Specific Features of Kinetics of Stochastically Gated, Diffusion-Controlled Reactions

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The kinetics of diffusion-controlled, stochastically gated biochemical reactions is analyzed within the markovian approximation for stochastic fluctuations of reaction rate. With the use of methods developed in the theory of magnetic field effects on chemical reactions, several general expressions for reaction rate and transient kinetics of geminate and bulk reactions are derived. In particular, it is shown that gating strongly manifests itself not only in steady-state reaction rates but also in the long time tail of kinetics. Specific features of gated reactions in the presence of attractive potential, resulting in the long-lived intermediate state (cage), are discussed. Two simple markovian models of gating are considered which allow significant simplification of the general expressions obtained. Within these models simple analytical formulas for reaction rate and reaction kinetics are derived and analyzed in detail.

I. Introduction

The well-known important feature of some biochemical reactions, such as protein−ligand binding, is the dependence of reaction rates on conformal transitions in reacting molecules.[1] These transitions give rise to fluctuations of reaction rates (gating). Investigations demonstrate that rate fluctuations strongly manifest themselves in kinetics of these so-called gated reactions (GRs).[2−4]

Possible manifestations of fluctuating reactivity in kinetics of GRs have been analyzed theoretically in many recent articles.[5−9] Naturally, the most direct methods of analysis are based on numerical solution of the corresponding equation.[1,5] Unfortunately, these methods are not very informative and do not give deep insight into the problem because of the numerous parameters in the problem under study. In this situation the analysis within simple analytically solvable models is of great value.

One such model, very popular at present, is the model of the first-order reaction whose time-dependent reaction rate $k(t) \sim k[s^2(t)]$, where $s(t)$ is a Gaussian stochastic variable which represents the effect of conformal transitions on reactivity.[6,7] This model has made it possible to reveal some interesting properties of GRs. However, it is rather limited, which implies the above-mentioned fairly special type of kinetics and fluctuations of $k(t)$.

Several works discuss the specific features of GRs within the markovian approximation for reactivity fluctuations.[4,5,8,9] This approximation has an advantage because it enables one to analyze the effect of gating on real nonexponential kinetics of diffusion-controlled reactions. In particular, this approach allowed Szabo and Zhou[5] to show that the effects of the gating of ligands and proteins on reaction kinetics are surprisingly different. Some details of these effects were analyzed in ref 8 within the simple markovian two-state model. Unfortunately, this model is clearly oversimplified. It is unable to take into account important features of realistic gating [for example, the large number (continuum) of gating states involved in the process, possible complicated spectrum of gating rates that cannot be approximated by the only rate, etc.]. They can strongly manifest themselves in the kinetics of GRs.

This work describes the general method of the analytical treatment of diffusion-controlled GRs within markovian approximation for gating. From mathematical and physical points of view, the theory of GRs is very close to the theory of magnetic field effects (MFEs) on chemical reactions of paramagnetic particles.[10,11] The main mechanism of MFEs is based on the assumption that the rates of reaction of these particles are spin selective,[12,13] i.e., reaction rates depend on the total spin (internal state) of pairs of reacting particles. A similar idea on the dependence of reactivity on internal states of reacting pairs underlies the theory of diffusion-controlled GRs.[3,5]

The treatment of MFEs reduces to solving the stochastic Liouville equation (SLE),[12−14] which is actually the system of a large number of differential equations represented in the matrix form. The general kinetic equation that describes GRs[3,5] is a particular case of the SLE corresponding to the absence of quantum transitions. This means that a lot of theoretical results obtained in the strongly developed theory of MFEs[10,11] can be straightforwardly applied to the analysis of GR kinetics.

The methods proposed in refs 10 and 11 are based on the idea of solving the SLE directly in the matrix form without any assumptions on the mechanism of spin-selective transitions during the reactions. It is shown that the general matrix expressions for observables obtained by these methods appear to be very useful for qualitative analysis of results. In particular, this approach helps to find general relations between observables which are valid irrespective of the mechanisms of the transitions. The obtained expressions also enable one to apply some models for transitions in which these expressions can be reduced to simple analytical formulas.

The main purpose of this work is to analyze some specific features of diffusion-controlled GRs by the methods of the theory of MFEs. These methods have permitted the elucidation of specific properties of GR kinetics. In particular, simple matrix expressions are obtained for the yield of geminate and bulk GR in the absence and presence of interparticle interaction potential. General analysis of the specific features of kinetics is carried out using these expressions. In the relaxation time model (RTM) and single reactive channel model (SRCM) well-known in the theory of MFE, these matrix expressions are reduced to simple analytical formulas for reaction kinetics.

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II. General Formulation

For the convenience of the presentation and introduction of notation, we start with geminate GRs.

A. Geminate Reactions. The kinetics of stochastically gated, diffusion-controlled reactions of proteins, hereafter called macromolecule (*m*), with ligand (*l*) is generally characterized by the vectors of parameters. These parameters are different for geminate and bulk reactions. The kinetics of geminate reactions is completely described by the vector $|\mathbf{p}(r,t)\rangle$ of probabilities to find the *ml*-pair at a distance *r* between reagents and in gating states $|m_\mu\rangle$ and $|l_\lambda\rangle$ of the macromolecule and ligand, respectively. In our discussion we use the Dirac's bra-ket notation for gating states. In particular, expansion of $|\mathbf{p}(r,t)\rangle$ in the complete bases of gating states is written as: $|\mathbf{p}(r,t)\rangle = \sum_{\mu,\nu} p_{\mu\nu}(r,t)|m_\mu\rangle|l_\lambda\rangle$.

The evolution of $|\mathbf{p}(r,t)\rangle$ is completely determined by the Green's function $\hat{g}_g(r,r'|t)$ of the SLE-type kinetic equation

$$\dot{\hat{g}}_g = D[\hat{L} - (\hat{W}_m + \hat{W}_l)/D]\hat{g}_g = D(\hat{L} - \hat{W}_g/D)\hat{g}_g \quad (1)$$

$$|\mathbf{p}(r,t)\rangle = \int \mathrm{d}^3 r' \hat{g}_g(r,r'|t)|\mathbf{p}_g(r')\rangle \quad (2)$$

where $|\mathbf{p}_g(r,t)\rangle = |\mathbf{p}(r,t=0)\rangle$.

In eq 1

$$\hat{L} = \nabla(\nabla + \beta\nabla U) \quad (3)$$

(with $\beta = 1/kT$) is the Smoluchowsky operator that controls diffusive relative motion of the *ml*-pair with the diffusion coefficients *D* in the interaction potential $U(r)$, which is assumed to be spherically symmetric. The matrix $\hat{W}_g = \hat{W}_m + \hat{W}_l$ describes the markovian fluctuations of the reaction rate caused by gating in macromolecules ($\hat{W}_m$) and ligands ($\hat{W}_l$).

For the convenience of our further discussion we need special notation for the equilibrium eigenvectors

$$|0_j\rangle = \sum_\nu p_{j\nu}|j_\nu\rangle \quad \text{and} \quad \langle 0_j| = \sum_\nu \langle j_\nu|, (j = m, l) \quad (4)$$

of the matrixes $\hat{W}_m$ and $\hat{W}_l$: $\hat{W}_j|0_j\rangle = \langle 0_j|\hat{W}_j = 0$ ($j = m, l$). In eq 4, $p_{j\nu}$ is the equilibrium probability to find the system in the gating state ν of the molecule *j*. Note that $|0_j\rangle \neq \langle 0_j|^+$ because the matrixes $\hat{W}_m$ and $\hat{W}_l$ are nonhermitian. Also, according to the definition (eq 4) $p_{j\nu} = \langle 0_j|j_\nu\rangle\langle j_\nu|0_j\rangle$. This relation enables one to interpret the matrix element $\langle 0_j|\hat{A}|0_j\rangle$ of any matrix $\langle\nu|\hat{A}|\nu'\rangle = A_\nu\delta_{\nu\nu'}$ diagonal in the basis of gating states as an average over the distribution $p_{j\nu}$.

$$\langle 0_j|\hat{A}|0_j\rangle = \langle A\rangle_0 = \sum_\nu A_\nu p_{j\nu} \quad (5)$$

Naturally, for the continuous distribution of eigenvalues ν the sum in eq 5 is replaced by the integral.

We also introduce the projection operators

$$\hat{P}_j = |0_j\rangle\langle 0_j| \quad \text{and} \quad \hat{Q}_j = \hat{E}_j - \hat{P}_j \, (j = m, l) \quad (6)$$

in which $\hat{E}_j$ is the unity matrix in the space of *j*-gating states.

The Green's function satisfies the reactive boundary condition

$$\partial\hat{g}_g/\partial r|_{r=d} = \hat{\kappa}_0\hat{g}_g \quad (7)$$

where the reactivity matrix $\hat{\kappa}_0$ is diagonal in the $|ml\rangle$-basis of gating states.

