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Complementary Variational Approximations for Intermittency and Reaction Dynamics in Fluctuating Environments

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We develop variational approximations to the survival probability for chemical reactions that are coupled to a Markovian stochastic environment. These approximations provide upper and lower bounds and are able to capture the correct asymptotic behavior for both a slowly fluctuating environment and a rapidly relaxing environment. Intermittency, as observed in single molecule experiments, can also be computed using the same approximations. We highlight the relationship of these approximations to previous approaches and compare variational results to exactly solvable examples.

I. Introduction

Traditionally, chemical kinetics concentrated on reactions with easily separable elementary steps, each with a high activation barrier. The individual elementary events therefore obeyed Poisson statistics producing exponential rate laws. The advent of faster experimental methods has led to a study of chemical processes lacking such barriers and having time scales comparable to the environmental fluctuations around each molecule. Examples of such processes include diffusion controlled reactions in polymers,[1] ligand binding in proteins,[2] and even traditionally slow reactions in glasses which provide an especially sluggish environment.[3] The environmental fluctuations lead to nonexponential ensemble kinetics and non-Poissonian statistics for the individual reaction rates. The deviation from Poisson statistics entails the possibility of "intermittency": periods of rapid successions of reaction events interposed between quiescent non-reactive periods.[4] Recent advances in sensitivity allowing experimental kinetics to penetrate the single molecule level[5] make these deviations from Poisson statistics directly observable. In this paper we explore some variational approaches that give both upper and lower bounds to the rates. We exploit the approximation scheme to study both the average rate and intermittency growth rates.

Chemical reactions influenced by fluctuating environments are fundamental in many diverse fields within physical chemistry and biological physics. (See refs 6 and 7 for an extensive compilation of applications.) Very often, the problem can be described in terms of a density that evolves in time according to the Smoluchowski equation coupled to a reactive sink, as Zwanzig[6] has recently emphasized, arising naturally whenever the rate coefficient is coupled to a stochastic variable whose dynamics is Markovian. A first-order chemical reaction can be represented by

$$\partial_t \Psi = -\epsilon k(\mathbf{r})\Psi \tag{1}$$

where the relaxation of the probability distribution $\Psi(\mathbf{r}, t)$ is coupled to the dynamics of the environment represented by $\mathbf{r}(t)$ through the first-order rate coefficient $\epsilon k(\mathbf{r})$. When the time evolution of $\mathbf{r}(t)$ is described by Markovian dynamics, $\Psi(\mathbf{r}, t)$ evolves according to

$$\partial_t \Psi = -\mathcal{D}\,\Psi - \epsilon k(\mathbf{r})\Psi \tag{2}$$

where $\mathcal{D}$ is the diffusion operator.[8] Wang and Wolynes[9] extended the formalism to include non-Markovian fluctuations through the path integral representation of the problem; their results were later rederived using a many-body diffusion equation.[10]

Exact solutions of eq 2 have been obtained for only a couple of specific forms of the reactive sink.[9,11,12] Additionally, some applications such as quenching of reactive groups on a polymer are inherently difficult to calculate even numerically due to complicated boundary conditions.[13] The latter problem is of importance in the experimental study of protein folding where it provides an important handle on the basic time scales of main chain motions.[14,15] To study these problems, approximate solutions are not only useful, but also necessary, for easy but accurate inversion of experimental data to model kinetic parameters.

Equation 2 couples two distinct time scales: the diffusional relaxation rate set by the diffusion coefficient D_0 and the reaction coefficient at a particular configuration of the environment, controlled by the strength of the reactive sink ϵ. Although exact solutions are often not possible, expressions for the survival probability are easily found in the limits where either time scale dominates.[8] We assume that the fluctuations of the environment are bounded by an external potential, providing a nonvanishing equilibrium probability distribution. When the reaction rate is slow compared to the rate of diffusion (the dynamically averaged limit), the system is always approximately in equilibrium giving exponential relaxation; conversely, in the limit of a very slowly relaxing environment (static limit), the survival probability is determined by the initial conditions resulting in a highly nonexponential decay. Explicitly, the survival probability in these limits is asymptotically

$$S(t) = \begin{cases} e^{-\langle \epsilon k \rangle t} & \epsilon/D_0 \rightarrow 0 \quad \text{(dynamically averaged)} \\ \langle e^{-\epsilon k t} \rangle_0 & \epsilon/D_0 \rightarrow \infty \quad \text{(static)} \end{cases} \tag{3}$$

where $\langle ... \rangle$ and $\langle ... \rangle_0$ denote averages over the equilibrium and

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initial distribution, respectively. Looking forward to our analysis, we offer two parenthetical comments about the case of equilibrium initial distributions: (1) at very short times the initial decay of $S(t)$ is given by $S(t) \approx 1 - \epsilon\langle k\rangle t$ regardless of the value of ϵ. (2) Jansen's inequality $\mathrm{e}^{-\langle x\rangle} \leq \langle \mathrm{e}^{-x}\rangle$ implies that, for a given ϵ, the dynamically averaged limit is always below the static limit; in fact, a result of our variational treatment is that the Laplace transforms of $\mathrm{e}^{-\langle \epsilon k\rangle t}$ and $\langle \mathrm{e}^{-\epsilon kt}\rangle$ are actually rigorous lower and upper bounds on the survival probability for a system initially at equilibrium.

In the intermediate regime of comparable reaction and environmental relaxation rates, achieving a universal approximation scheme has proved to be rather difficult, resulting in many different approaches. For the purposes of this paper, the first approach was the Wilemski–Fixman (WF) closure approximation applied to reaction dynamics in polymers.[16,17] Related subsequent work has focused on both the derivation and region of validity of the approximation. Higher order corrections to the WF approximation can be obtained through perturbation theory.[12,18] In another perturbative approach, the static and dynamically averaged limits can be well described separately, increasing the dynamical range that can be studied through interpolation.[19] Other, perturbative[20,21] and nonperturbative[22–25] approaches have also been employed for this problem. While the WF closure approximation is only applicable for the case of equilibrium initial conditions, many of the other approaches cited above do not require this restriction. Soon after the WF approximation was published, Doi showed that it could be derived from an variational upper bound on the decay rate of the survival probability.[26] Improvements to the WF closure can then be generated through different choices of the trial function.

In this paper we develop variational upper and lower bounds on the survival probability itself. Doi's variational approximation is related to the upper bound derived here, but the derivation is quite different. We follow the formulation of the problem given in ref 27, specialized to diffusion influenced reactions in systems with an environmental coordinate that has bounded fluctuations. Like the WF approximation, the bounds are rigorous only in the special case of an equilibrium initial distribution, though they can be of use in approximating the survival probability for nonequilibrium initial conditions as well. Much like the situation when using variational principles in quantum electronic structure, the errors in most observable for the nonequilibrium situation are of first order in the deviation from the exact result for the solution of the diffusion equation, while the equilibrium averaged functional itself has errors only to second order (like the energy in the ordinary variational problems of quantum mechanics).

We note that other related variational functionals have been introduced for the problem of diffusion through a porous material[28,29] and subsequent development of complementary variational bounds for this application can be found in refs 30–32. Although these studies are closely related to the present work, they are distinct. In those studies, the sinks, or traps, serve to define (complicated) absorbing boundary conditions within which particles *freely* diffuse. Accordingly, treatment of the boundary conditions become the central focus of these approximations, whereas in the model described above, the reaction enters as a sink function in the diffusion equation rather than being incorporated directly into the boundary conditions.

The organization of the paper is as follows. In section II, after formulating the average rate problem, we indicate how the intermittency observable in single molecule experiments can be quantified through the higher order moments of the survival probability. In this section, we also discuss the WF approximation and its relationship to perturbative approaches in order to put our approach into context. The derivation of our variational approximations to the survival probability is presented in section III and is similar to that found in ref 27. In section IV we offer a comparison between the exact solution of two solvable examples and our approximations. Explicit expressions needed to calculate the bounds for the examples, as well as the connection between the present work and Doi's variational functional are contained in Appendices. Throughout the paper both the formalism and examples focus on Markovian environments, though the method may be generalized to approximate non-Markovian processes as well.

