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Force-induced deformations and stability of biological bonds

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A deformation model of the forced-induced dissociation of biological bonds is developed. A simple illustration shows that protein deformations can change the receptor-ligand interaction linearly with applied force at small forces, either increasing or decreasing the bond stability, and that a minor external work can lead to notable changes in the interaction energy. The deformation-induced increase of bond stability is illustrated with the remarkable catch-bond phenomenon in P and L selections. Additionally, the model rationalizes the frequently seen disparity between the bond dissociation rates of many free complexes and the zero-force asymptotic rates measured by force spectroscopy.

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Binding of biological objects exhibits a number of fascinating phenomena that are not observed with small molecules or rigid macroscopic bodies and that originate from the internal structure and flexibility of biomolecules. The "catch-bond" phenomenon first predicted by Dembo *et al.* [1] is a vivid example demonstrated by leukocytes and bacteria in blood and receiving much recent attention due to its counter-intuitive behavior: The bond is strengthened rather than broken by a pulling force [2–8]. Ordinary bonds also show unexpected properties. The bond dissociation rates measured for free complexes disagree by orders of magnitude with the rates obtained by extrapolation of the force-spectroscopy [9–12] data to zero force [13–17].

The pioneering model [1] described either catch or slip behavior. In order to explain the catch-slip transition, a number of models have been proposed [4–8]. These models represent the interaction between rigid receptor and ligand using potential energy profiles, where barrier heights are linear with force, as proposed by Bell [18]. Recent studies indicate that the structures of both receptor and ligand can be modified during bond formation, e.g. [19]. The positions and orientations of the residues that come in contact inside the binding pocket change, thereby increasing or decreasing the binding interaction. It is logical then that application of an external force to the bound complex can also induce deformations, further increasing or decreasing the interaction. This type of impact of the force on the receptor-ligand bond acts in addition to the Bell mechanism. It will be called the deformation effect.

In order to illustrate how the binding energy of a biological complex changes due to the deformational effect, we consider a simple model of receptor-ligand interaction (Fig. 1), where the applied force alters only the ligand. The model is not meant to represent the complex nature the receptor-ligand interaction. It shows for small forces f that the deformation change in the binding energy should be linear f, motivating the functional form of the deformation energy (4) below. In addition, the model shows that a minor external work $(\sim f^2)$ can lead to notable changes in the interaction energy $(\sim f)$. We expect that the key conclusions of the simple model will be preserved in a more realistic description.

The ligand is composed of two particles bound by a spring with the spring-constant k. The potential created by a rigid receptor has two minima spaced distance b apart. The equilibrium distance between the particles equals $a \neq b$. The applied force pulls the second particle and stretches the spring.

The potential energy of the system contains three terms,

$$U(x_1,x_2) = U_i(x_1,x_2) + U_l(x_1,x_2) - x_2 f. \tag{1}$$

$U_i(x_1,x_2)=k_1x_1^2/2+k_1(b-x_2)^2/2$ is the receptor-ligand interaction energy, where x_1,x_2 are the coordinates of the two particles, and k_1 is the harmonic force constant of the potential-energy minima. The potential energy of the ligand equals $U_l(x_1,x_2)=k(x_2-x_1-a)^2/2$. The last term in Eq. (1) describes the change in the total energy due to the applied force. Minimization of the total energy (1) with respect to the two coordinates x_1,x_2 gives the interaction energy in the relaxed complex. In the absence of the force, the interaction energy equals $U_{i\min}(f=0)=k_1(b-a)^2/[2(1+0.5k_1/k)]$. Flexible ligands (small k) lower the energy and increase the interaction relative to rigid ligands (infinite k).

Two new terms are added to the above expression for $U_{i\min}$ at a finite force. One of the terms is quadratic in f and always remains positive. The other term is linear in f,

$$U_{i\min}(\sim f) = -\frac{(b-a)kk_1 f}{(k_1+2k)^2}, \tag{2}$$

and dominates the quadratic term for small forces. It follows from (2) that if $b>a$ then $U_{i\min}(\sim f)<0$, the force deepens

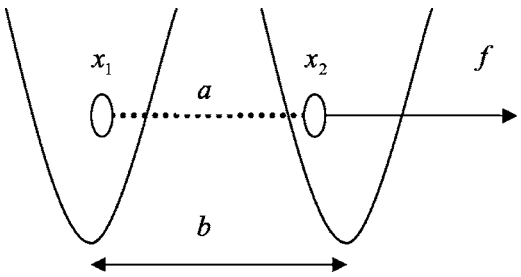

FIG. 1. The applied force can increase the receptor-ligand binding by optimizing the positions of atoms x_1 and x_2 in the binding potential.

the potential, and the binding strengthens. When $b<a$, the contribution of (2) to the total energy of the complex is positive and the receptor-ligand bond weakens. The force changes the interaction only for flexible ligands. The term (2) becomes zero in the limit $k\to\infty$ for rigid ligands.

