Transient kinetics of chemical reactions with bounded diffusion perpendicular to the reaction coordinate: Intramolecular processes with slow conformational changes

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Transient kinetics of chemical reactions with bounded diffusion perpendicular to the reaction coordinate: Intramolecular processes with slow conformational changes[a]

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Intramolecular reactions inside macromolecules (e.g., binding of ligands to iron inside heme proteins) may often be coupled to slow random fluctuations in the reaction center geometry. This motion is "perpendicular" to the reaction coordinate. It can be described as bounded diffusion in the presence of a binding potential field and an intramolecular rate constant which depends on the perpendicular degree of freedom. The diffusion equation is solved under the appropriate reflective boundary conditions. The transient decay of the total population is multiexponential (power law) for small diffusivity, changing to monoexponential kinetics for large diffusivity. For large times or large diffusivity, direct integration is very tedious, but an eigenvalue expansion converges rapidly. It also allows the calculation of the "average survival time" (an extension of the "first passage time") a natural candidate for replacing the reciprocal rate constant in multiexponential kinetics. An example is given for electron transfer between two loosely bound sites in a macromolecule. The average survival time shows a non-Kramers dependence on diffusivity, of the type found in the binding kinetics in heme proteins.

I. INTRODUCTION

The diffusion (Smoluchowski[1]) description of stochastic processes[2] has found numerous applications in solution-phase chemical and biochemical kinetics,[3-17] including such processes as unimolecular dissociation,[6-8] recombination of isolated ion pairs[14] and radicals,[15] fluorescence quenching,[16] and electron and electronic energy transfer.[17] Mathematically, the diffusion equation can be solved for steady-state conditions[6-10] deriving expressions for steady-state rate constants, or it can be solved for the transient time dependence.[14(c),14(f),14(g),15,17(c),17(d)] Physically, diffusion can be thought of as occurring along the reaction coordinate with reaction introduced as an appropriate boundary condition,[6-15] or as a process where diffusion and reaction occur along different coordinates, coupled by virtue of a coordinate dependent rate constant.[16,17]

The present work is motivated by the experiments on the binding kinetics of ligands to heme proteins.[18] In these experiments a sample of protein with a ligand like O_2 or CO bound to the heme is irradiated with a strong, short laser pulse. The rebinding kinetics is then followed over a large time regime by monitoring the total fraction of unligated hemes. Such decay curves are measured over a wide range of temperatures[18(a)] and solvent viscosities.[18(b)] In contrast to the prediction of Kramers' theory,[6] reaction takes place even at very large viscosities and low temperatures. The decay curves under such conditions are multiexponential (characterized by a distribution of barrier heights),

i.e., approaching a power-law dependence. At lower viscosities (and/or higher temperatures) the decay curves become exponential.

Our work differs from the discussion of the above results in the literature,[18,19] by attributing the above effects to random motion *perpendicular to the reaction coordinate*, when there is a configuration-dependent rate constant in the diffusion equation. Although no similar experimental results for other systems are yet available, we believe that they are not unique to heme proteins. Such effects are typical to intramolecular pro- processes in macromolecules where the reaction center can undergo slow, but relatively large, configurational changes.

As a concrete example consider an electron transfer reaction which depends exponentially on distance.[20] Suppose that the electron donor and electron acceptor are imbedded inside a large protein. In such a macromolecule many bonds can rotate, bend, or vibrate, leading to large fluctuations of donor—acceptor distance.[21] The random variations in this distance can be described by a diffusion equation. These variations are coupled to the electron transfer process because of the distance dependence of the rate constant.

A similar consideration is appropriate for the binding of ligands to heme proteins but requires a model for the dependence of the binding rate constant on the protein coordinate.[22] It is also complicated by the fact that at high diffusivity/temperature the ligand can escape out of the heme pocket into the solution or other protein site.

In contrast to most examples in the literature, configuration space is *bounded* by large potentials, preventing dissociation of the macromolecule. To keep problems finite in size, the potential at the boundary is replaced by an infinitely steep potential wall (re-

flective boundary conditions). The bound diffusion problem, characterized by the above boundry conditions, becomes an *eigenvalue problem*, in analogy to the Schrödinger equation for a bound particle. The *time course* of reaction can be calculated either by direct integration or by an eigenfunction expansion.

The paper is constructed as follows: Sec. II gives the mathematical theory, Sec. III discusses some numerical spects, and Sec. IV presents results for the electron transfer example. The theory is used in a subsequent publication[22] to discuss the kinetics of ligand binding to heme proteins.

II. THEORY OF BOUND DIFFUSION

A. The diffusion equation

We consider the diffusion (Smoluchowski)[1] equation in the presence of a coordinate dependent reaction

$$\frac{\partial p(x,t)}{\partial t} = D\frac{\partial^2 p}{\partial x^2} + \frac{D}{k_B T}\frac{\partial}{\partial x}\left(p\,\frac{\partial V}{\partial x}\right) - k(x)p \equiv -\mathcal{L}(p)\;. \tag{1}$$

$p(x,t)$ is the probability density for finding a value x for the independent coordinate at time t, D is the diffusion constant, k_B is Boltzmann's constant, and T the absolute temperature. The motion is under the influence of a potential $V(x)$ and a coordinate dependent rate constant[16,17] $k(x)$. Equation (1) also defines the diffusion operator $\mathcal{L}$.

The diffusion equation can be interpreted by saying that three physical processes contribute to the time and space variations of p. The first is free diffusion, which would widen any initial distribution until it becomes uniform. The second, a potential term, would carry an initial distribution down the gradient, until it becomes a delta function at the potential's minima. The last term describes a "total loss" of density due to reaction, which can occur from any point x with a different rate constant $k(x)$. It is the mathematical realization of the physical concept of diffusion perpendicular to the reaction coordinate: The perpendicular coordinate is x, while events along the reaction coordinate determine $k(x)$.

Equation (1) can also be written as the condition of flux conservation

$$-\partial p(x,t)/\partial t = \partial J(x,t)/\partial x + k(x)p(x,t)\;, \tag{2}$$

where the flux J and flux operator $\mathcal{J}$ are defined by

$$J(x,t) \equiv -D\left[\frac{\partial}{\partial x} + \frac{1}{k_B T}\frac{\partial V}{\partial x}\right]p(x,t) \equiv \mathcal{J}(p)\;. \tag{3}$$

In the absence of reaction, $k(x) = 0$, Eq. (1) admits a (time independent) equilibrium solution

$$p^{eq} = Z^{-1}\exp[-V(x)/k_B T]\;, \tag{4a}$$

where $Z \equiv \int \exp[-V(x)/k_B T]dx$. In the absence of diffusion, $D = 0$, each state x decays with its characteristic rate $k(x)$,

$$p(x,t) = p(x,0)\exp[-k(x)t] \tag{4b}$$

and Eq. (1) reduces to a conventional first order rate equation. Here we are concerned with the combined effect of reaction and diffusion.

In practice Eq. (1) may be only solvable numerically. The continuous coordinate x is divided into a grid of points $\{x_i\}$, with spacings $\Delta x \equiv x_{i+1} - x_i$. Defining $\overline{D} \equiv D/(\Delta x)^2$, $k_i \equiv k(x_i)$, $V_i \equiv V(x_i)$, and $p_i(t) \equiv p(x_i,t)\Delta x$ one can write[15] the diffusion equation in a finite-difference form

$$\frac{\partial p_i(t)}{\partial t} = \overline{D}(p_{i+1} - 2p_i + p_{i-1}) + \frac{\overline{D}}{k_B T}\left[(V_{i+1} - V_i)\frac{p_{i+1} + p_i}{2}\right.$$

$$\left. - (V_i - V_{i-1})\frac{p_i + p_{i-1}}{2}\right] - k_i p_i\;. \tag{5}$$

Little physical intuition is gained by Eq. (5). We therefore prefer the Master equation[2(b)] form

$$\partial p_i(t)/\partial t = p_{i-1}\Omega(i\,|\,i-1) + p_{i+1}\Omega(i\,|\,i+1),$$

$$-p_i[\Omega(i-1\,|\,i) + \Omega(i+1\,|\,i)] - k_i p_i\;, \tag{6}$$

where the transition frequencies from j to i are given by

$$\Omega(i\,|\,j) \equiv \overline{D}\exp[-(V_i - V_j)/2k_B T]\;. \tag{7}$$

Equation (5) follows from the first order Taylor approximation $\Omega(i\,|\,j) \cong \overline{D}[1 + (V_j - V_i)/2k_B T]$. In matrix notation

$$\frac{dp}{dt} = -Lp\;, \tag{6'}$$

where $p \equiv (p_1,\ldots,p_N)$ is a vector of probabilities and L is a $N \times N$ tridiagonal matrix: $L_{i\pm1,i} = -\Omega(i\pm1\,|\,i)$, $L_{ii} = \Omega(i+1\,|\,i) + \Omega(i-1\,|\,i) + k_i$.

