

Waiting time distribution and nonexponential relaxation in single molecule spectroscopic studies: Realization of entropic bottleneck in a simple model

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We study a dynamical disorder model for environmental modulation of rate processes where a need of dynamical cooperativity presents an entropy barrier, rather than an energy barrier. The rate depends on a control variable, Q , that describes the collective instantaneous state of the environment and is itself a random walker in finite discrete space with continuous time. We obtain the waiting time distribution for the relaxation by simulating the model. The time dependence of the average survival probability is derived there from and also by a numerical solution through the Liouville-master equation approach to the theoretical problem. We present an analytical treatment of the first passage time problem that is posed by a limiting case of our model. As the rate of the environmental fluctuation, τ_{env}^{-1} , slows down, the decay of the average survival probability is found to be more and more nonexponential in short times, but to change to exponential at longer times. The average survival time, τ , exhibits a fractional power law dependence on $\kappa (= \tau_{\text{env}} k_0)$, where time is scaled in terms of k_0^{-1} , k_0 being the intrinsic rate coefficient for the relaxation. The mean first passage time in the limiting case of the model exhibits an exponential dependence on the total number of the environmental subsystems N and a non-Arrhenious temperature dependence over the temperature range studied. We note the likely relevance of a part of this result to single molecule spectroscopic studies that reveal a tail in the waiting time distribution at long times.

I. INTRODUCTION

Environmental modulation of rate processes in complex dynamical systems, such as macromolecules, has been a topic of intense research interest in recent years. The stress has been on studies of passage through fluctuating bottleneck which can generally be either geometric¹⁻⁵ or energetic⁶⁻⁸ in character. Motivated by experimental studies of the kinetics of ligand binding in myoglobin, Zwanzig proposed a model¹ where the protein, which is known to fluctuate around its average structure when embedded in solvents at ambient temperature, is in a dynamical environment. In his model, the ligand binding is assumed to be governed by the passage through a geometrical bottleneck whose cross-sectional area fluctuates in time because of thermal noise. The model results in a decay of the molecular concentration which is non-exponential at short times, but changes to exponential at long times. If λ be the relaxation rate of the radius of the bottleneck, then the effective rate constant for the long time exponential decay was found to vary as $\lambda^{1/2}$.

The stochastic aspects of environmental fluctuation can be best studied at single molecule resolution. Single molecule fluorescence spectroscopy permits one to investigate the dynamical behavior of individual biomolecules in the condensed phase.⁹⁻¹¹ Single molecule spectroscopy (SMS), by definition, eliminates ensemble averaging involved in

conventional chemical kinetics. Study at single molecule level allows one to investigate the static disorder¹²⁻¹⁵ which arises from a distribution of rates among individual molecules. The local environment of a single molecule (SM) in a condensed phase fluctuates with time. If in a rate process with a single molecule this environmental fluctuation controls the rate of the occurrence of the event, dynamical disorder^{1,16} results. SMS allows to probe along a time trajectory dynamical disorder free from the static one.⁹ In contrast with ensemble-averaged measurements, single molecule experiments provide information on distribution^{9,17-19} that would otherwise be concealed under the mean value of the observable. The single molecule time trajectories for systems fluctuating under the equilibrium condition contain detail dynamical information including that on distribution.

The purpose of the present work, motivated by the single molecule spectroscopic studies^{9,19} that reveal a distribution of waiting time for an event to occur, is to develop a microscopic model capable of giving rise to experimentally observed distribution and also to investigate the accompanying features of such a model. In our model, the relaxation faces an entropy barrier, rather than an energy barrier. The entropic bottleneck arises from the need of a dynamical cooperativity in the environment. The model includes a control variable which, being a pointer of the collective instantaneous state of the environment, is a random walker in finite discrete space with continuous time as a result of environmental fluctuation. We study the waiting time distribution for the reactive event to occur by simulating the model and obtain the time depen-

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dence of the average survival probability there from and also by numerical solution of the theoretical problem formulated.

We also investigate the waiting time distribution as well as the time dependence of the average survival probability for an instantaneous death model which can be considered as a limiting case of the present model. The instantaneous death model can be treated analytically for the average survival time.

The rest of this paper is organized as follows. Section II describes the model. A theoretical analysis is contained in Sec. III. Section IV outlines the method of simulation. The results are presented in Sec. V with discussions. We conclude in Sec. VI with a few comments.

