Rupture of Multiple Parallel Molecular Bonds under Dynamic Loading

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Biological adhesion often involves several pairs of specific receptor-ligand molecules. Using rate equations, we study theoretically the rupture of such multiple parallel bonds under dynamic loading assisted by thermal activation. For a simple generic type of cooperativity, both the rupture time and force exhibit several different scaling regimes. The dependence of the rupture force on the number of bonds is predicted to be either linear, like a square root, or logarithmic.

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Single molecule force spectroscopy has made it possible to measure the binding strength of a pair of receptor-ligand ("lock-key") molecules using vesicles [1], the atomic force apparatus [2–4], or optical tweezers [5] as transducers. Thus, the essential constituents mediating biological adhesion have become accessible to quantitative physical experiments [6]. This experimental progress has fostered theoretical studies of the rupture of such pairs under dynamic loading. Thermal activation being a main contributing factor, Kramers-like descriptions of the rupture process with time-dependent potentials show that the rupture strength of such bonds depends on the loading rate [7–9]. Such behavior has been found experimentally indeed [10,11]. While unspecific theoretical models of the rupture process reveal generic features, molecular dynamic studies can address the details of the dynamics of the rupture of specific pairs [8,12].

Adhesive contact and the rupture thereof often involves not just one but several molecular pairs of the same or different species [13]. The equilibrium properties of the cooperative effects of such specific interactions are well studied both in theory [14–16] and in experiments [17–19]. Concerning the dynamics of rupture of such a contact under loading, detailed models for specific problems such as the peeling of a membrane [20,21] or the rolling of leucocytes in shear flow [22] have been solved numerically to extract a critical tension or shear rate for rupture. However, it is inherently difficult to separate generic dynamical properties from specific ones using such intricate models. As an example for a generic property consider the following question: How does the time and force necessary to break an adhesive contact under dynamic loading depend on the number of bonds initially present?

The present study addresses this question within a simple model that extends work on the dynamic failure of a single bond to that of a whole patch involving several bonds of the same type. Quite generally, two different limiting cases must be distinguished. If the load is primarily concentrated on one bond at a time with relaxation of the load when the first bond fails and subsequent loading of the next one, the rupture process basically is a sequence of similar single molecule events. The N_0 bonds initially present then act *in series*. The rupture time will be $\sim N_0$ whereas the force will exhibit a sawtoothlike pattern with a peak given by the rupture strength of a single bond. Such a behavior has been found and modeled in the related case of unfolding of proteins with several identical domains like titin [23]. The main purpose of the present paper is to analyze the other case where the load is distributed (almost) uniformly among several bonds such that these bonds act *in parallel*. As more and more bonds rupture, the force on the remaining ones increases. This simple type of cooperativity leads to different scaling regimes for the rupture time and rupture force.

Model.—We model the rupture geometry generically as shown in Fig. 1. One partner of the bond ("receptor") is confined to a substrate. The other ("ligand") is connected by a polymer to a transducer which is connected by an elastic element to a sled being pulled at velocity v. For simplicity, we model both the elasticity of the transducer and the polymers as Hookean springs with zero rest length and spring constants K_t and K_p, respectively. As long as a bond is intact the corresponding polymer is stretched to an extension x_p which we assume to be the same for all intact bonds. The elongation of the transducer from its resting position is x_t. Force balance on the transducer becomes $NK_p x_p = K_t x_t$, where N is the number of intact bonds. Geometry dictates the time dependence $x_p(t) + x_t(t) = vt$. From these two relations, we find the time-dependent force on an intact bond as

$$F_b(t) = K_p x_p(t) = \frac{K_p K_t}{N(t)K_p + K_t} vt\,. \tag{1}$$

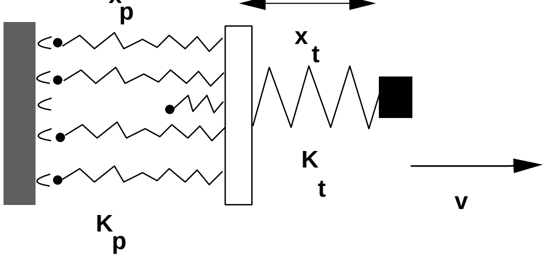

FIG. 1. Model geometry for the rupture of parallel bonds. Symbols are explained in the main text.