The merit of Eq. (6) is in describing the diffusion process as a biased (by the potential V_i) random walk process between nearest neighbors. This makes the determination of boundary conditions straightforward. For example, a reflecting boundary condition for a right boundary at $i = N$ would be $\Omega(N\,|\,N+1) = \Omega(N+1\,|\,N) = 0$. A second consequence of the presentation (6) is that the transition frequencies Ω obey detailed balance[2(b)]:

$$p_i^{eq}\Omega(j\,|\,i) = p_j^{eq}\Omega(i\,|\,j)\;. \tag{8}$$

B. The adjoint and backward equations

We now introduce the adjoint equation, and the adjoint operator $\mathcal{L}^\dagger$:

$$\frac{\partial q(x,t)}{\partial t} = D\left[\frac{\partial^2}{\partial x^2} - \frac{1}{k_B T}\frac{\partial V(x)}{\partial x}\frac{\partial}{\partial x}\right]q(x,t)$$

$$- k(x)q(x,t) \equiv -\mathcal{L}^\dagger(q)\;. \tag{9}$$

Left multiplying $\mathcal{L}(p)$ by q and $\mathcal{L}^\dagger(q)$ by p and integrating once by parts between any two points $x_1 < x_2$, one finds[13(a),14(d)]

$$\int_{x_1}^{x_2}[q\mathcal{L}(p) - p\mathcal{L}^\dagger(q)]dx = D\left[p\frac{\partial q}{\partial x} - q\frac{\partial p}{\partial x} - \frac{1}{k_B T}\frac{\partial V}{\partial x}pq\right]_{x_1}^{x_2}$$

$$= Dp\frac{\partial q}{\partial x} - q\mathcal{J}(p)\bigg]_{x_1}^{x_2} \tag{10}$$

which is the definition of an adjoint equation.[23]

There is a simple relation between the solutions p and q of Eqs. (1) and (9), respectively,

$$q(x,t) = \exp[V(x)/k_B T]p(x,t) = p/p^{eq}\;. \tag{11}$$

By direct substitution in Eq. (9) we find that

$$\mathcal{L}^\dagger(q) = \exp[V(x)/k_B T]\mathcal{L}(p) , \qquad (12)$$

implying that q is indeed a solution of the adjoint equation. In particular, if $k(x) = 0$, $p^{eq}(x) \propto \exp(-V/k_B T)$ or $q^{eq}(x) \propto 1$, as can be verified directly from Eq. (9). Similarly, using Eq. (11) one can write the flux [Eq. (3)] as[6]

$$\mathcal{J}(p) = -D\exp(-V/k_B T)\partial q/\partial x . \qquad (13)$$

Hence $\mathcal{L}$ is a Sturmian[23] operator in q.

The adjoint equation can be given an additional interpretation,[2] that of the (Kolmogorov) "backward" equation. Consider the transition probability $p(x, x', t)$. As a function of the final variable x it is a solution of the ("forward") equation (1) with an initial distribution concentrated at x' $p(x, 0) = \delta(x - x')$. To find its behavior as a function of the initial variable x' (the backward equation),[2(a)] one can take the transpose of L in Eq. (6') and go to the continuous limit. One finds that [also for the case $k(x) \neq 0$] the backward equation is the same as the adjoint[13(a),13(d),14(e)]:

$$-\partial p(x, x', t)/\partial t = \mathcal{L}_x(p) = \mathcal{L}_{x'}^\dagger(p) . \qquad (14)$$

The subscripts x and x' explicitly denote the variable for differentiation in the forward or backward equation, respectively.

C. Boundary conditions

In the physical problem, high potential energies of large excursions make it essentially impossible to leave a restricted spatial region. To keep the problem finite and easily computable, we restrict the diffusion problem by reflecting walls in a spatial region which has negligible probability. This prevents any flux from escaping out of the interval (x_a, x_b):

$$J(x_a, t) = J(x_b, t) = 0 , \qquad (15)$$

where $J(x, t)$ is given by Eq. (3). In the absence of reaction,

$$\frac{d}{dt}\int_{x_a}^{x_b} p(x, t)\,dx = J(x_a) - J(x_b) , \qquad (16)$$

the boundary conditions mean that the total probability in (x_a, x_b) is conserved.

For the solution $q(x)$ of the adjoint equation the reflecting boundary conditions become[13(a),13(d),14(e)] [cf. Eq. (13)] $\partial q/\partial x = 0$. Hence when p and q are solutions of the forward and backward equations, respectively, one can rewrite Eq. (10) as

$$\int_{x_a}^{x_b} q\,\mathcal{L}(p)\,dx = \int_{x_a}^{x_b} p\,\mathcal{L}^\dagger(q)\,dx . \qquad (10')$$

For bounded diffusion this condition holds for arbitrary $q(x)$, because due to infinite potentials outsides (x_a, x_b), $p(x)$ vanishes at the boundaries.

D. Time dependence of average quantities

Of prime interest in the present work is the fraction of unreacted reagents (the "survival probability")

$$Q(t) \equiv \int p(x, t)\,dx ,$$

$$Q(x', t) \equiv \int p(x, x'\,t)\,dx , \qquad (17)$$

where all integrals are between the two boundaries x_a and x_b. $Q(t)$ is the analog of the reagent's concentration for unit initial concentration. $Q(x', t)$, the survival probability when starting from x', is the solution of the backward (adjoint) equation, as evident by integrating Eq. (14) over x.[13(a),13(d)]

Next, we note[11] that $p(x, t)/Q(t)$ is the conditional distribution function over configurations for which no reaction has taken place. This probability density normalizes to unity at all times. Hence it is natural to define any reagent averaged quantity $\langle q \rangle$ using this conditional probability

$$\langle q \rangle \equiv Q(t)^{-1}\int q(x)\,p(x, t)\,dx . \qquad (18)$$

Using these definitions and Eq. (10') the time dependence of the survival probability[11]

$$-\frac{dQ(t)}{dt} = \int \mathcal{L}(p)\,dx = \int p\mathcal{L}^\dagger(1)\,dx$$

$$= \int k(x)p(x, t)\,dx = \langle k \rangle Q(t) \qquad (19)$$

is given by a unimolecular rate expression, with a positive "average rate" $\langle k \rangle$. Generally, $\langle k \rangle$ would be time dependent and the decay nonexponential. For a large diffusion constant D, of course p/Q approaches the equilibrium distribution, and a useful approximation for the rate constant follows:

$$\langle k \rangle \cong Z^{-1}\int k(x)\exp(-V/k_B T)\,dx . \qquad (20)$$

We shall reach the same conclusion below using an eigenfunctions expansion and perturbation theory, and be able to see when this approximation is adequate.

Next, we consider the time dependence of the average value $\langle q \rangle$ of an arbitrary function $q(x)$:

$$-\frac{d\langle q \rangle}{dt} = Q^{-1}\int q\mathcal{L}(p)\,dx + \langle q \rangle\,d\ln Q/dt$$

$$= \langle \mathcal{L}^\dagger(q) \rangle - \langle q \rangle\langle k \rangle . \qquad (21)$$

We use the above result to write down equations of motion for the first two moments (for a symmetric distribution—the peak location and width):

$$d\langle x \rangle/dt = -D\langle dV/dx \rangle/k_B T + [\langle x \rangle\langle k \rangle - \langle xk \rangle] , \qquad (22a)$$

$$\frac{d\langle x^2 \rangle}{dt} = 2D - \frac{2D}{k_B T}\left\langle x\frac{dV}{dx}\right\rangle + [\langle x^2 \rangle\langle k \rangle - \langle x^2 k \rangle] . \qquad (22b)$$

When $k(x) = $ const, the terms in the square brackets vanish and the equations reduce to familiar "macroscopic" equations, describing exponential decay of the moments to their steady state values. This is more transparent when we rewrite Eq. (22) for a harmonic potential, $V(x) = 1/2\,fx^2$ (or for an arbitrary potential close enough to its minimum):

$$\frac{d\langle x\rangle}{dt} = -\frac{Df}{k_B T}[\langle x\rangle - \langle x\rangle^{\mathrm{eq}}] + [\langle x\rangle\langle k\rangle - \langle xk\rangle] , \quad (22a')$$

$$\frac{d\langle x^2\rangle}{dt} = -\frac{2Df}{k_B T}[\langle x^2\rangle - \langle x^2\rangle^{\mathrm{eq}}] + [\langle x^2\rangle\langle k\rangle - \langle x^2 k\rangle] , \quad (22b')$$

where $\langle x\rangle^{\mathrm{eq}} = 0$ and $\langle x^2\rangle^{\mathrm{eq}} = k_B T/f$.

