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Dynamic disorder characteristics of single-molecule pulling experiments on two-dimensional free-energy landscape

Yue Zheng [a], Ruibin Ren [b], Junjun Xu [c,*]

[a] College of Chemical and Environmental Engineering, Liaoning University of Technology, Jinzhou, Liaoning 121000, China
[b] College of Mathematics, Southwest Jiaotong University, Chengdu 610031, China
[c] College of Chemistry and Chemical Engineering, Bohai University, Jinzhou, Liaoning 121013, China

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ABSTRACT

The dynamic characteristic of macromolecule is mainly subject to the fluctuation of rate constant and this phenomenon is usually considered as dynamic disorder (DD). In order to detect the DD nature in the bio-molecule system more accurately, here we propose a theoretical framework based on the two-dimensional (2D) free-energy landscape including the pulling coordinate and other slow conformational variables. The generalized Langevin equation (GLE) with fractional Gaussian noise (fGn) and the power-law memory kernel are used on this landscape for the research. The transition rate, which depends on both intrinsic barrier height and noise strength ratio, has been analyzed under the condition of external force. The particular discrepancies were investigated between the kinetics of the transitions with and without DD. We find that the discrepancies relied on the barrier height and the noise strength ratio. Taken together, our study illustrates the importance of the DD characteristics, which should be taken into account during the research into the single-molecule pulling experiments.

1. Introduction

Single-molecule pulling experiment provides a powerful tool to directly probe the kinetic information of the molecules during key processes in the living cell. This method has been used to study numerous fundamental biological problems widely distributed in the molecular system, from the mechanical properties of protein unfolding [1–3] and ligand dissociation [4,5] to the molecular dynamics during enzymatic catalysis [6,7]. Pulling experiments under the constant speed or constant force can directly measure the force-dependent rate coefficient $k(F)$ to detect the dynamic characteristics through monitoring the response of the bio-molecule by external pulling force F.

To accurately extract the kinetic information of molecular transitions, it is necessary to establish a reliable theory for irreversible transition rate under the condition of pulling force. To this end, two approaches have been widely used so far. One is the celebrated phenomenological Bell's formula [8] with exponential of F according to $k_{\mathrm{Bell}}(F) = k_0 \exp(\beta F x^{\ddagger})$, $\beta^{-1} = k_B T$ with k_B being Boltzmann's constant and T being 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 two basic parameters in the absence of applied force. However, the Bell's formula is only suitable for the conditions of low external force [9]. Kramers's theory [10] based on the generalized Langevin equation (GLE) [11,12] is another famous approach, which provides more information than Bell's formula. Besides k_0 and $x^{\ddagger}$, it also includes the free-energy of activation $\Delta G^{\ddagger}$. Especially, connected with fractional Gaussian noise (fGn) [13], this theory identified the dynamic disorder (DD) [14–16]. Compared with Zwabzig's approach [17] connected with Bell's rate formula, which assumes that fluctuating rate is dependent on time-varying control parameters, the GLE with fGn clearly reveals the conformational fluctuation caused by DD under the one-dimension (1D) condition.

However, the force-induced molecular rupture involves a huge number of degrees of freedom originated from both the pulling molecule and the surrounding environments. Theory dependent on the 1D assumption [18] means that the dynamic change along the pulling coordinate named x is slower than that along any other coordinate, which may not be the case in general [9,19]. It is necessary to note that even slower coordinate Q, for example the local conformational change, is decided by the dihedral angles [19,20] and other parameters. Therefore, it is important to propose a theoretical analysis based on a two-dimensional (2D) free-energy

* Corresponding author.
E-mail addresses: 543653649@qq.com (Y. Zheng), Airy_Ren@swjtu.edu.cn (R. Ren), xujunjun@bhu.edu.cn (J. Xu).

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landscape [21,22]. In the theory, the freedom Q not only can be as slow as change in the pulling direction x, but also represents the rate-limiting step of protein unfolding [23]. In the present study, the 2D free-energy landscape has been established to study the kinetic characteristics.