Following Bell [13], we assume that the main effect of such a force is to introduce an instantaneous, time-dependent dissociation rate $k_0(t)$ according to

$$k_0(t) = k_0 \exp[F_b(t) x_b / k_B T], \tag{2}$$

where k_0 is the dissociation rate in the absence of a force. The quantity x_b is of the order of the distance between the minimum of the binding potential and the barrier and $k_B T$ is the product of Boltzmann's constant and temperature.

We are mainly interested in the case of a *soft* transducer defined as $K_t \lesssim K_p$. In this case, Eq. (1) shows that the force on a bond is inversely proportional to the number of intact bonds for all $N(t)$. Hence, when a bond ruptures, the force on the remaining ones increases. We now discuss two different cases, irreversible and reversible bonds. In the former case, a bond, once ruptured, cannot rebind. Reversible bonds have a nonzero rebinding rate.

Irreversible bonds.—Initially $N(t=0) \equiv N_0$ bonds are present. The rate equation for their time-dependent decrease is

$$\partial_t N = -N(t) k_0 \exp[F_b(t) x_b / k_B T]. \tag{3}$$

We scale time with the dissociation rate in equilibrium k_0 according to $\tau \equiv t k_0$. The rate equation in the case of a soft transducer then becomes

$$\partial_\tau N = -N \exp[\mu \tau / N] \tag{4}$$

with the loading parameter

$$\mu \equiv K_t x_b v / k_B T k_0 . \tag{5}$$

This simple rate equation seems not to have an analytical solution. However, its scaling behavior can be extracted by the following analysis. With the substitution $u(\tau) \equiv \tau / N$ one obtains

$$\partial_\tau u = u(1/\tau + 1) + u(\exp[\mu u] - 1). \tag{6}$$

For small τ, $u(\tau) \approx \tau / N_0$ and the second term in (6) can therefore be neglected. The solution $u_1(\tau)$ of the corresponding equation becomes $u_1(\tau) = \tau e^{\tau} / N_0$ and hence a purely exponential decay for the number of intact bonds, $N(\tau) = N_0 e^{-\tau}$. This approximation breaks down for $\tau \gtrsim \tau_1$ with τ_1 implicitly defined by

$$\max(1/\tau_1, 1) = \exp[\mu u_1(\tau_1)] - 1 . \tag{7}$$

For $\tau > \tau_1$, we can then ignore both the first term and the "-1" in the second term of (6). The corresponding equation $\partial_\tau u = u \exp[\mu u]$ is solved by

$$E(\mu u_1) - E(\mu u) = \tau - \tau_1 , \tag{8}$$

where $E(x) \equiv \int_x^\infty dx' \, e^{-x'} / x'$ is the exponential integral and $u_1 \equiv u_1(\tau_1)$ is the crossover value of the first solution at the matching point τ_1. Hence the time necessary for complete rupture, τ^*, can be estimated by setting $u(\tau^*) = \tau^* / N = \infty$ which leads to

$$\tau^* = \tau_1 + \tau_2 = \tau_1 + E(\mu u_1). \tag{9}$$

Based on this approximative solution of (6), three subregimes can be identified.

(i) $\mu \lesssim 1$: In this case, the exponential decay holds till $N(\tau) \simeq 1$. Physically, the rupture is then complete. In this trivial regime, where the loading is too small to affect the rupture process at all, the time required for rupture is

$$\tau^* \sim \ln N_0 . \tag{10}$$

Note that the same result could have been obtained by analyzing the mean time required for the irreversible decay of N_0 independent bonds under no force.

(ii) $1 \lesssim \mu \lesssim N_0$: In this regime, the exponential decay persists till $\tau_1 \sim \ln(N_0/\mu)$. At this time the number of bonds has reached $N(\tau_1) \sim \mu$. The remaining bonds decay according to (8) which leads to an additional time τ_2 of order 1 which is small compared to τ_1. Hence the whole rupture time in this regime is of order

$$\tau^* \sim \ln(N_0/\mu) . \tag{11}$$

(iii) $N_0 \lesssim \mu$. In this case, the exponential decay applies till $\tau_1 \sim (N_0/\mu) \ln(\mu/N_0)$. According to (8) the remaining time $\tau_2 \sim (N_0/\mu)/\ln(\mu/N_0)$ is smaller than τ_1. Hence the total rupture time is

$$\tau^* \sim (N_0/\mu) \ln(\mu/N_0) . \tag{12}$$

Thus we find for small loading rates that the rupture time is logarithmic in the number of bonds initially present, whereas for large loading this time becomes linear in N_0. For fixed N_0 and increasing μ, the rupture time first is independent of μ. It then decays logarithmically in μ and finally becomes inversely proportional to μ.

