

# Entropic-elasticity-controlled dissociation and energetic-elasticity-controlled rupture induce catch-to-slip bonds in cell-adhesion molecules

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We develop a physical model to describe the kinetic behavior in cell-adhesion molecules. Unbinding of noncovalent biological bonds is assumed to occur by both bond dissociation and bond rupture. Such a decomposition of debonding processes is a space decomposition of the debonding events. Dissociation under thermal fluctuation is nondirectional in a three-dimensional space, and its energy barrier to escape is not influenced by a tensile force, but the microstates that could lead to dissociation are changed by the tensile force; rupture happens along the tensile force direction. An applied force effectively lowers the energy barrier to escape along the loading direction. The lifetime of the biological bond, due to the two concurrent off rates, may grow with increasing tensile force to a moderate amount and then decrease with further increasing load. We hypothesize that a catch-to-slip bond transition is a generic feature in biological bonds. The model also predicts that catch bonds in a more flexible molecular structure have longer lifetimes and need less force to be fully activated.

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## I. INTRODUCTION

Based on the kinetic theory of the strength of solids developed by Zhurkov [1], Bell [2] showed that the lifetime of biological bonds shortens exponentially with increasing tensile force. The model has been used broadly to depict the weakening of biological bonds [3,4], and a bond with such behavior is usually termed a “slip bond.”

In the last few years, progress in experimental techniques has enabled the mechanical activation of chemical bonds to be studied on both an individual basis [5–7] and in a cluster composed of multiple bonds. Experiments have revealed that a small tensile force could strengthen bonds of adhesion molecules in the sense that bond lifetimes are prolonged. A bond with such a binding behavior is termed a “catch bond,” and was first predicted by Dembo [8,9]. The prolonging of the lifetime of a bond cluster in response to tensile force was first observed by Thomas *et al.* [10]. They found that the adhesion of *Escherichia coli* bacteria binding to a mannose-coated surface via the adhesin FimH was enhanced by a moderate amount of shear force. The same trend was found on a single cell-adhesion molecule by Marshall *et al.* [7]. Their study revealed that bonds between P-selectin and P-selectin glycoprotein ligand-1 (PSGL-1) display a biphasic relationship between bond lifetime and applied force, whereby lifetime first increases and then decreases with increasing force. More recent work, including contact and separation tests on microspheres coated with a PSGL-1 ligand and P-selectin separately [11], flow chamber experiments [12–16], and laser trap tests [17], have all observed catch-to-slip transition in biological bonds.

Several phenomenological models have been proposed to interpret the transition from catch to slip bonds. Evans *et al.* [11] assumed that bond failure originates from two possible bound states with different dissociation pathways. Catch bonds are then explained by switching between the two path-

ways. Barsegov and Thirumalai [18] suggested that the observed catch-slip behavior in specific protein-protein complexes can be captured in general by using an energy landscape that allows for two bound states: one force-free state and another force-stabilized bound state. External forces redistribute the population in these two states and give rise to the catch-slip bond behavior. A common feature to these two models is that two bound states (or two energy wells) are assumed. External force changes the respective off rates of the two bound states, and gives rise to a catch-slip transition. Pereverzev *et al.* [19] suggested a four-parameter and two-pathway model for the catch-slip transition in biological adhesion. In their model, there is only one energy well in a biological bond but ligands can escape receptor binding sites via two alternative routes. An applied force will modify the possibilities of escaping via the two routes and result in a catch-slip transition.

The aforementioned models, more or less, are based on the conjecture that structure mechanisms play the critical role for the observed catch-slip transition in selectin-ligand bonds. This concept, first hypothesized by Konstantopolous *et al.* [20], suggests that conformational changes may alter either the population of different bound states or off rates along distinct pathways.

Recent experiments by Phan *et al.* [14] and Lou *et al.* [15] seem to support the viewpoint that conformational change induces catch bonds [21]. Their studies were motivated by differences in the unliganded versus the liganded crystal structures of the N-terminal calcium-dependent lectin domain and an epidermal-growth-factor- (EGF-)like domain of P-selectin [22]. The unliganded P-selectin has a relatively stiff “bent” conformation, while the ligand-bound structure shows a flexible “extended conformation [21,22]. Phan *et al.* [14] added a glycosylation site between the two domains to wedge the interdomain open and stabilize P-selectin in the extended conformation. They investigated altered binding properties that resulted from such conformational changes in P-selectin and showed that the extended selectin conformation has higher affinity for ligands. The authors also pre-

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dicted that adhesion via L-selectin would be enhanced by a mutation (N138G) in the interdomain region through the elimination of a hydrogen bond to favor the bent confirmation. Lou *et al.* [15] confirmed that eliminating a hydrogen bond to increase the flexibility of the interdomain in L-selectin increases tethering and prolongs the lifetime of the selectin-ligand bond. They postulated that this conformational change plays an important role in regulating the kinetic on-off rate of selectin-ligand interaction, as an applied tensile force is sufficient to switch the P-selectin from low- to higher-affinity conformations.

The experiments by these two groups have clearly established that the interdomain substantially influences the affinity of selectins for ligands. It remains hypothetical whether the original bend conformation could be shifted toward the extended conformation by small external forces alone. The observed catch bonds in single-molecule bonds for P-selectin with monomeric sPSGL-1 and PSGL-1 are in the force regions of 5–10 pN and 10–25 pN, respectively [7]; the lifetime for a single actomyosin bond also shows a catch bond in the force range about 1–6 pN [17]. Note that catch bonds occur in a force region of no more than three times the force due to thermal fluctuation (4–10 pN [7]). More importantly, experiments by Lou *et al.* [15] for both the low- (bent conformation) and high-affinity (extended conformation) bonds show catch-slip transitions, which may suggest either that there is further conformational change in high-affinity bonds, or that the catch-slip transition is a general behavior in the L-selectin and ligand interactions. We hypothesize that catch-slip bond transition is a feature in protein-protein complexes in general, and suggest a simple model mechanism to explain the observed mechanical behavior in noncovalent biological bonds. The most significant difference of our model from others is that debonding occurs via both bond dissociation and bond rupture through a space decomposition, as detailed in the next section.

## II. THEORY

Taking a sphere  $s$  around the bonding pocket of a bound molecule with the sphere radius  $\lambda_s$ , being the width of the energy well of the bond, the off rate  $k$  of the bound molecule is the summation of all debonding events found in the sphere during unit time. It can be expressed as

$$k = k_0 \oint_s \exp\left(\frac{\lambda_s \mathbf{f} \cdot \mathbf{n} - \varepsilon}{k_B T}\right) ds, \quad (1)$$

where  $k_0$  is a constant off rate,  $\varepsilon$  is the energy barrier of bond dissociation in the absence of external force,  $\mathbf{n}$  is the surface normal of  $ds$ —a unit vector,  $\mathbf{f}$  is the applied force and also a vector with magnitude  $f$ ,  $k_B$  is Boltzmann's constant, and  $T$  is the absolute temperature. Equation (1) is consistent with Kramers' theory [23] of chemical reactions in a field of force.

The whole surface in the integral [Eq. (1)] is divided into a “dissociation space” and a “rupture space” such that each subspace is dominated by one debonding mechanism. In the dissociation space, debonding is dominated by bond disso-

ciation, which is nondirectional and its energy barrier for escape is not influenced by a tensile force. However, the microstates that could lead to dissociation are changed by the tensile force. In the rupture space, the surface normal almost parallels the loading direction. Bond rupture happens mainly along the tensile force direction and the applied force effectively lowers the energy barrier to escape along the loading direction.

The integrated off rate in the dissociation space in Eq. (1) depends on the total number of possible conformations  $\Omega$  of a molecule under a given loading  $f$ . This statement is based on the fact that dissociation occurs preferentially in certain conformations, as shown by experiments by Zhang *et al.* [24] and molecular dynamics simulations by Lou and Zhu [25]. To connect the off rate by dissociation with the total accessible microstates of the molecule, we make the simple assumption that the bond dissociation rate  $k_d$  is proportional to  $\Omega$ , i.e.,

$$k_d = k_c \Omega, \quad (2)$$

where  $k_c$  is a referential off rate. We proceed to construct the relationship for the applied force, entropy, and  $\Omega$ .

For a polymer chain, the first law of thermodynamics states that

$$dU = dQ - dW, \quad (3)$$

where  $dU$  is the change in the system's internal energy, and  $dQ$  and  $dW$  are the heat and work exchanged between the system and its surroundings as the system undergoes differential change. In the specific case of uniaxial tensile force applied to a molecule, work done is given by force multiplied by distance, so the work done by a uniaxial force  $f$  (the scalar of  $\mathbf{f}$ ) is given by

$$dW = -f dl, \quad (4)$$

where  $dl$  is the extension of the molecule due to the force  $f$ . Further, assuming that the deformation process occurs reversibly in a thermodynamic sense, we obtain

$$dQ = T dS, \quad (5)$$

where  $dS$  is the differential change in entropy. For uniaxial tension with  $V$  and  $T$  constant, combining the above equations gives

$$dU = TdS + f dl \quad (6)$$

and leads to the expression of the tensile force

$$f = \left(\frac{dU}{dl}\right)_{T,V} - T \left(\frac{dS}{dl}\right)_{T,V}. \quad (7)$$

The first term on the right-hand side in Eq. (7) is the energy contribution to the tensile force, or energetic elasticity; see, e.g., Rubinstein and Colby [26]. The second term is the entropy contribution to the tensile force, or entropic elasticity. When the molecule is extended by small forces, the change in length (and energy) comes almost entirely from a change in conformation. Therefore, at constant temperature, it can be approximated that the internal energy of the bonds does not change, i.e.,  $dU=0$ , and that leads to

$$f = -T(dS/dl). \quad (8)$$

Thus, a tensile force applied to a molecule will elongate the molecule and reduce its entropy.

Based on the wormlike chain model, the entropy change in a molecule subjected to a uniaxial tensile force is given by

$$S - S_0 = -\frac{1}{2}Nk_B \left( \frac{2}{\lambda} + \lambda^2 - 3 \right), \quad (9)$$

where  $N$  is the number of chain segments of the molecule,  $\lambda$  the nominal stretch (current chain length  $l$  normalized by the original length  $L$ ), and  $S_0$  the initial entropy. From Eqs. (8) and (9), we obtain

$$f = \frac{Nk_B T}{L} \left( \lambda - \frac{1}{\lambda^2} \right). \quad (10)$$

We further linearize Eqs. (9) and (10) to get a simple relationship between  $f$  and  $(S - S_0)$  when the stretch is small. Assuming  $\lambda = 1 + x$  with  $x \ll 1$  and using Taylor expansion, we can get the relationship between entropy reduction and the tensile force  $f$ . After simple algebra, we arrive at

$$(S - S_0)T = -\frac{f^2}{2K} \quad \text{with} \quad K = \frac{3k_B T N}{L^2}, \quad (11)$$

where  $K$  is the stiffness of the molecule in the linear entropic elasticity regime. From Eq. (2), Eq. (11), and the general relation

$$S = k_B \ln(\Omega), \quad (12)$$

we have the off rate by bond dissociation, which is given by

$$k_d = k_c \exp\left(\frac{S_0}{k_B}\right) \exp\left(-\frac{f^2}{2Kk_B T}\right). \quad (13)$$

Lower entropy in the molecule means that there is less chance for the bond to dissociate under thermal fluctuation [see Fig. 1(a)], and results in a lower off rate. Isberg and Barnes [27] made an analogy between FimH adhesion as a catch bond and a piece of flexible rope caught in a hook. If one holds both ends of the rope and pulls it, the rope cannot be removed from the hook; when we stop pulling, the rope can be freed from the hook by an environmental perturbation like the wind. This is the low-end limit. On the other hand, the high-end limit is when we pull so hard that either the hook or the rope can be broken. Returning to the adhesion problem, a binding could be released by Brownian motion in the absence of external forces. A uniaxial force reduces the entropy (degrees of freedom) of the molecule, and the chance of bond dissociation triggered by thermal fluctuations gets smaller, so bond lifetime is prolonged.

