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Distinctive features of the biological catch bond in the jump-ramp force regime predicted by the two-pathway model

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The receptor-ligand unbinding in the biological catch bond is analyzed within a simple model that comprises a single bound state and two unbinding pathways. This model is investigated in detail for the jump-ramp force regime, where the pulling force quickly jumps to a finite value and then is ramped linearly with time. Two qualitative criteria are identified that distinguish the catch bond from the slip bond. First, the rupture force probability density of the catch-bond exhibits a maximum-minimum pair, which develops at finite forces. In contrast, the slip bond produces a maximum that first appears at zero force. Second, the catch bond can be identified over a wide range of ramp rates by high rupture probabilities at low forces relative to the probability at the maximum, in contrast to the slip bond, where the probability at the maximum always corresponds to the most likely rupture force. Both distinctive features of the catch bond are masked by large jump forces, indicating that the catch bond is best identified in experiments with moderate loading rates and small jump forces. The catch-bond lifetime in the constant force regime is related to the probability density in the jump-ramp regime, allowing one to determine the bond lifetime for a constant force by measuring the initial probability density in the jump-ramp experiments with different jump forces and a fixed ramp rate. The key analytic results are illustrated with the *P*-selectin/*P*-selectin glucoprotein ligand-1 bond.

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The binding of biological macromolecules through weak, noncovalent interactions is critical for the functioning of living organisms and their individual components. An understanding of the physics of the interactions can be achieved by consideration of a potential energy profile that governs the relative motion of receptor and ligand. The details of the receptor-ligand interaction profile, including the number of potential energy minima describing bound states, the types of unbinding pathways, the heights of the energy barriers along these pathways and so on, are of great interest to both experimentalists and theoreticians. The receptor-ligand binding can be probed experimentally by application of an external force. Current experimental measurements are performed on ensembles of receptor-ligand complexes perturbed by hydrodynamic shear stress [1–4] and with individual systems manipulated with atomic force microscopy (AFM) [5–8] or optical tweezers [9–11]. The applied forces can be both stationary [7,8] and time dependent [12,13]. The studies of catch-bond ensembles by hydrodynamic perturbations and investigations of individual bonds with AFM complement each other, creating a more complete picture of the receptor-ligand interaction.

Generic with the known biological receptor-ligand bonds, the bond lifetime decreases when a sufficiently strong force pulls the bond. This regime is known as the slip bond and occurs because the force lowers the energy barrier between the bound and free states [14,15]. In contrast to the slip bond, the catch bond is an unusual type of receptor-ligand binding, where an external force pulling the bond increases the binding strength [16]. The growth of the catch-bond lifetime with applied force is observed up to a critical force value, beyond which the bond transforms into the ordinary slip bond.

As discussed in [17], the catch-slip transition has been discovered in systems involving bacterial cell attachment to host cells via the lectinlike adhesin FimH [3] as well as in the binding of *P*- or *L*-selectins with *P*-selectin glucoprotein ligand-1 (PSGL-1). The FimH system has been investigated in flow chamber experiments, where the hydrodynamic shear stress creates a detaching force acting to break the bond. The selectin systems have been investigated both in flow chambers and by AFM. The constant force scenario used to study the *P*-selectin/PSGL-1 complex in [7,8] has been extended in [13] to the jump-ramp regime, revealing additional features of the biological catch-slip bond.

A model of the catch bond with a single bound state and two alternative pathways to the free state was considered in [18] and applied for the interpretation of the experimental data [7,8,13]. The model contains four independent parameters, one less than the model developed in [13]. A seven-parameter model was recently described in [19]. General features of two-pathway models were considered in [20]. Reference [8] rationalized the shape of the receptor-ligand interaction potential of the two-pathway model.