The force measured by the transducer is given by

$$F_t \equiv N(t) K_p x_p(t) \approx (k_B T / x_b) \mu \tau . \tag{13}$$

Thus, the total force experienced by the soft transducer is independent of the number of intact bonds and increases linearly in time. The dimensionless rupture force $f^* = \mu \tau^*$ is thus given by

$$\begin{aligned} f^* &\sim \mu \ln N_0 \quad \text{for } \mu \lesssim 1 , \\ &\sim \mu \ln(N_0/\mu) \quad \text{for } 1 \lesssim \mu \lesssim N_0 , \\ &\sim N_0 \ln(\mu/N_0) \quad \text{for } N_0 \lesssim \mu , \end{aligned} \tag{14}$$

in the three regimes, respectively.

Reversible bonds.—So far, we have neglected the possibility that broken bonds can reform. Hence, rupture from a genuine equilibrium situation where bonds form, break, and rebind requires a refined description where we add a term for rebinding. We assume that one species of the receptor/ligand couple is limited to a total number N_1 with $N(t)$ molecules bound and $N_1 - N(t)$ unbound, whereas the other species is available in excess. The rate equation becomes

$$\partial_t N = -N(t) k_0 \exp[\mu\tau/N(t)] + k_f (N_1 - N(t)), \tag{15}$$

where we assume for simplicity that the rate k_f for bond formation is not affected by the force. Without loading, the equilibrium number of bonds is

$$N_{\mathrm{eq}} = \gamma N_1/(1+\gamma), \tag{16}$$

where $\gamma \equiv k_f/k_0$. As loading starts, the number of bonds decreases from this equilibrium value. With $u(\tau) \equiv \tau/N$ as before, we get

$$\partial_\tau u = u(1/\tau + 1 + \gamma - \gamma N_1 u/\tau) + u(\exp[\mu u] - 1). \tag{17}$$

For $\mu = 0$, this equation is solved by

$$u_0(\tau) \equiv \tau/N_{\mathrm{eq}}, \tag{18}$$

which corresponds to the stationary equilibrium distribution. The loading term becomes relevant at a time $\tau = \tau_1$ for which

$$(\exp[\mu u_0(\tau_1)/N_1] - 1)u_0 \sim \partial_\tau u_0 = 1/N_{\mathrm{eq}}. \tag{19}$$

Two cases must then be distinguished.

(i) For $\mu \lesssim N_{\mathrm{eq}}$, $\tau_1 \sim (N_{\mathrm{eq}}/\mu)^{1/2}$. Up to this time, the loading has not significantly affected the number of bonds. The remaining time till all bonds are ruptured can be estimated to be of the same order as τ_1 using (17). Hence,

$$\tau^* \sim (N_{\mathrm{eq}}/\mu)^{1/2}. \tag{20}$$

In this case, the rupture time increases as a square root of the equilibrium bonds present and decreases as a square root of the loading parameter.

(ii) For $N_{\mathrm{eq}} \lesssim \mu$, $\tau_1 \sim (N_{\mathrm{eq}}/\mu)\ln(\mu/N_{\mathrm{eq}})$, with a remaining time of the same order. Hence in this case, we recover the irreversible result (12) with N_0 replaced by N_{eq}.

Since in both cases the rupture time $\tau^* \sim \tau_1$, we get easily for the rupture force

$$\begin{aligned} f^* = \mu\tau^* &\sim (\mu N_{\mathrm{eq}})^{1/2} \quad \text{for } \mu \lesssim N_{\mathrm{eq}}, \\ &\sim N_{\mathrm{eq}} \ln(\mu/N_{\mathrm{eq}}) \quad \text{for } N_{\mathrm{eq}} \lesssim \mu. \end{aligned} \tag{21}$$

