18.325 Final Project: CTRW study of Single-Molecule Spectroscopy

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Abstract

In this project, the continuous time random walk formalism is employed to model conformational fluctuations in single-molecule experiments. Specifically, the Scher-Lax model is applied to the random walks on the complex landscapes of energy states. The first-passage time distribution function is calculated to include geometric effects and non-diffusive scaling, which gives a generic interpretation of static disorders observed in recent quantum dot experiments. A four-state simple model of CTRW is formulated to consider the dynamic disorder and memory effects. For the exponential form of waiting-time distribution, it recovers the former work of multi-channel model.

In physical chemistry, traditional chemical kinetics assumes a clear separation of time scales. Under this assumption, the depletion from the reactant to the product is a Poisson process and the average population decays exponentially. However, in protein and glass system, chemical reactions are usually modulated by the geometric constraints, slow structural relaxation, hydrogen binding and complex network in aqueous systems. The competition between reaction process and the conformational dynamics leads to non-exponential kinetics and memory effects. Yet, conventional bulk measurement usually can not resolve the the conformational dynamics. In comparison, single-molecule measurements provide a unique probe of static and dynamical disorder in the environments. [2–6]

Advances in optical spectroscopy and microscopy have made it possible to directly measure the optical spectrum along single molecule trajectories and monitor the molecular dynamics and chemical kinetics of the simplest reactive system, a single molecule. [2–5] Early pioneering work was done by Moerner and co-workers in low temperature glasses. Recent progresses have extended the regime of single-molecule spectroscopy to room temperatures and biomolecules. New experiments can observe spectral fluctuations, translational and rotational diffusion motions, conformational dynamics. [5] These new experiments contain rich information that needs theoretical interpretations. Geva and Skinner used a stochastic two-level model to explain bi-exponential relaxation in these experiments. [14] Wang and Wolynes showed theoretical that the statistics of single reaction events exhibits intermittency and does not follow the Poisson law. [10] Onuchic and coworkers explored the possibility to use replica correlation functions along single-molecule trajectories to analyze the complex energy landscape. [12] Agmon introduced a diffusion model for the conformational cycle of a single working enzyme. [18]

Though much progresses has been made, it remains a challenge to quantify dynamic disorder. Inspired by a recent quantum dot experiment by M. Kuno and coworkers, I would like model the reaction kinetics by a general Scher-Lax model of continuous time random walk(CTRW) and try to explain the basics of the static and the dynamic disorders of single-molecule reactive systems. In Section I, I briefly review the diffusion controlled reaction model in various limit. In Section II, I solve a Scher-Lax model explicitly, and use the first-passage time to explain the power-law statistics observed by M. Kuno et al. [15] In Section III, I study the dynamic disorder with a CTRW model and show the memory effects induced by conformational dynamics. Then I briefly conclude and remark in section IV.

I. DIFFUSION MODEL

The diffusive reaction model was first introduced by Agmon and Hopfield to describe the ligand binding in myoglobin, later was analyzed by Zwanzig and elaborated by Wang and Wolynes. [7,8,10,11] The diffusion model describes a reactive system modulated by diffusive environmental variables, e.g., electron transfer in a sluggish solvent or in a fluctuating biomolecule.

In the diffusion model, the diffusion coordinate is described by the Smoluchowski operator

$$\hat{L}_D = \lambda\theta \frac{\partial}{\partial x}\left(\frac{\partial}{\partial x} + \frac{x}{\theta}\right), \tag{1}$$

where λ characterizes the relaxation time scale of the diffusive solvent, θ is the variance of the equilibrium distribution of the diffusion coordinate, and $\lambda\theta = D$ is the diffusion constant. The reaction rate $k(x)$ is related to the diffusion coordinate x by $k(x) = \kappa x^2$, with κ the proportionality coefficient, so that the survival probability satisfies

$$\frac{\partial}{\partial t} P(x,t) = -k(x)P(x,t) + \hat{L}_D P(x,t). \tag{2}$$

The corresponding Green's function is derived in Ref. [22], giving

$$G(x,y,t) = e^{-\frac{\lambda(s-1)t}{2}}\left[\frac{s}{2\pi\theta(1-e^{-2\lambda st})}\right]^{\frac{1}{2}} \exp\left[-\frac{s(x-ye^{-\lambda st})^2}{2\theta(1-e^{-2\lambda st})} + \frac{(s-1)(x^2-y^2)}{4\theta}\right], \tag{3}$$

where $s = \sqrt{1+4\kappa\theta/\lambda}$ represents the coupling of the two time scales associated with the diffusion and the rate processes. The equilibrium population obtained from $\hat{L}_D \rho_{eq}(x) = 0$ is a Gaussian function, $\rho_{eq}(x) = e^{-x^2/(2\theta)}/\sqrt{2\pi\theta}$.