The 2D model is usually applied with the white noise condition [24] based on the normal diffusion assumption and cannot account for DD characteristics caused by sub-diffusion that exhibits non-Markovian nature of the conformational changes. The sub-diffusion is a common phenomenon present in macromolecule pulling experiments [25]. The DD effect can be expressed by the non-exponential decay [26] of the waiting time. The GLE-fGn has already been used to analyze the immigration rate and the waiting time under external force [15,16] in our investigations. The key nature of the fGn is the power-law memory kernel according to $K(t) \sim |t|^{-\gamma}$. In this formula, the range $0 < \gamma < 1$ must correspond to the sub-diffusive behavior [27] and the DD effects have been analyzed. However, the fGn has not yet been taken into the multidimensional landscape [28] and the DD effect also has not been revealed in this situation [29].

Motivated by the above considerations, we aim to propose a framework based on 2D energy profile [19] involving both fGn and DD effect [30]. We analyze the transition rate under the pulling force and investigate how it changes with the barrier height $\Delta G^{\ddagger}$ and the noise strength ratio α_k. The formula of the ratio is written as $\alpha_k = \eta_Q/\eta_x$, η_Q and η_x represent the noise strength in the Q and x dimensions respectively [31]. In order to extract DD characteristics, it is necessary to introduce two power-law functions to form the kernel matrix which can present the properties of both x and Q noises. The results for both systems with and without DD are calculated and our results suggest that DD is an important factor of the dynamics of molecular transition.

2. Model and method

In our framework, the dynamic of the freedom Q other than the extension x is essential for the rupture kinetics. Under the condition of the mechanical work $-Fx$, the free energy of the molecular system is the sum of the intrinsic energy called $G(x, Q)$ and the external force F takes the role in the dimension x. The 2D free-energy landscape model is established including the effect from both pulling coordinate x and changes of the dihedral angle Q:

$$G(x, Q) = G_0(Q) + \frac{k(Q)}{2}\left[x - x_0(Q)\right]^2 - Fx \tag{1}$$

In the absence force condition, the curve in x coordination is assumed to reflect the distance between the bound state and the transition state. The curve in Q coordination is harmonic with the curvature $k(Q)$ and the minimum at $x_0(Q)$. $k(Q)$ represents the statistical dispersion in the values of the molecular extension at the coordinate of the Q and also means the stiffness of the molecule itself. $x_0(Q)$ is the most probable value of the extension at a given Q without any pulling force. $G_0(Q)$ is a linear-cubic function of the Q.

$$k(Q) = k_{\cup}^0 \frac{1 - \Delta k^{\ddagger}/k_{\cup}^0}{1 - (Q/\Delta Q^{\ddagger})(\Delta k^{\ddagger}/k_{\cup}^0)} \tag{2}$$

$$x_0(Q) = \varepsilon Q^2 - Q\frac{\Delta x^{\ddagger}}{\Delta Q^{\ddagger}}\left[1 + \varepsilon\frac{(\Delta Q^{\ddagger})^2}{\Delta x^{\ddagger}}\right] + \Delta x^{\ddagger} \tag{3}$$

$$G_0(Q) = \frac{2\Delta G^{\ddagger}}{(\Delta Q^{\ddagger})^3}\left[Q - \frac{\Delta Q^{\ddagger}}{2}\right]^3 - \frac{3\Delta G^{\ddagger}}{2\Delta Q^{\ddagger}}\left[Q - \frac{\Delta Q^{\ddagger}}{2}\right] \tag{4}$$

From Eq. (2) to Eq. (4), $\Delta x^{\ddagger}$ is the distance along x between transition and bound states and $\Delta k^{\ddagger}$ represents the difference of the molecular stiffness in the bound ($k_{\cup}^0$) and the transition states at $F = 0$. The $x_0(Q)$ is specified by ε and $\varepsilon = \Delta x^{\ddagger}/(\Delta Q^{\ddagger})^2$.