The current paper analyzes the two-pathway, single-bound-state model for the jump-ramp force regime. The experimental signatures of the time-dependent force that follow from the two-pathway description of the biological catch bond are considered in detail. The rupture force probability density is investigated as a function of the applied force for varying jump values and loading rates. The analytic results obtained with the two-pathway model in the jump-ramp force regime are illustrated with the experimental data on the *P*-selectin/PSGL-1 complex [13].

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Our previous work [18] focused on the two-pathway model represented by the receptor-ligand interaction potential, whose one-dimensional projection onto the direction of the applied force is shown Fig. 1. The ligand escapes from the bound state minimum 1 into the free state 0 by passing through either the slip, x_s, or catch, x_c, barrier. The bond survival probability distribution function $P(t)$ satisfies the rate equation

$$\frac{dP(t)}{dt} = -(k_{1s} + k_{1c})P(t), \tag{1}$$

where k_{1s} and k_{1c} are the rate constants for the escape over the slip and catch barriers, respectively. According to Bell [14], the effect of the pulling force on the rate constants can be explicitly represented by

$$k_{1s} = k_{1s}^0 \exp(x_{1s}f/kT), \quad k_{1c} = k_{1c}^0 \exp(-x_{1c}f/kT). \tag{2}$$

T is temperature and k is the Boltzmann constant. The coefficients k_{1s}^0 and k_{1c}^0 define the rates at zero force. The difference in the signs in the exponential force dependence in (2) is critical for the catch-slip transition. The catch barrier is lower than the slip barrier in the absence of the force (Fig. 1). The force raises the catch barrier and lowers the slip barrier, inverting their relative heights [18]. The parameters x_{1s} and x_{1c} are the distances between the minimum and the corresponding maxima, and determine the work carried by the force on the ligand as it covers these distances. The work is positive in the slip direction and negative in the catch direction.

The analysis of the model presented in [18] indicates that with a constant pulling force the probability distribution function obeying Eq. (1) has the simple form

$$P(t) = \exp[-t/\tau(f)], \tag{3}$$

with the inverse bond lifetime τ expressed by the sum of the slip and catch contributions

$$1/\tau(f) = k_{1s}^0 \exp(x_{1s}f/kT) + k_{1c}^0 \exp(-x_{1c}f/kT). \tag{4}$$

Reference [18] showed that the bond lifetime $\tau(f)$ exhibits a maximum as a function of the pulling force provided that

$$(k_{1c}^0 x_{1c})/(k_{1s}^0 x_{1s}) > 1.$$

Further discussion of the catch-bond model assumes that this condition holds. Equation (4) gives good agreement [18] with the experimental data [7,8] on binding of *P*- and *L*-selectins with PSGL-1 in both monomeric and dimeric forms.

This paper extends the analytic analysis of the two-pathway model to the widely used jump-ramp force scenario introduced and applied to the *P*-selectin/PSGL-1 complex by Evans and co-workers [5,12,13]. The experimental implications of the two-pathway model in the time-dependent regime are discussed. In jump-ramp experiments, the force rapidly, nearly instantaneously, increases to a jump value f_0 and then gradually grows with the loading rate constant r

$$f(t) = f_0 + rt. \tag{5}$$

The solution of Eq. (1) with the time-dependent force (5) is straightforward, but has a complicated analytic form. The experimental data is typically presented in terms of the force histograms [13] that are most conveniently described by a rupture force probability density. The latter is obtained by solving Eq. (1) and changing variable t to f

FIG. 1. Schematic representation of the two-pathway potential responsible for the catch-slip transition in the biological catch bond. A ligand in the bound state x_1 can escape to the free state 0 through either of the two transition states x_s, x_c. The vector indicates the direction of the force f applied to the ligand.

$$p(f,f_0) = \frac{1}{r\tau(f)} \exp\left[-\frac{kT}{r} g(f,f_0)\right], \tag{6}$$

where

$$g(f,f_0) = \varphi(f) - \varphi(f_0),$$
$$\varphi(f) = \frac{k_{1s}^0}{x_{1s}} \exp\left(\frac{x_{1s}f}{kT}\right) - \frac{k_{1c}^0}{x_{1c}} \exp\left(\frac{-x_{1c}f}{kT}\right). \tag{7}$$