The population at time t can be explicitly calculated with the above Green's function, yielding

$$P(t) = \int_{\infty}^{\infty} \int_{-\infty}^{\infty} G(x, y, t) \rho_{eq}(x) dx dy$$
$$= \exp[-\frac{\lambda}{2}(s-1)t][\frac{(s+1)^2 - (s-1)^2 e^{-2\lambda st}}{4s}]^{-\frac{1}{2}} \tag{4}$$

The occupancy time PDF, which can directly measured in single-molecule experiment, is related to $P(t)$ by

$$f(t) = -\frac{dP(t)}{dt} \tag{5}$$

Several limiting behavior of the above function is summarized as follows.

1. In the fast modulation limit, $\lambda \to \infty$, the distribution functions become

$$P(t) \longrightarrow \exp(-\kappa\theta t), \tag{6a}$$

$$f(t) \longrightarrow \kappa\theta \exp(-\kappa\theta t), \tag{6b}$$

   thus reducing to the single exponential kinetics with effective rate constant $k_{eff} = \kappa\theta$.

2. In the slow modulation limit, $\lambda \to 0$, the Green's function simplifies to

$$G(x, y, t) = \delta(x - y) \exp[-\kappa x^2 t]. \tag{7}$$

   Therefore, the event averaged distribution functions decay by power law,

$$P(t) \longrightarrow \frac{1}{(1 + 2\kappa\theta t)^{1/2}}, \tag{8a}$$
$$f(t) \longrightarrow \frac{\kappa\theta}{(1 + 2\kappa\theta t)^{3/2}}, \tag{8b}$$

   which is a result of inhomogeneous averaging of the rate distribution. The power-law line shape of the off-time distribution in the single quantum dot measurement may be interpreted as an inhomogeneous average of all possible kinetic pathways.

3. In the long time regime, $P(t)$ and $f(t)$, both decay exponentially as

$$P(t) \longrightarrow \frac{2\sqrt{s}}{s+1} \exp[-\frac{\lambda}{2}(s-1)t], \tag{9a}$$
$$f(t) \longrightarrow \frac{\lambda\sqrt{s}(s-1)}{s+1} \exp[-\frac{\lambda}{2}(s-1)t], \tag{9b}$$

   with the effective rate constant $k_{eff} = \lambda(s-1)/2$.

4. In the short time regime, direct expansion of the distribution functions to the first order in t leads to,

$$P(t) \longrightarrow 1 - \kappa\theta t + O(t^2), \tag{10a}$$

$$f(t) \longrightarrow \kappa\theta(1 - 3\kappa\theta t) + O(t^2), \tag{10b}$$

which predict the initial decay due to the reaction and the diffusion processes.

II. THE SCHER-LAX CONTINUOUS TIME RANDOM WALK MODEL

The Scher-Lax model generalizes the Montroll-Weiss continuous time random walk to include the spatial dependence of waiting-time distributions. [1] In the single-molecule fluorescence measurement, we may model the bright and dark states as ensembles of conformational states, which depend on the local energy landscapes of the bright and dark states. The single molecule performs random walks in the ensemble of conformational states while staying in the bright (dark) state. The "blinking" events are therefore associated with the passages between the bright and the dark states. We assume only one pathway connecting the bright and the dark states, which is of course not exactly right in real cases. Later I will show that this assumption is related to the static disorder limit. In the Scher-Lax model, if the walker arrives at site x' at time t', the probability that his next step is to site x from x' and occur at time $t' + t$ is given by the density function $\psi(x|x', t)$. The Montroll-Weiss walk is recovered in the special case where $\psi(x|x', t) = p(x|x')\psi(t)$. This factorization generally does not hold in the Scher-Lax model. The probability that the walker remains at site x' for time t at least and then steps to site x is then formulated as

$$\phi(x|x', t) = \int_t^\infty \psi(x|x', t)dt. \tag{11}$$

While the probability that the walker pauses at site x' for at least time t is

$$\phi(x', t) = \sum_x \phi(x|x', t). \tag{12}$$

Similarly we can define the waiting time density at site x' as the summation of the PDF to all other sites.