Stiff transducer.—So far, we have considered the case of a soft transducer ($K_t \lesssim K_p$) for which the force on a bond depends on the number of bonds. Another limiting case is a stiff transducer with $K_t \gtrsim N_0 K_p$ and $K_t \gtrsim N_{\mathrm{eq}} K_p$ for the case of irreversible and reversible rupture, respectively. According to Eq. (1), the force on a bond then is (almost) independent of the number of bonds. Hence, the rupture time is only weakly dependent on the number of bonds. An analysis of the corresponding rate equations along similar lines as above shows for the irreversible case two subregimes with

$$\begin{aligned} \tau^* &\sim \ln N_0 \quad \text{for } \bar\mu \lesssim 1, \\ &\sim \ln\bar\mu/\bar\mu \quad \text{for } \bar\mu \gtrsim 1 \end{aligned} \tag{22}$$

with a loading parameter

$$\bar\mu \equiv K_p x_b v / k_B T k_0 \tag{23}$$

dominated by the polymeric stiffness. For the dimensionless maximal force experienced by the transducer during the rupture process one finds

$$\begin{aligned} f^* &\sim \bar\mu N_0 \quad \text{for } \bar\mu \lesssim 1, \\ &\sim N_0 \ln\bar\mu \quad \text{for } \bar\mu \gtrsim 1 \end{aligned} \tag{24}$$

in the two cases.

Similarly, for a stiff transducer and *reversible* bonds, one gets

$$\begin{aligned} \tau^* &\sim (\ln N_{\mathrm{eq}})^{1/2}/\bar\mu^{1/2} \quad \text{for } \bar\mu \lesssim 1, \\ &\sim \ln\bar\mu/\bar\mu \quad \text{for } \bar\mu \gtrsim 1, \end{aligned} \tag{25}$$

and for the dimensionless maximal force experienced by the transducer

$$\begin{aligned} f^* &\sim \bar\mu^{1/2} N_{\mathrm{eq}} \quad \text{for } \bar\mu \lesssim 1, \\ &\sim N_{\mathrm{eq}} \ln\bar\mu \quad \text{for } \bar\mu \gtrsim 1. \end{aligned} \tag{26}$$

Finally, there is a crossover regime for $N_{0,\mathrm{eq}} K_p \gtrsim K_t \gtrsim K_p$, where the pulling starts as in the soft case. As the number of intact bonds decreases towards the value $\tilde N \equiv K_t/K_p$, the denominator in (1) becomes dominated by K_t and the rupture process proceeds as for a stiff transducer. For the *reversible* case, it turns out that both the rupture time and the rupture force are dominated by the soft part. Hence the results [(20) and (21)] apply for all $K_t \lesssim N_{\mathrm{eq}} K_p$. For the *irreversible* case, analysis of the crossover regime is slightly more involved. The different scaling regimes for rupture time and force are shown in Fig. 2 without explicit derivation.

Concluding perspective.—Based on an analysis of rate equations, the comprehensive scaling analysis presented in this paper has revealed several different regimes for the rupture time and force of parallel molecular bonds under dynamic loading. The most distinctive regime is

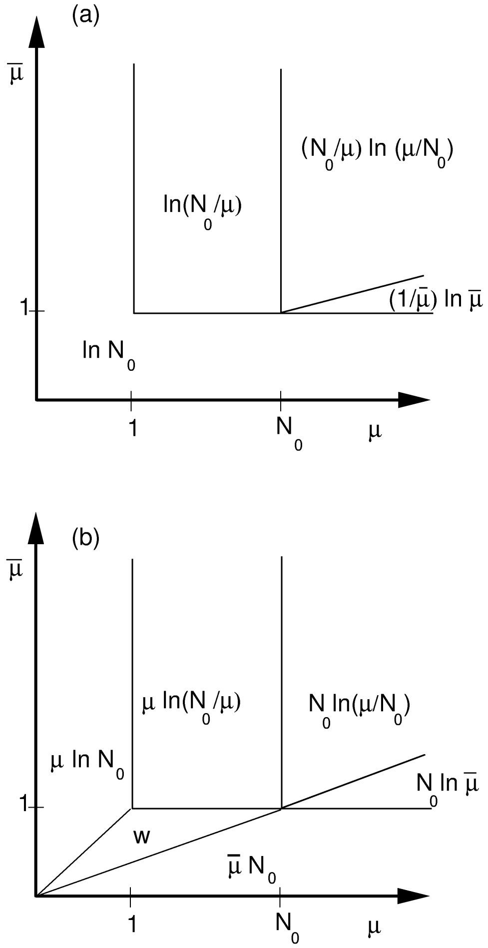

FIG. 2. Dynamical phase diagram for (a) the dimensionless rupture time τ^* and (b) the dimensionless rupture force f^* as a function of the two loading parameters μ (5) and $\bar{\mu}$ (23) in the case of irreversible rupture. In the region w, the rupture force is given by $f^* \sim \mu \ln(N_0\bar{\mu}/\mu)$.