II. Background

A. Formulation of the Problem. We begin with the Smoluchowski equation given in eq 2 that describes the time evolution of $\Psi(r, t)$, the probability of finding the system with environmental variable r at time t. (For consistency with the examples given below, r is taken to be a scalar variable, though the formalism remains the same when generalized to higher dimensions.) We assume that r is confined by an external potential $U(r)$. The diffusion operator in eq 2 is then given by $\mathsf{D} = -\partial_r D_0 \mathrm{e}^{-\beta U(r)} \partial_r \mathrm{e}^{\beta U(r)}$, where D_0 is the diffusion coefficient and $\beta = 1/k_{\mathrm{B}}T$ is the inverse temperature. In contrast to free diffusion in which the mean-square fluctuations are unbounded and the equilibrium distribution vanishes, diffusion confined by an external potential has finite mean-square fluctuations determined by the equilibrium Boltzmann distribution: $\Psi_{\mathrm{eq}}(r) = \mathrm{e}^{-\beta U(r)}$.

It is convenient to consider also the adjoint diffusion equation. Substituting $\Psi(r, t) = \Psi_{\mathrm{eq}}(r)\rho(r, t)$ in eq 2, and using the property $\mathsf{D}\Psi_{\mathrm{eq}}\rho = \Psi_{\mathrm{eq}}\mathsf{L}\,\rho$ for the adjoint operator L , gives the adjoint diffusion equation[33]

$$\partial_t \rho = -\,\mathsf{L}\,\rho - \epsilon k(r)\rho \tag{4}$$

with $\mathsf{L} = -\mathrm{e}^{\beta U(r)} \partial_r D_0 \mathrm{e}^{-\beta U(r)} \partial_r$. For use in future derivations, we note that that L is a semipositive definite, self-adjoint operator over the equilibrium distribution, i.e., $\langle A\mathsf{L}\,A\rangle \geq 0$, and $\langle A\mathsf{L}\,B\rangle$, for any functions $A(r)$ and $B(r)$.

Since $\rho(r, t)$ satisfies the adjoint (or backward) Smoluchowski equation, $\rho(r, t)$ can be interpreted as the probability that the system *initially* at r remains unreacted at time t.[33] The appropriate initial condition is then $\rho(r, 0) = 1$. The starting point for our discussion is the Laplace transform of eq 4

$$(\omega + \mathsf{L} + \epsilon k(r))\,\hat{\rho} = 1 \tag{5}$$

where we have denoted the Laplace transformed density by $\hat{\rho}(r, \omega) = \int_0^\infty \mathrm{d}t\ \mathrm{e}^{-\omega t}\ \rho(r, t)$.

The main quantity of interest is the survival probability $S(t)$, defined as the probability that the reaction has not occurred at time t, can be obtained by averaging $\rho(r, t)$ over the initial distribution, $\Psi_0(r)$: $S_0(t) = \int \mathrm{d}r\ \Psi_0(r)\rho(r, t) \equiv \langle \rho(t)\rangle_0$. The moments of the survival probability are also of interest since they define the mean nth moment passage times

$$\tau_0^{(n)} = -\int_0^\infty \mathrm{d}t\ t^n\ \dot{S}_0(t) \tag{6}$$

which are measures of the decay rate. $\tau^{(n)}$ can be conveniently written in term of the Laplace transform of the survival probability as

$$\tau_0^{(n)} = n\,(-1)^{(n-1)} \frac{\mathrm{d}^{n-1}}{\mathrm{d}\omega^{n-1}} \hat{S}_0(\omega)|_{\omega=0} \tag{7}$$

In particular, the mean first passage time (MFPT) is simply $\tau_0 = \hat{S}_0(0)$. For equilibrium initial conditions, $\Psi_0(r) = \Psi_{eq}(r)$, we denote the survival probability and MFPT by $S(t) = \langle \rho(t) \rangle$ and $\tau = \hat{S}(0)$, respectively.

B. Intermittency. For many chemical reactions, a large free energy barrier induces a time scale separation between the mean lifetime of an individual reactant molecule and the relatively fast elementary time scale of the environmental dynamics. Consequently, these reactions are in the dynamically averaged limit in which the rates are determined by near equilibrium stochastic processes. Here, the probability per unit time that an individual molecule undergoes the reaction is a constant equal to the average reaction rate. Thus, the kinetics are described by the usual first order rate law, and the statistics of the lifetimes of individual molecules obey Poissonian statistics.

However, this description breaks down when the stochastic dynamics of the environment become slow. Then, the lifetime of an individual reactant molecule is dominated by the rare configurations of the environment poised to react. As a result, the average lifetime is not determined by the most probable one, but primarily by the tails of the distribution. In this case, the statistics of the stochastic trajectories of the molecule can not be described merely by the average, but higher order moments are necessary as well, i.e., they are non-Poissonian. A measurement of the average rate from a large ensemble of molecules does not clearly indicate the extent to which the dynamics is determined by the tails of the environmental distribution. On the other hand, the origin of nonexponential relaxation in slowly fluctuating environments such as glasses is still incompletely understood. Consequently, monitoring single molecule reactions can give insights to this unresolved problem by elucidating the impact that rare configurations have on the mean reaction rate.

To describe the non-Poissonian character of single molecule time traces requires the evaluation of multitime correlation functions. These have been hard to describe in a simple way. Here we introduce the idea of an intermittency growth rate. Although the higher order corrections clearly will be multiexponential, the magnitude of the deviation can be roughly characterized by a typical growth rate. This is much like the time-honored procedure of characterizing even non-exponential decays by a mean first passage time.

Analyzing the statistics of a single molecule experiment that measures the apparent instantaneous lifetime associated with individual reaction events can distinguish between these types of reactions. Consider a hypothetical reaction in which the product, once formed, is recycled very rapidly back to the reactant state. The qualitative time traces for two single molecule experiments are illustrated in Figure 1. In contrast to the signal for a rapidly relaxing environment shown in Figure 1a, the signal for slowly fluctuating environments is intermittent: long periods of inactivity separating clustered measurements as shown in Figure 1b.

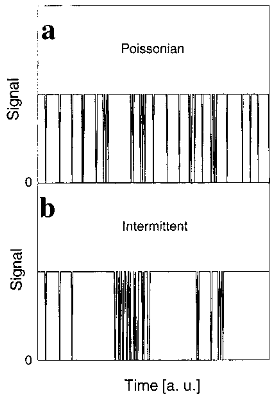

Figure 1. Schematic time traces of two single molecule experiments where a reaction event gives a vanishing signal. (a) Poissonian statistics. (b) non-Poissonian statistics.

There are several ways to characterize this intermittency quantitatively. Ideally the system should be recycled to the starting point instantaneously on the time scale of the environmental fluctuations. We can define a nearly instantaneous survival probability, $\rho(r_1, t_1; r_2, t_2)$, as the probability of no excursion being found between times t_1 and t_2 where the environmental variable is r_1 and r_2, respectively; that is, equivalently, none being found in the time $\tau = t_2 - t_1$ around $\bar{t}_{12} = (t_1 + t_2)/2$

$$\tilde{\rho}(\tau|\bar{t}_{12}) = \rho(r_1, t_1; r_2, t_2) \tag{8}$$

This probability can be correlated at different nonoverlapping times ($t_1 < t_2 < t_3 < t_4$)

$$\tilde{\rho}(\tau|\bar{t}_{12})\tilde{\rho}(\tau|\bar{t}_{34}) = \rho(r_1, t_1; r_2, t_2)\,\rho(r_3, t_3; r_4, t_4) \tag{9}$$

where $\bar{t}_{12} = (t_1 + t_2)/2$, and $\bar{t}_{34} = (t_3 + t_4)/2$ and where we take $\tau = t_2 - t_1 = t_4 - t_3$. We can approximate this as the limit $\bar{t}_{12} \rightarrow \bar{t}_{34}$ and averaging over environmental fluctuations which modulate the rate

$$S_2(\tau) = \langle \tilde{\rho}(\tau)^2 \rangle \tag{10}$$

The deviation of the ratio $R_2(\tau) = S_2(\tau)/S(\tau)^2$ from the Poissonian value $R_2(\tau) = 1$ is a measure of the intermittency. The intermittency ratio $R_2(\tau)$ can be evaluated by a path integral formalism.[34,35] Formally, the solution to eq 1 for a particular trajectory $r(t)$ can be written as

$$\Psi(r, t) = \exp\left[-\epsilon \int_0^t \mathrm{d}t\, k(r(t))\right] \tag{11}$$

The survival probability is then the average of this exponential over all possible paths (subject to specified initial and final conditions). From this path integral representation, it can be readily shown that $S_2(t)$ is simply the survival probability $S(t)$ with the replacement $\epsilon \rightarrow 2\epsilon$.[34,35] This correspondence allows us to investigate intermittency directly by analyzing the original Smoluchowski equation. We can then use any of our variational approximations to the survival probability for the problem with an enhanced sink strength 2ϵ to evaluate the growth rate of the intermittency ratio, $S_2(\tau)/S(\tau)^2$ defined in this way. While a limited characterization of the higher order statistics, the intermittency growth rate shows at a glance where big deviations from Poisson statistics are expected.