The role of a nonconstant $k(x)$ can be better understood if we assume that it is a decreasing function of x. Then, by Chebyshev's inequality

$$\langle x\rangle\langle k\rangle > \langle xk\rangle , \quad (23a)$$

$$\langle x^2\rangle\langle k\rangle < \langle x^2 k\rangle . \quad (23b)$$

Hence if $\langle x\rangle$ is smaller than its steady-state value the effect of $k(x)$ is to make it decay faster. Similarly, when $\langle x\rangle$ is larger that its steady-state value, it would decay slower than when $k(x) = \mathrm{const}$. This is intuitively clear, since a decreasing, positive $k(x)$ means that any distribution is "eaten up" by reaction more on the left than on its right. This would tend to shift the peak to the right and narrow the width.

E. Spectral theory of bounded diffusion

We now introduce results which are helpful in solving the bounded diffusion equation for the time dependence of the probability density, and for describing the decay of the survival probability.

The boundary conditions immediately imply [e.g., because of the Sturmian form,[23] Eqs. (2) and (13)] that the diffusion operator $\mathcal{L}$ has a discrete spectrum[8]

$$\mathcal{L}(g_n) = \lambda_n g_n , \quad n = 0, 1, \ldots . \quad (24a)$$

We normalize $g_n(x)$ so that (unless the integral vanishes) $\int g_n dx = 1$. Some properties of the eigenvalues λ_n and eigenfunctions g_n are given below:

(i) The diffusion equation and its adjoint have the same spectrum

$$\mathcal{L}^\dagger(h_n) = \lambda_n h_n . \quad (24b)$$

(ii) The nodal theorem[23]: The nth eigenfunction has n nodes (zeros) inside the interval (x_a, x_b).

(iii) When $k(x) = 0$, the "ground state" is $h_0(x) = 1$ or $g_0(x) = Z^{-1}\exp[-V(x)/k_B T]$, with $\lambda_0 = 0$. As in the theory of the Master equation with detailed balance[2(b)] all the other eigenvalues are real and positive. Normalization of $p(x, t)$ is conserved for all t, implying that $\int g_n dx = \delta_{n0}$.

(iv) When $k(x) > 0$ all eigenvalues are positive. For $n > 0$ one can assume $g_n(x) \geq 0$ between the left bound x_a and the first node x_1 writing

$$\lambda_n \int_{x_a}^{x_1} g_n dx = \int_{x_a}^{x_1} \mathcal{L}(g_n) dx = -D(\partial g_n/\partial x)_{x=x_1} + \int_{x_a}^{x_1} k(x) g_n dx . \quad (25)$$

But the derivative of a positive function at its first node must be negative, and $k(x) \geq 0$, which proves the assertion. For $n = 0$ we replace the upper limit by x_b,

$$\lambda_0 = \int \mathcal{L}(g_0) dx = \int g_0 \mathcal{L}^\dagger(1) dx = \int k(x) g_0(x) dx . \quad (25')$$

(v) As a corollary of Eq. (11) one has that

$$h_n(x) = \exp[V(x)/k_B T]g_n(x) . \quad (11')$$

(vi) Condition (10') ensures that $\{h_m\}$ and $\{g_n\}$ are biorthogonal (for $\lambda_n \neq \lambda_m$),[2(b)]

$$\int h_n g_m dx = \delta_{nm} . \quad (26)$$

The last property is essential for the spectral representation of $p(x, t)$, since it is generally impossible and unnecessary to calculate a complete set $\{g_n\}$. Hence[2(b)]

$$p(x, t) = \sum_n \omega_n g_n(x) \exp(-\lambda_n t) , \quad (27)$$

$$\omega_n \equiv \int h_n(x) p(x, 0) dx .$$

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$$\omega_n \equiv \int h_n(x) p(x, 0) dx .$$

$\int p(x, 0) dx = 1$ implies that $\sum_n \omega_n = 1$. From Eq. (27) follows the spectral representation of the survival probability

$$Q(t) = \sum_n \omega_n \exp(-\lambda_n t) \quad (28)$$

and of average values in general

$$Q(t)\langle q\rangle \equiv \int q(x) p(x, t) dx = \sum_n \gamma_n \exp(-\lambda_n t) , \quad (29)$$

$$\gamma_n \equiv \omega_n \int q(x) g_n(x) dx .$$

It is instructive to write the above expressions for the transition probabilities $p(x, x', t)$, i.e., for delta function initial distributions $p(x, 0) = \delta(x - x')$:

$$p(x, x', t) = \sum_n h_n(x') \exp(-\lambda_n t) g_n(x) , \quad (27')$$

$$Q(x', t) \equiv \int p(x, x', t) dx = \sum_n h_n(x') \exp(-\lambda_n t) . \quad (28')$$

In the eigenfunction method, solving for h_n or g_n requires the same amount of computational effort hence solving (the adjoint equation) directly for $Q(x', t)$ is basically equivalent to solving for $p(x, x', t)$.

F. Average survival time

We can extend the conventional role of a rate constant to nonexponential kinetics by defining an average survival time $\langle \tau\rangle$ as a generalization of the first passage time.[12] In the latter case one usually introduces an absorbing barrier: A particle that reaches that point is, with probability one, dumped into the "sink." From the viewpoint of Eq. (1) this can happen at any point x, with a probability (per unit time) $k(x)$.

The (cumulative) probability for not reacting until time t is $Q(t)$. The probability for not reacting between

t and $t + dt$ is $[dQ(t)/dt]dt$. The distribution function for reacting at time t (irrespective of the "internal state" x) is hence[12] $-dQ/dt$, and the average survival time is given by

$$\langle \tau \rangle \equiv - \int_0^\infty t\, \frac{dQ}{dt}\, dt = \int_0^\infty Q(t)\, dt = \sum_n \omega_n / \lambda_n \, , \qquad (30)$$

where we have used the eigenvalue expansion (28). In the special case of large D, $\langle \tau \rangle \cong \lambda_0^{-1}$, the reciprocal rate constant of conventional unimolecular kinetics. Generally it is a weighted average of the survival times λ_n^{-1} of the different eigenstates.

There is a more direct route to $\langle \tau \rangle$, by considering the average survival time $\tau(x)$ out of an initial state x,

$$\tau(x) \equiv \int_0^\infty Q(x, t)\, dt \, , \qquad (31a)$$

$$\langle \tau \rangle = \int_{x_a}^{x_b} p(x, 0) \tau(x)\, dx \, . \qquad (31b)$$

Since $Q(x, t)$ is a solution of the backward (adjoint) equation (14) one finds by its time integration [setting $Q(x, 0) = 1$, $Q(x, \infty) = 0$][13(a),13(d)]

$$\mathcal{L}^\dagger(\tau) = 1 \, . \qquad (32)$$

The boundary conditions for $\tau(x)$ are automatically satisfied in the Master equation approach [cf. Eq. (6′)] where Eq. (32) becomes a set of nonhomogeneous algebraic equations

$$\mathbf{L}^* \tau = 1 \, . \qquad (32')$$

($\mathbf{L}^*$ is the transpose of $\mathbf{L}$.) The solution of Eq. (32′) followed by the integration (31b) can be advantageous over the time integration of $Q(t)$ in the bounded diffusion theory, because the x integration is bounded while the t integration is not [especially for small D when $Q(t)$ is slowly varying].

G. Slow and fast diffusion limits

In the next section we consider the above results as a function of the magnitude of $k(x)$ for constant D, viewing $k(x)$ as a pertubation in the no-reaction diffusion equation. In the present section we consider these results as a function of D for a given $k(x)$, showing that they reduce to the correct asymptotic expressions in the slow and fast diffusion limits.

In the $D \to 0$ limit each configuration x reacts with a characteristic rate $k(x)$. In the $D \to \infty$ limit $h_0(x) \to 1$, $g_0(x) \to p^{eq}(x)$, $\omega_n \to \delta_{n0}$, and hence [cf. Eq. (25′)] all x values decay with the same average rate constant $\langle k \rangle$ of Eq. (20)[24]:

$$p(x, t) = p(x, 0) \exp[-k(x)t] \, , \qquad D \to 0 \, , \qquad (33a)$$

$$p(x, t) = p(x, 0) \exp\left[-t \int k(x) p^{eq}\, dx\right], \qquad D \to \infty \, . \qquad (33b)$$

Note that both limits are independent of D.

The survival probability is accordingly given by

$$Q(t) = \int p(x, 0) \exp[-k(x)t]\, dx \, , \qquad D \to 0 \, , \qquad (34a)$$

$$Q(t) = \exp\left[-t \int k(x) p^{eq}(x)\, dx\right], \qquad D \to \infty \qquad (34b)$$

and the mean survival time by

$$\langle \tau \rangle = \int p(x, 0) k(x)^{-1}\, dx \, , \qquad D \to 0 \, , \qquad (35a)$$

$$\langle \tau \rangle = \left[\int k(x) p^{eq}(x)\, dx\right]^{-1} \, , \qquad D \to \infty \, . \qquad (35b)$$

The observation that bounded diffusion perpendicular to the reaction coordinate interpolates between these two limits, is central in the present work.