The initial condition for $\hat{g}_g(r,r'|t)$ is

$$\hat{g}_g(r,r'|t=0) = \hat{g}_g^0(r,r') = \hat{E}\delta(r-r')/(4\pi rr') \quad (8)$$

where $\hat{E} = \sum_{\lambda,\mu}|m_\mu\rangle|l_\lambda\rangle\langle l_\lambda|\langle m_\mu| = \hat{E}_m \otimes \hat{E}_l$ is the unity matrix in the space of gating states that is the direct product of unity matrixes in *m*- and *l*-spaces.

Most of kinetic parameters of GRs can easily be represented in terms of the Laplace transform of $\hat{g}$:

$$\hat{G}_g(r,r'|\epsilon) = \int_0^\infty \mathrm{d}t\, \hat{g}_g(r,r'|t)\, \mathrm{e}^{-st} \quad (9)$$

which obeys the steady-state SLE

$$(\hat{q}^2 - \hat{L})G_g = \hat{g}_g^0/D \quad (10)$$

where

$$\hat{q} = \sqrt{(\epsilon + \hat{W}_m + \hat{W}_l)/D} \quad (11)$$

In geminate reaction the pair of reacting molecules is assumed to be formed at a distance $r_i \geq d$ in the equilibrium gating state $|0\rangle = |0_m\rangle|0_l\rangle$, i.e.,

$$|\mathbf{p}(r,t=0)\rangle = |\mathbf{p}_g(r)\rangle = \frac{1}{4\pi r_i^2}\delta(r-r_i)|0\rangle \quad (12)$$

The kinetics of geminate reaction is determined by the time-dependent *ml*-reaction yield

$$Y(t) = \int_0^t \mathrm{d}\tau\, \langle 0|\hat{\kappa}_0|\mathbf{p}(\mathrm{d},\tau)\rangle = \frac{1}{2\pi i}\{4\pi \mathrm{d}^2 \int_{-i\infty}^{i\infty} \mathrm{d}\epsilon\epsilon^{-1}\, \langle 0|\hat{\kappa}_0\hat{G}_g(d,r_i|\epsilon)|0\rangle\, \mathrm{e}^{st}\} \quad (13)$$

It is evident from eq 13 that the total reaction yield $Y(t \to \infty)$ is given by

$$Y(t\to\infty) = Y_\infty = 4\pi d^2\, \langle 0|\hat{\kappa}_0\hat{G}_g(d,r_i|0)|0\rangle \quad (14)$$

Note that eqs 13 and 14 are very similar to those obtained in the theory of MFEs.[10,11]

Equations 13 and 14 reproduce the expected behavior of $Y(t)$ both in the limit of slow and fast gating. In the slow gating limit, when the characteristic gating rates $\|\hat{W}_m\|$ and $\|\hat{W}_l\|$ are smaller than the characteristic reaction times, one can set $\hat{q} = \sqrt{(\epsilon+\hat{W}_g)/D} \approx \sqrt{\epsilon/D}$ and reduce the SLE (eq 10) to a system of uncoupled equations. According to eq 13 in this case $Y(t)$ is the yield averaged over independent gating states. In the opposite limit of fast gating in the SLE (eq 9) one can use the approximations $\hat{q} = \sqrt{(\epsilon+\hat{W}_g)/D} \approx \sqrt{\epsilon/D}\ |0\rangle\langle 0|$ and $\hat{\kappa}_0 = \langle 0|\hat{\kappa}_0|0\rangle|0\rangle\langle 0| = \langle\kappa_0\rangle_0|0\rangle\langle 0|$, where $\langle\kappa_0\rangle_0 = \sum_{\mu,\lambda}\kappa_{0\mu\lambda}p_\mu^m p_\lambda^l$ is the average reactivity of the *ml*-pair (see also eq 5) in which $\kappa_{0\mu\lambda} = \langle m_\mu|\langle l_\lambda|\hat{\kappa}_0|l_\lambda\rangle|m_\mu\rangle$. In other words, in the fast gating limit the kinetics of the gated reaction reduces to that of the reaction without gating, but corresponding to the average reactivity $\langle k_0\rangle_0$ of the pair. Some specific properties of geminate reaction kinetics are discussed below in two realistic models of relative motion of molecules.

B. Bulk Reactions. For bulk GRs the initial condition corresponds to the delocalized spatial distribution function of ligands $p_b(r)$ in the equilibrium gating state $|0\rangle = |0_m\rangle|0_l\rangle$:

$$|\mathbf{p}(r,t=0)\rangle = |\mathbf{p}_b(r)\rangle = c_l p_b(r)|0\rangle \quad (15)$$

where c_l is the bulk concentration of ligands. In our discussion we will assume the thermal initial distribution functions $p_b(r) = \exp[-\beta U(r)]$.

The kinetics of bulk GRs is characterized by the survival probability $P(t)$ of m-molecules. In the pair approximation the method of calculation of $P(t)$ for reacting molecules without internal degrees of freedom is well-known[15] and quite simple. The problem of proper treatment of internal degrees of freedom within the pair approximation is solved in the theory of MFEs.[11,16] The corresponding extension of the method leads to the expression for $P(t)$ in terms of the solution of the SLE similar to eq 1, but not the same. The analysis performed in ref 11, however, concerns reactions that lead to the simultaneous disappearance of both reacting molecules and the concentrations of both molecules are comparable. At the same time, in the considered reaction of macromolecule (m), whose concentration is low, with ligands (l) the m-molecule can be approximately considered as a sink for l-molecules. In this case some modification of the method proposed in ref 11 is required.

Following ref 11 let us treat the reaction of one m-molecule with l-molecules, distributed over the volume with the above-mentioned distribution vector $|\mathbf{p}(r,t=0)\rangle$, as a sequence of ml-encounters which are uncorrelated in time for different l-molecules. It is important to point out that the effect of l- and m-gating transitions should be treated in different way. First, we take into account only l-gating and evaluate the corresponding survival probability $P_l(t)$. In this case the average contribution of the encounter with one l-molecule to $P_l(t)$ is given by

$$P_l^{(1)}(t) = 1 - \frac{1}{V}\int_0^t \mathrm{d}\tau\, k(\tau) \tag{16}$$

where V is the volume of the system and

$$k(t) = \langle 0_l|\hat{k}_l(t)|0_l\rangle \tag{17}$$

is the average time-dependent reaction rate which is determined by the reaction rate matrix

$$\hat{k}_l(t) = 4\pi \mathrm{d}^2\, \hat{\kappa}_0 \hat{g}_l(d|t) = \frac{1}{2\pi i}\,[4\pi d^2\, \hat{\kappa}_0 \int_{-i\infty}^{i\infty} \mathrm{d}\epsilon\, \hat{G}_l(d|\epsilon)\, \mathrm{e}^{st}] \tag{18}$$

This matrix is expressed in terms of the Green's function $\hat{g}_l(r/t)$ satisfying the SLE

$$\dot{\hat{g}}_l = D(\hat{L} - \hat{W}_l/D)\hat{g}_l \tag{19}$$

with the initial condition

$$\hat{g}_l(r|t=0) = \hat{g}_l^0 = p_b(r)\hat{E}_l \tag{20}$$

or in terms of the corresponding Laplace transform $\hat{G}(d|\epsilon)$ that obeys the corresponding steady-state SLE

$$(\hat{q}_l^2 - \hat{L})G_l = \hat{g}_l^0/D \quad \text{with} \quad \hat{q}_l = \sqrt{(\epsilon + \hat{W}_l)/D} \tag{21}$$

Contribution of encounters with other l-molecules to $P_l(t)$ is similar to eq 16. These contributions can be summed up easily on the assumption that the blips of the reaction rate $k(t)$ caused by encounters with different l-molecules are uncorrelated. In so doing the survival probability resulting from n uncorrelated ml-encounters is given by

$$P_l^{(n)} = \left[1 - \frac{1}{V}\int_0^t \mathrm{d}\tau\, k(\tau)\right]^n \tag{22}$$

and therefore in the limit $n \to \infty$, $V \to \infty$, but $n/V = c_l$,

$$P_l(t) = \lim_{n\to\infty} P_l^{(n)}(t) = \exp[-c_l \int_0^t \mathrm{d}\tau\, k(\tau)] \tag{23}$$

Equation 23 describes the reaction kinetics for l-gating. The additional effect of fluctuations of the reaction rate $k(t)$ caused by markovian m-gating transitions can be described with the use of the well-known method of averaging of exponential functionals depending on markovian fluctuating parameters.[12−14] In our particular case the fluctuating parameter is the reactivity κ_0. This method enables one to reduce the problem of averaging of these functionals and evaluating the kinetics $P(t)$ in the presence of m-gating to solution of the SLE:

$$P(t) = \langle 0_m|\hat{R}(t)|0_m\rangle \tag{24}$$

where the $\hat{R}(t)$ is the matrix in the m-gating space $|m_\mu\rangle$ that satisfies the SLE

$$\dot{\hat{R}} = -\hat{K}(t)\hat{R} \tag{25}$$

where

$$\hat{K}(t) = c_l\hat{k}(t) + \hat{W}_m \tag{26}$$

and

$$\hat{k}(t) = \sum_\mu k_\mu |m_\mu\rangle\langle m_\mu| = 4\pi d^2\, \langle 0_l|\hat{\kappa}_0\hat{g}_l(d|t)|0_l\rangle \tag{27}$$

is the matrix of time-dependent reaction rates diagonal in the m-gating space. For each particular μ the rate k_μ is calculated by formulas 17 through 20, i.e., the effect of l-gating is completely incorporated in k_μ. It is clear that in the absence of l-gating $\hat{k}(t) = 4\pi d^2\, \hat{\kappa}_0\hat{g}_l(d|t)$.