The GLE with two coordinate effects of x and Q is given:

$$\frac{\partial \boldsymbol{G}(\boldsymbol{x})}{\partial \boldsymbol{x}} = -\int_0^t dt' \boldsymbol{K}(t - t')\frac{d\boldsymbol{x}}{dt'} + \boldsymbol{\theta}(t) \tag{5}$$

In this equation, the 2D free-energy landscape model is $\boldsymbol{G}(\boldsymbol{x}) = G(x, Q)$ and the matrix $\boldsymbol{x} = (x, Q)$ just contains two different freedoms, the extension effect from x coordinate and the change of angles from Q variable. The random force matrix $\boldsymbol{\theta}(t) = (\theta_x(t), \theta_Q(t))$ represents surrounding random forces which can affect both x and Q coordinates. The power-law memory kernel matrix $\boldsymbol{K}(t)$ is related to $\boldsymbol{\theta}(t)$ by fluctuation–dissipation theorem [32]:

$$\left\langle \boldsymbol{\theta}(t) \cdot \boldsymbol{\theta}^T(t') \right\rangle = k_B T \boldsymbol{K}(t - t') \tag{6}$$

$\boldsymbol{\theta}^T(t)$ is the transposed matrix of the $\boldsymbol{\theta}(t)$ and the $\langle\cdot\rangle$ means the trajectory averaging. Compared with the white noise condition, it would be better to reveal the DD characteristic if we assume that both coordinates reflect the fGn feature in the kernel matrix $\boldsymbol{K}(t)$:

$$\boldsymbol{K}(t) = \begin{pmatrix} \eta_x(2-\gamma)(1-\gamma)|t|^{-\gamma} & 0 \\ 0 & \eta_Q(2-\gamma)(1-\gamma)|t|^{-\gamma} \end{pmatrix} \tag{7}$$

This kernel matrix has the symmetrical characteristic with the power-law functions of time t in these two coordinates and only the noise strength η_x is different from η_Q. The γ in Eq. (7) is a key factor. If γ tends to 1, power-law functions behaves as the $\delta(t)$ functions and the Eq. (5) has to be reduced to the conventional Langevin equation with the WN condition. In this condition, the reduced formula is one kind of basic model used by Y. Suzuki and O.K. Dudko's theory [19]. If $\gamma = 0.5$, the kernel matrix is time-dependent, belonging to fGn condition and used in our model. It is proved that this kind of power-law function has been observed by single molecule pulling experiments [25] and it can be inferred from molecular dynamic (MD) simulation [33].

By applying the Kramers's theory [10], the migration rate equation with fGn in the condition of 2D free-energy landscape is deduced from Eq. (5):

$$k(t, F) = \frac{\Lambda_+(t, F)}{2\pi}\sqrt{\frac{\det \boldsymbol{H}_{\cup}(F)}{|\det \boldsymbol{H}_{\cap}(F)|}}\exp\left[-\frac{\Delta G^{\ddagger}}{k_B T}\right] \tag{8}$$

In Eq. (8), $\Delta G^{\ddagger} = G(x_{\cap}(F), Q_{\cap}(F)) - G(x_{\cup}(F), Q_{\cup}(F))$ is the height of the activation barrier with the pulling force. $\Lambda_+(t, F)$ can be expressed by the Mittag–Leffler function:

$$\Lambda_+(t, F) = \frac{E'_{\gamma}(|\lambda_-(F)|t^{\gamma})}{E_{\gamma}(|\lambda_-(F)|t^{\gamma})} \tag{9}$$

In Eq. (9), $E'_{\gamma}(|\lambda_-(F)|t^{\gamma})$ is the reciprocal value of $E_{\gamma}(|\lambda_-(F)|t^{\gamma})$. $\lambda_-(F)$ is the negative root of the function $\det[s\boldsymbol{I} + \check{\boldsymbol{K}}^{-1}(s)\boldsymbol{H}_{\cap}(F)]^{-1} = 0$ and then, $\check{\boldsymbol{K}}(s)$ is the Laplace transform of the fraction kernel matrix $\boldsymbol{K}(t)$. $\boldsymbol{H}_{\cup\cap}(F)$ is the Hessian matrix of $G(x, Q)$ at the transition and bound states:

$$\boldsymbol{H}_{\cup\cap}(F) = \begin{pmatrix} G_{xx}^{\cup/\cap}(F) & G_{xQ}^{\cup/\cap}(F) \\ G_{Qx}^{\cup/\cap}(F) & G_{QQ}^{\cup/\cap}(F) \end{pmatrix} \tag{10}$$

Because of adiabatic approximation [11], the survival probability $S(t)$ is defined that the given particle has not crossed the barrier up to time t. It follows the first order rate equation: $dS(t, F)/dt = -k(t, F)S(t, F)$. Thus: