First passage time approach to diffusion controlled reactions

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Association reactions involving diffusion in one, two, and three-dimensional finite domains governed by Smoluchowski-type equations (e.g., interchain reaction of macromolecules, ligand binding to receptors, repressor–operator association of DNA strand) are shown to be often well described by first-order kinetics and characterized by an average reaction (passage) time τ. An inhomogeneous differential equation is derived which, for problems with high symmetry, yields τ by simple quadrature without taking recourse to detailed cumbersome time-dependent solutions of the original Smoluchowski equation. The cases of diffusion and nondiffusion controlled processes are included in the treatment. For reaction processes involving free diffusion and intramolecular chain motion, the validity of the passage time approximation is analyzed.

I. INTRODUCTION

There are a variety of problems in chemical physics and biophysics where one wishes to calculate the average time τ required for a particle, generated at some point and diffusing under the influence of a potential, to reach and be bound to a certain target. For example consider the diffusion controlled interchain reaction of a polymer with two reactive groups attached, say at the ends.[1–3] The simplest description of the dynamics of the end-to-end distance of the polymer is to liken its time development to a diffusion under the influence of a potential (e.g., the harmonic spring model). Assuming that the reaction occurs with a certain rate whenever the ends are sufficiently close, one would typically like to know the fraction of unreacted molecules at time t and the average time needed for the ends to collide for the first time. Related well-known problems in biophysics include the work of Adams and Delbrück,[4] who studied the variation of the first passage time with dimension of the diffusion space in their analysis of the diffusion of ligand binding to receptor molecules. More recently, Karplus and Weaver in their model for protein folding[5] have developed estimates of the average time it takes two microdomains of a polypeptide chain to coalesce.

In this paper we develop a method which yields the average reaction time τ by simple quadrature for diffusion processes in a force field governed by a Smoluchowski-type diffusion equation with a space-dependent diffusion constant. The desired reaction time τ is related to the probability $\Sigma(t)$ that a system is still unreacted at time t in that one presupposes the approximation

$$\Sigma(t) \approx \Sigma_{\text{approx}}(t) = \exp(-t/\tau) , \tag{1.1}$$

i.e., a single exponential decay of $\Sigma(t)$. Approximation (1.1) is equivalent to the definition of τ most commonly stated

$$\tau = \int_0^\infty dt\, \Sigma(t) . \tag{1.2a}$$

$\Sigma(t)$ in turn is related to the distribution $p(\mathbf{r}, t)$ of finding the system at position $\mathbf{r}$ at time t:

$$\Sigma(t) = \int d\mathbf{r}\, p(\mathbf{r}, t) , \tag{1.3a}$$

where the integral extends over the whole diffusion space. $p(\mathbf{r}, t)$ is to obey the Smoluchowski equation

$$\frac{\partial}{\partial t} p(\mathbf{r}, t) = \nabla \cdot \mathbf{j}(\mathbf{r}, t) , \tag{1.4}$$

$$\mathbf{j}(\mathbf{r}, t) = D(\mathbf{r})[\nabla p(\mathbf{r}, t) + \beta p(\mathbf{r}, t) \nabla U(r)] ,$$

where $\mathbf{j}(\mathbf{r}, t)$ is the corresponding flux. $D(\mathbf{r})$ is the position dependent diffusion coefficient and $U(\mathbf{r})$ the interaction potential. For the sake of simplicity we assume that the system has spherical symmetry. The reader may note that Eq. (1.4) is of the Focker–Planck type.

Although $p(\mathbf{r}, t)$ is not explicitly needed for the calculation of τ, we need to discuss its properties as it is through Eq. (1.4) that the reaction behavior of the system enters. To describe the ring closure reaction of polymer or the absorption of a particle, one imposes the "radiation" boundary condition at $r = a$:

$$j(a, t) = \kappa p(a, t) , \tag{1.5}$$

where κ is a microscopic rate constant which is a measure of the effectiveness of the reaction at trapping the particle. If a reaction occurs whenever the particle reaches $a(\kappa \to \infty)$, this reduces to the so-called Smoluchowski boundary condition

$$p(a, t) = 0 . \tag{1.6}$$

We enclose our system and prevent any particles from escaping to infinity by erecting a reflective barrier at $r = R$:

$$j(R, t) = 0 . \tag{1.7}$$

The solution of Eq. (1.4) subject to the above boundary conditions for a δ-function initial condition, i.e., $p(\mathbf{r}, 0) = \delta(\mathbf{r} - \mathbf{r}_0)$, is the Green's function or the conditional probability $p(\mathbf{r}, t/\mathbf{r}_0, 0)$ that if the particle (we will use "particle" terminology from now on, also when the end-to-end distance is meant) was at $\mathbf{r}_0$ at $t = 0$, it

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will be at $\mathbf{r}$ at time t. The probability that a particle initially at $\mathbf{r}_0$ has not been absorbed at time t is denoted by $\Sigma(\mathbf{r}_0, t)$ and is given by

$$\Sigma(\mathbf{r}_0, t) = \int_{a \le r \le R} d\mathbf{r}\, p(\mathbf{r}, t/\mathbf{r}_0, 0) . \tag{1.3b}$$

