On Stochastic Models of Dynamic Disorder†

David R. Reichman

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York, 10025

Received: March 30, 2006; In Final Form: July 31, 2006

In this paper we investigate some general aspects of stochastic models of dynamic disorder. First, we reexamine the Zwanzig model for the kinetics of escape through a fluctuating hole. We show that this model is trivially connected to the canonical model of the broadening of the zero-phonon line (ZPL) in crystals. This provides a new perspective of the Wang−Wolynes expression for the rate of escape from a geometric bottleneck with non-Markovian Gaussian fluctuations. Motivated by recent single-molecule experiments, we examine more general examples of fluctuation processes from the perspective of cumulant expansions. Finally, we discuss recent single-molecule experiments probing enzyme turnover performed by Xie and co-workers.

I. Introduction

The stochastic theory of dynamic disorder has had a broad impact on many areas of physics, chemistry, and biology. Among the first successful theories of spectroscopy in condensed phases, the stochastic theory developed by Anderson and Kubo has had a major impact on our understanding of optical, vibrational, and NMR line shapes in liquid, crystalline, and glassy hosts.[1−6] Related problems, such as that of a particle escaping from a fluctuating bottleneck or surmounting a fluctuating barrier, have been used in a variety of physical and biophysical contexts.[7−11] With the emergence of single-molecule spectroscopic techniques, interest in such approaches has been revived.[12−16]

In this work, we investigate a variety of stochastic problems that are relevant for understanding certain biological processes. These problems may be simple, such as a particle escaping from a hole whose radius is free to fluctuate,[17] or more complex, where the fluctuating decay rate depends in a complicated manner on the stochastic variables.[18] The simple example is of importance in ligand binding kinetics, where the bottleneck to binding or unbinding is the ability of the binding entity to fit in a confined space that is continuously in motion.[19,20] There are manifold examples of situations that must be modeled by more complex stochastic processes. A timely example is that of enzyme kinetics that may be probed via single-molecule spectroscopy.[21−24] Here, exact solutions for reasonable stochastic models are difficult to find. Approximate solutions should be constructed with special attention paid to the nature of the stochastic process. When the available data are not amenable to direct calculation, models may be built that allow a gross rationalization of the data. Here, several stochastic problems are investigated. Our discussion will range from exact solution to the investigation of simple models.

This paper is organized as follows: In Section II, we discuss the Zwanzig model for the dynamics of a simple fluctuating stochastic bottleneck. In Section III, we discuss a memory function based technique for the approximate, infinite-order resummation of stochastic cumulants in cases where exact resummation is impractical. In Section IV, we discuss recent single-molecule experiments of Xie and co-workers on the flavin enzymatic system. We discuss a crude model that may be used to rationalize the experimental results. We discuss how the model may be experimentally distinguished from the schematic model commonly used to rationalize such experiments. In the last section we conclude.

II. Simple Fluctuating Bottleneck

Consider the problem, originally posed by Zwanzig, of a classical particle escaping from a localized region that depends stochastically on the radius of the bottleneck,

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = -K(r(t))P(t) \qquad \text{(II.1)}$$

with $K(r) = \kappa r^2$.[17] The variable $r(t)$ is assumed to have Gaussian fluctuations. In the Markovian limit, Zwanzig provided an exact solution for a slightly more general version of this problem. For the full non-Markovian case, Wang and Wolynes derived a closed form expression for the asymptotic rate of decay of the ensemble-averaged population using path integral techniques.[9] The Wang−Wolynes expression for the rate is given by $k_{\mathrm{eff}} = (1/2\pi)\int_0^\infty d\omega\ \ln[1 + 2\kappa\tilde{C}(\omega)]$ where where the angular brackets denote an average over the stochastic process, and $C(t) = \langle r(t)r(0)\rangle$. Bicout and Szabo considered this problem from the viewpoint of a multidimensional Fokker−Planck equation with a quadratic sink term.[25] The analysis of the Fokker−Planck equation leads to an eigenvalue problem from which the Wang−Wolynes rate is recovered. Bicout and Szabo extended the treatment of Wang and Wolynes by providing a practical algorithm for the full time dependence of the survival probability $\langle P(t)\rangle$. Below, we provide an alternate derivation of this expression via a direct method distinct from that of Wang and Wolynes as well as Bicout and Szabo.

