Statistical-Mechanical theory of Many-Body Effects in reaction rates

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Statistical-mechanical theory of many-body effects in reaction rates

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Many-body effects in reaction rates depend on the ratio ϵ of a rate coefficient to the product of a diffusion coefficient and a radius, and on the reduced volume fraction ϕ_0 of one or more reactants. We present a statistical-mechanical theory of the macroscopic kinetics (deterministic rates) of reactions in solutions, and fluctuations therefrom, for arbitrary ϵ and ϕ_0, by deriving expressions for effective forward and reverse rate coefficients and their dependence on ϵ, ϕ_0 to lowest order. We use an enzyme-catalyzed reaction as an example. There are two corrections to rate coefficients (for $\epsilon = 0$, $\phi_0 = 0$) at a given ϵ, $\phi_0 \neq 0$, and both are proportional to $\phi_0^{1/2}$ (the square root of the total enzyme density in the example). The first is an uncorrelated screening term described by the single enzyme distribution function, which increases the rate; and the second a term described by correlations among enzymes, which decreases the rate. In the limit of very fast reactions the correlation term is negligible, and the screening term reduces to that previously obtained for diffusion controlled reactions. For other cases both terms contribute: for example, in the range $\phi_0 \sim 10^{-2}$ to 10^{-1} and $\epsilon \sim 1$–10 the corrections vary from a few percent to 30%, as obtained from numerical solutions of the corrections for the enzyme example. We discuss a quasistationary state of the example and derive a generalization of the Michaelis–Menten equation for all ϵ, ϕ_0. Fluctuations from the deterministic motion are shown to be small for three-dimensional systems.

I. INTRODUCTION

The principal purposes of the present paper are the formulation of a statistical-mechanical theory for obtaining expressions for deterministic reaction rates in chemical systems in which there are density-dependent interactions among some species due to reaction, and for considering the effect of fluctuations on those interactions. Direct interactions, such as Coulomb forces on reacting ions, affect the rate of a reaction, and a simple model of a reaction fits experiments quite well (Bronsted–Bjerrum theory[1] of primary and secondary salt effect). Direct interactions in the gas phase have been considered by means of a cluster theory.[2] In this article we discuss indirect interactions, due to chemical reaction and diffusion. Consider, as an example, an enzyme reaction: let the density of enzymes be in a dilute range but sufficiently large that the reaction of a substrate with an enzyme molecule affects the substrate concentration field at a neighboring enzyme. The enzyme–substrate reaction obeys Michaelis–Menten kinetics[3] and the reaction scheme is taken to be

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} ES \overset{k_2}{\rightarrow} E + PR, \tag{1.1}$$

where E denotes the enzymes, S the substrates, ES the complexes, and PR the products, and k_1, k_{-1}, k_2 are steps as shown in Eq. (1.1). We define the reduced quantities

$$\epsilon = k_1/4\pi a D, \qquad \phi_0 = 4\pi a^3 E_0/3, \tag{1.2}$$

where ϕ_0 is the total enzyme volume fraction, D the diffusion coefficient of the substrate S, a the radius of reaction of the enzyme, and E_0 the total density of enzyme (complexed or not).

The Michaelis–Menten expression for an enzyme reaction, and the common formulation of macroscopic kinetics, hold for the conditions $\epsilon = 0$, $\phi_0 = 0$, that is ideal solutions, well stirred (homogeneous). The corrections to ideal rate coefficients for very fast reactions $\epsilon \rightarrow \infty$, have been discussed by many authors for $\phi_0 = 0$[4–10] and also for $\phi_0 \neq 0$.[11–17] The bimolecular reaction rates for arbitrary ϵ have been analyzed by a few authors,[18–21] but only in regard to the screening correction.

In this article we propose a statistical-mechanical theory of reaction rates for arbitrary ϵ and ϕ_0. To do so we must treat the many-body problem consistently and investigate the role of fluctuations. The analysis shows the presence of an intermediate time scale, on which both screening and correlation interactions are important, and a late time scale, on which the correlation interactions vanish. We outline here briefly our approach.

Consider a three-dimensional classical isothermal enzyme reaction consisting of substrate S, enzymes E, and complexes ES. The enzymes and complexes are much larger than the substrate; they are assumed to be spheres with a radius a, and the distribution of their positions are assumed to be stationary. The substrate moves by diffusion with the diffusion coefficient D. We suppose that reaction may occur when a substrate approaches within a radius a of an enzyme and that the reactions obey Michaelis–Menten kinetics. Let $C(r,t)$ denote the macroscopic local number density of substrate, $E(r,t)$ that of the enzyme, and $E_S(r,t)$ that of complex, all of which are coarse grained in space and time,

$$u(r,t) = \sum_k \int d\omega\, u_k(\omega) \exp(ik\cdot r + i\omega t) \tag{1.3}$$

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with approximately $|k| \leqslant 1/r_c$ and approximately $|\omega| \leqslant 1/t_c$, where $u = C, E, E_S$, and (r_c, t_c) are minimum values for the characteristic wavelength and time scales of the reaction-diffusion process. The length cutoff r_c and the time cutoff t_c in Eq. (1.3) must be chosen to be much larger than the microscopic (molecular) length and time scales, respectively.

For a sufficiently dilute enzyme reaction, the rate equations for the averaged functions $\langle u(r,t) \rangle$ are given, on a macroscopic space and time scale, by

$$\left(\frac{\partial}{\partial t}\right)\langle C(r,t)\rangle = D\nabla^2\langle C\rangle - k_1\langle E\rangle\langle C\rangle + k_{-1}\langle E_S\rangle, \tag{1.4a}$$

$$\left(\frac{\partial}{\partial t}\right)\langle E(r,t)\rangle = -k_1\langle E\rangle\langle C\rangle + (k_{-1}+k_2)\langle E_S\rangle \tag{1.4b}$$

with the conservation law $\langle E(r,t)\rangle + \langle E_S(r,t)\rangle = E_0$, where $E_0 = N/V$ is the total enzyme density, N the total number of enzymes, and V the total volume of the system. Here the average is taken over the initial enzyme distribution function.

From Eqs. (1.4), a characteristic length l_R and time τ_R of the macroscopic processes concerned are defined by

$$l_R = (4\pi a_R\langle E\rangle)^{-1/2}, \quad \tau_R = l_R^2/D = 1/k_1\langle E\rangle, \tag{1.5a}$$

where l_R represents a screening length of reactive–diffusive interactions among enzymes, and $a_R = \epsilon a = k_1/4\pi D$ is an effective radius of an enzyme. For typical values of various lengths, see Table I. We assume that the total enzyme volume fraction ϕ_0 is small. As is shown in Sec. III C, the rate equations (1.4) hold on the length scale of order l_R and time scale of order τ_R when $\epsilon \ll 1$. Therefore, we have

$$a_R/l_R = (3\phi_R)^{1/2} \ll 1, \quad \tau_0'/\tau_R = 3\phi_R \ll 1, \tag{1.5b}$$

where $\phi_R(t)$ represents the effective enzyme volume fraction and is given by $\phi_R(t) = 4\pi a_R^3\langle E(t)\rangle/3 = \epsilon^3\phi_0\{\langle E(t)\rangle/E_0\}$ and $\tau_0' = a_R^2/D$ is a microscopic time related to a_R. Then, there are two different choices of the cutoff r_c, depending on the process of interest. Equation (1.5b) suggests that there exist two characteristic macroscopic stages. The first is an intermediate stage where the space-time cutoffs are set as

$$l_R \gg r_c \gg a_R, \quad \tau_R \gg t_c \gg \tau_0'. \tag{1.6}$$

TABLE I. Macroscopic length and time scales calculated for $\phi_0 = 10^{-4}$, $k_2 = k_{-1}$, and $k_1\langle C\rangle/(k_2 + k_{-1}) = 1.0$ at different values of $\epsilon = 0.01$, 1.0, and 100.0.

Symbols	Definition	$\epsilon = 0.01$	1.0	100.0
l_R/a	Eqs. (1.5)	815	74	6
τ_R/τ_0		815^2	74^2	6^2
l/a	Eqs. (1.10)	818	94	58
τ/τ_0		818^2	94^2	58^2
l_D/a	Eq. (1.11a)	58	58	58
τ_D/τ_0		58^2	58^2	58^2
L/a	Eq. (1.12)	22	22	22

At some initial time substrate gradients are set up among enzymes by the reactions betwee enzymes and substrate, and by concentration fluctuations of substrate. Thus, a reaction–diffusion process with the characteristic length l_R and the characteristic time τ_R becomes dominant and this intermediate stage is described by Eqs. (1.4). In the late stage, the density of substrate has decreased substantially. The reaction process is slow compared to diffusion, and spatial inhomogeneity in the system is negligible. The macroscopic variables $\langle u(r,t)\rangle$ become homogeneous in space, which leads to $\langle u(r,t)\rangle = \langle u(t)\rangle$. Therefore, this second stage is characterized by the inequalities

$$r_c \gg l_R \gg a_R, \quad t_c \gg \tau_R \gg \tau_0', \tag{1.7}$$

and the rate equations

$$\left(\frac{d}{dt}\right)\langle C(t)\rangle = -k_1\langle E\rangle\langle C\rangle + k_{-1}\langle E_S\rangle, \tag{1.8a}$$

$$\left(\frac{d}{dt}\right)\langle E(t)\rangle = -k_1\langle E\rangle\langle C\rangle + (k_{-1}+k_2)\langle E_S\rangle \tag{1.8b}$$

with the conservation law $\langle E(t)\rangle + \langle E_S(t)\rangle = E_0$.

The rate equations (1.4) and (1.8) are valid only when the effective enzyme volume fraction given by $\phi_R(t)$ is sufficiently small. If this condition is not satisfied, reaction–diffusion interactions among enzymes become important and modify the rate equations and the rate coefficients. Because of the long range of these interactions, the macroscopic processes of interest are complicatedly coupled to the microscopic processes, which are associated with the enzyme sphere configurations. In order to find the analogs of Eqs. (1.4) and (1.8) for the case of nonzero enzyme volume fraction ($\phi_0 \neq 0$) with arbitrary values of ϵ beginning with a microscopic point of view, therefore, we must set up appropriate microscopic equations and then must eliminate the microscopic process by suitable averagings. In the present paper, this is done by the following two types of coarse-graining procedures. The first is the reduction of variables by averaging over the enzyme sphere configurations. This is accomplished in Sec. II, where we start with molecular equations and derive linear Langevin-type equations for $u(r,t)$;

$$\left(\frac{\partial}{\partial t}\right)C(r,t) = D\nabla^2 C + I(r,t), \tag{1.9a}$$

$$\left(\frac{\partial}{\partial t}\right)E(r,t) = I(r,t) + k_2 E_S(r,t) \tag{1.9b}$$

with the conservation law $E(r,t) + E_S(r,t) = E_0$, and the reaction term

$$I(r,t) = \int dr' \int_0^t dt' [-\varphi(r,r',t-t')C(r',t') + \psi(r,r',t-t')E_S'(r',t')] + R(r,t), \tag{1.9c}$$

where φ and ψ are memory functions, and $R(r,t)$ is a fluctuating force which satisfies $\langle R(r,t)\rangle = 0$. In order to calculate the memory functions φ and ψ, we also introduce the enzyme number density $N(p,r;t)$, where p denotes an occupation number such that $p = 1$ is associated with a position r occupied by an enzyme, while $p = 0$ is associated with a position r occupied by a complex [cf. Eq. (2.17b)]. Then, the

effective number density of complexes $E'_S(r,t)$ in Eq. (1.9c) is given by $E'_S(r,t) = \int_0^1 (1-p) bN(p,r;t)dp$, where $b = (1+\epsilon p)^{-1}$ [cf. Eq. (2.16)].

Equations (1.9) hold for any arbitrary value of ϵ, and thus the characteristic length l_R and time τ_R can be generalized so as to treat any case for arbitrary ϵ. We may define a new screening length l and its related time τ by

$$l = (4\pi a^* \langle E \rangle)^{-1/2}, \quad \tau = l^2/D = 1/k_1 \langle E' \rangle, \quad (1.10a)$$

and also introduce a new effective radius of an enzyme a^* and its related time τ_0^* by $a^* = \epsilon a \langle E' \rangle / \langle E \rangle$ and $\tau_0^* = a^{*2}/D$, which satisfy

$$a^*/l = [3\phi(t)]^{1/2} \ll 1, \quad \tau_0^*/\tau = 3\phi(t) \ll 1, \quad (1.10b)$$

where $\phi(t)$ represents the effective volume fraction and is given by $\phi(t) \equiv 4\pi a^{*3} \langle E(t) \rangle / 3 = \phi_0 (\epsilon^3 \langle E' \rangle^3 / \langle E \rangle^2 E_0)$. Here the effective number density of enzymes $\langle E' \rangle$ is given by $\langle E'(t) \rangle = \int_0^1 pb \langle N(p,r;t) \rangle dp$. Then, there are also two characteristic stages as discussed before, where (l_R, τ_R) and (a_R, τ_0') are now replaced by (l,τ) and (a^*, τ_0^*), respectively.

Depending on the value of ϵ, we have the following two further extreme cases. The first is the fast reaction case [A], where $\epsilon \gg 1$, and

$$l = l_D = (4\pi a E_0)^{-1/2} \gg a^* = a,$$
$$\tau = \tau_D \gg \tau_0^* = \tau_0 = a^2/D. \quad (1.11a)$$

Here l_D represents the screening length in case [A], and $\tau_D = l_D^2/D = 1/4\pi a D E_0$. In this case, Eq. (1.9a) reduces exactly to that obtained in Ref. 15, referred to as TC, on the study of diffusion-controlled reactions. Hence this is the so-called diffusion-controlled limit. The second is the slow reaction case [B], where $\epsilon \ll 1$, and

$$l = l_R \gg a^* = a_R, \quad \tau = \tau_R \gg \tau_0^* = \tau_0'. \quad (1.11b)$$

As the volume fraction ϕ_0 decreases, the screening length l becomes much larger than the interenzyme distance given by

$$L = a/\phi_0^{1/3}. \quad (1.12)$$

Therefore, the number of enzymes in the volume $l^3, E_0 l^3$, is very large even in the low density limit $E_0 \to 0$. The definition of the macroscopic lengths and times and their order of magnitude are given in Table I.

