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Dynamic disorder in receptor-ligand forced dissociation experiments

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Recently experiments showed that some biological noncovalent bonds increase their lifetimes when they are stretched by an external force, and their lifetimes will decrease when the force increases further. Several specific quantitative models have been proposed to explain the intriguing transitions from the "catch bond" to the "slip bond." In this work we propose that the dynamic disorder of the force-dependent dissociation rate can account for the counterintuitive behaviors of the bonds. A Gaussian stochastic rate model is used to quantitatively describe the transitions observed recently in the single bond P-selctin glycoprotein ligand 1–P-selectin force rupture experiment [Marshall *et al.*, Nature **423**, 190 (2003)]. Our model agrees well with the experimental data. We conclude that the catch bonds could arise from the stronger positive correlation between the height of the intrinsic energy barrier and the distance from the bound state to the barrier; classical pathway scenario or *a priori* catch bond assumption is not essential.

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Since Bell proposed the famous force induced dissociation rate [1],

$$k_{\mathrm{off}} = k_{\mathrm{off}}^{0} \exp[\beta f x^{\ddagger}], \tag{1}$$

where $k_{\mathrm{off}}^{0}=k_0 \exp(-\beta \Delta G^{\ddagger})$ is the intrinsic rate constant in the absence of force, $\Delta G^{\ddagger}$ is the height of the intrinsic energy barrier, $x^{\ddagger}$ is the projection of the distance from the bound state to the energy barrier along the applied external force f, and $\beta^{-1}=k_{\mathrm{B}}T$ with k_{B} the Boltzmann's constant and T absolute temperature, the expression has been demonstrated experimentally [2,3] and widely employed in various forced dissociation experiments. Later, at least four other models have been put forward to explain and understand recent forced dissociation experiments [4–6]. In particular, Dembo proposed a Hookean spring model [4,5] to describe force responses of receptor-ligand bonds. In addition to predicting that the dissociation rates of the bonds increase exponentially with the square of the force, the most important contribution of the model may be the finding of a "catch bond" which is defined as increasing its lifetime when the bond is stretched by the force. Correspondingly, a bond described by the Bell expression is defined "slip bond" for its lifetime decreases when the force is applying.

Until recently, the catch bond predicted mathematically was demonstrated in some biological adhesive bonds which include the lectinlike bacterial adhesion protein *FimH* [7], P-selctin glycoprotein ligand 1(PSGL-1)–P- or L-selectins [8,9] complex. However, these experiments also observed that the catch bonds always transit into slip bonds when the stretching force increases beyond a certain value, i.e., their lifetimes are shortened again. The counterintuitive catch-to-slip transition has attracted considerable attention from experimenters and theorists. Several kinetic models have been proposed to explain the intriguing observations in qualitative [9] and quantitative approaches [10–12]. We know that the interface between the ligand and receptor in the adhesive complex has been reported to be broad and shallow, such as the crystal structure of PSGL-1–P-selectin complex revealed in [13]. In addition, as one type of noncovalent bonds, the interactions between the molecules are weaker. Therefore it is plausible that the height and position of the energy barrier of the complex fluctuate with time due to the thermal motion of the whole macromolecular structure. Dissociation reactions with fluctuating energy barriers have been studied in terms of rate processes with dynamic disorder [14], which was proposed and theoretically investigated by Agmon and Hopfield [15]. Hence, it is of interest to determine whether the fluctuation of the height and position of the energy barrier induces the catch-to-slip transition. On the other hand, we also note that in Bell's initial work and in the other models developed later, the intrinsic rate constant k_0 and the distance $x^{\ddagger}$ were determined and time independent. It is possible to derive results from the relaxation of this restriction. Stimulated by the two considerations, in the present work we propose a stochastic Gaussian rate model to quantitatively describe the catch-to-slip bond transitions. In addition to predicting the experimental data, well, our model provides a possible physical origin of the catch bonds: they are likely to be induced by a stronger positive correlation between the fluctuating height of the energy barrier $\Delta G^{\ddagger}$ and the distance $x^{\ddagger}$.

Consider a simple molecular dissociation process under a constant force f,

$$\text{Binding state } (B) \xrightarrow{k_f} \text{unbinding state } (U), \tag{2}$$

where the time-dependent forced dissociation rate $k_f(t)$ is a stochastic variable. If the survival probability $P(t)$ of the state B is assumed to satisfy the first order decay rate equation then its formal solution is given by

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$$P(t) = \left\langle \exp\left(- \int_0^t k_f(\tau) d\tau \right) \right\rangle. \quad (3)$$

Cumulant expansion of the above equation [16] leads to

$$P(t) \approx \exp\left[- \int_0^t d\tau \langle k_f(\tau) \rangle + (\text{higher orders terms}) \right], \quad (4)$$

where the higher order terms mean the higher correlation functions of the rate $k(t)$, e.g., the double integral of the second order correlation function $\langle k_f(t_1) k_f(t_2) \rangle - \langle k_f(t_1) \rangle \langle k_f(t_2) \rangle$, etc.

