Dynamic disorder in receptor-ligand forced dissociation experiments

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(Dated: July 11, 2018)

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”. Different from the previous efforts, 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-selectin glycoprotein ligand 1 (PSGL-1) – P-selectin force rupture experiment [Marshall, et al. (2003) Nature 423, 190-193]. Our model agrees well to 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.

PACS numbers: 87.15.Aa, 82.37.Rs, 87.15.By, 82.20.Uv

Since Bell firstly proposed the famous force induced dissociation rate

\[ k_{\text{off}} = k_0 \exp(\beta f x^\dagger), \]  

where \( k_0 \) is the intrinsic rate constant in the absence of force, \( \Delta G^\dagger \) is the height of the intrinsic energy barrier, \( x^\dagger \) is projection of the distance from the bound state to the energy barrier along the applied external force \( f \), and \( \beta = k_B T \) with \( k_B \) the Boltzmann’s constant and \( T \) absolute temperature, the expression has been demonstrated experimentally and widely employed in various forced dissociation experiments. Later, at least four other models have been put forward to explain and understand newcoerced forced dissociation experiments. In particular, Dembo proposed a Hookean spring model 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 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 lectin-like bacterial adhesion protein FinH, P-selectin glycoprotein ligand 1 (PSGL-1) – P-selectin complex, or L-selectin complex. However, these experiments also observed that the catch bonds always transit into slip bonds when the stretching force increases beyond a certain values, 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 and quantitative approaches. 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 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 thermal motion of the whole macromolecular structure. Dissociation reactions with fluctuating energy barriers have been studied in terms of rate processes with dynamic disorder, which was first proposed and theoretically investigated by Agmon and Hopfield. 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 \( x^\dagger \) were determined and time-independent. It is possible to derive novel results from 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.

\[ k_{\text{off}} = k_0 \exp(-\beta \Delta G^\dagger), \]

\[ \Delta G^\dagger = k_B T \]
transitions. In addition to well predicting the experimental data, our model provides a new possible physical origin of the catch bonds: they are likely to be induced by stronger positive correlation between the fluctuating height of the energy barrier $\Delta G^2$ and the distance $x^\dagger$.

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

$$\text{Binding state (B) } \xrightarrow{k_f} \text{Unbinding state (U)},$$

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

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

Cumulant expansion of the above equation [18] leads to,

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

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 standard Arrhenius form, we rewrite the Bell expression as $\langle k_f(t) \rangle = k_0 \exp[-\beta(\Delta G^2(t) - fx^\dagger(t))]$. Now the characteristic of the Bell expression is determined by the two stochastic processes $\Delta G^2(t)$, the energy barrier height and the distance from the bound state to the barrier $x^\dagger(t)$. The simplest stochastic properties of them are listed below:

$$\begin{align*}
\langle \Delta G^2(t) \rangle &= \Delta G^2_0 \\
\langle x^\dagger(t) \rangle &= x^\dagger_0 \\
\langle x^\dagger(t)x^\dagger(0) \rangle &= K_g(t) \\
\langle \Delta G^2(t) \Delta G^2(0) \rangle &= K_g^2(t) \\
\langle \Delta G^2(t)x^\dagger(0) \rangle &= K_gx(t) \\
\langle \Delta G^2(t)x^\dagger(0) \rangle &= K_gx(t).
\end{align*}$$

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

$$\langle k_f(t) \rangle = k_0 \exp\left[-\beta\Delta G^2_0 + \frac{\beta^2}{2}K_g - \frac{(x^\dagger_0 - \beta K_gx^\dagger)^2}{2K_x}\right] \times \exp\left[\frac{\beta^2 K_x}{2} \left( f - \frac{\beta K_gx - x^\dagger_0}{\beta K_x}\right)^2 \right],$$

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 [19], and the second order truncations in variables $\Delta G^2$ and $x^\dagger$ are used, we name it Gaussian stochastic rate model (GSRM).

The average dissociation rate $\langle k_f(t) \rangle$ is so simple that we can immediately distinguish four different physical situations according to the definitions of the parameters: (i) if all $K_g$, $K_x$, and $K_{gx}$ vanish, then average rate is just the classical Bell expression Eq. (4); (ii) if both $K_g$ and $K_{gx}$ vanish or in the absence of the fluctuation of the distance $x^\dagger(t)$, $\langle k_f(t) \rangle$ still keeps the Bell formula except that the intrinsic dissociation rate changes into $k_0 \exp(-\beta\Delta G^2(0) + \beta^2 K_g/2)$, i.e., the fluctuation of the barrier height speeds up the dissociation process [17]. (iii) If both $K_g$ and $K_{gx}$ vanish or in the absence of the fluctuation of $\Delta G^2$, then we have

$$\langle k_f(t) \rangle = k_0 \exp(-\beta\Delta G^2) \exp\left[\beta x^\dagger_0 f + \frac{\beta^2 K_x}{2} f^2 \right].$$

