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Kinetics of molecular transitions with dynamic disorder in single-molecule pulling experiments

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Macromolecular transitions are subject to large fluctuations of rate constant, termed as dynamic disorder. The individual or intrinsic transition rates and activation free energies can be extracted from single-molecule pulling experiments. Here we present a theoretical framework based on a generalized Langevin equation with fractional Gaussian noise and power-law memory kernel to study the kinetics of macromolecular transitions to address the effects of dynamic disorder on barrier-crossing kinetics under external pulling force. By using the Kramers' rate theory, we have calculated the fluctuating rate constant of molecular transition, as well as the experimentally accessible quantities such as the force-dependent mean lifetime, the rupture force distribution, and the speed-dependent mean rupture force. Particular attention is paid to the discrepancies between the kinetics with and without dynamic disorder. We demonstrate that these discrepancies show strong and nontrivial dependence on the external force or the pulling speed, as well as the barrier height of the potential of mean force. Our results suggest that dynamic disorder is an important factor that should be taken into account properly in accurate interpretations of single-molecule pulling experiments. © *2013 AIP Publishing LLC*. [http://dx.doi.org/10.1063/1.4801331]

I. INTRODUCTION

Single-molecule pulling experiment is brilliantly designed to directly probe the intrinsic kinetic information of key processes in the living cell. This manipulation method has been intensively applied to the fundamental understanding of the inner world of molecular interactions in a wide variety of biological problems, ranging from the mechanical properties of protein unfolding[1–3] and ligand dissociation[4,5] to the dynamics associated with enzymatic catalysis.[6,7] Such experiments, at a constant speed or at a constant force, allow monitoring of the response of a single biomolecule to the external pulling force F, and therefore, can directly measure the force-dependent rate coefficient $k(F)$ of the system. In order to extract from the experimental data the intrinsic kinetic information about the apparent rate and free-energy landscape in the absence of loading force, two approaches so far have been widely adopted. One is the celebrated phenomenological Bell's formula[8] which scales $k(F)$ with the exponential of F according to $k_{Bell}(F) = k_0 \exp(\beta F x^{\ddagger})$, where $\beta^{-1} = k_B T$ with k_B being Boltzmann's constant and T the absolute temperature. The intrinsic reaction rate constant k_0 and the distance between the free-energy minimum and the transition-state $x^{\ddagger}$ are parameters of the system in the absence of the applied force. This formula is proven to be accurate only for sufficiently low forces.[9] Another approach is the application of Kramers' theory based on Langevin equation description[9–11] to study the rate of rupture in the presence of pulling. As a result, it provides a generalization of Bell's formula which can reveal richer information about not only k_0 and $x^{\ddagger}$, but also the apparent free-energy of activation $\Delta G^{\ddagger}$. In this microscopic interpretation of kinetics, pulling direction is assumed to be in accordance with the reaction coordinate of molecular transition, and the transition process is treated as a Brownian motion on the potential of mean force along this coordinate. The underlying barrier crossing process is assumed empirically on an *ad hoc* basis, to be Markovian governed by Langevin dynamics, resulting in an ever constant reaction rate.

Nevertheless, proteins are complex systems with many degrees of freedom and motions on a wide range of time scales, hence their biological reactions often exhibit dynamic disorder (DD)[12] with fluctuating rate. In particular, it has been recently found that the distance between a donor and an acceptor of electron transfer within a single protein molecule undergoes subdiffusion exhibiting typically non-Markovian characteristics of long-time memory.[13] Meanwhile, the enzymatic rate constants of single molecules are found to have large-amplitude fluctuations over a broad range of time scales.[14,15] The connection between fluctuations in protein conformation and those in reaction rate has also been investigated.[16–18] Taking these facts into account, the pulling coordinate, e.g., the end-to-end distance of a biopolymer,[19] which is in general in accordance with conformation coordinate, might be subject to subdiffusion, generating DD of the molecular transitions under pulling. However, most recent works on the analysis and interpretation of single-molecule pulling experiments were based on normal diffusion assumption[9–11] and thus did not account for the non-Markovian nature of conformational changes. Therefore, it is interesting to ask how the DD effects, resulting from

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subdiffusion of the conformation coordinate, would influence the kinetics associated with the pulling experiments.

To this end, in the present paper, we adopt a generalized Langevin equation (GLE) with fractional Gaussian noise (fGn) to describe the kinetics of the pulling coordinate. Compared with the fundamental Zwanzig's direct approach,[20] which assumes the fluctuating rate constant to be phenomenologically dependent on time-varying control parameters, GLE facilitates incorporating directly the subdiffusive nature of pulling coordinate, introduced via a power-law friction kernel $K(t) \sim t^{-\gamma}$ with $\gamma < 1$, into the resulting DD of reaction rate.[17,18] By using the Kramers' rate theory, we analytically calculate the fluctuating rate constants of molecular transition, as well as the experimentally accessible quantities such as the force-dependent mean lifetime, the rupture force distribution, and the speed-dependent mean rupture force. The discrepancies between the kinetics with DD and that without DD are particularly elaborated. We found that these discrepancies show strong and nontrivial dependence on the external force or the pulling speed. Our results therefore suggest that DD might be an important factor that should be taken into account in accurate interpretations of single molecular pulling experiments.

The remainder of the paper is organized as follows. In Sec. II, we introduce our model and method based on GLE and Kramers' rate theory. The barrier crossing rate, the mean lifetime at constant force, the rupture force distribution at constant pulling speed, as well as the relevant kinetic quantities will be explicitly derived. In Sec. III, we numerically calculate the specific results for two cases with and without DD. The DD effect will be specifically elucidated. Section IV concludes the paper.