The second coarse-graining procedure is a reduction of processes, that is the extraction of the macroscopic process characterized by (l,τ) from Eqs. (1.9) by suppression of the microscopic process characterized by (a^*, τ_0^*). This is done by the scaling expansion method[22] with the following central results: In the intermediate stage, we have the scaling

$$r \to Sr, \quad t \to S^2 t, \quad l \to Sl, \quad \tau \to S^2 \tau, \quad \phi \to S^{-2}\phi, \quad (1.13a)$$
$$\langle u(r,t) \rangle \to S^{-2} \langle u(r,t) \rangle, \quad \delta u(r,t) \to S^{-(d+2)/2} \delta u(r,t) \quad (1.13b)$$

with $S \gg 1$, and approximately $|r| \geqslant r_c$ and approximately $t \geqslant t_c$, where $\delta u(r,t) = u(r,t) - \langle u(r,t) \rangle$ denotes the fluctuations around the deterministic motion $\langle u(r,t) \rangle$, and the molecular quantities such as D and k_1 are all kept constant. Then, by applying the scaling (1.13) to Eqs. (1.9) and expanding them in powers of S^{-1}, we can carry out three expansions all consistent with each other. The first is the expansion in the small parameter $\phi^{1/2}$, Eq. (1.10b). The second is the expansion in the spatial gradients ∇, which permits us to write Eqs. (1.9) in a spatially local form such as in Eqs. (1.4). The third is the expansion in the slowness parameter $\partial/\partial t$, which leads to a Markov equation such as Eqs. (1.4). Thus, the scaling method carries out the space-time coarse graining in a manner consistent with the expansion in the small parameter $\phi^{1/2}$. From Eq. (1.13b), we have $|\delta u / \langle u \rangle| = \phi^{(d-2)/2}$. Therefore, the scaling method also enables us to evaluate the magnitude of the fluctuations relative to the deterministic motion.

In Sec. III, we discuss the intermediate stage for arbitrary ϵ and show that reactive–diffusive long-range interactions among enzymes separated by a distance of order $l (\gg L)$ cause two kinds of first-order corrections; an uncorrelated term $v(r,t)$, which is described by a deterministic part of a single-enzyme distribution function, $f(p,r;t) = \langle N(p,r;t) \rangle$, and a correlated term $w(r,t)$ which is described by a fluctuating part of the single-enzyme distribution function, $\delta N(p,r;t) = N(p,r;t) - f(p,r;t)$, and that in turn by an enzyme pair correlation function. Thus, we obtain for arbitrary values of ϵ, to order S^{-1},

$$\langle I(r,t) \rangle = -k_1 \langle E' \rangle \langle C \rangle + k_{-1} \langle E'_S \rangle + [3\phi(t)]^{1/2} [v(r,t) - w(r,t)], \quad (1.14)$$

where v and w are averaged functionals of E' and $\langle C \rangle$. We see from Eq. (1.14) that the first-order correction term is proportional to the square root of the enzyme volume fraction ϕ, i.e., the enzyme density $\langle E \rangle$. In case [A] where $\epsilon \gg 1$, the correction results only from the uncorrelated term v, since the uncorrelated term w is of order ϵ^{-1}. This is due to the fact that since the time scale of the reaction process is much shorter than that of the diffusion process, on the time scale of order τ_D the reactions are already completed and the fluctuations are averaged out. Then, Eq. (1.14) reduces to

$$\langle I(r,t) \rangle = -(4\pi a D) E_0 \times [1 + (3\phi_0)^{1/2}] \langle C(r,t) \rangle + O(\epsilon^{-1}). \quad (1.15)$$

This is identical to that obtained previously for diffusion-controlled reactions.[11–17] In all other cases the correction term results from both uncorrelated and correlated terms, both of which may play important roles. Estimates of magnitudes of the correction terms from screening and correlation terms are obtained for ranges of ϵ and ϕ for an enzyme reaction by numerical solution of the derived corrections.

In Sec. IV, we study the late stage characterized by the space-time cutoffs (r_c, t_c) which are prescribed by the condition $r_c \gg l$ and $t_c \gg \tau$. It is shown that the reaction process is described by the following nonlinear Fokker–Planck equation for the single-enzyme distribution function $f(p,r;t)$:

$$\left(\frac{\partial}{\partial t}\right) f(p,r;t) = \left(\frac{\partial}{\partial p}\right) \left[-y(p,z) + [3\phi(z)]^{1/2} \gamma(z) pb + \left(\frac{\partial}{\partial p}\right) pb \right] f, \quad (1.16)$$

where y is a drift term and is given by Eq. (4.7), and $\gamma(z)$ is a coefficient given by Eq. (4.5a). Here z is a scaled substrate

density given by $z(t) = k_1\langle C(t)\rangle/(k_{-1}+k_2)$. Thus, we find the deterministic rate equations

$$\left(\frac{d}{dt}\right)\langle C\rangle = -\tilde{k}_1(z)\langle E\rangle\langle C\rangle + \tilde{k}_{-1}(z)\langle E_S\rangle, \tag{1.17a}$$

$$\left(\frac{d}{dt}\right)\langle E(t)\rangle = -\tilde{k}_1(z)\langle E\rangle\langle C\rangle + [\tilde{k}_{-1}(z)+k_2]\langle E_S\rangle \tag{1.17b}$$

with the renormalized rate coefficients

$$\tilde{k}_1(z) = k_1\{1+[3\phi(z)]^{1/2}[A_1(z) + A_{-1}(z)]\}\langle E'\rangle/\langle E\rangle, \tag{1.18a}$$

$$\tilde{k}_{-1}(z) = k_{-1}[1+(3\phi(z)^{1/2}A_{-1}(z)]\langle E_s'\rangle/\langle E_s\rangle, \tag{1.18b}$$

where the coefficients A_1 and A_{-1} are averaged functionals of E and E', and depend only on the scaled parameters z, ϵ, and $\kappa = k_{-1}/(k_{-1}+k_2)$. The rate coefficients k_1 and k_{-1} are renormalized by the reactive–diffusive long-range interactions differently, and their deviations from the infinitely dilute limit go as the square root of the enzyme density E_0. When $k_2 \neq 0$ (i.e., irreversible reactions) the density $\langle C\rangle$ approaches the value zero in the long time limit $t\to\infty$. Hence $\tilde{k}_1$ and $\tilde{k}_{-1}$ reduce to

$$\tilde{k}_1 = [k_1/(1+\epsilon)]\{1+(3K_0\phi_0)^{1/2}[\epsilon/(1+\epsilon)]^{3/2}\}, \tag{1.19a}$$

$$\tilde{k}_{-1} = [k_{-1}/(1+\epsilon)]\{1+(3K_0\phi_0)^{1/2}[\epsilon/(1+\epsilon)]^{3/2}\}, \tag{1.19b}$$

respectively, where $K_0 = k_2(1+\epsilon)/[k_{-1}+k_2(1+\epsilon)]$. When $\epsilon = 0$, therefore, there is no correction to the rate coefficients. In the low density limit $E_0\to 0$, these coefficients reduce to those obtained for irreversible reactions by other authors.[4–6,18–21] On the other hand, when $k_2 = 0$ (i.e., reversible reactions), the scaled density $z(t)$ approaches the equilibrium value $z(\infty) = \langle E_S(\infty)\rangle/\langle E(\infty)\rangle$ in the $t\to\infty$ limit. Hence we obtain

$$\tilde{k}_1 = k_1[1+z(\infty)]/[1+z(\infty)+\epsilon], \tag{1.20a}$$

$$\tilde{k}_{-1} = k_{-1}[1+z(\infty)]/[1+z(\infty)+\epsilon]. \tag{1.20b}$$

Therefore, there is no correction to the rate coefficients for reversible reactions. These coefficients do not agree with those obtained in the low concentration limit $z(\infty)\to 0$ by previous authors.[18–21]

Under the quasistationary state approximation, $d\langle E(t)\rangle/dt = d\langle E_S(t)\rangle/dt = 0$, we also obtain

$$\left(\frac{d}{dt}\right)\langle C(t)\rangle = -\tilde{k}(z)E_0\langle C(t)\rangle \tag{1.21}$$

with the effective rate coefficient

$$\tilde{k}(z) = \tilde{k}_1k_2/(\tilde{k}_1\langle C\rangle + \tilde{k}_{-1} + k_2). \tag{1.22}$$

This is a generalization of the Michaelis–Menten equation (where $\epsilon = 0$, $\tilde{k}_1 = k_1$ and $\tilde{k}_{-1} = k_{-1}$) to first order in the small parameter $\phi^{1/2}$ given by Eq. (1.10b). Equations (1.16), (1.17), and (1.21) are the most important results in the present paper.

The outline of this paper is as follows. In Sec. II, we first transform the molecular equations into linear Langevin-type equations (1.9) and obtain microscopic expressions for the memory functions and fluctuating force by employing a similar formalism to that previously introduced by TC[15] to study diffusion-controlled reactions. In order to calculate the memory functions, we then define probability distribution functions of finding enzymes at given positions and derive a hierarchy of equations for them. In Sec. III, the intermediate stage is studied. The scaling method is first introduced to order all terms in the scaling parameter S^{-1}. By employing a similar approach to that introduced in Ref. 23, referred to as TK, on the study of particle growth, we derive kinetic equations for single-enzyme distribution function $f(p,r;t)$ and the variance $\langle\delta N(p,r;t)\delta N(p',r';t)\rangle$ systematically to order $\phi^{1/2}$ in the expansion in S^{-1}. It is shown that although the fluctuations $\delta N(p,r;t)$ are small as compared to the deterministic part $f(p,r;t)$ when $d>2$, they are important since they cause an appreciable correction to the rate coefficients to order $\phi^{1/2}$. The deterministic rate equations (1.9) with Eq. (1.14) are derived to order $\phi^{1/2}$. The fourth section focuses on the late stage. A nonlinear Fokker–Planck equation (1.16) is derived for the single-enzyme distribution function $f(p,r;t)$. The new rate equations (1.17) are found. The quasistationary state is further discussed and Eq. (1.21) is derived. The quasistationary distribution function and the renormalized rate coefficients are calculated numerically. The effects of the uncorrelated and correlated terms on the deterministic reaction rate are discussed. The theoretical values of the normalized rate coefficients $\tilde{k}_1(z)/k_1$ and $\tilde{k}(z)k_1$ are calculated, based on the experimental data for the catalase-hydrogen peroxide reaction by Strother and Ackerman[24] for a range of the parameters ϵ, ϕ_0. The volume fraction (ϕ_0) dependence of the rate coefficients is stressed. Section IV is devoted to a short summary and some remarks.

II. BASIC EQUATIONS

Let $P_i(t)$ denote an occupation number such that $P_i(t) = 1$ is associated with a position X_i occupied by an enzyme, while $P_i(t) = 0$ is associated with a position X_i occupied by a complex (enzyme and substrate). We assume that $P_i(t)$ is a smooth function of t which takes any value between zero and one. Then, the number density of enzymes is defined by

$$E(r,t) = (1/4\pi)\sum_{i=1}^{N}\int d\Omega_i\, P_i(t)\delta(r-r_i), \tag{2.1}$$

where Ω_i is the orientation of the vector $n_i = r_i - X_i$ from the center of the ith sphere X_i to a point on its surface r_i. Similarly, the number density of complexes is defined by

$$E_S(r,t) = (1/4\pi)\sum_{i=1}^{N}\int d\Omega_i\, Q_i(t)\delta(r-r_i), \tag{2.2}$$

where $Q_i(t) = 1$ when a position X_i is occupied by a complex, and $Q_i(t) = 0$ when occupied by an enzyme. Then, the reaction–diffusion processes at the molecular level are described by

$$\left(\frac{\partial}{\partial t}\right)C(r,t) = D\nabla^2C(r,t) + I(r,t), \tag{2.3a}$$

$$\left(\frac{\partial}{\partial t}\right)E(r,t) = I(r,t) + k_2E_S(r,t) \tag{2.3b}$$

with the reaction term

$$I(r,t) = -k_1 E(r,t) C(r,t) + k_{-1} E_S(r,t), \tag{2.4}$$

where $C(r,t)$ is the instantaneous number density of substrates and $E_S(r,t)$ satisfies the conservation law

$$E(r,t) + E_S(r,t) = E_0. \tag{2.5}$$

A. Reduced equations of motion for $C(r,t)$ and $E(r,t)$

Equations (2.3) are starting equations for studying interactive effects among enzymes due to the reaction of substrates with enzymes. The average of the reaction term I contains the correlation function $\langle EC \rangle$; since the total enzyme density E_0 is not dilute, this term cannot simply be decoupled. Therefore, we need to derive an equation for $\langle EC \rangle$ which also contains the higher correlation terms such as $\langle E^2 C \rangle$, and we have to deal with a hierarchy of equations for the correlation functions.

Rather than solve such equations directly, we first rewrite the reaction term (2.4) as

$$I(r,t) = \sum_{i=1}^{N} \int d\Omega_i \, \delta(r - r_i) \sigma_i(\Omega_i,t) \tag{2.6}$$

with

$$4\pi\sigma_i(\Omega_i,t) = -k_1 P_i(t) C(r_i,t) + k_{-1} Q_i(t), \tag{2.7}$$

where the density σ_i denotes the time-dependent source of reaction between the substrates and the ith enzyme at point Ω_i on its surface. In the following, we then solve the reaction–diffusion equation (2.3a) with Eq. (2.6) for $\sigma_i(\Omega_i,t)$ and express σ_i in terms of $C(r_i,t)$. We combine that result with Eq. (2.7) to obtain $C(r_i,t)$ in terms of $P_i(t)$. Thus, we write the reaction term $I(r,t)$ in terms of $P_i(t)$. Finally we separate I into a deterministic part and a fluctuating part by means of a coarse graining procedure and thus transform Eq. (2.3a) into the form of linear Langevin-type equations. The following porcedure is mostly the same as that introduced by TC.[15]

The formal solution of Eq. (2.3a) with Eq. (2.6) is given by

$$C(r,t) = C_0(r,t) + \sum_{i=1}^{N} \int_0^t dt' \int d\Omega_i' \, g_0(r - r_i', t - t') \times \sigma_i(\Omega_i', t') \tag{2.8}$$

with the free propagator

$$g_0(r,t) = (1/4\pi D)(2\pi i)^{-1}(2\pi)^{-3} \times \int dz \int dk \exp(ik\cdot r + zt)/[k^2 + (z/D)], \tag{2.9}$$

where $C_0(r,t)$ is the free concentration field in the absence of enzymes. In order to solve Eq. (2.8) for $\sigma_i(\Omega_i,t)$, it is convenient to introduce the inverse propagator $K_i(\Omega_i,\Omega_i',t,t')$ of the free propagator $g_0(r_i - r_i', t - t') = g_0(\Omega_i,\Omega_i';t - t')$ by

$$\int_{t'}^{t} dt'' \int d\Omega_i'' \, K_i(\Omega_i,\Omega_i'';t,t'') g_0(\Omega_i'',\Omega_i';t'' - t') = \delta(\Omega_i - \Omega_i')\delta(t - t'). \tag{2.10}$$

As is shown in Appendix A, use of Eqs. (2.8) and (2.10) then leads to

$$\sigma_i(\Omega_i,t) = \int_0^t dt' \int d\Omega_i' \, K_i(\Omega_i,\Omega_i';t,t') [C(r_i',t') - C_0(r_i',t') - \int_0^{t'} dt'' \int dr'' \, g_0(r_i' - r'', t' - t'') \times \theta(|r'' - X_i| - a) I(r'',t'')]. \tag{2.11}$$

Here the step function $\theta(x)$ of Eq. (2.11), $\theta(x) = 1$ for $x > 0$ and $\theta(x) = 0$ for $x \leqslant 0$, comes from the fact that the spheres are supposed to be nonoverlapping and nontouching.

