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Overview of Theoretical Models for Reaction Rates

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There is enormous recent interest in the development of models for rate processes because rates are an almost universal characterization in the physical and biological sciences. In this paper we provide an introduction to several of the problems to be discussed in greater depth by other speakers at a symposium held at the National Institutes of Health on May 6–8, 1985. This review will focus on (1) the Smoluchowski model for reaction rates together with its extension by Onsager, (2) first passage time formalism for discrete and continuous master equations and Fokker–Planck equations, (3) the Kramers model and its extensions, (4) diffusion in the presence of trapping centers.

KEY WORDS: Reaction rates; first passage times; Markov processes; random walks; trapping problems; Kramers model.

1. INTRODUCTION

There is an approximate gap of 50 years between the discovery of the mass action law and the first calculation of rate constants by Smoluchowski in terms of parameters characterizing the microscopic state of the reacting molecules. Since the time of Smoluchowski an enormous number of statistical mechanical and kinetic models for rate processes have been developed. These have served to deepen our understanding of the underlying physical processes and bring into focus occasionally profound mathematical problems whose solution are required to elucidate these processes. There is now so much and so varied an activity in this general subject area that it seemed reasonable to hold a meeting to summarize and put into perspective at least some of the current research in chemistry, physics, and mathematics, relating to the calculation of reaction rates. This meeting was held at the National Institutes of Health at Bethesda,

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Maryland, May 6–8, 1985, and the remaining papers in this volume are written by the invited speakers.

In this paper, introductory to the more advanced expositions, we summarize a few of the original papers on which contemporary research in the field of reaction rates and first passage times is based and indicate where some of the further research has led. It is by no means complete and would require far too much space to make it so. Successive sections will deal with the models of Smoluchowski and Onsager based on a diffusion picture, first passage time models based on equations adjoint to the Fokker–Planck and master equations, the Kramers model and the effects of traps on diffusion processes and random walks. The last section enumerates some of the omitted topics. A number of very useful reviews have appeared on one or more of these topics. The oldest of these, by Noyes,(1) on the relation between the Smoluchowski approach to the calculation of rates and the use of escape probabilities, is a classic in the field. The second, by Calef and Deutch(2) on diffusion-controlled reactions, covers much of the recent literature and overlaps the present paper to some extent, and the third, by Hynes(3) on the theory of reactions in solutions, discusses many of the issues involved in the solution to the Kramers equation from a physical point of view. In addition to these a number of recent monographs contain related and enlightening material. In particular we mention those of van Kampen(4) and Gardiner.(5)

2. THE SMOLUCHOWSKI AND ONSAGER MODELS

The modeling of chemical reaction rates in terms of diffusion in the presence of absorbing bodies seems first to have been suggested by Smoluchowski in his classic study of the kinetics of coagulation in colloidal solutions.(6) The Smoluchowski model consists of a single absorbing sphere of radius R, surrounded by a sea of infinitesimal diffusing particles initially scattered uniformly throughout space with concentration c. Smoluchowski calculates the rate at which particles react with (are absorbed to) the sphere finding

$$k = 4\pi DRc\left[1 + \frac{R}{(\pi Dt)^{1/2}}\right] \tag{2.1}$$

where D is the diffusion constant. The second time-dependent term in brackets represents the effect of the depletion of particles in the immediate neighborhood of the sphere. From this rather simple beginning the study of rate processes has led to the study of ever finer details of these processes using both diffusion theory and the theory of stochastic processes to model microscopic features of the underlying reactions. Many of these developments will be treated in greater detail in the following papers in this symposium volume.

Calculations for the Smoluchowski model are reasonably straightforward but even the simple expression in Eq. (2.1) has raised questions that have broadened our understanding of the basic assumptions in the Smoluchowski and related models. To calculate the rate constant in Eq. (2.1) one solves a diffusion equation subject to an absorbing boundary condition on the surface of the sphere. If $p(r, t \mid r_0, 0)$ is the probability density for the location of an unabsorbed particle at time t then the boundary condition for absorption is $p(R, t \mid r_0, 0) = 0$, from which Eq. (2.1) follows after some calculation. The $t^{-1/2}$ term is clearly bothersome at sufficiently short times. Collins and Kimball(7) therefore proposed the replacement of the absorbing boundary condition by a so-called radiation boundary condition which, in the present case is

$$\pi R^2 D \left.\frac{\partial p}{\partial r}\right|_{r=R} = \kappa p \tag{2.2}$$

where κ is a constant. Further work along these lines was performed by Frisch and Collins.(8) The radiation boundary condition is equivalent to the physical assumption that not all encounters of particles with the sphere lead to an absorption. The use of this (radiation) boundary condition indeed leads to a more reasonable formula for the rate constant, replacing Eq. (2.1). Debye(9) has generalized the Smoluchowski theory to allow an interaction potential between the reacting particles. Shoup and Szabo(10) have developed the corresponding rate constants for a two-step reaction of the form $A + B \rightleftarrows (AB)^* \rightleftarrows AB$, where $(AB)^*$ is an encounter complex. Some of the problems that arise in framing proper boundary conditions have recently been discussed by Monchick(11) in terms of detailed models of the encounter reaction. Agmon(12) has presented results on boundary conditions that allow for desorption as well as absorption, following earlier work by Goodrich(13) and others on this possibility.(13–17)

A diffusion-controlled reaction is one in which the time for two bodies to diffuse to the same neighborhood is the rate-limiting step, the reaction time itself being negligible in comparison. At first glance the Smoluchowski theory would appear to be deficient as a model for calculating rates in diffusion-controlled reactions because it is phrased in terms of a single central sphere and does not take correlations into account. Questions relating to the importance of correctly including many-body effects were first raised by Waite(18,19) and Noyes(1) and have been analyzed by many authors since.

The rate of a diffusion-controlled reaction refers, in the simplest case, to a reaction of the form $A+B\rightarrow P$ for which the mass-action equation is

$$[\dot{A}]=[\dot{B}]=-k(t)[A][B] \tag{2.3}$$

The object of any theory is to calculate $k(t)$ from a microscopic picture. Waite proposed to overcome the difficulty caused by the omission of correlations in the Smoluchowski model by solving an infinite hierarchy of equations for successive joint densities of 1, 2, 3,... of the particles. His development of the theory truncated the hierarchy at second order, replacing the three-particle density by the form implied by an assumption of pairwise interaction forces, thereby obtaining a linear second-order equation. Similar results were obtained at about the same time by Monchick, Magee, and Samuel.(20) The equation derived by Waite(18) for diffusion and reaction can be written in terms of the pair density $c(\mathbf{r}, t)$ as

$$\frac{\partial c}{\partial t}=D\nabla^2 c-f(\mathbf{r}, t)c \tag{2.4}$$

where the last term represents the effect of reaction. The function f in Waite's development is expressed in terms of singlet probability densities which arise from the superposition approximation. The important conclusion that follows from Waite's analysis is that his approximation implies the validity of the Smoluchowski approach. However, Smoluchowski's assumption of an absorbing boundary condition is to be replaced by the radiation boundary condition, Eq. (2.2), first suggested by Collins and Kimball.(7) Noyes(1) proposed to overcome the difficulty in Smoluchowski's theory in a more phenomological way by introducing an encounter density, $h(t)$, defined so that $h(t)\,dt$ is the probability that two particles separating from a nonreactive encounter at $t=0$ will react with each other for the first time between t and $t+dt$. Noyes then writes for $k(t)$, the expression

$$k(t)=k(0)\left[1-\int_0^t h(\tau)\,d\tau\right] \tag{2.5}$$

where $k(0)$ is the rate constant derived from equilibrium statistics. Szabo, Lamm, and Weiss(21) showed that in the presence of a potential, $V(r)$, the right-hand side of Eq. (2.5) is to be multiplied by the factor $\exp[-\beta V(R)]$. The exact interpretation and validity of Noye's results is still somewhat controversial as may be appreciated from some of the work of Monchick(11,12) and Razi Naqvi, Waldenström, and Mork.(23) Difficulties arise when passing from a microscopic to a macroscopic picture and in the reconciliation of elements of the atomic and continuum pictures of the kinetics of reaction rates. The results of these studies suggest that the choice of boundary conditions in the Smoluchowski picture may be much more complicated than believed earlier. A completely satisfactory resolution of the various difficulties associated with the choice of boundary conditions is not yet at hand and it is yet unclear whether any author has treated the microscopic analysis at a proper level. There have been no investigations of possible experimental techniques to help decide on the choice of appropriate boundary conditions.