II. MODEL AND METHOD

Force-induced biomolecular transition involves a vast number of degrees of freedom both of the molecule being pulled and of the surroundings. To make it a tractable problem, the instantaneous configuration of the molecule is coarse-grained by a single variable $x(t)$, for example, the end-to-end distance of the biopolymer chain. Moreover, the pulling coordinate that is acted on by force F is assumed to be in accordance with the reaction coordinate of configurational change in most cases.[9–11,21] It is worth noting here that this simple one-dimensional (1D) scenario only applies if the dynamics along the pulling coordinate $x(t)$ is slower than that along any other coordinate. In the case of more complex biomolecules where the pulling coordinate $x(t)$ might not be a good reaction coordinate, higher-dimensional approach may be considered.[22] In the present paper, however, for simplicity, we limit ourselves to 1D description. We assume the dynamics of $x(t)$ is governed by the following GLE:

$$m\frac{d^2x(t)}{dt^2} = -\int_0^t dt' K(t-t')\frac{dx(t')}{dt'} - \frac{\partial U(x,F)}{\partial x} + \theta(t), \tag{1}$$

where m is the reduced mass of the particle, $U(x, F)$ is the potential of mean force in the presence of force F, $\theta(t)$ is the random fluctuating force originating from the bath thermal motions. The friction kernel $K(t)$ is related to $\theta(t)$ by the fluctuation-dissipation theorem[23]

$$\langle \theta(t)\theta(t')\rangle = \beta^{-1}K(|t-t'|), \tag{2}$$

with $\langle\cdot\rangle$ denoting trajectory averaging.

Equation (1) is the starting point for the treatment of conformational fluctuations[24] and barrier crossing problem.[17] In these works, this equation is simplified further by neglecting the inertial contribution term, which is generally valid if the friction is high. This actually corresponds to an overdamped limit, which will be adopted here as well. The neglect of inertia in Eq. (1) leads to

$$\frac{\partial U(x,F)}{\partial x} = -\int_0^t dt' K(t-t')\frac{dx(t')}{dt'} + \theta(t). \tag{3}$$

As a free-energy surface of an applied force, $U(x, F)$ is a combination of a bare potential $U_0(x)$ and a force modification term, reading

$$U(x,F) = U_0(x) - Fx, \tag{4}$$

where we choose $U_0(x)$ a single-well free-energy surface in a specific linear-cubic form,[11]

$$U_0(x) = \frac{3}{2}\Delta G^{\ddagger}x/x^{\ddagger} - 2\Delta G^{\ddagger}(x/x^{\ddagger})^3, \tag{5}$$

which is characterized by a barrier height $\Delta G^{\ddagger}$, a distance $x^{\ddagger}$ between native state (well) and transition state (barrier), and an identical harmonic frequency ω in both well and barrier regions. According to Eq. (5), $m\omega^2 = 6\Delta G^{\ddagger}/x^{\ddagger 2}$. Two situations will be considered in this paper: F is a constant, and F grows linearly with time t at a constant pulling speed V as $F(t) = Vt$. It is assumed that under an external loading, $U(x, F)$ keeps its shape but is tilted relative to the natural profile. For convenience, we introduce a force correction factor $\epsilon(F) = \sqrt{1 - F/F_c}$, where $F_c = 3\Delta G^{\ddagger}/2x^{\ddagger}$ is the critical force at which the barrier disappears. Permissible values of the force are limited by F_c. Figure 1 depicts the bare free-energy surface $U_0(x)$ and the force-modified free-energy surface $U(x, F)$. As can be seen, due to the effect of F, the barrier

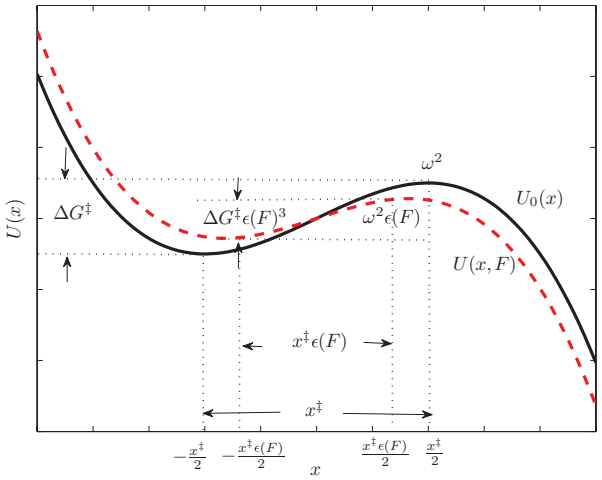

FIG. 1. The free energy profile with and without external force. See the context for details.

height and the well-barrier distance are decreased according to $\Delta G(F) = \Delta G^{\ddagger}\epsilon(F)^3$ and $x^{\ddagger}(F) = x^{\ddagger}\epsilon(F)$, respectively. In addition, the frequency at well and barrier is reduced to be $\omega(F)^2 = \omega^2\epsilon(F)$.

On the other hand, in view of that many studies up to date[17,18,24] have suggested that a GLE with a power-law friction kernel can describe well the protein conformational fluctuations and can account for the dynamic disorder in the relevant complex kinetics of biochemical reactions, we assume that the same friction kernel might hold for the dynamics involving the pulling coordinate, i.e., the reaction coordinate of configurational change. Following Refs. 24, 25, $K(t)$ in Eq. (1) takes the form

$$K(t) = \beta\eta(2-\gamma)(1-\gamma)|t|^{-\gamma}, \tag{6}$$

with $0 < \gamma < 1$. The friction coefficient $\eta(2-\gamma)(1-\gamma)$ depends on the exponent γ and includes a parameter η reflecting the interaction strength between system and bath.[26] Note that this power-law friction kernel has been observed by direct single molecule experiments,[13] and can be inferred from molecular dynamic (MD) simulations.[27] Besides, its microscopic origin has been also investigated in terms of polymer dynamics[28] and the fractal nature of protein.[29] Specifically, as $\gamma \to 1^-$, $K(t)$ in Eq. (6) behaves as a delta function. Thus, the GLE (1) reduces to a conventional Langevin equation with white noise.