The formal solution for k_{eff} is expressible in the cumulant-type series, making use of the Gaussian property of $r(t)$[25−27]

$$S(t) = \exp\left(-\frac{1}{2}\left[2\kappa t - \frac{(2\kappa)^2}{2}\int_0^t \mathrm{d}t_1 \int_0^t \mathrm{d}t_2 C(|t_1 - t_2|)C(|t_2 - t_1|) + \frac{(2\kappa)^3}{3}\int_0^t \mathrm{d}t_1 \int_0^t \mathrm{d}t_2 \int_0^t \mathrm{d}t_3 C(|t_1 - t_2|)C(|t_2 - t_3|)C(|t_3 - t_1|)\ \ldots\right]\right) \qquad \text{(II.2)}$$

† Part of the special issue "Robert J. Silbey Festschrift".

10.1021/jp061992j CCC: $33.50
Published on Web 09/21/2006

Since $C(|t|)$ is a real, even function of time, the cosine transform may be expressed

$$\tilde{C}(\omega) = \frac{1}{\pi}\int_0^\infty \mathrm{d}t\, C(t)\cos(\omega t) = \frac{1}{2\pi}\int_{-\infty}^{\infty}\mathrm{d}t\, C(|t|)\exp(i\omega t)$$

The nth term ($S_{(n)}(t)$) in the exponent may be expressed as

$$S_{(n)}(t) = \frac{(-\kappa)^n}{n(2\pi)^n}\int_{-\infty}^{\infty}\mathrm{d}\omega_1 \ldots \int_{-\infty}^{\infty}\mathrm{d}\omega_n\, \tilde{C}(\omega_1)\ldots\tilde{C}(\omega_n)\times \frac{\sin(\omega_1-\omega_n)t/2}{(\omega_1-\omega_n)}\ldots\frac{\sin(\omega_n-\omega_{n-1})t/2}{(\omega_n-\omega_{n-1})} \quad \text{(II.3)}$$

Since $\lim_{t\to\infty}[\sin(xt)/x] = \pi\delta(x)$, the long time limit of the nth cumulant is

$$S_{(n)}(t) \simeq \frac{(-\kappa)^n t}{2\pi n}\int_{-\infty}^{\infty}\mathrm{d}\omega\,[\tilde{C}(\omega)]^n \quad \text{(II.4)}$$

The cumulant series is seen to be that of the logarithm, and the sum can be performed, yielding exactly the expression derived by Wang and Wolynes.

The above derivation uses the methods developed by Nitzan and Persson,[26] as well as Skinner and Hsu for the calculation of line broadening on surfaces and in crystals.[27] In fact, the result for k_{eff} is seen to be a simple modification of the result presented by Skinner and Hsu. This finding is a particular example of the general relationship between stochastic line shape theory and the fluctuating rate problem discussed in ref 8. The isomorphism between the fluctuating bottleneck problem and the stochastic line shape problem has interesting applications to the calculation of line shapes of chromophores in condensed phases and at interfaces. For example, the Zwanzig result for the viscosity dependence of the relaxation rate in the Markov limit[17] immediately translates into the known result for the dependence of the broadening of the zero-phonon line on the dimensionless strength of the electron- phonon coupling in the weak-coupling, Redfield limit.[28] In fact, the analogy between the line broadening and the fluctuating bottleneck problem immediately suggests a solution to a quantum generalization of the Zwanzig problem, as well as an alternate solution of the full time dependence of the non-Markovian decay of the population to that presented by Bicout and Szabo.