Example. The following simple example is instructive in understanding the small and large D limits. Consider a system of two states (e.g., spin). Each state can convert to the other with the same rate constant D, but they react with different rate constants k_1 and k_2. Hence one solves for the eigenvalues of

$$\begin{pmatrix} k_1 + D & -D \\ -D & k_2 + D \end{pmatrix} \, .$$

From the solution to the resulting quadric equation for λ, one verifies directly that for $D \to 0$ the eigenvalues are k_1 and k_2, whereas for $D \to \infty$ $\lambda_0 = \frac{1}{2}(k_1 + k_2)$ while $\lambda_1 \to \infty$. In particular, for an initial equilibrium distribution $p^{eq} = (\frac{1}{2}, \frac{1}{2})$ one finds

$$Q(t) = \frac{1}{2}(e^{-k_1 t} + e^{-k_2 t}) \, , \qquad D \to 0 \, , \qquad (34a')$$

$$Q(t) = \exp[-1/2(k_1 + k_2)t] \, , \qquad D \to \infty \, . \qquad (34b')$$

H. Self-adjoint presentation

Up to this point we have discussed the solution using the diffusion equation and its adjoint. The substitution $p(x, t) = \exp(-V/2k_B T)\, \Phi(x, t)$ can convert the system to a self-adjoint (Hermitian) representation[8]:

$$\partial \Phi / \partial t = D \partial^2 \Phi / \partial x^2 - U(x) \equiv -\mathcal{H}(\Phi) \, , \qquad (36)$$

$$U(x) \equiv \frac{D}{2k_B T}\left(\frac{V'^2}{2k_B T} - V''\right) + k(x) \qquad (37)$$

(where a prime denotes differentiation with respect to x). We could have discussed the whole theory using this Schrödinger-like presentation. In particular, we see that the question whether the "effective potential" $U(x)$ is bound or not depends both on $V(x)$ and $k(x)$. For example, when $V(x)$ is linear in x, $U(x) = k(x) + \text{const.}$ and the answer depends solely on the x dependence of the rate constant. If $k(x)$ is monotonic in x, $V(x)$ must increase faster than a linear function in order that $U(x)$ be bound and possess a discrete spectrum. The eigenvalues of $\mathcal{H}$ are then the same as those of $\mathcal{L}$ and $\mathcal{L}^\dagger$ and the eigenfunctions $\phi_n = g_n/(p^{eq})^{1/2} = h_n(p^{eq})^{1/2}$.

Techniques of quantum mechanics can be applied to Eq. (36) to develop a perturbation approach to the solutions,[25] if $k(x)$ is adequately small. The first approximation is "zero order" perturbation theory for λ_n other than λ_0 [i.e., set $k(x) = 0$]. For λ_0 the zero order value is zero, and first order correction is independent of D,

$$\lambda_0^{(1)} \equiv \int \phi_0^{(0)} k(x) \phi_0^{(0)}\, dx = \int p^{eq}(x)\, k(x)\, dx \, , \qquad (39)$$

a result already derived in Eqs. (20) and (25'). Note that if ϕ_0 is normalized in the usual quantum mechanical way, p is normalized as a probability density. To extend the predictions to smaller diffusion constants we can add to λ_0 its second order perturbation correction $\Delta\lambda_0$:

$$\Delta\lambda_0 = -\sum_{n=1}^{\infty} \left[\int k(x) g_n^{(0)} dx \right]^2 / \lambda_n^{(0)} , \qquad (39)$$

where we have used the fact that $g_n^{(0)}$, the eigenfunctions of $\mathcal{L}$ for zero reaction are equal to $\phi_0^{(0)} \phi_n^{(0)}$. Equation (39) predicts that λ_0 would decrease with decreasing D. Equation (39) is often the second term in an asymptotic expansion rather than a convergent power series.

I. Kramers kinetics

The motivation for the above analysis has been to describe kinetics in which the diffusive motion is *not* along the reaction coordinate. Detailed results in this situation can be easily confused with Kramers' analysis[6-9] of diffusion along the reaction coordinate because, in spite of the very different physical situation, the *mathematics* of Kramers is a special case of the mathematics we have treated.

Kramers' approach is to set the probability distribution equal to zero at the transition state $x^{\neq}$ and solve for the lowest eigenvalue. (The actual solution is rather involved.[9]) The absorbing boundary condition $p(x^{\neq}) = 0$ is mathematically equivalent[10,11] to a reflecting boundary just beyond $x^{\neq}$ and a rate constant which is zero everywhere except at $x^{\neq}$ where it is very large:

$$k(x) = C\delta(x - x^{\neq}) , \quad C \to \infty . \qquad (40)$$

The rate constant is proportional to D because the lowest eigenfunction is independent of C for large C, and the rate of flow of probability out is D times the gradient of this eigenfunction. Thus, when the Kramers problem has an eigenvalue which behaves as

$$\lambda_0 \propto D \exp[- V(x^{\neq})/k_B T] , \qquad (41)$$

our problem with *transverse* diffusion and $k(x)$ given by Eq. (40) must also have this transition-state form.

Under most circumstances the problem of diffusion perpendicular to the reaction coordinate is expected to have a slowly varying $k(x)$. Then the reaction does not become vanishingly slow as $D \to 0$, in contrast to Kramers' case.

J. Example: Harmonic potential and exponential rate constant

We finally consider the special case

$$V(x) = 1/2 fx^2 , \qquad (42a)$$

$$k(x) = A \exp(- \alpha x) \qquad (42b)$$

which may describe an electron transfer reaction between two sites in a macromolecule. Under these conditions the no-reaction eigenfunctions $h_n^{(0)}$ of $\mathcal{L}^{\dagger}$ are the Hermite polynomials [compare Eq. (9) to Eqs. (5)–(6), p. 54 in Ref. 25]. The Schrödinger representation (36) reduces to the harmonic oscillator case with

$$U(x) = \frac{Df}{2k_B T} \left(\frac{fx^2}{2k_B T} - 1 \right) + k(x) . \qquad (43)$$

Hence, as a zero order $[k(x) = 0]$ approximation

$$\lambda_n^{(0)} = nDf/k_B T . \qquad (44)$$

For $k(x)$ given by Eq. (42b) the first order approximation to λ_0 [cf. Eq. (38)] can be evaluated by completing the exponent to squares:

$$\lambda_0^{(1)} = A (f/2\pi k_B T)^{1/2} \int_{-\infty}^{\infty} \exp(- \alpha x - fx^2/2k_B T) \, dx$$

$$= A \exp(\alpha^2 k_B T/2f) . \qquad (45)$$

Hence for a stiff bond $\lambda_0^{(1)} \cong A$, but for large fluctuations in a macromolecule f is small and $\lambda_0^{(1)}$ can be quite different from A. In such cases, even the large D, long times exponential kinetics is not a straightforward measurement to interpret.

The second order approximation [Eq. (39)], gives by completing to squares

$$\Delta\lambda_0 = -A^2 e^{\xi_0^2} \sum_{n=1}^{\infty} \left| \int_{-\infty}^{\infty} \phi_0(\xi + \xi_0) \phi_n(\xi) \, d\xi \right|^2 / \lambda_n^{(0)} . \qquad (46)$$

The harmonic oscillator functions[25] $\phi_n(\xi)$ depend on the reduced variable $\xi \equiv (f/2k_B T)^{1/2} x$. The displacement of the oscillators is $2k_B T\alpha/f$, i.e., $\xi_0^2 = 2k_B T\alpha^2/f$. The Franck–Condon overlap integrals for displaced oscillators are well known[26]:

$$\left| \int_{-\infty}^{\infty} \phi_0(\xi + \xi_0) \phi_n(\xi) \, d\xi \right|^2 = e^{-\xi_0^2/2}(\xi_0^2/2)^n/n! . \qquad (47)$$

On using Eq. (44) for $\lambda_n^{(0)}$ we find that

$$\Delta\lambda_0 = -A^2 \frac{k_B T}{Df} \exp(\alpha^2 k_B T/f) \sum_{n=1}^{\infty} \frac{1}{nn!} (\alpha^2 k_B T/f)^n . \qquad (48)$$

For large f or D (or very small T), this correction tends to zero. This is the case in conventional kinetics. Under the conditions of the examples given here, $\alpha^2 k_B T/f$ is of the order of unity, and the correction becomes appreciable at small diffusifity.

III. NUMERICAL CONSIDERATIONS

In practice we solve the Master equation (6'). In this we differ from other numerical approaches[14(c),14(g),15] which solve finite-difference equations of type (5). We have tried direct numerical integration, by setting

$$p(t + \Delta t) = p(t) - Lp\Delta t . \qquad (49)$$

There is a problem in choosing Δt, for part of the reaction is very fast, while part is slow. An increasing Δt is necessary to numerically integrate out to large times. This worked for the lowest value of $D \equiv \bar{D}(\Delta x)^2$, when the eigenfunction method is tedious, as it involves many eigenstates. As D increases, the off-diagonal terms in L increase, resulting in a too large loss of probability in one time step, making further integration impossible. One can drastically decrease Δt, but then integration becomes very time consuming (especially for large D). Under these conditions the eigenfunction technique is more useful, because with increasing

D less states contribute to the expansion. By using biorthogonality (Sec. II E) only a few lowest eigenfunctions need be calculated, diagonalization[15] of the complete matrix L is unnecessary. We now describe the numerical procedures involved and discuss some special problems.

Eigenvalues of L are found by solving numerically

$$d(\lambda) \equiv \det[\Delta t(L - \lambda I)] = 0 . \qquad (50)$$

We multiply by $\Delta t \ll 1$ to prevent overflow due to very large values of the determinant. The determinant of a tridiagonal matrix is evaluated using a simple recursion relation. Denote by $d_j(\lambda)$, $2 \le j \le N$, the determinant of the $j \times j$ matrix consisting of the first j rows and columns of $\Delta t(L - \lambda I)$. Then

$$d_j(\lambda) = \Delta t(L_{jj} - \lambda)d_{j-1}(\lambda) - (\overline{D}\Delta t)^2 d_{j-2}(\lambda) \qquad (51)$$

and $d(\lambda) \equiv d_N(\lambda)$. The zeros of the determinant are found numerically (in double precision) starting from the initial guess $\lambda_0^{(1)}$, $\lambda_n^{(0)}$ [Eqs. (44) and (45)], and using the method of bisections.

Once an eigenvalue λ_n is determined, its eigenvector g_n is calculated from a second recursion relation

$$(g_n)_{i+1} = -[L_{i i-1}(g_n)_{i-1} + (L_{ii} - \lambda_n)(g_n)_i]/L_{i i+1} . \qquad (52)$$

We start at the boundary where k_i is minimal, by choosing the first component of g_n arbitrarily (but small enough) and the second $(g_n)_2 = -(L_{11} - \lambda)(g_n)_1/L_{12}$. We then check that g_n has indeed n nodes.

It is important not to project g_n [using Eq. (52)], too far, where the finite accuracy in λ_n would cause g_n to diverge. Hence the calculation of g_n is terminated at the point past the nth node where it is closest to zero (not earlier, to prevent errors in the scalar products). Usually, the higher eigenfunctions can be extended slightly further out. The larger D, the further out the eigenvectors extend. After determining g_n, h_n can be calculated either from Eq. (11') or from a recursion relation similar to Eq. (52) using the transpose of L.

An accurate solution for the eigenproblem depends on a prudent choice of four parameters:

(i) Δt in Eq. (50) should be as large as possible to allow for a maximal number of iterations, determining all significant digits in λ_n. Δt which is too large would cause the determinant to diverge (usually one choice of Δt is suitable for the whole range of λ). The initial determination of Δt can be tricky, but then it can be determined easily for different diffusion constants, as it is inversely proportional to D. The interval of permissable Δt values decreases with decreasing D.

(ii) The choice of Δx (or the number of grid points N): Δx should be small so that the difference equation approaches a differential equation. Δx which is too small is troublesome, resulting in diverging determinants and difficulty in determining Δt. In the example calculated, we find $N = 250$ suitable for large D, while for small D we decrease N to about 100.

(iii) Choosing the boundaries. In principle the boundaries are at infinity. In practice we can choose them at

a finite distance without affecting the eigenvalues too much: Far enough so that the eigenvalues are boundary independent, but not too far, otherwise $(g_n)_i$ varies by too many orders of magnitude, resulting in an overflow. We have set the boundaries so that $(g_n)_i$ varies by 8–12 orders of magnitude.

(iv) The number of eigenfunctions involved is a decreasing function of D. Typical numbers for the example in Sec. IV are 3 for $D = 10^{10}$ Å²/s and 30 for $D = 10^7$ Å²/s. A useful criterion for convergence is $\sum_n \omega_n = 1$ (Sec. II E). Convergence can be faster for $Q(t)$ than for $p(x, t)$, or one can use direct integration for the very short time regime. Convergence for $\langle \tau \rangle$ is usually much faster than for the other quantities.

The problem can also be solved using the eigenvalues of the finite-time matrix $M \equiv I - \Delta t L$ [where we replace $1 - k_i \Delta t$ by $\exp(-k_i \Delta t)$]. Hence Eq. (49) becomes $p(t + \Delta t) = Mp(t)$. The eigenvalues μ_n of M are related to those of L: $\ln \mu_n = -\lambda_n \Delta t$. $0 < \mu_n \le 1$ with $\mu_0 = 1$ only when $k(x) = 0$. Again, a prudent choice of Δt, Δx, and the boundaries is necessary. We have compared the λ_n calculated from μ_n with those calculated directly for L. It seems that they provide upper and lower bounds for the correct values, bracketing them more tightly with decreasing Δx.

IV. RESULTS

We present as a simple illustrative example, results for electron transfer between two loosely bound sites in a macromolecule (see Sec. II J). It is closely related to problems such as electronic energy transfer between the ends of a polymer chain.[17(d)] The much more complex and specific problem of ligand binding to heme proteins is published separately.[22]

First we suggest reasonable parameters in Eq. (42). For the distance dependence of electron transfer we choose[20] $\alpha = 1.5$ Å⁻¹. We take $A = A_0 \exp(-\alpha x_e)$, where the equilibrium distance between the electron acceptor and donor $x_e = 10$ Å, and $A_0 = 10^{14}$ s⁻¹, a typical number[20] for fast electron transfer. The exact value of these two parameters is not very critical, as A simply sets the time scale. In choosing the force constant for the relative donor–acceptor motion we were guided by the experimental observation[21] that fluctuations of some groups in proteins around their x-ray configuration can have a mean square deviation as large as $\langle x^2 \rangle = 0.5$ Å². Therefore the relative donor–acceptor mean square deviation can be twice that number $[\langle (x_1 + x_2)^2 \rangle = \langle x_1^2 \rangle + \langle x_2^2 \rangle$ when x_1 and x_2 are uncorrelated]. For a Gaussian (equilibrium) distribution $\langle x^2 \rangle = k_B T/f$, hence we take $f = 0.5$ kcal/mol Å² for $T = 300$ K. The functions $V(x)$ and $k(x)$ for these parameters are shown in Fig. 1.

The initial distribution is set equal to the equilibrium distribution for no reaction, but displaced by a distance x_0 from the potential minimum $x = 0$. Such a displacement is physically plausible: Suppose charged reagents are prepared by inducing a fast electron transfer in the excited state of an uncharged precursor, while the reaction one follows is the back electron transfer to give the uncharged state. In such a case the ionic interac-
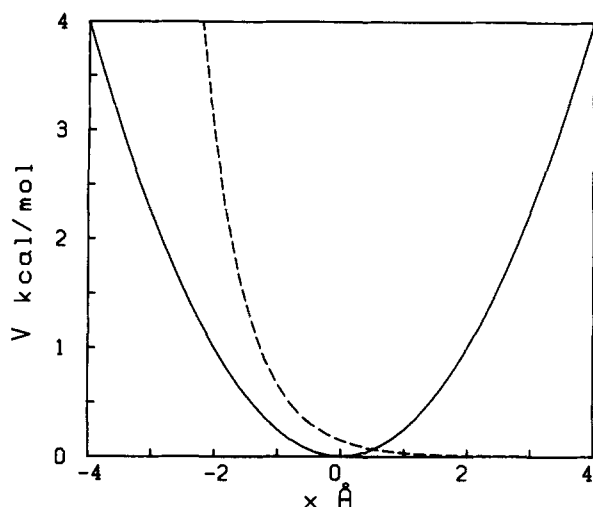
FIG. 1. The potential function $V(x)$—full line, and rate constant $k(x)$—dashed line, [cf. Eq. (42)] as a function of x. $f = 0.5$ kcal/molÅ^2, $\alpha = 1.5$ Å^{-1}, $A_0 = 14$ s^{-1}, $x_e = 10$ Å. The units of $k(c)$ are arbitrary.

tion in the reagents reduces x_e. Since the initial distribution is that of the precursor one has positive displacement.

For each displacement we calculated $p(x, t)$ and $Q(t)$ for different diffusion coefficients. For $D \le 10^6$ Å^2 s^{-1} (the absolute value of D has no physical significance, only its value relative to A) we have found it easier to use direct integration. For values of D larger than this we have used the eigenfunction method. Table I gives the first 15 eigenvalues. These need be calculated only once for the various initial conditions.