Concurrently, in the rupture space, the applied force can increase elastic energy in the bound pocket and so reduce the energy barrier and accelerate bond rupture, as predicted by the Bell model. Bond rupture under the influence of an applied force is demonstrated in Fig. 1(b). The bond has an initially high energy barrier. While  $f$  increases, the energy barrier decreases, and the probability of bond rupture by thermal fluctuation increases. Note that, while bond dissociation can occur along any direction, rupture of the bond is

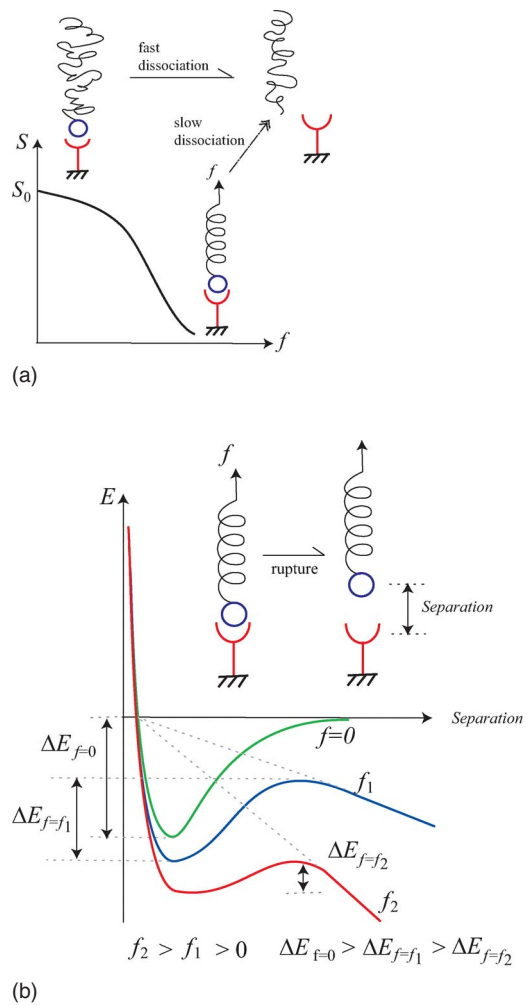


FIG. 1. (Color online) Schematic of the dependence of bond dissociation and bond rupture on external force  $f$ : (a) the applied force will reduce the bond configuration (controlled by entropic elasticity) and slow down bond dissociation; (b) energy increase in the bond pocket due to the applied force reduces the energy barrier for bond rupture, and shortens bond lifetime.

mainly due to bond separation along the tensile loading direction, as shown in Eq. (1). As predicted by the Bell model, in the rupture regime, the off rate  $k_r$  of biological noncovalent bonds subjected to a tensile force  $f$  follows

$$k_r = k_s \exp\left(\frac{f\lambda_s}{k_B T}\right), \quad (14)$$

where  $k_s$  is a referential rupture rate.

Based on Eq. (1), unbinding of a bond occurs by both dissociation and rupture. Considering that we are collecting debonding events in the dissociation space and rupture space, the overall off rate is a natural superimposition of bond dissociation [Eq. (13)] and bond rupture [Eq. (14)] and is given by

$$k = k_c \exp\left(-\frac{f^2}{2Kk_B T}\right) + k_s \exp\left(\frac{f\lambda_s}{k_B T}\right). \quad (15)$$

The pre-coefficient term  $k_c \exp(S_0/k_B)$  in Eq. (13) is for simplicity written as  $k_c$  in the above equation; it depends on the

TABLE I. Model parameters for bonds of P-selectin with specific ligands sPSGL-1, PSGL-1, and G1, obtained by fitting the lifetime versus force curve reported by Marshall *et al.* [7], with  $T=300$  K.

	$k_c$ (1/s)	$K$ (pN/nm)	$k_s$ (1/s)	$\lambda_s$ (nm)
sPSGL-1	20	2.5	0.45	0.4
PSGL-1	25	10	0.25	0.2
G1 <sup>a</sup>			0.2	0.45

<sup>a</sup>Only the bond rupture term in Eq. (15) is used to fit the experimental data for P-selectin with G1.

intrinsic structure of the bound molecule. If we assume that the rebinding rate is small in the presence of an applied force, the lifetime  $\langle\tau\rangle$  of a bond is approximated as the reciprocal of  $k$ . When  $f \rightarrow 0$ , the dissociation rate in Eq. (15) has the same meaning as that in a bonding reaction system, as described by Eq. (1). The rupture rate at zero external force can be interpreted as the dissociation rate in a particular region where the surface normal is almost parallel to the loading direction. Hence, it should be much less than the usual dissociation rate. Indeed, that is the case, as shown in our application (data listed in Tables I and II).

In Eq. (15),  $k_c$  and  $k_s$  need to be determined quantitatively by experiments. As discussed in Ref. [1], the strongest influences on  $\lambda_s$  are the properties of the bond pocket like bond angles and bond affinity. The physical meaning of  $\lambda_s$ , in our understanding, is the width of the energy well corresponding to a specific bond (the characteristic length between the minimum energy and the nearby saddle point). The high sensitivity of  $\lambda_s$  to various structural changes in a bond pocket makes it difficult to precisely quantify this parameter. We will fit Eq. (15) to experimental data and get estimates of these parameters in the next section.

### III. APPLICATION

We apply the model to representative published experimental data for P-selectin adhesion complexes with monomeric sPSGL-1, dimeric PSGL-1, and antibody G1. The model parameters in Eq. (15) were obtained by fitting the theoretical curves of  $\langle\tau\rangle$  vs  $f$  to the experimental data of

TABLE II. Model parameters for interactions of L-selectin with specific ligands sPSGL-1, PSGL-1, and DREG56, obtained by fitting the off rates versus force curve reported by Sarangapani *et al.* [13], with  $T=300$  K.

	$k_c$ (1/s)	$K$ (pN/nm)	$k_s$ (1/s)	$\lambda_s$ (nm)
sPSGL-1	50	15	2	0.1
PSGL-1	40	40	4	0.05
DREG56 <sup>a</sup>			0.8	0.3

<sup>a</sup>Only the bond rupture term in Eq. (15) is used to fit the experimental data for L-selectin with DREG56.

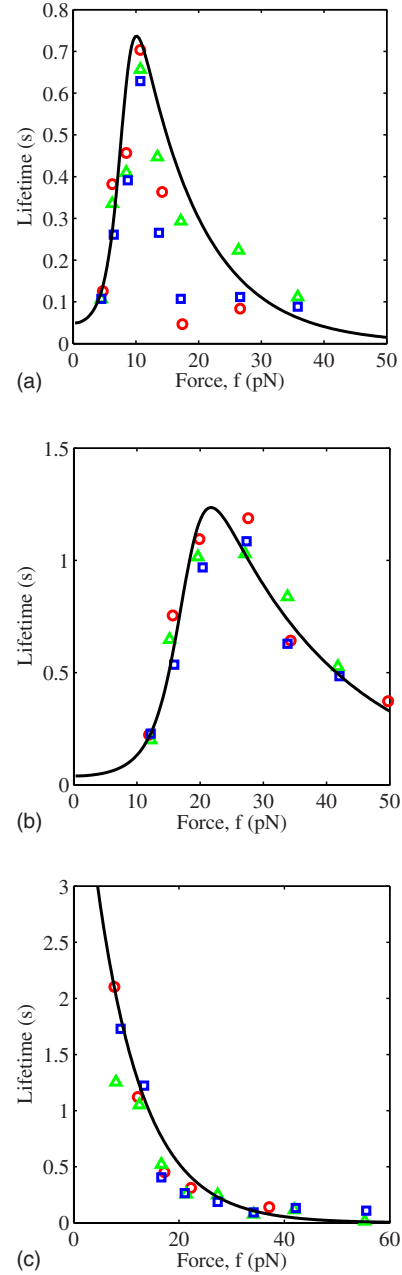


FIG. 2. (Color online) The lifetime versus force for bonds of dimeric P-selectin with monomeric sPSGL-1 (a), PSGL-1 (b), and G1 (c). The experimental data for lifetimes shown here were determined by Marshall *et al.* [7] with three types of definition: mean lifetime  $\langle\tau\rangle$  (blue squares), standard deviation of the lifetime (green triangles), and inverse negative slope for the off rate (red circles). The solid line is a fit generated from Eq. (15) with parameters listed in Table I.

