

## Kramers model with a power-law friction kernel: Dispersed kinetics and dynamic disorder of biochemical reactions

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Kramers' model for the rate of chemical reaction is generalized to explain the phenomena of dispersed kinetics and dynamic disorder in biochemical reactions, by incorporating the newly observed power-law friction kernel into the generalized Langevin equation for a one-dimensional reaction ordinate. This new model accounts for time scale overlap between conformational and chemical dynamics, and quantitatively describes the multi-exponential kinetics and memory effects of fluctuating rate constants, which have been revealed by recent single-molecule experiments.

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Proteins are complex systems with many degrees of freedom and motions on a wide range of time scales, hence their biological reactions often exhibit dispersed kinetics and dynamic disorder [1]. Dispersed kinetics refers to multi-exponential behaviors associated with heterogeneity, as was revealed in ensemble studies by Frauenfelder and coworkers on rebinding of CO to hemoproteins upon photodissociation [2]. Dynamic disorder refers to fluctuations of rate constants, which were inferred from ensemble studies [2] and have been directly observed by recent single molecule experiments [3]. In particular, enzymatic rate constants of single molecules are found to exhibit large-amplitude fluctuations over a broad range of time scales ( $10^{-3}$  to 10 s) [3]. Meanwhile, conformational fluctuations within a single protein have been recently observed at time scales comparable to and slower than the reaction time scale, which can be described well by a generalized Langevin equation (GLE) with a power law friction kernel [4,5]. However, the underlying connection between fluctuations in protein conformation and those in reaction rate constants, which coincide in time scales, is not well understood. Here we theoretically address the effect of conformational fluctuations on dispersed kinetics and dynamic disorder of biochemical reactions.

Dispersed kinetics and dynamic disorder has been the subject of intensive theoretical investigations [6–8]. Zwanzig discussed two approaches in his comprehensive review [7]. The first approach assumes the fluctuating rate constant is phenomenologically dependent on a time-varying control parameter, such as the activation barrier height [6] or the area of the bottleneck [7]. Although this approach is conceptually straightforward, the control parameters are usually not experimentally accessible. As a result, their dynamics is often assumed empirically on an *ad hoc* basis, for example, Brownian motion governed by Langevin dynamics. The second one assumes a kinetic scheme involving multiple discrete conformational states with different rate constants. However, there is often no sufficient information about the kinetic parameters or the connection topology among the

multiple states [9]. Here we seek for an alternative reaction rate theory based on a GLE.

Recent experiments on equilibrium conformational fluctuations within single protein molecules, such as fluorescein antibody [4] and flavin reductase [5], showed that the distance fluctuation between an electron donor and an acceptor is a Gaussian non-Markovian process, which can be well described by one-dimensional GLE [10]:

$$m \frac{d^2 x(t)}{dt^2} = -\zeta \int_0^t d\tau K(t-\tau) \frac{dx(\tau)}{d\tau} - \frac{dU(x)}{dx} + F(t), \quad (1)$$

where  $x(t)$  is the donor acceptor separation,  $m$  is the reduced mass moving in a potential of mean force  $U(x)$ , and  $F(t)$  is the random fluctuating force originating from bath thermal motion. Friction kernel  $K(t)$  is related to  $F(t)$  by fluctuation-dissipation theorem

$$\langle F(t)F(\tau) \rangle = k_B T \zeta K(t-\tau). \quad (2)$$

The friction constant,  $\zeta$ , reflects the interaction strength between system and bath [10].

For equilibrium fluctuation [4,5],  $U(x)$  was often determined to be a harmonic potential,  $F(t)$  is proved to be a Gaussian noise, and  $K(t)$  is determined to be a power law decay over at least four decades of timescales ( $10^{-3}$  to 10 s),

$$K(t-\tau) = 0.75 |t-\tau|^{-0.5} \quad (3)$$

This friction kernel has been observed for two different systems, fluorescein antibody [4] and flavin reductase [5] from sub-milliseconds to tens of seconds. A similar power-law kernel has also been inferred from MD simulations on lysozyme around a nanosecond time scale [11]. The microscopic origin has been investigated theoretically in terms of polymer dynamics [12](a) and the fractal nature of protein [12](b), respectively. All these studies have suggested the power law friction kernel could be a general description for protein dynamics for a wide range of time scales. Our premise is that the same friction kernel might hold for the reaction coordinate in Kramers' model for protein reactions.

