Eur Biophys J (2003) 31: 637–642
DOI 10.1007/s00249-002-0257-8

BIOPHYSICS LETTER

Alexei Boulbitch

Enforced unbinding of biomembranes whose mutual adhesion is mediated by a specific interaction

Received: 29 July 2002 / Revised: 26 August 2002 / Accepted: 9 September 2002 / Published online: 24 October 2002

Abstract The enforced unbinding of a biomembrane from a rigid substrate whose adhesion is mediated by a specific interaction has been studied theoretically. We argue that the unbinding takes place via motion of the adhesion rim. We account for the release of the elastic energy (stored in the membrane curvature) in the binding-unbinding process and obtain the dissociation constant at the rim. We further deduce an equation of motion for the rim. The solution exhibits an initial phase describing a slow motion followed by a regime of rapid motion and finally breaking of the adhesion. We show that the unbinding force depends on the rate of force application as $F_* \sim (F')^{\beta}$. When small forces are applied, $\beta = 1/2$, while in the case of large forces, $\beta = 1/3$.

Keywords Adhesion · Biomembranes · Unbinding · Specific forces · Ligand · Receptor

Introduction

It is important to study the physical characteristics of cellular adhesion since it represents an essential stage in various biological processes such as cell recognition, immune response, cell-tissue interaction, and endo- and exocytosis (Alberts et al. 1994). During many of these processes the membrane is under an external mechanical load. For example, keratocytes have been observed to exert forces of $\sim 10^{-8}$ N on the substrate during locomotion (Oliver et al. 1999), phagocytes generate forces of $\sim 10^{-8}$ N in order to drag an object being engulfed (Evans et al. 1993), leucocytes roll over endothelial cells of the blood vessels (Bongrand 1999) under the action of a force of $\sim 10^{-11}$ N arising from the flow of the blood (Bruinsma 1996), and forces in the range of $\sim 10^{-6}$ N are generated during cell division (Burton and Taylor 1997). These processes, and others, involve either adhesion taking place under the load or the enforced unbinding of cells.

Recently, experiments on enforced unbinding of single ligand-receptor bonds (Dammer et al. 1996; Lehenkari and Horton 1999; Merkel et al. 1999), vesicles (Evans 1985a; Guttenberg et al. 2000), and cells (Evans 1985b; Prechtl et al. 2002) have been reported. It has been shown that the force for the bond breaking is a statistical, rather than deterministic, parameter and that the most probable bond-breaking force F_* depends upon the rate of application of the force $F' = \partial F/\partial t$ (where t is the time) as $F_* \approx \log F'$ (Evans and Ritchie 1999; Merkel et al. 1999). For a system in which an array of elastic ligand-receptor bonds is stretched at a constant velocity by a rigid force transducer [for example, in AFM experiments (Dammer et al. 1996; Lehenkari and Horton 1999), the breaking of each successive bond increases the load on the rest, yielding:

$$F_* \approx (F')^{\beta} \tag{1}$$

with $\beta = 1$ when the force rate is small and up to $\beta = 0.5$ in the non-linear regime (Seifert 2000, 2002).

The adhesion of membranes mediated by generic interactions was studied using the example of lipid bilayer vesicles on substrates (Seifert 1997). Since the time of formation or breaking of a ''generic bond'' is negligibly small compared to the typical time scale of the experiments, the system is able to come to equilibrium. The shapes of adhered vesicles and their unbinding from the substrate can be understood on the basis of this fact (Seifert and Lipowsky 1990; Lipowsky 1991; Seifert 1991, 1995). Unlike the case of the vesicle-substrate interaction, adhesion between cells or between a cell and a tissue takes place via specific forces mediated by the interaction of ligands and receptors (Bell 1978), the generic forces being effectively screened out by the glycocalix which also plays a repulsive role (Bell et al. 1984).

A. Boulbitch
Department für Biophysik E22,
Technische Universität München,
James-Franck-Strasse, 85747 Garching, Germany
E-mail: alexei_boulbitch@physik.tu-muenchen.de

Accordingly, one should expect that the adhesion of biomembranes mediated by specific interactions are kinetically dominated, analogous to the case of the single and multiple specific bonds discussed above.

Adhesion and unbinding of cells have been studied both experimentally (Bongrand 1999) and theoretically using computer simulation techniques (Hammer and Lauffenburger 1987; Hammer 1991; Hammer and Apte 1992; Chang et al. 2000) and based on a theory that accounts for the reactions between ligands and receptors (Bell 1978; Bell et al. 1984). However, a number of unknown parameters have to be introduced into such simulations.

