PHYSICAL REVIEW E VOLUME 47, NUMBER 4 APRIL 1993

Competitive and noncompetitive reversible binding processes

Noam Agmon
Department of Physical Chemistry and the Fritz Haber Research Center, The Hebrew University, Jerusalem 91904, Israel

(Received 21 December 1992)

This work treats many-body aspects in an idealized class of reversible binding problems involving a static binding site with many diffusing point particles. In the noncompetitive limit, where no restriction exists on the number of simultaneously bound particles, the problem reduces to reversible aggregation. In the competitive limit, where only one particle may be simultaneously bound, it becomes a model for a pseudounimolecular reaction. The general formalism for both binding limits involves the exact microscopic hierarchy of diffusion equations for the N-body density functions. In the noncompetitive limit of independent particles, the hierarchy admits an analytical solution which may be viewed as a generalization of the Smoluchowski aggregation theory to the (idealized) reversible case. In the competitive limit, the hierarchy enables straightforward derivation of useful identities, determination of the ultimate equilibrium solution, and justification for several approximations. In particular, the utility of a density-expansion, short-time approximation is investigated. The approximation relies on the ability to solve the hierarchy numerically for a small number of particles. This direct-propagation algorithm is described in the numerical section.

PACS number(s): 05.40.+j, 82.20.Fd, 87.10.+e, 87.15.Rn

I. INTRODUCTION

The present work treats idealized many-body, reversible binding processes in condensed media. One assumes that noninteracting, point particles diffuse in a medium containing a static, spherical binding site. If only one particle may be bound at a given time the binding is termed "competitive" whereas if the site admits any number of particles the binding is "noncompetitive." Given an initial (out of equilibrium) distribution, one monitors the probability that one or more particles are bound at any later time. It is noted that competitive and noncompetitive binding are two extreme cases of a binding site which is limited to the binding of k particles at most. The general process may be termed binding of order k. Most physically significant are the cases $k = \infty$ (noncompetitive) and $k = 1$ (competitive binding), to be discussed below.

Noncompetitive binding is an idealized aggregation process. Aggregation was first considered by Smoluchowski [1] and reviewed by Chandrasekhar [2]. In this approach, irreversible aggregation of different size clusters is described by a set of rate equations with rate parameters obtained from steady-state diffusion theory. These depend on the radius and diffusion coefficient of the aggregates, which are functions of their size. The rate-equation approach has been extended to various cases [3] including reversible aggregation, which appears to be important for phospholipid vesicles [4, 5]. Recently, interest has shifted to the geometry of the clusters and their fractal nature [6]. With the exception of Ref. [7], mainly irreversible aggregation has been considered. In the present model, clusters have no geometry since they are comprised of point particles. Thus one has an ideal case where the only observable is the number of particles within an aggregate (the aggregate size). Additionally, for a static binding site cluster-cluster aggregation cannot occur. These limitations allow rigorous determination of the aggregate size distribution in the reversible case.

The Smoluchowski model was shown to be an exact description of the microscopic many-body dynamics in two limiting cases. The first is irreversible aggregation of point clusters on the line, provided that clusters of all sizes have the same diffusion coefficient [8]. This polymerization process includes both single-species annihilation and coalescence as special cases. For the latter, the exact interparticle distance distribution can also be obtained [9]. The other limiting problem is fluorescence quenching of a static excited molecule by moving point quenchers [10, 11]. This solution can be extended to a moving molecule by a density expansion [12]. Since the excited molecule is quenched irreversibly upon the arrival of the first quencher, the quenching process is isomorphic to irreversible binding of the first monomer in the noncompetitive binding model. It is therefore not totally surprising that an analytical solution can be obtained for all the aggregation states also in the reversible case.

Competitive binding represents a pseudounimolecular reaction in solution under conditions that one of the reactants is in large excess. This is a special case of a bimolecular reaction, the study of which was pioneered by Waite [13], Noyes [14], and others. Recent investigations of irreversible bimolecular reactions have focused on the effect of fluctuations in the initial particle distribution on the asymptotics of the reaction [15–19]. In reversible reactions initial fluctuations are not likely to be important because each dissociation event regenerates the free site with a distribution of particles around it which eventually becomes unrelated to the initial distribution.

Recently, attention has been directed to reversible diffusion-influenced reactions [20–35]. Among various approaches used are convolution relations [22, 24, 25, 27], a "bimolecular" boundary condition [29, 30], mean-field approaches [21, 31–33], occupation number formalism [31], and statistical-mechanical approaches [35]. These approaches usually do not specify the microscopic diffusion equations that form the starting point of the derivation. An exception is the occupation-number formalism of Szabo and Zwanzig [31], which should be obtainable from the exact hierarchy of diffusion equations presented below. When truncated after a single binding event the hierarchy describes competitive binding, while if not truncated it represents noncompetitive binding.

Several experimentally important situations fall under the title of competitive binding. Examples are substrates competing for binding to the active site of an enzyme or protons competing for binding to a bulky base molecule. In both cases a large molecule (enzyme, base) serves as the binding site and may therefore be considered static. We [36–38] have reported reversible geminate recombination of protons following the photodissociation of an excited hydroxyaryl molecule (*R*OH acid). The fluorescence intensity of the excited undissociated acid quantitatively fits the solution of the time-dependent Smoluchowski equation for a Coulomb field and with the back-reaction [39, 40] boundary condition imposed at the contact separation. A characteristic power-law ($t^{-3/2}$) decay is clearly observed [37,38(a)]. By lowering the *p*H, a competitive many-body environment is obtained where the homogeneous protons compete with the geminate proton for rebinding. Under such conditions we have found [41] that the binding probability follows a power-law approach to equilibrium. Unlike the prediction of some mean-field approximations [29, 31, 32] the asymptotic power seems to increase with increasing proton concentration. The origin of this discrepancy is currently unclear. Asymptotic analysis of the equations presented below (to be carried out separately) could shed some light on this problem.

This paper is structured as follows: Sec. II defines the quantities under investigation; Sec. III presents the general many-body binding equations; Sec. IV gives their solution in the limit of noncompetitive binding, where all the particles are mutually independent; Sec. V derives identities and approximations for competitive binding. Finally, Sec. VI discusses the direct propagation algorithm used to solve these equations numerically for a small number of particles.

II. DEFINITION OF THE BINDING PROBABILITIES

Let us consider N identical, noninteracting particles diffusing in a d-dimensional viscous medium with a reversible trap of radius a located at the origin. The introduction of an interaction between the particles will complicate the following equations considerably and is therefore not considered here. Correlations between particles are only introduced at the surface of the trap and then only for competitive binding. Otherwise the particles move freely and randomly with a diffusion constant D. The N-particle, time- (t) dependent probability density function will be denoted by $p_N(x_1, x_2, ..., x_N, t)$, where x_i is the distance of the ith particle from the origin. x_i may assume any value between a and R (which can possibly be infinite). In addition, the N spatial coordinates may each assume one discrete value representing a bound particle and denoted by an asterisk. For example, the vector $(*, x_2, ..., x_N)$ implies that particle 1 is bound while the others are free to diffuse. This differs from the situation described by the vector $(a, x_2, ..., x_N)$, where particle 1 has reached the trap surface but is yet unbound. Trapping and detrapping may occur at $r = a$ with the association and dissociation rate coefficients κ_a and κ_d, respectively. The following exposition concentrates primarily on the binding states of the site. These are described mathematically by the time-dependent probability for having m out of the N particles simultaneously bound, to be denoted by $q_{N,m}(t)$. Thus $0 \leq m \leq N$.

The binding-state probabilities are defined as follows: The probability of having no particle bound, sometimes called the survival probability and denoted by $S_N(t)$, is given by

$$q_{N,0}(t) = S_N(t) \equiv \int_a^R \cdots \int_a^R p_N(x_1, \ldots, x_N, t)\, dV_1 \cdots dV_N \,, \tag{2.1}$$

where $dV_i \equiv \gamma_d x_i^{d-1} dx_i$ is a volume element, $\gamma_d \equiv 2\pi^{d/2}/\Gamma(d/2)$ is the appropriate geometric factor, namely, 2, 2π, and 4π for d =1, 2, and 3, respectively (in one dimension, $\gamma_d = 1$ if only half the line is considered). The probability of having exactly one particle bound is the sum over all single binding configurations

$$q_{N,1}(t) = \int_a^R \cdots \int_a^R [p_N(*, x_2, \ldots, x_N, t)\, dV_2 \cdots dV_N + \cdots + p_N(x_1, \ldots, x_{N-1}, *, t)\, dV_1 \cdots dV_{N-1}] \,. \tag{2.2a}$$

When all N particles start from the same initial condition, for example when all are initially bound or initially randomly distributed, the N terms in (2.2a) become identical so that

$$q_{N,1}(t) = N \int_a^R \cdots \int_a^R p_N(*, x_2, \ldots, x_N, t)\, dV_2 \cdots dV_N \,. \tag{2.2b}$$

In a similar fashion one defines $q_{N,m}(t)$ for $1 < m \leq N$. For equivalent particles

$$q_{N,m}(t) = \binom{N}{m} \int_a^R \cdots \int_a^R p_N(*, \ldots, *, x_{m+1}, \ldots, x_N, t)\, dV_{m+1} \cdots dV_N \,. \tag{2.3}$$

The binomial factor,

$$\binom{N}{m} \equiv N(N-1)\cdots(N-m+1)/m!,$$

represents all the permutations leading to m bound particles. The above probabilities normalize initially to unity

$$\sum_{m=0}^{N} q_{N,m}(0) = 1 . \tag{2.4}$$

The equations introduced below will have the property that they conserve probability, so the normalization condition will be shown to hold for $t > 0$ as well. For competitive binding, only $q_{N,0}$ and $q_{N,1}$ differ from zero, whereas in the noncompetitive case all of the binding states are permissible.

III. THE MICROSCOPIC BINDING EQUATIONS

The N-particle density distribution obeys an N-dimensional diffusion equation with appropriate boundary conditions. The terms appearing in the boundary conditions themselves obey certain diffusion equations. In order to deduce these equations, consider first the one-particle equation which is to be generalized to 2 and subsequently to N particles.