presumably the square root dependence of rupture time and force [(20) and (21)] on loading rate and number of bonds derived for reversible bonds under small loading. Such a square root behavior on the loading rate is different from both the irreversible case and the dependence on loading rate for rupture of a single bond or bonds in series. An experimental result showing such an exponent could therefore be taken as a signature of breaking multiple parallel reversible bonds. Of course, it will be important to work with a model system where the number or density of bonds of at least one partner can be controlled in order to extract the dependence of rupture time and force on this crucial quantity.

An obvious theoretical refinement of the present model would be to include fluctuations of the rupture time for individual bonds. Other ramifications can include allowing lateral interactions between the bonds, combining the simplistic Hookean transducer with a membrane patch with its own elasticity, or modeling the rupture process more delicately than was done here to name just a few possibilities. It will be interesting to see how robust the scaling regimes derived in this paper will be under such modifications which can effectively lead to scenarios somewhere between the present "in parallel" case and the "in series" case described briefly at the beginning of the paper. Finally, it should be clear that in spite of—or rather because of—the progress made in understanding the single bond behavior, the cooperative effects of several bonds under dynamic loading deserve further attention both in theory and in experiment.

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[1] E. Evans, D. Berk, and A. Leung, Biophys. J. **59**, 838 (1991).
[2] E.-L. Florin, V. T. Moy, and H. E. Gaub, Science **264**, 415 (1994).
[3] V. T. Moy, E.-L. Florin, and H. E. Gaub, Science **266**, 257 (1994).
[4] G. U. Lee, D. A. Kidwell, and R. J. Colton, Langmuir **10**, 354 (1994).
[5] T. Nishizaka, H. Miyata, H. Yshikawa, S. Ishiwata, and K. Kinosita, Nature (London) **377**, 251 (1995).
[6] For a review, see P. Bongrand, Rep. Prog. Phys. **62**, 921 (1999).
[7] E. Evans and K. Ritchie, Biophys. J. **72**, 1541 (1997).
[8] S. Izrailev *et al.*, Biophys. J. **72**, 1568 (1997).
[9] J. Shillcock and U. Seifert, Phys. Rev. E **57**, 7301 (1998).
[10] R. Merkel, P. Nassoy, A. Leung, K. Ritchie, and E. Evans, Nature (London) **397**, 50 (1999).
[11] D. A. Simson, M. Strigl, M. Hohenadl, and R. Merkel, Phys. Rev. Lett. **83**, 652 (1999).
[12] H. Grubmüller, B. Heymann, and P. Tavan, Science **271**, 997 (1996).
[13] G. I. Bell, Science **200**, 618 (1978).
[14] G. I. Bell, M. Dembo, and P. Bongrand, Biophys. J. **45**, 1051 (1984).
[15] D. Zuckerman and R. Bruinsma, Phys. Rev. Lett. **74**, 3900 (1995).
[16] R. Lipowsky, Phys. Rev. Lett. **77**, 1652 (1996).
[17] D. A. Noppl-Simson and D. Needham, Biophys. J. **70**, 1391 (1996).
[18] A. Albersdörfer, T. Feder, and E. Sackmann, Biophys. J. **73**, 245 (1997).
[19] S. E. Chesla, P. Selvaraj, and C. Zhu, Biophys. J. **75**, 1553 (1998).
[20] M. Dembo, D. C. Tornby, K. Saxmann, and D. Hammer, Proc. R. Soc. London B **234**, 55 (1988).
[21] For an experimental study, see H. J. Ra, C. Picart, H. Feng, H. L. Sweeney, and D. E. Discher, J. Cell Sci. **112**, 1425 (1999).
[22] D. A. Hammer and D. A. Lauffenburger, Biophys. J. **52**, 475 (1987).
[23] M. Rief, J. M. Fernandez, and H. E. Gaub, Phys. Rev. Lett. **81**, 4764 (1998).