A recent quite interesting approach to the subject was taken by Torney and McConnell.(24) They used the formalism of lattice random walk theory to show that if the reactant particle is modeled as a perfectly absorbing point on a lattice, the geminate recombination approach of Noyes and the Smoluchowski diffusion (or random walk) models are identical. They also discuss two-dimensional reaction kinetics as might be appropriate for reactions occurring, e.g., in a phospholipid bilayer. The interesting result in two-dimensional reactions is that $k(t)$ is predicted to go to 0 as $(\ln t)^{-1}$. This phenomenon of the asymptotic decay of the rate constant undoubtedly corresponds to the known difference between random walks in two and three or more dimensions.(25)

The Smoluchowski model refers to the rate at which many diffusing particles react with a single target particle, neglecting interaction forces. Onsager(26) later considered the related problem in which he asks for the probability that a pair of ions at a given initial separation will recombine under the influence of a mutual Coulomb attraction. In this case the diffusion takes place in a nonuniform field. Although it may not appear initially that the reaction rate and recombination probabilities are necessarily related we will show later that they can be calculated in quite similar ways from the underlying mathematical models.

While the calculation of recombination rates does not lead to very difficult mathematical problems for the Coulomb potential, the time-dependent problem is significantly more difficult to solve. There has been considerable recent interest in the development of approximation techniques for the solution of the time-dependent Onsager problem with the Coulomb and more general potentials. The techniques include perturbation methods valid at short times, singular perturbation methods, and numerical solutions of the Smoluchowski equation. Pedersen and Larsen(27) have compared the results of several approximations to the solution of the Laplace transformed equation. Since the transforms are not easily inverted these authors compare the numerical and approximate solutions in the transform domain. The question of how error estimates in the s domain translate into errors in time is not easy to answer. The most comprehensive approach to the calculation of diffusion-controlled rate constants is that of

Sibani and Pedersen.(28) It leads to expansions in inverse powers of t, but as in the analysis by Pedersen and Larsen,(27) Sibani and Pedersen only calculate errors in the Laplace transform domain. An alternative approach to the calculation of the Laplace transform of $k(t)$ taking advantage of the fact that its transform satisfies a Ricatti equation has also been explored by these authors.(29) The most comprehensive time-dependent solution to the Onsager problem is that of Hong and Noolandi,(30) which has been applied to problems in the radiation chemistry of solids and liquids. A useful discussion of time-dependent geminate recombination as applied to photoconducting solids is given in the review article by Noolandi.(31)

If $\phi(r, \theta)$ is defined to be the probability that an electron will escape from its associated ion, and if the initial separation of the pair is equal to r and the angle with the electric field equal to θ, then Onsager shows that $\phi(r, \theta)$ satisfies

$$\nabla(e^{-\beta V}\nabla\phi)=0 \tag{2.6}$$

where $\beta=(kT)^{-1}$ and $V= -e^2/(\varepsilon r)-eRr\cos\theta$. This relation must be supplemented by boundary conditions which Onsager idealizes by assuming that the ion has a negligible radius. Thus he assumes that $\phi(0, \theta)=0$, which is the condition for an absorbing boundary, and $\phi(\infty, \theta)=1$. If one averages over all angles the solution given by Onsager is equivalent to

$$\langle\varphi\rangle=\frac{1}{2r}\int_0^2 dv\int_2^\infty \exp(-\tfrac{1}{2}Frv-u/r)\, I_0[(2Fuv)^{1/2}]\, du \tag{2.7}$$

where the parameter F is related to the magnitude of the electric field E by $F=eRr_c/(2kT)$, where $r_c=e^2/(\varepsilon kT)$ is known as the Onsager radius. In the absence of a field $\langle\phi\rangle=\exp(-r_c/r)$.

The Onsager theory has been generalized in a number of directions. Gösele and Seeger(32) calculated the reaction rate for a pair of radicals diffusing in an anisotropic medium. Tachiya(33) has shown that in an anisotropic medium, characterized by a diffusion tensor $\mathbf{D}$ Eq. (2.6) generalizes to

$$\nabla\cdot\mathbf{D}e^{-\beta V}\cdot\nabla\phi=0 \tag{2.8}$$

which is the adjoint of the appropriate Smoluchowski equation. When there is a partially absorbing surface at the ion the boundary condition at the surface of the ion is

$$\mathbf{n}\cdot\mathbf{D}\cdot\nabla\phi=\kappa\phi \tag{2.9}$$

where $\mathbf{n}$ is the outward normal to the surface and κ is a constant characterizing the reaction efficiency. A further generalization given by Sano(34) is to the recombination problem of an electron in the presence of a finite number of sinks. In the absence of a field the escape probability for an electron from a finite set of fixed cations is just the product of escape probabilities from the individual cations, i.e., the escape probabilities are independent provided the reaction radii are equal to zero. Recombination probabilities for a radical in the presence of two sinks was given by Sano.(34) Deutch and his collaborators(35-37) have analyzed, using approximate methods, recombination probabilities with many reactive sinks in an isotropic medium. An extensive analysis of the Onsager problem with imperfect reaction at the surface was made by Rice and Baird,(38) and Sano and Tachiya.(39) These also include the effects of scavenging, that is, the possibility that the electron will be removed by a uniformly distributed set of traps. Sano and Tachiya(40) have also examined the Onsager problem when the reactant particle is constrained to diffuse on a spherical surface and the theory has been applied to the analysis of data on reactions occurring on micellar surfaces.

A simple derivation of the relation for the escape probability, ϕ, that appears in the Onsager problem, and the infinite time bimolecular rate constant, $k(\infty)$, appearing in Eq. (2.6), is that of Berlin, Cordier, and Delaire.(41) They show that the relation can be found quite easily if the Smoluchowski equation is integrated over time from 0 to ∞. Quite recently the Onsager problem for particles constrained to perform a random walk on a lattice has been analyzed by Scher and Rackovsky.(42)

3. FIRST PASSAGE TIMES

Shortly before the work of Onsager discussed in the last section, Pontryagin, Andronow, and Witt(45) derived results that have proved to be of central importance for many models in the stochastic theory of rate reactions. In order to understand the contribution of these authors we must introduce some terminology. Let us assume that a particle moves in a space, S, that can be decomposed into an interior, I, together with a boundary, B. The first-passage time, $T(x)$, is defined to be the time at which the particle first reaches B starting from an arbitrary point, x, in I. Many processes in chemical physics can be modeled in terms of Markov processes, that is, processes in which knowledge of the state of the system at some time t is sufficient to predict its state at times $t' > t$. This prescription rules out cases in which a variable memory is necessary for prediction forward in time. These may be exemplified by models with excluded volume in which one needs the entire history of the process (discrete random walk or diffusion process) to predict its behavior in the future. A particular class of Markov processes is that in which the motion of a single particle can be described by a Fokker–Planck (henceforth abbreviated as FP) equation.(4,5)

Let the position of a particle at time t be denoted by $\mathbf{r}(t)$, and let $p(\mathbf{r}, t \mid \mathbf{r}_0, 0)\, dr$ be the probability density that $\mathbf{r}(t)$ is somewhere in the volume $(\mathbf{r}, \mathbf{r}+d\mathbf{r})$ at time t given that $\mathbf{r}(0)=\mathbf{r}_0$. The FP equation is obtained under the conditions

$$\begin{gathered}\lim_{\Delta t \to 0} \frac{1}{\Delta t} \int (\mathbf{r}-\mathbf{r}_0)_i\, p(\mathbf{r}, t+\Delta t \mid \mathbf{r}_0, t)\, d\mathbf{r} = b_i(\mathbf{r}_0, t) \\ \lim_{\Delta t \to 0} \frac{1}{\Delta t} \int (\mathbf{r}-\mathbf{r}_0)_i \cdot (\mathbf{r}-\mathbf{r}_0)_j\, p(\mathbf{r}, t+\Delta t \mid \mathbf{r}_0, t)\, d\mathbf{r} = a_{ij}(\mathbf{r}_0, t)\end{gathered} \tag{3.1}$$

with all of the higher-order infinitesimal moments, defined similarly to a_{ij} and b_i, being equal to zero. The resulting second order equation is

$$\frac{\partial p}{\partial t} = \frac{1}{2} \sum_i \sum_j \frac{\partial^2}{\partial x_i\, \partial x_j} (a_{ij} p) - \sum_i \frac{\partial}{\partial x_i} (b_i p) \equiv Lp \tag{3.2}$$

where L is the linear operator indicated by the spatial derivative terms. The important result of Pontryagin, Andronow, and Witt(45) is that if $p(\mathbf{r}, t \mid \mathbf{r}_0, 0)$ is regarded as a function of the initial position $\mathbf{r}_0$, then $p(\mathbf{r}, t \mid \mathbf{r}_0, 0)$ is the solution to the adjoint equation

$$\frac{\partial p}{\partial t} = L^+ p = \frac{1}{2} \sum_i \sum_j a_{ij} \frac{\partial^2 p}{\partial x_{0i}\, \partial x_{0j}} + \sum_i b_i \frac{\partial p}{\partial x_{0i}} \tag{3.3}$$