Consider an operator $\hat{r} = \sum_k h_k(b_k + b_{-k}^\dagger)$ where the spectrum of h_k is chosen so that $C(t) = \langle \hat{r}(t)\hat{r}(0)\rangle$ produces a $\tilde{C}(\omega)$ that reproduces the classical stochastic limit as $T \to \infty$, and $b_k(b_{-k}^\dagger)$ is a standard lowering (raising) operator for a harmonic process. The constant h_k may be taken to have the proper frequency factors such that $\hat{r}$ has units of length. The replacement of $r(t)$ with $\hat{r}(t)$ constitutes one possible quantum generalization of Zwanzig's fluctuating bottleneck problem.[29] While the mapping is not a unique one, it is guaranteed to provide the proper stochastic limit at infinite temperature. An exact solution to this problem, valid for all times (not just asymptotically) may be found by first noting that

$$\langle \hat{P}(t)\rangle = \langle \exp_{\mathrm{T}}[-\kappa\int_0^t \mathrm{d}\tau \hat{r}(\tau)^2]\rangle \quad \text{(II.5)}$$

where $\hat{P}(t)$ is the population operator, and T denotes a time-ordered exponential. The solution to this may be determined by noting that $\hat{P}(t)$ may be expressed as $\hat{P}(t) = \langle \exp(iH_{\mathrm{eff}}t)\exp(-i[H_{\mathrm{eff}} - i\kappa\hat{r}^2]t)\rangle$. Here, H_{eff} denotes the effective harmonic Hamiltonian that generates the Gaussian stochastic process. Since all averages involve harmonic stochastic operators, the exact average may be computed from the method of Balian and Brezin.[30] More specifically, if $\hat{\Theta}$ is an operator of the form $\hat{\Theta} = \exp[(\alpha\cdot\boldsymbol{S}\cdot\alpha)/2]$ where the vector $\alpha = (b_1, \ldots, b_N; b_1^\dagger, \ldots, b_N^\dagger)$ and $\mathbf{S}$ is a symmetric matrix, then $\langle\hat{\Theta}\rangle$ is given by $\langle\hat{\Theta}\rangle = \det([\hat{\Theta}] - 1)$ where $[\hat{\Theta}]$ is the matrix that represents this operator, namely, $[\hat{\Theta}] = \exp(\tau\cdot\boldsymbol{S})$ where τ is the $2N \times 2N$ block matrix

$$\tau = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix} \quad \text{(II.6)}$$

Combinations of more complicated products may be calculated as matrix products, and thus the full solution of $\hat{P}(t)$ may conveniently be given numerically as a determinant. The Wang–Wolynes expression (more precisely its quantum generalization) is guaranteed to emerge in the long-time limit and will yield the same classical behavior as that of the Bicout–Szabo approach, which is also exact in this limit. Like the Bicout–Szabo approach, our approach provides the full time dependence of $\hat{P}(t)$ and provides an alternate route to classical stochastically averaged population in the limit $T \to \infty$.

III. Complex Stochastic Processes

In most situations, the form of $K(r(t))$ is not simple enough to allow for an exact calculation of even the asymptotic form of the relaxation rate, as was possible for the case of the Zwanzig model discussed above. An important example that will be discussed further in the next section is the case of single molecule charge-transfer reactions for which we may model the fluctuating rate of population as $K(r(t)) \sim k_0\exp(-r(t)/r_0)$.[18,24] Here, higher-order cumulants quickly become very cumbersome to compute. Below, we develop an approach capable of approximately resumming the cumulant series. The approach is not limited to a particular form of $K(r(t))$, although the exponential form will be used as a concrete example.

