfactory results, but the theory using the Airy integral did.

The Monte Carlo results are very sensitive to the location of boundary I. Since the attractor Q_0 is within the separatrix tube, it is possible to choose boundary I so that the process will not hit I before II with probability close to 1. Thus, the Monte Carlo study of marginal (and critical) type systems is time consuming. On the other hand, the asymptotic calculations, although sensitive to the location of the boundary, are not any more difficult than in the normal case. In this sense, the Monte Carlo and asymptotic techniques are complementary.

C. Marginal bifurcation

When $k = 0.069979$ and $kx_r^1 = 0.25901$, the deterministic system exhibits the marginal bifurcation. In this case, the first exit probability is of little interest. The expected time that it takes the process to hit a specified curve R, given that $\bar{x}(0) = x$, is of more interest. Consequently, we calculate the time it takes to hit R, conditioned on hitting R and $\bar{x}(0) = x$. This case is treated elsewhere.[17]

D. The critical case

When $k = 0.08125$ and $kx_r^1 = 0.261199$, and the boundaries I and II are as shown in Fig. 5, the theory of the critical

TABLE II. Comparison of the theory with Monte Carlo experiments in the marginal case.

Test point	u^{theory} (Airy)	u^{MC} (# trials)	u^{theory} (error)
(0.2, 1.2)	0.29	0.24 (1650)	0.12
(0.3, 1.0)	0.63	0.67 (1040)	0.78
(0.5, 2.2)	0.38	0.41 (1710)	0.23
(0.32, 2.8)	0.17	0.14 (1150)	0.001
(0.53, 1.71)	0.57	0.55 (1100)	0.50
(0.6, 1.8)	0.62	0.65 (1430)	0.77

TABLE III. Comparison of theory and Monte Carlo experiments in the critical case.

Test point	u^{theory}	u^{MC} (# trials)
(0.7, 1.28)	0.67	0.71 (2040)
(0.5, 1.2)	0.63	0.68 (980)
(0.9, 2.0)	0.54	0.50 (980)
(0.6, 1.0)	0.76	0.76 (1060)
(0.5, .82)	0.78	0.77 (1060)
(0.9, 1.8)	0.59	0.61 (980)

case will be applicable. The parameters α and β were calculated using the method of characteristics. A double precision Runge–Kutta routine was used to calculate the rays. More sophisticated routines, with error control, gave similar results. Iterates of α_0 and β_0 were calculated using the method of false position. The values of ψ on the boundaries I and II were determined by Taylor expanding around the nodes and then following rays that hit the boundary. A similar technique was used in the marginal case and at the critical bifurcation. The value of ψ in a vicinity of the separatrix was calculated by a Taylor expansion. The derivative of ψ on S was calculated by integrating Eq. (4.14). A fourth order Runge–Kutta routine was used. In Table III, we compare the Monte Carlo experiments and the theoretical results.

The Monte Carlo results were very sensitive to the location of the boundary. Since both attractors P_0 and P_1 are contained by the separatrix tube, it is possible to choose I and II so that the probability of hitting either boundary is very small.

ACKNOWLEDGMENTS

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