The expression in eq 24 coincides with that obtained in ref 5. Notice, however, that in ref 5 this formula is derived by the complicated method of solving truncated systems of equations for reduced distribution functions of high order. The truncation was made within the superposition approximation for the triplet distribution function. The obtained nonlinear equation for the pair distribution function is then reduced to eq 25 in some additional approximation whose accuracy is in fact uncontrolled. The above-mentioned analysis has shown that the rigorous derivation is actually much simpler and does not appeal to any properties of the triplet and higher order distribution functions representing many-particle (three and more) correlations. The expression (eq 24) is easily and rigorously derived in the pair approximation.

Now let us briefly analyze the general specific features of the bulk reaction kinetics predicted by eqs 24 through 26. It is clear that these equations reproduce the limiting behavior of kinetics expected from the physical point of view. In particular, in the limit of fast gating transitions when $||\hat{W}_m|| \gg ||\hat{k}||$, one can use approximation $c_l\hat{k}(t) + \hat{W}_m \approx c_l\langle 0_m|\hat{k}(t)|0_m\rangle|0_m\rangle\langle 0_m|$, i.e., in this limit the kinetics of the bulk reaction reduces to that of reaction without gating corresponding to the average reactivity. In the opposite limit $||\hat{W}_m|| \ll ||\hat{k}||$, eq 24 describes the nonexponential kinetics of reaction in the uncoupled gating states with different reactivities.

In general, if the matrix $\hat{K}_\infty = \hat{K}(t\to\infty) = \hat{K}_b + \hat{W}_m$, in which $\hat{K}_b = c_l\hat{k}_\infty = c_l\hat{k}(t\to\infty)$ is the steady-state reaction rate matrix, has the lowest nonzero eigenvalue $K_{\lambda\infty}$, corresponding to the lowest eigenstate $|\lambda_m\rangle$, the long time asymptotic reaction kinetics is exponential:

$$P(t \gg K_{\lambda\infty}^{-1}) = p_m \exp(-K_{\lambda\infty} t) \quad (28)$$

where $p_m = \langle 0_m|\lambda_m\rangle\langle\lambda_m|0_m\rangle$ is the weight (probability) of the rate $K_{\lambda\infty} = \langle\lambda_m|\hat{K}_\infty|\lambda_m\rangle$. If, however, the eigenvalues of $\hat{K}_\infty$ are continuously distributed around zero, the kinetics $P(t)$ becomes strongly nonexponential (see section V).

Additional analysis of the various limits of eq 24 is made below within realistic models of relative motion.

III. Free Diffusion

The problem of the analytic solution of SLEs (eqs 1 and 10) is essentially simplified in the absence of interaction potential: $U(r) = 0$. In particular, the powerful method of analytical solution of the steady-state SLE (eq 10) was proposed.[10,11] We are not going to discuss the method, which was presented and thoroughly analyzed in refs 10 and 11, but analyze the final formulas.

A. Geminate Reactions. In geminate reactions the effects of *l*- and *m*-gating on reaction kinetics are similar and can be treated simultaneously. The method proposed in refs 10 and 11 gives the following expression for the matrix $\hat{G}_g$ (see eq 8):

$$\hat{G}_g(r,r_i|\epsilon) = \hat{G}_g^f(r,r_i|\epsilon) = [e^{\hat{q}|r-d|} + e^{-\hat{q}(r-d)}\hat{\Gamma}]/(8\pi\hat{q}rr_i) \quad (29)$$

where $\hat{\Gamma} = (\hat{q} + \hat{\kappa})^{-1}(\hat{q} - \hat{\kappa})\exp(-\hat{q}\Delta)$ with $\hat{q}$ defined by eq 11, $\hat{\kappa} = \hat{\kappa}_0 + 1/d$, and $\Delta = r_i - d$. Substituting eq 29 into eq 13 we get the final result for the yield $Y(t)$ in terms of the inverse Laplace transform. Equations 13 and 29 enable one to perform general analysis of geminate GRs. The final formulas are closely related to those derived in the MFE theory.[10,11]

For the initial state (eq 12) the expression for the reaction yield is written as:

$$Y^f(t) = \frac{d}{r_i}\left[\frac{1}{2\pi i}\int_{-i\infty+\sigma}^{i\infty+\sigma}\frac{d\epsilon}{\epsilon}\left\langle 0\left|\hat{\kappa}_0\frac{1}{\hat{\kappa} + \hat{q}(\epsilon)}\right|0\right\rangle e^{-\Delta\sqrt{\epsilon/D+st}}\right] \quad (30)$$

This formula shows that in strong reactivity $||\hat{\kappa}_0|| \gg 1/d$, $||\hat{q}||$ the gating effect is weak. The strongest effect is expected in the opposite limit of weak reactivity, when $||\hat{\kappa}_0|| \ll 1/d$ and reactivity can be treated pertubatively. Specific features of the yield in the more complicated intermediate case of $||\hat{\kappa}_0|| \sim ||\hat{q}|| \gg 1/d$ will be analyzed in section V in the relaxation time model.

According to eq 29, the total reaction yield Y_∞^f (see eq 14) is given by

$$Y_\infty^f = \langle 0|\hat{Y}_\infty^f|0\rangle = (d/r_i)\langle 0|\hat{\kappa}_0(\hat{\kappa} + \hat{q}_W)^{-1}|0\rangle \quad (31)$$

and $\hat{q}_W = \hat{q}(\epsilon = 0) = \sqrt{\hat{W}_g/D}$.

For our further discussion it is convenient to introduce two matrixes of effective reaction radii

$$\hat{L} = d\hat{\kappa}_0(\hat{\kappa} + \hat{q}_W)^{-1} \quad \text{and} \quad \hat{L}_* = d(\hat{\kappa} + \hat{q}_W)^{-1}\hat{\kappa}_0 \quad (32)$$

and corresponding reaction rates

$$\hat{k}_\infty = 4\pi D\hat{L} \quad \text{and} \quad \hat{k}_\infty^* = 4\pi D\hat{L}_* \quad (33)$$

The matrices $\hat{k}_\infty$ and $\hat{k}_\infty^*$ are composed of bimolecular reaction rates at $t \to \infty$ (see below). In principle, $\hat{k}_\infty \neq \hat{k}_\infty^*$ and $(\hat{k}_\infty)^T \neq \hat{k}_\infty^*$ because the gating rate matrices $\hat{W}_l$ and $\hat{W}_m$ generally are not hermitian. For slow gating, however, when $||q_W d|| \ll 1$, $\hat{L} \approx \hat{L}_* = \hat{L} = d(\hat{\kappa}_0/\hat{\kappa})$ and thus $\hat{k}_\infty \approx \hat{k}_\infty^* = 4\pi D\hat{L}$.

With the use of definitions 32 and 33, one can represent the yield Y_∞^f in the form $Y_\infty^f = (1/r_i)\langle 0|\hat{L}|0\rangle$.

In agreement with the general statement mentioned above, for strong reactivity $||\hat{\kappa}_0|| \gg 1/d$, $||\hat{q}_w||$ the yield $Y_\infty(r_i) \approx d/r_i$ is practically independent of gating transitions, whereas for weak reactivity $Y_\infty(r_i) \approx (d^2/r_i)\langle 0|\hat{\kappa}_0|0\rangle$, where $\langle 0|\hat{\kappa}_0|_{10}\rangle = \langle\kappa_0\rangle_0 = \sum_{\mu,\lambda}\kappa_{0\mu\lambda}p_\mu^m p_\lambda^l$ is the average reactivity.

Naturally, eq 31 reproduces the results expected in the fast- and slow-rate fluctuation limits:

(1). In the fast fluctuations limit, when all eigenvalues of $\hat{W}_g = \hat{W}_m + \hat{W}_l$, except the equilibrium one (which is equal to zero), are large enough to ensure inequality $||\hat{q}_W|| \gg ||\hat{\kappa}||$, $1/(\hat{\kappa} + \hat{q}_w) \approx |0\rangle\langle 0|/\langle 0|\hat{\kappa}|0\rangle$ and thus

$$Y_\infty^f = L_f/r_i \text{ and } L_f = d\langle\kappa_0\rangle_0/(1 + d\langle\kappa_0\rangle_0) \quad (34)$$

Clearly in this limit the yield (eq 34) coincides with that predicted for the reaction of particles with the average reactivity $\langle 0|\hat{\kappa}_0|0\rangle = \langle\kappa_0\rangle_0$ created at a distance r_i.[15]

(2). In the opposite limit of slow fluctuations, when $||\hat{q}_W|| \ll ||\hat{\kappa}_0||$,

$$Y_\infty^f = d^2\langle\kappa_0/(1 + d\kappa_0)\rangle_0/r_i \quad (35)$$

which is expected for reagents with a set of uncoupled states with different reactivity.