The average time required for absorption is

$$\tau(\mathbf{r}_0) = \int_0^\infty dt\, \Sigma(\mathbf{r}_0, t) . \tag{1.2b}$$

Often the situation arises that a system is made reactive, i.e., $\kappa \ne 0$, at times $t \ge 0$, but is unreactive, i.e., $\kappa = 0$, for $t < 0$. At $t < 0$, Eq. (1.4) then describes the relaxation of $p(\mathbf{r}, t)$ to the equilibrium or steady-state solution (three-dimensional case)

$$p_{\text{eq}}(\mathbf{r}) = c r^2 \exp[-\beta U(r)] , \tag{1.8}$$

where c is a normalization constant. The probability that a particle starting from the equilibrium distribution $p_{\text{eq}}(\mathbf{r})$ is still in the system at time $t > 0$ is [$p_{\text{eq}}(\mathbf{r})$ assumed normalized on the interval $a \le r \le R$]

$$\begin{aligned} \Sigma(t) &= \int_{a \le r_0 \le R} d\mathbf{r}_0\, p_{\text{eq}}(\mathbf{r}_0) \Sigma(\mathbf{r}_0, t) \\ &= \iint_{a \le r, r_0 \le R} d\mathbf{r}\, d\mathbf{r}_0\, p_{\text{eq}}(\mathbf{r}_0) p(\mathbf{r}, t/r_0, 0) \end{aligned} \tag{1.9}$$

and the corresponding average time for absorption is

$$\tau = \int_{a \le r_0 \le R} d\mathbf{r}_0\, p_{\text{eq}}(\mathbf{r}_0)\, \tau(\mathbf{r}_0) = \int_0^\infty dt\, \Sigma(t) . \tag{1.10}$$

When the boundary conditions, interaction potential, and the diffusion coefficient depend on a single coordinate in an arbitrary orthogonal curvilinear coordinate system (e.g., in situations of spherical symmetry), the evaluation of τ can be reduced to a simple quadrature. For free diffusion, the resulting integrals are elementary, and simple closed expressions for $\tau(r_0)$ and τ can, in fact, be obtained. The first passage time theory[6,7] addresses the case of the Smoluchowski boundary condition for which every encounter at $r = a$ leads to reaction, making $\tau(r_0)$ the average time required to reach $r = a$ for the first time starting from $r = r_0$. This theory shows for one-dimensional systems how one can determine $\tau(r_0)$ and τ without ever obtaining $p(\mathbf{r}, t/\mathbf{r}_0, 0)$.

The purpose of this paper is fourfold. First, we show that the existing theory is easily generalized to incorporate radiation boundary conditions and to handle problems of higher spatial dimensionality. In the case of radiation boundary conditions, the particle can reach $r = a$ many times before being absorbed. Thus, the name *first* passage time is no longer appropriate and we use *average* passage time instead. Second, we obtain several new exact results for the average passage time of a particle undergoing free diffusion and diffusion in a harmonic potential which reduce in certain limits to approximate expressions obtained previously by more cumbersome methods. Third, we investigate how the entire time course of the reaction, i.e., $\Sigma(t)$, is approximated by Eq. (1.1). For this purpose the Smoluchowski equation is solved numerically by an algorithm described in detail elsewhere.[8] Finally, we extend the first passage time treatment to obtain the area under autocorrelation functions for processes governed by the Smoluchowski diffusion equation.

The outline of this paper is as follows: In Sec. II we derive $\tau(\mathbf{r}_0)$ and τ (as well as the area under autocorrelation functions) as integrals over $p_{\text{eq}}(\mathbf{r})$ for a d-dimensional system with spherical symmetry. In Sec. III we obtain simple closed expressions for τ for free diffusion in one, two, and three dimensions, and compare $\Sigma(t)$ calculated exactly and approximated by Eq. (1.1). Finally, in Sec. IV we consider the ring closure reaction of polymers in the framework of the harmonic spring model using also potentials which mimic excluded volume effects.

II. THEORY

The Smoluchowski equation (1.4) can be rewritten as

$$\frac{\partial}{\partial t} p(\mathbf{r}, t/\mathbf{r}_0, 0) = \mathbf{L}(\mathbf{r}) p(\mathbf{r}, t/\mathbf{r}_0, 0) , \tag{2.1}$$

where

$$\mathbf{L}(\mathbf{r}) = \nabla \cdot D(\mathbf{r}) \nabla + \beta \nabla \cdot D(\mathbf{r}) (\nabla U) . \tag{2.2}$$

Instead of solving this equation for $p(\mathbf{r}, t/\mathbf{r}_0, 0)$ and then integrating over $\mathbf{r}$ to obtain $\Sigma(r_0, t)$ [see Eq. (1.3b)] we will derive a differential equation which determines $\Sigma(\mathbf{r}_0, t)$ directly. However, as the boundary conditions to describe reactive systems are given for Eq. (2.1), we need to consider initially the distribution function $p(\mathbf{r}, t/\mathbf{r}_0, 0)$ to derive the appropriate boundary conditions for $\Sigma(\mathbf{r}_0, t)$ and $\tau(\mathbf{r}_0)$.

For this purpose we consider the adjoint equation[9] to Eq. (2.1):

$$\frac{\partial}{\partial t} p(\mathbf{r}, t/\mathbf{r}_0, 0) = \mathbf{L}^+(\mathbf{r}_0) p(r, t/r_0, 0) , \tag{2.3}$$

which holds for the adjoint diffusion operator

$$\mathbf{L}^+(\mathbf{r}_0) = \nabla \cdot D(\mathbf{r}) \nabla - \beta D(\mathbf{r}) (\nabla U) \cdot \nabla \tag{2.4}$$

and the adjoint boundary conditions given below. For a formal derivation of Eq. (2.3) we start from the solution of Eq. (2.1):

$$p(\mathbf{r}, t/\mathbf{r}_0, 0) = \int_V d\mathbf{r}'\, \delta(\mathbf{r} - \mathbf{r}') \exp[t \mathbf{L}(r')]\, \delta(\mathbf{r}' - \mathbf{r}_0) . \tag{2.5}$$