This fact allows one to write simple looking equations for the moments of the first passage time. For example the mean first passage time, $\langle T(\mathbf{r}_0) \rangle$, defined by

$$\langle T(\mathbf{r}_0) \rangle = \int_0^\infty dt \int_I p(\mathbf{r}, t \mid \mathbf{r}_0, 0)\, d\mathbf{r} \tag{3.4}$$

can be shown to satisfy

$$L^+ \langle T(\mathbf{r}_0) \rangle = -1 \tag{3.5}$$

In one dimension one can solve this, as well as equations for higher order moments, explicitly. In the case of a D-dimensional spherical system with a potential $V(r)$, the first passage time, $\langle T(r) \rangle$ can be determined from the equation(46,47)

$$r^{1-D} \frac{d}{dr} \left[r^{D-1} D(r) \frac{d}{dr} \langle T(r) \rangle \right] - \beta D(r) \frac{dV}{dr} \frac{d}{dr} \langle T(r) \rangle = -1 \tag{3.6}$$

with appropriate boundary conditions. For example, the use of a radiation boundary condition at R and a reflecting boundary condition at R',

$$\begin{aligned} \left.\frac{d\langle T(r)\rangle}{dr}\right|_{r=R} &= \frac{\kappa}{D(R)}\langle T(R)\rangle \\ \left.\frac{d\langle T(r)\rangle}{dr}\right|_{r=R'} &= 0 \end{aligned} \tag{3.7}$$

leads to the solution

$$\langle T(r)\rangle = \int_R^r \frac{du}{D(u)\,p_{\text{eq}}(u)} \int_u^{R'} p_{\text{eq}}(y)\,dy + [\kappa p_{\text{eq}}(r)]^{-1} \tag{3.8}$$

where

$$p_{\text{eq}}(r) = r^{D-1}\exp[-\beta V(r)] \Big/ \int_R^{R'} \rho^{D-1}\exp[-\beta V(\rho)]\,d\rho \tag{3.9}$$

Some of the implications as well as generalizations of these formulas have been discussed by Schulten, and Szabo.(48) Mozumder has recently applied some of these results to problems in radiation chemistry.(49)

The foregoing analysis is mathematics rather than physics since we have not related it to a physical model underlying the calculation of reaction rates. Let us suppose that we have a one-dimensional potential barrier as shown in Fig. 1 and we wish to calculate the rate of escape of particles over the barrier. The diffusion of particles will be characterized by a density $p(x, t \mid x_0)$ such that $p(x, t \mid x_0)\,dx$ is the probability that a particle initially at x_0 will be in the interval $(x, x+dx)$ at time t. If B is the location of the barrier maximum then the number of unreacted particles at time t is defined to be

$$N(t) = N(0)\int_{-\infty}^{B}\int p(x, t \mid x_0)\,\varphi(x_0)\,dx\,dx_0 \tag{3.10}$$

where $\varphi(x_0)$ is the initial density. The relative net rate at which particles cross the barrier is

$$k(t) = -\dot{N}(t)/N(t) \tag{3.11}$$

In the single well case shown in Fig. 1 it is usually assumed that the backwards reaction rate is negligible so that particles that cross the barrier do not recross it in the opposite direction. If it is further assumed that $N(t)$

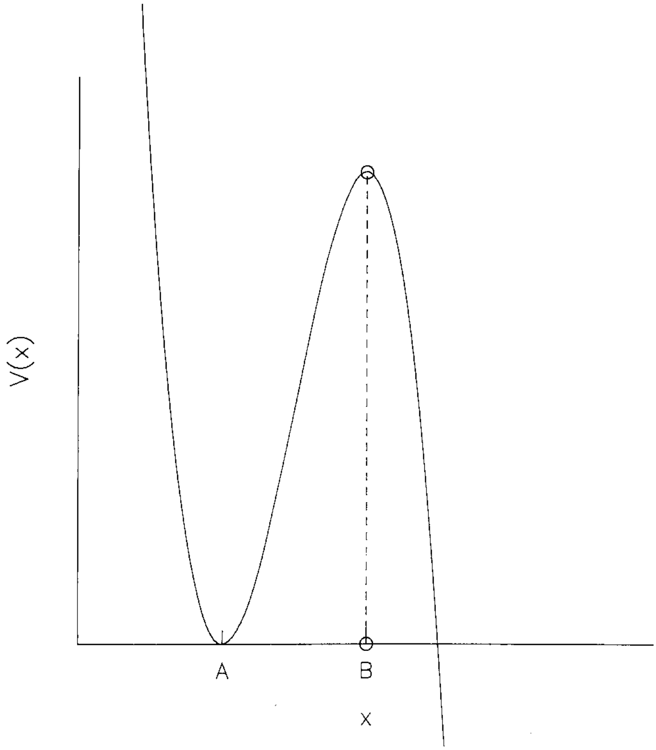

Figure 1

is exponential then $k(t) = k = \text{const}$, and since $N(t) = N(0)\exp(-kt)$ it follows that the mean residence time in the potential well is

$$\langle t \rangle = -\int_0^\infty t \frac{\dot{N}(t)}{N(t)}\, dt = \frac{1}{k} \tag{3.12}$$

Hence one can calculate the reaction rate k by calculating the average residence time in the well. This analysis can be extended to the double well case of Fig. 2 as shown by Northrup and Hynes,(50) and later with some emendation by Schulten, Schulten, and Szabo.(46)

We note that identification of the rate constant as the reciprocal of a first passage time is a consequence of assuming exponential decay for $N(t)$. Newell(51) was the first to discuss conditions under which the exponential approximation is a useful one for diffusion processes. Much of the rigorous theory is summarized in the book by Mandl(52) for diffusion processes and that of Keilson(53) for nearest-neighbor random walks on the line. A more heuristic approach to this class of problems for the Fokker–Planck

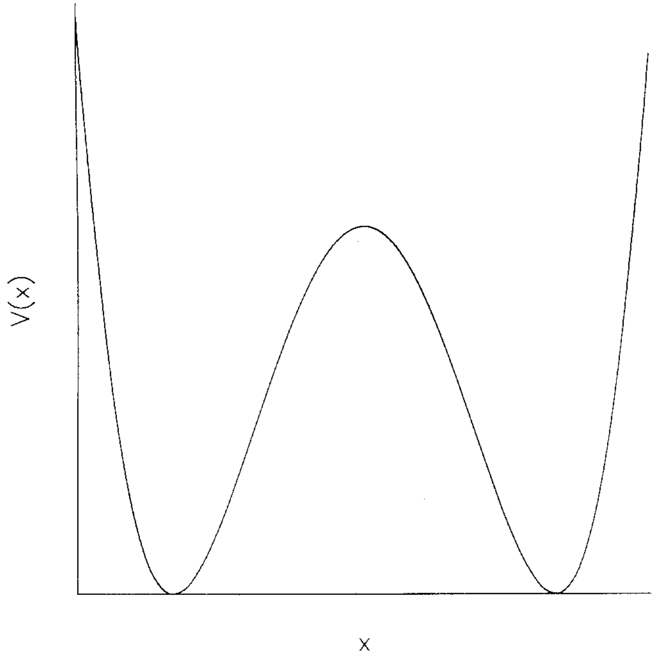

Figure 2

equation has been given by Lindenberg *et al.*(54) All of these analyses depend on successive eigenvalues for the relevant differential operator being widely separated in an appropriate sense. Since the Smoluchowski equation for motion in a time-independent field can be reduced to Sturm–Liouville form, one knows(55) that asymptotically $\gamma_n \sim n^2$. For many easily calculated examples $\lambda_2/\lambda_1 \sim 4$ in accordance with the asymptotic relation and for these the exponential approximation is extremely effective. The large separation property of the lowest eigenvalues can be shown to depend on the ratio of the distance of the initial position from that of the maximum potential to a representative displacement in a fixed time interval. The larger this ratio the greater is the separation of eigenvalues. So far there has not been any rigorous analysis to justify extensions of the method suggested by some authors,(48,56) but calculated results indicate that the generalizations might be quite useful provided that the necessary theory indicating the region of validity is developed.