To investigate the single-molecule mechanics under external force, we regard the irreversible molecular transition as a thermally activated barrier crossing process in a force-modified free-energy surface. By applying Kramers' theory,[30] the escape-over-a-barrier rate can be explicitly derived from the ratio of the stationary particle flux over the barrier top to the equilibrium particle population in the region of the potential well. To proceed further, Eq. (3) is now transformed to an equivalent generalized Smoluchowski equation for the probability density $P(x, t)$ that the particle is at the point x at time t. By using standard methods of functional calculus (see details in Ref. 18), we have near the barrier region[18]

$$\frac{\partial P(x,t)}{\partial t} = D(t,F)\left\{\beta\frac{\partial}{\partial x}\left[\frac{\partial U(x,F)}{\partial x}P(x,t)\right] + \frac{\partial^2}{\partial x^2}P(x,t)\right\}, \tag{7}$$

where $D(t, F)$ is the diffusion coefficient which is in general dependent on time. In the above expression, it follows

$$D(t,F) = \frac{1}{m\omega^2\beta\epsilon(F)}\frac{\dot{\chi}(t,F)}{\chi(t,F)}, \tag{8}$$

where $\dot{\chi}(t, F) = d\chi(t, F)/dt$ and $\chi(t, F)$ is given by the inverse Laplace transform of

$$\hat{\chi}(s,F) = \frac{\hat{K}(s)}{s\hat{K}(s) - m\omega^2\epsilon(F)}, \tag{9}$$

with $\hat{K}(s)$ the Laplace transform of the friction kernel $K(t)$. Taking into account Eq. (6), it takes a power law form with respect to s, i.e., $\hat{K}(s) = \beta\eta\Gamma(3-\gamma)s^{\gamma-1}$ (note that as $\gamma = 1$, $\hat{K}(s)$ becomes a constant, of which the inverse Laplace transformation is a delta function, representing a white noise). Thus, Eq. (9) can be carried out exactly to produce

$$\chi(t,F) = E_{\gamma}[(t/\tau(F))^{\gamma}], \tag{10}$$

where E_{α} is the Mittag-Leffler function defined by the series expansion $E_{\alpha}(x) = \sum_{j=0}^{\infty} x^k/\Gamma(\alpha j + 1)$, with $\Gamma(z)$ the gamma function. $\tau(F)$ is the relaxation time in form of

$$\tau(F) = \tau_0\epsilon(F)^{-1/\gamma}, \tag{11}$$

where $\tau_0 = (\frac{\eta\Gamma(3-\gamma)}{m\omega^2})^{1/\gamma}$ roughly sets the system's characteristic time scale in the absence of external force F. Obviously, this relaxation time scale is lengthened due to the effect of F.

On the basis of Eq. (7), following Kramers[30] and Hanggi,[31] we derive the time-dependent barrier crossing rate under external loading, given by

$$k(t,F) = \frac{1}{2\pi}\frac{\dot{\chi}(t,F)}{\chi(t,F)}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}. \tag{12}$$

Under adiabatic approximation,[10] the survival probability $S(t)$, which is defined as the probability that a given particle has not crossed the barrier up to time t, follows the first order rate equation: $\dot{S}(t, F) = -k(t, F)S(t, F)$. Thus,

$$S(t,F) = \exp\left[-\int_0^t dt' k(t',F)\right]. \tag{13}$$

Taking into account the specific expression of the reaction rate (12), $S(t, F)$ can be further expressed as

$$S(t,F) = \chi(t,F)^{-\frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}}. \tag{14}$$

Equations (12) and (13) [or (14)] describe molecular transition kinetics at both constant force and time-dependent linear force.

If the force F is a constant, what we concern is the distribution of barrier crossing time, i.e., the waiting time distribution $f(t, F)$, following $f(t, F) = -\dot{S}(t, F)$. In view of Eq. (14), $f(t, F)$ is easily found to be

$$f(t,F) = \frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}\frac{\dot{\chi}(t,F)}{\chi(t,F)^{[\frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}+1]}}. \tag{15}$$

Consequently, the mean waiting time is given by

$$\bar{t}(F) = \int_0^{\infty} t' f(t',F)dt' = \int_0^{\infty} dt\,\chi(t,F)^{-\frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}}. \tag{16}$$

In addition, if the force F grows linearly with time as $F = Vt$, the key quantity is the distribution of rupture forces $p(F)$ which is assumed to be related to the survival probability by[9]

$$-\dot{S}(t,F)dt = p(F)dF. \tag{17}$$

From Eq. (13), $p(F)$ can be calculated from

$$p(F) = \frac{k(t,F)|_{t\to F/V}}{V}e^{-\frac{1}{V}\int_0^F [k(t',F')|_{t'\to F'/V}]dF'}. \tag{18}$$

Then, the mean rupture force is given by $\bar{F}(V) = \int Fp(F)dF$.

III. SPECIFIC RESULTS AND DISCUSSIONS

On the basis of the general formulations given in Sec. II, we go forward to evaluate the specific results for the waiting time distribution and its resulting mean lifetime at constant force, as well as for the rupture force distribution and the resulting mean rupture force at constant pulling speed. The DD effect can be therefore quantitatively estimated. It is evident that all the kinetic quantities mentioned above are related to a common function $\chi(t, F)$ defined as Eq. (10), in terms of a Mittag-Leffler function where there is a factor γ introduced originally from the friction kernel Eq. (6). As a special case, $\gamma = 1/2$ will be explicitly analyzed, for which $x(t)$ undergoes subdiffusion and DD takes effect. In addition to it, for comparison, we will also evaluate the DD-free results. As already mentioned above, one can reproduce the white noise results by letting $\gamma = 1$, which is also adopted in Refs. 18 and 32, leading to a time-independent reaction rate, i.e., the DD-free case. We will compare the results with DD to those without DD, with particular attention to the dependence on F or V.

A. The case $\gamma = 1$

In this case, fGn reduces to white noise and the Mittag-Leffler function reduces to an exponential one. Thus, $\chi(t, F) = e^{t/\tau(F)}$, where $\tau(F) = \tau_0/\epsilon(F)$ with $\tau_0 = \frac{\eta}{m\omega^2}$. The reaction rate given by Eq. (12) will reduce to a well-defined Kramers' rate constant as follows:

$$k(F) = k_0\epsilon(F)e^{\beta\Delta G^{\ddagger}(1-\epsilon(F)^3)}, \tag{19}$$

where $k_0 = \frac{1}{2\pi\tau_0}e^{-\beta\Delta G^{\ddagger}}$ is the reaction rate constant in the absence of external force, which is determined by the system's characteristic time scale τ_0 as well as the barrier height $\beta\Delta G^{\ddagger}$.

In case of a constant force F, the survival probability and the waiting time distribution follow an obvious single-exponential decay: $S(t, F) = e^{-k(F)t}$ and $f(t, F) = k(F)e^{-k(F)t}$. The mean lifetime is just the reciprocal of $k(F)$,

$$\bar{t}(F) = 1/k(F). \tag{20}$$

While, in case of a linearly growing force $F = Vt$, the distribution of rupture force follows from Eqs. (18) and (19) analytically as

$$p(F) = \frac{k(F)}{V}\exp\left[\frac{k_0[1 - e^{\beta\Delta G^{\ddagger}(1-\epsilon(F)^3)}]}{\beta x^{\ddagger}V}\right]. \tag{21}$$

Equations (19)–(21) recover the expressions in literatures so far[9–11] based on Kramers theory under Langevin dynamics description, leaving out DD consideration, which we call therefore DD-free results in this paper.

B. The case $\gamma = 1/2$

When $\gamma \neq 1$, the derivative of the Mittag-Leffler function can no longer be expressed in a closed form, in general. However, there are some values of γ, for which such closed forms are known.[33] In particular, the case $\gamma = 1/2$ is of special significance. For this value, the friction kernel $K(t)$ decays following $|t|^{-1/2}$ [cf. Eq. (6)]. This exponent of γ has shown a highly satisfactory fit to experimental data on the time correlation function of distance fluctuations in proteins.[24] For $\gamma = 1/2$, the Mittag-Leffler function in Eq. (10) can be rewritten as $E_{1/2}(x) = \exp(x^2)\mathrm{erfc}(-x)$, where $\mathrm{erfc}(x)$ is the complementary error function. Therefore, we have

$$\chi(t, F) = E_{1/2}(\sqrt{t/\tau(F)}) = e^{t/\tau(F)}\mathrm{erfc}(-\sqrt{t/\tau(F)}), \tag{22}$$

$$\dot{\chi}(t, F) = \frac{1}{\tau(F)}\left[e^{t/\tau(F)}\mathrm{erfc}(-\sqrt{t/\tau(F)}) + \frac{1}{\sqrt{\pi}\sqrt{t/\tau(F)}}\right],$$

where $\tau(F) = \tau_0/\epsilon(F)^2$ with $\tau_0 = (\frac{3\sqrt{\pi}}{4}\frac{\eta}{m\omega^2})^2$. Substituting Eq. (22) into (12), we immediately have

$$k(t, F) = k^*(F)\left[1 + \frac{1}{\sqrt{\pi}\sqrt{t/\tau(F)}e^{t/\tau(F)}\mathrm{erfc}(-\sqrt{t/\tau(F)})}\right], \tag{23}$$

where the coefficient $k^*(F)$ is expressed as

$$k^*(F) = \frac{1}{2\pi\tau_0}\epsilon(F)^2e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}, \tag{24}$$

which can be thought as an effective or modified Kramers' rate constant. It is the last term in the square bracket in Eq. (23) that is responsible for the time dependence of the reaction rate, resulting in DD. This time-dependence behavior is closely related to the ratio of time t to the relaxation time scale $\tau(F)$. In particular, over a long time period, or more specifically, as $t/\tau(F) \gg 1$, $k(t, F)$ will effectively reduce to the modified Kramers' rate constant $k^*(F)$. Particularly, for the case $F = 0$, $k^*(F)$ will be exactly k_0.

The survival probability $S(t, F)$ and waiting time distribution $f(t, F)$ under a constant force loading are straightforwardly derived by inserting Eq. (22) into Eqs. (14) and (15). As a result, we have

$$\begin{aligned} S(t, F) &= E_{1/2}(\sqrt{t/\tau(F)})^{-k^*(F)\tau(F)}, \\ f(t, F) &= k(t, F)E_{1/2}(\sqrt{t/\tau(F)})^{-k^*(F)\tau(F)}, \end{aligned} \tag{25}$$

where $k(t, F)$ is given by (23). Both $S(t, F)$ and $f(t, F)$ are functions with respect to the ratio $t/\tau(F)$, and evidently exhibit non-exponential decay. According to Eq. (25), we can readily establish their short-time and long-time approximations as follows:

(a) $t/\tau(F) \ll 1$:

$$S(t, F) \approx \left(1 + \frac{1}{\sqrt{\pi}}\sqrt{t/\tau(F)}\right)^{-k^*(F)\tau(F)}, \tag{26a}$$

$$f(t, F) \approx k^*(F)\frac{1}{\sqrt{\pi}}\sqrt{t/\tau(F)}^{-1/2}. \tag{26b}$$

(b) $t/\tau(F) \gg 1$:

$$S(t, F) \approx 2^{-k^*(F)\tau(F)}e^{-k^*(F)t}, \tag{27a}$$

$$f(t, F) \approx k^*(F)2^{-k^*(F)\tau(F)}e^{-k^*(F)t}. \tag{27b}$$

These approximations indicate $S(t, F)$ and $f(t, F)$ will be initially non-exponential and then change to exponential at long times. Note here that the time scale is measured by the ratio $t/\tau(F)$ rather than t itself. To investigate the influence of the