II. THE MODEL

The model considers occurrence of an event in a central system, the rate being controlled by the degree of order or excitation present in the environment. The environment consists of N identical noninteracting two-state subsystems, each of which transits back and forth between its two states, labeled 0 and 1, in thermal equilibrium at temperature T . The waiting time before a transition can occur from the state i ($=0,1$) is random, but is drawn from a Poissonian probability density function given by

$$\psi_i(t) = \frac{1}{\tau_i} \exp(-t/\tau_i), \quad i=0,1, \quad (1)$$

where τ_i is the average time of stay in the state i . If p_i be the equilibrium probability of the state i being occupied, we have

$$p_0 = \frac{1}{1 + \exp[-\epsilon/(k_B T)]} \quad (2)$$

and

$$p_1 = \frac{\exp[-\epsilon/(k_B T)]}{1 + \exp[-\epsilon/(k_B T)]}, \quad (3)$$

where the 0 state is assumed to have a zero energy and the 1 state an energy ϵ , and k_B is the Boltzmann constant. The following relation, due to detailed balance, holds

$$K = \frac{p_1}{p_0} = \frac{\tau_1}{\tau_0}, \quad (4)$$

where K is the equilibrium constant for the two states. We define a variable $\zeta_j(t)$ ($j=1,2,\dots,N$), which takes on a value 0 if at the given instant of time t the state 0 of the two-state subsystem j is occupied and 1 if otherwise. $\zeta_j(t)$ is thus essentially an occupation variable. The control variable, $Q(t)$, is defined as

$$Q(t) = \sum_{j=1}^N \zeta_j(t). \quad (5)$$

$Q(t)$ is therefore a stochastic variable in the discrete integer space $[0,N]$ and carries information of the degree of order or excitation prevailing in the environment at time t . The environmental modulation of the rate of the occurrence of the event arises from a Q -dependent rate constant k . We assume the rate constant $k(Q)$ to be of the form

$$k(Q(t)) = k_0 [1 + \tanh(Q(t) - N_c)], \quad (6)$$

for all Q except for $Q=0$ and $k(0)=0$. Here k_0 has the dimension of time inverse and N_c is a fixed integer greater than the value where the equilibrium distribution of Q is peaked. A purely entropic bottleneck arises when $\epsilon=0$, whereby $\tau_0=\tau_1=\tau_{\text{env}}$.

In the context of our model, the event may be either the folding of a biomolecule or the reaction controlling an enzymatic turnover or the entry of a small ligand molecule in a pocket of a biomolecule while the subsystems may be the subunits of the biomolecule each of which has two possible conformations. The particular form of the Q dependence of the rate constant incorporates a dynamical cooperativity. The rate of the occurrence of the event is large when a major fraction of the subunits has a particular conformation. The present work mostly concentrates on the case where ϵ is also equal to zero, whence both the states are equally probable to be occupied at equilibrium with $\tau_0=\tau_1=\tau_{\text{env}}$.

A special case of the model arises when N_c is an absorbing barrier. This means that the event occurs with unit probability at the instant Q reaches N_c for the first time. This limiting case is thus a kind of instantaneous death model. This model can be solved analytically for the average relaxation time τ .

III. THEORETICAL ANALYSIS

The theoretical treatment of the dynamical disorder model starts with a rate equation for the time dependence of the average survival probability, $\langle S(t) \rangle$, which is

$$\frac{d\langle S(t) \rangle}{dt} = -k(Q(t))\langle S(t) \rangle, \quad (7)$$

where the Q dependence of the rate constant is given by Eq. (6). For our model, Q is a stochastic variable which undergoes a random walk in the discrete integer space $[0,N]$ in unit steps with time varying continuously. The average transition probabilities per unit time for the stochastic variable to make a jump from Q to Q' ($=Q\pm 1$) are $W(Q',Q)$, given by

$$W(Q+1,Q) = W^+(Q) = (N-Q)/\tau_0 \quad (8)$$

and

$$W(Q-1,Q) = W^-(Q) = Q/\tau_1. \quad (9)$$

We follow Zwanzig's prescription¹⁶ which first yields a Liouville-master equation to be satisfied by the noise-averaged probability density $g(S,Q;t)$ and then performs a stepwise averaging

$$\bar{S}(Q;t) = \int_1^0 dS S g(S,Q;t) \quad (10)$$

and subsequently

$$\langle S(t) \rangle = \sum_{Q=0}^N \bar{S}(Q;t). \quad (11)$$

In the present case, the Liouville-master equation reads as

$$\begin{aligned}
\frac{\partial g(S, Q; t)}{\partial t} = & k(Q) \frac{\partial}{\partial S} [Sg(S, Q; t)] \\
& + [(N - Q + 1)/\tau_0]g(S, Q - 1; t) \\
& + [(Q + 1)/\tau_1]g(S, Q + 1; t) \\
& - [(N - Q)/\tau_0]g(S, Q; t) - (Q/\tau_1)g(S, Q; t),
\end{aligned} \tag{12}$$

whence the partially averaged $\bar{S}(Q; t)$ satisfies

$$\begin{aligned}
\frac{\partial \bar{S}(Q; t)}{\partial t} = & -k(Q)\bar{S}(Q; t) + [(N - Q + 1)/\tau_0]\bar{S}(Q - 1; t) \\
& + [(Q + 1)/\tau_1]\bar{S}(Q + 1; t) - [(N - Q)/\tau_0]\bar{S}(Q; t) \\
& - (Q/\tau_1)\bar{S}(Q; t).
\end{aligned} \tag{13}$$

The set of equations given by Eq. (13) for $Q = 0, 1, \dots, N$ has a matrix representation

$$\frac{\partial \bar{\mathbf{S}}(t)}{\partial t} = \mathbf{D}\bar{\mathbf{S}}(t). \tag{14}$$

We solve numerically by finding the eigenvalues $\{\lambda\}$ and the right eigenvectors $\{\Phi_\lambda\}$ of the matrix \mathbf{D} and then expanding in terms of eigenvectors²⁰

$$\bar{\mathbf{S}}(t) = \sum_{\lambda} c_{\lambda} \Phi_{\lambda} \exp(\lambda t). \tag{15}$$

The set of coefficients $\{c_{\lambda}\}$ are determined by $\bar{\mathbf{S}}(0)$ which is in turn obtained from the simulations.