$$\psi(x', t) = \sum_{x} \psi(x|x', t), \tag{13}$$

then, we may define $\chi(x|x', t)$, the conditional probability that a walker at site x' steps to site x, given that his waiting time for the step is t,

$$\psi(x|x', t) = \chi(x|x', t)\psi(x', t), \tag{14}$$

Similarly, the step distribution can defined as

$$\phi(x|x', t) = \int_{0}^{\infty} \psi(x|x', t)dt, \tag{15}$$

and we can rewrite $\psi(x|x', t)$ as

$$\psi(x|x', t) = p(x|x')\psi(t|x, x'), \tag{16}$$

where $\psi(t|x, x')$ is the conditional probability density function for the waiting time t, given that the walker steps from site x' to x. we can use $p(x|x_0, t)$ to represent the site occupancy probability at site x and time t if the walk started at site x_0 at time 0. The first passage time density, denoted by $f(x|x_0, t)$, therefore is coupled to the site occupancy probabilities by

$$p(x|x_0, t) = \delta_{xx_0}\phi(x_0, t) + \int_{0}^{t} f(x|x_0, \tau)p(x|x, t-\tau)d\tau. \tag{17}$$

The Laplace transform of the above relation yields

$$\hat{p}(x|x_0, s) = \delta_{xx_0}\hat{\phi}(x_0, s) + \hat{f}(x|x_0, s)\hat{p}(x|x, s). \tag{18}$$

Therefore the first passage time can be deduced once we find the site occupancy probabilities.

At time t either the walker has never left the starting site, or he has made at least one step, and in the latter case we may partition all his possible motions over the outcome and time of occurrence of his first step. Thus

$$p(x|x_0,t) = \delta_{xx_0}\phi(x_0,t) + \sum_x \int_0^t p(x|x,t-\tau)\psi(x|x_0,\tau)d\tau, \tag{19}$$

in terms of Laplace transforms it becomes

$$\hat{p}(x|x_0,s) = \delta_{xx_0}\hat{\phi}(x_0,s) + \sum_x \hat{\psi}(x|x_0,s)\hat{p}(x|x,s). \tag{20}$$

In general, the site x can be a position vector in any geometry. To simplify the discussion, we only consider a translational invariant system, where $p(x|x_0,t) = p(x-x_0,t)$. Furthermore, we define the start position x_0 as the origin. Eq. (20) can be simplified from these assumptions as

$$\hat{p}(x,s) = \delta_{x0}\frac{1-\hat{\psi}(0,s)}{s} + \sum_{x'} \hat{p}(x-x',s)\psi(x',s), \tag{21}$$

where the relation $\hat{\phi}(x,s) = (1-\hat{\psi}(x,s))/s$ is applied. The Fourier transform of the spatial coordinates gives

$$\tilde{\hat{p}}(\vec{k},s) = \frac{1-\hat{\psi}(0,s)}{s} + \tilde{\hat{p}}(\vec{k},s)\tilde{\hat{\psi}}(\vec{k},s). \tag{22}$$

The Laplace transform of the waiting time density in Eq. (13) gives $\tilde{\hat{\psi}}(\vec{0},s) = \sum_x \hat{\psi}(x|x',s) = \hat{\psi}(0,s)$, which, combined with Eq. (22) leads to the expression of $\tilde{\hat{p}}(\vec{k},s)$,

$$\tilde{\hat{p}}(\vec{k},s) = \frac{1-\tilde{\hat{\psi}}(\vec{0},s)}{s(1-\tilde{\hat{\psi}}(\vec{k},s))}. \tag{23}$$

We can assume $\tilde{\hat{\psi}}(\vec{k},s)) \sim 1-s^\beta - s^{\beta-m}|\vec{k}|^\alpha$ in the small s and $|\vec{k}|$ limit, where β characterizes the scaling, and m denotes the time dependence in diffusion constant. [21] The site occupancy probability function at the origin can be estimated as

$$\hat{p}(0,s) \propto s^{m-1}\frac{1}{(2\pi)^d}\int \frac{k^{d-1}dk}{s^m + k^\alpha}, \tag{24}$$

where d is the dimensionality of the system under study. Evaluation of the integral leads to

$$\hat{p}(0,s) \propto s^{-1+\frac{m}{\alpha}d}. \tag{25}$$

From the Tauberian theorem for Laplace transforms, we can deduce the asymptotic behavior of $p(0,t)$ for large t,

$$p(0,t) \propto t^{-\frac{m}{\alpha}d}. \tag{26}$$

Similarly asymptotic estimation can be obtained for the first-passage time as well, explicit calculation shows that

$$\hat{f}(0,s) \sim 1 - s^{\beta - \frac{m}{\alpha}d}, \tag{27}$$

therefore $f(0,t)$ is asymptotically a Lévy distribution,

$$f(0,t) \sim l_{\beta - \frac{m}{\alpha}d}(t), \tag{28}$$

which relates the power of the time distribution to the dimensionality and the scaling of the random walk. In general, the scaling may be diffusive, sub-diffusive, super-diffusive or even ballistic. In the special case of diffusive motion in a one-dimensional lattice with fixed diffusion constant, $\alpha = 2$, $\beta = 1$, $m = 1$, and $d = 1$, the long time asymptotic distribution of the first-passage time is

$$f(0,t) \sim t^{-\frac{3}{2}}. \tag{29}$$

For the subdiffusive and superdiffusive motion on one-dimensional lattics with fixed diffusion constant, $\alpha = 2$, $m = 1$, and $d = 1$, the first-passage time scales

$$f(0,t) \sim t^{-(\beta + \frac{1}{2})}. \tag{30}$$

Fro the discussion of Scher-Lax model, I have generalized the power-law spectrum of the first-passage time to include dimensional effects and non-diffusive scaling.

III. FOUR-STATE CTRW MODEL AND DYNAMIC DISORDER

Modulated reaction models have been used for analyzing the fluctuating environment and its effects on chemical kinetics since a long time ago. Early examples include a series of papers by Hynes [16,17] on the influence of solvant relaxation on the reaction rate constant and Agmon-Hopfield model [7] for ligand binding to myoglobin. A recent application is the analysis of Xie's single enzyme turnover experiment. [4,18,19,22] Here I only consider a model consisting of two reaction channels connecting four states. As shown in Fig. 3, each reaction channel is associated with a forward reaction rate $k_{1,f}$ and a backward reaction rate $k_{1,b}$. The conformational dynamics is represented by the inter-conversion waiting-time distribution $\psi(t)$. We can denote $\phi(t)$ as

$$\phi(t) = \int_t^\infty \psi(\tau) d\tau. \tag{31}$$

Then $\phi(t)\exp(-k_{1,f}t)$ is the overall probability that the single molecule pauses at site A_1 for at least time t given that it arrives at site A_1 at time 0. The conditional waiting-time distribution defined in the previous section can be written as

$$\psi(B_1|A_1,t) = k_{1,f} e^{-k_{1,f}t}\phi(t), \tag{32}$$

$$\psi(A_2|A_1,t) = e^{-k_{1,f}t}\psi(t), \tag{33}$$

$$\psi(B_2|A_2,t) = k_{2,f} e^{-k_{2,f}t}\phi(t), \tag{34}$$

$$\psi(A_1|A_2,t) = e^{-k_{2,f}t}\psi(t). \tag{35}$$

For simplicity, I assume the same waiting-time distribution $\psi(t)$ for conformational dynamics in both bright and dark states. The probability $g_{ij}^{(f)}(t)$ represents the probability that the single molecule is at state i at time t while keeping in the bright states, given that it arrvies at state j at time 0. It is clear that $g_{ij}^{(f)}(t)$ includes various number of detours between two bright states, for example, $g_{11}^{(f)}(t)$ can be written as

$$\begin{aligned} g_{11}^{(f)}(t) = \phi(B_1|A_1,t) + \int_0^t d\tau_1 \int_0^{t-\tau_1} d\tau_2 \phi(B_1|A_1,t-\tau_1-\tau_2)\psi(A_1|A_2,\tau_1)\psi(A_2|A_1,\tau_2) \\ + \cdots \end{aligned} \tag{36}$$

The Laplace transform of $g_{11}^{(f)}(t)$ is therefore

$$\hat{g}_{11}^{(f)}(s) = \frac{\hat{\phi}(B_1|A_1,s)}{1-\hat{\psi}(A_1|A_2,s)\hat{\psi}(A_2|A_1,s)}. \tag{37}$$