(3). As for the time dependence of the yield $Y(t)$, in the limit of fast gating this dependence is the same as for reagents with nonfluctuating average reactivity (see eq 34). In the slow gating limit the time dependence can be determined by considering the gated reaction as a set of independent reactions with reactivities $\kappa_{0\mu\lambda}$.

A simple formula can be obtained for the long time tail of $\delta Y(t) = Y^f(t) - Y_\infty^f = \langle 0|\delta\hat{Y}(t)|0\rangle$ (at $t \gg d^2/D$). In the simplest case of small initial distance and long time, when $\Delta/\sqrt{Dt} \ll 1$, the expansion of the Laplace transform (eq 29) in small ϵ (or more correctly in small $||\delta\hat{q}||d \ll 1$, where $\delta\hat{q} = \hat{q} - \hat{q}_W$ and $\hat{q}_W = \sqrt{\hat{W}_g/D}$) and the subsequent inverse Laplace transformation yield

$$\delta\hat{Y}(t) = \hat{Y}^f(t) - \hat{Y}_\infty^f = \frac{1}{(4\pi D)\sqrt{\pi Dt}}\hat{k}_\infty\Phi(\hat{W}_g t)\hat{\Pi}_* \quad (36)$$

where $\hat{W}g = \hat{W}_m + \hat{W}_l$, $\hat{\Pi}_* = 1 - \hat{L}_*/r_i$ is the matrix of escaping probabilities and

$$\Phi(x) = e^{-x}[1 - \sqrt{\pi x}\, e^x \operatorname{erfc}(\sqrt{x})] \quad (37)$$

in which $\operatorname{erfc}(x) = (2/\sqrt{\pi})\int_x^\infty dz\, \exp(-z^2)$ is the error function.[17] The function $\Phi(x)$ is monotonically decreased as x is increased [with $\Phi(0) = 1$ and $\Phi(x \to \infty) \sim (2x)^{-1} e^{-x}$].

In principle, expansion in $||\delta\hat{q}||d \ll 1$ does not imply that $||\hat{q}_W||d \ll 1$, although if $||\hat{q}_W||d \sim 1$, eq 36 is valid only at relatively large times $t > 1/||\hat{W}||$.

Equation 36 is a generalization of the corresponding expression for diffusion-controlled reactions in the absence of gating.[15] It is clear from this equation that at $t \gg ||\hat{W}_{l,m}||$ we get $\Phi(\hat{W}t) \approx |0\rangle\langle 0|$; therefore, the asymptotic time behavior of $Y(t)$ coincides with that predicted by the conventional formula:[15] $Y(t) = (4\pi D\sqrt{\pi Dt})^{-1} k_\infty(1 - L_*/r_i)$, where $k_\infty = \langle 0|\hat{k}_\infty|0\rangle$ and $L_* = \langle 0|\hat{L}_*|0\rangle$. Note, however, that the form of the function $\Phi(\hat{W}_t)$, and thus the form of convergence of the yield $Y(t)$ to the conventional asymptotic one essentially depends on the spectrum of the matrix $\hat{W}$.

B. Bulk Reactions. The bulk GR kinetics is controlled by the matrix $\hat{K}(t)$ defined in eq 26. The main problem of analysis of the kinetics is in evaluating the time-dependent rate $\hat{k}(t)$. Specific features of this time dependence are determined by the analytical properties of the Green's function $\hat{G}_l(r|\epsilon)$, which satisfies eq 21. In the free diffusion model this function can be obtained analytically without difficulties by the method developed in ref 11:

$$\hat{G}_l(\mathrm{d}|\epsilon) = \hat{G}_l^f(\mathrm{d}|\epsilon) = \frac{1}{\hat{\kappa} + \hat{q}_l} \frac{(1 + d\hat{q}_l)}{d\hat{q}_l^2} \tag{38}$$

Hence, according to eqs 24−27 the problem reduces to some matrix operations and evaluation of the inverse Laplace transform. In general, this can be done only numerically. Analytical expressions can be derived only within simple models of rate fluctuations (see below). Equation 25, however, is very useful for qualitative analysis of the problem.

For the sake of convenience we will consider the cases of *l*- and *m*-gating separately.

1. Gated Ligands. For gated ligands (*l*-gating) the time-dependent survival probability $P(t)$ for *m*-molecules is given by eq 23: $P(t) = P_l(t)$, in which the time dependence of the reaction rate $k_l(t)$ is determined by $\hat{g}(d/t)$ (see eqs 17 and 18). In general, the function $k_l(t)$ can be obtained by numerical calculation. Here we analyze only the most important asymptotic (at $t \gg d^2/D$) specific features of $k(t)$.

As it follows from eqs 24−27, the long time asymptotic reaction kinetics is determined by the steady-state rate

$$k_{l\infty} = \langle 0_l|\hat{k}_{l\infty}|0_l\rangle = 4\pi d^2 D \lim_{\epsilon\to 0} [\epsilon\langle 0_l|\hat{\kappa}_0\hat{G}_l(\mathrm{d}|\epsilon)|0_l\rangle] = 4\pi d\, D\langle 0_l|\hat{\kappa}_0(\hat{\kappa} + \hat{q}_{W_l})^{-1}|0_l\rangle \tag{39}$$

in which $\hat{k}_{l\infty} = \hat{k}_l(t \to \infty) = 4\pi d\, D\hat{\kappa}_0(\hat{\kappa} + \hat{q}_{W_l})^{-1}$ with $\hat{q}_{W_l} = \sqrt{\hat{W}_l/D}$. The long time tail (at $t \gg d^2/D$) of the time-dependent rate $\delta k_l(t) = k_l(t) - k_{l\infty}$ can be calculated with eqs 24−27 using an approximate expression for $\hat{G}_l(r|\epsilon)$ obtained by expansion in small $||\hat{q}_l(\epsilon) - \hat{q}_{W_l}||d \ll 1$:

$$\delta k_l(t) = k_l(t) - k_{l\infty} = \langle 0_l|\delta\hat{k}_l(t)|0_l\rangle \tag{40}$$

Here

$$\delta\hat{k}_l(t) = \hat{k}_l - \hat{k}_{l\infty} = \frac{1}{4\pi D\sqrt{\pi Dt}}\hat{k}_{l\infty}\Phi(\hat{W}_l t)\hat{k}^*_{l\infty} \tag{41}$$

with $\Phi(x)$ defined in eq 37 and $\hat{k}^*_{l\infty} = 4\pi d\, D(\hat{\kappa} + \hat{q}_{W_l})^{-1}\hat{\kappa}_0$, in accordance with eq 32.

Equations 36 and 41 demonstrate the close relation of the long time dependencies of $\delta\hat{k}_l(t)$ and $\delta\hat{Y}(t)$ similar to that in the theory of diffusion-controlled ungated reactions.[15]

Equation 40 shows that *l*-gating strongly affects the long time kinetics $\delta k_l(t)$. This equation is the generalization of the well-known expression for the long time asymptotic behavior of $\delta k_l(t)$ in the absence of gating.[15] In general, eq 40 describes the relaxation of $\delta k_l(t)$ from $\delta k_<(t) = \langle k_{l\infty}k^*_{l\infty}\rangle_l(4\pi D\sqrt{\pi Dt})^{-1}$ at relatively small $t < 1/||\hat{W}_l||$ to $\delta k_>(t) = \langle k_{l\infty}\rangle_l\langle k^*_{l\infty}\rangle_l(4\pi D\sqrt{\pi Dt})^{-1}$ at $t > 1/||\hat{W}_l||$, where the average is taken over the reactivity distribution in the equilibrium *l*-gating state according to definition 5. The functional form of crossover from $\delta k_<(t)$ to $\delta k_>(t)$ depends on the specific features of the gating rate matrix $\hat{W}_l$. Some examples of this form will be analyzed in section V.