We now solve Eqs. (2.7) and (2.11) for $C(r_i,t)$. As is shown later, only the long–range interaction over a distance of order l is important. Therefore, the free propagator g_0 in Eq. (2.11) is a slowly varying function in space and time [cf. Eq. (3.19)]. On the other hand, as is seen from Eq. (2.10), $K_i(\Omega_i,\Omega_i';t,t')$ is related to a short-range interaction over a distance of order a through the free propagator $G_0(\Omega_i,\Omega_i';t,t')$, which has a time scale of order τ_0. Hence this is a rapidly varying function with the characteristic time τ_0. On the time scale of order τ, therefore, we can make a Markov approximation in Eq. (2.11) in which the time t' is replaced by t. This corresponds to an expansion in the slowness parameter $(\partial/\partial t)$; $C(r_i',t') = C(r_i',t) + O[(t - t')(\partial/\partial t)]$, where $(t - t')(\partial/\partial t)$ is of order τ_0/τ. Similarly, on the length scale of order l, we can replace the position vector r_i' by X_i in Eq. (2.11). This corresponds to an expansion in the spatial gradient ∇; $C(r_i',t') = C(X_i,t') + O(R_i\cdot\nabla_i)$, where $R_i\cdot\nabla_i$ is of order a/l. Since the error introduced by these expansions is of order ϕ, they have no effect on the first-order correction. However, these expansions must be verified self-consistently by means of the space-time coarse-graining procedure discussed in Sec. III A. As is shown in Appendix B, use of Eqs. (2.7), (2.10), and (2.11) thus leads to

$$C(X_i,t) = [1 + \epsilon P_i(t)]^{-1} \Big[C_0(X_i,t) + (k_{-1}/4\pi a D) Q_i(t) + \int_0^t dt' \int dr' g_0(X_i - r', t - t') \theta(|r' - X_i| - a) I(r',t') \Big] \tag{2.12}$$

where ϵ is given by Eq. (1.5). Inserting Eq. (2.12) into Eq. (2.7) and using Eq. (2.6), we can write the reaction term $I(r,t)$ as

$$I(r,t) = -k_1 \int_0^t dt' \int dr' \, T(r,t;r',t') C_0(r',t') + k_{-1} E_S'(r,t) - k_1 \int_0^t dt' \int dr' \, M(r,t;r',t') I(r',t') \tag{2.13}$$

with

$$T(r,t;r',t') = \int_0^1 dp\, T_p(r,t;r't') = \delta(r-r')\delta(t-t')E'(r,t), \quad (2.14)$$

$$M(r,t;r',t') = \int_0^1 dp\, M_p(r,t;r't') = E'(r,t)g_0(r-r',t-t')\theta(|r-r'|-a), \quad (2.15)$$

$$E'_S(r,t) = \int_0^1 dp\, E'_{Sp}(r,t) = \int_0^1 dp\, qbN(p,r;t), \quad (2.16)$$

where $q = 1-p$. Here $E'(r,t)$ is given by

$$E'(r,t) = \int_0^1 dp\, pbN(p,r;t) \quad (2.17a)$$

with the enzyme number density

$$N(p,r;t) = \sum_{i=1}^{N} \delta[p - P_i(t)]\delta[r - X_i(0)], \quad (2.17b)$$

where

$$b = (1+\epsilon p)^{-1}. \quad (2.17c)$$

For notational convenience, we introduce a coordinate-time matrix representation $I = [I(r,t)]$, $T = [T(r,t;r',t')]$, $M = [M(r,t;r',t')]$ and $A' = [A'(r,t)]$, etc. Then, Eq. (2.13) yields

$$I = -k_1 H\cdot C_0 + k_{-1}B, \quad (2.18)$$

where

$$H = [1 + k_1 M]^{-1}\cdot T, \quad (2.19)$$

$$B = [1 + k_1 M]^{-1}\cdot A'. \quad (2.20)$$

Thus the reaction term I is written in terms of $P_i(t)$, that is, in terms of $N(p,r;t)$.

We now separate $I(r,t)$ into a deterministic part and a fluctuating part by eliminating the microscopic processes associated with the enzyme sphere configurations. This is done by averaging over the initial enzyme distribution function $\rho_0\{[p_i(0),X_i(0)]\}$. As is shown in Appendix C, we can write the reaction term I as

$$I = -\varphi\cdot C + \psi\cdot E'_S + R \quad (2.21)$$

with the memory functions

$$\varphi = k_1[1 - k_1\langle H\rangle\cdot g_0]^{-1}\cdot\langle H\rangle, \quad (2.22)$$

$$\psi\cdot\langle E'_S\rangle = k_{-1}[1 - k_1\langle H\rangle\cdot g_0]^{-1}\cdot\langle B\rangle \quad (2.23)$$

and the fluctuating force

$$R = [1 - k_1\langle H\rangle g_0]^{-1}[-k_1(H - \langle H\rangle)\cdot C_0 + k_{-1}(B - \langle B\rangle)] - \psi\cdot(E'_S - \langle E'_S\rangle), \quad (2.24)$$

where $\langle R\rangle = 0$, and C_0 is configuration independent. The angular brackets denote the average over the initial distribution function $\rho_0\{[P_I(0),X_i(0)]\}$.

Thus, use of Eqs. (2.3a) and (2.21) leads to a linear Langevin-like equation for $C(r,t)$. In the limit of fast reaction, $\epsilon\to\infty$, this equation reduces exactly to Eq. (2.13) of Ref. 15 obtained by TC for diffusion-controlled reactions, since $\epsilon pb\to 1$ and $b\to 0$ as $\epsilon\to\infty$ [cf. Eq. (2.17c)].

B. Decomposition into a deterministic and a fluctuating motion

We wish to decompose the time evolution of $C(r,t)$ into a deterministic part $\langle C(r,t)\rangle$ and a fluctuating part $\delta C(r,t)$;

$$C(r,t) = \langle C(r,t)\rangle + \delta C(r,t). \quad (2.25)$$

This decomposition is essential since the ϕ dependence of the fluctuations differs from that of the deterministic motion.[21] In the next section we show that the relative magnitude of the fluctuations compared to the deterministic part is of order $\phi^{1/2}$ when $d = 3$. From Eqs. (2.3a) and (2.21), we then obtain

$$\left(\frac{\partial}{\partial t}\right)\langle C(r,t)\rangle = D\nabla^2\langle C\rangle + \langle I(r,t)\rangle, \quad (2.26a)$$

$$\left(\frac{\partial}{\partial t}\right)\delta C(r,t) = D\nabla^2\delta C + \delta I(r,t) \quad (2.26b)$$

with

$$\delta I = I - \langle I\rangle = -\varphi\cdot\delta C + \psi\cdot\delta E'_S + R, \quad (2.27)$$

where $\delta E'_S = E'_S - \langle E'_S\rangle$. Similarly to Eqs. (2.26), from Eqs. (2.3b) and (2.5), we also have

$$\left(\frac{\partial}{\partial t}\right)\langle E(r,t)\rangle = \langle I(r,t)\rangle + k_2\langle E_S(r,t)\rangle, \quad (2.28a)$$

$$\left(\frac{\partial}{\partial t}\right)\delta E(r,t) = \delta I(r,t) + k_2\delta E_S(r,t) \quad (2.28b)$$

with the conservation laws

$$\langle E(r,t)\rangle + \langle E_S(r,t)\rangle = E_0, \quad (2.29a)$$

$$\delta E(r,t) + \delta E_S(r,t) = 0, \quad (2.29b)$$

where $\delta E(r,t) = E(r,t) - \langle E(r,t)\rangle$ and $\delta E_S(r,t) = E_S(r,t) - \langle E_S(r,t)\rangle$.

Thus, our study of the reaction–diffusion process reduces to two analyses: one of the memory functions φ and ψ, and the other of the correlation function $\langle R(r,t)R(r',t')\rangle$ which determines the stochastic properties of the fluctuations.

C. Kinetic equations for distribution functions

The correlation functions are the averaged functionals of the product of the enzyme number density $N(p,r;t)$ given by Eq. (2.17b). In order to calculate such functions, therefore, we finally need to discuss the time evolution of $N(p,r;t)$.

We first derive an equation for the occupation number of the ith enzyme $P_i(t)$. The total flux density of the substrates across a sphere of radius a around the ith enzyme is given by

$$j_i(t) = -Da\int d\Omega_i(n_i\cdot\nabla C)_{ri}. \quad (2.30)$$

We assume that reaction may occur when a substrate approaches within a radius a of the center of an enzyme. Then, $P_i(t)$ obeys

$$\left(\frac{d}{dt}\right)P_i(t) = j_i(t) + k_2 Q_i(t), \quad (2.31)$$

where $Q_i(t) = 1 - P_i(t)$ from the definition of $P_i(t)$. We note from Eq. (2.30) that the rate coefficients k_1 and k_{-1}

appear in the flux $j_i(t)$ through the solution $C(r,t)$ of Eq. (2.3a).

Next let us introduce the m-enzyme distribution function by

$$f_m(1,...,m;t) = \prod_{i\neq j}^{m} \theta(|r_{ij}| - 2a) \times \langle N(1,t)\cdots N(m,t)\rangle \tag{2.32a}$$

with

$$\int d(1) f_1(1) = N, \quad \int d(m+1) f_{m+1}(1,...,m+1) = N f_m(1,...,m), \tag{2.32b}$$

where $r_{ij} = r_i - r_j$, and $m = (p_m, \Upsilon_m)$ represents the specific value of the occupation number and position of the mth enzyme. Similarly to Eq. (2.25), we decompose $N(i;t)$ as $N(i;t) = f_1(i;t) + \delta N(i;t)$; the ϕ dependence of the fluctuations δN will turn out to differ from that of the deterministic part f_1. Therefore, it is convenient further to introduce the correlation functions $G_m(1,...,m;t)$ through the Ursell–Mayer procedure

$$\begin{aligned}
f_2(1,2) &= f(1)f(2) + G_2(1,2),\\
f_3(1,2,3) &= f(1)f(2)f(3) + (1 + e_{12} + e_{13}) f(1) G_2(2,3) + G_3(1,2,3),\\
f_4(1,2,3,4) &= f(1)f(2)f(3)f(4) + (1 + e_{23} + e_{24}) G_2(1,2) G_2(3,4) + (1 + e_{13} + e_{14} + e_{23} + e_{24} + e_{13}e_{24})\\
&\quad \times f(1)f(2) G_2(3,4) + (1 + e_{12} + e_{13} + e_{14}) f(1) G_3(2,3,4) + G_4(1,2,3,4),
\end{aligned} \tag{2.33}$$

and so on, where $f(i) = f_1(i)$, and e_{ij} is the exchange operator between i and j. Then, we have

$$\langle E(r,t)\rangle = \int_0^1 dp\, p f(p,r;t), \tag{2.34a}$$

$$\langle \delta E(r_1,t)\delta E(r_2,t)\rangle = \int_0^1 dp_1 \int_0^1 dp_2\, p_1 p_2 \chi(1,2;t) \tag{2.34b}$$

with the variance

$$\chi(1,2;t) = \langle \delta N(1;t)\delta N(2;t)\rangle = \delta(1-2) f(1;t) + G_2(1,2;t). \tag{2.35}$$

Thus, the time evolution of $E(r,t)$ is described by f and χ.

By taking the time derivative of Eq. (2.32a) and then using Eqs. (2.31), (2.33), and (2.35), we obtain

$$\left(\frac{\partial}{\partial t}\right) f(1) = -\left(\frac{\partial}{\partial p_1}\right)[J_1(1) + k_2 q_1 f(1)], \tag{2.36a}$$

$$\left(\frac{\partial}{\partial t}\right) G_2(1,2) = -(1 + e_{12})\left(\frac{\partial}{\partial p_2}\right)[J_2(2,1) - f(1)J_1(2) + k_2 q_2 G_2(1,2)], \tag{2.36b}$$

$$\left(\frac{\partial}{\partial t}\right)\chi(1,2) = -(1 + e_{12})[\delta(1-2)J_1(2) + J_2(2,1) - f(1)J_1(2)\, k_2 q_2 \chi], \tag{2.37}$$

and so on, with

$$J_m(2,1,...,m) = \prod_{j\neq i}^{m} \theta(|r_{ij}| - 2a)\langle I_p(r_2;t) \times N(1,t)\cdots N(m,t)\rangle, \tag{2.38}$$

where

$$I_p(r;t) = \sum_{i=1}^{N} j_i(t)\delta[p - P_i(t)]\delta[r - X_i(0)]. \tag{2.39}$$

From Eqs. (2.3b) and (2.31) we have $\int I_p(r,t)dp = I(r,t)$. As is shown in Appendix D, we can write I_p as

$$I_p = -k_1 H_p \cdot (1 + g_0\cdot\varphi)\cdot\langle C\rangle + k_{-1}[B_p + k_1 H_p\cdot(1 + g_0\cdot\varphi)\cdot g_0\cdot\langle B\rangle] \tag{2.40}$$

with

$$H_p = T_p - k_1\cdot M_p\cdot H, \tag{2.41a}$$

$$B_p = E'_{Sp} - k_1 M_p\cdot B. \tag{2.41b}$$

From Eq. (2.37), we then obtain

$$J_1(p) = -\varphi_p\cdot\langle C\rangle + \Psi_p, \tag{2.42}$$

where

$$\varphi_p = k_1\langle H_p\rangle\cdot(1 + g_0\cdot\varphi), \tag{2.43a}$$

$$\Psi_p = \psi_p\cdot\langle E'_S\rangle = k_{-1}[\langle B_p\rangle + \varphi_p\cdot g_0\cdot\langle B\rangle]. \tag{2.43b}$$

Here $\int \varphi_p\, dp = \varphi$ and $\int \psi_p\, dp = \psi$.