The instantaneous death model, considered as a limiting case of our dynamical disorder model, poses an interesting first passage time problem. The average survival probability in this case is given by

$$\langle S(t) \rangle = \sum_{Q=0}^{N_c-1} P(Q; t), \tag{16}$$

where $P(Q; t)$, the probability of the collective environmental state to be at Q at time t , satisfies the master equation²⁰

$$\begin{aligned}
\frac{dP(Q; t)}{dt} = & [(N - Q + 1)/\tau_0]P(Q - 1; t) \\
& + [(Q + 1)/\tau_1]P(Q + 1; t) \\
& - [(N - Q)/\tau_0]P(Q; t) - (Q/\tau_1)P(Q; t).
\end{aligned} \tag{17}$$

The set of differential equations, given by Eq. (17), for $Q = 0, 1, \dots, N_c - 1$, has a compact matrix representation

$$\frac{d\mathbf{P}(t)}{dt} = \mathbf{A}\mathbf{P}(t). \tag{18}$$

Note that apart from having a $k(Q)$ term in its diagonal element, the matrix \mathbf{D} differs from \mathbf{A} in dimension. We numerically find the time dependence of the average survival probability by diagonalizing the matrix \mathbf{A} and then following

the method of eigenvector expansion, whence the coefficients of the expansion are determined from $\mathbf{P}(0)$ which is again obtained from the simulations.

For the instantaneous death model, we follow the procedure outlined in Ref. 21 to find an expression for the mean first passage time $\tau(l)$ which is the mean time elapsed before the stochastic variable Q (starting from an initial value $l \leq N_c - 1$) reaches N_c for the first time. $\tau(l)$ satisfies the equation related to the backward master equation

$$W^+(l)[\tau(l+1) - \tau(l)] + W^-(l)[\tau(l-1) - \tau(l)] = -1, \tag{19}$$

subject to an absorbing boundary condition at $Q = N_c$, $\tau(N_c) = 0$, and a reflecting boundary condition at $Q = 0$, $\tau(-1) = \tau(0)$. We define

$$U(l) = \tau(l+1) - \tau(l), \tag{20}$$

$$\Theta(l) = \prod_{m=1}^l \frac{W^-(m)}{W^+(m)}, \tag{21}$$

and

$$\Psi(l) = U(l)/\Theta(l). \tag{22}$$

Using these definitions, one can rewrite Eq. (19) as

$$W^+(l)\Theta(l)[\Psi(l) - \Psi(l-1)] = -1, \tag{23}$$

which is solved for $\Psi(l)$ to obtain

$$\Psi(l) = - \sum_{m=0}^l \frac{1}{W^+(m)\Theta(m)}, \tag{24}$$

where the reflecting boundary condition is used. Then with the help of the absorbing boundary condition we get the following:

$$\tau(l) = \sum_{n=l}^{N_c-1} \Theta(n) \sum_{m=0}^n \frac{1}{W^+(m)\Theta(m)}. \tag{25}$$

Substitution for $W^+(m)$ and $\Theta(m)$ by Eqs. (8) and (9) and subsequent simplification yield

$$\tau(l) = \frac{\tau_0}{N} \sum_{n=l}^{N_c-1} \binom{N-1}{n}^{-1} \sum_{m=0}^n \binom{N}{m} K^{m-n}, \tag{26}$$

where $\binom{N}{n} = N!/n!(N-n)!$. For the special case of $\tau_0 = \tau_1 = \tau_{\text{env}}$, $K = 1$. We turn into a new index $r = N - m$ for the inner sum, whence Eq. (26) reads as

$$\tau(l) = \frac{\tau_0}{N} \sum_{n=l}^{N_c-1} \binom{N-1}{n}^{-1} \sum_{r=N-n}^N \binom{N}{r} K^{N-n-r}. \tag{27}$$

Use of an integral identity²² allows one to rewrite the above equation

$$\tau(l) = \tau_0 \int_0^1 dx (1-x)^{N-n-1} (1+x/K)^n, \tag{28}$$

and then introducing the variable $y = (1+x/K)/(1-x)$, one gets

$$\tau(l) = \tau_0(1 + 1/K)^N \sum_{n=l}^{N_c-1} \int_1^\infty dy y^n (y + 1/K)^{-N-1}. \quad (29)$$

On integration one ends up with a sum over hypergeometric functions $F(a, b; c; z)$

$$\tau(l) = \tau_0(1 + 1/K)^N \times \sum_{n=l}^{N_c-1} \frac{F(N+1, N-n; N-n+1; -1/K)}{N-n}. \quad (30)$$