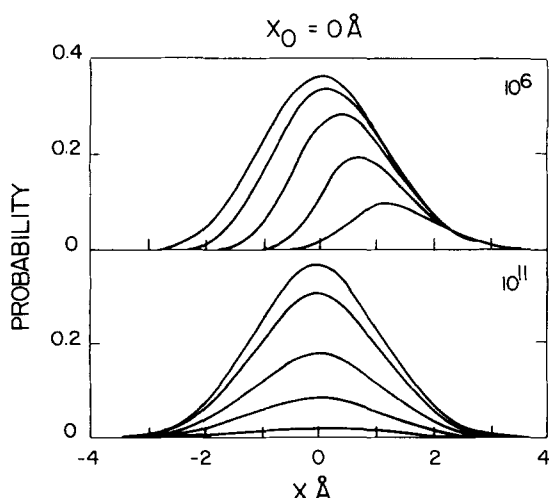Figures 2–4 show the distribution functions $p(x, t)$ as

FIG. 2. Probability distribution ($\alpha = 1.5$ Å^2, $f = 0.5$ kcal/molÅ^2. $T = 300$ K) for zero displacement and two extreme D values. For the upper panel ($D = 10^6$ Å^2 s^{-1}) times are: 6.3×10^{-10}, 3.1×10^{-9}. 1.2×10^{-8}, 3.9×10^{-8}, and 1.3×10^{-7} s. For the lower panel ($D = 10^{11}$ Å^2 s^{-1}) times are: 0, 1.6×10^{-9}, 6.3×10^{-9}, 1.3×10^{-8}, and 2.5×10^{-8} s.
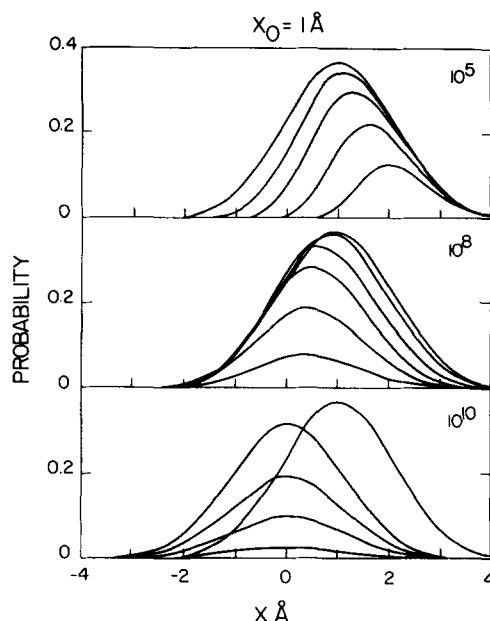

FIG. 3. Same as Fig. 2 for positive displacement $x_0 = 1$ Å. For the upper panel ($D = 10^5$ Å^2/s) times are the same as for upper panel, Fig. 2. For the two lower panels times are the same as for the lower panel, Fig. 2 (for $D = 10^8$ Å^2/s we added a curve for $t = 10^{-7}$ s).

a function of x at several different times, for several values of D and x_0. When $D < 10^6$ Å^2 s^{-1} all x motion is practically frozen and $p(x, t)$ [Eq. (33a)] decays more on the left, where $k(x)$ is larger, leading to distributions peaked to the right of the potential well. The effect is larger when the initial distribution is displaced to the

TABLE I. Eigenvalues[a] λ_m (in s^{-1}) for electron-transfer pro- problem.

$n/D(\text{Å}^2\text{s}^{-1})$	10^6	10^7	10^8	10^9	10^{10}
0	2.33(6)[b]	1.06(7)	3.62(7)	7.94(7)	1.08(8)
1	4.09(6)	2.53(7)	1.55(8)	1.05(9)	8.77(9)
2	5.83(6)	3.99(7)	2.77(8)	2.06(9)	1.77(10)
3	7.66(6)	5.47(7)	4.02(8)	3.12(9)	2.68(10)
4	9.78(6)	7.03(7)	5.30(8)	4.21(9)	3.63(10)
5	1.23(7)	8.77(7)	6.64(8)	5.34(9)	4.60(10)
6	1.51(7)	1.08(8)	8.12(8)	6.53(9)	5.61(10)
7	1.83(7)	1.30(8)	9.77(8)	7.81(9)	6.67(10)
8	2.18(7)	1.55(8)	1.12(9)	9.22(9)	7.82(10)
9	2.56(7)	1.83(8)	1.36(9)	1.08(10)	9.06(10)
10	2.97(7)	2.13(8)	1.59(9)	1.25(10)	1.04(11)
11	3.42(7)	2.45(8)	1.83(9)	1.43(10)	1.19(11)
12	3.87(7)	2.79(8)	2.08(9)	1.63(10)	1.35(11)
13	4.36(7)	3.15(8)	2.35(9)	1.84(10)	1.52(11)
14	4.87(7)	3.53(8)	2.64(9)	2.06(10)	1.69(11)
15	5.41(7)	3.93(8)	2.95(9)	2.30(10)	1.88(11)

[a]$f = 0.5$ kcal/molÅ^2, $\alpha = 1.5$ Å^{-1}, $T = 300$ K. The exact value of λ_n for large n can be somewhat sensitive to boundary location and grid size. For the above results the right boundary is at 6.5 Å and the left is at -1.2, -2.9, -4.2, -4.8, and -4.9 Å for $D = 10^6$, 10^7, 10^8, 10^9, and 10^{10} Å^2/s, respectively. $\Delta x = 0.08$ Å (totol of 130 grid points), 0.07 Å (170 points) and 0.05 Å (250 points) for $D = 10^6$, 10^7, and $\ge 10^8$ Å^2/s.
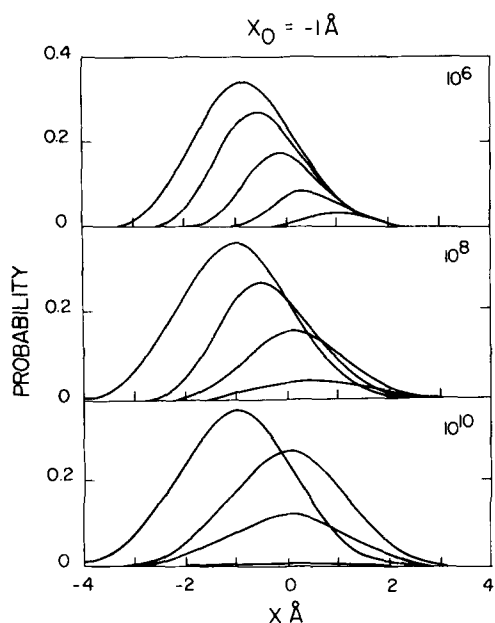[b]Exponent in parentheses.

FIG. 4. Same as Fig. 2 for negative displacement $(x_0 = -1$ Å$)$. Times: upper panel $(D = 10^6$ Å^2 s$^{-1})$ same as upper panel, Fig. 2. Two lower panels: 0, 2.5×10^{-8}, and 4.0×10^{-8} s.

left (upper panel Fig. 4), resulting in faster decay, and is smaller for positive displacements (upper panel Fig. 3).

As the diffusion constant D is increased the population moves downhill in addition to reacting. For zero or positive displacements (Figs. 2 and 3) this results in faster overall decay, as the distribution moves towards larger $k(x)$. For negative displacements (Fig.

4) the population first moves under the influence of the potential to the right, resulting in slower initial decay. Once the peak reaches its steady state value, the force works to prevent it from drifting further to the right, resulting in faster final decay.

The above behavior could also be understood through the "macroscopic" equations of motion (Sec. II D): Since $k(x)$ is decreasing with x, the second term on the right-hand side of Eq. (22a) is positive, pushing the peak of the right. If initially $\langle x \rangle < 0$, the first term would also be positive, so that the peak would move even faster to the right, resulting in slower initial decay.

As a demonstration of Eq. (22a) we show in Fig. 5 $\langle x \rangle$ as a function of t, for several values of D. The four lines in each panel are the results for four different initial displacements. We see that at long times $\langle x \rangle$ tends to a steady state value, independent of the initial conditions. At the zero diffusion limit $\langle x \rangle$ tends to infinity with t. For $D \to \infty$ $\langle x \rangle \to 0$ (its zero reaction equilibrium value) as $t \to \infty$. For intermediate values of D, $\langle x \rangle$ tends to a (positive) steady-state value, as a compromise between the two terms in Eq. (22a).

We now turn to the survival probability (the area under the curves in Figs. 2–4). Our central result is Fig. 6 which shows the survival probability on a log–log (base 10) plot for four different displacements. The value of $\log D$ is marked on each curve: There is little change in $Q(t)$ if D is decreased below 10^5 Å^2 s^{-1} or increased above 10^{10} Å^2 s^{-1}.