Marshall *et al.* [7]. The results shown in Fig. 2 were obtained by using the model parameters listed in Table I.

With Eq. (15), the theoretical parameters (listed in Table I) for P-selectin with sPSGL-1 and PSGL-1 are  $k_s = 0.2-0.45$  s<sup>-1</sup> and  $\lambda_s = 0.2-0.45$  nm, which are in the range suggested by experiments [7,13,28,29]. The stiffnesses fitted using Eq. (15) for P-selectin with monomeric sPSGL-1 and dimeric PSGL-1, are about 2.5 and 10 pN/nm, respectively,

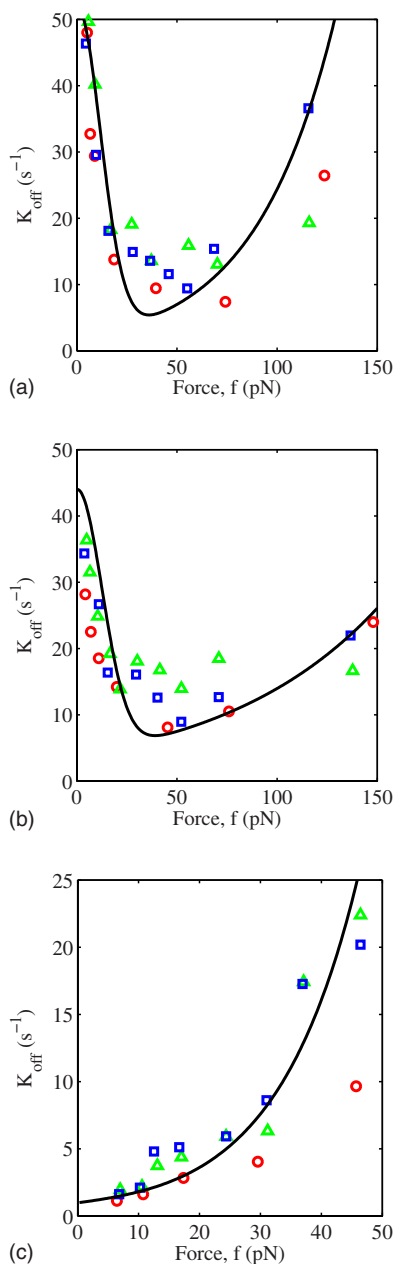


FIG. 3. (Color online) Off rates as a function of the applied force for bonds of L-selectin with monomeric sPSGL-1 (a), PSGL-1 (b), and DREG56 (c). The experimental data on off rates are obtained from Sarangapani *et al.* [13]. Off rates are estimated from the reciprocal mean lifetime  $\langle \tau \rangle$  (blue squares), the reciprocal standard deviation of the lifetime (green triangles), and negative slope for the off rate (red circles). The solid line is the fitted curve generated from Eq. (15) with parameters listed in Table II.

which are in the range of the stiffness for proteins 1–40 pN/nm [30]. The difference in  $K$  also reflects the structural change between monomeric sPSGL-1 and dimeric PSGL-1; the latter is about four times stiffer than the former. Based on Eq. (15), the off rate due to bond dissociation at zero external force  $k_c$  is about two orders of magnitude larger than  $k_s$ . This reflects the fact that, in the absence of or at very small forces, bond lifetime is dominated by dissociation. As  $f$  increases, bond rupture takes over gradually and becomes the primary