Equations (2.36) and (2.37) give the system of kinetic equations which describe not only the deterministic motion in the reaction–diffusion processes but also the fluctuations around it, since the averaged reaction term $\langle I\rangle$ is determined by $J_1(p,r,t) = \langle I_p(r,t)\rangle$, and the fluctuations are described by χ through Eq. (2.34b).

III. MACROSCOPIC RATE EQUATIONS FOR REACTION–DIFFUSION PROCESSES

In the present section we derive the system of macroscopic rate equations in the intermediate stage which describe the reaction–diffusion processes characterized by the space cutoff r_c as prescribed by the condition $l \gg r_c \gg a^*$, Eq. (1.10b).

A. Scaling method

We first discuss a scaling method[21] which can be used systematically to extract the reaction–diffusion processes described by the length and time scale (l,τ), given by Eq. (1.10a), from the microscopic processes characterized by (a^*,τ_0^*). Since $l \gg a^*$ and $\tau \gg \tau_0^*$, we introduce a scale transformation

$$l \to Sl \quad \tau \to S^{\theta}\tau, \quad \phi^{1/2} = (a^*/l) \to S^{-1}\phi^{1/2} \tag{3.1}$$

with $S \gg 1$, where (a^*, τ_0^*) and all molecular quantities such as D, k_1, and ϵ are fixed. Here the time exponent θ is given by $\theta = 2$ since $\tau = l^2/D$. Then, the space-time coarse graining is given by the scaling

$$r \to Sr, \quad t \to S^2 t \tag{3.2}$$

for approximately $|r| \gtrsim r_c$ and approximately $t \gtrsim \tau_c$. Use of Eqs. (1.10a), (3.1), and (3.2) thus leads to

$$\langle E' \rangle \to S^{-2}\langle E' \rangle, \quad k_{-1} \to S^{-2}k_{-1}, \quad k_2 \to S^{-2}k_2 \tag{3.3a}$$

which is combined with Eqs. (2.17a), (2.32b), and (2.34a) to give

$$\langle E \rangle \to S^{-2}\langle E \rangle, \quad f \to S^{-2}f, \quad E_0 \to S^{-2}E_0,$$
$$N \to SN, \quad V \to S^d V. \tag{3.3b}$$

The enzyme density E_0 approaches zero in the scaling limit $S \to \infty$. The number of enzymes in a volume $r_c^d, E_0 r_c^d$, however, increases in proportion to $\phi^{(2-d)/2}$ when $d > 2$. This suggests that the fluctuations δC, δE, and χ may be characterized by a Gaussian process but not by a Poisson process even in the low-density limit $E_0 \to 0$.[22]

Since the $\langle I \rangle$ term in Eq. (2.26a) must balance the left-hand side of Eq. (2.26a) and that of Eq. (2.28a), respectively, we find

$$\langle I \rangle \to S^{-4}\langle I \rangle, \ \langle C \rangle \to S^{-2}\langle C \rangle. \tag{3.4}$$

From Eqs. (2.29a) and (3.3b), we also obtain $\langle E_S \rangle \to S^{-2}\langle E_S \rangle$ and $\langle E_S' \rangle \to S^{-2}\langle E_S' \rangle$. Then, the macroscopic scale invariance under the scaling (3.1) and (3.2) leads to the following scaled forms:

$$\langle u(r,t) \rangle = \phi \tilde{u}(r/l, t/\tau), \tag{3.5}$$

$$f(p,r;t) = \phi \tilde{f}(p, r/l; t/\tau). \tag{3.6}$$

where $\tilde{u}$ and $\tilde{f}$ are scale invariants. Here $\langle E' \rangle$ and $\langle E_S' \rangle$ have the same scaled form as Eq. (3.5).

The ϕ dependence of the fluctuations will turn out to differ from that of the deterministic motion, and hence we also define a scaling exponent β by

$$\delta u(r,t) = \phi^{\beta/2} \delta \tilde{u}(r/l, t/\tau), \tag{3.7}$$

where δC, δE, and δA have the same exponent β from Eqs. (2.26b), (2.28b), and (2.29b).

We next discuss the correlation function G_m. There are two types of correlation functions which originate from different interactions. One is the spatial correlation due to the short-range interactions over a distance of order a, which gives a higher-order contribution in ϕ. The other correlation comes from the long-range interactions over a distance of order l, due to reaction; this has the invariant form

$$G_m(1,\ldots,m;t) = \phi^{\mu} m/2 \tilde{G}_m(p_1,\ldots,p_m; r_1/l, r_{21}/l, \ldots, r_{m1}/l; t/\tau). \tag{3.8a}$$

Here the exponent μ_m can be obtained by integrating G_m with respect to $r_1 \ldots r_m$ over the volume l^d. Since G_m is nonvanishing only for relative distances shorter than l, we have $\int d(1) \cdots \int d(m) G_m \approx E_0 l^d$. This is combined with Eq. (3.8a) to obtain $\mu_m = 2 + (m-1)d$. From Eq. (2.34b) and (3.7), therefore, we find $\beta = (d+2)/2$, and

$$\chi(p_1,r_1,p_2,r_2;t) = \phi^{\beta} \tilde{\chi}(p_1,p_2,r_1/l, r_{21}/l; t/\tau). \tag{3.8b}$$

Thus, we have

$$|\delta C/\langle C \rangle|^2 \approx |G_2/f^2| \approx |G_3/fG_2| \approx \phi^{(d-2)/2}. \tag{3.9}$$

Therefore, if $d > 2$, then the higher-order correlations become less important and the hierarchy of Eqs. (2.36) can be truncated. Thus, the fluctuations δu are negligible compared to their average values $\langle u \rangle$; nonetheless, they are important since they affect the rate coefficients k_1 and k_{-1} to order $\phi^{1/2}$ [see Eq. (3.25b)].

We apply the scaling (3.1) and (3.2) to the deterministic equations (2.26a) and (2.36a), and obtain

$$\left(\frac{\partial}{\partial t}\right)\langle C(r,t) \rangle = D\nabla^2 \langle C(r,t) \rangle + Y^S(r,t), \tag{3.10a}$$

$$\left(\frac{\partial}{\partial t}\right) f(p,r;t) = -\left(\frac{\partial}{\partial p}\right)[S^4 J_1^S(p, Sr, S^2 t) + k_2 q f(p,r;t)] \tag{3.10b}$$

with the scaled reaction term

$$Y^S(r,t) = S^4 \int_0^1 dp\, J_1^S(p, Sr, S^2 t). \tag{3.11}$$

Here J_i^S means that J_i also depends on S through ϕ included in it. Similarly, we scale the stochastic equations (2.26b), (2.36), and (2.37) with a scaling exponent η

$$R(r,t) = \phi^{\eta/2} \tilde{R}(r/l, t/\tau). \tag{3.12}$$

Then, we find

$$\left(\frac{\partial}{\partial t}\right)\delta C(r,t) = D\nabla^2 \delta C(r,t) + \delta Y^S(r,t), \tag{3.13a}$$

$$\left(\frac{\partial}{\partial t}\right) G_2(1,2;t) = -(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)\{S^{d+4}[J_2^S(p_2, Sr_2, p_1, Sr_1; S^2 t) - S^{-2} f(1) J_1^S(p_2, Sr_2, S^2 t)] + k_2 q_2 G_2\}, \tag{3.13b}$$

$$\left(\frac{\partial}{\partial t}\right)\chi(1,2;t) = -(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)\{S^{d+4}[S^{-d}\delta(1-2) J_1^S(p, Sr_2; S^2 t) + J_2^S(p_2, p_1, Sr_2, Sr_1; S^2 t) - S^{-2} f(1) J_1^S(p, Sr_2; S^2 t)] + k_2 q_2 \chi\} \tag{3.13c}$$

with

$$\delta Y^S(r,t) = S^{d+4}\int_0^t dt' \int dr'[-\varphi^S(Sr,S^2t;Sr',S^2t')\delta C(r',t') + \psi^S(Sr,S^2t;Sr',S^2t')\delta E'_S(r',t')] + S^{\beta+2-\eta}R(r,t), \tag{3.14}$$

where, in order to derive Eq. (3.14), we have changed the integration variables r' and t' to Sr' and S^2t', respectively.

B. Expansion of scaled functions in powers of S^{-1}

We first discuss the expansion of the scaled function J_1^S in Eq. (3.10b) in powers of S^{-1}. Since J_1 has a complicated form, it is convenient to expand J_1 formally in powers of free propagators and then investigate each term by applying the scaling (3.1) and (3.2). The following procedure is mostly the same as that introduced by TK[23] for problems of particle growth at nonzero volume fraction.

From Eq. (2.42), we have

$$J_1(p) = \sum_{m=0}^{\infty} J_{1m}(p) = \sum_{m=0}^{\infty}(-k_1)^m[-k_1\Phi_m(p)\cdot\langle C\rangle + k_{-1}\Psi_m(p)], \tag{3.15}$$

where Φ_m and Ψ_m contain m free propagators. The first few terms of Φ_m are given by

$$\begin{aligned}\Phi_0 &= \langle T_p\rangle, \quad \Phi_1 = \langle M_pT\rangle - \Phi_0 g_0\varphi_0,\\ \Phi_2 &= \langle M_pMT\rangle - \Phi_1 g_0\varphi_0 - \Phi_0 g_0\varphi_1 - \Phi_0(g_0\phi_0)^2,\\ \Phi_3 &= \langle M_pM^2T\rangle - \Phi_2 g_0\varphi_0 - \Phi_0 g_0\varphi_2 - \Phi_1 g_0\varphi_1 - \Phi_1(g_0\varphi_0)^2 - \Phi_0 g_0\varphi_1 g_0\varphi_0\\ &\quad - \Phi_0 g_0\varphi_0 g_0\varphi_1 - \Phi_0(g_0\varphi_0)^3,\end{aligned} \tag{3.16}$$

where φ_m is given by $\varphi_m = \int \Phi_m(p)dp$ and has the same expansion forms as Eq. (3.16), except that T_p and M_p are now replaced by T and M, respectively. Here $\Psi_0(p) = \langle E'_{Sp}\rangle$, and $\Psi_m(p)$ $(m\geqslant 1)$ has the same expansion form as $\Phi_m(p)\cdot\langle C\rangle$, except that $T\cdot\langle C\rangle$ is now replaced by E'_S in Ψ_m. The expansion in powers of g_0 is merely formal since the higher order terms are not necessarily small compared to the lower order terms. By using Eqs. (2.14) and (2.15), we can write $\langle M_pM^{m-1}T\rangle$ as

$$\begin{aligned}\langle M_pM^{m-1}T\rangle_{rr't'} &= pb\int dp'p'b'\int d(1)p_1b_1\cdots\int d(m-1)p_{m-1}b_{m-1}\\ &\quad\times\int_0^t dt_1\int_0^{t_1}dt_2\cdots\int_0^{t_{m-2}}dt_{m-1}\, g_0(r-r_1,t-t_1)g_0(r_1-r_2,t_1-t_2)\cdots\\ &\quad\times g_0(r_{m-1}-r',t_{m-1}-t')F_{m+1}(p,r,t;1,t_1;2,t_2,\ldots,m-1,t_{m-1};p',r',t'),\end{aligned} \tag{3.17}$$

where $m>1$, and

$$F_m(1,t_1;\ldots;m,t_m) = \prod_{i=1}^{m-1}\theta(|r_{i+1}-r_i|-2a)\langle N(1,t_1)\cdots N(m,t_m)\rangle. \tag{3.18}$$

Here let us make a simple approximation in Eq. (3.17) that all times t_i and t' in F_{m+1} may be replaced by t. In fact, as will be shown later, φ_m $(m\geqslant 1)$ are the correction terms to φ_0 and become important on a longer time scale $\tau' = \tau/\lambda$ than τ. Since only the long-range interaction over a distance of order l is important in Eq. (3.17), the free propagator g_0 is scaled as

$$g_0(r,t) = \phi^{3/2}\tilde{g}_0(r/l,t/\tau). \tag{3.19}$$

On the time scale of order τ', therefore, we can replace the times t_i and t' in F_{m+1} by t. Since the error introduced by this expansion in $\partial/\partial t$ is of order $\tau/\tau' = \phi^{1/2}$ and φ_m $(m>0)$ are at least of order $\phi^{1/2}$, it has no effect on the first-order correction.

The function F_m is in general different from f_m [cf. Eqs. (2.32) and (3.18)]. However, F_m can be written in terms of f_i $(2\leqslant i\leqslant m)$. A few explicit forms of F_m are

$$\begin{aligned}F_2(1,2) &= f_2(1,2),\\ F_3(1,2,3) &= f_3(1,2,3) + \delta(1-3)f_2(1,2),\\ F_4(1,2,3,4) &= f_4(1,2,3,4) + \delta(1-3)f_3(1,2,4) + \delta(1-4)f_3(1,2,3)\\ &\quad + \delta(2-4)f_3(1,2,3) + \delta(1-3)\delta(2-4)f_2(1,2)\end{aligned} \tag{3.20}$$

and so on. Using Eqs. (2.33), (3.17), and (3.20), we can write $J_{1m}(p)$, to order S^{-1}, as

$$S^4J_{10}(p,Sr,S^2t) = h(p,r,t)f(p,r;t), \tag{3.21a}$$

$$S^4J_{11}(p,Sr,S^2t) = -S^{-1}k_1pb\int_0^t dt'\int dr'\int dp'\, g_0(r-r',t-t')\times G_2(p,r,p'r';t)h(p',r',t'), \tag{3.21b}$$

$$S^4 J_{12}(p,Sr,S^2t) = S^{-1}k_1^2 pb \int_0^t dt' \int dr' \int dp' \int d(1)p_1 b_1 \int_0^t dt_1$$

$$\times g_0(r-r_1,t-t_1)g_0(r_1-r',t_1-t')f(1;t)[G_2(p,r,p',r';t)$$

$$+\delta(r-r')\delta(p-p')f(p,r;t)]h(p',r',t'), \tag{3.21c}$$

$$S^4 J_{13}(p,Sr,S^2t) = S^{-1}k_1^3 pb \int_0^t dt' \int dr' \int dp' \int d(1)p_1 b_1 \int d(2)p_2 b_2$$

$$\times \int_0^t dt_1 \int_0^{t_1} dt_2\, g_0(r-r_1,t-t_1)g_0(r_1-r_2,t_1-t_2)g_0(r_2-r',t_2-t')$$

$$\times f(1;t)f(2;t)[G_2(p,r,p',r';t)+\delta(r-r')\delta(p-p')f(p,r;t)]h(p',r',t') \tag{3.21d}$$

with

$$h(p,r,t) = -k_1 pb\,\langle C(r,t)\rangle + k_{-1}qb, \tag{3.22}$$

where we have used Eqs. (3.9) and (3.19) and changed the integration variables r_i and t_i to Sr_i and S^2t_i, respectively. Thus, the first-order correction of interactive effects due to reaction is of order S^{-1} and consists of two kinds of terms. One is a correlated term such as Eq. (3.21b) which contains the correlation function G_2, and the other is an uncorrelated term such as the last term of Eq. (3.21c), which has the product of the single distribution functions.