C. WF and Related Approximations. In this subsection, we will discuss the WF approximation to reaction dynamics[16,17] and indicate some connections to previous work on this problem. Not only does this put the present method into proper context, it also provides an opportunity to define the quantities of interest throughout the paper.

The derivation of the WF approximation consists of two steps. First, averaging eq 5 over $\Psi_{eq}(r)$ gives the Laplace transformed survival probability $\hat{S}(\omega)$ in terms of $\langle k\,\hat{\rho} \rangle$

$$\hat{S}(\omega) = \frac{1}{\omega}\,(1 - \epsilon\langle \mathrm{k}\ \hat{\rho}\rangle) \qquad (12)$$

where we have used $\langle \mathsf{L}\ \hat{\rho}\rangle = 0$, and the self-adjoint property of L. On the other hand, eq 5, can be written as the integral equation

$$\hat{\rho} = \frac{1}{\omega + \mathsf{L}} - \epsilon\,\frac{1}{\omega + \mathsf{L}}\ k\hat{\rho} \qquad (13)$$

Multiplying this equation by k and taking the average yields an alternative equation involving $\langle k\ \hat{\rho}\rangle$,

$$\langle k\ \hat{\rho}\rangle = \frac{1}{\omega}\,\langle k\rangle - \epsilon\langle k\,(\omega + \mathsf{L}\,)^{-1}\,k\hat{\rho}\rangle \qquad (14)$$

In the WF closure approximation, it is assumed that the system is always nearly in local equilibrium, implying that the reduced probability density has no spatial dependence, $\hat{\rho}(r, \omega) = \hat{v}(\omega)$. Requiring that this approximation gives a consistent expression for $\langle k\ \hat{\rho}\rangle$ leads to the approximation $\hat{v}(\omega) \approx \langle k\ \hat{\rho}\rangle/\langle k\rangle$. Applying the approximation to right-hand side of eq 14, together with eq 12, gives the WF approximation to the survival probability

$$\hat{S}_{\mathrm{WF}}(\omega) = \frac{1}{\omega}\left(1 - \frac{\epsilon\langle k\rangle^2}{\omega(\langle k\rangle + \epsilon\hat{D}(\omega))}\right) \qquad (15)$$

where $\hat{D}(\omega) = \langle k(\omega + \mathsf{L}\,)^{-1}\ k\rangle$.

Here, a remark about notation is necessary. If h_1 and h_2 are two arbitrary functions of the dynamical variable r, then $\langle h_1(\omega - \mathsf{L}\,)^{-1}h_2\rangle$ denotes the Laplace transform of the time correlation function between $h_1(r(t))$ and $h_2(r(0))$. Explicitly,

$$\langle h_1(\omega - \mathsf{L}\,)^{-1}h_2\rangle = \int_0^\infty \mathrm{d}t\ \mathrm{e}^{-\omega t}\,\langle h_1(t)\ h_2(0)\rangle \qquad (16)$$

where

$$\langle h_1(t)\ h_2(0)\rangle = \int\int \mathrm{d}x\mathrm{d}y\ h_1(x)G(x, t|y)\ \Psi_{\mathrm{eq}}(y)\ h_2(y) \quad (17)$$

and $G(x, t|y) = \mathrm{e}^{-\mathcal{D}t}\ \delta(x - y)$ is the Green's function in the absence of the sink term. Thus, $\hat{D}(\omega)$ in eq 15 is identified as the Laplace transform of the sink−sink correlation function, $D(t) = \langle k(t)k(0)\rangle$.

Since the WF approximation assumes that the system is always near equilibrium, it becomes exact in the dynamically averaged limit (small ϵ/D_0). However, the approximation works surprisingly well in some cases even when this equilibration assumption is violated.[29] The integral equation in eq 13 can be expanded in a perturbation series about the dynamical limit in powers of ϵ. The closure approximation is a particular summation of higher order terms, as shown in ref 12. Consequently, this resummation of the perturbation series accounts for the success of the approximation even when the assumption that the system is approximately in equilibrium is not valid.

The WF approximation becomes less accurate as the environmental relaxation slows. The alternative integral equation

$$\hat{\rho} = \frac{1}{\omega + \epsilon k(r)} - \frac{1}{\omega + \epsilon k(r)}\,\mathsf{L}\ \hat{\rho} \qquad (18)$$

is a more useful representation to study the problem near the static limit (large ϵ/D_0); this can also be expanded in a perturbation series for $\langle\hat{\rho}\rangle$, but this time the expansion is about the static density in powers of D_0. In order to increase the accuracy over a wider range of parameters, interpolation schemes have been proposed incorporating the lowest order terms obtained from eqs 13 and 18 in a hybrid Padé approximant.[19] We approach this same issue by employing a variational procedure to generate this interpolation.

III. Variational Bounds

In this section we derive the variational bounds

$$F[\varphi] \le \langle\hat{\rho}\rangle \le K[\xi] \qquad (19)$$

valid for any functions $\xi(r, \omega)$ and $\varphi(r, \omega)$. These are complementary bounds on the survival probability for equilibrium initial conditions $\hat{S}(\omega) = \langle\hat{\rho}(\omega)\rangle$. The lower bound is based on eq 5, whereas the upper bound is derived from the equivalent integral equations, eq 13 or eq 18. In order to present the operator algebra clearly, we set the initial condition $\rho(r, 0) = f(r)$ and set $f(r) = 1$ at the end of the derivation. Then, the exact solution for the probability density is formally $\hat{\rho} = (\omega + \mathsf{L}\ + \epsilon k(r))^{-1}\ f$, and the bound in eq 19 is on the quantity $\langle\hat{\rho}\ f\rangle$.

We first consider the lower bound $F[\varphi]$. We want to construct a functional such that its functional derivative is

$$\delta F[\varphi] = (\omega + \mathsf{L}\ + \epsilon k(r))\ \varphi - f \qquad (20)$$

Consequently, the stationary condition $\delta F[\varphi^*] = 0$ implies that φ^* satisfies eq 5, i.e., the exact density optimizes $F[\varphi]$. Since L is self-adjoint, the functional

$$F[\varphi] = -\ \langle\varphi\ (\omega + \mathsf{L} + \epsilon k)\ \varphi\rangle + 2\ \langle\varphi\ f\rangle \qquad (21)$$

satisfies eq 20 and has the optimal solution $\varphi^* = \hat{\rho}$ with $F[\varphi^*] = \langle\hat{\rho}\ f\rangle$. The positive-definite property of L ensures that the quadratic term of $F[\varphi]$ is negative. Therefore, the stationary solution maximizes $F[\varphi]$, proving the lower bound inequality in eq 19.