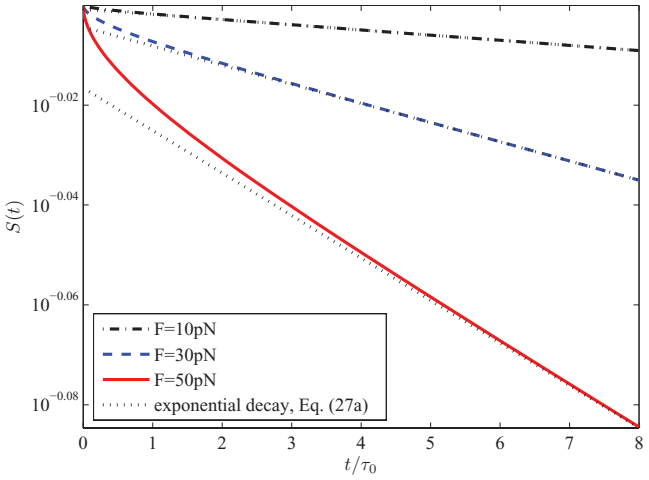

FIG. 2. The survival probability $S(t, F)$ for $\gamma = 1/2$ and $F = 10$, 30, and 50 pN. Other parameters are $\beta\Delta G^{\ddagger} = 5$, $x^{\ddagger} = 0.4$ nm, $T = 300$ K, and $\tau_0 = 0.001$ s.

external force on the behavior of these quantities, we vary the value of F, but keep the intrinsic characteristic time τ_0 and the bare free energy profile to be unaltered. According to Eq. (11), at small forces, the ratio $t/\tau(F)$ is relatively large for any fixed interval of time t, so the system is effectively in the long time regime, where $S(t, F)$ and $f(t, F)$ behave as an exponential. At large forces, the ratio $t/\tau(F)$ is relatively small for any fixed interval of time t, so the system is in the short time regime, where $S(t, F)$ and $f(t, F)$ decay non-exponentially initially, until the time t is sufficiently large that the system crosses over into the long time regime. As an illustration, Fig. 2 depicts the time evolution of the survival probability at different values of F, but common parameters τ_0, $\Delta G^{\ddagger}$, and $x^{\ddagger}$. Indeed, it is evident from this figure that as force is small, a clear time scale separation $t/\tau(F) \gg 1$ that holds almost over the whole time scales results in single exponential $S(t, F)$ [in accordance with Eq. (27a)], while as force is large, time scale overlap, i.e., $t \sim \tau(F)$, leads to multiexponential $S(t, F)$, the signature of DD. Moreover, this DD effect becomes more pronounced for larger forces.

Furthermore, the mean waiting time under the influence of a constant force can be obtained from Eqs. (16) and $(22)_1$, yielding

$$\bar{t}(F) = \int_0^{\infty} dt e^{-k^*(F)t}[1 + \mathrm{erf}(-\sqrt{t/\tau(F)})]^{-\frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}}. \tag{28}$$

If the barrier height is large and the external force is small, such that the exponent $-\frac{1}{2\pi}e^{-\beta\Delta G^{\ddagger}\epsilon(F)^3}$ is small, Eq. (28) reduces to

$$\bar{t}(F) = 1/k^*(F) \tag{29}$$

in close analogy to DD-free expression (20). Nevertheless, in general cases, if the barrier height of the free-energy is not very large and/or the external force is not very small, the last term in Eq. (28) will cause a certain deviation of $\bar{t}(F)$ from Eq. (29), demonstrating the DD effect. In particular, if $\Delta G^{\ddagger}$ is enough small, this deviation is observable even at null force.[17,18]

Finally, at a constant speed pulling, the distribution of rupture forces $p(F)$ in this case of $\gamma = 1/2$ can be directly evaluated by inserting Eq. (12) into the general expression (18), i.e.,

$$p(F) = \frac{k^*(F)}{V}\left[1 + \frac{1}{\sqrt{\pi}\sqrt{t/\tau(F)}e^{t/\tau(F)}\mathrm{erfc}(-\sqrt{t/\tau(F)})}\right]_{t\to F/V} \times e^{-\frac{1}{V}\int_0^F k^*(F')[1+\frac{1}{\sqrt{\pi}\sqrt{t'/\tau(F')}e^{t'/\tau(F')}\mathrm{erfc}(-\sqrt{t'/\tau(F')})}]_{t'\to F'/V}dF'}. \tag{30}$$

Unlike $\gamma = 1$ case, the evaluation of $p(F)$ is not analytically tractable, and a numerical integration is thus necessary. Equations (23)–(30) can account for the DD effect, which we call therefore DD results.

C. The comparison between $\gamma = 1/2$ and $\gamma = 1$

To roughly estimate how the DD affects on the reaction kinetics under external force, we go forward to numerically evaluate the mean lifetime at constant forces, as well as the rupture force distribution and the corresponding mean rupture force at constant pulling speeds, in both $\gamma = 1/2$ and $\gamma = 1$ cases. The relevant quantities will be compared quantitatively. In comparison, we assume that both cases are prescribed by an identical characteristic time scale τ_0.

We first consider the constant force situation. Now the most relevant quantity is the mean lifetime $\bar{t}(F)$. For comparison, we introduce the absolute and relative differences regarding $\bar{t}(F)$ as follows:

$$\Delta\bar{t}(F) = \bar{t}(F)^{\mathrm{DD}} - \bar{t}(F)^{\mathrm{DD\text{-}free}} \tag{31}$$

and

$$\alpha_{\bar{t}}(F) = \frac{\bar{t}(F)^{\mathrm{DD}} - \bar{t}(F)^{\mathrm{DD\text{-}free}}}{\bar{t}(F)^{\mathrm{DD\text{-}free}}}, \tag{32}$$

where the superscripts denote the results with and without DD, given by Eqs. (28) and (20), respectively.