2. Gated Macromolecule. It follows from eqs 24−28 that the long time asymptotic kinetics of *m*-gated reactions is determined by the matrix $\hat{K}_\infty = \hat{K}(t \to \infty) = c_l\hat{k}_\infty + \hat{W}_m = \hat{K}_b + \hat{W}_m$ in the space of *m*-gating states $|m_\mu\rangle$. In general, this kinetics is nonexponential, however, if the matrix $\hat{K}_\infty$ has well-separated eigenvalues and the minimum eigenvalue $k_{\lambda\infty}$, corresponding to the eigenstate $|\lambda_\mathrm{m}\rangle$, is nonzero, then at fairly long times $t \gg 1/||\hat{K}_\infty||$ the kinetics becomes exponential and the rate

$$k_{\lambda\infty} = \langle\lambda_m|\hat{K}_\infty|\lambda_m\rangle = \langle\lambda_m|\hat{K}_b + \hat{W}_m|\lambda_m\rangle \tag{42}$$

In principle, the rate $K_\lambda(t)$ depends on time, and this dependence is typical for diffusion-controlled reactions. At sufficiently long times $t \gg d^2/D$ the time-dependent term $\delta k_\lambda(t) = k_\lambda(t) - k_{\lambda\infty}$ of the total rate can be evaluated similarly to eq 40.

$$\delta k_\lambda(t) = k_\lambda(t) - k_{\lambda\infty} = c_l\langle\lambda_m|\hat{k}(t) - \hat{k}_\infty|\lambda_m\rangle = c_l\langle\lambda_m|\hat{k}^2_\infty|\lambda_m\rangle/(4\pi D\sqrt{\pi Dt}) \tag{43}$$

Analysis shows, however, that if the spectrum of the matrix $\hat{W}_m$ is continuous near zero (corresponding to the equilibrium state $|0_\mathrm{m}\rangle$), the reaction kinetics is strongly nonexponential at long times. Some additional discussion of this effect will be continued in section V.

Equations 42 and 43 demonstrate the important specific feature of GRs: in the presence of *m*-gating there is no relation between parameters of geminate and bulk GRs. For example, according to eq 34 the total geminate reaction yield $Y^f_\infty = L/r_\mathrm{i}$, where L is the effective reaction radius. In the absence of *m*-gating this radius determines the asymptotic (at $t \to \infty$) bulk reaction rate: $k_\infty = 4\pi dDL$ in agreement with general rules for diffusion-controlled reactions.[15] This relation, however, is not valid for *m*-gated reactions as evident from eq 42. Furthermore, in this case there is no relation between amplitudes of the long-time asymptotic dependencies $\delta k_\lambda(t)$ and $Y(t)$, although in some cases discussed above the long time dependence $\delta k_\lambda(t) \sim 1/\sqrt{t}$ in agreement with that known in the theory of diffusion-controlled reactions.[15]

IV. The Effect of Interaction. Exponential Model

A. Geminate Reactions. In general, in the presence of interaction $U(r)$ the analytical solution of the SLE (eq 1) is impossible. However, in the realistic limit of localized potentials in the shape of a deep well, in which $\xi = a||\hat{q}|| \ll 1$, where a is the Onzager radius defined by the relation $\beta U(a) = 1$, the SLE (eq 1) can be solved by expansion in small ξ.[18,19] In this limit the reaction kinetics is completely determined by the probability of staying within the well (cage), which, when pairs are created in the well, is given by

$$|\mathbf{n}(t)\rangle = \int_d^a \mathrm{d}^3\, r|p(r|t)\rangle = \frac{1}{2\pi i}\int_{-i\infty}^{i\infty} \mathrm{d}\epsilon\, \mathrm{e}^{st}\hat{G}_c(\epsilon)|\mathbf{n}_0\rangle \tag{44}$$

where $|\mathbf{n}_0\rangle = \int_d^a \mathrm{d}^3 r|p_g^0(r)\rangle = |0\rangle$ and

$$\hat{G}_c(\epsilon) = [\epsilon + \hat{W} + w_d a\hat{q}(\epsilon)]^{-1} \tag{45}$$

In eq 45

$$\hat{W} = \hat{W}_m + \hat{W}_l + \hat{W}_r + w_d \tag{46}$$

is the sum of matrices of gating rates ($\hat{W}_m$ and $\hat{W}_l$), the matrix of cage reaction rates $\hat{W}_r = D(\mathrm{d}^2\hat{\kappa}_0\mathrm{e}^{\beta U(d)})/\int_d^a \mathrm{d}r\, r^2\, \mathrm{e}^{-\beta U(r)}$ and

the cage dissociation rate $w_d = D/(\int_{r_e}^{\infty} \mathrm{d}r\, r^{-2}\, \mathrm{e}^{\beta U(r)} \int_d^a \mathrm{d}r\, r^2\, \mathrm{e}^{-\beta U(r)})$ in which r_e is the radius of the bottom of well.

Equations 45 and 46 show that in the presence of sufficiently deep potential well the exponential stage of evolution of pairs for a relatively long period up to $t \sim t_c \approx (w_d + ||W_r||)^{-1} \ln(D/w_d a^2)$ appears, which at $t > t_c$ is replaced by the inverse power type one: $|n(t)\rangle \sim t^{-3/2}$, corresponding to free diffusion outside the well.[18,19] This means that the effect of slow rate fluctuations, for which $||\hat{W}_l + \hat{W}_m||t_c < 1$ is properly described by the free diffusion model, i.e., using the results of section III, whereas in the opposite limit of fast rate fluctuations, when $||\hat{W}_l + \hat{W}_m||t_c > 1$, this effect can be treated within the exponential model. Here we concentrate on the exponential model, which allows the description of specific features of gated reactions in the presence of strong interaction.

In the exponential model, evolution of the matrix $\hat{g}_g^e$ is described by eq 47:

$$\hat{g}_g^e = -\hat{W}\hat{g}_g^e \tag{47}$$

with the initial condition $\hat{g}_g^e = \hat{E}$. The geminate reaction yield is written as

$$Y^e(t) = \langle 0|\hat{W}_r\hat{W}^{-1}[1 - \exp(-\hat{W}t)]|0\rangle = \frac{1}{2\pi i}\int_{-i\infty}^{i\infty} \mathrm{d}\epsilon\, \epsilon^{-1}\, \langle 0|\hat{W}_r\hat{G}_e(\epsilon)|0\rangle\, \mathrm{e}^{st} \tag{48}$$

where

$$\hat{G}_e(\epsilon) = \hat{G}_c(\epsilon, a = 0) = (\epsilon + \hat{W})^{-1} \tag{49}$$

evidently coincides with $\hat{G}_c(\epsilon)$ in the limit $||\hat{W}_l + \hat{W}_m||t_c < 1$ when the term $w_d a\hat{q}(\epsilon)$ can be neglected.

Equation 48 is conveniently represented in the form

$$Y^e(t) = Y_\infty^e - [\phi(t) - W_d \int_t^\infty \mathrm{d}\tau\, \phi(\tau)] \tag{50}$$

where $\phi(t) = \langle 0|\exp(-\hat{W}t)|0\rangle$ and

$$Y_\infty^e = Y^e(t \to \infty) = \langle 0|\hat{W}_r\hat{G}_e(0)|0\rangle = \langle 0|\hat{W}_r\hat{W}^{-1}|0\rangle \tag{51}$$

is the total reaction yield.

Equations 48−51 reproduce correctly both limits of fast and slow fluctuations discussed within the free diffusion model in section III. These equations reduce the problem of calculating the yield $Y(t)$ to matrix operations and the inverse Laplace transform. For some simple gating models this can be done analytically (see section V).

B. Bulk Reactions. The kinetics of bulk reactions is determined by the corresponding matrix, which satisfies eq 52:

$$\dot{\hat{g}}_l^e = -\hat{W}_e\hat{g}_l^e + K_c\hat{E}\, \mathrm{e}^{-\hat{W}t} \tag{52}$$

where $\hat{W}_e = \hat{W}_l + \hat{W}_r + w_d$ and K_c is the rate of capture into the cage. The last term in the SLE (eq 52) describes the flux of gated *l*-molecules into the cage. The initial condition for eq 52, corresponding to the equilibrium distribution within the well, is written as $\hat{g}_b^e(t = 0) = \hat{g}_b^0 = (K_c/w_d)\hat{E}$. The general theory[18,19] shows that in the presence of the potential well (cage) the expression (eq 23) for the survival probability is still valid, but the GR rate is given by

$$\hat{k}(t) = \frac{1}{2\pi i}\int_{-i\infty}^{i\infty} \mathrm{d}\epsilon\, \epsilon^{-1}\langle 0_l|\hat{W}_r\hat{G}_l^0(\epsilon)|0_l\rangle\, \mathrm{e}^{st} \tag{53}$$

with

$$\hat{G}_l^0(\epsilon) = (\epsilon + \hat{W}_l)\hat{G}_l(\epsilon) = K_c(\epsilon + \hat{W}_e)^{-1} \tag{54}$$

It is clear from eq 53 that the steady-state GR rate

$$k_\infty = \langle 0_l|\hat{k}_\infty|0_l\rangle = \langle 0_l|K_c/\hat{W}_e|0_l\rangle \tag{55}$$

V. Simple Models for Gating

Formulas derived above in the free diffusion and exponential (cage) models still require some matrix operations, which cannot be carried out without specification of the gating mechanism (the form of matrices $\hat{W}_m$ and $\hat{W}_l$). In section V we consider two simple models in which the matrix operations are performed and some analytical formulas for specific parameters of GR kinetics are obtained.