We have used the symbol V as a remainder that the integration is over $a \le r \le R$. For some functions $u(\mathbf{r})$ and $v(\mathbf{r})$ one has

$$v \mathbf{L} u - u \mathbf{L}^+ v = \nabla \cdot \mathbf{P}[u, v] , \tag{2.6a}$$

where

$$\mathbf{P}[u, v] = v D \nabla u - u D \nabla v + \beta D (\nabla U) u v \tag{2.6b}$$

is the bilinear concomitant of $\mathbf{L}$. Since $\mathbf{P}[\delta(\mathbf{r} - \mathbf{r}'), \delta(\mathbf{r}' - \mathbf{r}_0)]$ for $\mathbf{r}$ and $\mathbf{r}_0$ *inside* V vanishes on the surface of V, we can rewrite Eq. (2.5) as

$$p(\mathbf{r}, t/\mathbf{r}_0, 0) = \int_V d\mathbf{r}'\, \delta(\mathbf{r}' - \mathbf{r}_0) \exp[t \mathbf{L}^+(r')]\, \delta(\mathbf{r} - \mathbf{r}') .$$

Differentiation of this equation with respect to t yields Eq. (2.3). Equation (2.3) has to be complemented, however, by boundary conditions which guarantee P to vanish on the boundary of V. This requires Eq. (2.6b) to vanish on the surface of V. If we identify u and v with the solutions of Eqs. (2.1) and (2.3), respectively, we require in the case of the *Smoluchowski boundary condition* (1.6), $u(a)=0$, that $v(a)=0$, i.e., $[D(a)\neq 0]$,

$$p(\mathbf{r}, t/\mathbf{r}_0, 0)=0\ , \quad r_0=a\ . \tag{2.7}$$

In the case of the *radiation boundary condition* (1.5), $\nabla u+\beta(\nabla U)u=[\kappa/D(a)]\,u$, we have $\nabla v=[\kappa/D(a)]\,v$, i.e., $[D(a)\neq 0]$,

$$\nabla_{\mathbf{r}_0} p(\mathbf{r}, t/\mathbf{r}_0, 0)=\frac{\kappa}{D(r_0)}\, p(\mathbf{r}, t/\mathbf{r}_0, 0)\ , \quad r_0=a\ . \tag{2.8}$$

The differential equation for $\Sigma(\mathbf{r}_0, t)$ can now be derived readily by integrating Eq. (2.3) over $\mathbf{r}$ to yield

$$\frac{\partial}{\partial t}\Sigma(\mathbf{r}_0, t)=\mathbf{L}^{+}(\mathbf{r}_0)\,\Sigma(\mathbf{r}_0, t)\ . \tag{2.9}$$

This equation in a somewhat different form has been given by Pontryagin *et al.*[10] The boundary conditions (2.7) and (2.8) become $[D(a)\neq 0]$

$$\Sigma(\mathbf{r}_0, t)=0 \quad (r_0=a) \tag{2.10}$$

and

$$\nabla\Sigma(\mathbf{r}_0, t)=\frac{\kappa}{D(r_0)}\,\Sigma(\mathbf{r}_0, t) \quad (r_0=a)\ , \tag{2.11}$$

respectively.

To obtain a differential equation for $\tau(\mathbf{r}_0)$ defined by Eq. (1.2b), we integrate Eq. (2.9) over all time and obtain by virtue of $\int_0^\infty dt(\partial/\partial t)\Sigma(\mathbf{r}_0, t)=\Sigma(\mathbf{r}_0, \infty)-\Sigma(\mathbf{r}_0, 0)=-1$ the following:

$$\mathbf{L}^{+}(\mathbf{r}_0)\,\tau(\mathbf{r}_0)=-1\ . \tag{2.12}$$

While this equation is general, it can be solved analytically only for problems where the boundary conditions, the potential, and the diffusion coefficient in an orthogonal curvilinear coordinate system depend solely on a single coordinate. In particular, for *d dimensions* employing spherical coordinates we have

$$r_0^{1-d}\frac{d}{dr_0}\left[r_0^{d-1}D(r_0)\frac{d}{dr_0}\,\tau(r_0)\right]-D\beta\frac{dU}{dr_0}\frac{d}{dr_0}\,\tau(r_0)=-1\ . \tag{2.13}$$

The radiation boundary condition (2.11) and the reflective boundary condition at $r=R$, i.e., $\kappa=0$, imply

$$\left[\frac{d}{dr_0}\,\tau(r_0)\right]_{r_0=a}=\frac{\kappa}{D(a)}\,\tau(a)\ , \tag{2.14a}$$

$$\left[\frac{d}{dr_0}\,\tau(r_0)\right]_{r_0=R}=0\ . \tag{2.14b}$$

Since Eq. (2.13) represents a first-order inhomogeneous differential equation for $d\tau/dr_0$, it is easily solved subject to the above boundary conditions. One obtains

$$\tau(r_0)=\int_a^{r_0}dx\,\frac{x^{1-d}}{D(x)}\exp[\beta U(x)]\int_x^R dy\,y^{d-1}\exp[-\beta U(y)]$$
$$+\frac{1}{\kappa}\,a^{1-d}\exp[\beta U(a)]\int_a^R dy\,y^{d-1}\exp[-\beta U(y)]\ . \tag{2.15}$$