4. KRAMERS' THEORY

One of the seminal papers in the theory of reaction kinetics is that of Kramers,(57) which appeared in 1940. Kramers considered the problem of a one-dimensional Brownian particle moving in an external field of force characterized by a potential $V(x)$. The particle is initially caught in a potential hole and can only escape by passing over a potential barrier. Kramers proposed studying the rate of the escape of particles over the barrier, and in particular the dependence of this rate on temperature and viscosity. The new feature of the Kramers model, in contrast to those of Smoluchowski and Onsager, is that it describes diffusion in phase space. It gives, as the equation of motion of the Brownian particle in one dimension,

$$\ddot{x} + (\gamma/m)\dot{x} + (1/m)\, dV/dx = \xi(t)/m \tag{4.1}$$

where m is the mass, γ is the viscosity, and $\xi(t)$ is a Langevin, or fluctuating, term. The fluctuating term $\xi(t)$ is assumed to be white noise. Relaxation of this assumption leads to considerably greater complications in the analysis. Equation (4.1) can be rewritten as the first-order stochastic system

$$\begin{aligned} \dot{x} &= v \\ \dot{v} &= -\frac{\gamma v}{m} - \frac{1}{m}\frac{dV}{dx} + \frac{1}{m}\xi(t) \end{aligned} \tag{4.2}$$

Let $\rho(x, v, t)\, dx\, dv$ be the probability that the Brownian particle is to be found in an infinitesimal area in the phase space centered at the point (x, v). After making the appropriate assumption on the fluctuating force one can derive the following equation for ρ:

$$\frac{\partial \rho}{\partial t} = V'(x)\frac{\partial \rho}{\partial v} - v\frac{\partial \rho}{\partial x} + \gamma\frac{\partial}{\partial v}\left(v\rho + \frac{kT}{m}\frac{\partial \rho}{\partial v}\right) \tag{4.3}$$

Van Kampen has attributed this equation to Klein.(58)

The difficulty with dealing with Eq. (4.3) is that it is two dimensional. Kramers therefore examined the regimes characterized by high and low viscosities. The high-viscosity regime is one in which the acceleration term, $\ddot{x}$, can be neglected in Eq. (4.1), in comparison with the remaining terms. This will generally be true for times $t \gg m/\gamma$. In that situation the phase space density attains its equilibrium Maxwell distribution in velocity in a much shorter time than it takes to reach spatial equilibrium, so that $\rho(x, v, t)$ can be factorized as

$$\rho(x, v, t) = g(x, t) \exp[-mv^2/(2kT)] \tag{4.4}$$

provided that the force, $V'(x)$, does not vary appreciably over distances that are $O[(kTm/\gamma^2)^{1/2}]$. The function $g(x, t)$ can then be shown to satisfy the Smoluchowski equation[(59,60)] in one spatial dimension:

$$\frac{\partial g}{\partial t} = \frac{\partial}{\partial x}\left[D\frac{\partial g}{\partial x} - \frac{mV'(x)}{\gamma}g\right] \tag{4.5}$$

An instructive and systematic procedure for effecting the reduction from Eq. (4.3) to Eq. (4.5) is presented in Gardiner's monograph,[(5)] which also shows how to calculate systematic corrections to the Smoluchowski equation using the method of adiabatic elimination of fast variables. In the high-viscosity regime Kramers makes the assumption that the escape rate is determined mainly by details of the potential near the minimum at A in Fig. 1, and near the barrier maximum at B. This is equivalent to the assumption that the transition times from the initial Boltzmann equilibrium state to the barrier are much shorter than the time spent in making the transition through the barrier. Thus Kramers approximates the potential in the neighborhood of these two points by

$$\begin{aligned} V(x) &\sim \frac{m\omega_A^2}{2}(x - x_A)^2, && x \sim x_A \\ V(x) &\sim V_0 - \frac{m\omega_B^2}{2}(x - x_B)^2, && x \sim x_B \end{aligned} \tag{4.6}$$

and by calculating the (one-way) current through the barrier, finds that the equilibrium rate is

$$k = \frac{m\omega_A\omega_B}{2\pi\gamma}\exp(-\beta V_0) \tag{4.7}$$

In a more precise treatment of the high-viscosity Kramers model Chandrasekhar[(60)] assumes that the steady state solution to Eq. (4.3) can be written in the form $\rho(x, v, t) \sim f(x, v)\exp[-m(v^2/2 + V)/(kT)]$ where $f(x, v)$ satisfies an easily derived steady state equation. The current through B is calculated as

$$k = \int_{-\infty}^{\infty} v\rho(x_B, v, t)\, dv \tag{4.8}$$

which is found to be

$$k = \frac{\omega_A}{2\pi\omega_c}\left\{\left[\frac{\gamma^2}{4m^2} + \omega_c^2\right]^{1/2} - \frac{\gamma}{2m}\right\}\exp(-\beta V_0) \tag{4.9}$$

This reduces, in the limit $\gamma \gg 2m\omega_c$ to Eq. (4.7) as it should, but reduces in the limit $\gamma \ll 2m\omega_c$ to

$$k' = \frac{\omega_A}{2\pi} \exp(-\beta V_0) \tag{4.10}$$

which is the prediction of transition rate theory.(61) This prediction is almost certainly unreliable at sufficiently low friction in the cases like unimolecular decomposition or isomerization, in which there are reactant or product wells in the potential curve. Kramers obtained a result for the low-viscosity limit by deriving an equation for the action. Because only a small amount of energy is lost per period of oscillation in a neighborhood of the initial equilibrium in the potential well, one can define action-angle variables, and average over a single cycle. The slow dissipation process makes it plausible that the phases become uniformly distributed after a short time so that only an equation for the energy remains. His result in using this equation is

$$k = \frac{\gamma I \omega_A}{2\pi m k T} \exp(-\beta V_0) \tag{4.11}$$

where I is an action integral whose evaluation is discussed by Matkowsky, Schuss, and Tier.(62) A slightly more accurate version of Kramers' theory in the high-friction limit is due to Edholm and Leimar,(63) who show that the retention of higher-order terms in the expansion of the potentials in Eq. (4.6) can lead to a considerable gain in accuracy compared to the quadratic approximation of Kramers. The physical interpretation and deficiencies of Kramers' theory are very clearly discussed in the comprehensive review by Hynes.(3)

Kramers' original theory has stimulated an enormous amount of research, both in the improvement of the mathematical analysis and in the formulation of new, physically less restrictive models. The most satisfactory mathematical analysis of the original Kramers model is that of Matkowsky, Schuss, and Tier,(62) who formulate the problem in terms of first passage times. These authors start by observing that the rate, k, can be expressed as

$$k = (\tau_1 + 2\tau_2)^{-1} \tag{4.12}$$

where τ_1 is the mean time for a particle to go from A to B in Fig. 1, and τ_2 is the mean time to go from B to the appropriate separatrix in the phase plane and then escape the well. The authors show, by means of a singular perturbation analysis of the equations for mean first passage time, that with their detailed results for τ_1 and τ_2, Eq. (4.12) goes over into the limiting forms in Eqs. (4.7), (4.9), and (4.11) obtained by Kramers for appropriate regimes in the parameter γ. Carmeli and Nitzan(64) and Büttiker, Harris, and Laudauer(65) have alternative more physical theories that allow one to bridge the gap between the two limiting forms provided by Kramers. Numerical calculations by Matkowsky, Schuss, and Tier(62) on a particular potential show that the Carmeli–Nitzan approximation agrees quite well with their own while the Büttiker–Harris–Landauer(65) form differs considerably from it. The numerical comparison, however, was made only for a particular potential. Whether the agreement that was found holds more generally is not known at present. Visscher(66) has also derived an empirical connection formula from numerical solutions to the Kramers–Klein equation. Mangel(67) has discussed the theory of rate constants in the high friction limit by using the backwards version of the Smoluchowski equation. This can be solved exactly for the mean first passage time and yields the Kramers expression to lowest order. Because of the many competing theories it would be advantageous to develop both numerical and molecular dynamics models against which to test each of the approximations so has to have a better feeling for their range of validity.