We focus now on the similar derivation for the upper bound. Multiplying eq 13 by $\epsilon k(r)$ (to make the second term symmetric) gives the starting point for this derivation

$$\epsilon k\hat{\rho} = \epsilon k\,\frac{1}{\omega + \mathsf{L}}\ f - \epsilon k\,\frac{1}{\omega + \mathsf{L}}\ \epsilon k\ \hat{\rho} \qquad (22)$$

Proceeding as before, we want a functional $M[\xi]$ whose variational derivative is

$$\delta M[\xi] = \left(\epsilon k + \epsilon k\,\frac{1}{\omega + \mathsf{L}}\ \epsilon k\right)\xi - \epsilon k\,\frac{1}{\omega + \mathsf{L}}\ f \quad (23)$$

so that $\delta M[\xi^*] = 0$ implies ξ^* is the solution to eq 22, i.e., $M[\xi]$ is optimized by $\xi^* = \hat{\rho}$. The self-adjoint property of L ensures that the functional

$$M[\xi] = \epsilon\langle k\ \xi^2\rangle + \epsilon^2\ \langle\xi\ k\ (\omega + \mathsf{L}\,)^{-1}\ k\ \xi\rangle - 2\epsilon\langle\xi\ k\ (\omega + \mathsf{L}\,)^{-1}\ f\rangle \quad (24)$$

satisfies eq 23. Here, the stationary value is a minimum of $M[\xi]$, since this time the quadratic term is positive. The minimum is at $\xi^* = \hat{\rho}$ with $M[\xi^*] = -\ \langle\xi^*\ \epsilon k(\omega + \mathsf{L}\,)^{-1}\ f\rangle$. Using $(\omega + \mathsf{L} + \epsilon k)\ \hat{\rho} = f$ to eliminate $\xi^*\ \epsilon k$ in this expression for $M[\xi^*]$ gives the upper bound

$$\langle\hat{\rho}\ f\rangle - \langle f\,(\omega + \mathsf{L}\,)^{-1}\ f\rangle \le M[\xi] \qquad (25)$$

This proves the upper bound inequality in eq 19, with

$$K_{\mathrm{dyn}}[\xi] = M[\xi] + \langle f\,(\omega + \mathsf{L}\,)^{-1}\ f\rangle \qquad (26)$$

The subscript stands for "dynamical" referring to diffusion propagator of the integeral equation (eq 13).

From our discussion in the previous section, it is natural to consider the other integral equation (eq 18) as the starting point of the derivation. This gives an alternative upper bound. Since the derivation is analogous to the derivation of $K_{\mathrm{dyn}}[\xi]$, we just quote the result: $\langle\hat{\rho}\rangle \leq K_{\mathrm{st}}[\xi]$, where $K_{\mathrm{st}}[\xi]$ can be obtained by making the replacement $\mathsf{L} \leftrightarrow \epsilon k$ in the expression for $K_{\mathrm{dyn}}[\xi]$ (see eq 30 below). Here, the subscript stands for "static", referring to static propagator $(\omega + \epsilon k)^{-1}$ of the integeral equation (eq 18).

Setting $f(r) = 1$, we have the final results for the complementary bounds

$$F[\varphi] \leq \hat{S}(\omega) \leq K[\xi] \tag{27}$$

where

$$F[\varphi] = -\langle\varphi\,(\omega + \mathsf{L} + \epsilon k)\,\varphi\rangle + 2\langle\varphi\rangle \tag{28}$$

and $K[\xi]$ is either of the following expressions

$$K_{\mathrm{dyn}}[\xi] = \epsilon\langle k\,\xi^2\rangle + \epsilon^2\,\langle\xi\,k(\omega + \mathsf{L}\,)^{-1}\,k\,\xi\rangle + \frac{1}{\omega} - 2\epsilon\,\frac{\langle\xi\,k\rangle}{\omega} \tag{29}$$

$$K_{\mathrm{st}}[\xi] = \langle\xi\,\mathsf{L}\,\xi\rangle + \langle\xi\,\mathsf{L}\,(\omega + \epsilon k)^{-1}\,\mathsf{L}\,\xi\rangle + \langle(\omega + \epsilon k)^{-1}\rangle - 2\langle\xi\,\mathsf{L}\,(\omega + \epsilon k)^{-1}\rangle \tag{30}$$

The expression for $K_{\mathrm{dyn}}[\xi]$ has been simplified using $\langle\mathsf{L}\,A\rangle = 0$, for arbitrary $A(r)$.

As stated above, this bound applies only to the case of an equilibrium initial condition. It may appear that this restriction can be relaxed by using a nonequilibrium weight to define the averages in the derivation of $F[\varphi]$ and $K[\xi]$. However, the bounded character of the result depends on the self-adjoint and positive definite properties of L which fail to hold for arbitrary initial distributions. Nevertheless, the variational equations for an equilibrium initial distribution can be used to approximate $\hat{\rho}(r, \omega)$ by the trial function that optimizes $\langle\hat{\rho}(\omega)\rangle$, e.g., $\hat{\rho}(r, \omega) \approx \xi^*(r, \omega)$. Naively, one expects that the approximation should be valid for regions of low potential, since the equilibrium distribution used to determine the optimized wave function suppresses errors for large r.

Before considering specific examples of this approach, it is instructive to look at these bounds for the most elementary trial function, a constant (with respect to r).

For $\varphi = c(\omega)$, the lower bound becomes $F[c] = -c^2(\omega + \epsilon\langle k\rangle) + 2c$. The maximum of $F[c]$ is at $c^* = (\omega + \epsilon\langle k\rangle)^{-1}$, giving the optimum value $F[c^*] = c^*$. Thus, we see that the lower bound is $\langle\hat{\rho}_{\mathrm{dyn}}(\omega)\rangle = (\omega + \epsilon\langle k\rangle)^{-1}$, the Laplace transform of the dynamically averaged limit given in eq 3.

We now consider the upper bound given by $K_{\mathrm{st}}[\xi]$, when $\xi = c(\omega)$. Since $K_{\mathrm{st}}[c] = \langle(\omega + \epsilon k)^{-1}\rangle$ is independent of c, the upper bound is simply $\langle\hat{\rho}_{\mathrm{st}}(\omega)\rangle = \langle(\omega + \epsilon k)^{-1}\rangle$, the Laplace transform of the static limit given in eq 3. Combining these limits, we have the result

$$\langle\hat{\rho}_{\mathrm{dyn}}\,(\omega)\rangle \leq \hat{S}(\omega) \leq \langle\hat{\rho}_{\mathrm{st}}(\omega)\rangle \tag{31}$$

giving rigorous bounds on the survival probability consistent with Jansen's inequality applied to eq 3, as indicated in the Introduction. Notice that this result depends on equilibrium initial conditions; obviously, for a given sink function, it is possible to choose initial conditions that result in a very rapidly decaying survival probability, even in the static limit.

Finally, we consider the upper bound given by $K_{\mathrm{dyn}}[\xi]$, when $\xi = c(\omega)$. $K_{\mathrm{dyn}}[c]$ has a minimum at $(c^*)^{-1} = \omega\,(\langle k\rangle + \epsilon\langle k\,(\omega + \mathsf{L}\,)^{-1}\,k\rangle)/\langle k\rangle$. Evaluating the upper bound at c^* recovers the WF approximation to the survival probability (eq 15), $K_{\mathrm{dyn}}[c^*] = \hat{S}_{\mathrm{WF}}(\omega)$. Combining this with the lower bound give the limits

$$\langle\hat{\rho}_{\mathrm{dyn}}(\omega)\rangle \leq \hat{S}(\omega) \leq \hat{S}_{\mathrm{WF}}(\omega) \tag{32}$$

This result is reminiscent of Doi's variational bound on the decay rate. Indeed, it is shown in Appendix A that Doi's formula is related to the upper bound obtained by setting $\omega = 0$ in $K_{\mathrm{dyn}}[\xi]$, i.e., the bound of the MFPT, $\tau = \hat{S}(0)$.

For general trial functions, we expect that whether $K_{\mathrm{st}}[\xi]$ or $K_{\mathrm{dyn}}[\xi]$ gives a more stringent upper bound depends on the relative rates of the environmental relaxation and sink parameter strength. For example, near the static limit, $K_{\mathrm{st}}[\xi]$ will presumably provide a smaller upper bound than $K_{\mathrm{dyn}}[\xi]$ *for the same trial function*. However, it is important to note that either $K_{\mathrm{st}}[\xi]$ or $K_{\mathrm{dyn}}[\xi]$ is capable of determining the survival probability to arbitrary accuracy, limited only by the flexibility of the trial function. For the purposes of demonstrating the approach, it is enough to consider only one of these bounds. For clarity of presentation, we will focus on the bound given by $K_{\mathrm{dyn}}[\xi]$ in the remainder of this paper.