Figure 3 presents the dependence of $\Delta\bar{t}(F)$ (a) and $\alpha_{\bar{t}}(F)$ (b) for relatively low barrier heights, $\beta\Delta G^{\ddagger} = 1.5, 2, 3, 4$. Both $\Delta\bar{t}(F)$ and $\alpha_{\bar{t}}(F)$ increase monotonically with F. Note that even for $F = 0$, large discrepancies already exist between the two cases $\gamma = 1$ and 1/2. We emphasize here that this depends on the choice of criteria to compare the two situations, i.e., we have chosen that the characteristic time scale τ_0 should be the same with or without DD. Physically, this means that in the long time limit, the system under consideration, described by simple Langevin equation or GLE, should have the same rate constant (see the context around Eq. (24)). With this choice, the mean lifetime $\bar{t}(F)$ might be different for $F = 0$. Our results show that $\bar{t}(F = 0)^{\mathrm{DD}}$ is smaller than $\bar{t}(F = 0)^{\mathrm{DD\text{-}free}}$ for these small barrier heights. When external force is present, the inset in Fig. 3(a) shows that $\bar{t}(F)$ decreases quickly with F. This is reasonable because F will reduce the barrier height and make the barrier-crossing easier. Interestingly, when DD is present ($\gamma = 1/2$), $\bar{t}(F)$ decreases more slowly than the DD-free case ($\gamma = 1$). This seems to imply that DD can weaken the effects of barrier-reducing induced by force, which might be due to the subdiffusion nature.

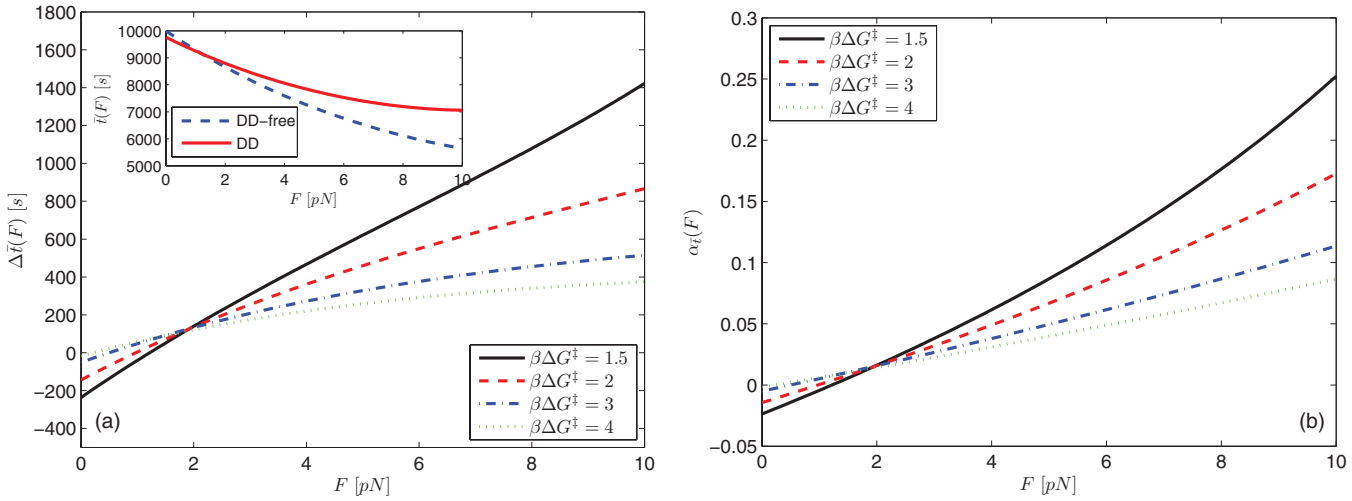

FIG. 3. The absolute (a) and relative (b) deviations of the mean lifetime as functions of external force for $\beta\Delta G^{\ddagger} = 1.5, 2, 3, 4$. The inset shows the mean lifetime with and without DD for $\Delta G^{\ddagger} = 1.5$. Other parameters are $x^{\ddagger} = 0.4$ nm, $T = 300$ K, and τ_0 chosen so that $k_0 = 10^{-4}$ s^{-1}.

Consequently, at a certain value of F, $\Delta\bar{t}(F)$ will go across zero from below, and a further increasing F will increase $\Delta\bar{t}(F)$. Thus, for small barrier heights, DD seems to play a nontrivial role to the barrier-crossing process: for small external forces, DD tends to accelerate the transition compared to the DD-free case, but it tends to slow down the transition process if external force is large.

The situation is different if the free energy barrier is high. In Fig. 4, we show the results for $\beta\Delta G^{\ddagger} = 5, 10, 15, 25$. In these cases, the differences at small forces are negligibly small. We may understand this as follows. If the barrier is high, the system bears a clear time scale separation between the barrier-crossing process and the inside-well dynamics, at least for small enough forces. Therefore, the system behaves like in the long-time limit, such that the DD does not take effect and $\Delta\bar{t}(F = 0) \simeq 0$. This picture may also illustrate why $\Delta\bar{t}(F)$ is so evident for $F = 0$ in Fig. 3, where time scale separation is not so remarkable if barrier height is low. With increasing F, we observe an interesting variation of $\Delta\bar{t}(F)$, i.e., it shows a clear-cut maximum at a certain force. This is not observed for $\alpha_{\bar{t}}(F)$, which grows monotonically with F, demonstrating an ever-increasing relative discrepancy between DD and DD-free results. For these relatively large barrier heights, $\Delta\bar{t}(F)$ is always positive, indicating that DD is not favorable for the barrier crossing compared to the DD-free case. We can also see that the discrepancy is more pronounced for smaller barrier heights.