Recently, a simple but versatile experimental model system was reported in which the specific adhesion process can be studied. It consists of a giant vesicle with reconstituted ligands/receptors and which acts as a test cell. To mimic the target cell, either a supported membrane with reconstituted conjugated receptors/ligands or a substrate coated by them is used (Boulbitch et al. 2001; Guttenberg et al. 2001). Using this system, the spontaneous adhesion of a biomembrane, mediated by a single type of ligand-receptor couple, was studied (Boulbitch et al. 2001). Recently, such vesicles with reconstituted lipo-ligands (recognized by the integrin receptors of the endothelial cell) were used to study the enforced unbinding of vesicles from living endothelial cells (Prechtl et al. 2002). A vesicle was sucked into a micropipette and brought into contact with an endothelial cell, resulting in their mutual adhesion (Fig. 1a). After that, the unbinding experiment was performed at a constant force rate (Fig. 1b). The measurements yielded the dependence of the unbinding force on the loading rate in the form of Eq. (1) with $\beta_{\mathrm{exp}} \approx 0.4$.

In this letter we describe the kinetics of the enforced unbinding of a membrane from a substrate for the case of adhesion mediated by specific interactions. We deduce the equation of motion of the adhesion rim and solve it for the case of a constant loading rate. We predict that there are two regimes for the rim displacement during the enforced unbinding. The first regime is that of slow displacement at early times, while in the second regime at late times the rim exhibits an exponential acceleration. We show that the unbinding force exhibits a power law dependence Eq. (1) upon the force rate with $\beta = 1/2$ for small, and $\beta = 1/3$ for large, loads, in accord with the results reported by Prechtl et al. (2002).

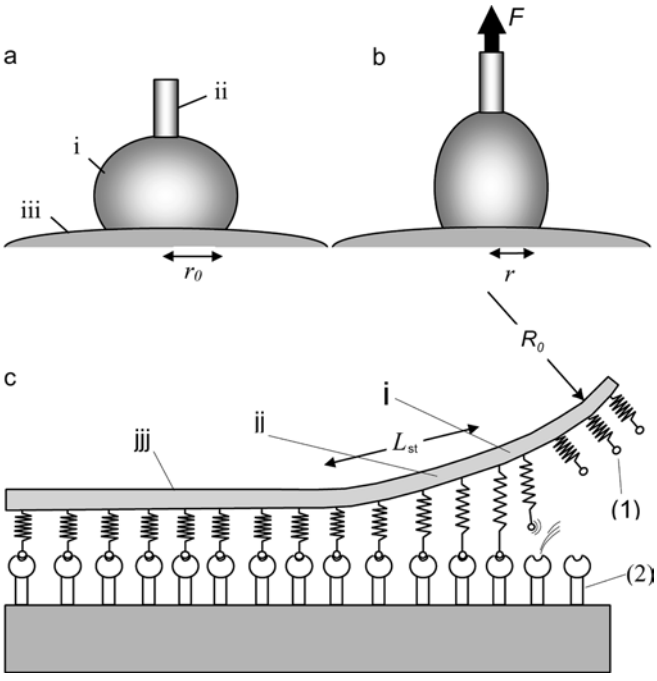

Fig. 1 **a**, **b** Geometry of the experiment on the enforced unbinding of a vesicle (*i*) aspirated into a micropipette (*ii*) from an endothelial cell (*iii*) (Prechtl et al. 2002). **a** The adhesion stage. **b** The regime of enforced unbinding under the action of the force F. The contact contour is a circle of radius r. The vesicle plays the role of a force transducer. **c** The adhesion front. The ligands (*1*) are reconstituted into the vesicle membrane and are selectively recognized by the receptors (*2*) of the endothelial cell; (*j*) shows the reaction zone, where most of the dissociation events take place, (*jj*) the prestressed zone, of length L_{st}, and (*jjj*) the region of unstressed ligand-receptor pairs

Results

Consider a vesicle possessing reconstituted lipo-ligands (L) adhering to a rigid substrate covered with receptors (R). This corresponds to the experimental geometry reported by Prechtl et al. (2002), since the endothelial cells used as the substrate in this work exhibited no deformation during unbinding. We assume that the ligand-receptor pairs (LR) are homogeneously distributed in the adhesion interface and do not form clusters [in agreement with the observations reported by Guttenberg et al. (2001) and Boulbitch et al. (2001)]. The difference between the enforced unbinding of multiple bonds by AFM [as reported by Lehenkari and Horton (1999)] and that of a specifically adhering vesicle or cell is that, in the latter case, the load on the ligand-receptor bonds is transferred via the flexible biomembrane. This results in a stress concentration in the membrane in the vicinity of the adhesion rim (region (j) in Fig. 1c), which manifests itself as a large membrane curvature in this area. In addition, the elastic ligand-receptor bonds at the rim (region (jj) in Fig. 1c) are stretched (Evans 1985b; Hammer and Lauffenburger 1987; Dembo et al. 1988). During the propagation of the rim the release of the energy stored in the stretched bonds, as well as that stored in the curved membrane, results in the breaking of the bonds. Because of the stress concentration, this occurs mainly in the vicinity of the rim rather than in the rest of the adhesion area. The membrane unbinding is therefore dominated by the rim motion.

Estimate the relative contribution of the energy released from the curved membrane and from the stretched bonds for the unbinding geometry shown in Fig. 1a and b. The energy per unit rim length, $E_{\mathrm{b}}\delta r$, released

during the process of membrane unbinding during rim propagation through a distance δr has been calculated in Landau and Lifshitz (1959): $E_b = M^2/2\kappa$, where M is the elastic torque of the membrane at the rim per unit rim length and κ is the membrane bending elasticity.

If the vesicle adhering to the substrate is in equilibrium, the membrane has a certain radius of curvature R_0 at the contact point in accord with the condition $\kappa/2R_0^2 = \varepsilon_{adh}$ (Seifert and Lipowsky 1990), where ϵ_{adh} is the adhesion energy. This corresponds to an equilibrium torque per unit rim length $M_0 = (2\kappa\epsilon_{adh})^{1/2}$ (Fig. 1a). If a force F is applied to the micropipette, it is balanced by the force $f = F/2\pi r$ per unit length at the rim, where r is the radius of the rim. Applying the lever rule of Archimedes (Guttenberg et al. 2000) one finds ΔM, the contribution of the balancing force to the torque at the rim: $\Delta M = fr = F/2\pi$. The total torque at the rim, $M = M_0 + \Delta M$, takes the form:

$$M = M_0 + \frac{F}{2\pi} \tag{2}$$

(see Fig. 1b). Estimating $\epsilon_{adh} \approx 10^{-5}$ J/m^2 and $\kappa \approx 4\times10^{-19}$ J (Guttenberg et al. 2001), one finds $M_0 \approx 10^{-12}$ N, which is much smaller than the minimal yield force measured by Prechtl et al. (2002). This justifies the estimate $E_b = F^2/8\pi\kappa$.

The stretching of ligand-receptor bonds takes place within a distance $L_{st} \sim (\kappa a/k)^{1/4}$ from the rim (Fig. 1c, jj) (Landau and Lifshitz 1959), where k is the spring constant of the single ligand and a is the area per single bond. The number of the stretched bonds is $N \sim rL_{st}/a$. The energy per unit area stored in stretched bonds takes the form $E_{st} \sim F^2(2kNL_{st}r)^{-1}$. One finds the ratio $\phi = E_{st}/E_b \sim 4\pi r^{-2}(a\kappa/k)^{1/2}$. Since the integrin receptors tend to cluster in the adhesion area (Dustin et al. 1996), one can estimate a as the area per ligand-receptor head as $a \sim 100$ nm^2 (Tangemann and Engel 1995). This corresponds to the estimate for the area per selectin bond (Hammer and Lauffenburger 1987). No direct measurements of the spring constant of a single ligand-receptor bond have been reported. We assume it to be of the same order of magnitude as the spring constant of a myosin molecule reported by Veigel et al. (1998), i.e. $k \sim 10^{-3}$ N/m, which is in the range of estimates for a selectin bond (Hammer and Lauffenburger 1987). One finds $\kappa \sim 10^{-18}$ J (Sackmann 1995). During the initial stage of the unbinding, $r \sim 10^{-5}$ m. This yields $L_{st} \sim 10^{-8}$ m, which is below the distance between receptors. Thus, the region with the stretched bonds can be considered as an infinitely thin line. The estimate for the ratio E_{st}/E_b is $\phi \sim 10^{-5}$, which means that during the initial stage of unbinding the energy stored in the stretched bonds is negligible with respect to that stored in the curved membrane.