This expression entails a major result of our paper. The second term of Eq. (2.15), i.e., the one proportional to κ^{-1}, bears a simple physical interpretation. The probability $p_{\mathrm{eq}}(r)$ of finding a particle at equilibrium in the absence of any reaction at r is

$$p_{\mathrm{eq}}(r)=\left\{\int_a^R dy\,y^{d-1}\exp[-\beta U(y)]\right\}^{-1} r^{d-1}\exp[-\beta U(r)]\ . \tag{2.16}$$

Equation (2.15) can then be rewritten as

$$\tau(r_0)=\int_a^{r_0}dx[D(x)p_{\mathrm{eq}}(x)]^{-1}\int_x^R dy\,p_{\mathrm{eq}}(y)+[\kappa p_{\mathrm{eq}}(a)]^{-1}\ . \tag{2.17}$$

In the limit $\kappa\to\infty$ corresponding to the Smoluchowski boundary condition, the second term vanishes. In the opposite limit $\kappa\to 0$, i.e., small probability of reaction, $\tau(r_0)$ becomes independent of r_0:

$$\tau(r)=[\kappa p_{\mathrm{eq}}(a)]^{-1} \quad (\kappa\to 0)\ . \tag{2.18}$$

The physical interpretation of this equation is the following: For small κ the particles react slowly, and starting at r_0 first assume and then during the reaction maintain the equilibrium distribution; in line of this argument the effective reaction rate constant $[\tau(r_0)]^{-1}$ is proportional to $p_{\mathrm{eq}}(a)$ and to the microscopic reaction rate constant κ.

Finally, to obtain τ [Eq. (1.10)] we average $\tau(r_0)$ over the equilibrium initial distribution in the region $a\leq r\leq R$, i.e.,

$$\tau=\left\{\int_a^R dy\,y^{d-1}\exp[-\beta U(y)]\right\}^{-1}\int_a^R dr_0\,r_0^{d-1}\exp[-\beta U(r_0)]\,\tau(r_0)\ .$$

By virtue of Eq. (2.17) and changing orders of integration we have

$$\tau=\left\{\int_a^R dx\,x^{d-1}\exp[-\beta U(x)]\right\}^{-1}\int_a^R dx\,\frac{x^{1-d}}{D(x)}\exp[\beta U(x)]\left\{\int_x^R dy\,y^{d-1}\exp[-\beta U(y)]\right\}^2+[\kappa p_{\mathrm{eq}}(a)]^{-1}\ . \tag{2.19}$$

By means of Eq. (2.16) this can be written

$$\tau=\int_a^R dx[D(x)p_{\mathrm{eq}}(x)]^{-1}\left[\int_x^R dy\,p_{\mathrm{eq}}(y)\right]^2+[\kappa p_{\mathrm{eq}}(a)]^{-1}\ . \tag{2.20}$$

In subsequent applications of this equation we shall assume that D(x) is independent of position.

Before considering these applications we like to indicate briefly how the above procedure can be used to calculate the area under autocorrelation functions when the dynamics of the underlying process is described by a

TABLE I. Analytical formulas for average passage times describing reactions involving free diffusion in one, two, and three dimensions.[a]

Dimension	$\tau D/R^2$
1	$(1-x)^2/3+D(1-x)/\kappa R$
2	$(x^2-3)/8-(\ln x)/2(1-x^2)+D(1-x^2)/2\kappa Rx$
3	$(1-x)^2(5+6x+3x^2+x^3)/15x(1+x+x^2)+D(1-x^3)/3\kappa Rx^2$

[a]With radiation boundary conditions $\partial\tau/\partial r=(\kappa/D)\tau$ imposed at $r=a$ and reflection boundary condition $\partial\tau/\partial r=0$ at $r=R$, $x=a/R$.

Smoluchowski-type equation. The autocorrelation function $C_A(t)$ for a certain property $A(r)$ is

$$C_A(t)=\iint d\mathbf{r}_0\, d\mathbf{r}\, A(\mathbf{r})A(\mathbf{r}_0)p_{\mathrm{eq}}(\mathbf{r}_0)p(\mathbf{r},t/\mathbf{r}_0,0), \quad (2.21)$$

where $p_{\mathrm{eq}}(\mathbf{r})=\lim_{t\to\infty}p(\mathbf{r},t/\mathbf{r}_0,0)$. We can assume without loss of generality that $C_A(0)=1$ and $\langle A\rangle=0$ with

$$\langle F\rangle=\int d\mathbf{r}_0\, p_{\mathrm{eq}}(\mathbf{r}_0)F(\mathbf{r}_0)\,. \quad (2.22)$$

The previous theory can immediately be generalized to reduce the calculation of

$$\tau_A=\int_0^\infty dt\, C_A(t) \quad (2.23)$$

to quadrature. For this purpose we write Eq. (2.23) as

$$\tau_A=\int d\mathbf{r}_0\, p_{\mathrm{eq}}(\mathbf{r}_0)A(\mathbf{r}_0)\tau_A(\mathbf{r}_0)\,, \quad (2.24)$$

where

$$\tau_A(\mathbf{r}_0)=\int_0^\infty dt\int d\mathbf{r}\, A(\mathbf{r})p(\mathbf{r},t/\mathbf{r}_0,0)\,. \quad (2.25)$$

In complete analogy to the derivation of Eq. (2.12) one can show

$$\mathbf{L}^+(\mathbf{r}_0)\,\tau_A(\mathbf{r}_0)=-A(\mathbf{r}_0)\,, \quad (2.26)$$

with $\mathbf{L}^+$ given by Eq. (2.4). Solving this differential equation subject to the appropriate boundary conditions, τ_A can be obtained by evaluating the integral in Eq. (2.24). Finally, in analogy to Eq. (1.1), the autocorrelation function can be approximated as

$$C_A(t)\cong\exp(-t/\tau_A)\,. \quad (2.27)$$

III. APPLICATION TO PROBLEMS INVOLVING FREE DIFFUSION

We consider a particle, diffusing freely, which is trapped between two concentric spheres of radii a and R. We describe the absorption of the particle at $r=a$ by a radiation boundary condition. The boundary at $r=R$ is assumed to be impenetrable, i.e., described by a "reflective" boundary condition. For $U(r)=0$ the integrals in Eq. (2.19) determining the average passage time τ are all elementary. The expressions for τ thus obtained for motion in one, two, and three dimensions are given in Table I. The result for the one-dimensional case, when $\kappa\to\infty$, had been obtained previously by Adam and Delbrück[4] using an approach based on solving the time-dependent diffusion equation. For the cases of two- and three-dimensional motion these authors were unable to obtain simple answers. For example, for the two-dimensional situation they found (for $\kappa\to\infty$)[1]

$$D\tau/R^2=\sum_{n=0}^{\infty}\frac{4}{y_n^4(1-x^2)}\,\frac{[J_1(y_n)]^2}{[J_0(xy_n)]^2-[J_1(y_n)]^2}\,, \quad (3.1)$$

where y_n are the roots of the transcendental equation

$$J_0(xy)Y_1(y)-Y_0(xy)J_1(y)=0\,,$$

$x=a/R$, and $J_n(y)$ and $Y_n(y)$ are Bessel functions. This expression is identical to the simple result in Table I.

Karplus and Weaver[5] generalized the approach of Adam and Delbrück to radiation boundary conditions. By a rather involved analysis these authors determined τ in the limit $\kappa\to 0$. Their results agree with those in Table I in this limit.

In Fig. 1 we compare for a reaction involving free one-dimensional diffusion and described by a Smoluchowski boundary condition ($\kappa\to\infty$) the exact[1] $\Sigma(t)$ defined in Eq. (1.3a) with its first passage time approximation [Eq. (1.1)]:

$$\Sigma_{\mathrm{approx}}(t)=\exp[-3Dt/(R^2-a^2)]\,.$$

Considering the simplicity of this expression the agreement appears satisfactory, except at short times. It should be emphasized, however, that the example of Fig. 1 constitutes the most demanding test for the passage time approximation for free diffusion processes. If κ were finite or for diffusion in higher-dimensional spaces, better agreement is obtained. This is demonstrated in Tables II and III which compare the exact and approximate $\Sigma(t)$ for three-dimensional free diffusion. Table II contains the results for a small diffusion space with $a/R=0.5$. In case of the Smoluchowski boundary condition the agreement between $\Sigma(t)$ and $\Sigma_{\mathrm{approx}}(t)$ is clearly better than in Fig. 1. Finite κ leads to a slow down of the reaction and drastically improves the agreement. Increasing the diffusion space likewise slows

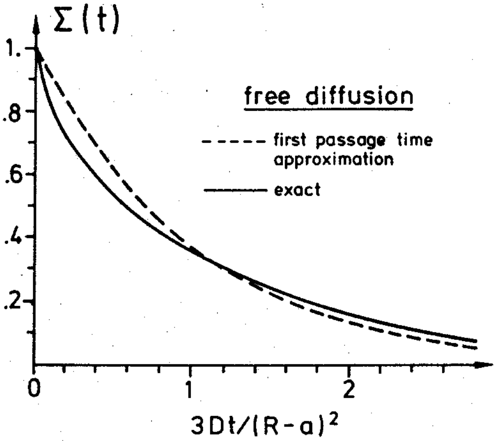

FIG. 1. Comparison of $\Sigma(t)$ and $\Sigma_{\mathrm{approx}}(t)$ for a reaction involving one-dimensional free diffusion in the interval $[a,R]$ assuming a reflective boundary at $x=R$ and a Smoluchowski boundary condition at $x=a$.

TABLE II. Comparison of exact and approximate $\Sigma(t)$ for reactions involving three-dimensional free diffusion between two concentric spheres ($x = 0.5$).

	$\kappa R/D \to \infty$		$\kappa R/D = 0.1$	
Dt/R^2	Exact[a]	Approx[b]	Exact[c]	Approx[b]
0	1.000	1.000	1.000	1.000
0.02	0.829	0.888		
0.04	0.738	0.789		
0.06	0.661	0.701		
0.10	0.532	0.553		
0.20	0.309	0.306		
0.40	0.104	0.094		
0.60	0.035	0.029		
1.00	0.004	0.003	0.917	0.919
2.00			0.844	0.845
4.00			0.714	0.713
10.00			0.435	0.430
20.00			0.189	0.185

[a] According to Adam and Delbrück.
[b] $\exp(-Dt/R^2\tau)$ with τ according to Table I.
[c] Numerical integration of the diffusion equation.

down the reaction process and hence improves the passage time approximation as demonstrated in Table III with $a/R = 0.1$.

The association of the repressor and the operator situated on a DNA strand, a reaction puzzling for its short time course, has been described by Schranner and Richter[11] as a two step process: (1) the diffusion of the repressor between two concentric cylinders to be trapped on the interior cylinder, i.e., the DNA strand; (2) one-dimensional diffusion of the repressor along the DNA strand to be bound by the operator. In the case that the trapping to the DNA strand is irreversible, the overall process entails two first-order reactions with rates τ_1^{-1} and τ_2^{-1}, say. One can readily show that in this case the overall reaction is approximately described by a single rate constant τ^{-1} given by

$$\tau = \tau_1 + \tau_2 \, . \tag{3.2a}$$

From Table I we have ($\kappa \to \infty$)

$$\tau_1 = \frac{R^4 \ln(R/b)}{2D_1(R^2 - b^2)} - \frac{3R^2 - b^2}{8D_1} \, , \tag{3.2b}$$

$$\tau_2 = L^2/3D_2 \, , \tag{3.2c}$$

where D_1 and D_2 represent the diffusion coefficients for reaction steps (1) and (2), respectively, and $2L$ is the length of the DNA molecule with the operator at the center. Equations (3.2) agree with the result of Ref. 11 which were obtained by means of an involved analysis. Consulting Table I, it is simple to account approximately for the effect of a finite κ, i.e., a situation in which the repressor is not trapped with unit probability to the DNA strand.

IV. INTRACHAIN REACTIONS OF POLYMERS

The theory of intrachain reactions of polymers has been discussed in detail by Wilemski and Fixman[1] and further analyzed by Doi[2,3] both for the Rouse–Zimm and the harmonic spring model. The quantity of interest is $\Sigma(t)$, the fraction of polymers yet unreacted at time t. In what follows we choose $\Sigma(t)$ to be normalized such that $\Sigma(0) = 1$. We assume that the dynamics of the end-to-end distance r is described by a Smoluchowski-type equation. Although we will be mainly concerned with the harmonic spring model, i.e., $U(r) \sim r^2$, the theory presented in this section applies to any effective potential $U(r)$. In particular, one may employ a potential which accounts for excluded volume effects. The major defect of the Smoluchowski-type polymer models for the chain dynamics is the implicit assumption that the relaxation of the distribution of end-to-end distances towards the equilibrium distribution in the absence of reaction is governed by a single time constant, i.e., the "diffusion coefficient." The purpose of this section is to show that the average passage time τ is easily calculated for such description and that $\Sigma_{\text{approx}}(t)$ [Eq. (1.1)] provides an excellent approximation to the corresponding time course of the reaction.

In the harmonic spring model for a d-dimensional polymer the potential appearing in the Smoluchowski equation is

$$U(r) = dr^2/2\beta L^2 \, , \tag{4.1}$$

where L is the mean distance between the polymer ends, i.e., $L^2 = \langle r^2 \rangle$. The corresponding equilibrium end-to-end distribution is

$$p_{\text{eq}}(r) = cr^{d-1}\exp(-dr^2/2L^2) \, , \tag{4.2}$$

representing a Gaussian chain. For a calculation of the average passage time on the basis of Eq. (2.19) we introduce the dimensionless parameters

$$\alpha = (d/2)^{1/2} a/L \, , \tag{4.3a}$$

$$\lambda = (d/2)^{1/2} \alpha^{d-1} \kappa L/D \, , \tag{4.3b}$$

TABLE III. Comparison of exact and approximate $\Sigma(t)$ for reactions involving three-dimensional diffusion between two concentric spheres ($x = 0.1$).

	$\kappa R/D \to \infty$		$\kappa R/D = 0.1$	
Dt/R^2	Exact[a]	Approx[b]	Exact[c]	Approx[b]
0	1.000	1.000	1.000	1.000
0.2	0.925	0.929		
0.4	0.860	0.863		
0.6	0.800	0.803		
0.8	0.744	0.746		
1.0	0.692	0.694		
2.0	0.481	0.481	0.992	0.994
4.0	0.233	0.232	0.986	0.988
8.0	0.055	0.054	0.975	0.976
10.0	0.026	0.026	0.969	0.971
20.0	0.001	0.001	0.941	0.942
100.0			0.744	0.742
200.0			0.554	0.551

[a] According to Adam and Delbrück.
[b] $\exp(-Dt/R^2\tau)$ with τ values according to Table I.
[c] Numerical integration of the diffusion equation.

and take the limit $R \to \infty$. This yields

$$(dD/2L^2)\tau = \left[\int_\alpha^\infty dx\, x^{d-1} \exp(-x^2)\right]^{-1} \int_\alpha^\infty dx\, x^{1-d} \exp(x^2) \left[\int_x^\infty dy\, y^{d-1} \exp(-y^2)\right]^2 + \lambda^{-1} \exp(\alpha^2) \int_\alpha^\infty dy\, y^{d-1} \exp(-y^2) . \tag{4.4}$$

We want to consider first the simplest case, the end-end reaction of a one-dimensional polymer described by the Smoluchowski boundary condition $\lambda \to \infty$. Assuming the reaction occurs every time the ends meet, i.e., $\alpha = 0$, Eq. (4.4) becomes

$$(D/2L^2)\tau = \left[\int_0^\infty dx \exp(-x^2)\right]^{-1} \int_0^\infty dx \exp(x^2) \times \left[\int_x^\infty dy \exp(-y^2)\right]^2 . \tag{4.5}$$

By virtue of[12]

$$\left[\int_x^\infty dy \exp(-y^2)\right]^2 = \int_1^\infty dt\, (1+t^2)^{-1} \exp[-x^2(1+t^2)]$$

the integral is evaluated readily to yield

$$\tau = L^2 \ln 2/D \tag{4.6}$$

and thus

$$\Sigma_{\text{approx}}(t) = \exp(-Dt/L^2 \ln 2) . \tag{4.7}$$

In the Appendix we derive an analytical expression for the exact $\Sigma(t)$:

$$\Sigma(t) = (2/\pi) \sin^{-1}[\exp(-Dt/L^2)] . \tag{4.8}$$

Figure 2 compares the expressions (4.7) and (4.8) to demonstrate that the passage time approximation is satisfactory indeed. However, just as for the case of free diffusion the correspondence between the exact and the approximate $\Sigma(t)$ improves on going to higher dimensions and to radiation boundary conditions.