According to the standard Arrhenius form, we rewrite the Bell expression as $\langle k_f(t) \rangle = k_o \langle \exp\{-\beta[\Delta G^{\ddagger}(t) - f x^{\ddagger}(t)]\} \rangle$. Now the characteristic of the Bell expression is determined by the two stochastic processes $\Delta G^{\ddagger}(t)$, the energy barrier height and the distance from the bound state to the barrier $x^{\ddagger}(t)$. The simplest stochastic properties of them are listed below,

$$\langle \Delta G^{\ddagger}(t) \rangle = \Delta G_0^{\ddagger},$$

$$\langle x^{\ddagger}(t) \rangle = x_0^{\ddagger},$$

$$\langle x^{\ddagger}(t) x^{\ddagger}(0) \rangle - \langle x^{\ddagger}(0) \rangle^2 = K_x(t),$$

$$\langle \Delta G^{\ddagger}(t) \Delta G^{\ddagger}(0) \rangle - \langle \Delta G^{\ddagger}(0) \rangle^2 = K_g(t),$$

$$\langle \Delta G^{\ddagger}(t) x^{\ddagger}(0) \rangle - \langle \Delta G^{\ddagger}(0) \rangle \langle x^{\ddagger}(0) \rangle = K_{gx}(t). \quad (5)$$

Here a stationary process and finite time correlation functions are assumed. Then using cumulant expansion of $\langle k_f(t) \rangle$ again and truncating it to second order, we have

$$\langle k_f(t) \rangle = k_0 \exp\left[- \beta \Delta G_0^{\ddagger} + \frac{\beta^2}{2} K_g - \frac{(x_0^{\ddagger} - \beta K_{gx})^2}{2K_x} \right] \times \exp\left[\frac{\beta^2 K_x}{2} \left(f - \frac{\beta K_{gx} - x_0^{\ddagger}}{\beta K_x} \right)^2 \right], \quad (6)$$

where K_g, K_x, and K_{gx} are the variance and covariance of and between the two stochastic variables at the same time point. Because the above consideration has a similar spirit with the Kubo-Anderson's stochastic line-shape theory [17], and the second order truncations in variables $\Delta G^{\ddagger}$ and $x^{\ddagger}$ are used, we name it Gaussian stochastic rate model (GSRM).

The average dissociation rate Eq. (6) is so simple that we can immediately distinguish four different physical situations according to the definitions of the parameters: (i) If all K_x, K_g, and K_{gx} vanish, then the average rate is just the classical Bell expression Eq. (1); (ii) If both K_x and K_{gx} vanish or in the absence of the fluctuation of the distance $x^{\ddagger}(t)$, $\langle k_f(t) \rangle$ still keeps the Bell formula except that the intrinsic dissociation rate changes into $k_0 \exp(-\beta \Delta G^{\ddagger} + \beta^2 K_g / 2)$, i.e., the fluctuation of the barrier height speeds up the dissociation process [15]. (iii) If both K_g and K_{gx} vanish or in the absence of the fluctuation of $\Delta G^{\ddagger}$, then we have

$$\langle k_f(t) \rangle = k_0 \exp(-\beta \Delta G^{\ddagger}) \exp\left[\beta x_0^{\ddagger} f + \frac{\beta^2 K_x}{2} f^2 \right]. \quad (7)$$

Different from the Bell expression, when the force is larger, the dissociate rate increases exponentially with the square of force. This conclusion is very similar with that of Dembo *et al.* [4]. However the physical origin is completely different: The square of the force here arises from the fluctuation of the distance $x^{\ddagger}$. It also means the bond is still slip and the lifetime of the bond is shorter than that predicted by the Bell formula. Of course, if the variance of the distance K_x is very small, the modification to the Bell expression can be neglected. Although the result is interesting, in the following part we only focus on the fourth case, in which (iv) both the distance and the barrier height are stochastic variables. Because the force is positive at the beginning, if $K_{gx} \leqslant 0$ or $(\beta K_{gx} - x_0^{\ddagger}) \leqslant 0$, the behavior of the average dissociation rate is then similar to the case in (iii). However if $x_e^{\ddagger} \equiv \beta K_{gx} - x_0^{\ddagger} > 0$, we see that the rate first decreases with the increasing of the force, and then increases when the force is beyond $f_c \equiv x_e^{\ddagger} / \beta K_x$, where the new parameters $x_e^{\ddagger}$ and f_c are defined for they have same dimensions of distance and force. Hence, our model predicts the possibility of the catch-slip bond transition at some critical transition force f_c.