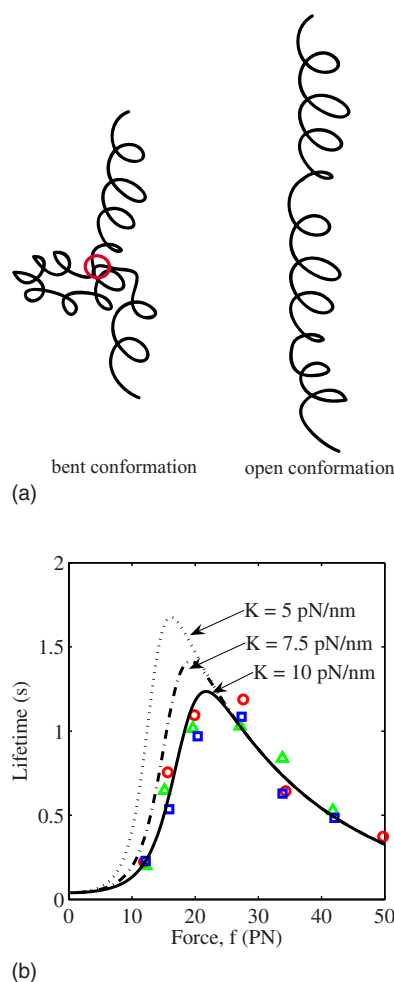


FIG. 4. (Color online) The influence of conformational change in a complex on its bond lifetime. (a) The diagram shows a structure with a hinge (red circle) between two domains (bent conformation), as well as the same structure without the hinge (extended conformation). We expect that the structure in the extended conformation is more flexible than that in the bent conformation; (b) Model prediction for the effect of bond complex stiffness on the bond lifetime. As stiffnesses decrease, catch bonds have longer lifetimes and require less force to be fully activated. Such a trend is consistent with observations by Lou *et al.* [15]. Other parameters used in Eq. (15) for these curves are the same as those in Fig. 2(b) for the P-selectin–PSGL-1 interaction.

mechanism that controls bond lifetime. The competition of these two off rates gives rise to the observed catch-slip transition in noncovalent biological bonds.

The model is also applied to experimental results for L-selectin with sPSGL-1, PSGL-1, and DREG56. The off rate  $k$  versus  $f$  reported by Sarangapani *et al.* [13] and fitted curves using our theory are shown in Fig. 3 with fitted parameters as listed in Table II. Equation (15) can fit the experimental data quite well. Also, the stiffnesses of the bond complex for L-selectin with monomeric sPSGL-1 (13 pN/nm) and dimeric PSGL-1 (42 pN/nm) indicate that the latter is stiffer.

We use Eq. (15) to show the influence of conformational change of a bond complex on bond lifetime. For L-selectin

or P-selectin, the crystal structures show bent and extended conformations. Experiments [14,15] have shown that an extended selectin conformation can strengthen selectin-ligand bonds. The extended structure of the bond complex, in contrast to its bent status, should be more flexible, as demonstrated in Fig. 4(a). We simply reduce the stiffness  $K$  in Eq. (15) to reflect a bond complex conformation change from bent to extended. Figure 4(b) shows several curves of bond lifetime versus force for different stiffness  $K$  of the bonding complex based on model parameters used in Fig. 2(b). In the case where the stiffness in a complex is lower, the catch bonds have longer lifetimes and require less force to be fully activated. Such a trend is consistent with observations by Lou *et al.* [15], as shown in their Fig. 4. Experiments and analysis by Nguyen-Duong *et al.* [31] have also shown that a stiffer force probe can reduce the lifetime of a molecular complex dramatically.

#### IV. CONCLUSION

In this paper we have developed a theoretical model for the analysis of the mechanical activation of chemical bonds between specific molecules. Unbinding of biological bonds is assumed to take place through dissociation and bond rup-

ture. Both dissociation and rupture are thermally activated escapes over a transition state barrier. The difference lies in the fact that dissociation is nondirectional, and its energy barrier for escape is not influenced by a tensile force, but the microstates that could lead to dissociation are changed by the tensile force. On the other hand, rupture happens along the tensile force direction. The applied force effectively lowers the energy barrier to escape along the loading direction. The lifetime of the biological bond, due to the combination of both off rates, grows with increasing tensile force and then decreases with further increasing force. We hypothesize that a catch-to-slip bond transition is a common feature in biological bonds. We showed that modification in the stiffness  $K$  of the bond complex changed the effect of force on bond lifetimes: a reduced  $K$  can lead to catch bonds with longer lifetimes, and it does not require as much force to be fully activated. The features predicted by the model are consistent with the experimental observations by Lou *et al.* [15] and Nguyen-Duong *et al.* [31].

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