The Taylor expansion of Eq. (4.8) in terms of $\exp(-Dt/L^2)$, i.e.,

$$\Sigma(t) = \frac{2}{\pi} \sum_{k=0}^{\infty} (2k)! [2^{2k} (k!)^2 (2k+1)]^{-1} \exp[-(2k+1)Dt/L^2)] , \tag{4.9}$$

corresponds to the eigenvector expansion of the one-dimensional polymer reaction. This yields the eigenvalues

$$\lambda_k = -(2k+1)D/L^2 , \quad k = 0, 1, 2, \ldots . \tag{4.10}$$

The passage time approximation describes $\Sigma(t)$ as a single exponential decay corresponding to a decay constant $\lambda \approx -1.4\ D/L^2$. The validity of this description depends (1) on a large spacing between the eigenvalues such that $\Sigma(t)$ over most of its decay is dominated by $\lambda_0 \approx \lambda$; (2) on the condition for the coefficients c_k multiplying $\exp(\lambda_k t)$ in Eq. (5.9): $c_0 \gg c_k$, $k \neq 0$. Evaluation yields for c_k, $k = 0, 1, 2, \ldots$ the values 0.64, 0.11, 0.05, 0.03, 0.02, ..., i.e., the lowest eigenvalue accounts for only 64% of the total particle decay, and the remaining particles decay faster. The first passage time approximation assumes that all particles decay with a single rate λ, albeit somewhat larger than λ_0 to account for the fast decay contribution to $\Sigma(t)$. These observations actually reflect general conditions for the validity of the passage time approximation.

We next consider three-dimensional polymers. For the integrals in Eq. (4.4) to exist, α cannot be taken zero. This would also be physically unreasonable as $\alpha = 0$ implies a vanishingly small reaction domain. For $\alpha > 0$, the integrals in Eq. (4.4) cannot be evaluated analytically. However, for most situations of interest, α is small and hence an expansion of τ in terms of α yields accurate passage times. For example, a polymer with $L = 50$ Å and a reaction radius $a = 5$ Å yields $\alpha = 0.12$. The required expansion is

$$(3D/L^2)\tau = \sqrt{\pi}/2\alpha + (\ln 2 - 1) - \alpha\sqrt{\pi}/2 + 4\alpha^2/3 + \sqrt{\pi}(1+\alpha^2)/2\lambda + 0(\alpha^3) . \tag{4.11}$$

We have established by direct numerical integration of Eq. (4.4) that this expansion is accurate to within 6% for $\alpha < 0.5$ and $\lambda > 1$; for $\alpha < 0.3$ the error is smaller than 1%. The leading term in expansion (4.11), which is proportional to α^{-1}, has been derived previously by Sunagawa and Doi[3] employing a rather cumbersome approach.

In Table IV the exact and approximate $\Sigma(t)$ for a three-dimensional polymer are compared. For the Smoluchowski boundary condition ($\lambda \to \infty$), the most stringent test, the agreement found is much better than that for the one-dimensional case presented in Fig. 2, the agreement holding even at relatively short times. For smaller values of α the agreement should be even better. For larger values of α it becomes poorer. For example, when $\alpha = 0.7$ (this is a rather unphysical value since it implies the reaction occurs when the ends approach 57% of the root mean square end-to-end distance) at $3\ Dt/L^2 = 0.5$, the exact $\Sigma(t)$ is 0.465 while the approximate value is 0.527. Table IV shows that for smaller reaction probabilities ($\lambda = 0.1$) the agreement between $\Sigma(t)$ and $\Sigma_{\text{approx}}(t)$ is dramatically improved.

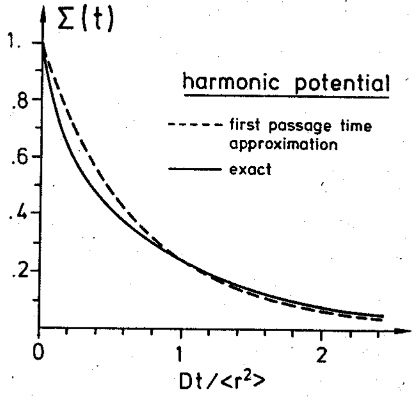

FIG. 2. Comparison of $\Sigma(t)$ and $\Sigma_{\text{approx}}(t)$ for a reaction involving the ends of a one-dimensional Gaussian chain assuming a Smoluchowski boundary condition at $x = 0$.

TABLE IV. Comparison of exact and approximate $\Sigma(t)$ for the reaction of a three-dimensional polymer with $\alpha = 0.2$.[a]

	$\lambda \to \infty$		$\lambda = 0.1$	
$3Dt/L^2$	Exact	Approx[b]	Exact	Approx[b]
0	1.000	1.000	1.000	1.000
0.5	0.858	0.882	0.960	0.963
1.0	0.757	0.779	0.924	0.927
2.0	0.593	0.606	0.855	0.859
4.0	0.364	0.368	0.734	0.738
6.0	0.224	0.223	0.629	0.634
8.0	0.138	0.135	0.540	0.545
10.0	0.085	0.082	0.463	0.468
20.0			0.215	0.219
40.0			0.046	0.048

[a] This value of α implies that the reaction can occur when the polymer ends reach 16% of the root mean square end-to-end distance.

[b] $\exp(-3Dt/L^2\tau)$ with τ standing for the average mean passage time.