A great many authors have considered the Kramers' problem for physical models that differ from the one discussed by Kramers. In the original Kramers' analysis the potential contains a single well. Brinkmann,(68) and shortly thereafter, Landauer and Swanson(69) and Langer,(70) treated the two-well problem in which there may be a current in both directions over the potential barrier. The Kramers analysis in the high-friction limit leads to results that depend on local behavior of the potential function in the neighborhoods of the minimum and maximum, for the single-well case. A number of authors have considered parametric forms for the potential in an attempt both to describe the time course of the kinetics and to check the validity of Kramers' results. One of the first of these investigations is a paper by van Kampen(71) which studies a double square well potential for which eigenvalues and eigenfunctions can be calculated explicitly. A detailed calculation of flow rate across the separating barrier shows that Kramers' calculation does indeed lead to the correct value. Larson and Kostin(72,73) have considered both the high-friction or Smoluchowski limit as well as the moderate-friction case. In the first of their papers(72) they treated high-friction limit together with the quartic potential

$$V(x) = V(0)(x^2 - a^2)^2/a^4 \tag{4.13}$$

which allowed them to obtain approximate eigenvalues by using a singular perturbation analysis for the lowest ones, and by local approximations to the potential curve for the higher ones. They also consider the

Smoluchowski case for a quartic potential in three dimensions by using variational methods. This work was continued in a second paper(73) which treats the full Kramers equation for the quartic potential by similar methods. At low-friction values their techniques are not accurate but they propose an empirical formula, following Visscher(66) which leads to agreement within 3% with accurate numerically calculated values for the rate constant. How much these results can be generalized is not at all clear from the exposition. Larson(74) has recently examined the problem posed by a sharp potential barrier, rather than the case contemplated originally by Kramers. The source of the problem in this situation is that the Smoluchowski equation is a valid approximation to the full Kramers equation provided that the force, $V'(x)$, does not change appreciably over intervals of length $(kT/(m\gamma^2))^{1/2}$. Clearly this cannot be satisfied by potential surfaces that have discontinuous slopes. Larson uses singular perturbation techniques to show that approximations obtained from the Smoluchowski equation are useful only when the potential energy peak is extremely high compared to kT. Results related to the sharp barrier were obtained by Matkowsky and Schuss,(75) Ludwig,(75a) and by Matkowsky, Schuss, and Ben-Jacob.(76) There is still room for further analysis of the sharp potential function problem as evidenced by the numerical results given by Larson(74) and compared by him to the results of his and other theories.

One of the most active current areas of research in generalizing the Kramers theory is that in which the Markovian assumption implicit in the Langevin form of Eq. (4.1) is relaxed, and replaced by a more complicated form involving a memory. Several authors(77–81a) have considered generalized Langevin equations, of which

$$m\ddot{x}(t) = F(t) - \gamma \int_0^t \xi(\tau)\, x(t-\tau)\, d\tau + \xi(t) \tag{4.14}$$

is typical, where $\beta = (kT)^{-1}$, $\xi(t)$ is the (nonwhite) noise, $F(t)$ the external force, and $c(t)$ is the correlation function

$$c(t) = \langle n(0)\, n(t)\rangle \tag{4.15}$$

The original Kramers equation is believed to be adequate for a large particle in Brownian motion, but not for a system in which the size of the molecule being followed is of the same order of magnitude as the solvent molecules.(3) Equation (4.14) is sometimes referred to as a generalized Langevin equation. In several analyses of non-Markovian effects the investigators found that the form of the Kramers' expression for the reaction rate is valid except that the parameters γ/m and ω_c are replaced by suitably defined functions of time.(77–81) It is generally agreed that non-Markovian processes must be important for reactions in a solvent.(3) This also seems to be implied by data of Fleming and his collaborators(82–84) on the isomerization of DODCI. The utility of the non-Markovian theory for interpreting these data has also been pointed out by Bagchi and Oxtoby.(85) However, it is not presently known whether the formulation of the problem represented by Eq. (4.14) is a satisfactory one, or whether the experiments cited above are adequately represented in terms of the one-dimensional models that form the starting points of all of the analyses cited thus far.

There have only been a few attempts to generalize the Kramers theory to multidimensional nonpotential systems, the earliest of these being the work of Landauer and Swanson,(69) Langer,(70) and Matkowsky and Schuss.(75) A recent generalization by Gardiner(5,86) gives a reasonably simple generalization of Kramers' theory. Gardiner closely follows an idea first introduced by Northrup and Hynes(50) and by Skinner and Wolynes.(87) Gardiner's analysis essentially divides the space into two subspaces and calculates the rates of interchange between the two subspaces by first-order relaxation equations. While the formalism in this calculation is relatively simple it requires a knowledge of the equilibrium probability distribution. In the absence of a potential this requirement can pose severe practical problems. Multivariate systems for which the drift force cannot be derived from a potential may, for example, be open systems which have dissipative structures or bistable systems described by fields such as magnetic systems. The calculations of Schuss and Matkowsky(88) for multidimensional systems are also formulated in terms of a potential. Implicit in most calculations is the assumption of low noise. Up to this time there has been no extension of Gardiner's approach to the non-Markovian case. One advantage that singular perturbation methods have over Gardiner's technique is that the calculation of correction terms is relatively straightforward. Caroli, Caroli, and Roulet(89) have also analyzed multidimensional systems using the assumption that the nonpotential part of the force term is small enough to be treated by perturbation theory. They how that in the high-friction limit the relaxation time characterizing interchange rates between two basins decreases when a nonpotential term is included in the force. This is related to a more general result proved by Risken.(90) Another variation on the Kramers analysis is that involving a time-dependent potential. Some of the complicated interactions of time scales in this problem have been considered by Caroli *et al.*(91) Clearly much more work is required, both theoretical and experimental, before the Kramers theory can be reliably applied to kinetic data.

Another approach to the derivation of both Markovian and non-

Markovian equations that allows one to calculate reaction rates and other dynamic properties of reacting systems is that developed by Adelman and his collaborators.(92–99) This theory differs from the ones described so far, in that an attempt is made to model the many-body properties of the system more precisely than is done in theories based on a diffusion picture. Adelman divides his picture of a condensed phase reaction into a primary system containing the molecules of interest, and a heat bath. The heat bath is represented as a set of coupled harmonic oscillators which interacts with the primary system molecules. One can then write a reduced set of Langevin equations for molecules in the primary system, in which the Langevin terms depend on the behavior of the heat bath. Because of the nonlinear coupling between the heat bath and primary system the resulting equations must generally be solved numerically. The implications of this theory are still being explored, and are summarized in several review articles,(98,99) as well as by an article in this Proceedings by Professor Adelman.