Consider the case of a stochastically fluctuating population

$$\frac{\mathrm{d}P(t)}{\mathrm{d}t} = -(m + A(t))P(t) \quad \text{(III.1)}$$

where $m = \langle K(r(t))\rangle$, and $A(t) = K(r(t)) - m$. Using projection operator techniques, an *exact* equation of motion for the stochastically average population may be derived[31,32]

$$\frac{\mathrm{d}\langle P(t)\rangle}{\mathrm{d}t} = -m\langle P(t)\rangle + \int_0^t \mathrm{d}\tau D(t-\tau)\frac{\mathrm{d}\langle P(\tau)\rangle}{\mathrm{d}\tau} \quad \text{(III.2)}$$

where the memory function $D(t-\tau)$ is given by

$$D(t-\tau) = \exp(-r(t-\tau))\langle A(t)U(t,\tau)A(\tau)\rangle \quad \text{(III.3)}$$

where $U(t,\tau) = \exp[-\int_\tau^t \mathrm{d}t'\mathbf{Q}A(t')]$, and $\mathbf{Q}h(t) = h(t) - \langle h(t)\rangle$, where $h(t)$ is an arbitrary stochastic process.

The memory kernel may be expanded by expanding the exponential operator that contains $\mathbf{Q}$. To lowest order, $D(t-\tau) = \langle A(t)A(\tau)\rangle$. In a previous work, an identical average was denoted "memory function" by Yang and Cao; however, their derivation utilized a different set of cumulants, and in fact the equation of motion derived for $\langle P(t)\rangle$ does not contain explicit memory effects.[31] The distinction between these two approaches is that the method of Yang and Cao utilizes "partially ordered cumulants" which are exact at lowest nontrivial order for Gaussian processes, while the equation we have just derived uses "completely ordered cumulants" which are exact for sudden-jump stochastic processes.[32] Thus, depending on the particular problem, a proper choice of cumulants will greatly simplify the problem. For the simple Zwanzig model considered