Similarly $\hat{g}_{12}^{(f)}(s)$, $\hat{g}_{21}^{(f)}(s)$ and $\hat{g}_{22}^{(f)}(s)$ can be formulated explicitly as

$$\hat{g}_{12}^{(f)}(s) = \frac{\hat{\phi}(B_1|A_1,s)\hat{\psi}(A_1|A_2,s)}{1-\hat{\psi}(A_1|A_2,s)\hat{\psi}(A_2|A_1,s)}, \tag{38}$$

$$\hat{g}_{21}^{(f)}(s) = \frac{\hat{\phi}(B_2|A_2,s)\hat{\psi}(A_2|A_1,s)}{1-\hat{\psi}(A_2|A_1,s)\hat{\psi}(A_1|A_2,s)}, \tag{39}$$

$$\hat{g}_{22}^{(f)}(s) = \frac{\hat{\phi}(B_2|A_2,s)}{1-\hat{\psi}(A_2|A_1,s)\hat{\psi}(A_1|A_2,s)}. \tag{40}$$

Therefore the forward propagator is

$$\hat{G}(s) = \frac{1}{1-\hat{\psi}(s+k_{1,f})\hat{\psi}(s+k_{2,f})} \begin{pmatrix} \hat{\phi}(s+k_{1,f}) & \hat{\phi}(s+k_{1,f})\hat{\psi}(s+k_{2,f}) \\ \hat{\phi}(s+k_{2,f})\hat{\psi}(s+k_{1,f}) & \hat{\phi}(s+k_{2,f}) \end{pmatrix} \tag{41}$$

The single event distribution function of on-time, $f(t)$, is given by

$$f(t) = \sum K^{(f)} G^{(f)}(t) \begin{pmatrix} f_{A_1}^{eq} \\ f_{A_2}^{eq} \end{pmatrix}, \tag{42}$$

where $f_{A_i}^{eq}$ denotes the equilibrium flux from the dark states to the bright states, and $K^{(f)}$ denotes the forward reaction rate matrix.

$$K^{(f)} = \begin{pmatrix} k_{1,f} & 0 \\ 0 & k_{2,f} \end{pmatrix}. \tag{43}$$

The backward rate matrix is defined in the same fashion. The two-event distribution function of on-time, $f(t_2, t_1)$, is defined by

$$f(t_2,t_1) = \sum K^{(f)} G^{(f)}(t_2) K^{(b)} \hat{G}^{(b)}(0) G^{(f)}(t_1) \begin{pmatrix} f_{A_1}^{eq} \\ f_{A_2}^{eq} \end{pmatrix}, \tag{44}$$

which can be used to analyze the memory effect. If there is no memory, i.e., no dynamic disorder, $f(t_2,t_1) = f(t_2)f(t_1)$, therefore $\langle t_2 t_1 \rangle = \langle t_2 \rangle \langle t_1 \rangle$. To further simplify the model, I assume the forward and the backward rates are the same in each reaction channel, i.e., $k_{1,f} = k_{1,b} = k_1$ and $k_{2,f} = k_{2,b} = k_2$. Therefore the equilibrium population will be equally distributed in four sites due to symmetry argument. Then, the equilibrium fluxes to the bright states are

$$\begin{pmatrix} f_{A_1}^{eq} \\ f_{A_2}^{eq} \end{pmatrix} = \begin{pmatrix} \frac{k_1}{k_1+k_2} \\ \frac{k_2}{k_1+k_2} \end{pmatrix}. \tag{45}$$

In the case that there is only one reaction channel, for example, $k_2 = 0$, the equibilrium flux $f_{A_2} = 0$, and $f_{A_1} = 1$. Explicit calculation shows that

$$f(s_2, s_1) = f(s_2)f(s_1), \tag{46}$$

Therefore

$$\begin{aligned}\langle t_2 t_1\rangle &= \int\int t_1 t_2 f(t_2, t_1) dt_1 dt_2 \\ &= \frac{\partial}{\partial s_2}|_{s_2=0}\frac{\partial}{\partial s_1}|_{s_1=0}\hat{f}(s_2, s_1) \\ &= \langle t_1\rangle\langle t_2\rangle,\end{aligned} \tag{47}$$

which means no memory will be observed in the case of one reaction channel. Thus, the one-channel model only considers the static disorder. In the simple case when $\psi(t) = \gamma\exp(-\gamma t)$, the forward propagator is exactly the same the result in Ref. 19. The on-time distribution of two events $f(t_2, t_1)$ and $f(t_1)$ can be explicitly calculated. The difference function $\delta(t_2, t_1) = f(t_2, t_1) - f(t_2, t_1)$ is plotted in the diagonal direction in Fig. 3. The two-event echo is found at $2/(k_s + \gamma)$ where $k_s = (k_1 + k_2)/2$ is the average rate, exactly the same as the results in Ref. 21.

Therefore the continuous time random walk model at least provides an alternative approach to modulated reaction model. Furthermore, the waiting-time distribution may include non-exponential functional forms with long-time tails, which is extremely meaningful for conformational dynamics.

IV. BRIEF CONCLUSION AND REMARKS

I hereby conclude that the continuous time random walk model with spatial dependant waiting-time distrbitution is a good model to study the conformational dynamics in single-molecule measurements. Conformations of biomolecule in general are complicated energy states, which can not always modeled by single kinetic cheme. Environmental fluctuations, especially in room temperature, faciliate the crossing of energy barrier on complex energy landscapes. The waiting-time distribution ignores the details of the barrier crossing while keeping the correct scaling; therefore gives a simplified phenomelogical description of complicated dynamics.

However, the problem of dynamic disorders has not been completely solved. How to decouple the conformational dynamics from the reaction scheme and directly obtain the functional form of the waiting-time distribution is still unclear. Further theoretical work is still necessary to clarify the decouple mechanism and to explicitly detect the dynamic disorder.

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FIGURES

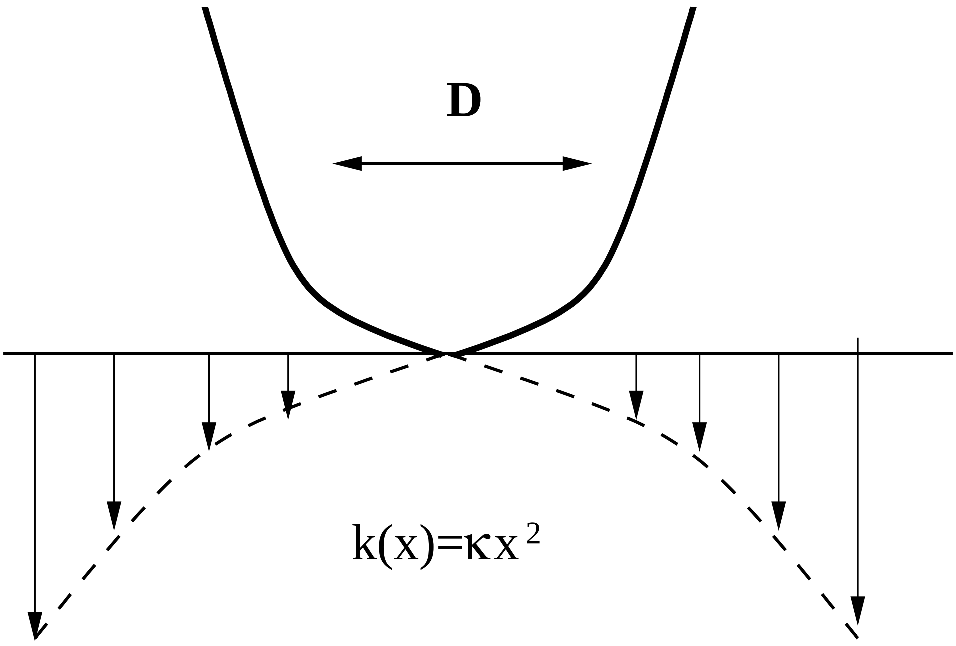

FIG. 1. The diffusion controlled reaction scheme. The reaction rate $k = \kappa x^2$ quadratically depends on the diffusion coordinate x.

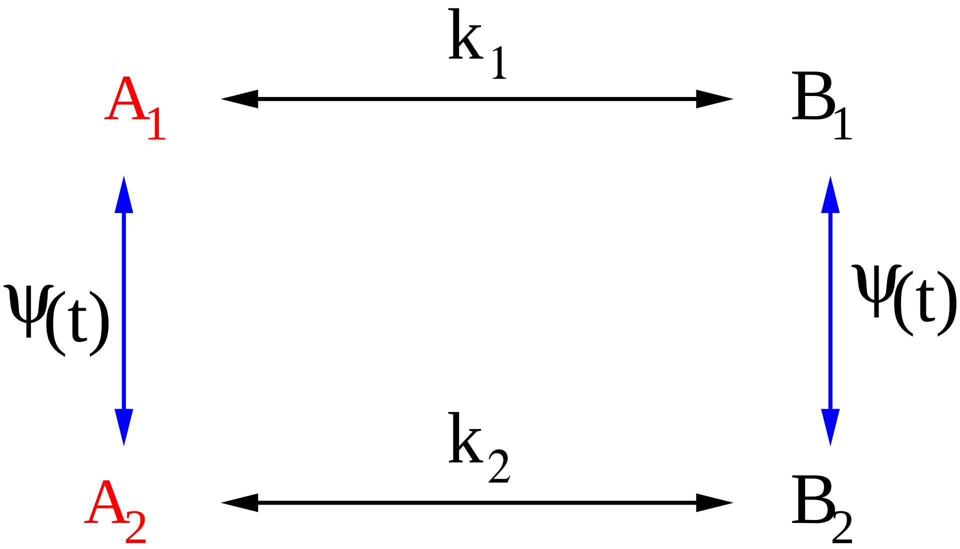

FIG. 2. The two-channel reaction scheme with four states. $\psi(t)$ is the waiting-time distribution characterizes the conformational fluctuations.

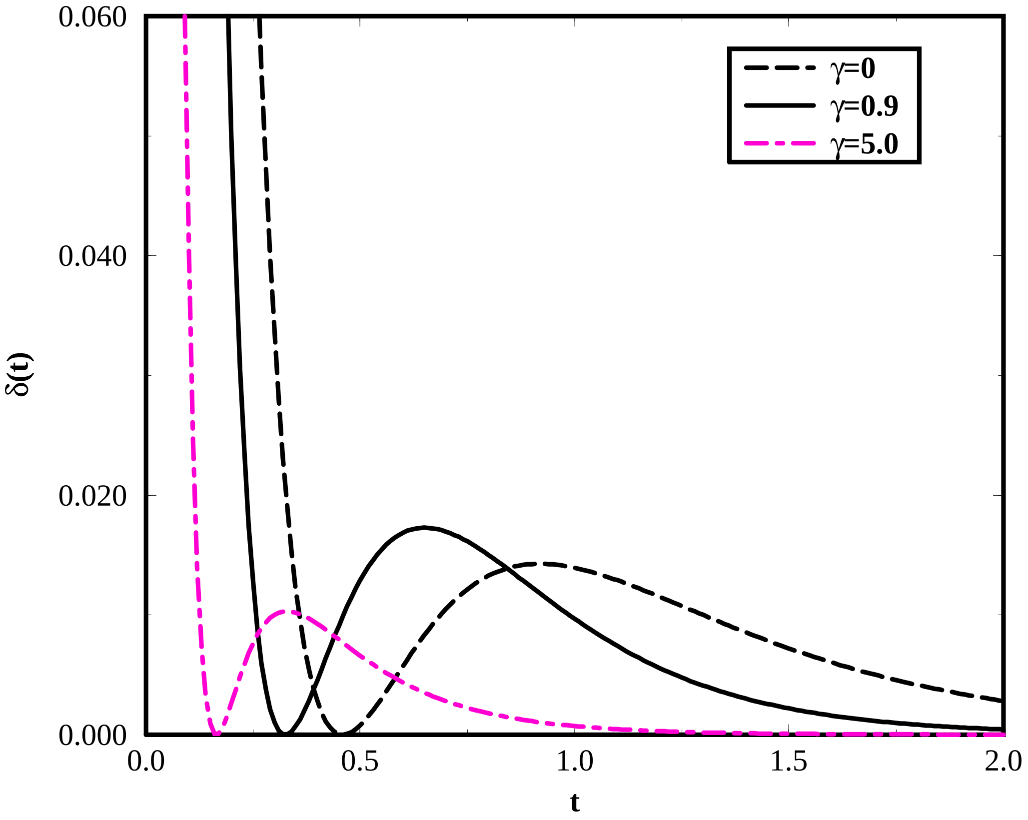

FIG. 3. The same-time difference function in the two-channel model when $k_1 = 1$, and $k_2 = 4$. A two-event echo is reached at time $2/(k_s + \gamma)$, as predicted in Ref. 21 . The echo time decreases as the modulation rate γ increases.