5. FIRST PASSAGE TIMES FOR MASTER EQUATIONS

Thus far we have described systems whose properties are most naturally described by the solution to diffusion equations or generalized diffusion equations. Physical systems in which quantum effects may be important suggest that problems involving discrete energy levels, or lattice variables, may also be useful in theories of reaction rates. Montroll and Shuler(100) were apparently the first to analyze first passage time problems for a master equation in the context of chemical kinetics. They consider a gas of diatomic molecules each of which can be represented as a harmonic oscillator. That is, the energy state space consists of equally spaced levels, $E_n = nh\nu$, and dissociation occurs when a single bond accumulates sufficient energy, i.e., reaches level N for the first time. If the interaction of the molecule with the heat bath is sufficiently weak so that first order perturbation they can be used Landau and Teller(101) show that the transition rates between levels can be written

$$k_{mn} = [(m+1)\,\delta_{n-1,m} + m\delta_{n+1,m}]\,k_{10} \tag{5.1}$$

The energy of the system is characterized by the quantum level n. The probability that the energy level at time t is n will be denoted by $p_n(t)$. These probabilities satisfy

$$\dot{p}_n = \sum_m (k_{nm}\,p_m - k_{mn}\,p_n) \tag{5.2}$$

which is a simple example of a physically significant master equation. The probability that dissociation has not occurred by time t for this model is

$$S(t)=\sum_{n=0}^{N-1} p_n(t) \tag{5.3}$$

and the mean time till dissociation, or mean first passage time is

$$\langle T_D\rangle=\int_0^\infty S(t)\,dt \tag{5.4}$$

Montroll and Shuler[(100)] were able to calculate quantities like the mean first passage time, although the calculation of the survival probability is much harder in general. Under appropriate conditions akin to those first given by Newell,[(51)] the survival probability can be approximated by a single exponential decay. Early discussions of the first passage formalisms for master equations were given by Kim[(102)] and Weiss.[(103)] It is now well known that the formalism for calculating moments of first passage times for one-dimensional systems with transitions allowed to nearest neighbors only is formally identical with the theory developed in Section 3 for the FP equation. For discrete master equations the matrix transpose takes the place of the adjoint operator in Eq. (3.3). Explicit expressions can be written down for the first passage time moments of such systems, exemplified by the result in Eq. (5.11) below. Possibly the simplest derivation of these results is that given in Ref. 104, where it is shown that the second-order differential equations appearing in the analysis of the Fokker–Planck problem are replaced by second-order difference equations in the lattice case. One can deal in this way with first passage time problems for continuous time random walks.[(104)] For example, if we have a continuous time random walk for which one or both of the end points, 0 or N, are absorbing, and $a_r(t)\,dt[b_r(t)\,dt]$ is the joint probability that the sojourn time at r is between t and $t+dt$ and that the succeeding transition is a step to the right (left), and $Q_r(t)$ is the probability density for the first passage time to absorption starting from lattice point r, then the Q's satisfy

$$Q_r(t)=\int_0^t a_r(\tau)\,Q_{r+1}(t-\tau)\,d\tau+\int_0^t b_r(\tau)\,Q_{r-1}(t-\tau)\,d\tau \tag{5.5}$$

This system must be solved subject to boundary conditions exemplified by $Q_N(t)=0$, $Q_0(t)=\int_0^t a_0(\tau)\,Q_1(t-\tau)\,d\tau$, for a single absorbing point at $r=N$. If one introduces Laplace transforms for the functions in Eq. (5.5), letting $\hat{a}(s)=\mathscr{L}\{a(t)\}$, $\hat{b}(s)=\mathscr{L}\{b(t)\}$, $\hat{Q}_r(s)=\mathscr{L}\{Q_r(t)\}$ then Eq. (5.5) is equivalent to the system

$$\hat{a}_r\Delta^2\hat{Q}_{r-1}+(2\hat{a}_r-1)\,\Delta\hat{Q}_{r-1}+(\hat{a}_r+\hat{b}_r-1)\,\hat{Q}_{r-1}=0 \tag{5.6}$$

where $\Delta f_r = f_{r+1} - f_r$. In discrete time units the Laplace transforms are replaced by generating functions with respect to time.

While Eq. (5.6) is not easily solvable in general it can be used to generate moments. The mean first passage time to absorption for a random walk that starts from r, for example, can be expressed as

$$\langle t(r) \rangle = \int_0^\infty t Q_r(t)\, dt = -\left.\frac{d\hat{Q}_r}{ds}\right|_{s=0_+} \tag{5.7}$$

Hence if we set

$$\begin{aligned} \theta_r &= \int_0^\infty a_r(t)\, dt \\ \mu_r &= \int_0^\infty t[a_r(t) + b_r(t)]\, dt \end{aligned} \tag{5.8}$$

the equation satisfied by the $\langle t(r) \rangle$ is

$$\theta_{r+1} \Delta^2 \langle t(r) \rangle + (2\theta_{r+1} - 1)\, \Delta \langle t(r) \rangle = -\mu_{r+1} \tag{5.9}$$

which can be solved in closed form. In the simplest case in which

$$a_r(t) = \theta_r \lambda \exp(-\lambda t), \qquad b_r(t) = (1 - \theta_r)\lambda \exp(-\lambda t) \tag{5.10}$$

so that θ_r is just the probability of moving to the right from lattice site r, $\mu_r = \lambda^{-1}$. The solution for the $\langle t(r) \rangle$ when the lattice sites are $r = 0, 1, \ldots, N$, N corresponding to an absorbing point, is

$$\lambda \langle t(r) \rangle = \sum_{j=r}^{N-1} [\theta_j p_{\text{eq}}(j)]^{-1} \sum_{s=0}^{j} p_{\text{eq}}(s) \tag{5.11}$$

in which

$$p_{\text{eq}}(r) = p_{\text{eq}}(0) \prod_{j=0}^{r-1} \frac{\theta_j}{(1 - \theta_{j+1})} \tag{5.12}$$

are the equilibrium probabilities in the absence of absorption. The probability $p_{\text{eq}}(0)$ is found by requiring the probabilities to be properly normalized.

The formalism just described is readily extended to provide equations similar to Eq. (5.11) for higher moments. Many applications have been made of relations similar to Eq. (5.11) other than the straightforward solution of problems like those posed by the Montroll–Shuler model. To name a few, Oppenheim, Shuler, and Weiss(105) have used such relations to develop an asymptotic analysis of rate processes with multiple stationary states, van Kampen(106) first derived the discrete analog of the Kramers theory, and Hänggi *et al.*(107) have recently used a similar analysis to discuss the transition between the master equation and the FP equation. Seshadri, West, and Lindenberg(108) have discussed approximations derived from Eq. (5.11), and their application to problems in unimolecular decomposition. Hänggi and Talkner(109) derived analogous results for processes with steps to second nearest neighbors, but these lead to relations not nearly as compact nor as useful as those for nearest-neighbor processes.

Thus far, although a few solutions are known for model master equations with long-range steps, they have not proved to be as generally useful as those for nearest-neighbor steps, because the longer-range models usually have a specific parametric form. The next type of generalization adopted by many authors involves an approximation to the master equation by an FP equation, which can be obtained by assuming that the system is large in some sense. These investigators then introduce scaling variables in terms of the appropriate large parameter.(110) This approximation is not unambiguous as shown recently by Grabert, Hänggi, and Oppenheim,(111) and Hänggi *et al.*(107) The FP equation can be regarded as a continuous analog of the nearest-neighbor random walk in the sense that one is able to find expressions for the moments in closed form as discussed in Section 3. An interesting alternative approach to the problem of calculating moments of the first passage times for master equations has recently been suggested by Matkowsky *et al.*(112) and Knessl *et al.*(112a) These authors point out that just as a master equation can be formally related to a Kramers–Moyal expansion so can the backwards master equation, whose solutions gives the distribution times, be expanded formally as an infinite-order differential equation. They work in discrete time, but the analysis is easily translated into continuous time. Let the position of a random walkers at step n be denoted by x_n. The sequence of steps follows from a recursion $x_{n+1} = x_n + \varepsilon\eta_n$, where η_n is a random variable governed by transition densities $w(z \mid x)$, where $w(z \mid x)\,dz = \text{Prob}\{z < \eta_n < z + dz \mid x_n = x\}$. The master equation for $p(y, n \mid x)$, the probability density for position at step n, given the initial position x, can be expressed as

$$\begin{aligned} &p(y, n+1 \mid x) - p(y, n \mid x) \\ &\quad = \int_{-\infty}^{\infty} [p(y - \varepsilon z, n \mid x)\, w(z \mid y - \varepsilon z) - p(y, n \mid x)\, w(z \mid y)]\, dz \\ &\quad = \sum_{k=1}^{\infty} (-1)^n \frac{\varepsilon^k}{k!} \frac{\partial^k}{\partial y^k} [\mu_k(y)\, p] \end{aligned} \tag{5.13}$$

where the $\mu_k(y)$ are moments of $w(z \mid y)$

$$\mu_k(y) = \int_{-\infty}^{\infty} z^k w(z \mid y)\, dz \tag{5.14}$$

The second line of Eq. (5.13) is just the usual Kramers–Moyal expansion. The backwards master equation can be analyzed in exactly the same way to yield an expansion similar to Eq. (5.13). Matkowsky *et al.*(112) show that, for example, the mean first passage time from a point x, $\langle T(x) \rangle$, satisfies

$$\sum_{k=1}^{\infty} \frac{\varepsilon^k}{k!} \mu_k(x) \frac{d^k \langle T(x) \rangle}{dx^k} = -1 \tag{5.15}$$

They then analyze this equation using singular perturbation theory for small ε, in principle taking account of all terms in the series. This allows development of a theory which can be used for processes with large deviations, as opposed to the Fokker–Planck approximation which amounts to the truncation of Eq. (5.15) at the $k = 2$ term. A multidimensional generalization of the theory has been promised.