The celebrated Kramers' theory models chemical reaction as thermally activated crossing of a barrier [13]. Specifically,  $U(x)$  was assumed to be an inverted parabola connecting

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harmonic wells, and  $F(t)$  to be white noise with a delta function  $K(t)$ . As an important extension, Grote and Hynes employed a GLE for the Kramers problem, in which  $F(t)$  is treated as colored noise, reflecting a realistic bath with finite relaxation times [14]. However, because a clear separation of time scales is assumed at the onset, namely, the relaxation of the reaction coordinate is always fast compared to the reaction time scale [15], both Kramers and Grote-Hynes theories give a well-defined rate constant, and therefore cannot account for dispersed kinetics or dynamic disorder. Such a clear separation of time scale is no longer true for proteins, which are sluggish systems as demonstrated by the fluctuation observed at the slow and broad range of time scales [4,5].

In this Rapid Communication, we provide a quantitative model for dispersed kinetics and dynamic disorder in the framework of barrier crossing dynamics. To do so, we incorporate the power law friction kernel, Eq. (3), into Eq. (1), and take  $U(x)$  to be an inverted parabola connecting two harmonic wells, Fig. 2(a). Note that the barrier height does not fluctuate with time, which is different from the theory assuming the barrier height as a fluctuating control parameter [6]. Instead, the fluctuation is introduced into  $F(t)$  in a self-consistent way, satisfying the fluctuation dissipation theorem.

This model offers several appealing features. First, the use of GLE formalism is based on the Hamiltonian of the system-bath interaction, rather than *ad hoc* assumptions. Secondly, a one-dimensional description, though simple, makes the complex many-body problem tractable. Thirdly, compared with Kramers' theory, the description only introduces one more parameter: the power law friction kernel.

We carry out stochastic simulations using a sampling algorithm for  $F(t)$  based on a circulant matrix method that was designed for the simulation of fractional Gaussian noise, which has a characteristic power law autocorrelation function [16]. As a check on the sampling algorithm,  $\langle F(t)F(\tau) \rangle$  is computed from a simulated  $F(t)$  trace, and is in good agreement with  $t^{-1/2}$ , as shown in Fig. 1(a). With the simulated  $F(t)$  trace, the GLE is readily integrated in time to give the progression of dynamics using standard algorithms.  $m=1$ ,  $k_B T=1$ , and all the times are given in units of  $1/\omega_a$ . The integration step size has been chosen to be 0.1 time units for stability reasons. In the overdamped limit where acceleration can be neglected, Eq. (1) reduces to

$$\frac{dU(x(t))}{dx} = - \int_0^t d\tau M(t-\tau) \frac{dx(\tau)}{d\tau} + F(t) \quad (4)$$

To validate the GLE simulation, we compute  $x(t)$  dynamics within a harmonic well (without the inverted parabola) using Eq. (4) and then compare the simulation with the analytical result derived in Ref. [4]:

$$C_x(t) \equiv \langle x(0)x(t) \rangle = (k_B T / m\omega_a^2) e^{t/t_0} \operatorname{erfc}(\sqrt{t/t_0}) \quad (5)$$

where  $t_0 \equiv (\Gamma(5/2)\zeta/m\omega_a^2)^2$  is a characteristic time scale of the system, and  $\Gamma$  is the gamma function,  $\operatorname{erfc}$  is the complementary error function. As shown in Fig. 1(b), the simulated  $C_x(t)$  agrees well with Eq. (5) ( $\zeta=1$  and  $t_0=1.8$ ), proving the validity of our simulation. It is important to note that, though

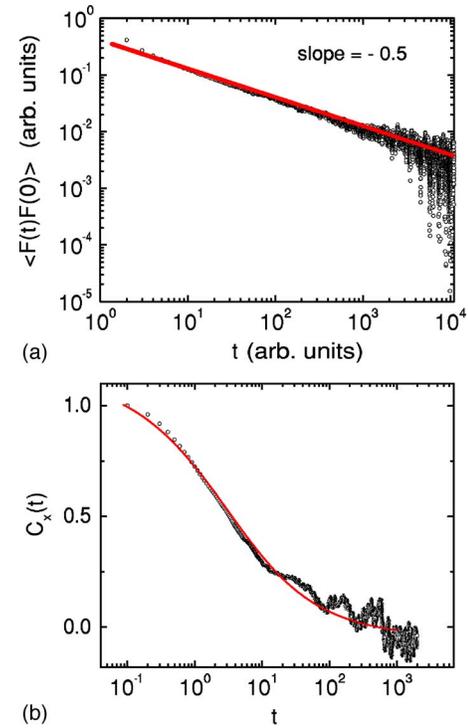


FIG. 1. (Color online) (a) Autocorrelation function  $\langle F(t)F(0) \rangle$  (open circle) of  $F(t)$  simulated by the circulant matrix method described in Ref. [16], overlaid with a power law decay  $t^{-1/2}$  (solid curve in red). (b)  $C_x(t)$  (open circle) calculated from a simulated  $x(t)$  trajectory undergoing diffusion in a harmonic potential with  $\zeta=1$ , overlaid with  $C_x(t) = (k_B T / m\omega_a^2) e^{t/t_0} \operatorname{erfc}(\sqrt{t/t_0})$  (solid curve in red) with  $t_0 \equiv (\Gamma(5/2)\zeta/m\omega_a^2)^2 = 1.8$ . The good agreement with the analytical expression proves the reliability of the GLE simulation.

the fluctuation of  $x(t)$  spans over multiple time scales, it is roughly controlled by  $t_0$  through Eq. (5). The stronger the system-bath coupling strength  $\zeta$ , the slower the  $x(t)$  relaxes, for fixed  $m\omega_a^2$ .

We now set out to simulate dispersed kinetics and dynamic disorder, which is often manifested in the waiting time distribution and the correlation function of waiting times in an enzymatic turnover time trace. Single molecule experiments showed that the former exhibits multi-exponential decay, and the latter fluctuates over a broad range of time scales, displaying a strong “memory effect” [3].

We first calculate the waiting time distribution  $f(t)$  for barrier crossing in the double well potential, which has a barrier height  $E_a$ , well frequency  $\omega_a$ , and barrier frequency  $\omega_b$  ( $\omega_b=1$ ), shown in Fig. 2(a). The initial conditions of  $x$  are drawn from Boltzmann distribution. As the trajectory is propagated from the reactant well, a waiting time is recorded when  $x(t)$  crosses over the bottom of the product well. 10 000 independent trajectories were sampled to give a smooth  $f(t)$  distribution. The simulation was done for not too large  $E_a=2k_B T$ , with which sufficient events of barrier crossing can be achieved with reasonable computational efforts.

As shown in Fig. 2(b),  $f(t)$  is monoexponential for small coupling strength. This corresponds to a well defined rate constant described in Kramers-Grote-Hynes theory. However,  $f(t)$  becomes multi-exponential at large coupling

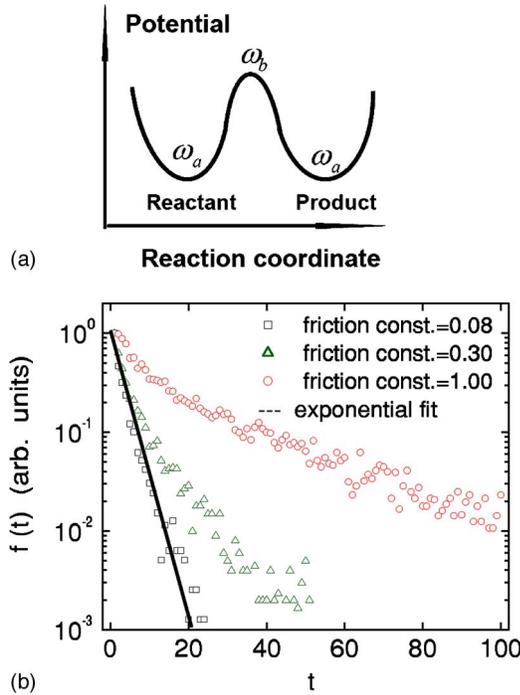


FIG. 2. (Color online) (a) Symmetric double well potential with well frequency  $\omega_a$ , barrier frequency  $\omega_b$ , and barrier height  $E_a$  for simulations of barrier crossing. (b) Waiting time distribution  $f(t)$  (normalized by their first points) for three friction constants  $\zeta=0.08, 0.30$  and  $1.00$ , respectively.  $f(t)$  for small  $\zeta=0.08$  can be fitted well by a mono-exponential decay (solid curve).  $f(t)$  for large  $\zeta=1.00$  displays multi-exponential decay, indicating dispersed kinetics.

strength, indicating dispersed kinetics. Specifically, the reaction time scale  $\tau_R$  is calculated from the first moment of  $f(t)$ ,  $\tau_R \equiv \int_0^\infty t f(t) dt$ ,  $\tau_R \sim 3, 4$ , and  $10$  for  $\zeta=0.08, 0.3$  and  $1.0$ , respectively. Meanwhile, as discussed before,  $t_0 \equiv (\Gamma(5/2)\zeta/m\omega_a^2)^2$  roughly sets the system's characteristic time scale,  $t_0=0.01, 0.07$ , and  $1.8$  for  $\zeta=0.08, 0.3$ , and  $1.0$ , respectively. It is evident from Fig. 2(b) that a clear time scale separation  $t_0 \ll \tau_R$  results in single exponential  $f(t)$ , while time scale overlap  $t_0 \sim \tau_R$  leads to multiexponential  $f(t)$ , the signature of dispersed kinetics.

To highlight the lack of time-scale separation, we calculate time-dependent transmission coefficient  $\kappa(t)$  according to the reactive flux formalism [17], which samples reaction events by starting trajectories directly on the top of the barrier:

$$\kappa(t) = \frac{\langle \delta(x(0) - x^\ddagger) \dot{x}(0) \theta(x(t) - x^\ddagger) \rangle_\#}{\langle \delta(x(0) - x^\ddagger) \dot{x}(0) \theta(x(0) - x^\ddagger) \rangle_\#} \quad (6)$$

where  $\langle \dots \rangle_\#$  specifies an average with  $x$  constrained to the transition state  $x^\ddagger$ , and  $\theta(x(t) - x^\ddagger)$  is a step function that equals 1 when  $x(t) > x^\ddagger$  and is 0 otherwise. Eq. (6) is based on Onsager's regression hypothesis, which is always true regardless whether there is a clear time scale separation. As before,  $E_a=2k_B T$  and  $\omega_b=1$ . The initial velocities  $\dot{x}(0)$  are sampled from the Maxwell distribution. Three  $\kappa(t)$  for

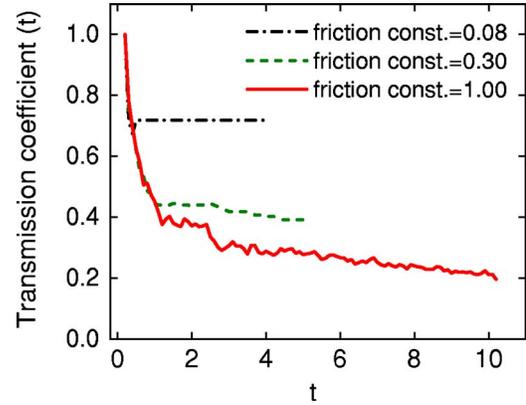


FIG. 3. (Color online) Time-dependent transmission coefficient  $\kappa(t)$  evaluated by reactive flux formalism for  $\zeta=0.08, 0.30$ , and  $1.00$ , respectively.  $\kappa(t)$  exhibits a plateau in  $\zeta=0.08$ . However, due to time scale overlap  $t_0 \sim \tau_R$  in  $\zeta=1.00$ ,  $\kappa(t)$  keeps decaying and does not reach a plateau before the reaction time scale. The absence of a plateau indicates the lack of a well-defined rate constant, leading to dispersed kinetics and dynamic disorder.

$\zeta=0.08, 0.3$ , and  $1.0$  are averaged over 1000 independent trajectories, and propagated up to their corresponding reaction time scales  $\tau_R \sim 3, 4$ , and  $10$ , respectively (Fig. 3).

In case of time scale separation between  $t_0(=0.01)$  and  $\tau_R(=3)$  for  $\zeta=0.08$ , after a transient relaxation at short times,  $\kappa(t)$  decays rapidly and reaches a plateau value  $\kappa_0$ , which represents the fraction of crossings of the transition state that are productive. In this case, the phenomenological rate constant  $k$  is well defined as  $k = \kappa_0 k^{TST}$  where  $k^{TST}$  is the transition state theory result [15]. However, in the case of time scale overlap between  $t_0(=1.8)$  and  $\tau_R(=10)$  for  $\zeta=1.0$ ,  $\kappa(t)$  keeps decaying and does not reach a plateau on any time scales faster than the reaction time scale  $\tau_R$ . The absence of a plateau value clearly demonstrates that there does not exist a well-defined rate constant, indicating the breakdown of time scale separation in Kramers-Grote-Hynes theories and the emergence of dispersed kinetics and dynamic disorder in biochemical reactions.

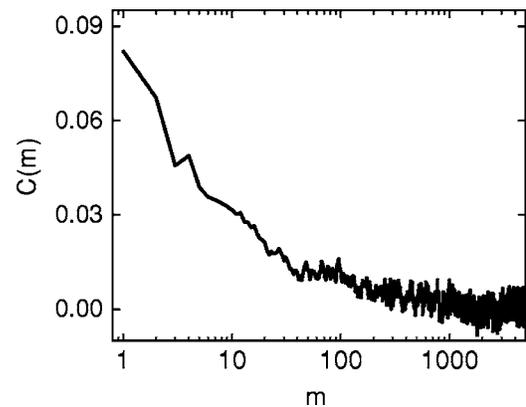


FIG. 4. Autocorrelation function  $C(m) = \langle \Delta\tau(0)\Delta\tau(m) \rangle / \langle \Delta\tau^2 \rangle$  of a simulated trajectory consisting of 10 000 consecutive turnovers.  $\Delta\tau(m) \equiv \tau(m) - \langle \tau \rangle$ ,  $\tau$  is the waiting time and  $m$  is the turnover index number.  $E_a=0.1k_B T$ ,  $\zeta=1$ . The waiting time correlations span over a broad range of time scales, resembling the memory effect reported in Ref. [3].

We now discuss dynamic disorder unraveled in recent single-enzyme turnover experiments: the autocorrelation function of waiting times of a single enzyme turnover trajectory decays over a broad range of times ( $10^{-3}$  to  $10$  s) [3]. Although such a single-molecule “memory effect” is beyond the conventional reaction rate theory, it can be naturally explained by our model when  $t_0 \sim \tau_R$  or  $t_0 > \tau_R$ . The consecutive enzymatic turnover trajectory is simulated by first starting a trajectory from the reactant well, and then repetitively resetting  $x$  back to its initial Boltzmann distribution in the reactant well when  $x(t)$  reaches the bottom of the product well. Such an instantaneous reset of  $x$  is to mimic the cyclic enzymatic turnovers. Importantly, during the resetting process,  $F(t)$  evolves continuously in time according to Eqs. (2) and (3), giving rise to the memory effect. This is the picture of how slow conformational fluctuations modulate the long time memory of enzymatic reaction. Figure 4 depicts the autocorrelation function  $C(m)$  of waiting times  $\tau(m)$  from a simulated 10 000 turnovers trajectory,  $C(m) = \langle \Delta \tau(0) \Delta \tau(m) \rangle / \langle \Delta \tau^2 \rangle$ , as a function of  $m$ , the turnover index number, and  $\Delta \tau(m) \equiv \tau(m) - \langle \tau \rangle$ .  $C(m) = 0$  should hold for  $m > 0$  in the case of no rate fluctuation. The multi-exponential decay of  $C(m)$  over three decades of time scales is shown in Fig. 4, which resembles the experimental results [3].

The simulations above are performed for a low energy barrier due to the limit of computation time. However, as we have shown, the emergence of dispersed kinetics and dynamic disorder only depends on the overlap of time scales  $t_0$  and  $\tau_R$ , which is also true for high barriers. In measurements of protein conformational dynamics,  $t_0$  is determined to be  $\sim 0.9$  sec for fluorescein antibody [4], and  $\sim 0.07$  s for flavin reductase [5]. Meanwhile,  $\tau_R$  on which enzymatic reactions normally occur is around  $10^{-4}$ – $10$  sec [18]. This time scale overlap between  $t_0$  and  $\tau_R$  corroborates multi-exponential kinetics and memory effect, as observed in single enzyme turnover experiments [3].

The incorporation of the experimentally determined power-law friction kernel into the GLE description of barrier crossing dynamics naturally accounts for multi-exponential waiting time distribution and multi-time-scale waiting time correlations. The observed dispersed kinetics and dynamic disorder are not due to the fluctuation of barrier heights but rather due to the conformational dynamics occurring on a wide range of time scales at which the assumption of time scale separation between conformational dynamics and enzymatic reactions breaks down.

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