A. Relaxation Time Model. In the RTM the matrices $\hat{W}_m$ and $\hat{W}_l$ are taken in the form

$$\hat{W}_j = w_j(\hat{E}_j - \hat{P}_j) = w_j\hat{Q}_j \tag{56}$$

where the projection operators $\hat{P}_j$ and $\hat{Q}_j$ are defined in eq 6, and w_m and w_l are the fluctuation rates of reactivities of the macromolecule and ligand, respectively. RTM makes it possible to significantly simplify the expressions for kinetics of geminate and bulk GRs. The main simplifications result from the special relation that is valid for the projection operators $\hat{P}_j$ and $\hat{Q}_j$

$$F(x\hat{P}_j + y\hat{Q}_j) = \hat{P}_jF(x) + \hat{Q}_jF(y) \tag{57}$$

where $F(x)$ is any smooth function.

The general expressions obtained in the gating of both ligands and macromolecules is too cumbersome so that here we restrict ourselves to analysis of gating in only one kind of reagent: either ligands ($j = l$) or macromolecules ($j = m$).

1. Geminate Reactions. a. Diffusion Model. Substituting relation 57 into the general formula (eq 30), one obtains the simple expression for the total yield of the geminate GR in the free diffusion model:

$$Y_\infty^f = \frac{L}{r_i} = \frac{d}{r_i}\left[1 - \frac{\Lambda_0}{1 - q_\mu^0 d\Lambda_0}\right] \tag{58a}$$

Here $q_\mu^0 = \sqrt{w_\mu/D}$,

$$\Lambda_0 = \int \mathrm{d}\kappa_0 \frac{p(\kappa_0)}{1 + d(\kappa_0 + q_\mu^0)} \tag{58b}$$

and $p(\kappa_0)$ is the distribution function of reaction rates κ_0, which for the sake of generality is assumed to be a continuous function of κ_0. This formula reproduces all general specific features of the total yield discussed in section IIIA. It can be considered as a simple and reasonable interpolation formula correctly describing all general limiting relations discussed above.

RTM also allows significant simplification of the eq 36 for the long time tail of the yield:

$$\delta Y^f(t) = \frac{1}{(4\pi D)\sqrt{\pi Dt}}[k_\infty\Pi + (\langle 0|\hat{k}_\infty\hat{\Pi}|0\rangle - k_\infty\Pi)\Phi(wt)] \tag{59}$$

where the function $\Phi(x)$ is defined by eq 37, $\Pi = \langle 0|\hat{\Pi}|0\rangle$ is the escaping probability in the equilibrium gating state (for definition see eq 36), and $k_\infty = \langle 0|\hat{k}_\infty|0\rangle$. It is important to note that in RTM $k_\infty^* = k_\infty$ (see eq 61) and thus $\Pi = \Pi_*$.

b. Cage (Exponential) Model. Formulas similar to eqs 58 and 59 can also be obtained in the exponential model. In particular, the total yield of GR

$$Y^e_\infty = 1 - \frac{w_d \tau_0}{1 - w_\mu \tau_0} \quad \text{with} \quad \tau_0 = \int dW_r \frac{p(W_r)}{w_\mu + w_d + W_r} \tag{60}$$

where μ = m,l and $p(W_r)$ is the (continuous) distribution function of reaction rates. Equation 60, similar to eq 58, reproduces all general specific features of the total yield mentioned in section IV.

As for the time dependence of the yield $Y(t)$, according to eq 48 calculation of this dependence reduces to evaluating the average of the exponential operator over the equilibrium gating state. This problem will be discussed in detail in section VA.2b (see eq 66). Here we only present the main results. In accordance with the general statement of section IIB the characteristic features of time behavior of this average is determined by the spectrum of the operator $\hat{W}$. The definition (eq 46) shows that all eigenvalues of $\hat{W}$ are nonzero; thus, at long times the yield $Y(t)$ decreases exponentially at $t > 1/w_d$. However, the behavior of $Y(t)$ at smaller times $t < 1/w_d$ depends on specific features of the spectrum of $\hat{W}$ in the region of eigenvalues larger than w_d.

2. Bulk Reactions. The general analysis in section IIB demonstrates that the kinetics of bulk GRs is essentially different for the gated ligands (*l*-gating) and macromolecules (*m*-gating).[5] The kinetics of *l*-GRs is exponential at $t \gg d^2/D$. The transient time dependence of the rate constant shows itself in this case as a deviation of bulk *l*-GR kinetics from the exponential at finite times. As for *m*-GRs, the kinetics of these reactions is significantly nonexponential at all times. In that case the contribution of the transient nonexponential part of the process can hardly be distinguished from the main nonexponential kinetics describing *m*-GRs. In other words calculation of the small asymptotic transient part of kinetics eq 41 is nearly useless for *m*-GRs, and for *m*-gating we restrict ourselves to evaluating only the long time behavior of $P(t)$ determined by $\hat{K}_\infty = \hat{K}(t \rightarrow \infty)$ (defined in eq 26) both in the diffusion and cage (exponential) models.

a. Gated Ligands. 1. Diffusion Model. In *l*-gating the steady-state rate constant of bulk GR is determined by eq 33 which predicts in RTM

$$k_{l\infty} = k^*_{l\infty} = 4\pi DL \tag{61}$$

with $L = d[1 - \Lambda_0/(1 - q_l^0\, d\Lambda_0)]$, in agreement with eq 58a. The parameter Λ_0 is given by eq 58b but with q^0_μ replaced by $q^0_l = \sqrt{w_l/D}$. The expression (eq 36) for the long tail $\delta k_l(t)$ is also represented within RTM in very simple form

$$\delta k_l(t) = \frac{1}{(4\pi D)\sqrt{\pi D t}} [k^2_{l\infty} + (\langle 0|\hat{k}^2_{l\infty}|0\rangle - k^2_{l\infty})\Phi(w_l t)] \tag{62}$$

where $\Phi(x)$ is defined by eq 37. In accordance with the remark in section III.B1 and definition (eq 33), the term in square brackets in eq 62 decreases from $\langle 0|\hat{k}^2_{l\infty}|0\rangle = \langle k^2_{l\infty}\rangle_l$ to $k^2_{l\infty} = \langle k_{l\infty}\rangle^2_l \le \langle k^2_{l\infty}\rangle_l$.

2. Cage Model. In this model the asymptotic (at $t \rightarrow \infty$) steady-state rate of the bulk GR is written as (eq 55) $k_{l\infty} = K_c Y^e_\infty$, where Y^e_∞ is the total yield of geminate GR given by eq 60 in which w_μ should be replaced by w_l. Evaluation of the time-dependent part $\delta k_l(t)$ reduces to the average of the matrix exponential operator, as seen in eq 53. The methods of calculation of this average as well as its dependence on the specific features of $\hat{W}_l$ and $\hat{W}_r$ are discussed below.

b. Gated Macromolecules. As pointed out in the beginning of this section, in *m*-gating the most important nonexponential behavior of kinetics of bulk GRs results from the spread of the steady-state rates determined by the matrix $\hat{K}_\infty = \hat{K}(t \rightarrow \infty) = c\hat{k}_\infty + \hat{W}_m = \hat{K}_b + \hat{W}_m$ (see eq 26). Neglecting the transient part of GR kinetics, we can write the expression for survival probability as $P(t) = \langle 0_m|\ \exp(-\hat{K}_\infty t)|0_m\rangle$. RTM allows the analysis of some interesting features of $P(t)$.

In RTM the Laplace transform

$$\tilde{P}(\epsilon) = \langle 0_m|(\epsilon - \hat{K}_\infty)^{-1}|0_m\rangle = \tau(\epsilon)/[1 - w_m\tau(\epsilon)] \tag{63}$$

where

$$\tau(\epsilon) = \int_0^\infty \mathrm{d}k_b \frac{p_0(k_b)}{\epsilon + w_m + k_b} \tag{64}$$

in which $p_0(k_j) = \langle 0_m|j\rangle\langle j|0_m\rangle$ is the distribution function of eigenvalues (reaction rates) of $\hat{K}_b = c\hat{k}_\infty$ in the equilibrium state $|0_m\rangle$. In general, eq 63 predicts the exponential asymptotic behavior of $P(t)$ with the rate equal to the lowest nonzero (positive) root of the equation $w_m\tau(-\epsilon) - 1 = 0$.

Equations 63 and 64 show that the specific features of $P(t)$ are determined by the distribution function $p_0(k)$. We have already mentioned that the function $P(t)$ can be calculated analytically[5,8] in the markovian two-state model of gating, which is a particular case of the proposed RTM. The general RTM (eq 56), however, enables one to obtain the analytical expression for $P(t)$ in some more realistic models assuming a continuum of gating states.

Here we analyze one of these models in which the distribution function

$$p_0(k) = \frac{(1/\pi)}{k_0 + k}\sqrt{\frac{k_0}{k}} \tag{65}$$

This strange (at first sight) distribution function is actually similar to that implied in the model discussed in refs 6 and 7. The model suggests that $k = s^2$, where s is the Gaussian fluctuating parameter for which the distribution function $p_0(s)$ is naturally Gaussian: $p_0(s) = \exp[-(s/s_0)^2]$. In this s-parametrization ($k = s^2$) the model function (eq 65) corresponds to the Lorentzian distribution function: $p_0(s) = (s_0^2 + s^2)^{-1}$ with $s_0 = \sqrt{k_0}$.

Calculation of the function $\tau(\epsilon)$ with the use of $p_0(k)$ (eq 65) and the subsequent inverse Laplace transformation yield

$$P(t) = \frac{2f_-}{f_- + f_+}\,\mathrm{e}^{-\nu_0\tau} + \frac{1}{f_- + f_+}\,\mathrm{e}^{-\tau}[f_+\mathrm{e}^{f_+^2\tau}\,\mathrm{erfc}(f_+\sqrt{\tau}) - f_-\mathrm{e}^{f_-^2\tau}\,\mathrm{erfc}(f_-\sqrt{\tau})] \tag{66}$$

where $f_\pm = \sqrt{1+(k_0/4w_m)} \pm \sqrt{k_0/4w_m}$, $\nu_0 = 1 - f_-^2 < 1$, and $\tau = w_m t$. Note that the long time behavior of $P(t)$ (for $f_\pm\tau \gg 1$) is determined by the first term in eq 66; therefore, the long time tail of kinetics is exponential with the rate $w_m\nu_0 < w_m$. The rate $w_m\nu_0$ is especially small for $k_0/w_m \ll 1$: $w_m\nu_0 = w_m\sqrt{k_0/4w_m} \ll w_m$. In the opposite case $k_0/w_m \gg 1$, we have $f_+ \gg f_-$; therefore, the kinetics is, in fact, determined by the second term in eq 66, whose amplitude is much larger than that of the

first term, although the behavior is still nearly exponential: $P(t) = t^{-3/2} \exp(-w_m t)$. Time dependence of the preexponential factor appears to be determined by the behavior of $p_0(k)$ at small k. In particular, for $p_0(k) = k^{-\nu}$ ($\nu > 0$), eq 63 predicts $P(t) = t^{-(1+\nu)} \exp(-w_m t)$.

B. Single Reactive Channel Model. The SRCM assumes that only one state $|r\rangle$ is reactive, i.e.,

$$\hat{\kappa}_0 = \kappa_r |r_\nu\rangle\langle r_\nu| \quad \text{and} \quad \hat{W}_r = w_r |r_\nu\rangle\langle r_\nu| \ (\nu = \text{m,l}) \tag{67}$$

It is convenient for our further discussion to introduce the distribution function of gating rates:

$$p_\nu(w) = \langle r_\nu | j_\nu\rangle\langle j_\nu | r_\nu\rangle \tag{68}$$

The normalization condition for $p_\nu(w_j)$ is fulfilled automatically because $\sum_j p_\nu(w_j) = \sum_j \langle r_\nu|j_\nu\rangle\langle j_\nu|r_\nu\rangle = \langle r_\nu|r_\nu\rangle = 1$.

For further analysis of the problems it is convenient to represent the distribution function $p_\nu(w)$ in the form

$$p_\nu(w) = p_0 \delta(w) + (1 - p_0) p_\nu^n(w) \tag{69}$$

in which $p_\nu^n(w)$ is the distribution of nonzero gating rates (assumed to be continuous). Similar to the definition (eq 33), we introduce a special definition for the matrix element $\langle r|F(\hat{W})|r\rangle$ which is actually the average of $F(w)$ over $p_\nu(w)$:

$$\langle r|F(\hat{W})|r\rangle = \langle F\rangle_r = \int \mathrm{d}w\, p_\nu(w) F(w) = p_0 F(0) + (1 - p_0) \int \mathrm{d}w\, p_\nu^n(w) F(w) \tag{70}$$

1. Geminate Reactions. It is clear that the model (eq 66) leads to matrix expressions similar to those discussed in section VA from mathematical point of view; in these matrices some terms are proportional to the projection operator on one of states. Therefore SRCM permits the significant simplification of general matrix expression for RG kinetics similar to those derived in RTM.

a. Diffusion Model. The expression for the total yield

$$Y_\infty^f = \frac{L}{r_i} = \frac{1}{r_i}\left(\mathrm{d}\, \frac{p_0 d\kappa_r}{1 + d\kappa_r\, \Lambda_r}\right) \tag{71}$$

where $\Lambda_r = \langle\Lambda\rangle_r$ is the average defined by eq 70 in which $\Lambda(w) = (1 + d\sqrt{w/D})^{-1}$.

In SRCM the general expression (eq 36) for the long time tail $\delta Y^f(t)$ can also be represented in analytical form:

$$\delta Y(t) = \frac{1}{4\pi D \sqrt{\pi D t}}\, k_\infty \left(1 - \frac{L}{r_i}\, \Theta(t)\right) \tag{72}$$

with $k_\infty = 4\pi D L$ and

$$\Theta(t) = 1 + p_0^{-1}(1 - p_0)\Theta_n(t) \tag{73}$$

in which

$$\Theta_n(t) = \int \mathrm{d}w\, p_\nu^n(w) \Lambda^2(w) \Phi(wt) \tag{74}$$

It is easily seen that $\Theta_n(t) \to 0$ and $\Theta(t) \to 1$ as $t \to \infty$ because of the small weight of the equilibrium state in the distribution function $p_\nu^n(w)$. The asymptotic behavior of $\Theta_n(t)$ at large t depends on specific features of the function $p_\nu^n(w)$ at small w.

b. Cage (Exponential) Model. In this model for the total yield of GR SRCM gives

$$Y_\infty^e = p_0 \frac{w_r/w_d}{1 + p_0(w_r/w_d) + (1 - p_0) w_r \tau_n} \tag{75}$$

with $\tau_n = \int \mathrm{d}w\, p_\nu^n(w)(w_d + w)^{-1}$. In the limit of slow relaxation, when $\tau_n \approx 1/w_d$ is determined by the rates $w \ll w_d$, eq 75 reduces to the evident expression $Y_\infty^e = p_0 w_r/(w_d + w_r)$, which means that the yield is controlled by the only reactive channel whose statistical weight is p_0.

The transient part of geminate reaction kinetics is given by eq 50 and includes averaging of exponential matrix in $\phi(t)$. Specific features of this average and thus the transient part of the yield are discussed in section VB2.

2. Bulk Reactions. Similar to the consideration in RTM, in SRCM we will discuss separately the gated ligands and macromolecules, and for *m*-gating we will only analyze the long time behavior of $P(t)$ determined by $\hat{K}_\infty = \hat{K}(t \to \infty)$.

a. Gated Ligands. 1. Diffusion Model. Calculation of the steady-state rate of *l*-GR with the use of eq 30 gives

$$k_{l\infty} = k_{l\infty}^* = 4\pi D L \tag{76}$$

where $L = p_0 \kappa_r d^2/(1 + \kappa_r\, d\Lambda_r)$ and Λ_r is defined in eq 71.

In SRCM simple analytical can also be derived for the long time tail (eq 41):

$$\delta k_l(t) = \frac{1}{(4\pi D)\sqrt{\pi D t}}\, k_{l\infty}^2 \Theta(t) \tag{77}$$

where the function $\Theta(t)$ is defined by eq 73. It was mentioned earlier that $\Theta(t) \to 1$ as $t \to \infty$. This means that, in agreement with the general statement in section IIIB, at very large times $t \gg 1/\|\hat{W}_\nu\|$, the relation for $\delta k_l(t)$ is predicted by the theory[15] for the ungated reactions with the steady-state rate $k_{l\infty}$ given by eq 76. SRCM, however, enables one to obtain behavior $\delta k_l(t)$ at large times independently of the relation between t and $1/\|\hat{W}_\nu\|$.

2. Cage (Exponential) Model. As in RTM, in SRCM the steady-state rate of *l*-GR is proportional to the yield Y_∞^e (eq 75) of geminate GR: $k_{l\infty} = K_c Y_\infty^e$. The time-dependent part $\delta k_l(t)$ is determined by the average matrix exponential operator as it follows from eq 53. The main features of this kind of average will be analyzed somewhat later in the discussion of kinetics of *m*-GRs.

b. Gated Macromolecules. In accordance with the general consideration of section IIB the long time behavior of the survival probability for gated macromolecules is given by $P(t) = \langle 0_m| \exp(-\hat{K}_\infty t)|0_m\rangle$, where $\hat{K}_\infty = \hat{K}(t \to \infty) = \hat{K}_b + \hat{W}_m$, regardless of the model of relative motion. For simplicity we assume that $\hat{K}_b = c\hat{k}_{m\infty} = k_r |r\rangle\langle r|$, although, strictly speaking, it is not implied by eq 67. This model allows the analysis of specific features of $P(t)$ within some general assumptions on behavior of $p_r(w)$.

Simple calculation for the Laplace transform $\tilde{P}(\epsilon)$ gives:

$$\tilde{P}(\epsilon) = \langle 0_m|(\epsilon - \hat{K}_\infty)^{-1}|0_m\rangle = \left[\epsilon + k_r \frac{p_0}{1 + (1 - p_0) k_r \tau_n(\epsilon)}\right]^{-1} \tag{78}$$

where

$$\tau_n(\epsilon) = \int \mathrm{d}w_m\, p_m^n(w_m)(\epsilon + w_m)^{-1} \tag{79}$$

In principle, the kinetics $P(t)$ can be obtained numerically for any function $\tau_n(\epsilon)$ by inverse Laplace transform of $\tilde{P}(\epsilon)$ (eq

78). However, here we analyze only the qualitative specific features of $P(t)$.

(a) If $\tau_n(\epsilon)$ is the analytic function of ϵ possessing a number of poles [in particular, for a finite number of gating states $\tau_n(\epsilon) = \sum_j \omega_j/(\epsilon + \epsilon_j)$], then the formula predicts the exponential long time behavior of $P(t)$:

$$P_e(t) \sim \exp(-k_e t) \tag{80}$$

with the rate equal to the lowest positive root of the equation

$$k_e - k_r \frac{p_0}{1 + (1 - p_0)k_r \tau_n(-k_e)} = 0 \tag{81}$$

In general, this root must be obtained numerically. In some limits, however, it can be found analytically.

(b) It is evident that if $1 - p_0 \ll 1$, so that $(1 - p_0)k_r\tau_n(-k_r) \ll 1$, then $k_e = p_0 k_r$.

(c) If $p_0 \ll 1$ and $\tau_n(\epsilon)$ is finite at $\epsilon = 0$, with high accuracy one can set $\tau_n(\epsilon) \approx \tau_n(0) = \tau_0$, in eq 78 for $\tilde{P}(\epsilon)$ thus arriving at the exponential reaction kinetics (eq 80) with

$$k_e = \frac{p_0 k_r}{1 + k_r \tau_0} \int \mathrm{d}w_m \, p_m^n(w_m)/w_m \tag{82}$$

(d) If $p_0 \ll 1$ and $\tau_n(\epsilon)$ is a finite but nonanalytic function of ϵ at $\epsilon = 0$, for example, $\tau_n(\epsilon \to 0) = \tau_0 + \tau_1(\epsilon/\epsilon_1)^\alpha$ with $0 < \alpha < 1$, the exponential asymptotics (eq 80) is intermediate. At very large t it is replaced by the final dependence $P(t) \approx t^{-(1+\alpha)}$. This is because in this case at small ϵ, $\tilde{P}(\epsilon)$ is represented as

$$\tilde{P}(\epsilon) = \left[\epsilon + k_e + k_e \frac{k_r \tau_1}{1 + k_r \tau_0} (\epsilon/\epsilon_1)^\alpha\right]^{-1} \tag{83}$$

It is easy to see that the inverse Laplace transform of this function gives the above-mentioned inverse power type long time tail of $P(t)$.

(e) If the distribution function $p_r^n(w_m)$ is singular at $w_m \to 0$: $p_r^n(w_m) = w_m^{-\alpha}$ with $0 < \alpha < 1$; $\tau_n(\epsilon)$ is also singular at $\epsilon \to 0$: $\tau_n(\epsilon) = \epsilon^{-\alpha}$. Such a behavior of $\tau_n(\epsilon)$ leads to the strongly nonexponential long time tail of $P(t)$: $P(t) = P_>(t) = t^{\alpha-1}$. The above-mentioned exponential kinetics is observed only at relatively short times $t < t_*$, where t_* is defined by the relation $P_e(t_*) = P_>(t_*)$.[18,19]

VI. Discussion

In this work we proposed a general method to describe the effect of gating on the kinetics of stochastically gated, diffusion-controlled reactions. The method is based on application of the theory of MFEs on liquid-phase chemical reactions.[10,11] The treatment with MFEs reduces the solution of the SLE which is actually a system of coupled differential equations of the second order.[12−14] One of important ideas of the theory of MFEs is to solve the complicated SLEs (for the spin-density matrix) just in the matrix form without any assumptions on mechanisms of transitions between spin states of reacting molecules, i.e., the mathematical form of the coupling of differential equations. It appears to be much easier to analyze these mechanisms in the final matrix expressions for observables. The fairly simple and general method of solution of the SLE developed in refs 10 and 11 is applied quite successfully in the theory of MFEs.

The basic eq 1, which describes the effect of gating on reaction kinetics in the markovian approximation for reaction rate fluctuations, is very similar to the SLE used in the theory of MFEs. Therefore the above-mentioned method of solving the SLE in the matrix form can be applied straightforwardly to the analysis of GRs. This method is described comprehensively in refs 10 and 11. In our work, we have restricted ourselves to the presentation and application of final formulas.

In section II with this method we obtained some general expressions for GR kinetics that seem to be useful for the analysis of kinetics. Analysis of kinetics in the free diffusion and exponential (cage) models, carried out in sections III and IV, has demonstrated the great capabilities of the proposed method that allows the derivation of expressions for observables in the compact matrix form. These expressions were used in section V to obtain simple analytical formulas within the two markovian models of gating, RTM and SRCM.

To clarify some important points of the analysis performed, we would like to add some general comments on our results.

(1) Expressions 36 and 40 for the transient parts of diffusion-controlled geminate and bulk GRs were obtained for the first time. These formulas clearly reveal the above-mentioned advantages of the method proposed in refs 10 and 11. This method has enabled us to derive the formulas without any assumptions based on the mechanism of gating (the form of $\hat{W}_g$). The expressions obtained generalize the corresponding expressions for the transient part of reaction kinetics known in the theory of diffusion-controlled, ungated reactions. They show that gating strongly interferes with the diffusion-controlled relaxation of the spatial distribution function of reagents giving rise to strong change of the long time tail of GRs kinetics. These general matrix expressions are reduced to very simple analytical ones in RTM and SRCM.

(2) In the presence of the attractive interaction potential well, when the long-lived intermediate state in the well is formed, the statistics of re-encounters and thus reaction kinetics substantially change.[18,19] At a relatively small initial time it becomes exponential and then it changes by conventional inverse power one. The effect of gating appears to be very sensitive to the statistics of re-encounters and, in particular, at relatively short times the universal relations (eqs 36 and 40) should be replaced by eqs 50 and 53, corresponding to the exponential model. In our work we did not analyze in detail the long time tail of transient kinetics predicted by the exponential model. The problem was reduced to evaluating the average of matrix exponential functions. Within the considered models of gating it can be done with the use of formulas describing bulk reaction kinetics, which is determined by the averages of similar types.

(3) Most recent theoretical works concentrate on analysis of gating either in the model based on the assumption the first-order reaction rate $k(t) = k[s^2(t)]$, where $s(t)$ is the Gaussian stochastic process,[6,7] or in the markovian two-state model.[5,8] The main difficulty in the treatment of first-order reactions lies in averaging the exponential functional $\langle \exp[\int^t \mathrm{d}\tau \, k(\tau)]\rangle_k$ over fluctuations of the rate constant $k(t)$. The markovian RTM and SRCM proposed in section V essentially extend the number of analytically solvable models for these first-order GRs. They permit the detailed analysis of some interesting specific features of GRs. In particular, in the most reasonable case of smooth (analytic) behavior of probability distributions $p_0(k)$ (in RTM) and $p_r^n(w)$ (in SRCM) the long time kinetics of bulk GRs is exponential with the rate obtained from general expressions 63 and 78, respectively. However, if $p_r^n(w)$ is singular at small w SRCM predicts strongly nonexponential long time tail of kinetics $P(t)$ (see discussion in the end of sections VA.2 and VB.2). New analytically solvable models such as eqs 65 and 83 are of special interest because they make it possible to describe the

changeover from the exponential bulk GR kinetics to nonexponential one at long times.

(4) In our work we have considered the simple variants of RTM and SRCM. Their combination provides the simplest models of gating. However, one can easily generalize these two models. For example, in SRCM the number of reactive channels can be increased but at the cost of complicating the problem. Some intermediate gating states can also be added in RTM by treating them as reactive channels with the use of SRCM, although assuming, for the sake of generality, that the reactivity in these channels is reversible. In this way a large variety of different simple and flexible models of gating can be formulated to describe realistic gating processes.

(5) In this work we have not discussed the effect of anisotropy of reactivity on GRs. This effect is expected to be quite important.[4] The method of analytical treatment of the interference of reactivity anisotropy and gating is actually well known in the theory of MFEs.[20] Analysis of this interference by the method developed in ref 20 will be presented in a separate publication.

VII. Conclusion

This work concerns the analysis of the kinetics of stochastically gated, diffusion-controlled GRs within the markovian approximation for fluctuations of reactivity. In this analysis we have discussed some basic properties of GR kinetics, although predictions of two particular models are thoroughly analyzed as well. The proposed method is fairly general and can be applied to many other models of gating. Some of them were mentioned in the Discussion. The proposed models are flexible enough and quite convenient for application to the analysis of experimental kinetic data.

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