IV. Examples

In this section we apply the complementary variational bounds to two problems in one dimension. One advantage of a variational formulation is that it may facilitate analytic approximations to the problem in higher dimensions provided the trial function is simple enough. We have used the present variational method for a highly multidimensional problem involving fluorescence quenching in a chain polymer which is partially ordered. This latter problem models fluorescence resonance energy transfer in partially denatured proteins. A report of that work will appear elsewhere. In the examples presented below we evaluate the bounds numerically for chosen trial functions. Admittedly, in one dimension it is easier to integrate eq 2 directly to obtain a numerical solution than to evaluate the bounds presented here. However, the purpose of these examples is to illustrate this variational approach and to provide a foundation for analyzing more difficult problems.

We assume a harmonic confining potential centered at the origin, $\beta U(r) = r^2/2\theta^2$. In this potential, the average position vanishes, but the mean-square displacement is finite, $\langle r^2\rangle = \theta^2$. The Green's function for the diffusion operator, used to calculate the correlation functions in our approximations, is given by

$$G(x, t|y) = \frac{1}{\sqrt{2\pi\theta^2\,(1 - \phi^2(t))}}\exp\left[\frac{-\,(x - \phi(t)y)^2}{2\theta^2\,(1 - \phi^2(t))}\right] \tag{33}$$

where $\phi(t) = \langle r(t)\ r(0)\rangle/\theta^2$ is the pair correlation function describing the dynamics of the environmental fluctuations. The form of the Green's function is determined by the harmonic potential, not the nature of the fluctuational dynamics. For Markovian dynamics, the fluctuations decay exponentially, $\phi(t) = \exp(-t/\tau_r)$, where $\tau_r = \theta^2/D_0$ sets the time scale of the diffusion within the harmonic well. However, since eq 33 is the Green's function for non-Markovian fluctuations,[10] these dynamics can be considered within the variational formalism as well, if in fact these fluctuations are a projection of a higher dimensional Markov process in r space itself.

In these examples, we assume Markovian dynamics for simplicity, as well as equilibrium initial conditions. We consider two forms of the sink function: quadratic, $k(r) = r^2/\theta^2$, and exponential, $k(r) = e^{-\alpha r}$. Both forms of reaction sink (with a harmonic confining potential) have applications that can found in in the literature. The diffusion−reaction problem with a quadratic sink has been used to model diffusion through a fluctuating bottleneck of radius r and can be solved explicitly.[11,12] The exponential sink has been used to model the dynamics of ligand binding in myoglobin; here, the environmental variable r describes the binding free energy barrier, where the fluctuations arise from transitions between different conformational substates of the protein.[8] This problem can be solved numerically by integrating the differential equation directly.[19] Even though this solution is numerical, we will still refer to it as the exact survival probability to easily distinguish it from our variational bounds.

To proceed, the trial function must be specified. Motivated by the limiting expressions for the survival probability, we choose a trial function that is a linear combination of $\hat{\rho}_{st}(\omega, r) = 1/(\omega + \epsilon k(r))$ and its inverse: $\xi = c_1(1 + \epsilon k(r)) + c_2\rho_{st}(\omega, r)$. Allowing the coefficients of the first two terms to vary independently gives the trial function

$$\xi_1 = c_1 + c_2 k(r) + c_3\rho_{st}(\omega, r) \tag{34}$$

where the coefficients $\{c\}$ are variational parameters. Choosing coefficients as variational parameters, rather than other functional forms has the advantage that the optimization of $F[\varphi]$ and $K[\xi]$ can be done explicitly, leading directly to interpolation formulae. For ξ_1 the expressions for the bounds are given in Appendix B with $\mathbf{g} = (1, k(r), \hat{\rho}_{st}(\omega, r))$.

TABLE 1: Symbols for Bounds Considered in Examples

lower bound	upper bound
$F[\varphi]$	$K_{dyn}[\xi]$
$\langle\hat{\rho}_{dyn}\rangle = (\omega + \epsilon\langle k\rangle)^{-1}$	$\langle\hat{\rho}_{st}\rangle = \langle(\omega + \epsilon k)^{-1}\rangle$
	$\hat{S}_{WF}(\omega)$

More flexible trial functions can lead to still more accurate approximations. As an example, we choose the trial function

$$\xi_2 = c_1\hat{\rho}_{st}(\omega_p, r) = c_1/(\omega_p + \epsilon k(r)) \tag{35}$$

where the coefficient c_1 and ω_p are now both variational parameters. ξ_2 interpolates between $\xi_2 = \hat{\rho}_{st}(\omega, r)$ at $\omega_p = \omega$ and ξ_2 approximately constant for sufficiently large ω_p. To find the optimal bounds, we first express the stationary value c_1 as a function of ω_p (from the results of Appendix B with $\mathbf{g} = (\hat{\rho}_{st}(\omega_p, r))$) and then optimize this expression with respect to ω_p.

We note that, technically, the lower bound is somewhat less involved to calculate than the upper bound, since $F[\varphi]$ only requires calculation of various equilibrium averages, whereas $K[\xi]$ needs the Laplace transform of time correlations as well.

Below, we compare the exact (or numerical) survival probability to the bounds $F[\{c\}]$ and $K_{dyn}[\{c\}]$ given eq 27. We also consider the bounds in eqs 32 and 31; they serve as a reference, placing our results into context. (Recall that the latter bounds were obtained by setting $c_2 = c_3 = 0$ in the trial function ξ_1). For reference, the quantities of interest are collected in Table 1.

A. Harmonic Sink. For a harmonic sink, many of the quantities needed to calculate the bounds can be obtained analytically. However, these exact formulae are not very