Finally, we mention the theorem of Wald(113) that allows one to derive approximations for moments of the first passage time. Let us consider a one-dimensional random walk in discrete time, let N be the first passage time, and let X_N be the point at which absorption occurs, so that $X_N \leqslant -a$ or $X_N \geqslant b$. Let $w(z \mid x) = w(z)$ be independent of x, where $w(z \mid x)$ is the transition density defined earlier, and let $\hat{w}(s)$ be the two-sided Laplace transform of $w(z)$. Wald showed that

$$\langle \hat{w}^{-N}(s) \exp(-sX_N) \rangle = 1 \tag{5.16}$$

holds exactly. This identity has been extensively used in sequential analysis(114,115) and can be used to generate approximations to the distribution of first passage times.

6. TRAPPING PROBLEMS

The final topic to be mentioned in any detail is that of trapping, which may be regarded as a form of reaction-diffusion process in which fixed reaction centers are randomly distributed through space. The subject was first analyzed in the framework of random walks on a lattice, as a model for the kinetics of annealing by Beeler and Delaney(116,117) and later by Rosenstock,(118) as a model of luminescent emission from an organic solid with impurities. Since these early analyses, many other investigators have applied the model to phenomena in chemical physics. We mention just a few contributions to this widely studied subject. The main focus of interest in this class of problems has been the survival time or time to trapping of a random walker, or diffusing particle, in a space in which traps are randomly embedded. Even a calculation of the survival function leads to mathematical problems of great complexity, and few exact results are known. Let us first consider the problem of traps on a lattice, in which each lattice point can be a trap with probability c. Let us suppose that the random walk takes place in discrete time, and let S_n be the distinct number of sites visited by a random walker in n steps. Then the probability that random walker will survive for at least n steps is exactly equal to

$$P(n) = \langle (1-c)^{S_n} \rangle \tag{6.1}$$

where the average is both over all trap configurations and random walks.

Although Eq. (6.1) is exact it is not too useful because it is difficult to calculate statistical properties of S_n. Rosenstock(118) has suggested that $P(n)$ be approximated by

$$P(n) \sim (1-c)^{\langle S_n \rangle} \tag{6.2}$$

which is a potentially useful form since the asymptotic dependence of $\langle S_n \rangle$ on n has been known since the work of Dvoretzky and Erdös.(119) However, the higher moments of S_n cannot be calculated by the same technique as used to find $\langle S_n \rangle$ and so the approximation in Eq. (6.2) is not easily correctable. An asymptotic Gaussian(120) distribution for S_n has been derived for $D \geqslant 3$ dimensions. The mean $\langle S_n \rangle$ is asymptotically proportional to n in these dimensions. In $D=3$ the variance, $\sigma^2(S_n) \sim bn \ln n$ while for $D > 3$, $\sigma^2(S_n) \sim bn$, where in each case b is a computable constant. This has been applied(121) to the calculation of the survival function, $P(n)$, but since the form of the distribution of S_n is not known for n small, the results are best valid for very low trap concentrations. An asymptotically exact result for $P(n)$ has been derived by Donsker and Varadhan(122) for large n. They show that

$$\ln P(n) \sim -a\left(\ln \frac{1}{1-c}\right)^{2/(D+2)} n^{D/(D+2)} \tag{6.3}$$

where D is the dimension and a is a constant depending on the lattice. This form for the result has been suggested by a number of investigators usually starting from a heuristic argument whose main point is that long-term survival is primarily determined by large voids.(123,124) Support for this contention has been provided by results of an exact calculation in one dimension by Weiss and Havlin,(125) who showed that by varying the distribution of gap-free intervals, one can obtain a different asymptotic form for the survival function. A difficulty with both the result in Eq. (6.3), and that based on the Gaussian form for the distribution of S_n is that in the absence of correction terms no one knows how large n must be to insure the utility of the asymptotic form. Klafter, Zumofen, and Blumen(126) suggest, from their simulations, that Eq. (6.3) is valid for values of n such that $P(n) \leqslant 10^{-21}$ in $D = 2$ dimensions. Using a very accurate combination of exact enumeration and simulation,(127) Havlin *et al.*(128) have found that Eq. (6.3) is valid for $P(n) \leqslant 10^{-13}$. Fixman(129) has studied a continuum analog in which traps are modeled as absorbing spheres, not necessarily located on a lattice. He finds Eq. (6.3) to be valid only for $P(n) \leqslant 10^{-67}$, but is able to fit his simulated data very well at low trap concentrations by using an effective medium approximation.(130) The Fixman model, it should be noted, is a many-body version of the Smoluchowski problem, and his analysis implies that the Smoluchowski model is valid only at extremely low trap concentrations. Otherwise Fixman has shown that taking approximate account of trap interactions leads to good agreement with simulated results over the measureable range in $P(n)$.

The Fixman analysis is, of course, not the first to use effective medium approximations in the context of the continuum random trapping problem. This approach has been pursued by Cukier and his collaborators,(131–134) by Calef and Deutch,(135) and Muthukumar.(136) Muthukumar and Cukier(132) have applied a multiple scattering formalism to the same problem. The results of these investigations are usually presented in terms of the macroscopic diffusion constant and reaction rate k, and their dependence on the concentration of trapping spheres. Other techniques such as those based on the t-matrix approximation(137) have also been used to study this problem.(138,139)

Of particular interest is the appearance of nonanalytic dependence of the diffusion constant D, and the rate k, on the concentration of traps, although there is still some disagreement between different authors(2,35,140,140a,140b) on some of the coefficients in the approximate expansions. In a recent mathematically rigorous calculation den Hollander(141) has shown, using the methods of Jain and his collaborators,(120) that one also finds nonanalytic behavior for the mean trapping time as a function of trap concentration for low concentrations.

Aside from investigations of diffusion and rate constants there have been a number of papers dealing with time-dependent solutions in the presence of trapping centers. Results along this line can be obtained in closed form in one dimension when traps are perfectly absorbing, because of the simple geometry but even in one dimension it does not seem possible to derive comparable results for imperfect traps. Many versions of the trapping problem are currently being investigated. Representative of these are problems involving trap motion and trap annihilation.(24,142–145) The mobile trap model is clearly a more realistic model for chemical reaction rates than is the classical fixed trap picture. In the annihilating trap model a trapping event leads to the disappearance of both the trap and the diffusing particle. Most of the information on these systems is derived from simulation studies since the problems are even more complex than the so-far unsolved static trapping problem. Finally, these problems have also been tackled for diffusion on fractal structures.(143,144,146)

There have been many simulation studies of the lattice trapping problem but Fixman(129) is the only one to have concentrated mainly on the continuum problem. Simulation has been the only way of beginning to understand the effects of inhomogeneity of the underlying lattice. Such studies are suggested by models for the kinetics of photosynthesis, and have been energetically pursued by Kopelman and his collaborators. Reviews of some of this work is to be found in Ref. 147 and 148 as well as in an article in this volume.(149) In any case, considerable computing power would be necessary to properly check the extensive theoretical analyses that have so far appeared in the literature, and supercomputers would certainly be needed to check higher-order terms or possible logarithmic corrections in the expansions that have been found by approximate methods. Not only is it difficult to solve problems involving randomly placed traps but even deterministically placed traps can pose considerable problems. Scher and Wu(150) and Montroll and West(151) have developed formalisms for the motion of a random walk on a lattice in which traps occur on a sublattice. For this special case one can obtain closed form expressions for many quantities of interest.