Equations (6) and (7) are defined for forces greater than the jump force

$$f \geqslant f_0. \tag{8}$$

The rupture force probability density (6) evaluated at f_0 immediately gives the bond lifetime (4) $\tau(f_0) = 1/[rp(f_0,f_0)]$ of the constant force regime [7,8]. This result directly relates the constant force experiments [7,8] to the jump-ramp experiments [13] allowing one to determine the bond lifetime $\tau(f)$ under a constant force by measuring the initial probability density $p(f_0,f_0)$ in the jump-ramp experiments with different jump forces f_0 and a fixed ramp rate r.

Further, it is well known for the simple slip-bond model ($k_{1c}^0 = 0$) that the probability density $p(f,f_0)$ is maximized at a certain force value that depends on r. It is important to establish what force values maximize the probability density in the two-pathway catch-slip model. The extrema are determined by setting the derivative of (6) with respect to f equal to zero,

$$[1/\tau(f)]_f' - r^{-1}[1/\tau(f)]^2 = 0. \tag{9}$$

Since the lifetime $\tau(f)$, Eq. (4), contains no f_0, Eq. (9) proves that the extrema in the probability density are independent of the initial force jump f_0. The extrema will be observed if they fall within the force interval (8).

The extrema in the rupture force probability density will be observed only for sufficiently large loading rates, since with small r, the second term in Eq. (9) is greater than the first, and Eq. (9) has no solutions. When r is sufficiently large, the value $f_{\max}$ of the force that maximizes the probability density grows with r, and the contributions of the

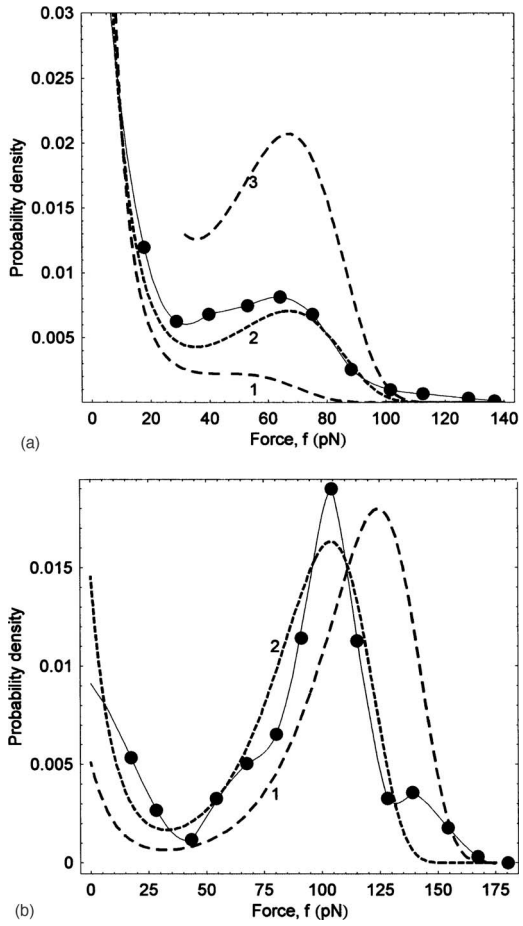

FIG. 2. Bond rupture force probability densities. The points (●) show the experimental data by Evans *et al.* [13] connected by an interpolation curve. The dashed lines represent the theoretical results, Eq. (6). (a) Experimentally: $r=210$ pN/s and $f_0=0$. The theoretical lines correspond to: (1) critical ramp rate $r=r_c=95.6$ pN/s characterizing the onset of the maximum-minimum pair in the probability density and $f_0=0$; (2) $r=210$ pN/s and $f_0=0$ as in the experiment; (3) $r=210$ pN/s and $f_0=30$ pN illustrating the effect of finite jump force. (b) Experiment: $r=1400$ pN/s, $f_0=0$. Theory: (1) $r=4000$ pN/s, $f_0=0$; (2) $r=1400$ pN/s, $f_0=0$.