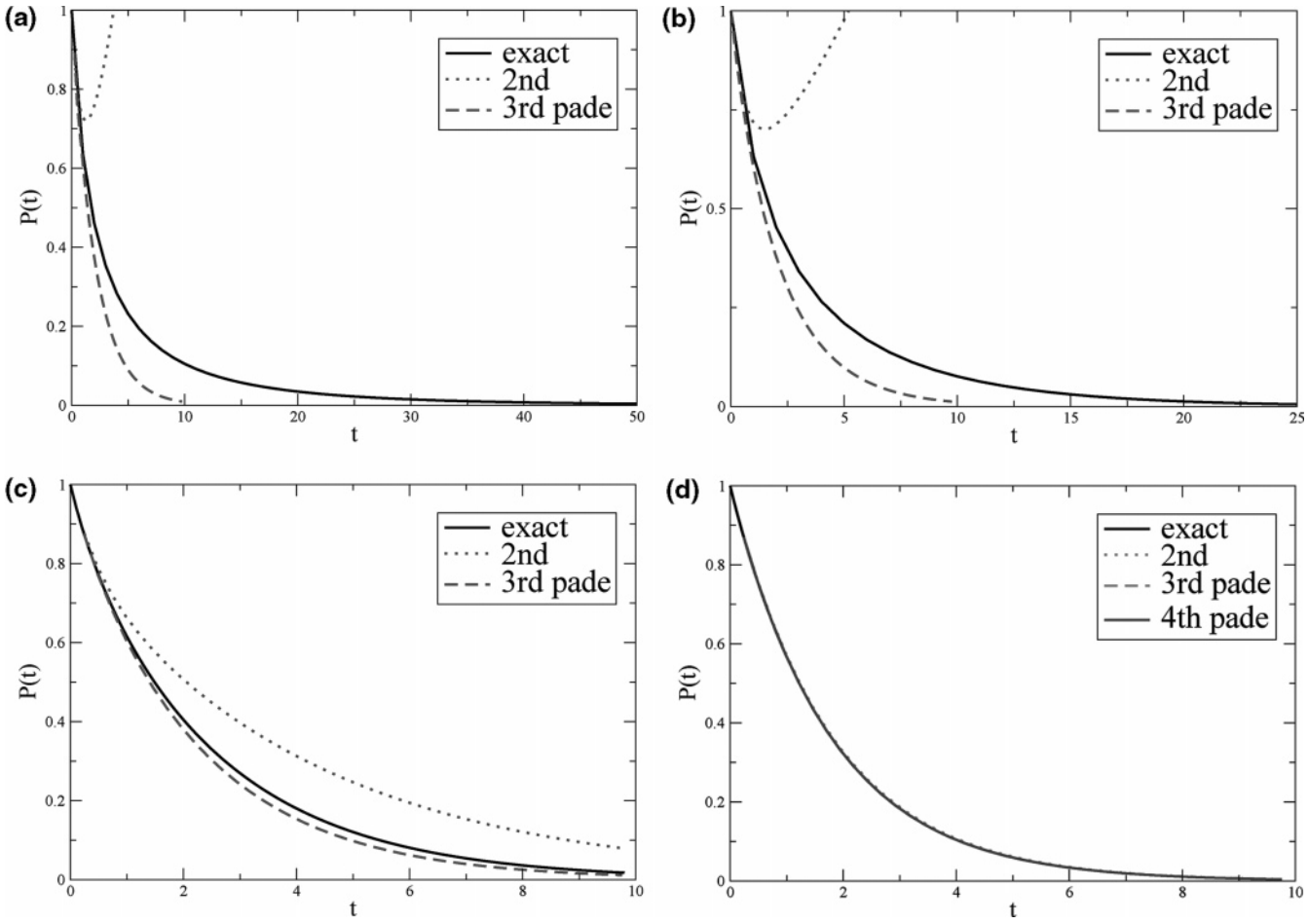

Figure 1. (a−d) Behavior of $\langle P(t)\rangle$ for model of III.1 with $K(t) \sim k_0 \exp(-r(t)/r_0)$ and $\langle r(t)r(0)\rangle = \exp(-\lambda t)$ for different λ comparing the exact result, the third-order Padé approximation and the second-order cumulant result. The values of λ are 0.01, 0.1, 1, 10 in (a)−(d), respectively.

in the last section, we demonstrated that a complete resummation of partially ordered cumulants easily led to the exact asymptotic rate expression. For the more complex case where $K(r(t)) \sim k_0 \exp(-r(t)/r_0)$, it is trivial to show that if $r(t)$ has Gaussian fluctuations, then the statistics of $K(r(t))$ has statistics closer to that of a sudden-jump process than a Gaussian one. Thus, it is advantageous in this case to use the approach outlined in this section, where it is expected that truncation of the expanded memory function expression at finite order will be much more successful than truncation of the usual Gaussian cumulant series.

A further advantage of the approach outlined above is that it is amenable to approximate, infinite-order resummation in Fourier−Laplace space. Defining the transform $D(\omega) = -i\int_0^\infty dt \exp(i\omega t)D(t)$, the solution to the equation of motion for the stochastically averaged population may be expressed as

$$\langle P(\omega)\rangle = \frac{-1}{[i\omega + m + D(\omega)]} \qquad \text{(III.4)}$$

We then approximately sum the infinite series for $D(\omega)$ using Padé techniques.[33] The simplest variant of Padé yields

$$D(\omega) \approx \frac{[D^{(2)}(\omega)]^2}{[D^{(2)}(\omega) - D^{(3)}(\omega)]} \qquad \text{(III.5)}$$

where $D^{(2)}(\omega)$ is the Fourier−Laplace transform of $D^{(2)}(t-\tau) = \langle A(t)A(\tau)\rangle$ and $D^{(3)}(\omega)$ is the Fourier−Laplace transform of $D^{(3)}(t-\tau) = -\int_\tau^t dt'\langle A(t)A(t')A(\tau)\rangle$.