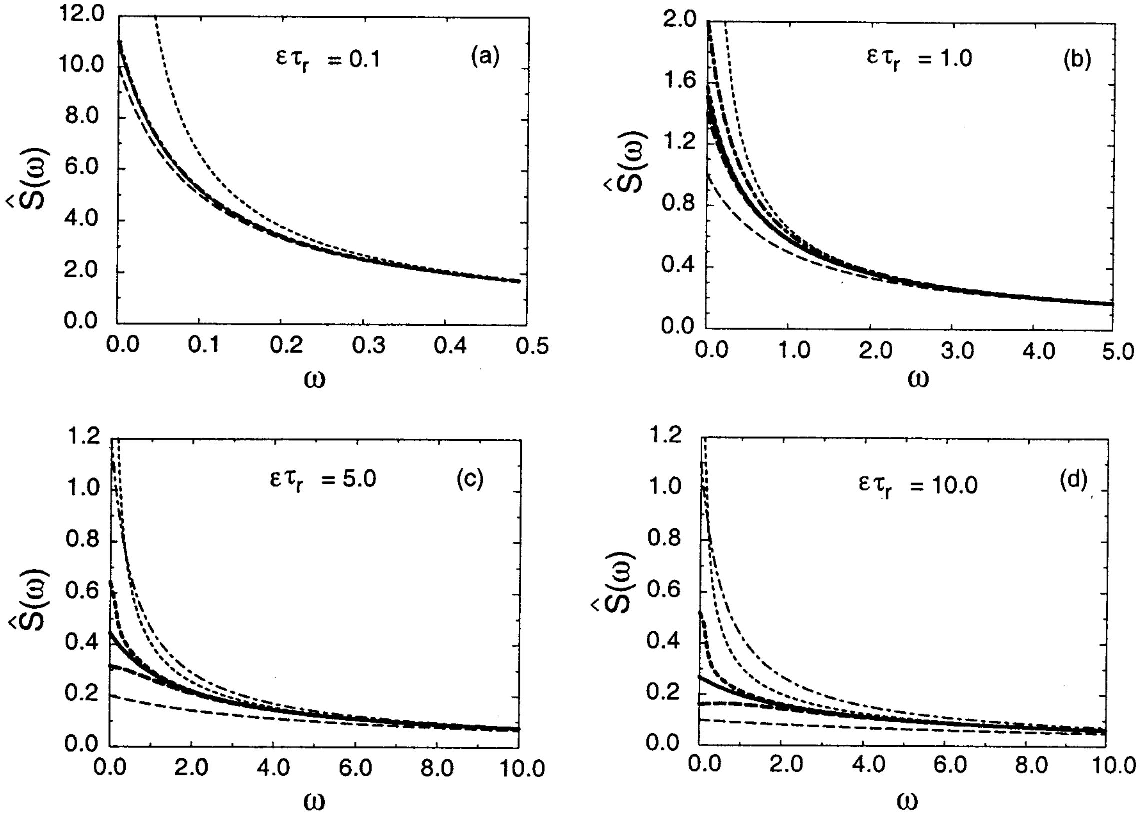

Figure 2. Survival probability as a function of frequency ω for selected values of the strength parameter ϵ (a−d) for the harmonic sink. Heavy lines correspond to exact (solid), $F[\{c\}]$ (long dashed), $K_{dyn}[\{c\}]$ (dashed). Light lines correspond to $\langle\hat{\rho}_{st}\rangle$ (dashed), $\hat{S}_{WF}$ (dotted-dashed), $\langle\hat{\rho}_{dyn}\rangle$ (long dashed). ω is in units of $1/\tau_r = D_0/\theta^2$. Not all lines are distinct in every plot, since they may overlap. Only the bound from ξ_1 are shown, since the bounds from ξ_2 are not easily distinguishable from the exact solution at the scale of the plot.

enlightening for our purposes. We note here that, for this problem, the equilibrium average of static density $\langle\hat{\rho}_{\mathrm{st}}(\omega)\rangle$ diverges at $\omega = 0$. This is relevant to our discussion, since our trial function contains this term, affecting the variational bounds at small ω. This is a peculiarity of this specific form of potential and reaction sink.

In Figure 2 we show the survival probability as function of frequency for increasing values of the reaction strength ϵ. As noted in the Introduction, for short enough times $\langle\rho_{\mathrm{st}}(t)\rangle$ and $\langle\rho_{\mathrm{dyn}}(t)\rangle$ agree for any value of ϵ; for correspondingly large ω, eq 31 implies that the variational bounds solve the survival probability exactly, as can be seen in the each of the plots in Figure 2.

For $\epsilon\tau_r = 0.1$, the system is near the dynamically averaged limit. Figure 2a shows that all approximations except $\langle\hat{\rho}_{\mathrm{st}}\rangle$ are in good agreement with the exact answer. As ϵ increases, the approximations become less accurate, particularly for small ω. The variational bounds F and K_{dyn} are much closer to the exact survival probability than the other bounds as ϵ increases. For $\epsilon\tau_r = 10.0$, Figure 2d, the environmental relaxation is slow enough that the WF approximation is inadequate. At this value of ϵ it is clear that the full variational bounds are accurate down to $\omega \approx 2.0$; for smaller frequencies, the lower bound $F[\xi_1]$ decreases slowly and the upper bound $K_{\mathrm{dyn}}[\xi_1]$ increases rapidly as $\omega \rightarrow 0$. This behavior is due to the diverging static density, as mentioned above. The variational bounds from the trial function ξ_2 does not show this behavior at small ω, and approximates the survival probability well throughout the parameter range, with a maximum deviation from the exact survival probability of only 5% for the upper bound at $\omega = 0$ for $\epsilon = 10$.

B. Exponential Sink. In this example, we consider the sink function $k(r) = e^{-\alpha r}$. While our methods are still applicable to the full survival probability, for brevity we will focus on the MFPT, $\tau = \hat{S}(0)$. Figure 3a shows the dependence of τ on reaction strength ϵ for $\alpha = 1/\theta$. The agreement between τ from the dynamically averaged and static limit (τ_{dyn} and τ_{st}) with the exact MFPT clearly indicates that ϵ covers the full range from the dynamically averaged to static limit. Consequently, the bounds given by both trial function ξ_1 and ξ_2 on the MFPT are close to the numerical result for both small and large values of ϵ as well. These bounds are in reasonable agreement with the numerical solution in the entire range, with a fractional error only as large as 30% for trial function ξ_1. The bounds from the trial function ξ_2 have excellent agreement with integrated result, giving a fractional error of less than 1%.

For larger α, the probability distribution for $r < 0$ is depleted very rapidly, potentially shifting the distribution further from equilibrium; of course, this still depends on the strength ϵ. Figure 3b shows the MFPT as a function of ϵ for $\alpha = 3/\theta$. While qualitatively similar to Figure 3a (with $\alpha = 1/\theta$), the bounds from trial function ξ_1 are hardly more restrictive than the bounds determined from τ_{st}, τ_{WF}, and τ_{dyn}. Trial function ξ_2 provides a much stricter bound, with a with fractional error of 10%.

We now consider the question of intermittency in this example. A simple approximation for intermittency ratio $R_2(t) = S_2(t)/S(t)^2$ defined in section IIb can be obtained using exponential fits to the individual survival probability moments expected from the mean first passage times: $S(t) \approx e^{-t/\tau}$. Then, the intermittency growth rate $\kappa_{\mathrm{I}} = -t^{-1} \log R_2(t)$ can be written as a function of the reaction strength as

$$\kappa_{\mathrm{I}} \approx 2\tau_{\epsilon}^{-1} - \tau_{2\epsilon}^{-1} \qquad (36)$$

where τ_ϵ is the MFPT for the reaction strength ϵ. A deviation in the growth rate from zero indicates that the statistics are non-Poissonian. Figure 4 shows the intermittency growth rate as a function of ϵ for the exact solution and the upper and lower bound, as well as the exact inverse MFPT. The intermittency growth rate has the expected behavior of vanishing in the dynamically averaged limit (small ϵ) and increasing as the environment slows (ϵ increases). The intermittency growth rate is smaller over most of the range than the rate itself, so small errors in τ are amplified in κ_{I}. The estimates from the upper and lower bounds with trial function ξ_1 agree qualitatively with the numerical result, but only within a factor of 2 of κ_{I}. The

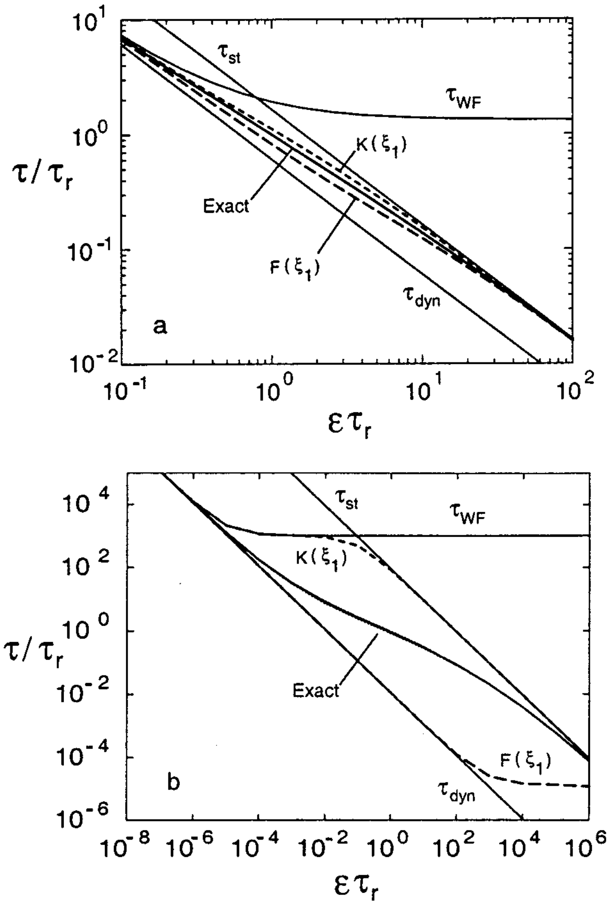

Figure 3. MFPT (τ/τ_r) as a function of the strength of the sink $\epsilon\tau_r$, where $\tau_r = \theta^2/D_0$, for the exponential sink with (a) $\alpha = 1/\theta$ and (b) $\alpha = 3/\theta$. Plots for the exact, upper, and lower bounds are labeled on graph. As in Figure 2, only the bounds from ξ_1 are shown.