In all of the references to this point the traps have been represented in the diffusion equations in terms of absorbing boundary conditions at the appropriate surfaces. Wilemski and Fixman in a series of widely cited papers(152) take a different tack by representing the effects of traps or reaction centers by a space dependent term in the diffusion equation itself. This is in addition to a possible constant radiation term which is easily handled. The resulting equation is then written

$$\frac{\partial p}{\partial t} = Lp - k(\mathbf{r})\,p \tag{6.4}$$

where L is the relevant diffusion operator and $k(\mathbf{r})$ represents the effects of traps. Equation (6.4) is a forward equation. In order to study disappearance rates, one calculates properties of the survival function

$$P(t) = \iint p(\mathbf{r}, t \mid \mathbf{r}_0, 0)\, \varphi(\mathbf{r}_0)\, d\mathbf{r}\, d\mathbf{r}_0 \tag{6.5}$$

where $\varphi(\mathbf{r}_0)$ is the initial density. Let us note that Eq. (6.4) can be regarded as the lowest order of an infinite hierarchy of equations as pointed out in Wilemski and Fixman's original article.(152) Higher-order equations allow for many-body effects. However, even Eq. (6.4) poses difficult mathematical problems in general. Wilemski and Fixman suggest an approximate solution for $P(t)$ when the initial condition, $\varphi(r_0)$, is assumed to be the equilibrium density $p_{\mathrm{eq}}(x_0)$ so that it satisfies $Lp_{\mathrm{eq}}(x)=0$. Several further justifications exist for the Wilemski–Fixman approximation. Doi,(153) for example, shows that it corresponds to the simplest choice of trial function in a variational formulation, and Battezati and Perico(154) develop a perturbation theory based on the smallness of the trap radius relative to other significant dimensions. A further approach is to assume that Eq. (6.4), in nondimensional form is

$$\frac{\partial p}{\partial \tau}=Lp-\varepsilon k(\mathbf{r})\,p \tag{6.6}$$

where ε is a small parameter. Straightforward perturbation theory(155) combined with a renormalization step suffices to obtain the Wilemski–Fixman form. An exact solution obtainable in one dimension for $k(x)=x^2$ and $V=0$ compared to the approximation shows that an increase in ε degrades the accuracy of the approximation. Since the Wilemski–Fixman approximation is exact for all ε when $k(x)=\delta(x-x_0)$ but not in general when $k(x)$ is the sum of two δ functions one sees that its validity depends both on the localization of $k(x)$ and on ε being a legitimate perturbation parameter. Agmon and Hopfield(156) use a separation of variables to show that when the operator L in Eq. (6.4) has the Smoluchowski form

$$L=D\frac{\partial}{\partial x}\left(e^{-\beta V}\frac{\partial}{\partial x}e^{\beta V}\right) \tag{6.7}$$

a solution to Eq. (6.4) is easily found in the limits $D\to 0$ and $D\to\infty$ for a general initial condition $p(x,0)$. These are

$$\begin{aligned} p(x,t)&=p(x,0)\exp[-k(x)t], \qquad D\to 0\\ p(x,t)&=p(x,0)\exp\left[-t\int k(x)\,p_{\mathrm{eq}}(x)\,dx\right] \end{aligned} \tag{6.8}$$

A formalism related to that developed for the solution of Eq. (6.4) was recently used in an interesting analysis of the effects of viscosity on electronic relaxation processes in which the intramolecular potential does not have a barrier to the motion of an initially formed excited state.(157) Thus the process is a complement to the Kramers model. The authors consider the motion of a solute particle on a one-dimensional potential surface, with a position dependent sink term in addition to the radiative decay constant. If momentum can be neglected so that one has the analog of conditions under which the Smoluchowski equation is valid in the Kramers problem then the starting point of the analysis by Bagchi, Fleming, and Oxtoby is

$$\frac{\partial p}{\partial t} = A\frac{\partial^2 p}{\partial x^2} + B\frac{\partial}{\partial x}(xp) - [k_{nr}S(x) + k_r]\, p \tag{6.9}$$

where A and B are inversely proportional to the viscosity and k_r and k_{nr} are constants. Three specific forms for $S(x)$ are considered, a sink at the origin, a Gaussian, and a Lorentzian. While the latter two cases cannot be solved exactly they nevertheless allow one to infer how the nonradiative decay rate varies with viscosity. The results are in qualitative agreement with experimental data on radiationless decay of the excited singlet state of triphenyl methane dyes.(158,159) Alternative approaches to this problem are those of Skinner and Wolynes.(160)

7. A MISCELLANY OF TOPICS

Limitations of space prevent our discussing many further topics that have attracted recent attention. Among these we mention the derivation of proper boundary conditions for diffusion equations starting from discrete random walk limits,(161,162) and the effects of radiation boundary conditions as opposed to absorbing boundary conditions for these equations.(12) There have been a few papers(163,164) dealing with situations in which the reactivity of a molecule fluctuates (e.g., the accessibility of a binding site of a protein is modulated by internal motions). The problem of extending the theory of diffusion-influenced reactions to nonuniformly reactive species (e.g., the ligand binding site of a macromolecule covers only a portion of its surface) has been considered by a number of authors.(165-169) The mathematical difficulty underlying these problems is that the relevant partial differential equations must be solved subject to so-called mixed boundary conditions (i.e., the boundary conditions are different on different parts of the molecular surface). The only exact solution available is that for the steady-state association constant to a circular reactive site on an infinite inert plane(169,170) and for a few terms in the short- and long-time expansions of the corresponding time dependent rate.(171) For more complicated geometries progress can be made by replacing the usual mixed boundary conditions by the requirements that the radiation boundary condition is satisfied on the average and the flux is constant above the reactive part of the molecule.(165) This appears to be an excellent approximation and allows a class of problems to be solved analytically. Recently it has been used to quantitate the role of surface diffusion as a rate-enhancing mechanism for a small reactive site on a plane and a sphere.(172) The problem of competition between a large number of small reactive sites on an inert spherical surface (e.g., receptors on a cell) has also been approximately treated.(165,170,173) Another set of problems that has recently engaged the attention of several investigators is that of the analysis of the Kramers equation in the presence of absorbing boundaries.(174–181) Because there are no solutions in closed form to the Kramers equation even in the absence of boundaries, only the barest beginnings have been made into the study of the effects of boundaries.

Many papers have appeared on the kinetics of decay from an unstable initial state to a stable final state.(182–184) Some of the complexity of detail of such processes can be appreciated from the work of Suzuki, who suggests that the decay process can be divided into at least three regimes, in which the fluctuating forces and nonlinearities alternately play the more significant roles. Different approaches exist for obtaining approximate solutions to this problem, and it is not yet clear whether all of the qualitative features of such systems are completely understood.

Several first passage time problems, in addition to those related to ligand binding to cells, have arisen in modeling of biological processes. One of the most widely cited of these by Adam and Delbrück(185) relates to diffusion of a particle to a target area. In that paper the authors suggest that such diffusion is facilitated in many cases by the presence of surfaces in which the target is imbedded. In their assumed process diffusion to the target then takes place in two stages. In the first the particle diffuses to the surface, and in the second it diffuses on the surface to the target. The major idea behind this formulation of target seeking as two-stage process is that a significant reduction in mean first passage time to the target can be achieved over that attainable by fully three-dimensional diffusion. An extension of these ideas has been made to intramicellar kinetics by Frank, Gratzel, and Kozak,(186) and by Hatlee *et al.*(187) A second application of first passage time formalism in a biological framework is the theory of protein folding as developed by Karplus and Weaver.(188) These authors suggest that a protein consists of several microdomains which move by diffusion and must coalesce in order to form a structure. This work has been continued by Weaver(189) and Zientara, Nagy, and Freed.(190) The general problem of energy transfer to either static or moving acceptors is suggested by the modeling of the photosynthetic reaction.(191–195) Models for this phenomenon have been extensively developed by Blumen, Zumofen, and their collaborators,(196–199) and by others.(200–207)

Finally, we note that many problems in determining maximal displacements of random walks or diffusion processes are closely related to first passage time problems. For example, the probability that the maximum displacement of a diffusion process on a line is less than X at time t is equal to the probability that the first passage time of the process to (X, ∞) exceeds t. This duality has been exploited by a number of authors.(208–211) Further applications of some of the analysis discussed in this paper abound in the physical and biological sciences. Many of these will be more thoroughly discussed in the remaining papers appearing in these Proceedings.

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