catch pathway can be neglected in view of the negative sign in front of the force in the catch exponents. This leads to the known expression

$$f_{\max}=\frac{kT}{x_{1s}}\ln\frac{rx_{1s}}{kTk_{1s}^0} \tag{10}$$

that maximizes $p(f)$ for the slip system, when $k_{1c}^0=0$ and $r>kTk_{1s}^0/x_{1s}$, and maximizes $p(f)$ for the catch-slip system with sufficiently large loading rates.

While the force $f_{\max}$ [Eqs. (9) and (10)], is independent of the jump value f_0, the maximum value of the density itself strongly depends on f_0

$$p(f_{\max},f_0)\sim\exp\left[\frac{kTk_{1s}^0}{rx_{1s}}\exp\left(\frac{x_{1s}f_0}{kT}\right)\right]. \tag{11}$$

Since the probability density is normalized, its growth in one region must be accompanied by decline in another region.

Equation (9) for the catch-bond system has a pair of solutions above the critical value $r>r_c$. In addition to Eq. (10), the second solution $f_{\min}$ corresponds to a minimum in the probability density. The minimum is absent in purely slip-bond systems and appears due to the catch barrier. The dependence of $f_{\min}$ on r is more complex compared to $f_{\max}$ and could not be found analytically. With decreasing r the maximum and minimum merge at a critical force $f=f_c$. At loading rates below the critical value r_c, the probability density is a monotonically decreasing function of force. The critical values of the loading rate r_c and force f_c are found by setting the first and second derivatives of $p(f,f_0)$, Eq. (6), with respect to f equal to zero. Combination of Eq. (9) for the first derivative with the corresponding equation for the second derivative leads to the following equation that defines the critical force:

$$[1/\tau(f)]_f''-2r^{-2}\tau(f)^{-3}=0. \tag{12}$$

The simultaneous solution of Eqs. (9) and (12) gives the critical loading rate

$$r_c=[1/\tau(f_c)]^2/[1/\tau(f)]'_{f=f_c}. \tag{13}$$

The catch-slip-bond system can be easily identified and distinguished from the slip-bond system by the following two features of the bond rupture probability density at loading rates above the critical value (13). First, the catch-bond density exhibits a pair of extrema, a maximum and a minimum, that simultaneously develop at a finite force $f\neq 0$ when $r=r_c$. In contrast, the slip bond develops only a maximum, which first appears at $f=0$. Second, the catch-bond shows significantly higher rupture probabilities at low forces than the slip bond. In particular for $f_0=0$, the ratio of the initial probability density to the density in the maximum is always less than one for the slip bond

$$p_{slip}(0,0)/p_{slip}(f_{\max},0)<1,\quad f_{\max}\neq 0, \tag{14}$$

and, within a wide range of loading rates $r<2kTk_{1c}^0/x_{1s}$, is greater than one for the catch bond

$$p_{catch}(0,0)/p_{catch}(f_{\max},0)\approx d\exp d>1,\quad d=(kTk_{1c}^0)/(rx_{1s}). \tag{15}$$

In addition, considering the hypothetical slip bond as the limit of the present model in the absence of the catch pathway ($k_{1c}^0=0$), it is straightforward to show that the ratio of the initial probability densities for the catch and slip bonds

$$p_{catch}(0,0)/p_{slip}(0,0)=1+k_{1c}^0/k_{1s}^0 \tag{16}$$

is significantly greater than one, since the catch barrier is smaller than the slip barrier, $k_{1c}^0/k_{1s}^0>1$. For instance, in the *P*-selectin/PSGL-1 system $k_{1c}^0/k_{1s}^0\approx 60$.