The expansion as ordered in Eqs. (3.21) then suggests the introduction of a renormalized propagator g defined through

$$g(r-r',t-t') = g_0(r-r',t-t') - k_1 \int_0^t dt_1 \int d(1)p_1 b_1 g_0(r-r_1,t-t_1)g(r_1-r',t_1-t')f(1;t). \tag{3.23}$$

Then, $S^4 J_1^S$ can be written, to order S^{-1}, as

$$S^4 J_1^S(p_1,Sr_1,S^2t) = h(1,t)f(1;t) + S^{-1}[V(1,t) - W(1,t)] \tag{3.24}$$

with the uncorrelated term

$$V(p,r,t) = k_1^2 pbf(p,r;t)\int_0^t dt' \int_0^t dt_1 \int dr_1 g_0(r-r_1,t-t_1)g(r_1-r,t_1-t')h(p,r,t')J\,\langle E'(r_1,t)\rangle \tag{3.25a}$$

and the correlated term

$$W(p,r,t) = k_1 pb \int_0^t dt' \int dr' \int dp'\, g(r-r',t-t')G_2(p,r,p',r';t)h(p',r',t'). \tag{3.25b}$$

From Eq. (3.11), we thus find

$$Y^S(r_1,t) = \int_0^1 dp_1\{h(1,t) + S^{-1}[V(1,t) - W(1,t)]\}. \tag{3.26}$$

Here $\{V(1,t) - W(1,t)\}$ represents the first-order correction of reactive–diffusive long-range interactions between enzymes separated by a distance of order l. There could also be a short-range interaction between enzymes separated by a distance of order a. As is easily shown, however, such an effect is of order ϕ. We also note that an interaction between two touching enzymes does not occur since we assume that the centers of the enzymes are fixed.

Since the correlated term is determined by the correlation G_2, we next discuss the asymptotic equation for G_2. In order to analyze the scaled functions J_2^S, we first expand the I_p term given by Eq. (2.40) in powers of the bare propagator g_0, similarly to Eqs. (3.15). Inserting the expanded I_p into Eq. (2.38), using Eqs. (2.33) and (3.20), and applying the scaling (3.1) and (3.2), we then find the similar expansion forms as in Eqs. (3.21). Up to order S^{-1}, we thus obtain

$$S^{d+4}[J_2^S - S^{-2}fJ_1^S] = m_{22}(t)G_2(1,2;t) - k_1 p_2 b_2 \int_0^t dt_3\, g(r_{21},t-t_3)h(1,t_3)f(1;t)f(2;t), \tag{3.27}$$

where the screening operator is given by

$$m_{ij}(t) = h(i,t) - k_1 p_i b_i \int_0^t dt_n \int d(n)g(r_{in},t-t_n)h(n,t)e_{nj}f(n). \tag{3.28}$$

We have used Eq. (3.9) to obtain Eq. (3.27) and retained only the terms up to order S^0 since the correlated terms in $S^4 J_1$ and Y^S are already of order S^{-1}. In the scaling limit $S\to\infty$, use of Eqs. (3.13b) and (3.27) thus leads to the asymptotic equation

$$\left(\frac{\partial}{\partial t}\right)G_2(1,2;t) = -(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)\left\{[m_{22}(t)+k_2q_2]G_2(1,2;t) - k_1\int_0^t dt'\, g(r_{21},t-t')h(1,t')p_2b_2f(1)f(2)\right\} \tag{3.29a}$$

which is integrated to give a formal solution

$$G_2(1,2;t) = \int_0^t ds \exp_+\left\{ -\int_0^s d\tau(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)[m_{22}(t-\tau)+k_2 q_2]\right\}$$
$$\times(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)k_1 p_2 b_2 \int_0^{t-s} dt'\, g(r_{21},t-s-t')h(1,t-t')f(1;t-s)f(2;t-s)$$
$$+\exp_+\left\{ -\int_0^t ds(1+e_{12})\left(\frac{\partial}{\partial p_2}\right)[m_{22}(s)+k_2 q_2]\right\}G_2(1,2;0), \tag{3.29b}$$

where $\exp_+$ denotes the time-ordered exponential.

There are two kinds of contributions due to the correlation function G_2 to the reaction–diffusion processes to order S^{-1}. One is a contribution to the deterministic motion through the correlated term [cf. Eq. (3.25)]. The other is a contribution to the fluctuations through the variance χ [cf. Eq. (2.35)].

C. Derivation of deterministic rate equations

Before we derive the deterministic rate equations with the corrections due to reaction, we first discuss under what conditions Eqs. (1.4) hold. In the scaling limit $S\to\infty$, or in the dilute limit $\phi_0\to 0$, use of Eqs. (3.10), (3.24), and (3.26) leads to

$$\left(\frac{\partial}{\partial t}\right)\langle C(r,t)\rangle = D\nabla^2\langle C\rangle - k_1\langle E'\rangle\langle C\rangle + k_{-1}\langle E'_S\rangle, \tag{3.30a}$$

$$\left(\frac{\partial}{\partial t}\right)\langle E(r,t)\rangle = -k_1\langle E'\rangle\langle C\rangle + k_{-1}\langle E'_S\rangle + k_2\langle E_S\rangle, \tag{3.30b}$$

$$\left(\frac{\partial}{\partial t}\right)f(p,r;t) = -\left(\frac{\partial}{\partial p}\right)[h(p,r,t)+k_2 q]f(p,r;t). \tag{3.30c}$$

These are the kinetic equations which hold for all ϵ on the length scale of order $l(\gg L)$ and the time scale of order τ. The interactive effects due to reaction are negligible on this space-time scale. When $\epsilon=0$, Eqs. (3.30a) and (3.30b) exactly reduce to Eqs. (1.4). Therefore, Eqs. (1.4) hold for $\phi_0\ll 1$ and $\epsilon\ll 1$.

The contribution due to the spatial correlation G_2 to the deterministic equations is of order $\phi^{1/2}$ [cf. Eqs. (3.10) and (3.26)]. If ϕ is not sufficiently small, however, this contribution becomes important on the time scale $\tau'=\tau/\phi^{1/2}$ longer than τ. Balancing $(\partial/\partial t)\langle C\rangle$ and the next dominant term of Eq. (3.10a) leads to the time exponent $\theta=3$. Hence there are two macroscopic time scales. One is the time scale τ on which the effect of neighboring enzymes is negligible. The other is τ' on which the interactive effects due to reaction become important. On the time scale of order τ', therefore, the densities $\langle u\rangle$ and the single distribution function f consist of a double-time process and Eqs. (3.5) and (3.6) can be generalized to

$$\langle u(r,t)\rangle = \phi\tilde{u}(r/l;T_0,T_1), \tag{3.31a}$$
$$f(p,r;t) = \phi\tilde{f}(p,r/l;T_0,T_1), \tag{3.31b}$$

where $u=C,E,E_S$, and E'_S, and $T_n\,(n=0,1)$ are scale invariants defined by $T_n=\phi^{n/2}(t/\tau)$. Then, the time derivative of Eq. (3.31a) leads to

$$\left(\frac{\partial}{\partial t}\right)\langle u(r,t)\rangle = (1/\tau)\left[\left(\frac{\partial}{\partial T_0}\right)+\phi^{1/2}\left(\frac{\partial}{\partial T_1}\right)\right]\langle u(r;T_0,T_1)\rangle. \tag{3.32}$$

The first term of Eq. (3.32) balances the first term of Eq. (3.26), respectively, and the second term balances its second term. Thus, the double-time scaling leads, in the scaling limit $S\to\infty$, to

$$\left(\frac{\partial}{\partial t}\right)\langle C(r,t)\rangle = D\nabla^2\langle C\rangle - k_1\langle E'\rangle\langle C\rangle + k_{-1}\langle E'_S\rangle + v(r,t) - w(r,t), \tag{3.33a}$$

$$\left(\frac{\partial}{\partial t}\right)\langle E(r,t)\rangle = -k_1\langle E'\rangle\langle C\rangle + k_{-1}\langle E'_S\rangle + k_2\langle E_S\rangle + v(r,t) - w(r,t), \tag{3.33b}$$

$$\left(\frac{\partial}{\partial t}\right)f(1;t) = -\left(\frac{\partial}{\partial p_1}\right)\{[h(1,t)+k_2 q_1]f(1;t) + v(1,t) - w(1,t)\} \tag{3.33c}$$

with the uncorrelated term

$$v(1,t) = k_1^2 p_1 b_1 h(1,t)f(1;t) \times\int dr_2\, g_0(r_{12})g(r_{21})\langle E'(r_2,t)\rangle \tag{3.34}$$

and the correlated term

$$w(1,t) = k_1^2 p_1 b_1\left[\hat{O}(1,t)\left(\frac{\partial}{\partial p_1}\right)p_1 b_1 + \hat{O}'(1,t)h(1,t)\right]f(1;t), \tag{3.35a}$$

where $v(r,t)=\int v(p,r,t)dp$ and $w(r,t)=\int w(p,r,t)dp$. Here $\hat{O}$ and $\hat{O}'$ are operators given by

$$\hat{O}(1,t) = \int d(2)h(2,t)g(r_{12})\hat{\Gamma}_{12}(t)g(r_{12}) \times h(2,t)f(2;t), \tag{3.35b}$$

$$\hat{O}'(1,t) = \int d(2)h(2,t)g(r_{12})\hat{\Gamma}_{12}(t)g(r_{21}) \times\left(\frac{\partial}{\partial p_2}\right)p_2 b_2 f(2;t), \tag{3.35c}$$

where $g(r)$ is a time-independent renormalized propagator given by

$$g(r) = \int_0^\infty dt\, g(r,t), \tag{3.36}$$

and $\hat{\Gamma}_{12}(t)$ is an operator given by

$$\hat{\Gamma}_{12}(t) = \int_0^\infty ds \exp\Big\{ -s(1+e_{12}) \times \Big(\frac{\partial}{\partial p_1}\Big)[m(1,t) + k_2 q_1]\Big\} \tag{3.37a}$$

with

$$m(1,t) = h(1,t) - k_1 p_1 b_1 f(1) \times \int d(3) g(r_{13}) h(3,t) e_{31}. \tag{3.37b}$$

We have neglected the initial correlation of Eq. (3.29b) in the long time limit $t \to \infty$, since it represents the correlation of the two enzymes separated far apart initially before the diffusive interaction due to reaction.

The deterministic rate equations (3.33) are generalizations of Eqs. (3.30) to order $\phi^{1/2}$ and hold for all ϵ on the length scale of order l and the time scale of order τ'. We see from Eqs. (3.34) and (3.35) that the correlated term $w(p,r,t)$ is quite different from the uncorrelated term $v(p,r,t)$. First, the correlated term decreases the rate, while the uncorrelated term increases it. This is shown numerically in Sec IV B. Second, the correlated term contains the square of the operator $(\partial/\partial p_1)$ through the operator (3.37a). Therefore, it leads to a kinetic equation for $f(p,r;t)$ with higher derivatives than the second order, while the uncorrelated term leads to a kinetic equation for $f(p,r;t)$ with only the first-order derivative. Thus, the correlated term makes the distribution function $f(p,r;t)$ broader than the uncorrelated term.

D. Macroscopic rate equations in diffusion-controlled case [A]

In order to compare the present results with those previously obtained for diffusion-controlled reactions, we discuss the asymptotic forms of Eqs. (3.33) in case [A], given by Eq. (1.11a). In this case we have $pb = \epsilon^{-1}$, from Eq. (2.17c). The macroscopic space-time scales are then given by (l_D, τ_D), where $l_D = (4\pi a E_0)^{-1/2}$ $(\gg a)$, and $\tau_D = l_D^2/D$ $(\gg \tau_0)$. Since $l_D/l_R = \sqrt{\epsilon} \gg 1$, on the length scale of order l_D and the time scale of order τ_D, therefore, the density $\langle E(r,t)\rangle$ and the distribution function $f(p,r;t)$ are already at equilibrium. In fact, in Eq. (3.33c), $h(p,t)f(p,r;t)$ is negligible compared to $k_2 q f(p,r;t)$ since $h = -4\pi a D\langle C\rangle \ll k_2 \sim k_1\langle C\rangle$. From Eqs. (3.33b) and (3.33c), therefore, we find the stationary solutions $\langle E(r,t)\rangle = E_0$ and $f(p,r;t) = E_0\delta(p-1)$. Use of Eqs. (3.23) and (3.36a) then leads to the renormalized propagator

$$g(r_{12}) = (4\pi D|r_{12}|)^{-1} \exp(-|r_{12}|/l_D). \tag{3.38}$$

From Eq. (3.34), therefore, we obtain $v(1,t) = -\sqrt{3\phi_0} \times (4\pi a D)\langle C\rangle f(p,r;t)$. Since $k_2 \gg 4\pi a D\langle C\rangle$, from Eq. (3.29a), we also find $G_2 \sim O(\phi_0^{5/2}/\epsilon)$, which leads to the correlated term $w \sim O(\phi_0^{1/2}/\epsilon)$. Hence the correlated term w is negligible compared to the uncorrelated term v, which is of order $\phi_0^{1/2}$. On the length scale of order l_D and the time scale of order $\tau_D' = \tau_D/\sqrt{\phi_0}$, from Eq. (3.33a), we thus obtain

$$\Big(\frac{\partial}{\partial t}\Big)\langle C(r,t)\rangle = D\nabla^2\langle C\rangle - (4\pi a D)E_0(1+\sqrt{3\phi_0})\langle C\rangle. \tag{3.39}$$

Equation (3.39) is identical, to order $\phi_0^{1/2}$, to that obtained in several prior articles for diffusion-controlled reactions.[11–17] This is reasonable since the starting linear Langevin equation for $C(r,t)$ given by Eq. (2.3a) with Eq. (2.21) reduces exactly to that obtained by TC. In fact, repeating the same procedure as that employed by TC to order ϕ_0, we also find the second-order correction term to Eq. (3.39) as

$$(3\phi_0)\Big\{(2/3)D\nabla^2\langle C\rangle - 4\pi a D E_0[(3/2) + \ln(3/2)]\langle C\rangle - (4\pi)^3 a D^4 E_0 \int \theta(|r'| - 2a) g(r')^3 \langle C(r-r',t)\rangle dr'\Big\}. \tag{3.40}$$

The term in square brackets in expression (3.40) is different from that obtained by TC because a series of nondivergent-type diagrams is missing in their calculation. Hence their result must be corrected as shown in Eq. (3.40).