A. The single-particle equations

The one-particle equation is frequently used to treat the reversible geminate recombination problem [36–38]

$$\frac{\partial p_1(x,t)}{\partial t} = \mathcal{L} p_1(x,t) , \quad a \le x \le R , \tag{3.1}$$

where the diffusion operator is defined by

$$\mathcal{L} \equiv x^{1-d} \frac{\partial}{\partial x} D x^{d-1} \frac{\partial}{\partial x} = -\gamma_d^{-1} x^{1-d} \frac{\partial}{\partial x} \mathcal{J} . \tag{3.2}$$

Here $\mathcal{J} \equiv -\gamma_d x^{d-1} D \partial/\partial x$ is the diffusive-flux operator. Equation (3.1) is augmented by boundary conditions. At $x = R$ the boundary is reflective,

$$\mathcal{J} p_1(x,t)|_{x=R} = 0 , \tag{3.3}$$

so that particles cannot leak through the outer sphere. At the "contact separation" a, a backreaction (reversible) boundary condition [39, 40, 37] is imposed

$$\mathcal{J} p_1(x,t)|_{x=a} = \kappa_d p_1(*,t) - \kappa_a p_1(a,t) . \tag{3.4}$$

As compared with other notations in the literature [36], $\kappa_a = \gamma_d a^{d-1} \kappa_r$. Equation (3.4) states that the flux into the binding site is the difference between an association (trapping) term and a dissociation (detrapping) term. When no dissociation occurs, $\kappa_d = 0$ and the backreaction boundary condition reduces to the "radiation" boundary condition which depicts irreversible association. When, in addition, $\kappa_a \to \infty$ the radiation boundary condition reduces to the absorbing (Smoluchowski) boundary condition, $p_1(a,t) = 0$.

To complete the single-particle equations, one needs to consider the bound fraction, $p_1(*,t)$. It obeys a simple kinetic equation

$$\frac{dp_1(*,t)}{dt} = \kappa_a p_1(a,t) - \kappa_d p_1(*,t) , \tag{3.5}$$

containing no diffusive terms. One expects that the total probability of finding the particle somewhere (either bound or unbound) normalizes to unity, therefore

$$p_1(*,t) = 1 - S_1(t) . \tag{3.6}$$

This identity follows by integrating (3.1) over space, substituting (3.3)–(3.5) to obtain

$$\frac{dS_1(t)}{dt} = \int_a^R dV \mathcal{L} p_1(x,t) = \mathcal{J} p_1(x,t)|_{x=a} = -\frac{dp_1(*,t)}{dt} , \tag{3.7}$$

and integrating over time. In the literature [36, 24], $1 - S_1(t)$ is often used for $p_1(*,t)$. In the notations introduced in Sec. II, $q_{1,0}(t) = S_1(t)$ while $q_{1,1}(t) = p_1(*,t)$. Therefore $q_{1,0}(t) + q_{1,1}(t) = 1$, in agreement with (2.4).

It is possible to join the backreaction boundary condition (3.4) with the diffusion equation (3.1) into a single relation

$$\frac{\partial p_1(x,t)}{\partial t} = \mathcal{L} p_1(x,t) + [\, \kappa_d p_1(*,t) - \kappa_a p_1(a,t)] \, \delta(x-a)/(\gamma_d a^{d-1}) , \tag{3.8}$$

which is subject to reflective boundary conditions

$$\mathcal{J} p_1(x,t)|_{x=a} = \mathcal{J} p_1(x,t)|_{x=R} = 0 , \tag{3.9}$$

at *both* ends. Indeed, when $x > a$ (3.8) reduces to (3.1). To show that it leads also to the backreaction boundary condition (3.4), one integrates it from a to $a + \epsilon$ and takes the limit $\epsilon \to 0$. The left-hand side (lhs) is of order ϵ. The right-hand side (rhs) gives $-\mathcal{J} p_1(x,t)|_{x=a+\epsilon} + \kappa_d p_1(*,t) - \kappa_a p_1(a,t)$. This is because the flux at $x = a$ now vanishes. In the limit, (3.4) is recovered. This is a generalization of the Wilemski-Fixman derivation [42] to a reversible reaction.

It is interesting to note that (3.8) can be formally extended to cover also (3.5). To do so, assume that x may also assume the value $*$. Since $p_1(*,t)$ is x independent, the diffusion term on the rhs of (3.8) vanishes. By formally defining

$$\delta(x-a)/(\gamma_d a^{d-1})|_{x=*} \equiv -1 , \tag{3.10}$$

one obtains (3.5) as a special case of (3.8) when $x = *$. Therefore *all* the one-particle equations, (3.1) through (3.5), are summarized in the single equation (3.8).

B. Two-particle equations

The generalization of the above equations to two particles is almost straightforward. The two-particle density function obeys

$$\frac{\partial p_2(x_1,x_2,t)}{\partial t} = \sum_{i=1}^{2} \mathcal{L}_i\, p_2(x_1,x_2,t)\,, \quad a \le x_i \le R, \tag{3.11}$$

where $\mathcal{L}_i$ is a diffusion operator in the coordinate x_i. The boundary conditions are

$$\mathcal{J}_i\, p_2(x_1,x_2,t)\big|_{x_i=R} = 0, \quad i=1,2 \tag{3.12}$$

at the outer sphere and

$$\mathcal{J}_1\, p_2(x_1,x_2,t)\big|_{x_1=a} = \kappa_d\, p_2(*,x_2,t) - \kappa_a\, p_2(a,x_2,t)\,, \tag{3.13a}$$

$$\mathcal{J}_2\, p_2(x_1,x_2,t)\big|_{x_2=a} = \kappa_d\, p_2(x_1,*,t) - \kappa_a\, p_2(x_1,a,t) \tag{3.13b}$$

for describing reversible binding at the inner sphere. In the above boundary conditions, $\mathcal{J}_i$ is the flux operator in x_i.

The only nontrivial extension of the one-particle equations occurs upon generalization of (3.5). Unlike $p_1(*,t)$, which can vary only due to association or dissociation, both $p_2(*,x_2,t)$ and $p_2(x_1,*,t)$ vary also due to diffusion of the unbound particle. Hence one has

$$\frac{\partial p_2(*,x_2,t)}{\partial t} = \mathcal{L}_2\, p_2(*,x_2,t) + \kappa_a\, p_2(a,x_2,t) - \kappa_d\, p_2(*,x_2,t)\,, \tag{3.14a}$$

$$\frac{\partial p_2(x_1,*,t)}{\partial t} = \mathcal{L}_1\, p_2(x_1,*,t) + \kappa_a\, p_2(x_1,a,t) - \kappa_d\, p_2(x_1,*,t)\,. \tag{3.14b}$$

When one particle is bound the appropriate density functions become one dimensional as compared with the two-dimensional density for two unbound particles. For each additional bound particle the dimensionality of the relevant density function decreases by unity.

The above equations are also subject to boundary conditions. The outer boundary condition is again reflective, while those at $x_i = a$ depend on whether the binding process is competitive or not. For the noncompetitive process, binding of the second particle is analogous to that of the first. Therefore

$$\mathcal{J}_2\, p_2(*,x_2,t)\big|_{x_2=a} = \kappa_d\, p_2(*,*,t) - \kappa_a\, p_2(*,a,t)\,, \tag{3.15a}$$

$$\mathcal{J}_1\, p_2(x_1,*,t)\big|_{x_1=a} = \kappa_d\, p_2(*,*,t) - \kappa_a\, p_2(a,*,t)\,. \tag{3.15b}$$

When binding is competitive, only a single particle may bind at a time. In this case, $p_2(*,*,t) \equiv 0$ and $\kappa_a = 0$ whenever the trap is occupied. The boundary conditions reduce to

$$\mathcal{J}_2\, p_2(*,x_2,t)\big|_{x_2=a} = \mathcal{J}_1\, p_2(x_1,*,t)\big|_{x_1=a} = 0\,. \tag{3.16}$$

For competitive binding, the hierarchy of equations ends at this level. In noncompetitive binding, one needs to consider also the equation obeyed by $p_2(*,*,t)$. This zero-dimensional density is the probability of the single event that both particles are simultaneously bound. It therefore obeys a simple kinetic equation, containing no diffusional terms

$$\frac{dp_2(*,*,t)}{dt} = \kappa_a\,[p_2(*,a,t) + p_2(a,*,t)] - 2\kappa_d\, p_2(*,*,t)\,. \tag{3.17}$$

This accounts for the possible binding of each of the two particles.

As in the single-particle case, the diffusion equation and backreaction boundary condition may be joined together to give

$$\begin{aligned}\frac{\partial p_2(x_1,x_2,t)}{\partial t} = {} & \sum_{i=1}^{2} \mathcal{L}_i\, p_2(x_1,x_2,t) + [\kappa_d\, p_2(*,x_2,t) - \kappa_a\, p_2(a,x_2,t)]\,\delta(x_1-a)/(\gamma_d\, a^{d-1}) \\ & + [\kappa_d\, p_2(x_1,*,t) - \kappa_a\, p_2(x_1,a,t)]\,\delta(x_2-a)/(\gamma_d\, a^{d-1})\,,\end{aligned} \tag{3.18}$$

which is subject to reflective boundary conditions at *both* ends

$$\mathcal{J}_i\, p_2(x_1,x_2,t)\big|_{x_i=a} = \mathcal{J}_i\, p_2(x_1,x_2,t)\big|_{x_i=R} = 0\,. \tag{3.19}$$

The proof follows that of (3.8). It is amusing to note that by allowing the states $x_i = *$ and adopting the convention in (3.10), the single relation (3.18) replaces all of (3.11) through (3.17).

The above equations can be presented graphically by the kinetic scheme of Fig. 1. Here two particles are assumed to diffuse on a finite interval discretized as the five uniformly spaced grid points (full circles). A point (i,j) on the two-dimensional lattice represents particle 1 on site i and particle 2 on site j. The transition probabilities (per unit time) between the lattice sites (full arrows) are all equal to $D/(\Delta x)^2$, where Δx is the grid spacing. The sites marked by asterisks represent one particle bound, and the second free to diffuse. They are connected among themselves by the same transition probabilities of magnitude $D/(\Delta x)^2$, while the transition probabilities to or from the regular sites (circles) are proportional to the dissociation and recombination rate coefficients (dashed arrows). The whole difference between competitive and noncompetitive binding is that in the first case the origin (0,0) has to be excluded since it represents two-particle binding. The scheme in Fig. 1 represents, in fact, the Master operator used in a numerical solution of the spatially discretized diffusion equations (see Sec. VI).