The expressions derived above provide valuable tools for analysis of the experimental data. Consider the jump-ramp experiments with the *P*-selectin/PSGL-1 complex [13]. Direct fit [18] of the experimental data yielded the following set of parameter values $k_{1s}^0=0.34\ s^{-1}$, $k_{1c}^0=20\ s^{-1}$, $x_{1s}=2.1$ Å, $x_{1c}=3.8$ Å. Solution of Eqs. (12) and (13) for the critical values of r_c, f_c with these parameters and temperature $kT=40.8$ pN Å gives $r_c=95.6$ pN/s, $f_c=45.6$ pN. For load-

ing rates $r \leqslant 95.6$ pN/s the survival probability density of the *P*-selectin/PSGL-1 bond is a monotonic function of force [see curve 1 in Fig. 2(a)] computed with $r=r_c$. For loading rates above 95.6 pN/s the probability density shows a maximum-minimum pair [curves 2, 3 in Fig. 2(a)].

The theoretical results are compared with the original experimental data reported by Evans *et al.* in the form of force histograms [13]. The histograms of Figs. 2(b) and 2(c) in [13] were normalized to obtain the probability densities and are represented in Figs. 2(a) and 2(b) of this paper by black dots connected with interpolation lines. The corresponding experimental loading rate values equal $r=210$ pN/s and $r=1400$ pN/s. The jump force is zero in both cases. The dashed lines in Fig. 2(a) and 2(b) represent the prediction of the two-pathway model (6). The short-dashed lines 2 in Figs. 2(a) and 2(b) are computed for the experimental jump and ramp values and show good agreement with the experimental data.

The effect of a nonzero jump force is illustrated in Fig. 2(a) by line 3, for which $f_0=30$ pN and $r=210$ pN/s. Compared to line 2 with $f_0=0$ and $r=210$ pN/s, the probability density corresponding to the nonzero jump is notably increased at large forces $f \geqslant 30$ pN at the expense of the low force region. Line 1 in Fig. 2(b) demonstrates the shift of the probability maximum with loading rate. For rates $r > 200$ pN/s, the location of the maximum is well described by the slip-pathway limit (10); however, the overall shape of the probability density, including the existence of the minimum in the low-force region, requires both slip- and catch-pathway contributions.

In summary, the present paper presented a detailed analysis of the biological two-state catch-bond dissociation under the action of the time-dependent force (5). The catch-slip transition in the receptor-ligand binding is described by a simple model involving a single bound state and two dissociation pathways. The analysis of the bond survival probability density function revealed two distinctive features that can be easily used for experimental identification of biological catch and slip bonds. First, the rupture force probability density of the catch bond exhibits both a minimum and a maximum as a function of the applied force, in contrast to the slip bond, which develops only a maximum. The minimum and maximum of the catch bond exist above a critical loading rate $r > r_c$, and merge and disappear at the critical point $r = r_c$. The critical force at which the catch-bond minimum-maximum pair disappears is finite, in contrast to the slip bond, where the maximum vanishes at zero critical force. Below the critical point $r < r_c$ the probability densities of both catch and slip bonds are monotonous and decreasing functions of force. Second, the catch bond exhibits high rupture probabilities at low forces relative to the maximum. While the maximum in the probability density distribution always corresponds to the most likely rupture force for the slip bond, the catch bond remains more likely broken by a low force within a wide range of loading rates. The fact that a low-force probability density is greater than the density in the maximum provides a clear indication of a catch bond. Both features that distinguish the catch bond from the slip bond are masked by large jump forces f_0. It is, therefore, desirable to study the catch-bond unbinding at relatively large loading rates and small jump forces. The analytic results obtained with the two-pathway model in the jump-ramp force regime were illustrated with the experimentally well-studied *P*-selectin/PSGL-1 receptor-ligand complex.

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