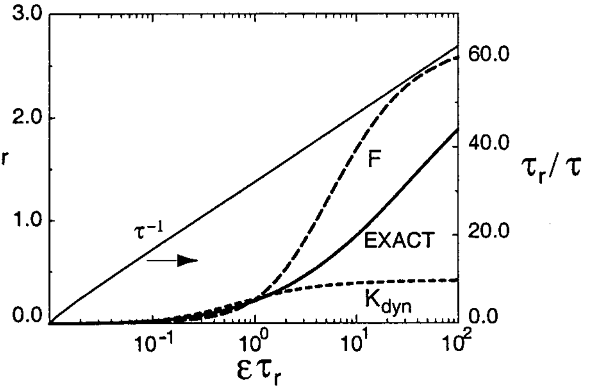

Figure 4. Intermittency growth rate $\kappa_{\mathrm{I}}\tau_r$ as a function of the strength of the sink $\epsilon\tau_r$, where $\tau_r = \theta^2/D_0$, for exponential sink ($\alpha = 1/\theta$). Results for exact, lower bound F, and upper bound K_{dyn} are labeled on graph. Also shown, is the inverse MFPT τ_r/τ (scale on the right). As in Figure 2, only the bounds from ξ_1 are shown.

trial function ξ_2 provides however a highly accurate estimate for the intermittency growth rate (within 3%). We note that the intermittency growth rate as analyzed here is not bounded by either approximation since we have taken the difference between the each bound at two values of ϵ. It is possible to develop more refined variational bounds involving the moments of the survival probability explicitly which we hope to pursue in the future.

V. Conclusion

Fluctuating environments greatly influence the kinetics of chemical reactions, when their relaxation is slow. Motivated by such problems, we have developed approximations based on a varitional principle that provides bounds for survival probability. The rigorous bounds are quite general and can be usefully applied to many dimensional problems which have more elusive solutions. For example, the variational approximations developed here have been generalized to treat reactions with more complicated fluctuational dynamics, such as fluorescence quenching between monomers in a polymer chain, where the polymer is usually modeled as a chain of monomers connected sequentially by harmonic potentials, resulting in pair correlations that contain a broad distribution of relaxation rates. This situation is described by a corresponding multi-dimensional diffusion problem that is difficult to solve numerically, but can treated with our variational approximations. These approximations also allow us to quantify intermittency which can be observed using single molecule techniques. An application to fluorescence resonance energy transfer in single-molecule folding experiments is described elsewhere.

Appendix A: Relation to Doi's Variational Bound

In ref 26, Doi presented a variational lower bound on the decay rate κ. Both the form of this bound as well as its derivation is apparently very different than the one given in the present paper. The expression for this bound is greatly simplified when κ is small. We show here the simplified bound in ref 26 is in fact the same bound obtained for the MFPT given by $K_{\mathrm{dyn}}[\xi]$.

In the notation of the present paper, eq 47 of ref 26 gives the bound

$$\kappa \geq I_0[\xi] = \frac{\epsilon\langle k\xi\rangle^2}{\langle k\xi^2\rangle + \epsilon\sum_{n\neq 0}\lambda_n^{-1}\langle k\varphi_n\xi\rangle^2} \qquad \text{(A1)}$$

Here, $\{\lambda_n\}$ and $\{\varphi_n\}$ are the respective eigenvalues and eigenfunctions of the adjoint operator: $\mathcal{L}\,\varphi_n = \lambda_n\varphi_n$. The sum in eq A1 excludes the lowest eigenvalue λ_0, which vanishes since the system eventually comes to equilibrium. In operator notation,

$$\sum_{n\neq 0}\lambda_n^{-1}\,\langle k\varphi_n\xi\rangle^2 = \hat{H}_{k\xi}(\omega = 0) \qquad \text{(A2)}$$

where

$$\hat{H}_{k\xi}(\omega) = \langle \xi\, k\,(\omega + \mathcal{L}\,)^{-1}\,k\,\xi\rangle - \langle k\,\xi\rangle^2/\omega \qquad \text{(A3)}$$

$\hat{H}_{k\xi}(\omega)$ is the Laplace transform of $\langle\delta[k(t)\xi(t)]\ \delta[k(0)\xi(0)]\rangle$, where $\delta[k\xi] \equiv k\xi - \langle k\xi\rangle$. The equilibrium correlation $\langle k\ \xi\rangle$ has been subtracted, since λ_0 is excluded in the summation. Thus, eq A1 can be written as

$$\kappa \geq \frac{\epsilon\langle k\,\xi\rangle^2}{\langle k\,\xi^2\rangle + \epsilon\hat{H}_{k\xi}(0)} \qquad \text{(A4)}$$

Now consider the bound given by $\hat{S}(\omega) \leq K_{\mathrm{dyn}}[\xi]$. Minimizing $K_{\mathrm{dyn}}[\alpha\xi]$ with respect to α gives the equivalent bound

$$\hat{S}(\omega) \leq \frac{1}{\omega} - \frac{\epsilon^2\langle k\,\xi\rangle^2}{\omega^2(\epsilon\langle k\,\xi^2\rangle + \epsilon^2\langle \xi\,k\,(\omega + \mathcal{L}\,)^{-1}\,k\xi\rangle)} \qquad \text{(A5)}$$

Written in terms of $\hat{H}_{k\xi}(\omega)$ this becomes

$$\hat{S}(\omega) \leq \frac{\langle k\,\xi^2\rangle + \epsilon\hat{H}_{k\xi}(\omega)}{\omega(\langle k\,\xi^2\rangle + \epsilon\hat{H}_{k\xi}(\omega)) + \epsilon\langle k\,\xi\rangle^2} \qquad \text{(A6)}$$

(For an alternative derivation of eq A6, set $\mathbf{g} = (\xi)$ in eq B9). Since the long time limit of $\langle\delta[k(t)\xi(t)]\ \delta[k(0)\xi(0)]\rangle$ vanishes, $\hat{H}_{k\xi}(0)$ is finite. Consequently, evaluating eq A6 at $\omega = 0$ gives the bound on the MFPT $\tau = \hat{S}(0)$:

$$\tau \leq \frac{\langle k\,\xi^2\rangle + \epsilon\hat{H}_{k\xi}(0)}{\epsilon\langle k\,\xi\rangle^2} \qquad \text{(A7)}$$

Thus, eq A4 and eq A7 are equivalent provided that κ^{-1} is identified as the MFPT τ.

Appendix B: Explicit Expressions

We show the explicit expressions for the optimum $F[\{c^*\}]$ and $K_{\mathrm{dyn}}[\{c^*\}]$ using the trial function of the form $\xi = \sum c_i g_i(r, \omega)$. In the derivations below, we make use of the definition of two vectors: the vector of variational parameters $\mathbf{c} = \{c_i\}$ and the vector of basis functions $\mathbf{g} = \{g_i\}$. In this notation the trial function can be written as $\xi = \mathbf{J}^\dagger\cdot\mathbf{c}$, where "†" denotes the matrix transpose.

1. Lower Bound $F[\{c_i^*\}]$. To find the maximum of $F[\{c\}]$ with respect to c_i, we first write eq 21 in matrix form

$$F[\mathbf{c}] = -\mathbf{c}^{\,\dagger}\cdot\mathbf{A}\cdot\mathbf{c} + 2\langle\mathbf{g}^\dagger\rangle\cdot\mathbf{c} \qquad \text{(B1)}$$

where the matrix $\mathbf{A}$ has elements

$$A_{ik} = \langle g_i\,(\omega + \mathcal{L}\ + \epsilon k)\,g_k\rangle \qquad \text{(B2)}$$

The maximum of F is then straight-forward: $(\mathbf{c}^*)^\dagger = \langle\mathbf{g}^\dagger\rangle\cdot\mathbf{A}^{-1}$ and

$$F[\mathbf{c}^*] = \langle\mathbf{g}^\dagger\rangle\cdot\mathbf{A}^{-1}\cdot\langle\mathbf{g}\rangle \qquad \text{(B3)}$$