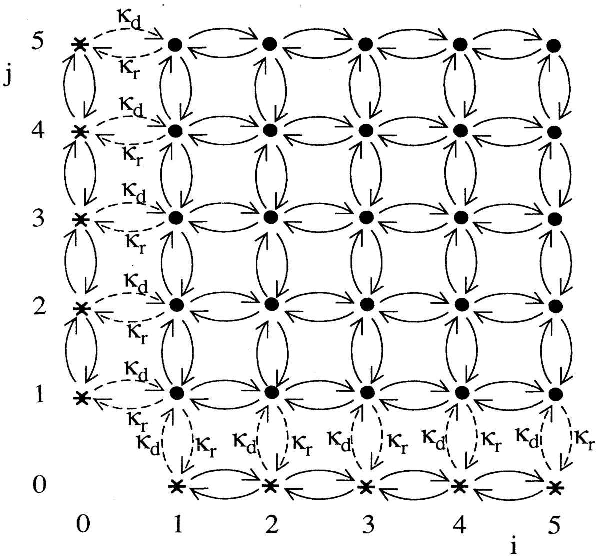

FIG. 1. Discrete spatial grid and transition probabilities for one-dimensional competitive binding of two particles.

C. Consistency checks

The consistency of the hierarchy presented above can be checked by considering first the density integrated over one of the coordinates and subsequently over both coordinates. One expects these quantities to obey physically sensible equations. Such relations are obtained below.

Define a density which is integrated over one coordinate by

$$\bar{p}_2(x_1,t) \equiv \int_a^R p_2(x_1,x_2,t)\,dV_2\,. \tag{3.20}$$

Integration of (3.11) over x_2 and insertion of (3.13b) gives

$$\begin{aligned}\frac{\partial \bar{p}_2(x_1,t)}{\partial t} &= \mathcal{L}_1\,\bar{p}_2(x_1,t) + \kappa_d\,p_2(x_1,*,t)\\ &\quad -\kappa_a\,p_2(x_1,a,t)\,.\end{aligned} \tag{3.21}$$

Adding this to (3.14b) gives

$$\frac{\partial[\bar{p}_2(x_1,t)+p_2(x_1,*,t)]}{\partial t} = \mathcal{L}_1[\bar{p}_2(x_1,t)+p_2(x_1,*,t)]\,, \tag{3.22}$$

which is a single-particle diffusion equation, see (3.1). Since the sum $\bar{p}_2(x_1,t)+p_2(x_1,*,t)$ represents the total probability of finding particle 1 at x_1, irrespective of particle 2, it is indeed expected to obey a simple diffusion equation in the coordinate x_1.

The form of the backreaction boundary condition imposed on (3.22) depends on whether the process is competitive or not. By integrating (3.13a) over x_2 and adding either (3.15b) or (3.16) one gets

$$\begin{aligned}&\mathcal{J}_1[\bar{p}_2(x_1,t)+p_2(x_1,*,t)]|_{x_1=a}\\ &\quad= \kappa_d\,[\bar{p}_2(*,t)+p_2(*,*,t)] - \kappa_a\,[\bar{p}_2(a,t)+p_2(a,*,t)]\end{aligned} \tag{3.23a}$$

for the noncompetitive case, but

$$\mathcal{J}_1[\bar{p}_2(x_1,t)+p_2(x_1,*,t)]|_{x_1=a} = \kappa_d\,\bar{p}_2(*,t) - \kappa_a\,\bar{p}_2(a,t) \tag{3.23b}$$

for competitive binding. Thus $\bar{p}_2(x,t)+p_2(x,*,t) = p_1(x,t)$ for noncompetitive binding (see below), but not for competitive binding. Similar results hold in x_2.

By further integrating the above equations and substituting sequentially, it can be verified that

$$\begin{aligned}S_2(t) &= 1 - \int_a^R p_2(x_1,*,t)\,dV_1\\ &\quad - \int_a^R p_2(*,x_2,t)\,dV_2 - p_2(*,*,t)\\ &= 1 - q_{2,1}(t) - q_{2,2}(t)\end{aligned} \tag{3.24a}$$

in the noncompetitive case, and

$$\begin{aligned}S_2(t) &= 1 - \int_a^R p_2(x_1,*,t)\,dV_1 - \int_a^R p_2(*,x_2,t)\,dV_2\\ &= 1 - q_{2,1}(t)\end{aligned} \tag{3.24b}$$

in the competitive case. Unlike the one-particle case, where no distinction between the two binding processes exists, (3.6) generalizes in different ways for competitive and noncompetitive binding. To obtain the above results use was made of (2.4). Thus by assuming initial normalization, the binding probabilities are properly normalized at all subsequent times. This verifies that the hierarchy of diffusion equations indeed conserves probability as it should.

D. Many-particle equations

The many-particle equations may be obtained from the two-particle equations by induction. For completeness, they are summarized below. The zeroth level of the hierarchy is the N-particle diffusion equation

$$\frac{\partial p_N(x_1,\ldots,x_N,t)}{\partial t} = \sum_{i=1}^{N} \mathcal{L}_i\,p_N(x_1,\ldots,x_N,t)\,,\qquad a \le x_i \le R \tag{3.25}$$

which is subject to outer and inner boundary conditions. The outer boundary conditions are reflective

$$\mathcal{J}_i\,p_N(x_1,\ldots,x_N,t)|_{x_i=R} = 0\,,\quad i=1,\ldots,N \tag{3.26}$$

while the inner boundary conditions depict backreaction in each and every coordinate. In x_1 one has

$$\begin{aligned}&\mathcal{J}_1\,p_N(x_1,\ldots,x_N,t)|_{x_1=a}\\ &\quad= \kappa_d\,p_N(*,x_2,\ldots,x_N,t) - \kappa_a\,p_N(a,x_2,\ldots,x_N,t)\end{aligned} \tag{3.27}$$

and similarly in $x_2,\ldots,x_N$. The density function for particle 1 bound obeys a diffusion equation in the remaining coordinates. For any value of $x_2,\ldots,x_N$ it may increase or decrease due to association or dissociation of particle 1. Therefore

$$\frac{\partial p_N(*,x_2,\ldots,x_N,t)}{\partial t} = \sum_{i=2}^{N} \mathcal{L}_i\, p_N(*,x_2,\ldots,x_N,t) + \kappa_a\, p_N(a,x_2,\ldots,x_N,t) - \kappa_d\, p_N(*,x_2,\ldots,x_N,t)\,. \quad (3.28)$$

Again, analogous equations hold in all other coordinates. The term involving $p_N(a,x_2,\ldots,x_N,t)$ couples the zeroth and first levels of the hierarchy. One reason for checking the consistency of the two-particle equations was to establish (3.28) as the first level of the hierarchy: Further levels then follow by induction. On this level there are again outer and inner boundary conditions. The outer boundary conditions are, of course, reflective

$$\mathcal{J}_i\, p_N(*,x_2,\ldots,x_N,t)|_{x_i=R} = 0\,, \quad i=2,\ldots,N. \quad (3.29)$$

For competitive binding, the inner boundary conditions are also reflective

$$\mathcal{J}_i\, p_N(*,x_2,\ldots,x_N,t)|_{x_i=a} = 0\,, \quad i=2,\ldots,N \quad (3.30)$$

and therefore binding of a second particle is disallowed. Hence for competitive binding the hierarchy terminates here. For binding processes of higher order, in particular for noncompetitive binding, the inner boundary conditions again depict reversible binding of a second particle and the hierarchy continues.

E. Detailed balancing

So far there was no reason to specify the initial condition, because the equations presented were valid for any initial condition. The notation (|) will be adopted in cases where the initial condition is important. The regions to the left and right of the vertical bar will then be used to specify the final and initial coordinates, respectively. Thus $p_N(x_1,\ldots,x_N,t|y_1,\ldots,y_N)$ designates the N-particle density function given the initial values $(y_1,\ldots,y_N)$ of the coordinates

$$p_N(x_1,\ldots,x_N,0|y_1,\ldots,y_N)\,dV_1\cdots dV_N = \prod_{i=1}^{N}\delta(x_i-y_i)\,dx_i\,. \quad (3.31)$$

Note that this can be formally used to define the initial density when one or more particles are initially bound, by adopting (3.10) with an opposite sign indicating that it is the initial rather than final location which is being equated to "*". Thus $p_N(x_1,\ldots,x_N,t|y_1,\ldots,y_N)$ is mathematically a Green's function and physically a transition probability, depicting transitions from an initial to a final value of the coordinates in a time interval t.

As is well known [43], transition probabilities in diffusion processes obey the detailed balance condition. For the presently considered case of free diffusion (no interaction potential) the detailed balance condition for any two unbound configurations is simply

$$p_N(x_1,\ldots,x_N,t|y_1,\ldots,y_N) = p_N(y_1,\ldots,y_N,t|x_1,\ldots,x_N)\,. \quad (3.32a)$$

When one of the particles (for example, particle 1) is bound, the detailed balance condition becomes

$$\kappa_a\, p_N(x_1,\ldots,x_N,t|*,y_2,\ldots,y_N) = \kappa_d\, p_N(*,y_2,\ldots,y_N,t|x_1,\ldots,x_N)\,. \quad (3.32b)$$

This identity is valid for both competitive and noncompetitive processes, both of which allow the single-particle binding state. Detailed balancing is useful in deriving the backward equations and boundary conditions corresponding to the hierarchy proposed above (cf. Ref. [24]) as well as for obtaining certain identities (see Sec. V B).

IV. NONCOMPETITIVE BINDING

A. General solution

A multiparticle binding site may be considered as a nucleation center for reversible aggregation of point particles. Diffusing particles attach to or detach from it, regardless of the aggregate size or its spatial structure. Since the N particles are completely independent of each other, it is natural to expect that the solution simply factors as

$$p_N(x_1,\ldots,x_N,t) = \prod\nolimits_{i=1}^{N} p_1(x_i,t)\,, \quad x_i \in [a,R]\cup[*]\,. \quad (4.1)$$

Here x_i may also assume the value $*$ and $p_1(x_i,t)$ is the single-particle density, namely, the solution of (3.1) through (3.5). For $N=2$ it can readily be checked that insertion of the factorization (4.1) into any of (3.11) through (3.15b) and (3.17) indeed leads to one of the one-particle equations or their sum. For example, (3.14b) becomes the sum of (3.1) and (3.5). This proof generalizes to $N>2$. Therefore (4.1) is an exact solution of the hierarchy presented in Sec. III D.

For $N=2$ again, integration of (4.1) over x_1 gives $\bar{p}_2(x_2,t) = [1-p_1(*,t)]p_1(x_2,t)$. Substituting an asterisk for x_1 gives $p_2(*,x_2,t) = p_1(*,t)p_1(x_2,t)$. Adding these two relations gives $\bar{p}_2(x_2,t) + p_2(*,x_2,t) = p_1(x_2,t)$, as concluded following (3.23b). Generalizing to N particles, one concludes that the condition

$$\bar{p}_N(x_2\ldots,x_N,t) + p_2(*,x_2,\ldots,x_N,t) = p_{N-1}(x_2,\ldots,x_N,t)\,, \quad (4.2)$$

when applied also to particles $2,\ldots,N$, is equivalent to (4.1).

As a result of the factorization (4.1), the binding probabilities for noncompetitive binding reduce to simple expressions in $p_1(*,t)$. These expressions simplify when all particles possess the same initial distribution and are hence all equivalent (see above). For equivalent particles, inserting (4.1) into (2.1) and integrating gives

$$q_{N,0}(t) \equiv S_N(t) = S_1(t)^N = [1 - p_1(*,t)]^N . \quad (4.3)$$

It can be checked that this result agrees with the more general expression for the survival probability given in (3.24a) for $N = 2$. In the limit of equivalent particles (3.24a) reads

$$\begin{aligned} S_2(t) &= 1 - 2S_1(t)\, p_1(*,t) - p_1(*,t)^2 \\ &= 1 - 2p_1(*,t) + p_1(*,t)^2 . \end{aligned}$$

The rhs indeed equals the binomial expansion of $[1 - p_1(*,t)]^2$, see (4.3). It admits a simple interpretation in terms of Fig. 1 (with the origin included as the two-particle binding case): $p_1(*,t)$ is the probability that one particle is bound, irrespective of the second particle. It is therefore the sum of the probabilities of all starred states on one side of the square, including the origin. $p_1(*,t)^2$ is the probability that both particles are simultaneously bound, i.e., the probability of the state represented by the origin in Fig. 1. Since by subtracting $2p_1(*,t)$ the probability $p_1(*,t)^2$ has been subtracted twice, it has to be added once as the last term in the above equation.

The probability $q_{N,1}(t)$ of having exactly one particle bound can be discussed in a similar fashion. By substituting (4.1) into (2.2b) and integrating, one gets

$$\begin{aligned} q_{N,1}(t) &= Np_1(*,t)\, S_1(t)^{N-1} \\ &= Np_1(*,t)\, [1 - p_1(*,t)]^{N-1} . \end{aligned} \quad (4.4)$$

Indeed, $p_1(*,t)$ is the binding probability of a single particle, $S_1(t)^{N-1}$ is the probability of having the remaining $N - 1$ particles unbound, and the factor N reflects the fact that all particles are identical hence any of the N particles may be the bound one. For $N = 2$, (4.4) reduces to

$$q_{2,1}(t) = 2[p_1(*,t) - p_1(*,t)^2] .$$

This again admits an interpretation in terms of Fig. 1: $p_1(*,t) - p_1(*,t)^2$ is the probability that exactly one particle (and no more) is bound. This is the probability of being at the starred side of the square in Fig. 1, excluding the origin. The factor 2 takes care of the two sides of the square.

Continuing in this fashion, the general expression for the binding probability for equivalent particles is gotten by inserting (4.1) into (2.3). This produces the Bernoulli distribution

$$q_{N,m}(t) = \binom{N}{m} p_1(*,t)^m\, [1 - p_1(*,t)]^{N-m} . \quad (4.5)$$

The average number of bound particles reduces, as expected, to

$$\langle q_N(t) \rangle \equiv \sum_{m=1}^{N} m\, q_{N,m}(t) = Np_1(*,t) , \quad (4.6)$$

where the second equality follows by the insertion of (4.5) and summation of the series. For a finite system of volume $V = \gamma_d\,(R^d - a^d)/d$, the equilibrium (zero flux) limit of (3.1) is the uniform (coordinate independent) distribution, $p_1(x,\infty) = [1 - p_1(*,\infty)]/V$. This relation already incorporates the normalization condition. Since the flux vanishes also at the boundary, (3.4) gives $\kappa_a\, p_1(a,\infty) = \kappa_d\, p_1(*,\infty)$. Taken together, one has that

$$p_1(*,\infty) = \kappa_a/(\kappa_a + V\kappa_d) . \quad (4.7)$$

This result is independent of the initial condition as it should be. The equilibrium limit for a finite system is therefore obtained by inserting (4.7) into (4.5).

B. The thermodynamic limit

Of considerable interest is the thermodynamic limit, involving an infinite system with all particles initially randomly distributed. Starting from a finite system, one lets $N \to \infty$ and $V \to \infty$ so that the concentration $c \equiv N/V$ remains constant. Taking the appropriate limit in (4.5) gives

$$q_m(t|\mathrm{eq}) = [cp_1(*,t|\mathrm{eq})]^m \exp[-cp_1(*,t|\mathrm{eq})]\, /m! \quad (4.8)$$

for the probability of having exactly m particles bound. The notation $p_1(*,t|\mathrm{eq})$, representing an initial equilibrium (random) distribution outside the trap, is defined from

$$\begin{aligned} p_1(*,t|\mathrm{eq}) &\equiv \gamma_d \int_a^\infty p_1(*,t|y)\, y^{d-1}\, dy \\ &= \lim_{V\to\infty} V\, p_1(*,t|\mathrm{uni}) . \end{aligned} \quad (4.9)$$

Here $p_1(*,t|y)$ is the single-particle binding probability given that the particle was initially located at y, see Eq. (3.31). The difference between the "uniform" and "equilibrium" solutions is that $p_1(\ |\mathrm{uni})$ is defined over a finite domain so that $p_1(x,0|\mathrm{uni}) = 1/V$, while $p_1(\ |\mathrm{eq})$ is defined over an infinite domain assuming that $p_1(x,0|\mathrm{eq}) = 1$.

In the notations of Ref. [24], $p_1(*,t|\mathrm{eq})$ is related to the reversible time-dependent rate coefficient $k_{\mathrm{rev}}(t)$ by

$$k_{\mathrm{rev}}(t) \equiv dp_1(*,t|\mathrm{eq})/dt , \quad (4.10a)$$

$$\begin{aligned} p_1(*,t|\mathrm{eq}) &= \int_0^t k_{\mathrm{rev}}(t')\, dt' \\ &= K_{\mathrm{eq}}\, S_1(t|*) , \end{aligned} \quad (4.10b)$$

$$\int_0^\infty k_{\mathrm{rev}}(t)\, dt = K_{\mathrm{eq}} \equiv \kappa_a/\kappa_d . \quad (4.10c)$$

Here $k_{\mathrm{rev}}(t)$ denotes the generalization of the more customary irreversible time-dependent rate coefficient, $k_{\mathrm{rad}}(t)$, which is the radiation-boundary-condition limit of $k_{\mathrm{rev}}(t)$ when $\kappa_d = 0$. The second identity follows by using the detailed balance condition (3.32b) in (4.9). This is a special case of the "generalized mass-action law" discussed below (Sec. V B). The third identity follows because for an infinite system $\lim_{t\to\infty} S_1(t|*) = 1$. It also defines the equilibrium coefficient K_{eq}. The above identities were obtained in Ref. [24].

The equilibrium limit of the binding probability for an infinite system may be obtained by using the identity (4.10c) in (4.8). This gives the Poisson distribution

$$q_m(\infty) = (cK_{\mathrm{eq}})^m \exp(-cK_{\mathrm{eq}})\, /m! , \quad (4.11)$$

which depends on the equilibrium constant K_{eq} but not on the diffusion constant D. Alternately, (4.11) can be obtained by inserting the equilibrium density for a finite system, Eq. (4.7), into (4.9) and taking the limit $V \to \infty$.

C. Analysis of the binding curves

For irreversible aggregation, the probability of observing an m aggregate rises and decreases due to the consecutive growth of the $m-1$ and m aggregates, respectively. Thus all the binding curves $q_m(t)$ go through a maximum which appears at later times for larger m values. This is no longer true in the reversible case, where aggregates may also dissociate. In this case, some of the binding curves increase monotonically to equilibrium. To analyze this behavior, consider the time derivative of the binding probability (4.8), which is given by

$$dq_m(t)/dt = ck_{\rm rev}(t)\,[q_{m-1}(t) - q_m(t)]\,, \tag{4.12}$$

with the time-dependent rate coefficient $k_{\rm rev}(t)$ defined in (4.10a). Since $k_{\rm rev}(t) > 0$ at any finite t, the necessary condition for a maximum in $q_m(t)$ at $t = t_{\rm max}$ is that $q_{m-1}(t_{\rm max}) = q_m(t_{\rm max})$, or

$$cp_1(*, t_{\rm max}|{\rm eq}) = m\,. \tag{4.13}$$

The identity (4.10b) shows that $p_1(*, t|{\rm eq})$ grows monotonically with time to a maximal value $K_{\rm eq}$ obtained at $t = \infty$. One therefore concludes that if

$$m < cK_{\rm eq} \le m + 1\,, \tag{4.14}$$

the first m binding states, $q_1(t), \ldots, q_m(t)$, show a maximum as a function of time, whereas the remaining binding states increase monotonically to equilibrium. In particular, in the irreversible case $\kappa_d = 0$ and $K_{\rm eq} = \infty$ so that all $q_m(t)$ exhibit a maximum.

D. Explicit results for one-dimensional aggregation

Closed-form results for aggregation in one dimension follow from the analytic solutions for p_1 in this case [37, 40]. The following solutions for Eqs. (3.1)–(3.5) are valid for diffusion on half the line, $0 \le x \le \infty$, $\gamma_d = 1$ and $a = 0$. Diffusion on both sides of the binding site is equivalent to multiplying c and κ_d by 2. For a particle which is initially bound [37]

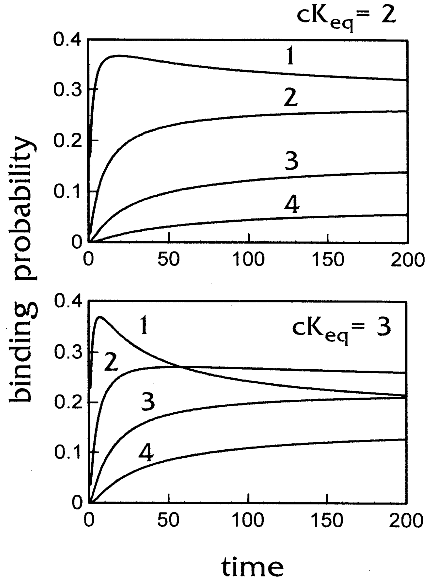

FIG. 2. Transient aggregation-state probabilities in one dimension. The parameters utilized in Eqs. (4.8) and (4.18) are $D = 1$, $\kappa_r = 1$, $\kappa_d = 0.2$, and $c = 0.4$ and 0.6 for the top and bottom panels, respectively.

$$p_1(*, t|*) = [\lambda_+\phi(\lambda_-\sqrt{t/D}) - \lambda_-\phi(\lambda_+\sqrt{t/D})]\,/\Delta\,, \tag{4.15}$$

where $\lambda_\pm \equiv (\kappa_r \pm \Delta)/2$, $\Delta \equiv (\kappa_r^2 - 4D\kappa_d)^{1/2}$, $\kappa_r = \kappa_a$ for $d = 1$, and

$$\phi(z) \equiv \exp(z^2)\,{\rm erfc}(z)\,. \tag{4.16}$$

erfc is the complementary error function. The notation $(\,|*)$ stands for an initial bound state. Insertion of (4.15) into (4.5) gives the binding probability for N particles initially bound at the origin of a semi-infinite line.

When a particle is initially unbound and placed at a distance y from the binding site, the following expression holds [40]:

$$p_1(*, t|y) = \frac{\kappa_r}{\Delta}\exp(-y^2/4Dt)\left[\phi\left(\frac{y}{2\sqrt{Dt}} + \lambda_-\sqrt{t/D}\right) - \phi\left(\frac{y}{2\sqrt{Dt}} + \lambda_+\sqrt{t/D}\right)\right], \tag{4.17}$$

where $0 \le y \le \infty$ and ϕ is defined by (4.16). The integral of (4.17) can be obtained in closed form. Insertion into (4.9) gives

$$p_1(*, t|{\rm eq}) = \int_0^\infty p_1(*, t|y)\,dy = \frac{D\kappa_r}{\Delta}\left[\frac{1}{\lambda_+}\phi(\lambda_+\sqrt{t/D}) - \frac{1}{\lambda_-}\phi(\lambda_-\sqrt{t/D})\right] + K_{\rm eq}\,. \tag{4.18}$$

In agreement with (4.10b) and (4.10c), $p_1(*, t|{\rm eq}) \to K_{\rm eq}$ as $t \to \infty$. The equilibrium coefficient $K_{\rm eq}$ is defined in (4.10c). Equation (4.18) can also be obtained directly from (4.15) by noting that $\lambda_+\lambda_- = D\kappa_d$ and applying identity (4.10b).

In the thermodynamic limit, Eqs. (4.8) and (4.18) give an exact analytical solution for the aggregate size distribution for reversible aggregation of point particles in one dimension. This solution is demonstrated in Fig. 2 for m = 1–4 and two values of $cK_{\rm eq}$. In agreement with the condition (4.14), when $cK_{\rm eq} = 2$ only $q_1(t)$ exhibits a maximum while for $cK_{\rm eq} = 3$ both $q_1(t)$ and $q_2(t)$ go through a maximum. In the latter case the maximum in $q_2(t)$ occurs exactly when $q_1 = q_2$, see (4.12).

E. Connection with the Smoluchowski theories

Smoluchowski [1] has discussed two related theories, that of density fluctuations and that of coagulation. Both theories were applied to colloid suspensions and were reviewed by Chandrasekhar [2]. It is interesting that in the limit of noncompetitive binding, both lead to (4.8).

The first theory describes equilibrium density fluctuations within some observation region. It is interesting to derive the thermodynamic limit (4.8) using the Smoluchowski arguments (compare Sec. III.1 in Ref. [2]). Denote by $S_1(t|*)$ the probability that a single, initially bound particle will have dissociated by time t. Suppose that initially n-independent particles were bound. The probability that during the time interval t, m particles will exit ("ausgang") the trap $A_m^{(n)}$ is given by the Bernoulli distribution

$$A_m^{(n)}(t) = \binom{n}{m} S_1(t|*)^m \, [1 - S_1(t|*)]^{n-m} . \qquad (4.19)$$

The probability that m particles will have entered the binding site during t, denoted above by $q_m(t|\text{eq})$, must be equal under equilibrium conditions to the average number of dissociating particles. Since cK_{eq} is the average number of particles bound under equilibrium conditions, the probability for having n particles simultaneously bound is given by the Poisson distribution q_n, Eq. (4.11). Taking the average of $A_m^{(n)}$ with respect to this distribution gives

$$\begin{aligned} q_m(t|\text{eq}) &= \sum_{n=m}^{\infty} A_m^{(n)}(t)\, q_n(\infty) \\ &= [cK_{\text{eq}} S_1(t|*)]^m \, \exp[-cK_{\text{eq}} S_1(t|*)]\,/m! \, . \end{aligned} \qquad (4.20)$$

Applying the identity (4.10b) shows that (4.20) is identical to (4.8). Although the derivation assumed an equilibrium distribution of particles within the site, the fact that the particles are independent makes $q_m(t|\text{eq})$ the probability of binding m (randomly distributed) particles in time t, *irrespective* of the initial number of particles in the site. This demonstrates that the probabilistic arguments of Smoluchowski are equivalent to the thermodynamic limit of the hierarchy of diffusion equations suggested in Sec. III.

A second Smoluchowski theory treats aggregation kinetics by rate equations. For the problem under consideration an exact solution exists, see Eq. (4.12). Thus one may check the validity of the rate-equation approach. In the case of irreversible aggregation (4.12) reduces to

$$dq_m(t)/dt = ck_{\text{rad}}(t)\,[q_{m-1}(t) - q_m(t)] \, , \qquad (4.21)$$

where $k_{\text{rad}}(t)$ is the (time-dependent) rate coefficient for irreversible recombination, i.e., the radiation-boundary-condition limit of $k_{\text{rev}}(t)$, obtained when $\kappa_d = 0$. The result (4.21) is a classical rate equation for irreversible aggregation, since the first term describes the addition of a monomer (concentration c) to a cluster of $m-1$ particles and the second term depicts growth of the m-particle cluster. Therefore the observation [10, 11] that the Smoluchowski theory is exact for $q_0(t)$ extends to arbitrary values of m.

For reversible aggregation a simple rate-equation approach suggests that [4(b)]

$$\begin{aligned} \frac{dq_m(t)}{dt} &= ck_{\text{rad}}(t)\,[q_{m-1}(t) - q_m(t)] \\ &\quad + \kappa_d\,[(m+1)q_{m+1}(t) - mq_m(t)] \, . \end{aligned} \qquad (4.22)$$

The second term on the rhs of (4.22) represents, in the rate-equation approach, dissociation of a monomer from clusters in which all monomers have equal dissociation probabilities. In the limit of $t \to \infty$ one has that $k_{\text{rad}}(t)^{-1} \to \kappa_a^{-1} + (4\pi Da)^{-1}$. For a slow, "reaction-controlled" reaction $k_{\text{rad}}(\infty) \approx \kappa_a$ and the equilibrium solution of Eq. (4.22) coincides with (4.11). Thus a rate equation approach is useful for intrinsically slow reactions. Otherwise, a better approximation for the reversible case may possibly be achieved by extending (4.12) rather than (4.22). In other words, starting from kinetic equations for irreversible aggregation, one replaces everywhere $k_{\text{rad}}(t)$ by $k_{\text{rev}}(t)$.

V. COMPETITIVE BINDING

Competitive binding is the more difficult case because the particles are no longer independent and therefore no analytical solution exists. The discussion of noncompetitive binding served to establish the hierarchy of diffusion equations. It is expected that this hierarchy, when truncated at the level of (3.30), provides the precise formulation of competitive binding. In the competitive case, it is precisely (3.30) which excludes the simple factorization (4.1) as a valid solution indicating that the particles are no longer independent. The formalism is used below as an alternate route to known identities and approximations and in extending the utility of the density expansion [12] to reversible reactions.

A. The equilibrium density

When R is finite, so that the N-particle system is contained in a finite volume V, an equilibrium solution is approached as $t \to \infty$. The exact equilibrium solution of (3.25)–(3.30) is

$$\begin{aligned} V^N p_N(x_1, \ldots, x_N, \infty) &= 1/(1 + cK_{\text{eq}}), \\ V^N p_N(*, x_2, \ldots, x_N, \infty) &= K_{\text{eq}}/(1 + cK_{\text{eq}}) \, , \end{aligned} \qquad (5.1)$$

irrespective of the initial condition and the identity of the bound particle. As always, $c \equiv N/V$ and $K_{\text{eq}} = \kappa_a/\kappa_d$. Upon insertion into (2.1) and (2.2b) one gets

$$\begin{aligned} q_{N,0}(\infty) &= 1/(1 + cK_{\text{eq}}), \\ q_{N,1}(\infty) &= cK_{\text{eq}}/(1 + cK_{\text{eq}}), \end{aligned} \qquad (5.2)$$

for the probability of having zero or one particles bound at equilibrium, respectively. This equilibrium solution was suggested in Ref. [24] based on chemical intuition and the convolution approximation.

It was noted [24] that solution (5.2) conforms to the usual thermodynamic definition of the equilibrium coefficient

$$K_{\text{eq}} = q_{N,1}(\infty)/[c q_{N,0}(\infty)], \tag{5.3}$$

namely, the concentration of products (bound particles) divided by the product of the concentration of reactants (free particles and unoccupied site). This is sometimes known as the "law of mass action." The validity of this relation is not limited to competitive binding. By using the equilibrium solution (4.11) for noncompetitive binding one can verify that the relation (5.3) holds in this case as well. Insertion of the equilibrium solution (4.7) into the Bernoulli distribution (4.5) shows that (5.3) holds also for aggregation in finite systems.

The proof that (5.1) is indeed the equilibrium solution follows from three observations: First, this solution is constant so that

$$\begin{aligned}\frac{\partial p_N(x_1,\ldots,x_N,\infty)}{\partial t} &= \frac{\partial p_N(*,x_2,\ldots,x_N,\infty)}{\partial t} = 0,\\ \mathcal{J}_i\, p_N(x_1,\ldots,x_N,\infty) &= \mathcal{J}_i\, p_N(*,x_2,\ldots,x_N,\infty) = 0,\\ \mathcal{L}_i\, p_N(x_1,\ldots,x_N,\infty) &= \mathcal{L}_i\, p_N(*,x_2,\ldots,x_N,\infty) = 0\,,\end{aligned} \tag{5.4a}$$

and similarly for $x_i = *, i = 2,\ldots,N$. Second, the flux at the contact distance, $x_1 = a$, vanishes

$$\kappa_a\, p_N(a,x_2,\ldots,x_N,\infty) = \kappa_d\, p_N(*,x_2,\ldots,x_N,\infty)\,, \tag{5.4b}$$

and similarly for $x_i = a$, $i = 2,\ldots,N$. Finally, (5.2) implies that the total probability is normalized,

$$q_{N,0}(\infty) + q_{N,1}(\infty) = 1\,. \tag{5.4c}$$

Since this proof is valid for any N and V, it holds also in the thermodynamic limit.

Rigorous equilibrium solutions thus exist for both competitive and noncompetitive binding. A comparison of solutions (4.11) and (5.2) shows that they coincide in the infinite dilution limit, $c \to 0$. In this limit the difference between competitive and noncompetitive binding vanishes. For finite concentrations, the equilibrium solutions for the two cases differ.

B. The generalized-mass-action law

It was shown above that the equilibrium solution for both competitive and noncompetitive binding obeys the mass-action law (5.3). In the time domain, a generalized-mass-action law holds

$$\begin{aligned}K_{\text{eq}} &= q_{N,1}(t|\text{uni})/[c q_{N,0}(t|*)]\\ &= q_1(t|\text{eq})/[c q_0(t|*)]\,,\end{aligned} \tag{5.5}$$

where $q_{N,1}(t|\text{uni})$ denotes the probability of having exactly one particle bound, given that initially all N particles were uniformly distributed in V and $q_{N,0}(t|*)$ denotes the probability of having no particle bound by time t, given that initially one was bound and the remaining $N-1$ particles were uniformly distributed. $q_1(t|\text{eq})$ and $q_0(t|*)$ are the $V \to \infty$ limits of these probabilities. When $t \to \infty$ Eq. (5.5) reduces to (5.3), while for $N = 1$ it reduces to (4.10b). The identity (5.5) was suggested from a convolution approach to competitive binding [24], proven using an occupation number formalism [31] and demonstrated in numerical random-walk simulations [30]. It will now be shown to be a direct consequence of the detailed balancing condition (3.32b).

Using the Green's function defined in (3.31) one may rewrite (2.1) as

$$q_{N,0}(t|*) = \frac{1}{V^{N-1}} \int_a^R \cdots \int_a^R dV_1 \cdots dV_N \int_a^R \cdots \int_a^R dU_2 \cdots dU_N\, p_N(x_1,\ldots,x_N,t|*,y_2,\ldots,y_N)\,. \tag{5.6}$$

Here $dU_i \equiv \gamma_d\, y_i^{d-1} dy_i$ and $\prod_i (dU_i/V)$ is the initial uniform probability. Similarly, from (2.2b) one has

$$q_{N,1}(t|\text{uni}) = \frac{N}{V^N} \int_a^R \cdots \int_a^R dV_2 \cdots dV_N \int_a^R \cdots \int_a^R dU_1 \cdots dU_N\, p_N(*,x_2,\ldots,x_N,t|y_1,\ldots,y_N)\,. \tag{5.7}$$

Use of (3.32b) now completes the proof. Since the detailed balance condition (3.32b) holds for all binding processes, the generalized-mass-action law (5.5) is indeed very general. It is valid for both competitive and noncompetitive binding in finite or infinite systems. It is most useful for competitive binding, where no analytical solution is available, since it shows that the solution for only one of the two initial conditions needs to be calculated (or measured).

C. The effective-rate equation

It is possible to reduce the solution of the hierarchial diffusion equations, Sec. III D, to a single effective-rate equation. This equation, which can be deduced from the convolution relations of Ref. [24], has been shown to be rigorous by Szabo and Zwanzig [31] using their occupation number formalism. It involves the survival probability for one particle (say, particle 1) which is initially at the contact distance a, while the other $N-1$ particles are uniformly distributed. In analogy to (5.6), this quantity is defined by

$$q_{N,0}(t|a) \equiv S_N(t|a) \equiv \frac{1}{V^{N-1}} \int_a^R \cdots \int_a^R dV_1 \cdots dV_N \int_a^R \cdots \int_a^R dU_2 \cdots dU_N\, p_N(x_1,\ldots,x_N,t|a,y_2,\ldots,y_N)\,. \tag{5.8}$$

The definition and subsequent derivation can be easily extended to other initial conditions of particles $2,\dots,N$, provided that they are the same for all particles (i.e., the particles are equivalent).

To derive the desired identity, differentiate (5.7) with respect to t and insert the $N-1$ particle diffusion equation (3.28). This gives

$$dq_{N,1}(t|\mathrm{uni})/dt = \frac{N}{V^N}\int_a^R\cdots\int_a^R dV_2\cdots dV_N \int_a^R\cdots\int_a^R dU_1\cdots dU_N \times\left[\left(\sum_{i=2}^{N}\mathcal{L}_i-\kappa_d\right)p_N(*,x_2,\dots,x_N,t|y_1,\dots,y_N)+\kappa_a\,p_N(a,x_2,\dots,x_N,t|y_1,\dots,y_N)\right]. \tag{5.9}$$

The integral of the diffusive terms on the rhs equals the difference of the fluxes at R and a, which vanish because the outer boundary is always reflective while the inner boundary is reflective whenever a particle is already bound, see (3.30). Here explicit use of competitiveness is made. For the last term on the rhs one uses the detailed balance condition (3.32a) and definition (5.8) to write

$$\frac{1}{V^N}\int_a^R\cdots\int_a^R dV_2\cdots dV_N\int_a^R\cdots\int_a^R dU_1\cdots dU_N\,p_N(a,x_2,\dots,x_N,t|y_1,\dots,y_N) = S_N(t|a)/V\,. \tag{5.10}$$

Inserting into (5.9), one finally obtains the effective-rate equation

$$\frac{dq_{N,1}(t|\mathrm{uni})}{dt} = c\kappa_a\,S_N(t|a) - \kappa_d\,q_{N,1}(t|\mathrm{uni})\,. \tag{5.11}$$

This is supplemented by the initial condition $q_{N,1}(0|\mathrm{uni})=0$. Since (5.11) is valid for any N and V, it is valid also in the thermodynamic limit where, dropping the subscript N, one has

$$\frac{dq_1(t|\mathrm{eq})}{dt} = c\kappa_a S(t|a) - \kappa_d\,q_1(t|\mathrm{eq})\,. \tag{5.12}$$

Unlike the generalized-mass-action law, the validity of (5.12) does not extend beyond the competitive case; for example, contrast it with (4.12). This is due to the use made of (3.30).

Equation (5.12) is exact but formal, since it depends on the unknown survival probability $S(t|a)$. One may turn it into a starting point for approximations by writing

$$S(t|a) = f(t)\,S(t|\mathrm{eq}) = f(t)\,[1-q_1(t|\mathrm{eq})]\,. \tag{5.13}$$

Different functions $f(t)$ give rise to different approximate solutions. Several of the approximations discussed by Szabo [32] indeed have this form.

It is interesting to note that (5.12) may be written as a convolution relation

$$q_1(t|\mathrm{eq}) = c\kappa_a\int_0^t \exp[-\kappa_d(t-t')]\,S(t'|a)\,dt'\,. \tag{5.14}$$

Alternately, one may use identity (5.5) to convert (5.12) into

$$\frac{dS(t|*)}{dt} = \kappa_d\,[S(t|a)-S(t|*)] \tag{5.15a}$$

and (5.14) into its convoluted form

$$S(t|*) = \kappa_d\int_0^t \exp[-\kappa_d(t-t')]\,S(t'|a)\,dt'\,. \tag{5.15b}$$

The probability that an initially bound particle will appear at contact between t and $t+dt$ is $\kappa_d\exp(-\kappa_d t)$. From contact, it evolves according to $S(t|a)$, therefore the convolution relation. The identity (5.15b) is identical with Eq. (4.29) in Ref. [24], which is therefore exact. It is useful in connecting solutions for the two different initial conditions.

D. The convolution approach

Starting from the formal but rigorous results of Sec. V C, the convolution approach of Agmon and Szabo [24] may be justified as follows: In the convolution relation (5.15b), $1-S_{\mathrm{irr}}(t|*)\equiv\exp(-\kappa_d t)$ is the binding probability for the irreversible dissociation of an initially bound particle. For clarity, let us attach the subscript rev to the solution which is subject to the more general reversible boundary conditions. Then (5.15b) may be rewritten as

$$S_{\mathrm{rev}}(t|*) = \kappa_d\int_0^t [1-S_{\mathrm{irr}}(t-t'|*)]\,S_{\mathrm{rev}}(t'|a)\,dt'\,. \tag{5.16}$$

It is impossible to solve this rigorous relation explicitly because two different initial conditions are involved, namely that of a particle bound and at contact. However, (5.16) relates not only two initial conditions, but also two different boundary conditions (the reversible and irreversible ones). A reasonable approximation may involve switching the two indices on the rhs of (5.16) to obtain

$$S_{\rm rev}(t|*) \approx \kappa_d \int_0^t [1 - S_{\rm rev}(t-t'|*)]\, S_{\rm irr}(t'|a)\, dt' . \tag{5.17}$$

In contrast to (5.16), in (5.17) both reversible terms refer to the *same* initial condition, that of a bound particle. A solution for reversible binding may now be obtained provided that a solution for the simpler, irreversible problem is known. In our previous notations $S_{\rm irr}(t|a) \equiv S_{\rm rad}(t|a)$ and (5.17) is identical with Eq. (4.14) in Ref. [24].

E. The density expansion

An expansion similar to that introduced by Haan and Zwanzig [44] has been proposed [12] for approximating the survival probability for irreversible binding

$$\begin{aligned} q_{N,1}(t) = {}& Nq_{1,1}(t) + \tfrac{1}{2}N(N-1)[q_{2,1}(t) - 2q_{1,1}(t)] \\ & + \frac{1}{3!}N(N-1)(N-2) \\ & \times [q_{3,1}(t) - 3q_{2,1}(t) + 3q_{1,1}(t)] + \cdots . \end{aligned} \tag{5.18}$$

This expansion is an exact identity for any finite value of N provided that all N terms are included. For large N, it is desirable to truncate the series at some value $n < N$. While such an approximation may be useful for any initial condition, the following discussion is limited to the case of equivalent particles which are initially uniformly distributed.