In addition to the constant force situation, we have also considered the case when the external force is loaded at a constant speed. Now the relevant quantities are the rupture force distribution and the mean rupture force. Similarly, results for both DD and DD-free cases are evaluated for comparison. We first obtain the rupture force distribution according to Eqs. (30) and (21), and then calculate the mean rupture force via averaging over all permitted forces. Similar to Eqs. (31) and (32), we analyze the absolute difference of mean rupture force

$$\Delta\bar{F}(V) = \bar{F}(V)^{\mathrm{DD}} - \bar{F}(V)^{\mathrm{DD\text{-}free}} \tag{33}$$

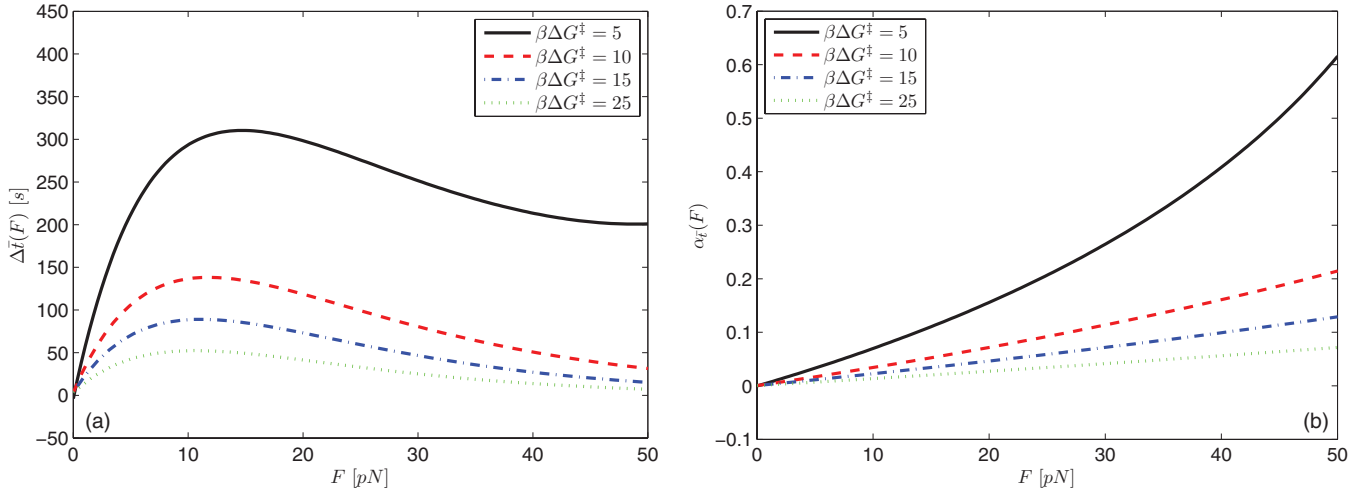

FIG. 4. The absolute (a) and relative (b) deviations of the mean lifetime as functions of external force for $\beta\Delta G^{\ddagger} = 5, 10, 15, 25$. Other parameters are the same as those in Fig. 3.

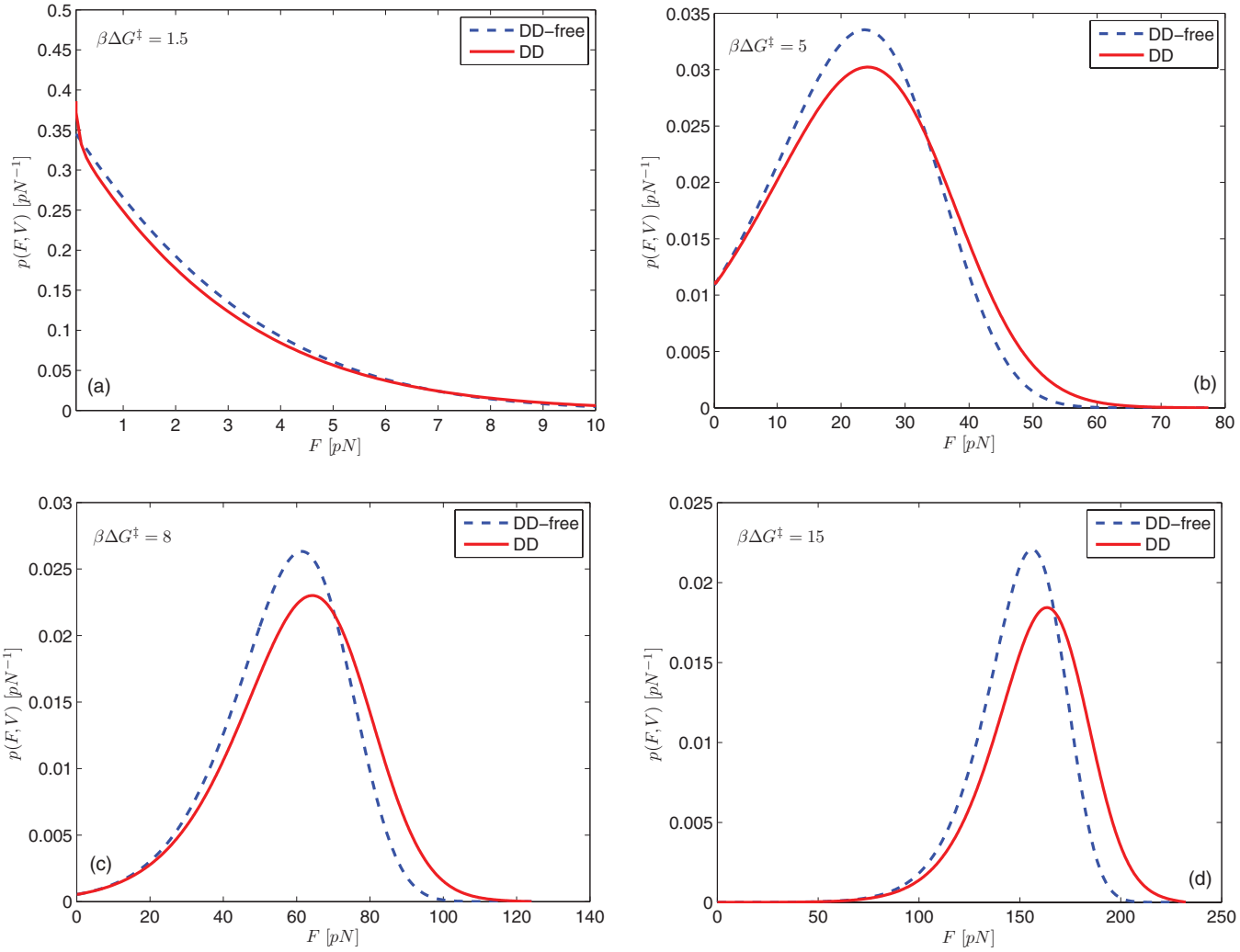

FIG. 5. The rupture force distribution for $V = 0.1$ pN/ms and $\beta\Delta G^{\ddagger} =$ (a) 1.5, (b) 5, (c) 8, (d) 15. DD and DD-free results are shown by solid and dashed lines. Other parameters are $x^{\ddagger} = 0.4$ nm, $T = 300$ K, and $\tau_0 = 0.001$ s.