An approximation, which is valid when $N-n \gg 1$, can simplify the cumbersome sum to an extent. It is then reasonable to approximate $F(N+1, N-n; N-n+1; -1/K) \approx F(N+1, N-n; N-n; -1/K) = (1 + 1/K)^{-(N+1)}$, whence the expression for the mean first passage time reduces to

$$\tau(l) \approx \tau_0(1 + 1/K)^{-1} \sum_{n=l}^{N_c-1} \frac{1}{N-n}. \quad (31)$$

It is then obvious that N_c must be much smaller than N for the validation of this expression. A small K value ensures that N_c remains larger than the most probable value for Q . This leads to a very weak dependence on N .

IV. COMPUTER SIMULATION

An outline of the method of simulation is presented here. Each of the two-state subsystems (TSSs) in the environmental space was initially allowed to be occupied according to the bias, if any, depending upon the value of ϵ . The waiting time for a transition to occur in each TSS was drawn from a normalized exponential distribution with the corresponding mean value. The transition was executed in the TSS having the least waiting time. Next waiting time was then drawn from the same distribution for that TSS and the waiting times of the rest of the TSSs were adjusted by subtracting the least one from the existing waiting times. The next transition was then executed in the same way. The process was thus repeated until sufficient number of initial configurations in the environmental space with waiting time for the next transition to occur in each TSS were stored.

For each trajectory, an initial configuration was chosen from the stored ones. The temporal evolution of the environment was executed in the same fashion as effected while generating the initial configurations. For the sake of generality, time was scaled by setting k_0 equal to unity. Each time a TSS having the least waiting time was picked for a transition to occur, a time period was obtained during which $Q(t)$ had a definite value. The time was advanced in discrete steps of Δt unless Δt included the instant when $Q(t)$ underwent a change; whenever it did, the time step was shortened accordingly to avoid any change in $Q(t)$ during it. In each step, a random number generator was called to get a random number uniformly distributed between zero and unity. If the drawn random number was less than or equal to $k(Q)\Delta t$, the trajectory was terminated. Otherwise, the simulation of the trajectory was continued. For the instantaneous death model, time was advanced in steps of the least waiting times and the trajectory was terminated as soon as Q reaches N_c for the first time.

On repeating the simulation of the trajectory N_s ($= 50\,000$) times and recording the time of the termination of the trajectory, the immediate outcome of the simulation was a set of waiting times t_i ($i = 1, 2, \dots, N_s$) for the event to occur. The histogram obtained from this set gave the waiting time distribution. The time dependence of the average survival probability, $\langle S(t) \rangle$, was then derived from

$$\langle S(t) \rangle = \frac{1}{N_s} \sum_{i=1}^{N_s} H(t - t_i), \quad (32)$$

where H is Heaviside step function. Equation (32) needs to be understood. If $w(t')$ be the waiting time density function, $w(t')dt'$ gives the probability that the event occurs between time interval t' and $t' + dt'$. The survival probability is then given by²³

$$S(t) = 1 - \int_0^t w(t') dt'. \quad (33)$$

For a simulated trajectory $w(t')$ has a δ -function form, and therefore, the survival probability in the i th simulation is

$$S^i(t) = 1 - \int_0^t \delta(t' - t_i) dt'. \quad (34)$$

On averaging over trajectories, one gets

$$\langle S(t) \rangle = \frac{1}{N_s} \sum_{i=1}^{N_s} S^i(t). \quad (35)$$

Equations (34) and (35) together result in Eq. (32).

A dimensionless parameter κ , defined as $\kappa = k_0 \tau_{env}$, was introduced and the set of simulations was repeated for different values of κ with k_0 kept constant. As κ changes, the time step Δt needs to be reset accordingly. We set the time step to be equal to $5 \times 10^{-3} \kappa$ for a particular value of $\kappa \leq 10$. For higher values of κ , we set $\Delta t = 0.5$. This gives an almost perfect agreement of the simulation result with the numerical solution of the time dependence of the average survival probability.

V. RESULTS AND DISCUSSIONS

The *dynamical disorder model* with a purely entropic bottleneck corresponding to $\tau_0 = \tau_1 = \tau_{env}$ is simulated with $N = 10$ and $N_c = 8$ for a range of values of κ between 1 and 500. The nonexponentiality in both the waiting time distribution and the decay of the average survival probability becomes progressively prominent as κ increases. For $\kappa = 1$, the waiting time distribution is Poissonian and this results in an exponential decay of the average survival probability as shown in Figs. 1(a) and 1(b). As κ increases, the waiting time distribution exhibits a longer tail as evident from Fig. 2. This is reflected in the decay of the average survival probability which is nonexponential at short times, but changes to exponential at longer times. Fig. 3 which shows $\langle S(t) \rangle$ in the logarithmic scale against time t illustrates this behavior. When the average rate of the environmental fluctuation, τ_{env}^{-1} , is comparable to the intrinsic rate k_0 , the reactive event occurs infrequently and the average survival probability decays exponentially. As the environmental fluctuation slows