The range of validity of the first passage time approximation can be rationalized as follows: For slow end-end reactions, i.e., if the ratio of the minimum reaction distance over the average polymer length L and/or the reaction probability (i.e., κ) are small, the polymer diffusion maintains the equilibrium end-to-end distribution at each instance of the reaction course and the polymer appears to react by a first-order process like a species without any internal degrees of freedom.

Within the framework of a Smoluchowski-type description of polymers one is not limited to the harmonic spring model $[U(r) \sim x^2]$. Haas *et al.*,[13] for example, fitted the end-to-end distribution as measured by fluorescence energy transfer to a function suggested by Edwards[14]:

$$p_{eq}(r) = cr^2 \exp[-\gamma(r-\delta)^2] . \tag{4.12}$$

For a polymer with $L = 22.5$ Å these authors determined the parameter values $\gamma = 0.01$ and $\delta = 16.7$. Thus, the measured end-to-end distribution is markedly non-Gaussian. Abstracting the free energy $U(r)$ from Eq. (4.12), the first passage time $(\lambda \to \infty)$ can be determined by numerical integration. Assuming that a reaction occurs when the end-to-end distance is 6 Å, we found $D\tau = 1200$ Å^2. The corresponding evaluation for a Gaussian polymer yields a much shorter first passage time $D\tau = 380$ Å^2. Thus, for the same diffusion coefficient the chain is predicted to react three times more slowly when excluded volume effects are accounted for in an approximate manner. This is primarily a consequence of the fact that sterical interactions partially hinder the two polymer ends from reaching each other.

V. CONCLUSION

We have considered in this paper reaction systems governed by a Smoluchowski-type diffusion equation. In many applications single relaxation (passage) times can account for the behavior of such systems. On the basis of the theory of first passage times, we have derived differential equations and appropriate boundary conditions which yield directly the desired relaxation times. For the case of the particle number of reactive systems undergoing various diffusion processes, we have shown that these differential equations are solved by elementary quadrature. In particular, we could generalize the Smoluchowski boundary condition, describing diffusion controlled reactions, to the radiation boundary condition, accounting for non-diffusion controlled processes. We have also demonstrated, for a few cases amenable to either analytical or numerical solution, to what extent processes involving diffusion and reaction can be described by a single relaxation time, i.e., as first-order reactions. Our applications considered reactions involving free diffusion over finite one-, two, and three-dimensional domains, e.g., the repressor-operator association, and intramolecular reactions of polymer end groups. In all these applications the concept of a single relaxation (passage) time appeared very suitable. It is expected that this concept, because of its mathematical simplicity and its close correspondence to experimental observations, which in most cases do not yield the fine details of more complete descriptions, will prove fruitful for many further applications.

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APPENDIX

In the following we will derive the simple analytical expression (4.8) for $\Sigma(t)$ describing the end-to-end reaction of a one-dimensional Gaussian chain. The Smoluchowski equation for this problem is

$$\frac{\partial}{\partial t} p(x, t/x_0, 0) = D\left(\frac{\partial^2}{\partial x^2} + L^{-2}\frac{\partial}{\partial x}x\right) p(x, t/x_0, 0) . \tag{A1}$$

The reaction will be accounted for by a Smoluchowski boundary condition imposed at $x = 0$. The normalized equilibrium distribution for the chain without reaction is $(-\infty < x < \infty)$

$$p_{eq}(x) = (2\pi L^2)^{-1/2} \exp(-x^2/2L^2) , \tag{A2}$$

with $\langle x^2 \rangle = L^2$. The solution of Eq. (A1) in the absence of reaction is[17]

$$\hat{p}(x, t/x_0, 0) = (2\pi L^2 T)^{-1/2} \exp[-(x - x_0 e^{-Dt/L^2})^2/2L^2 T] , \tag{A3}$$

where $T = 1 - \exp(-2Dt/L^2)$. The Green's function satisfying the Smoluchowski boundary condition at $x = 0$ is constructed readily by the method of images $(x > 0,\ x_0 > 0)$:

$$p(x, t/x_0, 0) = \hat{p}(x, t/x_0, 0) - \hat{p}(x, t/-x_0, 0) . \tag{A4}$$

The reaction rate is then

$$-\frac{\partial}{\partial t}\Sigma(x_0, t) = -\int_0^\infty dx \frac{\partial}{\partial t} p(x, t/x_0, 0)$$

$$= D\left[\frac{\partial}{\partial x} p(x, t/x_0, 0)\right]_{x=0}$$

$$= \frac{2Dx_0}{L^2 T(2\pi L^2 T)^{1/2}} \exp(-x_0^2 e^{-2Dt/L^2}/2L^2 T) . \tag{A5}$$

Averaging over $p_{eq}(x_0)$, $x_0 > 0$ yields

$$\frac{\partial}{\partial t}\Sigma(t) = - \frac{2D\exp(-Dt/L^2)}{\pi[1-\exp(-2Dt/L^2)]^{1/2}} . \tag{A6}$$

A factor of 2 has been included because $p_{eq}(x_0)$ given by Eq. (A2) is normalized on the interval $-\infty < x < \infty$. Integrating Eq. (A6) subject to the initial condition $\Sigma(0) = 1$ gives finally

$$\Sigma(t) = 2\pi^{-1}\sin^{-1}[\exp(-Dt/L^2)] . \tag{A7}$$

As a test one may evaluate from this result the first passage time τ according to the definition $\tau = \int_0^\infty \Sigma(t)\,dt$. Substitution of $y = e^{-x}$ yields, by virtue of $\int_0^1 dy\, y^{-1}\sin^{-1} y = (\pi/2)\ln 2$, expression (4.6) which in Sec. IV had been obtained by integrating the passage time equation.

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