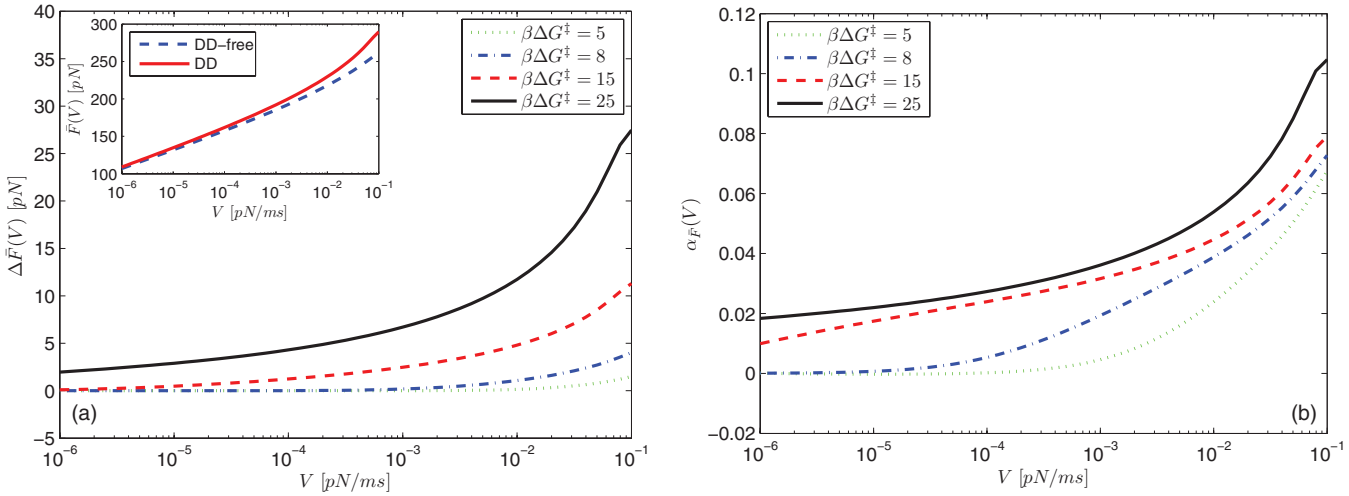

FIG. 6. The absolute (a) and relative (b) deviations of the mean rupture force as functions of pulling speed for $\beta\Delta G^{\ddagger} = 5, 8, 15, 25$. Other parameters are the same as those in Fig. 5.

as well as its relative deviation

$$\alpha_{\bar{F}}(V) = \frac{\bar{F}(V)^{\mathrm{DD}} - \bar{F}(V)^{\mathrm{DD\text{-}free}}}{\bar{F}(V)^{\mathrm{DD\text{-}free}}}. \quad (34)$$

$\bar{F}(V)^{\mathrm{DD}}$ is obtained from the distribution given by Eq. (30) and $\bar{F}(V)^{\mathrm{DD\text{-}free}}$ from Eq. (21).

As a result, Fig. 5 displays the comparison of the rupture force distribution for varying barrier height $\beta\Delta G^{\ddagger} = 1.5, 5, 8, 15$. We see that the distribution is exponential-like if the barrier is low. With increasing barrier height, the distribution evolves to a Gaussian-like shape. The physical insight underlying these observations is still open to us. Compared to the DD-free case, the distribution is lowered with a right-shifted peak when DD is accounted for, corresponding to a relatively larger mean rupture force. In accordance with this, the results of $\Delta\bar{F}(V)$ and $\alpha_{\bar{F}}(V)$ for varying barrier heights $\beta\Delta G^{\ddagger} = 5, 8, 15, 25$ are shown in Fig. 6. Clearly, the deviation is negligible for small speed V, while remarkable deviation appears at fast speeds. In addition, the DD curve lies above the DD-free curve, which means that DD tends to increase the mean rupture force. Remarkably, the deviation is more pronounced for larger barrier heights, which is quite different from the case of constant force as show in Fig. 4.

IV. CONCLUDING REMARKS

In summary, we have proposed a theoretical framework based on a GLE with fGn and power-law memory kernel to study the kinetics of macromolecular transitions in the presence of external force relevant to single molecular pulling experiments. By applying Kramers' theory, we have derived an analytical expression for the reaction rate which fluctuates in time in general, presenting DD. This expression and the resultant reaction kinetics are determined by a key function $\chi(t, F)$ in terms of a factor γ, the exponent of the memory kernel. Two cases of $\gamma = 1$ and $\gamma = 1/2$, respectively, corresponding to results without and with DD effects, are particularly analyzed. We explicitly evaluate the mean lifetime at a constant force, the rupture force distribution at constant pulling speed, and the resulting speed-dependent mean rupture force. Significant discrepancies are observed between the DD and DD-free results, especially for large force or large loading speeds. Generally, DD will slow down the barrier-crossing, thus leading to a relatively larger mean lifetime or larger mean rupture force compared to the DD-free case. Nevertheless, barrier height may have a subtle influence on this picture, in that the mean lifetime with consideration of DD could be smaller, when the barrier height is small and the force is small enough. Our analysis thus reveals a nontrivial role played by DD in macromolecular conformation transition, which should be taken into account carefully in proper interpretation of single molecular pulling experiments.

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