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 $x^\dagger$. 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 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 $K_{gx} \leq 0$ or $(\beta K_gx - x^\dagger_0) \leq 0$, the behavior of the average dissociation rate is then similar to the case in (iii). However if $x^\dagger_0 \equiv \beta K_gx - x^\dagger_0 > 0$, we see that the rate first decreases with the increasing of the force, and then increases when the force is beyond $f_c \equiv x^\dagger_0/\beta K_x$, where the new parameters $x^\dagger_c$ 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 [11], 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 $\tilde{t}(f) = 1/(\langle k_f \rangle)$. There are six parameters in this model. But in fact we can combine them into only three: the intrinsic dissociation rate $k_0 \equiv k_0 \exp\left[-\beta\Delta G^2_0 + \beta^2 K_g/2\right]$, which is the parameter that experiments can measure in practice, and the effective distance $x^\dagger_c$ defined above, and $K_x$; they are in-
dependent of each other. The average time then is

$$
\bar{t}(f) = N^{-1} \exp \left[ \frac{-(f-f_c)^2}{2\sigma^2} \right] 
= \left\{ t_0^d \exp \left[ -\frac{x_c^2}{2K_x} \right] \right\}^{-1}
\times \exp \left[ -\left( f - \frac{x_c^2}{\beta K_x} \right)^2 / 2(\beta^{-2} K_x^{-1}) \right].$$

(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 $\sigma$ and a prefactor $N^{-1}$; their corresponding definitions see the above equation. 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 $k_0^d \approx 133.0 / s$, $x_c^2 \approx 2.88$ nm, and $K_x \approx 1$ nm$^2$, whereas the important correlation coefficient $K_{px} \geq 12.0$ pN·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 $f_c$ [10]. Interestingly, 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.

![Figure 1](image1.png)

**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) [10] and the rescaled dimeric PSGL-1 (red circle symbols) from Ref. [14]. The blue solid line is given by GSRM. The definitions of the symbols $N$, $\sigma$, and $f_c$ see Eq. (9).

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 ramp rate [12]. 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 time-dependent force case still provides insightful results [6], it is of interest to see what we can get by extending Eq. (9) 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 $P(f, f_0)df = -(dS/dt)dt$, which is given below,

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

(9)

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

We calculate the force distributions of the steady ramps ($f_0 = 0$ pN) at ramp rates 210 and 1400 pN/s to compare with the experiment performed by Evans et al. [12] (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 $f_{\text{min}}$ and $f_{\text{max}}$ respectively. This observation could be understood by setting the derivative of Eq. (9) with respect to $f$ equal to zero,

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

(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

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

(11)

Then $r_c = N(f^* - f_c)/(f^* - f_c)^2/2\sigma^2)$, here $f^*$ is the force at which the minimum and maximum merge. We estimate $r_c \approx 9$ pN/s using the current parameters. If $r \leq r_c$, then the distribution is monotonous and decreasing function. Another important prediction is that the values of $f_{\text{min}}$ and $f_{\text{max}}$ must be larger than the catch-slip transition force $f_c$. Indeed the experimental observation shows that the force values at the minimum force histogram are around a certain values even the ramp rates change 10 folds. (see Figs. 2 and 4 in Ref. [12]). According to Eq. (10), when the ramp rate is sufficiently large, we easily obtain

$$
f_{\text{min}} \approx f_c + \frac{N\sigma}{r}$$

(12)

by linear expansion. Therefore we predict that $f_{\text{min}}$ observed in Evans et al. experiment [12] are almost the...
catch-slip transition force observed in the constant force rupture experiment performed by Marshall et al. [12, 21]. Unfortunately, simply analytic relationship between \( f_{\text{max}} \) and \( r \) cannot be found from Eq. (10). Even so, the extrema equation implies that \( f_{\text{max}} \) is a monotonous and increasing function of the ramp \( r \), but the increasing is very slow and is about \( f_{\text{max}} \propto \sqrt{\ln r} \) instead of \( f_{\text{max}} \propto \ln r \) [12, 14].

In conclusion, we proposed a stochastic dissociation rate model to explain the intriguing catch-slip bond transition 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 [12], seven [13] and four parameters [14] involved, our model only requires three physical parameters: \( k_{0,0}^d \), \( x^\ddagger \), and \( K_x \). Moreover, GSRM does not need the classical pathway concept or a priori catch bond. 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.

F.L. would like to thank Tokyo Institute of Technology for hospitality, where this work was completed.

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\[ f_c = h \ln \frac{f_{\text{min}}}{f_{\text{max}}} \]

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 [12], 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.

We know that the rupture force distribution of simple slip bond only has a maximum at a certain force value that depends on the ramp rate [22]. Therefor 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 nonvanished force. Because the above analysis is independent 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 \( f_c \).

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