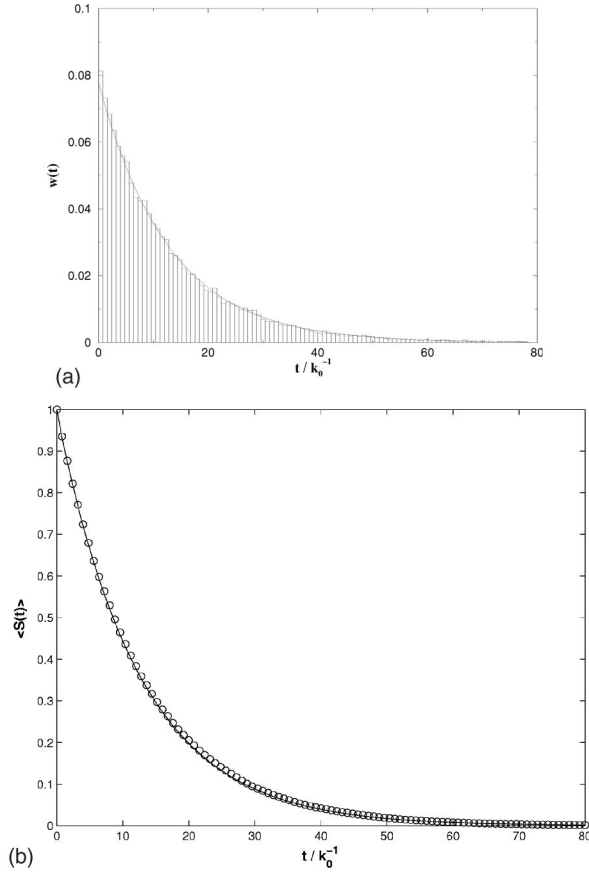


FIG. 1. (a) Waiting time histogram for the dynamical disorder model with $N=10$, $N_c=8$, and $\kappa=1$. The solid line is a fit to a normalized exponential waiting time distribution with the mean equal to 12.84. (b) The circles are the data point for the time dependence of the average survival probability obtained from the waiting time distribution shown in (a) and the solid line corresponds to the numerical solution. The agreement is nearly perfect.

down, the event occurs from a broader window leading to nonexponentiality. Fig. 4 shows a plot of $\ln\langle S(t) \rangle$ versus t for two values of N_c with N kept fixed at 10. It is evident that the nonexponentiality is more pronounced with a less severe entropic bottleneck.

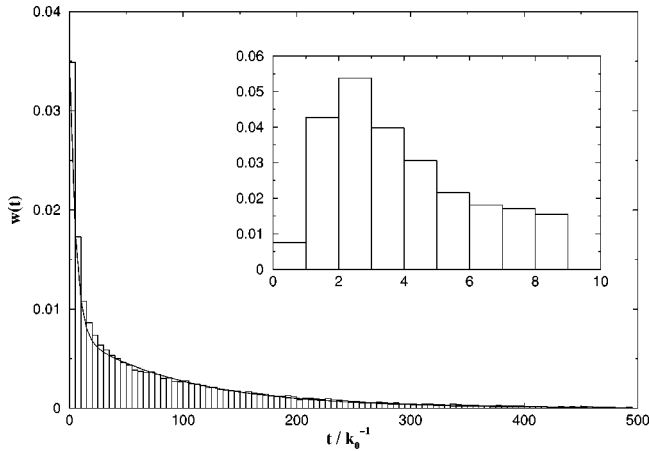


FIG. 2. (a) Waiting time histogram for the dynamical disorder model with $N=10$, $N_c=8$, and $\kappa=100$. The solid line is a fit to the biexponential $ae^{t/\tau_a} + be^{t/\tau_b}$ with $a=0.0075$, $\tau_a=97.99$, $b=0.027$, and $\tau_b=5.56$. (Inset) Expansion of the first two bins of the main histogram.

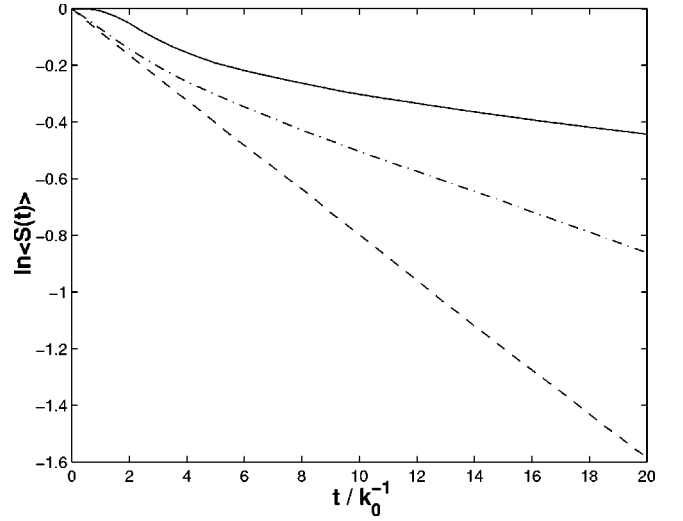


FIG. 3. $\ln\langle S(t) \rangle$ plotted as a function of time t for $\kappa=1, 10, 100$ (dashed line, dashed-dotted line, and solid line, respectively) in the case of the dynamical disorder model with $N=10$ and $N_c=8$. The change over from the short time nonexponential decay to long time exponential decay of the average survival probability is notable.