As an example of the utility of this approach, we consider the form $K(r(t)) \sim k_0 \exp(-r(t)/r_0)$ with $k_0 = 1$ and $r_0 = 1$, which sets the natural units of the problem. The stochastic process for the fluctuating coordinate is chosen to be Gaussian and defined as $\langle r(t)r(0)\rangle = \exp(-\lambda t)$. Even with this simple form, the exact behavior of $\langle P(t)\rangle$ is not amenable to analytic calculation and must be simulated. In Figure 1 we show the results for four different decorrelation time scales from exact simulation, the third-order Padé, and the second-order cumulant expansion. It is clear that the third-order Padé approach gives a substantial improvement over the second-order cumulant approach. Indeed, for $\lambda \sim 1$ the approach converges toward the exact answer. It may also be seen that for some values of λ the low-order cumulant approach is unstable. This is true as well for the partially ordered cumulant approach of ref 31.

Even when the above approach yields an accurate result for the quantity $\langle P(t)\rangle$, it should be reserved for cases where the nature of the stochastic process is well understood. The ensemble-averaged population is generally dominated by the lowest eigenvalues of the stochastic Liouvillian, and thus exponential decay is expected regardless of the stochastic process involved. Here, simpler theoretical treatments may even be more accurate.[34] In experiments performed on complex biological systems, the nature of the stochastic process is generally unknown, and an observable that is more sensitive to the nature of the fluctuations should be sought, as is discussed below.

IV. Slow Dynamical Fluctuations Probed by Single-Molecule Experiments

Recently, Xie and co-workers have probed single-molecule electron transfer in the flavin protein system.[24] Their studies

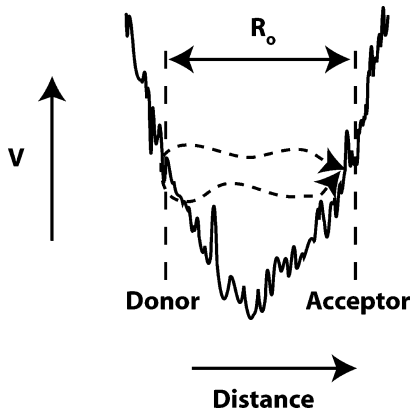

Figure 2. Two of many pathways that the system may use to navigate its way around a rough landscape. The projection of these paths onto the single stochastic coordinate $x(t)$ can give rise to slow dynamical behavior.

show that dynamical fluctuations are slow and nonexponential, resembling those found in glassy systems. The single-molecule nature of these experiments rules out static heterogeneity as a cause of the nonexponential decay of fluctuations. Similar results have been found for the fluctuations in catalytic activity of single DNA exonuclease molecules.

In the previous section, we discussed the stochastic average of population fluctuations that may occur if the stochastic rate $K(r(t))$ is a complicated function of the stochastic variable $r(t)$. In the experiments of Xie and co-workers, where electron transfer is used as a dynamical probe of single protein molecules, $K(r(t))$ may be taken as $K(r(t)) \sim k_0 \exp(-r(t)/r_0)$. This is precisely the form considered in the previous section. As discussed there, the long-time decay of $\langle P(t)\rangle$ will be of an exponential form. This implies that even single-molecule studies of this quantity will not yield a complete, detailed picture of the nature of dynamical fluctuations in this system. Xie and co-workers overcome this difficulty with a novel experimental technique that measures not the population, but the fluctuations of the lifetime $C(t) = [\langle A(t)A(0)\rangle]/[\langle (A(0))^2\rangle]$, where $A(t) = K(r(t)) - \langle K(r(t))\rangle$ was defined in the previous section. This quantity shows an approximate stretched exponential decay over several decades of time, although it may be fit with other functional forms. It is not consistent, however, with a simple Gaussian process for the variable $r(t)$ with an exponential decay of correlations $\langle r(t)r(0)\rangle \sim \theta \exp(-\eta t)$. A stochastic process of this type would lead to a dynamical portion of $C(t)$ that behaves as $C(t) \sim \exp[(\theta/r_0^2)\exp(-\eta t)]$.

To rationalize this behavior, we assume that the fluctuations occur at equilibrium and that there are essentially no long-lived substates that the system visits as it fluctuates around an average donor−acceptor distance of $\theta = R_0$. The latter assumption differs in philosophy from that often used to rationalize nonexponential relaxation in the context of single-molecule experiments. This point will be discussed further below. We assume that there is a primary coordinate $r(t)$ whose average is given by $\langle r(t)\rangle = \theta$ but whose dynamics is complex due the myriad of pathways on a high dimensional, rough energy landscape that the system may take such that the *instantaneous* distance between donor and acceptor is $r(t)$.[35,36] Thus, the donor−acceptor distance that is probed in the experiment is merely one particular coordinate that is projected out of the large dimensional space comprised of the other protein and solvent degrees of freedom in the problem. A cartoon of this physical situation is given in Figure 2. Our caricature of the motion in the rough landscape will be that of a particle moving in a random potential in large dimensions.[35] In the infinite limit, the dynamical correlations may be solved exactly as[35]

$$\frac{\partial G(t)}{\partial t} = -\mu G(t) - \frac{1}{T}\int_0^t d\tau \hat{V}'[G(t-\tau)]\frac{\partial G(\tau)}{\partial \tau} \qquad \text{(IV.1)}$$

where $\hat{V}(x)$ is the form of the random potential, $\hat{V}'(x)$ denotes the spatial derivative of the random potential, T is the temperature, and $G(t) = \langle dr(t)\delta r(0)\rangle$ where $\delta r(t) = r(t) - \theta$. Thus, $G(t)$ measures the correlations of the fluctuations of the donor−acceptance distance $r(t)$; these fluctuations may be complex because this primary distance coordinate results from the projection of a tremendous number of unseen variables whose motion takes place in a complex potential landscape. Near the onset temperature of glassy behavior T_0 the decay of $G(t)$ will show power-law relaxation with two noticeable regimes.[35,36] At short times $G(t) \sim q + c_1 t^{-b}$ and a longer-time relaxation $G(t) \sim q - c_2 t^a$, with q given by $(1-q^2)^2\hat{V}''(q) = T_0^2$ and a and b given through $(\Gamma^2[1+a])/(\Gamma[1+2a]) = (\Gamma^2[1-b])/(\Gamma[1-2b]) = (T/2)[\hat{V}'''(q)]/[\hat{V}''(q))^{3/2}]$. The constants c_1 and c_2 are not important for our discussion. Note that the long-time result for the time-dependent portion of $C(t)$ that results from our model for the behavior of $G(t)$ is given as

$$C(t) \sim \exp(-c_2 t^a) \qquad \text{(IV.2)}$$

This is the form that has been used to fit $C(t)$ as measured in the single-molecule experiments of Xie and co-workers. For the flavin system studied by Xie and co-workers the exponent $a \approx 0.3$; however, this value is likely to depend on temperature and solvent viscosity. The model presented above easily provides exponents in this range.

The nonexponential nature of the decay of $C(t)$ has been invoked by Xie and co-workers as evidence that the flavin system visits several long-lived conformers as it fluctuates. The simple model presented above demonstrates that this need not be the case. Here, stretched exponential relaxation of $C(t)$ results from the plethora of pathways that the system may take as it fluctuates around a fixed distance. In this "mode-coupling" picture, the system never remains near a basin of attraction for significant periods of time. Xie and co-workers have invoked the fractional Fokker−Planck approach of Klafter and co-workers.[37] This picture is isomorphic to a trap model with an exponential distribution of trapping energies.[38] These differing pictures are sketched in Figure 3. Note that the distinction between the pictures is not merely academic. First, it should be noted that for an exponent of $a = 0.3$ to hold in the trap picture, the single-molecule experiment must be waiting-time dependent. That is, the system must be aging. This is in contrast to the stationary character of the model presented above. It would be interesting to see if the single-molecule traces indeed yield nonstationary averages. Second, it may be possible to observe evidence of transient trapping by visual inspection of the single-molecule traces themselves. While such evidence is not clear from the trace presented in ref 24, it may indeed exist upon closer inspection of several independent traces. Recent simulations Luo, Andricioaei, Xie and Karplus[39] do demonstrate relatively long-lived trapped conformations. On the other hand, it should be noted that the temporal decay of $C(t)$ found in their simulations do exhibit the distinct temporal regimes predicted by the picture outlined above. Thus, as is typical in glassy systems,[40] combinations of the pictures in Figure 3 are likely to be operative. It should also be noted that the slow decay seen in the experiments of Xie and co-workers may find a description based on direct calculation of temporal correlations