The utility of the approximation depends on the convergence properties of the series. For noncompetitive binding, where an analytical solution is available, it is seen that (4.4) is equivalent to

$$q_{N,1}(t) = -\sum_{n=1}^{N} \binom{N}{n} n\, [-p_1(*,t)]^n . \tag{5.19}$$

This has the identical form to (5.18) with the expansion coefficients being equal to $-n[-p_1(*,t)]^n$. The fact that the series has alternating signs enhances its convergence properties. Convergence is expected to be fast under the condition that the single-particle density obeys $p_1(*,t) \ll 1$. For an initial uniform distribution, $p_1(*,0|{\rm uni}) = 0$. Hence the condition holds for short times. Since for $K_{\rm eq}/V \ll 1$, $p_1(*,\infty|{\rm uni}) \approx K_{\rm eq}/V$ the condition holds also for small $K_{\rm eq}/V$. In the general case one concludes that $cK_{\rm eq}$ should be small. Therefore the expansion should be useful for short times, infinite dilution, or slow binding.

If the leading term in (5.18) is already exact, $q_{N,1}(t) = Nq_{1,1}(t)$ and each of the higher coefficients cancels identically. This occurs for an approximation in which $\int_a^R \cdots \int_a^R p_N(*,x_2,\ldots,x_N,t)\, dV_2 \cdots dV_N \approx p_1(*,t)$, see (2.2b). In order that the leading term in the expansion will correspond to the more physical limiting case of noncompetitive binding, one exponentiates (5.18) to obtain

$$\ln S_N(t) \approx -Nq_{1,1}(t) + \tfrac{1}{2}N(N-1)[S_2(t) - S_1(t)^2] + \frac{1}{3!}N(N-1)(N-2)[S_3(t) - 3S_2(t)S_1(t) + 2S_1(t)^3] + \cdots . \tag{5.20}$$

This result is again valid for N equivalent particles. By performing a Taylor expansion and resuming the terms one verifies that this result is indeed equivalent to (5.18). Indeed, for noncompetitive binding $S_N = S_1^N$, see (4.3), so that all terms except the first vanish identically.

Figure 3 shows the utility of the expansion (5.20) for estimating the binding probability of 20 particles diffusing on a finite line segment. The binding probability, $q_{20,1}(t|{\rm uni})$, is shown for three different values of κ_d. The full curves are the results of a lattice random-walk simulation [30]. The dotted, dashed, and dash-dotted curves are calculated from the expansion truncated at $n = 1$, 2, and 3, respectively. These involve the exact binding probabilities, $q_{n,1}(*,t|{\rm uni}) = 1 - S_n(t|{\rm uni})$, for $n = 1$, 2, and 3 particles as calculated from the numerical propagation of Eqs. (3.25) through (3.30), using the algorithm described in the next section. It is seen that convergence to the exact 20-particle solution is very good for small t and/or small $cK_{\rm eq}$. Only for the longest times and the smallest κ_d is the third-order term required.

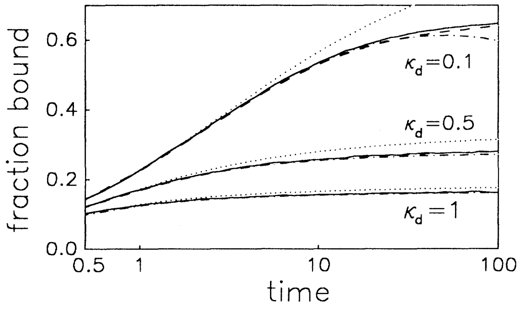

FIG. 3. The binding probability for competitive binding on the line. Simulations of 20 particles on an $L = 100$ long lattice (with a reversible binding site at the origin and periodic boundary conditions [30]) are compared with the first three terms in the density expansion. Note the logarithmic time scale. The parameters involved are $D = 1$, $\kappa_r = 1$, and $c = 0.2$. The average of 100 000 stochastic trajectories was required to produce the level of statistical noise shown by the simulated curves.

VI. THE DIRECT-PROPAGATION METHOD

In a numerical propagation of the partial-differential equations, the spatial coordinates are discretized so that the diffusive hierarchy is converted into a Master equation of transition probabilities obeying detailed balancing. These equations are detailed below for the case $N = 2$, see Sec. III B and $d = 1$. The discrete coordinate system is shown in Fig. 1 (for $L = 5$). The index i describes the location of the first particle and assumes the values $0, 1, \ldots, L$. $i = 0, 1$, and L represent the bound state $*$, the particle at the contact distance, $x_1 = a$, and at the outer boundary, $x_1 = R$, respectively. The second particle is described by the index j assuming analogous values. The grid spacing is Δx in both coordinates and one denotes $\bar{D} \equiv D/\Delta x^2$ and $\bar{\kappa_r} \equiv \kappa_r/\Delta x$. $p_{i,j}(t)$ is the appropriately discretized density $p_2(x_1, x_2, t)$. It is normalized such that

$$\sum_{i,j=0}^{L} p_{i,j}(t) = 1 . \tag{6.1}$$

An initial uniform distribution for the unbound state reads

$$p_{i,j}(0|\text{uni}) = 1/L^2 , \quad 1 \leq i, j \leq L \tag{6.2}$$

and zero otherwise. In the following, reflecting boundary conditions are imposed at L. The equations may be easily modified to account for other boundary conditions at L, for example, periodic [30].

The Master equations assume the following form: For the free state one has

$$\frac{dp_{i,j}(t)}{dt} = \begin{cases} \bar{D}\,(p_{i-1,j} + p_{i+1,j} + p_{i,j-1} + p_{i,j+1} - 4p_{i,j}), & 2 \leq i, j \leq L-1 \\ \bar{D}\,(p_{i-1,j} + p_{i+1,j} + p_{i,j-1} - 3p_{i,j}\,) , & j = L, \;\; 2 \leq i \leq L-1 \\ \bar{D}\,(p_{i-1,j} + p_{i,j-1} - 2p_{i,j}) , & i, j = L . \end{cases} \tag{6.3a}$$

At the contact distance ($j = 1$) one has

$$\frac{dp_{i,j}(t)}{dt} = \begin{cases} \bar{D}\,(p_{i-1,j} + p_{i+1,j} + p_{i,j+1}) + \kappa_d p_{i,j-1} - (3\bar{D} + \bar{\kappa_r})\, p_{i,j} , & j = 1, \;\; 2 \leq i \leq L-1 \\ \bar{D}\,(p_{i+1,j} + p_{i,j+1}) + \kappa_d (p_{i,j-1} + p_{i-1,j}) - 2(\bar{D} + \bar{\kappa_r})\, p_{i,j} , & i, j = 1 \\ \bar{D}\,(p_{i,j+1} + p_{i-1,j}) + \kappa_d p_{i,j-1} - (2\bar{D} + \bar{\kappa_r})\, p_{i,j} , & j = 1, \;\; i = L . \end{cases} \tag{6.3b}$$

Finally, for the bound state ($j = 0$) one has

$$\frac{dp_{i,j}(t)}{dt} = \begin{cases} \bar{D}\,(p_{i-1,j} + p_{i+1,j}\,) + \bar{\kappa_r}\, p_{i,j+1} - (2\bar{D} + \kappa_d)\, p_{i,j} , & j = 0, \;\; 2 \leq i \leq L-1 \\ \bar{D}\, p_{i+1,j} + \bar{\kappa_r}\, p_{i,j+1} - (\bar{D} + \kappa_d)\, p_{i,j} , & j = 0, \;\; i = 1 \\ \bar{D}\, p_{i-1,j} + \bar{\kappa_r}\, p_{i,j+1} - (\bar{D} + \kappa_d)\, p_{i,j} , & j = 0, \;\; i = L . \end{cases} \tag{6.3c}$$

Similar equations hold when the indices i and j are interchanged.

The above equations can be summarized in a tensor form

$$\frac{d\mathbf{p}(t)}{dt} = \mathbf{M}\mathbf{p}(t), \tag{6.4}$$

where $\mathbf{p}$ is the matrix of probabilities $p_{i,j}(t)$ and $\mathbf{M}$ is the tensor of transition probabilities in the above scheme. The formal solution is

$$\mathbf{p}(t) = \exp(t\mathbf{M})\,\mathbf{p}(0). \tag{6.5}$$

In ordinary finite differencing in time, the exponent is expanded in a Taylor series around $t = 0$. The drawback of this approach is the pointwise convergence at $t = 0$, which limits the size of the time step. In the Chebyshev propagation [45], routinely used in the geminate limit [36], the exponent is expanded in a Chebyshev series which converges uniformly over a whole interval. Scaling the eigenvalues of $\mathbf{M}$ to the size of this interval allows an arbitrarily large time step to be taken. The binding probability is finally obtained from the density $\mathbf{p}(\mathrm{t})$ by

$$q_1(t) = \sum_{i=1}^{L} p_{i,0}(t) + \sum_{j=1}^{L} p_{0,j}(t). \tag{6.6}$$

This algorithm has been coded for 1, 2, and 3 particles. Results of sample propagations (full curves) are compared in Fig. 4 with lattice random-walk simulations (squares), generated using the algorithm of Ref. [30]. The larger N, the more special cases need be considered at the boundary of the N-dimensional cube so that the Master equation (6.3a) complicates considerably. This is one limitation in increasing N. A second limitation involves computer memory requirements, since at each time step some three copies of $\mathbf{p}$ are retained in memory, each requiring the storage of $(L + 1)^N$ real numbers.