The analysis shows that the force-induced deformations of the receptor-ligand complex change the energy of the minimum of the binding potential. The change (2) is linear in the applied force, as has been schematically suggested in [3]. Note that the Dembo model [1] gives quadratic dependence. The sign of the deformation term depends on the relative positions of receptor-ligand points of contact. In contrast to the Bell term [18], where the linear dependence appears with rigid receptor and ligand due to anharmonicity of the interaction potential reflected in coexisting bound and transition states, the deformation term gives linear variation already in the harmonic model. The regime where the deformation and Bell terms have opposite signs can describe the biological catch bond.

The work W performed on the system while shifting the second particle is quadratic in force, $W=(k_1+k)/[k_1(k_1+2k)]f^2$. For sufficiently small forces, the work is significantly smaller than the absolute magnitude of (2). The energy conservation is not violated, since the internal energy of the ligand also varies with force, offsetting the change of the interaction energy.

Motivated by the simple analysis presented above we propose the following expression for the bond dissociation rate constant:

$$k(f) = k_0 \exp\left[-\frac{\Delta E_d(f) - x_{12} f}{k_B T}\right], \tag{3}$$

where k_0 is the rate constant in the absence of the force. The force modifies the barrier through the Bell term $(-x_{12}f)$, where x_{12} is the distance between the bound state minimum and the transition state maximum [9]. The change in the binding energy due to the force-induced deformation of the bond is described by the $\Delta E_d(f)$ term. As shown above (2), $\Delta E_d(f)$ should be linear for small f. It is assumed that the deformation energy $\Delta E_d(f)$ reaches a limit α at a certain force f_0, beyond which the force stops affecting the interaction, for instance, if the system resists further deformation, or if the deformations occur outside the binding pocket. In order to retain the linear dependence at small forces and achieve the limit at large forces, the change in the bond energy due to the force-induced deformation is postulated to have the following functional form:

$$\Delta E_d(f) = \alpha[1 - \exp(-f/f_0)], \tag{4}$$

where α can be positive or negative.

Provided that $\alpha>0$ and exceeds the critical value $\alpha_c = x_{12}f_0$, Eqs. (3) and (4) describe the catch bond [2–8]. Indeed, if the force is time independent, the average bond lifetime $\tau(f)=1/k(f)$ is maximized at $f_{\max}=f_0\ln[\alpha/x_{12}f_0]$. The ratio of the maximum lifetime to the lifetime at zero force

$$\tau(f_{\max})/\tau(0) = \exp\{[\alpha - x_{12}(f_0 + f_{\max})]/k_B T\}$$

characterizes the efficiency of the catch bond [7]. The efficiency ratio can significantly exceed one, if the deformation contribution to the binding energy is greater than the Bell term, $\alpha > x_{12}(f_0+f_{\max})$.

The strong disagreement between the force-free measurements and the extrapolation of the finite-force results to zero force [13–17] is rationalized by the present model due to the nontrivial behavior of the bond dissociation barrier at small forces. Figure 2 illustrates the overall change in the barrier height due to both Bell and deformation mechanisms as a function of force. The lines are shown for three characteristic values of the deformation energy α and differ around f_0. The maximum in line 1 describes the catch bond; line 2 is convex with no maximum; line 3 is concave. The extrapolation of the high-force data to zero force misses the maximum in line 1. Therefore, high-force measurements cannot detect the catch-bond.

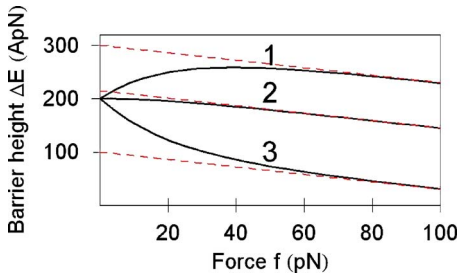

FIG. 2. (Color online) Bond-dissociation barrier as a function of applied force. The bond deformation energy α equals to (1) 100, (2) 15, and (3) −100 A pN. f_0=20 pN, x_{12}=0.7 A. Dashes show asymptotes of the high force data.

TABLE I. Deformation contribution to the binding energy α deduced from the true k_0 and asymptotic k_{as} rate constants.

Receptor/ligand	k_0 / s^{-1}	k_{as} / s^{-1}	α / A pN
Hexa-histidin/nitrilotriacetic acid	3×10^{-4} [13]	0.07 [13]	−218
DNA hairpins	~100 [14]	~1 [14]	−200
Protein A/immunoglobulin G	1.7×10^{-3} [13]	0.12 [13]	−170
Protein G/immunoglobulin G	3×10^{-4} [13]	0.01 [13]	−140
Fluorescein/4D5-Flu	0.062 [15]	0.1 [15]	−19
Fluorescein/FITS-E2	4.4×10^{-3} [15]	3×10^{-3} [15]	15
P-selectin/PSGL-1	1.4 [16]	0.022 [17]	172

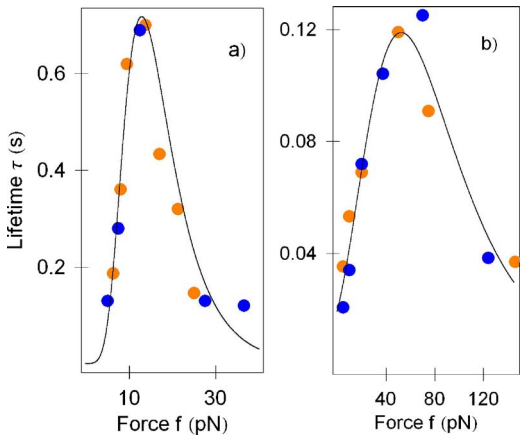

FIG. 3. (Color online) Bond lifetimes of (a) P and (b) L selectins with monomeric sPSGL-1 (blue circles) and dimeric PSGL-1 (orange circles) as functions of the applied constant force [2,3,7]. The solid lines are obtained using Eqs. (3) and (4) with $\alpha = 521.1 \pm 193.5$ ApN, $f_0 = 4.2 \pm 0.5$ pN, $x_{12} = 5.7 \pm 1.2$ A, $k_{as} = 0.13 \pm 0.02$ s^{-1} for P selectin and $\alpha = 152.9 \pm 7.7$ ApN, $f_0 = 31.8 \pm 4.5$ pN, $x_{12} = 0.92 \pm 0.3$ A, $k_{as} = 1.29 \pm 0.2$ s^{-1} for L selectin.

The deviations between the asymptotic $k_{as} = k_0 \exp(-\alpha / k_B T)$ and true k_0 zero-force rate constants is determined by the deformation contribution to the binding energy, which may be extracted directly from experiments

$$\alpha = k_B T \ln(k_0 / k_{as}). \tag{5}$$

Since α can be either positive or negative, the asymptotic rate can be much greater or much less than the true rate k_0.

The α value reflects whether the force-induced deformation optimizes or destabilizes the bond and to what extent. Small α's indicate that the bond is either not deformable or stiffer than other parts of the system. Large negative α's imply that the receptor-ligand interaction is highly optimized, and the bond is deformed unfavorably, by distorting the precise arrangement of the bond components. Large positive α's describe bonds which are favorably deformed by the applied force. Note that even if a deformation stabilizes the bond and the force-free rate constant exceeds the extrapolated value, the bond is not necessarily a catch bond, as illustrated with case 2 in Fig. 2, compared to case 1 that gives a catch bond. The larger the deformation contribution to the binding energy α and the smaller the force f_0 at which the deformation saturates, the more likely the corresponding line in Fig. 2 has a maximum, e.g., line 1, and the bond is a catch bond.

Table I shows the deformation contributions to the binding energy, Eq. (5), for several biological bonds. The hexahistidin/nitrilotriacetic acid system gives a large negative α, which is consistent with the very tight molecular arrangement of this manmade recognition pair. Similarly, unzipping of DNA is also characterized by a large negative α. Interactions in both systems are highly optimized, and distortions destabilize the bonds. The immunoglobulin examples show slightly less negative α. The protein-protein bonds are not as tight and, therefore, are less destabilized by deformation. The α values in the fluorescein systems are close to 0. These bonds can be stiff, since the fluorescein ligand is a relatively small rigid molecule.

The selectin system in Table I presents the unusual case of large positive α, indicating that the receptor-ligand interaction is further optimized by the force-induced bond deformation. The selectin catch bonds have developed to help leukocytes attach and penetrate through blood vessel walls and combat inflammations. The catch mechanism can create a higher population of leukocytes on the thick aorta walls than on the thin capillary walls and prevent blocking of narrow capillaries by multiple immobile leukocytes.

Figure 3 compares the present model with the experimental data of Marshall *et al.* [2] and Sarangani *et al.* [3], who were the first to clearly demonstrate the catch-bond behavior for P and L selectins, respectively. The comparison indicates that the deformation model quantitatively accounts for the catch-slip transition. Note that the α value for the P-selectin systems that follow from the ratio of the force-free and asymptotic dissociation constants, Table I, is three times smaller than the corresponding value obtained by fitting the data in Fig. 3(a). The discrepancy likely arises due to the difference in the experimental setups [2,17], in which the AFM lever spring constants differed by over an order of magnitude, and the bond components were attached to the measurement apparatus through different tip functionalization and with or without a lipid bilayer. In addition, the two sets of data were obtained in different force regimes: The table value of α is based on high force experiments, while the figure fit is performed to the low force data. Both α values predict a strong catch bond.

In summary, the communication proposes a quantitative model for force-induced deformations that alter the strength of biological bonds. The presented analysis shows that a small external work can lead to notable changes in the interaction energy. In combination with the traditional force dependence of the bond dissociation barrier proposed by Bell [18], the deformation model quantitatively describes the catch-slip transition. In contrast to the alternative catch-bond models [4–8], the deformation model operates with only one bound and one transition state. Applied to a range of systems, the deformation effect explains the disparity in the dissociation rates obtained in the force-free experiments and by extrapolation of the finite-force data. The model classifies biological bonds into stiff and deformable, and predicts whether or not the receptor-ligand interaction is well optimized. It may be expected that the deformation effect can rationalize other experiments, for instance the force history dependence of the catch bond [20] and the sensitivity of the actin bond to torsion [21].

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[1] M. Dembo, D. C. Torney, K. Saxman, and D. Hammer, Proc. R. Soc. London, Ser. B **234**, 55 (1988).
[2] B. T. Marshall, M. Long, J. W. Piper, T. Yago, R. P. McEver, and C. Zhu, Nature (London) **423**, 190 (2003).
[3] K. K. Sarangapani, T. Yago, A. G. Klopocki, M. B. Lawrence, C. B. Fieger, S. D. Rosen, R. P. McEver, and C. Zhu, J. Biol. Chem. **279**, 2291 (2004).
[4] D. Bartolo, I. Derenyi, and A. Ajdari, Phys. Rev. E **65**, 051910 (2002).
[5] E. Evans, A. Leung, V. Heinrich, and H. Zhu, Proc. Natl. Acad. Sci. U.S.A. **101**, 11281 (2004).
[6] V. Barsegov and D. Thirumalai, Proc. Natl. Acad. Sci. U.S.A. **102**, 1835 (2005).
[7] Y. V. Pereverzev, O. V. Prezhdo, M. Forero, E. V. Sokurenko, and W. E. Thomas, Biophys. J. **89**, 1446 (2005).
[8] Y. V. Pereverzev, O. V. Prezhdo, W. E. Thomas, and E. V. Sokurenko, Phys. Rev. E **72**, 010903(R) (2005).
[9] E. Evans, Annu. Rev. Biophys. Biomol. Struct. **30**, 105 (2001).
[10] G. Hummer and A. Szabo, Acc. Chem. Res., **38**, 504 (2005).
[11] P. C. Li and D. E. Makarov, J. Chem. Phys. **119**, 9260 (2004).
[12] M. Arya, A. B. Kolomeisky, G. M. Romo, M. A. Cruz, J. A. Lopez, and B. Anvari, Biophys. J. **88**, 4391 (2005).
[13] M. Nguyen-Duong, K. W. Koch, and R. Merkel, Europhys. Lett. **61**, 845 (2003), and references therein.
[14] F. Schwesinger, R. Ros, T. Strunz, D. Anselmetti, H.-J. Guntherodt, A. Honegger, L. Jermutus, L. Tiefenauer, and A. Pluckthun, Proc. Natl. Acad. Sci. U.S.A. **97**, 9972 (2000).
[15] P. Mehta, R. D. Cummings, and R. P. McEver, J. Biol. Chem. **273**, 32506 (1998).
[16] J. A. Fritz, G. Katopodis, F. Kolbinger, and D. Anselmetti, Proc. Natl. Acad. Sci. U.S.A. **95**, 12283 (1998).
[17] J. Manthe, H. Visram, V. Vasnoff, Y. Rabin, and A. Meller, Biophys. J. **87**, 3205 (2004).
[18] G. I. Bell, Science **200**, 618 (1978).
[19] S. Hayward, J. Mol. Biol. **339**, 1001 (2004).
[20] B. T. Marshall, K. K. Sarangapani, J. Lou, R. P. McEver, and C. Zhu, Biophys. J. **88**, 1458 (2005).
[21] Y. Tsuda, H. Yasutake, A. Ishijima, and T. Yanagita, Proc. Natl. Acad. Sci. U.S.A. **93**, 12937 (1996).