We first consider the single molecule constant force rupture experiment [8], where the average lifetime of the bond sPSGL-1–P-selectin was measured. Because the average dissociation rate $k_f(t)$ is time independent, the survival probability $P(t)$ is a simple exponential function $\exp[-t \langle k_f \rangle]$. Following the general definition, the average lifetime of the bond is just $\bar{t}(f) = 1 / \langle k_f \rangle$. There are six parameters in this model. But in fact we can combine them into only three: the intrinsic dissociation rate $k_0^d = k_0 \exp[-\beta \Delta G_0^{\ddagger} + (\beta^2/2) K_g]$, which is the parameter that experiments can measure in practice, and the effective distance $x_e^{\ddagger}$ defined above, and K_x; they are independent of each other. The average time then is

$$\bar{t}(f) = N^{-1} \exp\left[- \frac{(f - f_c)^2}{2\sigma^2} \right] = \left\{ k_0^d \exp\left[- \frac{x_e^{\ddagger 2}}{2K_x} \right] \right\}^{-1} \exp\left[- \left(f - \frac{x_e^{\ddagger}}{\beta K_x} \right)^2 / 2(\beta^{-2} K_x^{-1}) \right]. \quad (8)$$

It is unexpected to find that the average lifetime of the bond is a Gaussian-like function with respect to the force: the mean value is f_c, the variance σ, and a prefactor N^{-1}. Their corresponding definitions see the above equation and are introduced for convenience. Apparently they are still independent. According to the characteristic of Gaussian function, we can easily estimate the relevant parameters from the experimental data even without numerical methods; see Fig. 1: they are respectively $k_0^d \approx 133.0/\text{s}$, $x_e^{\ddagger} \approx 2.88$ nm, and $K_x \approx 1$ nm^2, whereas the important correlation coefficient $K_{gx} \geqslant 12.0$ pN$\times$nm^2 and the catch-slip transition force $f_c \approx 12$ pN which is directly read out from the experimental data. Here the estimation is performed at room temperature. We see that our prediction agrees with the data very well, in particular when the force is lower than f_c [18]. Interestingly,

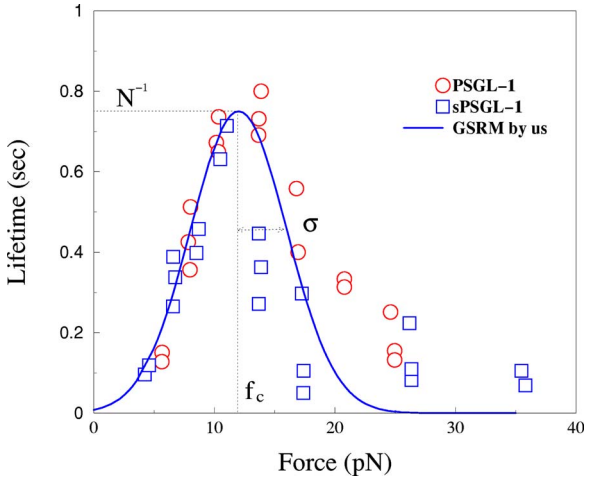

FIG. 1. (Color online) Average lifetime as a function of the applied constant force for bonds of dimeric P-selectin with monomeric sPSGL-1 (blue square symbols) [8] and the rescaled dimeric PSGL-1 (red circle symbols) from Ref. [12]. The blue solid line is given by GSRM. For the definitions of the symbols N, σ, and f_c see Eq. (9).

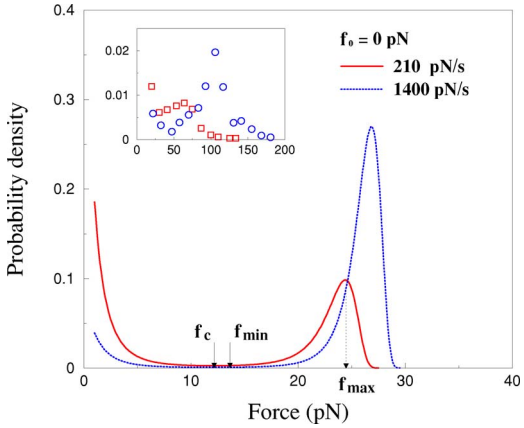

FIG. 2. (Color online) The distribution of rupture forces under two loading rates predicted by our model for binding of P-selectin to sPSGL-1. The symbols of inset are the steady ramp experimental data [10], where the loading rates are 210 pN/s (red squares) and 1400 pN/s (blue circles), respectively. We must point out that the experimental data is for binding of P-selectin to PSGL-1, while our parameters are for sPSGL-1.

the above result also shows that, only through forced dissociation experiment, we cannot isolate the precise information about the variance of the energy barrier height and the cross variance of the height and the distance.