The effects discussed in connection with Figs. 2–4 are manifested here. For small D the decay is faster for more negative initial displacements. For very large D, $Q(t)$ becomes independent of the initial condi-
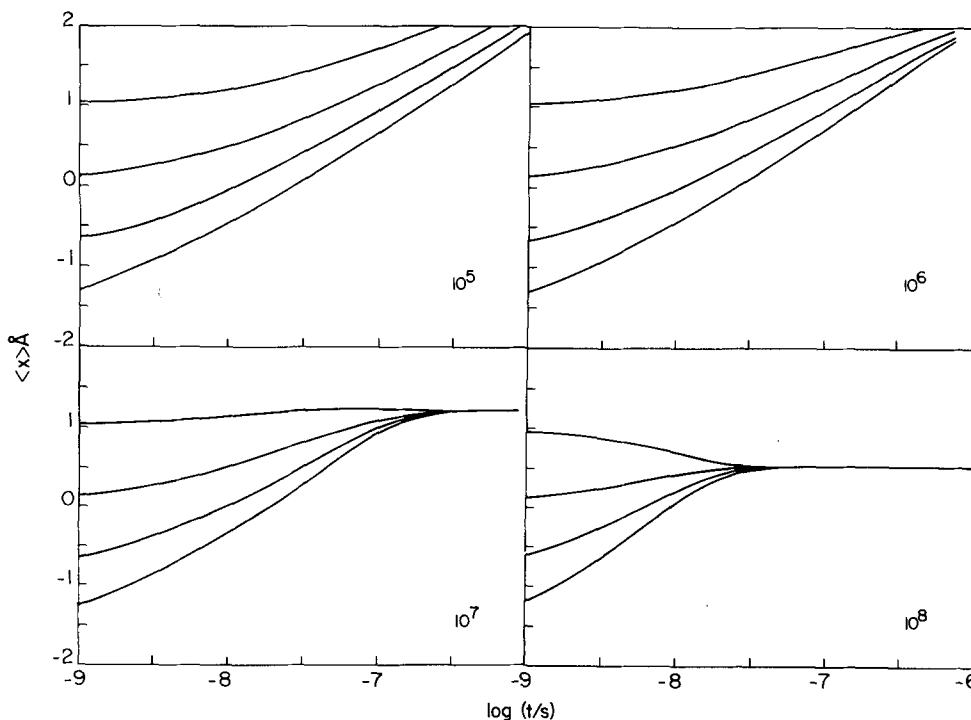

FIG. 5. Variations of the average value of the coordinate (the location of the peak of the distribution function) with time. Each panel is for a different value of D (in units of Å^2/s). The four curves in each panel are (down upwards): $x_0 = -2$, -1, 0, and 1 Å.
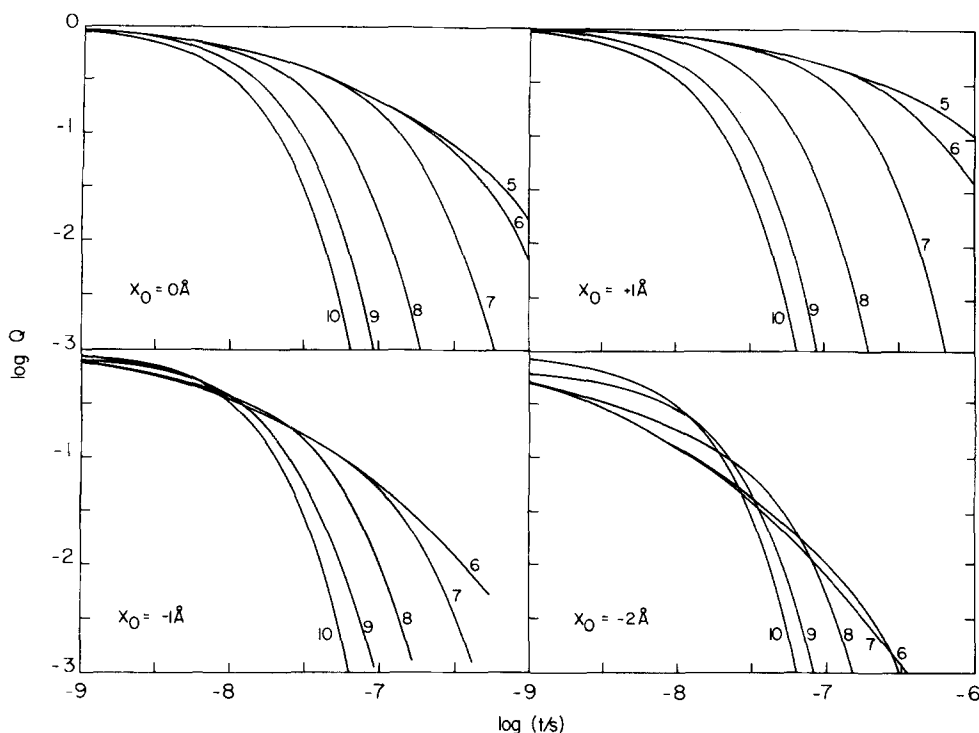
FIG. 6. Survival probabilities [Eqs. (17) and (28)] as a function of times for different values of D and x_0. The curves are marked by values of $\log_{10}D$ (D in $\text{Å}^2/\text{s}$), $\alpha = 1.5\ \text{Å}^{-1}$, $f = 0.5\ \text{kcal/mol}\ \text{Å}^2$ and $T = 300\ \text{K}$.

tions: It tends to a pure exponential, with an exponent λ_0 [cf. Eq. (45)].

For negative displacements we observe the effect discussed above: As D increases there is slower initial decay and faster final decay, resulting in the curves crossing over (e.g., $x_0 = -2\ \text{Å}$). This is the type of behavior observed in heme proteins.[18]

All the curves shown in Fig. 6 are given by the analytic expression (28), with λ_n in Table I, and some of the weights ω_n collected in Table II. For small D ω_0

is largest for $x_0 = 1$, which is indeed the slowest to decay (Fig. 6). The higher ω_n fall off very slowly (or may even have a maximum as a function of n)—a quantitative manifestation of the multiexponential kinetics. At the larger D values ω_n diminishes much faster with increasing n. The table shows that the first few terms do not have a simple dependence on n, and they can even change sign. At still higher values of D (not shown in the table) $\omega_0 \to 1$ and $\omega_n \to 0$ for $n \geq 1$.

Figure 7 examines the effect of increasing f from 0.5 to 1.0 kcal/mol Å^2 for two displacements. It is clear

TABLE II. Expansion coefficients[a] ω_n, Eq. (27).

n/D	$10^6\ \text{Å}^2\,\text{s}^{-1}$				$10^8\ \text{Å}^2\,\text{s}^{-1}$	
0	0.3400	6.98(−2)[b]	9.40(−3)	1.1604	0.8118	0.4689
1	8.49(−2)	5.50(−2)	1.10(−2)	−0.2183	8.73(−2)	0.1549
2	7.87(−2)	4.74(−2)	1.18(−2)	6.27(−2)	3.60(−2)	8.95(−2)
3	6.24(−2)	4.57(−2)	1.35(−2)	−1.04(−2)	1.94(−2)	5.84(−2)
4	5.60(−2)	4.66(−2)	1.59(−2)	3.42(−3)	1.19(−2)	4.13(−2)
5	4.91(−2)	4.65(−2)	1.81(−2)	3.43(−4)	8.18(−3)	3.16(−2)
6	4.26(−2)	4.51(−2)	1.98(−2)	6.02(−4)	6.00(−3)	2.56(−2)
7	3.64(−2)	4.29(−2)	2.10(−2)	3.00(−4)	4.50(−3)	2.13(−2)
8	3.11(−2)	4.03(−2)	2.18(−2)	2.74(−4)	3.38(−3)	1.76(−2)
9	2.65(−2)	3.75(−2)	2.23(−2)	1.50(−4)	2.54(−3)	1.45(−2)
10	2.27(−2)	3.48(−2)	2.24(−2)	1.36(−4)	1.92(−3)	1.19(−2)
11	1.94(−2)	3.21(−2)	2.24(−2)	7.47(−5)	1.46(−3)	9.80(−3)
12	1.67(−2)	2.96(−2)	2.22(−2)	7.02(−5)	1.12(−3)	8.09(−3)
13	1.44(−2)	2.73(−2)	2.19(−2)	3.87(−5)	8.65(−4)	6.70(−3)
14	1.25(−2)	2.51(−2)	2.14(−2)	3.82(−5)	6.74(−4)	5.58(−3)
15	1.08(−2)	2.32(−2)	2.09(−2)	2.09(−5)	5.30(−4)	4.66(−3)

[a]Three entries are for (left to right) $x_0 = 1$, 0, and $-1\ \text{Å}$. The exact value of ω_n is even more sensitive to the boundary location and Δx than λ_n. See footnote of Table I for exact conditions used.
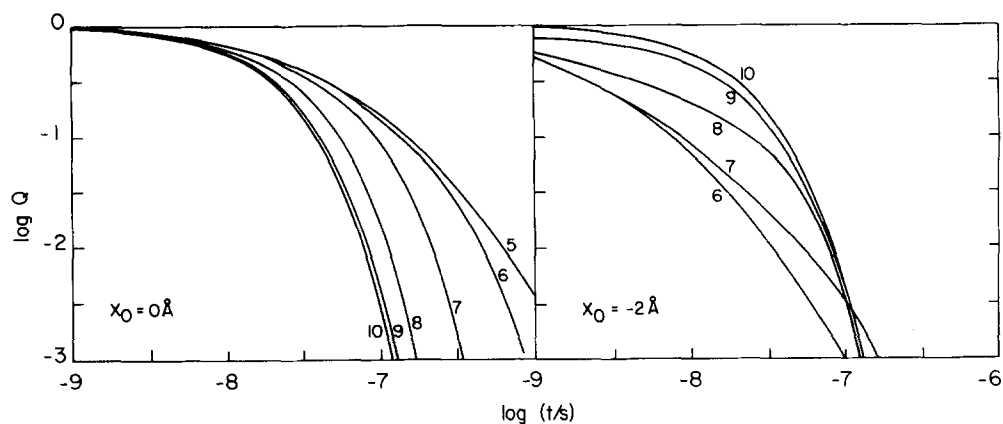[b]Exponent in parentheses.

FIG. 7. Same as Fig. 6 but with $f = 1.0$ kcal/molÅ^2.
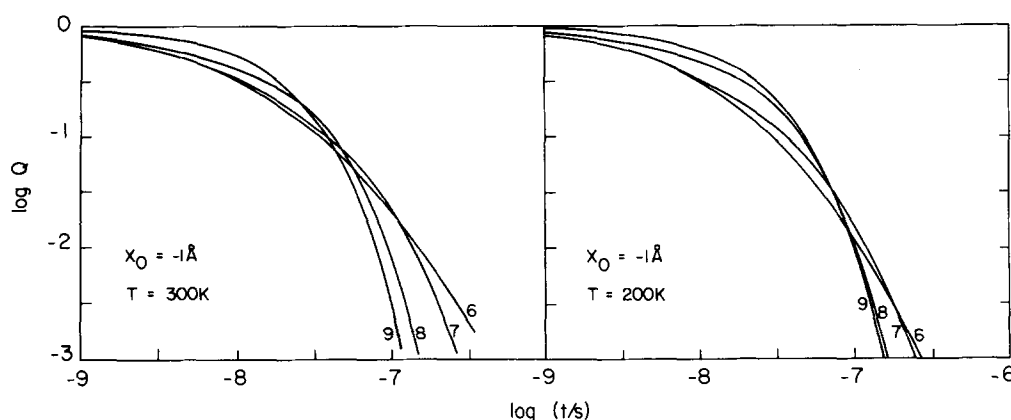

FIG. 8. Same as Fig. 7, for two different temperatures.

(e.g., for $x_0 = 0$ Å) that the variation in the decay curves due to diffusion diminishes as f increases. This is a result of the narrower initial distribution causing faster decay for small D. The effect of the larger force field is to diminish the difference between the high D results.
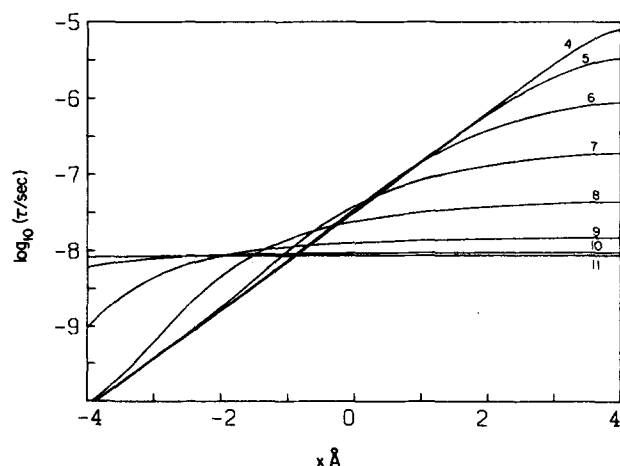

FIG. 9. Average survival times for starting from a given value of the coordinate, Eq. (31a). Each curve is for a different value of $\log_{10}(D)$.

Figure 8 examines the influence of temperature variations. The effect of decreasing T is similar to that of increasing f (Fig. 7), and due to a narrower initial distribution and faster downhill motion. In any real situation, the main effect of temperature variations is through the (Arrhenius-type) variations in A and D. But since A simply sets the time scale (and the relative D/A scale), and the effect of varying D is shown in the figures, one has all desired information for predicting the complete temperature effect.

Finally we discuss the average survival time. Figure 9 shows $\tau(x)$, the survival time when starting from x [Eq. (31a)] as calculated by solving the algebraic equation (32'). It is seen that for $D \to 0$, $\tau(x)$ is simply $k(x)^{-1}$, whereas for $D \to \infty$, $\tau(x)$ becomes independent of initial conditions.

The integral (31b) of $\tau(x)$ for the four initial distributions of Figs. 5 and 6 is shown in Fig. 10. $\langle \tau \rangle$ is D independent as D tends to zero or infinity, the asymptotic limits are given by Eq. (35). The $D \to \infty$ limit is also independent of the initial distribution, and tends to λ_0^{-1}, which is accurately predicted by Eq. (45) ($\lambda_0 = 1.15 \times 10^8$ s). The $D \to 0$ limit does depend on initial conditions: It is large for positive displacements where $k(x)$ is smaller and $\tau(x)$ larger.
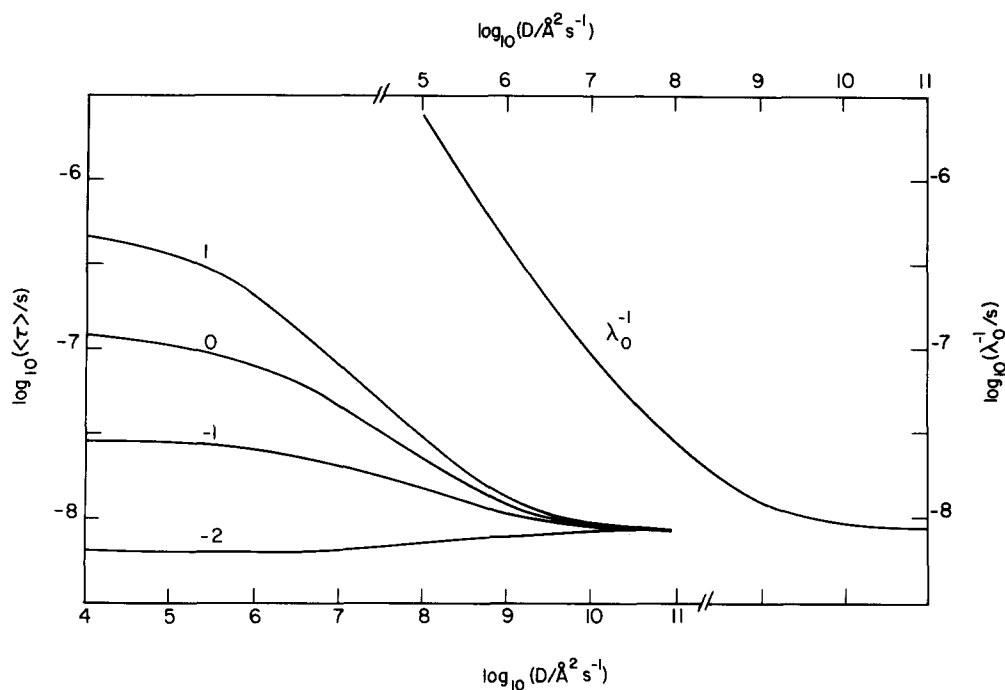
FIG. 10. Average survival times for starting from a given value of the coordinate, Eq. (31g)] as a function of diffusion constant (left and lower scales) for the examples shown in Fig. 6. x_0 (in Å) is denoted near each curve. The results are compared with $1/\lambda_0$ (right and upper scales), where λ_0 is the smallest eigenvalue of the diffusion operator.

$\langle \tau \rangle$ is always a measure of the average survival time, whereas λ_0^{-1} looses this measuring as $D \rightarrow 0$, and tends to infinity. It is therefore clear that for multiexponential kinetics the role of a rate constant as a measure for how fast things react, is taken over by $\langle \tau \rangle^{-1}$.

It is interesting to note that for intermediate D values (say, between 10^6 and 5×10^8 Å^2/s) $\log \langle \tau \rangle$ is almost linear in $\log D$. This means that $\langle \tau \rangle$ is proportional to some power of D (which depends on x_0). This is a "modified Kramers' relation" of the type empirically deduced from the heme binding results.[18(b)] Such a relation is expected even if there is no difference between "internal" and "external" viscosities.[19(b)] It is a consequence of diffusion perpendicular to the reaction coordinate.

V. CONCLUSION

In this paper we have examined the consequences of bounded diffusion perpendicular to the reaction coordinate on the transient decay kinetics of an intramolecular process. The main requirement for observing such effects is that the initial distribution be wide in comparison to the variations in the rate constant. This would usually imply a weak force constant for the diffusive motion, allowing slow but large conformational charges. These requirements are likely to be met in large biomolecules, and we expect these theoretical considerations will be often applicable to biochemical kinetics. For example, in an experimental investigation[17(d)] of Brownian motion of polymer chain ends, fluorescence decay curves from a donor attached at one end of the chain deviate from exponential when an acceptor is attached to the other end. This effect of coupling diffusion to electronic energy transfer should become more dramatic at lower temperatures. In a subsequent publication[22] we apply the present theory to

binding of CO to heme proteins. It is not an ideal testing ground for the ideas, but a great wealth of relevant data is available[18] in this case at present.

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