E. Fluctuations

We turn to an investigation of the properties of the fluctuations around the deterministic motion discussed in the previous section. In order to determine the exponent η defined in Eq. (3.12), we first consider the correlation function of the fluctuating force $R(r,t)$ given by Eq. (2.24). By using Eq. (2.24) and applying the scaling (3.1) and (3.2), we find, to lowest order in S^{-1},

$$\langle R^S(Sr,S^2t) R^S(Sr',S^2t)\rangle = S^{2(\eta-\beta-2)} k_1^2 \int_0^1 dp_1 \int_0^1 dp_2\, p_1 b_1\, p_2 b_2 \times \chi(1,2;t) C_0(r_1,t) C_0(r_2,t), \tag{3.41}$$

which leads to $\eta = \beta + 2 = (d+6)/2$ in the scaling limit $S \to \infty$. Similarly to Eqs. (3.30), in the scaling limit $S \to \infty$, use of Eqs. (3.13) thus leads to

$$\Big(\frac{\partial}{\partial t}\Big)\delta C(r,t) = D\nabla^2\delta c - k_1\langle E'\rangle \delta C + k_{-1}\delta E_S'(r,t) + R(r,t), \tag{3.42a}$$

$$\Big(\frac{\partial}{\partial t}\Big)\chi(1,2;t) = -(1+e_{12})\Big(\frac{\partial}{\partial p_2}\Big) \times [m_{22}(t) + k_2 q_2]\chi. \tag{3.42b}$$

Equations (3.42) hold on the length scale of order l and the time scale of order τ. From Eq. (3.19), we have $\langle(\delta C)^2\rangle / \langle C\rangle^2 \approx |\chi/f^2| \approx \phi^{1/2} \ll 1$ when $d = 3$. Therefore, the fluctuations are negligible compared to the averaged values. However, they are important since they affect the rate coefficients through the fluctuation–dissipation relation, to order $\phi^{1/2}$, and their effect is the same order as that of the uncorrelated term. They are also important since they might be observed by light scattering experiments.

Equations (3.42b) for the variance does not have a source term. On the time scale of order τ, therefore, the fluctuations $\chi(1,2;t)$ are generated only by an initial randomness related to $\chi(1,2;t=0)$, which originates from thermal

fluctuations. Similarly to Eq. (3.33), on the time scale of order $\tau' = \tau/\phi^{1/2}$, we can generalize Eqs. (3.42) to order $\phi^{1/2}$ by including the next-dominant terms of order $\phi^{1/2}$ such as $v(1,t)$ and $w(1,t)$. Then, the equation for the variance has a source term which is related to the correlated term $w(1,t)$. On the time scale of order τ', therefore, the fluctuations are generated not only by the initial randomness but also by the long-range interactions due to reaction. This situation is exactly the same as that discussed by TK on the particle growth problem.[23,25] In the present paper, however, we do not go further into this problem.

IV. DETERMINISTIC RATE EQUATIONS IN THE LATE STAGE

In the present section, we discuss a spatially homogeneous reaction process in the late stage which is characterized by the space-time cutoffs prescribed by $r_c \gg l$ and $t_c \gg \tau$. Similarly to the intermediate stage, we may also apply the scaling method to the starting equations (2.26a) and (2.36a) to obtain new deterministic nonlinear rate equations for arbitrary values of ϵ, which hold on the length scale of order l and on the time scale of order τ'. In the present section, however, we show that we can derive the same equations as those from Eqs. (3.33) by just neglecting the spatial inhomogeneities in the number densities $\langle u(r,t)\rangle$ and the single distribution function $f(p,r;t)$.

Since the spatial gradients are negligible relative to the reaction process, we can put $\langle u(r,t)\rangle = \langle u(t)\rangle$ and $f(p,r;t) = f(p,t)$. Then, use of Eqs. (3.23) and (3.36a) leads to

$$g(r_{12}) = (4\pi D\,|r_{12}|)^{-1} \exp[-|r_{12}|/l(t)] \tag{4.1}$$

with the screening length $l(t) = 1/\sqrt{4\pi a^* \langle E(t)\rangle}$. From Eqs. (3.34) and (3.35), therefore, we have

$$v(1,t) = \sqrt{3\phi(t)}\,p_1 b_1 (\langle E\rangle/\langle E'\rangle) h(1,t) f(p_1,t), \tag{4.2a}$$

$$w(1,t) = \sqrt{3\phi(t)}\,p_1 b_1 \Big[\hat{o}(p_1,t)\Big(\frac{\partial}{\partial p_1}\Big) p_1 b_1 + \hat{o}'(p_1,t) h(1,t)\Big] f(p_1,t) \tag{4.2b}$$

with the operators

$$\hat{o}(p_1,t) = (4\pi/\langle E'\rangle) \int d(2) h(2,t) g_{12} \hat{\Gamma}_{12}(t) \times g_{12} h(2,t) f(p_2,t), \tag{4.3a}$$

$$\hat{o}'(p_1,t) = (4\pi/\langle E'\rangle) \int d(2) h(2,t) g_{12} \hat{\Gamma}_{12}(t) \times g_{21} \Big(\frac{\partial}{\partial p_2}\Big) p_2 b_2 f(p_2,t), \tag{4.3b}$$

where the propagator g_{12} is given by $g_{12} = \exp(-|r_{12}|)/4\pi|r_{12}|$.

A. Renormalized rate equations

As is shown in Appendix E, we can transform Eq. (4.2b) into the following simple form:

$$w(p,r,t) = (k_{-1}+k_2)\sqrt{3\phi}\,[(1-\nu) pb\tilde{h} + \eta\tilde{h} + \gamma(z) pb \Big(\frac{\partial}{\partial p}\Big) pb\Big] f(p,t) \tag{4.4}$$

with

$$\gamma(z) = (\nu - \nu')[\langle \tilde{h}^2\rangle_f - z\nu\nu' \langle \tilde{h}\rangle_f]/(z+\kappa)\langle E'\rangle, \tag{4.5a}$$

$$\tilde{h}(p,z) = (\langle E\rangle/\langle E'\rangle) h(p,z)/(k_{-1}+k_2) = [-(z+\kappa) pb + \kappa b]\langle E\rangle/\langle E'\rangle, \tag{4.5b}$$

where

$$\nu(z) = \sqrt{1-\zeta(z)}, \quad \eta(z) = (\nu - \nu')[1+\epsilon(1-\kappa)\bar{p}]/[z+1+\epsilon(1-\kappa)\bar{p}](1+\epsilon\bar{p}), \quad \nu'(z) = \sqrt{1-2\zeta(t)},$$

$$\zeta(z) = (z+\kappa)/2[z+1+\epsilon(1-\kappa)\bar{p}],$$

and

$$\bar{p}(z) = \langle E(t)\rangle/E_0.$$

The angular brackets $\langle\cdots\rangle_f$ denotes the average over the distribution function $f(p,r;t)$. Here we have introduced the dimensionless variables $\kappa = k_{-1}/(k_{-1}+k_2)$, and $z(t) = k_1\langle C(t)\rangle/(k_{-1}+k_2)$. Use of Eqs. (3.33c), (4.2), and (4.4) then leads to a nonlinear Fokker–Planck equation

$$\Big(\frac{\partial}{\partial t}\Big) f(p,t) = (k_{-1}+k_2)\Big(\frac{\partial}{\partial p}\Big)[-y(p,z) + \sqrt{3\phi}\,\gamma(z) pb \Big(\frac{\partial}{\partial p}\Big) pb\Big] f(p,t) \tag{4.6}$$

with the drift term

$$y(p,z) = [\kappa - (z+\kappa)p] b + \sqrt{3\phi}\,[\nu pb - \eta]\tilde{h}(p,z) + (1-\kappa) q, \tag{4.7}$$

where $f(p,t)$ satisfies the boundary condition $\int_0^1 dp f(p,t) = E_0$. Equation (4.6) is a new kinetic equation which describes the reaction process in the late stage to order $\phi^{1/2}$. It is interesting to note that Eq. (4.6) is equivalent to the following multiplicative nonlinear stochastic equation,

$$\Big(\frac{d}{dt}\Big) P(t) = (k_{-1}+k_2)\{y[P(t),z] + P(t) b(t) \xi(t)\} \tag{4.8a}$$

with the Gaussian white noise $\xi(t)$ which satisfies

$$\langle \xi(t)\rangle = 0,$$

$$\langle \xi(t)\xi(t')\rangle = 2[\sqrt{3\phi}\,\gamma(z)/(k_{-1}+k_2)]\delta(t-t'), \tag{4.8b}$$

where $b(t) = [1+\epsilon P(t)]^{-1}$, and the noise is generated by the reactive–diffusive long-range interactions among enzymes. The average enzyme density $\langle E\rangle$ is then given by $\langle E\rangle = \langle P(t)\rangle E_0$.

By using Eqs. (3.33) and (4.6), we thus obtain the deterministic rate equations

$$\Big(\frac{d}{dt}\Big)\langle C(t)\rangle = \tilde{k}_1(z)\langle C\rangle\langle E\rangle + \tilde{k}_{-1}(z)\langle E_S\rangle, \tag{4.9a}$$

$$\Big(\frac{d}{dt}\Big)\langle E(t)\rangle = -\tilde{k}_1(z)\langle C\rangle\langle E\rangle + [\tilde{k}_{-1}(z) + k_2]\langle E_S\rangle \tag{4.9b}$$

with the renormalized rate coefficients

$$\tilde{k}_1(z) = k_1\{1 + \sqrt{3\phi}\,[A_1(z) + A_{-1}(z)]\}\langle E'\rangle/\langle E\rangle, \tag{4.10a}$$

$$\tilde{k}_{-1}(z) = k_{-1}[1 + \sqrt{3\phi}A_{-1}(z)]\langle E'_S/\langle E_S\rangle, \quad (4.10b)$$

where we have used Eq. (4.5) to obtain Eqs. (4.9), and

$$A_1(z) = [\nu/(\nu - \nu')(1 + \epsilon\bar{p}) - (n_{13}/n_{11})]\gamma/z, \quad (4.11a)$$

$$A_{-1}(z) = \{\nu[\kappa(n_{12}/n_{11}) - z\nu\nu'/(1 + \epsilon\bar{p})]/(z + \kappa) - \eta\}\langle E\rangle/\langle E'\rangle \quad (4.11b)$$

with $n_{ij}(z) = \langle p^i b^j\rangle_f/E_0$. Equations (4.9) hold on the length scale longer than l and on the time scale of order $\tau' = \tau/\phi^{1/2}$ for arbitrary values of ϵ and small ϕ. We see that long-range interactive effects due to reaction renormalize the rate coefficients k_1 and k_{-1} differently, while they do not change the rate coefficient k_2. In the long time limit $t \to \infty$, Eqs. (4.10) reduce to Eqs. (1.19), respectively, since z and γ/z go to zero [cf. Eq. (4.5)]. The effect of the uncorrelated and correlated terms on the deterministic reaction rate is investigated numerically in Sec. IV B.

B. Quasistationary state

Next let us discuss the asymptotic behavior of the distribution f and the densities $\langle C\rangle$ and $\langle E\rangle$. We asume that the substrate density $\langle C\rangle$ is much larger than the enzyme density $\langle E\rangle$. Then, the time scale $[k_1\langle C\rangle]^{-1}$ of the enzyme density $\langle E\rangle$ is much shorter than the time scale $[k_1\langle E\rangle]^{-1}$ of the substrate density $\langle C\rangle$. Therefore, for long time t the change in the density $\langle E\rangle$ and the distribution $f(p,t)$ as functions of t are assumed to be equal to zero. Making the quasistationary state approximation, $(\partial/\partial t)\, f(p,t) = 0$, from Eq. (4.6), we thus find

$$f(p,t) = E_0 F(p), \quad (4.12a)$$

$$F(p) = (\epsilon + p^{-1})p^{-\alpha(z)}e^{-\beta(p;z)}/\int_0^1 (\epsilon + p^{-1})p^{-\alpha(z)}e^{-\beta(p;z)}dp \quad (4.12b)$$

with

$$\alpha(z) = \{z + 1 - \lambda[\kappa\nu + (z + \kappa)\eta] - \epsilon[2 - \kappa - \lambda\kappa\eta]\}/\sqrt{3\phi}\gamma, \quad (4.13a)$$

$$\beta(p;z) = \{[1 - \lambda\kappa\eta]p^{-1} + \lambda\nu(z + \kappa)p + (1 - \kappa)\epsilon^2(1 - p)^2/2 + \epsilon p[(1 - \lambda\eta)(z + \kappa) + 2(1 - \kappa)]\}/\sqrt{3\phi}\gamma, \quad (4.13b)$$

where $\lambda = (3\phi)^{1/2}\langle E\rangle/\langle E'\rangle$. The normalized distribution function $F(p)$ depends on the time through $z(t)$.

Similarly to Eqs. (4.12), making the quasistationary state approximation, $(d/dt)\langle E(t)\rangle = 0$, from Eqs. (4.9b), we also find

$$\langle E_S(t)\rangle = z(t)\langle E(t)\rangle/\Delta(z) \quad (4.14)$$

which is combined with the conservation law $\langle E\rangle + \langle E_S\rangle = E_0$ to obtain

$$\langle E(t)\rangle = \Delta(z)E_0/[z(t) + \Delta(z)], \quad (4.15)$$

where

$$\Delta(z) = k_1[\tilde{k}_{-1}(z) + k_2]/\tilde{k}_1(z)(k_{-1} + k_2). \quad (4.16)$$

By using Eqs. (4.9a), (4.14), and (4.15), we thus obtain the rate equation

$$-V = \left(\frac{d}{dt}\right)\langle C(t)\rangle = -k_2\langle E_S(t)\rangle = -\tilde{k}(z)E_0\langle C(t)\rangle \quad (4.17)$$

with the effective rate coefficient

$$\tilde{k}(z) = k_1(1 - \kappa)/[z + \Delta(z)] = \tilde{k}_1 k_2/(\tilde{k}_1\langle C\rangle + \tilde{k}_{-1} + k_2). \quad (4.18)$$

This is a generalization of the Michaelis–Menten equation for which $\epsilon = 0$ and $\Delta(z) = 1$, to order $\phi^{1/2}$.

Equation (4.12) has no adjustable parameters but contains the moment n_{ij}. In order to calculate the distribution $F(p)$, therefore, we must determine such moments self-consistently. To do this, we first choose the values obtained by the uncorrelated term v only for the moments n_{ij} as the initial values. By taking into account the uncorrelated term (4.2a) only, similarly to Eqs. (4.12), we obtain the quasistationary distribution function $F(p) = \delta(p - p_u)$, where the most probable value of p is determined by the solution of the following equation

$$\epsilon^2(1 - \kappa)p_u^3 + [(z + \kappa)(\lambda + \epsilon) + \epsilon(2 - \epsilon)(1 - \kappa)]p_u^2 + [z + 1 + \epsilon(\kappa - 2) - \kappa\lambda]p_u - 1 = 0, \quad (4.19)$$

where $\lambda = (3\phi)^{1/2}\langle E\rangle/\langle E'\rangle$. Then we have $n_{ij} = p_u^i/(1 + \epsilon p_u)^j$. Thus, we calculate $F(p)$ from Eq. (4.12) and determine new values for the moments n_{ij}. We iterate this procedure, which converges rapidly, to obtain the accurate self-consistent values.

In Fig. 1 the quasistationary distribution function $F(p)$ vs p is shown for typical values of the scaled substrate density $z = k_1\langle C\rangle/k_{-1} + k_2)$. At high substrate density, such that $z \gg 1$, all corrections of order $\phi^{1/2}$ disappear and the distribution function $F(p)$ approaches the quasistationary solution of a δ-function type, $F(p) = \delta(p)$ (see also Fig. 3). This is due to the fact that the enzyme is saturated with substrate for large substrate density and the reactive–diffusive long-range interactions are negligible. At low density, such that $z \ll 1$, the correction due to the correlated term, Eq. (4.4), disappears and the distribution $F(p)$ approaches the solution of a δ-function type, $F(p) = \delta(p - 1)$ (see also Fig. 3). This follows from the reaction being fast and the fluctuations being averaged out for small z. Since the substrate density $\langle C\rangle$

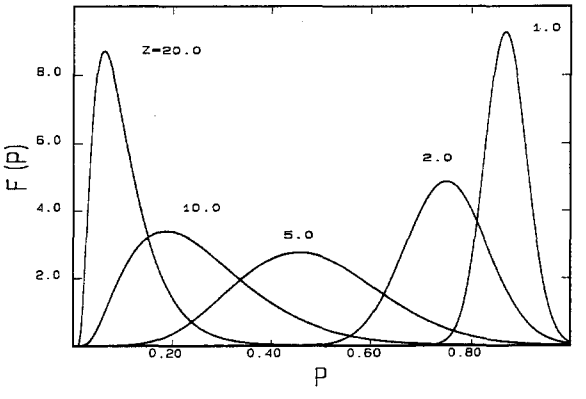

FIG. 1. The normalized distribution function $F(p)$, Eq. (4.12), vs p at the volume fraction $\phi_0 = 0.1$, $\epsilon = 10.0$, and $k_2 = 99k_{-1}$ for typical values of $z = k_1\langle C\rangle/(k_{-1} + k_2)$.

decreases as time t increases [cf. Eq. (4.5)], Fig. 1 thus describes the relaxation of the enzyme distribution function from the quasistationary state to the equilibrium state.

In Figs. 2(A) and 2(B) the normalized ratios of rate coefficients $\tilde{k}_1/k_1$, Eq. (4.10a), and $\tilde{k}/k_1$, Eq. (4.18), are plotted against $1/\epsilon$, respectively. We see that as the volume fraction ϕ_0 increases, both ratios of rate coefficients increase. We also see that as $\epsilon \to 0$, both corrected rate coefficients become independent of diffusion and reduce to the Michaelis–Menten result, where all corrections disappear, while as $\epsilon \to \infty$, they become independent of z, and reduce to the result obtained for diffusion-controlled reactions, where the correction due to the correlated term disappears. When $\phi_0 = 0$, from Eq. (4.6), we have the quasistationary distribution function $f(p,t) = E_0\delta(p - p_0)$, where the most-probable value of p is given by

$$p_0 = 2/\{z + 1 - \epsilon(1-\kappa) + \sqrt{[z+1-\epsilon(1-\kappa)]^2 + 4\epsilon(1-\kappa)}\}. \quad (4.20)$$

From Eqs. (4.10) and (4.16), we then obtain $\Delta = \Delta_0 = 1 + \epsilon(1-\kappa)p_0$, and

$$\tilde{k}_1(z) = k_1/(1+\epsilon p_0) \quad (4.21a)$$

$$\tilde{k}(z) = k_1(1-\kappa)/(z+\Delta_0). \quad (4.21b)$$

In the long time limit $t \to \infty$, therefore, we have $\tilde{k}_1 = k_1/(1+\epsilon)$ and $\tilde{k} = k_1(1-\kappa)/[1+\epsilon(1-\kappa)]$ since $z \to 0$ and $p \to 1$. Even in the low volume fraction limit $\phi_0 \to 0$, the rate coefficients are noticeably affected by diffusion when ϵ is of order 1. This kind of diffusion effect on the rate has been studied by several authors.[4–6,18–21]

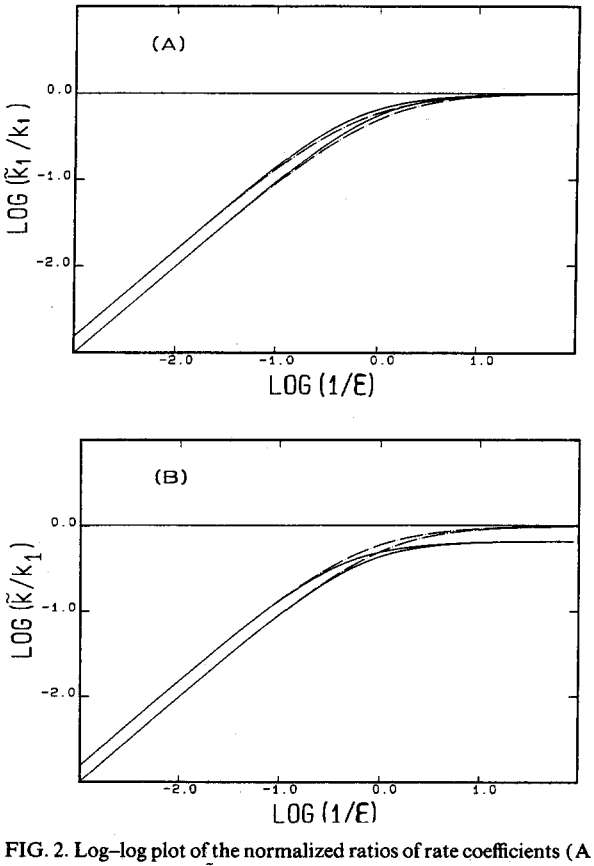

FIG. 2. Log–log plot of the normalized ratios of rate coefficients (A) $\tilde{k}_1/k_1$, Eq. (4.10a), and (B) $\tilde{k}/k_1$, Eq. (4.18) vs ϵ. In each plot the upper solid curve indicates the result for $(\phi_0, k_2/k_{-1}) = (0.1, 99)$ at $z = 0.5$, and the lower one for $(0.0, 99)$ at $z = 0.5$. The upper dot–dashed curve indicates the result for $(0.1, 99)$ at equilibrium $z = 0.0$, and the lower one for $(0.0, 99)$ at $z = 0.0$.

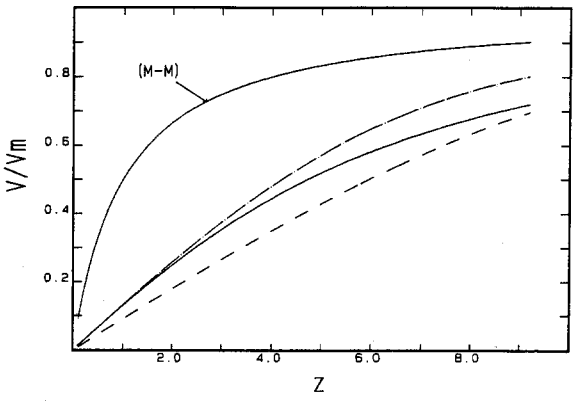

FIG. 3. A plot of the scaled reaction rate V/V_m, Eq. (4.17) vs the scaled substrate density $z = k_1\langle C\rangle/(k_{-1}+k_2)$ for the parameter values $\phi_0 = 0.1$, $\epsilon = 10.0$, and $k_2 = 99k_{-1}$. The dot–dashed curve indicates the result with the uncorrelated term only, the solid curve with both correlated and uncorrelated terms, and the dashed curve without both terms. (M–M) indicates the Michaelis–Menten result.

In Fig. 3 the scaled reaction rate V/V_m is plotted against the scaled substrate density z for the parameter values $\phi_0 = 0.1$, $\epsilon = 10.0$, and $\kappa = 0.01$, where the maximum reaction rate V_m is given by $V_m = k_2E_0$. The scaled reaction rate due to the uncorrelated term v and that obtained in the dilute volume fraction limit are also shown in Fig. 3 for comparison. We see that the correction due to the uncorrelated term v increases the rate, while that due to the correlated term w decreases it (see also Fig. 4).

In order to see a deviation of Eq. (4.17) from the infinitely dilute volume fraction limit $\phi_0 \to 0$ clearly, it is convenient to introduce a correction to the rate by

$$\Xi(z) = 100[z(z+\Delta)^{-1} - z(z+\Delta_0)^{-1}]/z(z+\Delta_0)^{-1},$$
$$= 100[\Delta_0 - \Delta]/(z+\Delta). \quad (4.22)$$

In Fig. 4 the correction is plotted against z for different pa-

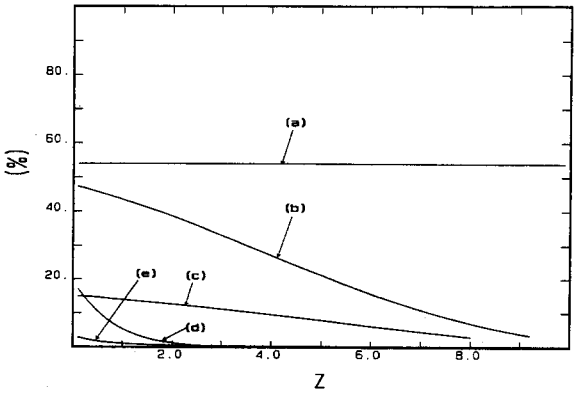

FIG. 4. The correction, Eq. (4.22) vs z for the parameter values (a) $(\phi_0, \epsilon, k_2/k_{-1}) = (0.1, 100.0, 99.0)$, (b) $(0.1, 10.0, 99.0)$, (c) $(0.01, 10.0, 99.0)$, (d) $(0.1, 1.0, 99.0)$, and (e) $(0.1, 10.0, 0.01)$.

rameter values of ϕ_0, ϵ, and κ_2/κ_{-1}. We see that the correction becomes noticeable, depending not only on the value of the volume fraction ϕ_0 but also on the values of the parameters z, ϵ, and κ_2/κ_{-1}.

The theoretical values (UC) of the normalized rate coefficients $\tilde{k}_1/k_1$ and $\tilde{k}/k_1$ are listed in Table II. They were calculated from Eqs. (4.10a) and (4.18), respectively, based on the experimental data for the bacterial catalase–hydrogen peroxide reaction by Strother and Ackerman.[23] The results (U) due to the uncorrelated term v and those (0) obtained in the low volume fraction limit $\phi_0 \to 0$ are also listed in Table II for comparison. The equilibrium values of the rate coefficients are also calculated from Eqs. (1.19). The experimental data are as follows. The catalase concentration is $E_0 = 1.2\times10^{-7}$ M, and the hydrogen peroxide concentration $\langle C \rangle = 1.3\times10^{-6}$ M, and the radius of the catalase $a = 52.2\times10^{-8}$ cm. Since the formation of the enzyme–substrate complex is diffusion independent for values of the viscosity η of the hydrogen peroxide up to about 6 cP,[24] we have $k_1 = 1.0\times10^7\,\mathrm{M^{-1}\,s^{-1}}$, $k_{-1} = 0.0\,\mathrm{s^{-1}}$, and $k_2 = 208.0\,\mathrm{s^{-1}}$, which lead to $z = 0.625$, $\kappa = 0$, and $\phi_0 = 4.3\times10^{-5}$. At $\eta = 63$ cP, we also have $\tilde{k}_1 = 0.19\times10^7\,\mathrm{M^{-1}\,s^{-1}}$.

From Eq. (4.21), the value of ϵ is then estimated as $\epsilon = 4.766$, leading to $k_D = 0.21\times10^7\,\mathrm{M^{-1}\,s^{-1}}$. The values of the volume fraction $\phi_0 = 4.3\times10^{-4}$, 4.3×10^{-2}, and 1.0×10^{-1} correspond to the values of the catalase concentration $E_0 = 1.2\times10^{-6}$, 1.2×10^{-4}, and 2.8×10^{-4} M, respectively. The higher values of the volume fraction ϕ_0, or total enzyme density E_0, correspond to estimates of in vivo enzyme concentrations (see Ref. 26). The theoretical values of the rate coefficients at $\epsilon = 0.4766$ ($k_D = 2.1\times10^7\,\mathrm{M^{-1}\,s^{-1}}$) are also listed in Table II for comparison. We see that if ϵ is larger, the correction is not negligible even for a smaller value of ϕ_0 and the effect of the correlated term w becomes important. The correction to $\tilde{k}_1$ is 27.3% (UC) and 28.9% (U) for $\phi_0 = 4.3\times10^{-2}$ and $\epsilon = 4.766$ at $z = 0.625$, and 27.2% (UC) and 27.2% (U) at equilibrium ($z = 0.0$). If the volume fraction ϕ_0 is large enough, the correction is also not negligible even for a small value of ϵ. The correction is 4.7% (UC) and 7.2% (U) for $\phi_0 = 1.0\times10^{-1}$ and $\epsilon = 0.4766$ at $z = 0.625$, and 10.0% (UC) and 10.0% (U) at equilibrium. In the long time limit $t \to \infty$, $\tilde{k}_1$ decreases to its equilibrium value, while $\tilde{k}$ increases to the same value (see also Fig. 2).

TABLE II. Theoretical values of $\tilde{k}_1/k_1$, Eq. (4.10a) and $\tilde{k}/k_1$, Eq. (4.18) for the bacterial catalase–hydrogen peroxide reaction. (UC) indicates the result with both correlated and uncorrelated terms (U) with the uncorrelated term only, and (0) without both terms. The numbers in the brackets denote the equilibrium values.