A more challenging experiment to our theory is force jump-ramp case, where the force increases linearly in time from a initial jump force f_0, $f=f_0+rt$, and r is the ramp rate [10]. In general, the stationary assumption of the forced dissociation processes should be more reasonable for the constant case. Considering that the direct extension of the Bell expression to the time-dependent force case still provides insightful results [6]. It is of interest to see what we can get by extending Eq. (6) to force jump-ramp cases. Because the experimental data is typically presented in terms of the force histogram, we calculate the rupture force distribution $P(f,f_0)$ according to definition $P(f,f_0)df=-(dS/dt)dt$ below,

$$P(f,f_0)=\frac{N}{r}\exp\left[\frac{(f-f_c)^2}{2\sigma^2}-\frac{N}{r}\int_{f_0}^{f}df' e^{(f'-f_c)^2/2\sigma^2}\right]. \quad (9)$$

We see that the average lifetime can be extracted from the above equation by setting $f=f_0$, i.e., $\bar{t}(f)=1/rP(f_0,f_0)$.

We calculate the force distributions of steady ramps ($f_0=0$ pN) at ramp rates 210 and 1400 pN/s to compare with the experiment performed by Evans *et al.* [10]; see Fig. 2, where we use the same parameters obtained above. We find that the main qualitative characteristics of the predictions and the experimental data are the same: the distributions and the force histograms reach the maximum and minimum at two distinct forces, which are named $f_{\min}$ and $f_{\max}$ respectively. This observation could be understood by setting the derivative of Eq. (9) with respect to f equal to zero,

$$f-f_c=\frac{N\sigma^2}{r}\exp\left[\frac{(f-f_c)^2}{2\sigma^2}\right]. \quad (10)$$

Interestingly, Eq. (10) has no solutions when the loading rate is smaller than a critical ramp rate r_c, which can be obtained by simultaneously solving the above equation and its first derivative,

$$1=\frac{N}{r}(f-f_c)\exp\left[\frac{(f-f_c)^2}{2\sigma^2}\right]. \quad (11)$$

Then $r_c=N(f^*-f_c)\exp[(f^*-f_c)^2/2\sigma^2]$, here f^* is the force at which the maximum and minimum merge. We estimate $r_c\approx 9$ pN/s using the current parameters. If $r\leqslant r_c$, then the distribution is monotonous and decreasing function. Another important prediction is that the values of $f_{\min}$ and $f_{\max}$ must be larger than the catch-slip transition force f_c. Indeed the experimental observation shows that the force value at the minimum force histogram are around a certain value even the ramp rates change ten fold. (see Figs. 2 and 4 in Ref. [10]). According to Eq. (10), when the ramp rate is sufficiently large, we easily obtain

$$f_{\min}\approx f_c+\frac{N\sigma}{r} \quad (12)$$

by linear expansion. Therefore we predict that $f_{\min}$/s observed in Evans *et al.* experiment [10] are almost the catch-slip transition force observed in the constant force rupture experiment performed by Marshall *et al.* [8,19]. Unfortunately, a simple analytic relationship between $f_{\max}$ and r cannot be found from Eq. (10). Even so, the extrema equation implies that $f_{\max}$ is a monotonous and increasing function of the ramp r, but the increase is very slow and is about $f_{\max}\propto\sqrt{\ln r}$ instead of $f_{\max}\propto\ln r$ [10,12].

We know that the rupture force distribution of a simple slip bond only has a maximum at a certain force value that depends on the ramp rate [20]. Therefore the catch-slip bond can easily be distinguished from the slip case by the presence of a minimum on the force rupture density function at a nonvanished force. Because the above analysis is indepen-

dent of the initial force jump f_0, in order to track the catch behaviors in the force jump-ramp experiments, the initial force f_0 should be smaller than f_c.

In conclusion, we proposed a stochastic dissociation rate model to explain the intriguing catch-slip bond transitions observed in the single molecule forced dissociation experiments, while the fluctuating rate is dependent on the two correlated stochastic control variables, the energy barrier height $\Delta G^{\ddagger}$ and the distance $x^{\ddagger}$ between the bound state and the energy barrier. Compared to the previous models with five [10], seven [11], and four parameters [12] involved, our model only requires three physical parameters: k_0^d, $x_e^{\ddagger}$, and K_x. Moreover, GSRM does not need the classical pathway concept or *a priori* catch bond [10–12,21]. Because there is no direct experiments or molecular structures supporting the pathway scenario, a change in concept would be important for further experimental study of the catch-slip bonds.

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[18] Equation (9) predicts that the averge lifetime of the bond is symmetric relative to the critical force f_c, while the experimental data are clearly skewed towards a large force. We simply attribute the discrepancy to the second-order truncation approximations of the rate in Eq. (3) and the variables $\Delta G^{\ddagger}$ and $x^{\ddagger}$ in Eq (6). Further analysis is needed to give a quantitave conclusion about the effects of the approximations.
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