2. Upper Bound $K_{\mathrm{dyn}}[\{c^*\}]$. The expressions for the stationary values of $K_{\mathrm{dyn}}[\mathbf{c}]$ and $F[\mathbf{c}]$ are similar. Here, the minimum of $K_{\mathrm{dyn}}[\mathbf{c}]$ is at $(\mathbf{c}^*)^\dagger = \langle\mathbf{g}^\dagger k\rangle/\omega\cdot\tilde{\mathbf{A}}^{-1}$, and

$$K_{\mathrm{dyn}}[\mathbf{c}^*] = \frac{1}{\omega} - \frac{1}{\omega^2}\langle\mathbf{g}^\dagger\,k\rangle\cdot\tilde{\mathbf{A}}^{-1}\cdot\langle k\,\mathbf{g}\rangle \qquad \text{(B4)}$$

where the components of $\tilde{\mathbf{A}}$ are

$$\tilde{A}_{ik} = \epsilon\langle g_i\,k\,g_k\rangle + \epsilon^2\langle g_i\,k\,(\omega + \mathcal{L}\,)^{-1}\,k\,g_k\rangle \qquad \text{(B5)}$$

As it is written, this formula cannot be naively evaluated at $\omega = 0$. To write this in a more convenient form, we explicitly subtract the equilibrium component of the correlation function in the second term:

$$\epsilon^2\langle g_i\,k\,(\omega + \mathcal{L}\,)^{-1}\,k\,g_k\rangle = \epsilon^2\langle\delta[g_ik]\,(\omega + \mathcal{L}\,)^{-1}\,\delta[kg_k]\rangle + \frac{\epsilon^2}{\omega}\langle g_i\,k\rangle\,\langle k\,g_k\rangle \qquad \text{(B6)}$$

where we have used the notation $\delta[g_ik] = g_ik - \langle g_i\,k\rangle$. This allows us to write $\tilde{\mathbf{A}}$ as the sum of two matrixes, $\tilde{\mathbf{A}} = \tilde{\mathbf{A}}_1 + \tilde{\mathbf{A}}_2$ with

$$\tilde{A}^1_{ik} = \epsilon\langle g_i\, k\, g_k\rangle + \epsilon^2\,\langle \delta[g_i k]\,(\omega + L)^{-1}\,\delta[k g_k]\rangle \qquad \text{(B7)}$$

and $\tilde{\mathbf{A}}_2$ is the direct product of $\epsilon\langle k\,\mathbf{g}\rangle/\sqrt{\omega}$ with itself (second term of eq B6). Breaking up $\tilde{\mathbf{A}}$ in this way allows us to use the Sherman−Morrison formula[36] to express $\tilde{\mathbf{A}}^{-1}$ in terms of $\tilde{\mathbf{A}}_1^{-1}$:

$$\tilde{\mathbf{A}}^{-1} = \tilde{\mathbf{A}}_1^{-1} + \epsilon^2\,\frac{(\tilde{\mathbf{A}}_1^{-1}\cdot\langle k\,\mathbf{g}\rangle)\otimes(\langle \mathbf{g}^\dagger\, k\rangle\cdot\tilde{\mathbf{A}}_1^{-1})}{\omega + \epsilon^2\langle \mathbf{g}^\dagger\, k\rangle\cdot\tilde{\mathbf{A}}_1^{-1}\cdot\langle k\,\mathbf{g}\rangle} \qquad \text{(B8)}$$

Substituting this into eq B4 leads to our final result,

$$K_{\text{dyn}}[\mathbf{c}^*] = \frac{1}{\omega + \epsilon^2\langle \mathbf{g}^\dagger\, k\rangle\cdot\tilde{\mathbf{A}}_1^{-1}\cdot\langle k\,\mathbf{g}\rangle} \qquad \text{(B9)}$$

Since the equilibrium correlations have been subtracted in the definition of $\tilde{\mathbf{A}}_1$ (eq B7), it is clear that eq B9 is finite at $\omega = 0$.

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References and Notes

(1) Sunagawa, S.; Doi, M. *Polymer J*. **1975**, *7*, 604.

(2) Frauenfelder, H.; Parak, H.; Young, R. D. *Annu. Rev. Biophys. Biophys. Chem*. **1988**, *17*, 451.

(3) Stein, D. L.; Doering, C. R.; Palmer, R. G.; van Hemmen, J. L.; McLaughlin, R. M. *J. Phys. A* **1990**, *23*, L203.

(4) Zeldovich, Y. B.; Ruzmaikin, A. A.; Sokoloff, D. D. *The Almighty Chance*; World Scientfic: Singapore, 1990; Chapter 8.

(5) Edman, L.; Földes-Papp, Z.; Wennmalm, S.; Riggler, R. *Chem. Phys*. **1999**, *247*, 11.

(6) Zwanzig, R. *Acc. Chem. Res.* **1990**, *23*, 148.

(7) Pagitsas, M. *J. Chem. Phys.* **1992**, *96*, 8497.

(8) Agmon, N.; Hopfield, J. J. *J. Chem. Phys.* **1983**, *78*, 6947.

(9) Wang, J.; Wolynes, P. G. *Chem. Phys. Lett*. **1993**, *212*, 427.

(10) Bicout, D. J.; Szabo, A. *J. Chem. Phys*. **1998**, *108*, 5491.

(11) Zwanzig, R. *J. Chem. Phys*. **1992**, *97*, 3587.

(12) Weiss, G. H. *J. Chem. Phys*. **1984**, *80*, 2880.

(13) Pastor, R. W.; Zwanzig, R.; Szabo, A. *J. Chem. Phys*. **1996**, *105*, 3878.

(14) Hagen, S. J.; Hofrichter, J.; Szabo, A.; Eaton, W. A. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 11615.

(15) Hass, E. *IEEE J. Quantum Electon*. **1996**, *2*, 1088.

(16) Wilemski, G.; Fixman, M. *J. Chem. Phys*. **1973**, *60*, 866.

(17) Wilemski, G.; Fixman, M. *J. Chem. Phys*. **1973**, *60*, 878.

(18) Battezzati, M.; Perico, A. *J. Chem. Phys*. **1981**, *74*, 4527.

(19) Rabinovich, S.; Agmon, N. *Chem. Phys*. **1990**, *148*, 11.

(20) Agmon, N. *J. Chem. Phys*. **1989**, *90*, 3765.

(21) Gitterman, M.; Weiss, G. H. *Chem. Phys.* **1994**, *180*, 319.

(22) Basilevsky, M. V.; Davidovitch, G. V. *J. Chem. Phys*. **1995**, *102*, 1607.

(23) Pechukas, P.; Ankerhold, J. *J. Chem. Phys*. **1997**, *107*, 2444.

(24) Berezhkovskii, A. M.; D'yakov, Yu. A.; Zitserman, V. Yu. *J. Chem. Phys*. **1998**, *109*, 4182.

(25) Seki, K.; Barzykin, A. V.; Tachiya, M. *J. Chem. Phys*. **1999**, *110*, 7639.

(26) Doi, M. *Chem. Phys*. **1975**, *11*, 107.

(27) Arthurs, A. M. *Complementary Variational Principles*, 2nd ed; Oxford University Press: Oxford, 1980; Chapter 2.

(28) Stieder, W.; Aris, R. *Variational Methods Applied to Problems of Diffusion and Reaction*; Springer Tracts in Natural Philosophy 24; Springer-Verlag: Berlin, 1973.

(29) Doi, M. *J. Phys. Soc. Jpn.* **1976**, *40*, 567.

(30) Rubinstein, J.; Torquato, S. *J. Chem. Phys*. **1988**, *88*, 6540.

(31) Torquato, S.; Rubinstein, J. *J. Chem. Phys*. **1989**, *90*, 1644.

(32) Given, J. A.; Blawzdziewicz, J.; Stell, G. *J. Chem. Phys*. **1990**, *93*, 8156.

(33) Risken, H. *The Fokker-Plank Equation*; 2nd ed.; Springer-Verlag: Berlin, 1989.

(34) Wang, J.; Wolynes, P. G. *Phys. Rev. Lett*. **1994**, *74*, 4317.

(35) Wang, J.; Wolynes, P. G. *J. Chem. Phys.* **1999**, *110*, 4812.

(36) Press, W. H.; Teukolsky, S. A.; Vetterling, W. T.; Flannery, B. P. *Numerical Recipes in Fortran*, 2nd ed.; Cambridge University Press: Cambridge, 1992; Chapter 2.