We have obtained the average survival time τ , defined as $\tau = \int_0^\infty dt \langle S(t) P \rangle$, from the area under the $\langle S(t) \rangle$ versus t curve for the range of values of κ . The average survival time is found to have a fractional power law dependence on κ , $\tau \sim \kappa^\alpha$, with the exponent $\alpha=0.52$ for large κ . This follows from the $\ln(\tau/k_0^{-1})$ versus $\ln\kappa$ plot shown in Fig. 5. The rate of the environmental fluctuation slows down as the viscosity η of the solvent is increased. It is then reasonable to assume that τ_{env} is proportional to η , whence we end up with an *inverse fractional power law* dependence of the average rate of the occurrence of the event, τ^{-1} , on the solvent viscosity. Such fractional viscosity dependence has been earlier predicted by Zwanzig in a different model of dynamical disorder¹ with geometric bottleneck. However, Zwanzig's

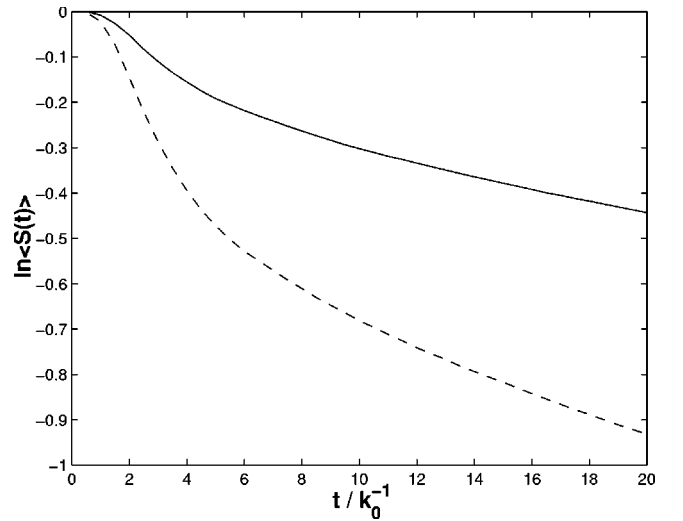


FIG. 4. $\ln\langle S(t) \rangle$ versus t plot at short times for $N_c=7$ and 8 (dashed line and solid line, respectively) with N held fixed at 10. With an enhanced time resolution at short times initial slow decay of the average survival probability is evident in both the cases.

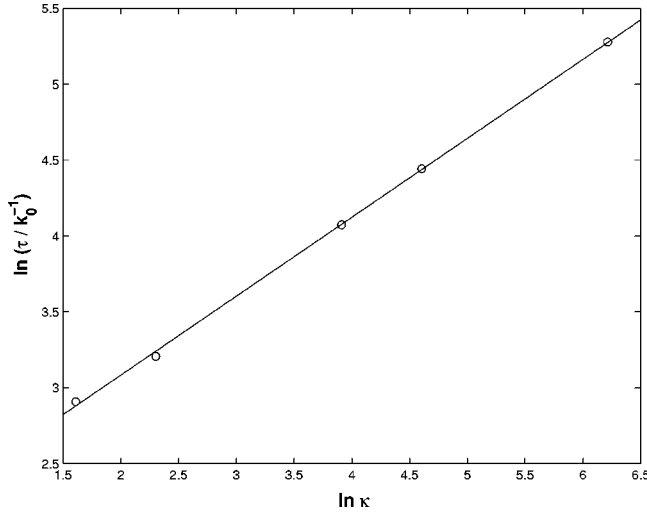


FIG. 5. Log-log plot of τ/k_0^{-1} vs κ . The solid line is a linear fit with slope $\alpha=0.52$. This means a fractional power law dependence of τ on κ with the exponent α .

treatment is in the context of ensemble-averaged experiments and discusses in terms of molecular concentration.

However, when the *instantaneous death model* (with only the entropy constraint) is simulated for $N=10$ and $N_c=8$, both the waiting time distribution and the decay of the average survival probability, shown in Figs. 6(a) and 6(b), are found to be exponential. We have studied the system size dependence of the average survival time τ by simulating the model for different N values with the fraction ϕ , defined as $\phi=N_c/N$, kept fixed at 0.8. For the instantaneous death model, the average survival time is essentially the mean first passage time. The mean first passage time observed in simulation, τ_{obs} , is a weighted average as $\tau_{\text{obs}} = \sum_{l=0}^{N_c-1} P(l;0) \tau(l)$. An exponential dependence of τ_{obs} on N is evident from Fig. 7 which shows a linear dependence of $\ln(\tau_{\text{obs}}/\tau_{\text{sc}})$ on N , τ_{sc} being the scaling unit.

The instantaneous death model has also been simulated to study the temperature dependence of the mean first passage time for a nonzero value of ϵ . In this case, time is scaled in terms of τ_{sc} , which equals τ_1 for the lowest temperature studied. The scaling is based on the assumption that the proportionality constant c in $p_i = c \tau_i$, $i=0$ and 1, is independent of temperature. The curvature in the plot of $\ln(\tau_{\text{obs}}/\tau_{\text{sc}})$ against $\epsilon/(k_B T)$, shown in Fig. 8, indicates a non-Arrhenius behavior. The observed mean first passage time τ_{obs} can be fitted well to the form

$$\ln(\tau_{\text{obs}}/\tau_{\text{sc}}) = 2.8 + 2.6(\epsilon/k_B T) + 0.89(\epsilon/k_B T)^2. \quad (36)$$

Several single molecule experiments^{9,19} have recently measured the distribution of the waiting time for the relaxation to occur. The waiting time distribution predicted by our dynamical disorder model for slow environmental fluctuation qualitatively resembles the folding time distribution observed in RNA folding [Note the similarity between Fig. 5(B) of Ref. 19 and Fig. 2 of the present work.] It is worth mentioning here that a recent experiment on single-molecule enzymatic dynamics has revealed at long times a power law distribution of reaction time.²⁴

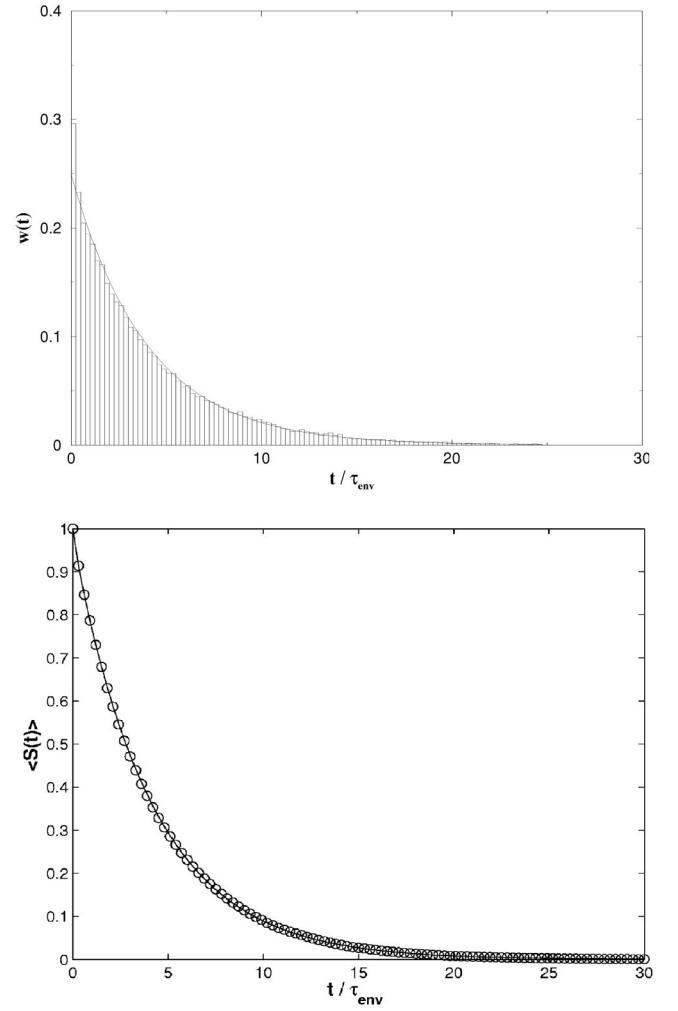


FIG. 6. (a) First passage time histogram for the instantaneous death model with $N=10$, $N_c=8$ and a purely entropic bottleneck. The solid line is a fit to the normalized exponential distribution with the mean equal to 4.01. (b) The corresponding decay of the average survival probability. The data points obtained from the simulation are marked with circles and the solid line is the numerical solution. The agreement between the two is almost perfect.

VI. CONCLUDING REMARKS

Let us first summarize the main aspects of this paper. We have introduced and studied a model of dynamical disorder. The salient feature of this model is the dynamical cooperativity between the central system and its environment. The entropic bottleneck is severe when a large fraction of the environmental subsystems needs to be in a particular state for the relaxation to happen. The waiting time distribution, obtained by simulating the model, exhibits a long time tail for slow environmental fluctuation. The numerical solution for the time dependence of the average survival probability is in agreement with the simulation result. A limiting case of the model is treated analytically for the average survival time. The waiting time distribution for slow environmental fluctuation looks alike with the experimentally observed folding time distribution in RNA folding.¹⁹

We note the resemblance of the qualitative predictions that our dynamical disorder model makes to those of Zwanzig's model¹, in spite of several differences between the two. Apart from the difference of the particular form of the con-

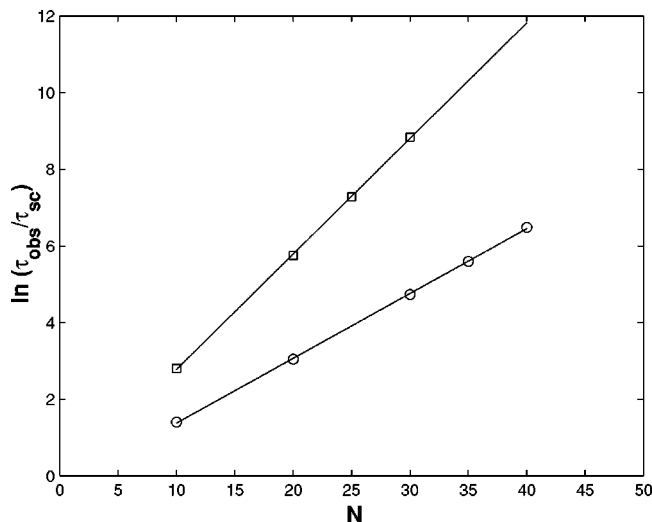


FIG. 7. $\ln(\tau_{\text{obs}}/\tau_{\text{sc}})$ vs N plot with the fraction $\phi = N_c/N$ held fixed at 0.8 for the instantaneous death model. The data points for sole entropy constraint, when time is scaled by $\tau_{\text{sc}} = \tau_{\text{env}}$, are within circles. The squares mark the data points for the case with an energy bias having $K=2/3$, whence $\tau_{\text{sc}} = \tau_1$. A linear fit in each case, with slopes 0.17 and 0.30, respectively, illustrates an exponential dependence of τ_{obs} on N . The dependence is stronger with an energy constraint.

control variable dependence of the rate constant, the main difference is that the control variable in our model moves in discrete space while its variation in Zwanzig's model is continuous. In addition, an element of dynamical cooperativity is present in our model. The resemblance thus suggests that the qualitative findings are more general in nature than it appears from a particular model being under consideration. An advantage with our model is that an energy barrier can be easily incorporated into it. While the dependence of the rate constant on the control variable enters our model naturally through a requirement of a dynamical cooperativity, the assumed form of the dependence is not so obvious at a first

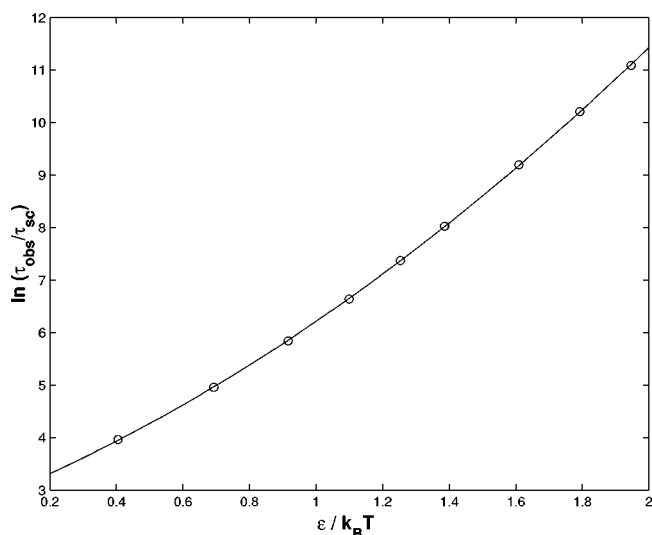


FIG. 8. Logarithmic plot of the scaled mean first passage time τ_{obs} against the reduced inverse temperature $\epsilon/(k_B T)$ for the instantaneous death model with $N=10$ and $N_c=8$. The solid line is quadratic fit to the data indicating non-Arrhenius behavior.

glance. We, however, emphasize that this particular form is quite effective to provide a properly placed window where from the event can occur with variable rates. The instantaneous death model comes naturally as a limiting case of this. The existence of the two parameters N and N_c in the present dynamical disorder model opens up the scope of the study of the dependence on the system size and on the required degree of cooperativity, respectively.

In a typical ensemble-averaged measurement with bulk samples, it is difficult, if not impossible, to distinguish whether the nonexponential behavior is intrinsic to each individual molecule or is due to inhomogeneous averaging over large population where each individual member displays different single exponential behavior. Single molecule study has, however, proved to be valuable in this regard. Slow conformational dynamics can be best probed at single molecule level.

The present study has explored the applicability of a dynamical disorder model in the context of slow conformational dynamics, where an entropy barrier rather than an energy barrier controls the relaxation. Since the content of the model is rather general, we envisage its applications to several different problems where entropy crisis slows down the dynamics. The two-state subsystems (TSSs) could be the representative of the fluctuating states of the subunits of a biopolymer (rotational isomers). It could also represent, with a nonzero value of ϵ , the bonded and nonbonded states of a hydrogen bond between two groups. A well known model of biochemical reactions employs the opening of a gate for the relaxation to occur.²⁵ The opening of the reaction gate is, in turn, determined by the environment. The model developed here provides a more general description of the dynamics of gate opening and also of configurational modulation of rate processes.²⁶ Another application of the present model could be to the area of cooperative dynamics in supercooled liquids near the glass transition. We hope to address these issues in future.

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