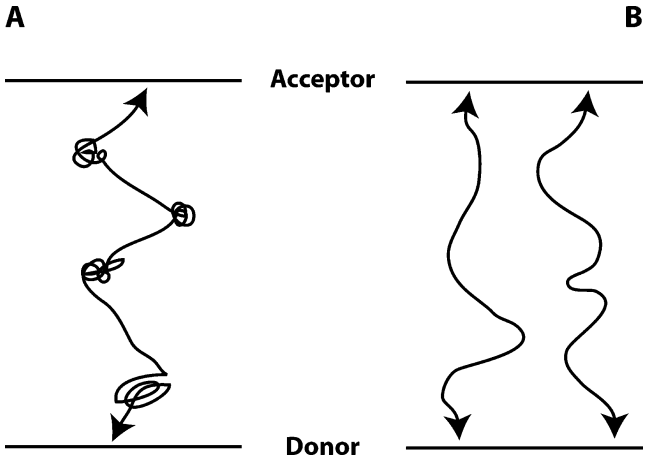

Figure 3. Depiction of two extreme landscape scenarios for the fluctuations of the effective lifetime in single-molecule experiments. Panel A shows a situation where the system visits many conformational "traps" as it fluctuates around an average fixed distance. Here, a distribution of trap times gives rise to slow dynamics. Panel B shows the schematic mode-coupling perspective of a particle in a high-dimensional, random potential. Here, the system is never stranded in conformational substates. Slow dynamics result due to the numerous fluctuation pathways that exist as the system fluctuates around a fixed distance.

in a polymer dynamics context.[41,42] Perhaps these and other models may be distinguishable via the computation of higher-order correlation function from the single-molecule data, as suggested in refs 10 and 43. While older, ensemble averaged experiments performed on biomolecules in water are fully consistent with the two power-law decays described above, it remains to be seen if either of these simplified models hold up to the experimental data found in recent single-molecule experiments.

V. Conclusions

In this work we have discussed several aspects of stochastic formulations of dynamic disorder models with applications to biophysical problems. We have reinvestigated the Zwanzig model of a system escaping a fluctuating, two-dimensional region. We have shown that one can sum the cumulant series exactly in the asymptotic limit, allowing for a re-derivation of the result of Wang and Wolynes. This derivation illustrates that the Zwanzig problem is trivially isomorphic to problems considered in optical line shape theory. This mapping provides new insight into both problems and allows us to extend the solutions of the Zwanzig problem into the quantum regime, as well as find a convenient exact expression for the *full* time dependence of the population decay. We then discussed more complex situations where exact solutions are impossible. We demonstrated how approximate, infinite-order resummations may be constructed to calculate the stochastically averaged population. Last, we have discussed a simple schematic model that is consistent with data from recent single-molecule experiments performed on the flavin system. It should be strongly emphasized that this model is not a *theory*, it is simply a picture that may be used to organize the gross features of a complex experiment. On the other hand, the model contains features that strongly differentiate it from other schematic models that might be used as a cartoon of the complex motion in protein systems. A realistic future goal should be the analysis of the single-molecule data, which contains information sufficient to distinguish between the trap and random-landscape pictures presented here. A more ambitious goal is the construction of more realistic models that reveal subtle details related to protein dynamics and function.[41,42] Work along these lines is underway.

Acknowledgment. The author would like to thank Dr. A. Golosov for all of the numerical calculations presented in Figure 1. He would also like to thank Professor X. S. Xie and Professor J. Klafter for discussion.

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