	$\tilde{k}_1/k_1$			$\tilde{k}/k_1$		
ϕ_0	(UC)	(U)	(0)	(UC)	(U)	(0)
$\epsilon = 4.766$						
4.3×10^{-4}	0.196	0.196	0.190	0.174	0.174	0.170
	(0.178)	(0.178)	(0.173)	(0.178)	(0.178)	(0.173)
4.3×10^{-3}	0.207	0.207	0.190	0.183	0.184	0.170
	(0.188)	(0.188)	(0.173)	(0.188)	(0.188)	(0.173)
4.3×10^{-2}	0.242	0.245	0.190	0.210	0.213	0.170
	(0.220)	(0.220)	(0.173)	(0.220)	(0.220)	(0.173)
1.0×10^{-1}	0.270	0.275	0.190	0.230	0.235	0.170
	(0.245)	(0.245)	(0.173)	(0.245)	(0.245)	(0.173)
$\epsilon = 0.4766$						
4.3×10^{-4}	0.758	0.759	0.755	0.514	0.515	0.513
	(0.682)	(0.682)	(0.677)	(0.682)	(0.682)	(0.677)
4.3×10^{-3}	0.763	0.767	0.755	0.517	0.518	0.513
	(0.691)	(0.691)	(0.677)	(0.691)	(0.691)	(0.677)
4.3×10^{-2}	0.779	0.791	0.775	0.524	0.529	0.513
	(0.722)	(0.722)	(0.677)	(0.722)	(0.722)	(0.677)
1.0×10^{-1}	0.791	0.809	0.755	0.529	0.537	0.513
	(0.745)	(0.745)	(0.677)	(0.745)	(0.745)	(0.677)

V. SUMMARY AND REMARKS

We have presented a statistical-mechanical derivation of expression for deterministic reaction rates of chemical reactions in solution for any value of $\epsilon = k_1/4\pi aD$, Eq. (1.2) and finite (but small) volume fraction ϕ_0 of a reactant. As a typical example, we have studied the effect of neighboring enzymes on the rates in a nondilute enzyme system. Since the present formalism is general, however, its formal application to other chemical systems is straightforward.

There are two important features in the present theory. First, to complete the separation of the macroscopic and microscopic processes, the space-time coarse graining is carried out in a manner consistent with the expansion in the small parameter $\phi^{1/2}$. This gives a systematic expansion for finding first-order correction.[15,21] Second, the dynamics of fluctuations around the deterministic motion is explored explicitly. This is indispensable since the derivation and validity of deterministic rate equations is closely related to the asymptotic behavior of fluctuations. Although the fluctuations are small compared to the deterministic motion when $d > 2$, they are important since they can cause an appreciable effect on the reaction rate through the fluctuation–dissipation relation of the second kind.[27] On the time scale of order τ' (see Table I) fluctuations have two origins: an initial randomness and a reactive–diffusive long-range interaction among enzymes.

In the late stage where the spatial inhomogeneities are negligible, we derive the renormalized deterministic rate equations (4.9) and obtained explicit expressions for the volume-fraction dependent forward and reverse rate coefficients $\tilde{k}_1$ and $\tilde{k}_{-1}$, Eqs. (4.10). Employing the quasistationary state approximation, we also derive the deterministic rate equation (4.17), which is a generalization of the Michaelis–Menten equation when $\epsilon = 0$, to order $\phi^{1/2}$, and obtain the overall rate coefficient $\tilde{k}$, Eq. (4.18). The normalized rate coefficients $\tilde{k}_1/k_1$, $\tilde{k}_{-1}/k_{-1}$, and $\tilde{k}/k_1$ depend on the scaled parameters ϕ_0, $\epsilon, z = k_1\langle C \rangle/(k_{-1} + k_2)$ and $\kappa = k_{-1}/(k_{-1} + k_2)$ only.

The reactive–diffusive long-range interactions among enzymes cause two kinds of first-order corrections to the rate coefficients, both of which are proportional to the square root of the enzyme density; the uncorrelated term (3.34) and the correlated term (3.35a) with quite different properties for each. The correlated term leads to a Fokker–Planck equation for $f(p,r;t)$ while the uncorrelated term leads to a kinetic equation for $f(p,r;t)$ with a first derivative only. The correlated term decreases the rate coefficients while the un-

correlated term increases them (see Fig. 3). Many-body effect becomes noticeable, depending not only on the magnitude of the volume fraction ϕ_0 and ϵ, but also on the smallness of z and κ (see Fig. 4).

We have calculated the theoretical values of the normalized rate coefficients $\tilde{k}_1(z)/k_1$, Eq. (4.10a) and $\tilde{k}(z)/k_1$, Eq. (4.18), based on the experimental data for the bacterial catalase–hydrogen peroxide reaction. The many-body effects are noticeable even for a small value of ϵ when the volume fraction ϕ_0 is at least of order 10^{-2}, and also noticeable even for a small value of ϕ_0 when ϵ is at least of order 1 (Table II). In both cases the effect of the correlated term on the rate is also important. In order to obtain still larger many-body effect on the rate, therefore, enzyme–substrate reactions are needed with a larger value of $\epsilon(=k_1/k_D)$, a smaller value of κ (i.e., $k_2 \gg k_{-1}$), a smaller value of the substrate concentration $z[=k_1\langle C\rangle/(k_{-1}+k_2)]$, and a larger value of the enzyme concentration $\phi_0\ (=4\pi a^3 E_0/3)$.

ACKNOWLEDGMENTS

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APPENDIX A: DERIVATION OF EQ. (2.11)

By using Eq. (2.10), we first invert Eqs. (2.8) to

$$\sigma_i(\Omega_i,t)=\int_0^t dt'\int d\Omega_i' K_i(\Omega_i,\Omega_i';t,t')\Big[C(r_i',t')-C_0(r_i',t') - \sum_{j\neq 1}\int_0^{t'} dt''\int d\Omega_j'' g_0(r_i'-r_j'',t'-t'')\sigma_j(\Omega_j'',t'')\Big] \tag{A1}$$

Since the enzymes are assumed to be nonoverlapping and nontouching spheres, we can write the last term of Eq. (A1) as

$$\begin{aligned}&\sum_{j\neq i}\int d\Omega_j'' g_0(r_i'-r_j'',t'-t'')\sigma_j(\Omega_j'',t'')\\ &=\sum_{j=1}\theta(|r_j''-X_i|-a)\int d\Omega_j'' g_0(r_i'-r_j'',t'-t'')\sigma_j(\Omega_j'',t'') \qquad \text{(A2)}\\ &=\int dr''\, g_0(r_i-r'',t'-t'')\theta(|r''-X_i|-a)\sum_{j=1}\int d\Omega_j''\,\delta(r'-r_j'')\sigma_j(\Omega_j'',t'').\end{aligned}$$

Then, use of Eqs. (2.7) and (A2) yields Eq. (2.11).

APPENDIX B: DERIVATION OF EQ. (2.12)

As was shown in Appendix C of Ref. 15, K_i is a rapidly varying function in time. On the other hand, C and g_0 are the slowly varying functions in space and time. Therefore, on the length scale of order l and the time scale of order τ, we can replace the position r_i' and the time t' in Eq. (2.11) by X_i and t, respectively. Then, we can write Eq. (2.11) as

$$\sigma_i(\Omega_i,t)=\int_0^t dt'\int d\Omega_i' K_i(\Omega_i,\Omega_i';t,t') \times\Big[C(X_i,t)-C_0(X_i,t) - \int_0^t dt''\int dr'' g_0(X_i-r'',t-t'') \times\theta(|r''-X_i|-a)I(r'',t'')\Big]. \tag{B1}$$

As was shown in Appendix C of Ref. 15, we also have, on the time scale of order τ,

$$\int_0^t dt'\int d\Omega_i\, d\Omega_i' K_i(\Omega_i,\Omega_i';t,t')=4\pi a D. \tag{B2}$$

Integrating Eq. (B1) and using Eqs. (2.7) and (B2) thus lead to Eq. (2.12).

APPENDIX C: DERIVATION OF EQ. (2.26)

From Eqs. (2.6) and (2.10), we have the formal solution

$$C=C_0+g_0\cdot I. \tag{C1}$$

Use of Eqs. (2.20) and (2.23) then leads to

$$C=[1-k_1 g_0\cdot H]\cdot C_0+k_{-1}g_0\cdot B, \tag{C2}$$

$$=[1+g_0\cdot\varphi]^{-1}\cdot[C_0+g_0\cdot\psi\cdot E_S'+g_0\cdot R], \tag{C3}$$

respectively. Comparing the average of Eq. (C2) with that of Eq. (C3), we thus find Eqs. (2.24) and (2.25). Similarly, comparing Eq. (C2) with Eq. (C3) also leads to Eq. (2.26).

APPENDIX D: DERIVATION OF EQ. (2.39)

Since $g_0(r_i-r_i',t-t')$ is of order ϕ^2 while $g_0(r_i-r_j,t-t')$ $(j\neq i)$ is of order $\phi^{3/2}$, use of Eqs. (2.8) and (2.10) leads, to lowest order in $\phi^{1/2}$, to

$$j_i(t)=Da\int_0^t dt'\int d\Omega_i\int d\Omega_i' g_0(r_i-r_i',t-t') \times\sigma_i(\Omega_i',t'). \tag{D1}$$

By using Eqs. (2.12), (2.13), and (2.14), we then obtain

$$j_i(t) = -k_1 P_i(t) b_i(t) C_0(r_i,t) + k_{-1} Q_i(t) b_i(t) - k_1 P_i(t) b_i(t) \int_0^t dt' \int dr'\, g_0(r_i - r', t - t') \times \theta(|r' - X_i| - a) I(r',t'). \quad \text{(D2)}$$

Inserting Eq. (D2) into Eq. (2.39) thus leads to

$$I_p = -k_1 T_p \cdot C_0 + k_{-1} E'_{Sp} - k_1 M_p \cdot I. \quad \text{(D3)}$$

From the average of Eq. (C2), we have

$$C_0 = (1 + g_0 \cdot \varphi) \cdot (\langle C \rangle - k_{-1} g_0 \cdot \langle B \rangle), \quad \text{(D4)}$$

where we have used the fact that $1 + g_0 \cdot \varphi = [1 - k_1 g_0 \cdot \langle H \rangle]^{-1}$. Therefore, use of Eqs. (D3) and (D4) leads to Eq. (2.39).

APPENDIX E: DERIVATION OF EQ. (4.4)

Using the Fourier–Laplace transformation, we can write Eq. (4.2b) as

$$w(p,t) = \lim_{\delta \to 0} \sqrt{3\phi}\,[4\pi / \langle E' \rangle (2\pi)^3] \times \int dk (k^2 + 1)^{-2} X_k(p,\delta), \quad \text{(E1)}$$

$$X_k(p_1,\delta) = p_1 b_1 \int dp_2\, h(p_2) [\delta + L_1 - M_1(k) + L_2 - M_2(k)]^{-1} \times [h(p_2) f(p_2) u_1 + u_2 h(p_1) f(p_1)] \quad \text{(E2)}$$

with the operators

$$L_1 = \left(\frac{\partial}{\partial p_1}\right)[h(p_1) + k_2 q_1], \quad \text{(E3)}$$

$$M_1(k) = [u_1 / \langle E' \rangle (k^2 + 1)] \int dp_3\, h(p_3) e_{13}, \quad \text{(E4)}$$

where $u_1 = \partial [p_1 b_1 f(p_1)] / \partial p_1$. By using the operator identity

$$[\partial\delta + L_1 - M_1]^{-1} = [\delta + L_1]^{-1} + [\delta + L_1]^{-1} \times M_1 [\delta + L_1 - M_1]^{-1}, \quad \text{(E5)}$$

we can write Eq. (E2) as

$$\begin{aligned} X_k(p_1,\eta) = {} & 2\alpha\zeta \langle E' \rangle \{ p_1 b_1 / (\delta + \alpha + \beta + L_1) \\ & + [k_{-1} + k_2(1 + \epsilon\bar{p})] / (\delta + \beta + L_1) \\ & \times (\delta + \alpha + \beta + L_1)(1 + \epsilon\bar{p})^2 \} h(p_1) f(p_1) \\ & + p_1 b_1 \left(\frac{\partial}{\partial p_1}\right) [(1 + \epsilon\bar{p})(k^2 + 1) \\ & \times \langle h^2 \rangle_f / (k^2 + 1 - 2\zeta) - (2\zeta/\alpha) k_1 k_2 \\ & \times \langle C \rangle \langle h \rangle_f (k^2 + 1) / (k^2 + 1 - 2\zeta)^2 \\ & - k_1 k_2 \langle C \rangle \langle h \rangle_f (k^2 + 1) / \\ & \times (k^2 + 1 - 2\zeta)(\delta + \alpha + L_1)] (1 + \epsilon\bar{p})^{-1} \\ & \times (\delta + \alpha + \beta + L_1)^{-1} p_1 b_1 f(p_1). \end{aligned} \quad \text{(E6)}$$

where $\beta = \alpha(k^2 + 1 - 2\zeta)/(k^2 + 1)$ and $\alpha = [k_1 \langle C \rangle + k_{-1} + k_2(1 + \epsilon\bar{p})]$. In order to derive Eq. (E6), we have used the following relations:

$$h(p_1)[\delta + L_1]^{-1} = [\delta + \alpha + L_1]^{-1} h(p_1) - k_1 k_2 \langle C \rangle / (\delta + L_1)(\delta + \alpha + L_1)(1 + \epsilon\bar{p}), \quad \text{(E7a)}$$

$$p_1 b_1 [\delta + L_1]^{-1} = [\delta + \alpha + L_1]^{-1} p_1 b_1 + [k_{-1} + k_2(1 + \epsilon\bar{p})] / (\delta + L_1)(\delta + \alpha L_1)(1 + \epsilon\bar{p}), \quad \text{(E7b)}$$

where we have replaced b_1 by $(1 + \epsilon\bar{p})^{-1}$ to obtain the second terms of Eqs. (E7), since the error introduced by this simplification is less than one percent for long times.

Equation (E6) still contains the operator L_1. However, such an operator can be omitted under the Markov approximation discussed in Sec. III. In fact, from Eq. (3.30c), we have $e^{-sL} 1 f(p_1,t) = f(p_1, t - s) = f(p_1,t) + O(\phi^{1/2})$, on the time scale of order τ'. By neglecting all operator L_1 in Eq. (E6) and inserting Eq. (E6) into Eq. (E1), we thus obtain Eq. (4.4).

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