VII. CONCLUSION

In this paper a class of ideal reversible binding problems has been considered, in which a static, spherical binding site in a d-dimensional space is surrounded by diffusing point particles which may both attach and detach from the binding site. The case of unrestricted binding is noncompetitive, involves independent particles, and cor-

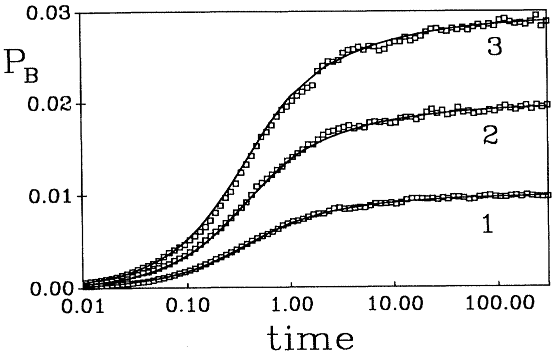

FIG. 4. Comparison of the binding probability, $P_B \equiv q_{N,1}(t|\text{uni})$, from the direct propagation method (curves) with random-walk simulations (squares) of competitive binding on the line for three different values of N. Parameters involved are $D = 1$, $\kappa_r = 1$, $\kappa_d = 1$, and $L = 100$. Periodic (rather than reflective) boundary conditions were imposed at the end of the interval. The number of simulations averaged varies from 100 000 for $N = 1$ to 60 000 for $N = 3$.

responds to an idealized picture of reversible aggregation. In contrast, when only one particle may bind at a time, one obtains the limit of competitive binding as an idealized case of a pseudo-first-order reaction. This work established a unified binding formalism through a hierarchy of diffusion equations. When truncated, these describe competitive binding and otherwise correspond to noncompetitive binding. The hierarchy serves as a convenient starting point for deriving identities and constructing approximations.

For noncompetitive binding, the binding probabilities may be obtained explicitly in terms of the single-particle solution. Since the aggregating particles are point particles, the aggregate has no spatial structure and may grow or diminish in size only by the addition or subtraction of a monomer. While this may be too restrictive for some realistic aggregation problems, the analytical expressions obtained for the binding states may serve as a useful reference point much like the properties of ideal gases are used in analyzing real gases. Additionally, the analytical solution suggests that a natural extension of irreversible aggregation kinetics to the reversible case is by replacing the time-dependent rate coefficient by its reversible counterpart rather than by adding dissociation terms to the equation. It would be interesting to apply this observation as a starting point for approximating realistic reversible aggregation problems.

For competitive binding the restriction imposed at the entry to the binding site introduces correlations between particle motions, so that no analytical solution is available even when the particles are otherwise noninteracting. In this case it was demonstrated how the exact hierarchy may be used to derive identities in a most straightforward way. These include an effective-rate equation, itself a basis for various approximations, and the generalized mass-action law whose generality indeed extends to binding processes of all orders. While these identities are known [24], their derivation is new. The simplicity of the derivations helps establish the diffusive hierarchy as the preferred description of these problems. Additionally, a density expansion has been applied to reversible binding for the first time. It uses the ability to solve (numerically) the exact many-body equations for a small number of particles. This provides a useful description of the binding probability for short times.

The asymptotic long-time behavior involves the convoluted motions of all particles and is hence inaccessible by means of a simple density expansion. It is exactly in this limit that many-body effects on these reactions become dominant, which motivates a careful study of the long-time behavior. So far, the asymptotic behavior has been obtained from mean-field approximations [32] and random-walk simulations [30]. The binding probability for competitive binding is predicted to approach its equilibrium limit through power-law decay, with a universal (concentration independent) power of $-d/2$. It is interesting that such power-law behavior has been recently observed experimentally in a reversible reaction of excited-state proton transfer to solvent [41]. The intriguing experimental observation is that the asymptotic power seems to increase with increasing concentration. The origin of this discrepancy has not yet been clarified.

It is hoped that the presently established hierarchy can be utilized for deriving the asymptotic behavior without the need to recourse to mean-field approximations. This involves taking both limits of infinite time and an infinite system (the "thermodynamic limit"). The result will allow us to verify the adequacy of the predicted mean-field behavior. However, the discrepancy between the experimental result [41] and the mean-field prediction could follow from several other factors, such as the neglect of anion diffusion or proton-proton Coulomb repulsions. The rigorous introduction of such interactions is extremely demanding. Nevertheless, joint advances in analytical theory and computer simulations and experiment promise to provide interesting insights on the many-body aspects of chemical and biochemical reactivity.

ACKNOWLEDGMENTS

I thank Shlomo Nir and Ruth Peled for comments on the manuscript. This work was supported by the Hebrew University Internal Funds. The Fritz Haber Research Center is supported by the Minerva Gesellschaft für die Forschung, München, FRG.

[1] M. von Smoluchowski, Phys. Z. **17**, 557 (1916); **17**, 585 (1916); Z. Phys. Chem. **92**, 129 (1917).

[2] S. Chandrasekhar, Rev. Mod. Phys. **15**, 1 (1943), Sec. III.

[3] F. Leyvraz, Phys. Rev. A **29**, 854 (1984); F. Leyvraz and S. Redner, *ibid.* **36**, 4033 (1987).

[4] (a) J. Bentz and S. Nir, Proc. Acad. Sci. USA **78**, 1634 (1981); S. Nir, J. Bentz, J. Wilschut, and N. Duzgunes, Prog. Surf. Sci. **13**, 1 (1983); (b) R. A. Parente, S. Nir, and F. C. Szoka, Biochem. **29**, 8720 (1990).

[5] P. D. Nguyen and E. A. O'Rear, Ann. Biomed. Eng. **18**, 427 (1990).

[6] H. E. Stanley and N. Ostrowsky, *On Growth and Form* (Nijhoff, Boston, 1986); R. Jullien and R. Botet, *Aggregation and Fractal Aggregates* (World Scientific, Singapore, 1987).

[7] R. Botet and R. Jullien, Phys. Rev. Lett. **55**, 1943 (1985); M. Kolb, *ibid.* **56**, 2769 (1986).

[8] J. L. Spouge, Phys. Rev. Lett. **60**, 871 (1988).

[9] C. R. Doering and D. ben-Avraham, Phys. Rev. A **38**, 3035 (1988); Phys. Rev. Lett. **62**, 2563 (1989).

[10] M. Tachiya, Rad. Phys. Chem. **21**, 167 (1983).

[11] A. Szabo, J. Phys. Chem. **93**, 6929 (1989).

[12] A. Szabo, R. Zwanzig, and N. Agmon, Phys. Rev. Lett. **61**, 2496 (1988).

[13] T. R. Waite, Phys. Rev. **107**, 463 (1957).

[14] R. M. Noyes, Prog. React. Kinet. **1**, 129 (1961).

[15] A. A. Ovchinnikov and Ya. B. Zeldovich, Chem. Phys. **28**, 215 (1978).

[16] D. Toussaint and F. Wilczek, J. Chem. Phys. **78**, 2642 (1983).

[17] K. Kang and S. Redner, Phys. Rev. A **32**, 435 (1985).

[18] D. ben-Avraham, Philos. Mag. **56**, 1015 (1987).

[19] V. Kuzovkov and E. Kotomin, Rep. Prog. Phys. **51**, 479 (1988).

[20] N. N. Lukzen, A. B. Doktorov, and A. I. Burshtein, Chem. Phys. **102**, 289 (1986).

[21] S. Lee and M. Karplus, J. Chem. Phys. **86**, 1883 (1987).

[22] K. Sienicki and M. A. Winnik, J. Chem. Phys. **87**, 2766 (1987); J. M. G. Martinho and M. A. Winnik, J. Phys. Chem. **91**, 3640 (1987); J. C. André, F. Baros, and M. A. Winnik, *ibid.* **94**, 2942 (1990).

[23] M. A. Burschka, C. R. Doering, and D. ben-Avraham, Phys. Rev. Lett. **63**, 700 (1989).

[24] N. Agmon and A. Szabo, J. Chem. Phys. **92**, 5270 (1990).

[25] J. Vogelsang and M. Hauser, J. Phys. Chem. **94**, 7488 (1990).

[26] P. M. Richards, J. Chem. Phys. **92**, 1963 (1990).

[27] M. N. Berberan-Santos and J. M. G. Martinho, J. Chem. Phys. **95**, 1817 (1991); Chem. Phys. Lett. **178**, 1 (1991).

[28] W. Naumann, Chem. Phys. **150**, 187 (1991); J. Chem. Phys. **98**, 2353 (1993).

[29] S. F. Burlatsky, G. S. Oshanin, and A. A. Ovchinnikov, Chem. Phys. **152**, 13 (1991).

[30] N. Agmon, H. Schnörer, and A. Blumen, J. Phys. Chem. **95**, 7326 (1991).

[31] A. Szabo and R. Zwanzig, J. Stat. Phys. **65**, 1057 (1991).

[32] A. Szabo, J. Chem. Phys. **95**, 2481 (1991).

[33] P. M. Richards and A. Szabo, J. Stat. Phys. **65**, 1085 (1991).

[34] J. F. Garst, J. Am. Chem. Soc. **114**, 1168 (1992).

[35] (a) J. Keizer, J. Am. Chem. Soc. **112**, 7952 (1990); (b) A. Molski and J. Keizer, J. Chem. Phys. **96**, 1391 (1992); (c) A. Molski, Chem. Phys. Lett. **191**, 59 (1992).

[36] E. Pines, D. Huppert, and N. Agmon, J. Chem. Phys. **88**, 5620 (1988).

[37] N. Agmon, E. Pines, and D. Huppert, J. Chem. Phys. **88**, 5631 (1988). Note the typographical error involving D in Eq. (C8) there.

[38] (a) D. Huppert, E. Pines, and N. Agmon, J. Opt. Soc. Am. B **7**, 1545 (1990); (b) E. Pines, D. Huppert, and N. Agmon, J. Phys. Chem. **95**, 666 (1991); (c) N. Agmon, D. Huppert, A. Masad, and E. Pines, *ibid.* **95**, 10 407 (1991); **96**, 2020(E) (1992).

[39] F. C. Goodrich, J. Chem. Phys. **22**, 588 (1954).

[40] N. Agmon, J. Chem. Phys. **81**, 2811 (1984).

[41] D. Huppert, S. Y. Goldberg, A. Masad, and N. Agmon, Phys. Rev. Lett. **68**, 3932 (1992); A. Masad, S. Y. Goldberg, D. Huppert, and N. Agmon, in *Proceedings of the 8th Symposium on Ultrafast Phenomena* (Springer-Verlag, Berlin, in press).

[42] G. Wilemski and M. Fixman, J. Chem. Phys. **58**, 4009 (1973).

[43] N. G. van Kampen, *Stochastic Processes in Physics and Chemistry* (North-Holland, Amsterdam, 1981).

[44] S. W. Haan and R. Zwanzig, J. Chem. Phys. **43**, 1978 (1965).

[45] R. Kosloff, J. Phys. Chem. **92**, 2087 (1988) and references therein.