The concentrations of the components of the reaction $L + R \rightleftarrows LR$ obey the equation:

$$\frac{\partial C_{LR}}{\partial t} = k_+ C_L C_R - k_- C_{LR} \tag{3}$$

where k_+ is the forward reaction rate, k_- is the dissociation rate, and C_i (i = L, R, LR) are the molar concentrations of the reagents with the dimension mol/L. Since during unbinding the elastic torque has the highest values in the vicinity of the contact line (Fig. 1c, j) and much smaller values away from this line (Fig. 1c, jjj), dissociation takes place mainly in a narrow area in the vicinity of the contact line referred to as the ''reaction zone'' (Fig. 1c, i) (Evans 1985a). The variables C_i and the rates $k_\pm$ in Eq. (3) are coordinate-dependent. In general, in order to describe the unbinding process using Eq. (3) one should additionally account for the lateral motion of ligands and receptors (cf. Boulbitch et al. 2001) and thus the problem is spatial. However, in the regime of high concentration of ligands considered here, the unbinding results in the displacement of the adhesion rim, rather than the variation in the lateral distributions of the concentrations. This corresponds to the automodel approach proposed by Dembo et al. (1988). Variation of the surface number density of the of the ligand-receptor pairs $\delta\rho_{LR}$ determines the variation of their number as $\delta N_{LR} = \delta\rho_{LR} bD$, where b is the width of the reaction zone and D is the rim length. On the other hand, according to the above assumption, this variation is related to the displacement of the contact line as $\delta N_{LR} = \rho_{LR} D\delta r$. The surface number density of the pairs, ρ_{LR}, is related to their molar concentration, C_{LR}, as:

$$\rho_{LR} = \frac{C_{LR} N_A}{A d_{LR}} \tag{4}$$

Here N_A is the Avogadro number, A is the membrane area, and d_{LR} is the thickness of the layer of the ligand-receptor pairs. Analogously for the surface number density of ligands, ρ_L, one finds $\rho_L = C_L N_A/A d_L$, where d_L is the thickness of the membrane. Making use of Eq. (4) one finds that:

$$\frac{b}{C_{LR}}\frac{\partial C_{LR}}{\partial_t} = \frac{\partial r}{\partial t} \tag{5}$$

This yields:

$$\frac{\partial r}{\partial t} = v\left(1 - \frac{K_d}{K_d^{(0)}}\right) \tag{6}$$

where $K_d = k_-/k_+$ is the dissociation constant, and $K_d^{(0)} = C_L C_R/C_{LR}$ is the ratio of the concentrations in front of the reaction zone (Fig. 1c, jj). $v = bk_+K_d^{(0)} = bk_-^{(0)}$ characterizes the unbinding velocity. Transition from Eq. (3) to Eq. (6) essentially simplifies the description of the unbinding. In general, the dissociation constant K_d may depend on the position r of the rim. Thus Eq. (6) defines the equation of motion $r = r(t)$ of the rim in the implicit form.

The condition of equilibrium for the reaction $L + R \rightleftarrows LR$ has the form $\mu_L + \mu_R - \mu_{LR} = 0$ (Landau and Lifshitz 1958). Assuming an ideal solution, one finds the chemical potentials of the receptors and the ligand-receptor pairs in the form $\mu_i = \mu_{0i} + k_B T \ln(N_i/N)$, where

$i = \mathrm{R}$ and LR, μ_{0i} are the chemical potentials at standard conditions, N_i is the number of receptors or pairs, and N is the number of lipids in the membrane. Since the membrane bending takes place in the unbound part of the vesicle (i.e. the ligand-containing part of the membrane), the chemical potential μ_L of the ligands must, in addition, account for the release of the membrane bending energy, equal to $-E_b$ per unit area (Landau and Lifshitz 1959), which takes place during the unbinding followed by the rim propagation: $\mu_L = \mu_{0L} + k_B T \ln(N_L/N) - M^2 a/2\kappa$, where N_L is the number of ligands. In general, one should also take into account the contribution of the variation of the membrane entropy during the unbinding. The latter, however, decreases with tension and under the tension of $\sim 10^{-4}$ N/m (as used by Prechtl et al. 2002) can be neglected (Evans and Rawicz 1990). Denoting $\mu_{0L} + \mu_{0R} - \mu_{0LR} = \epsilon_0$, one finds that the dissociation constant has the form:

$$K_d = \frac{N}{N_A V_m} \exp\left\{\frac{1}{k_B T}\left(\frac{M^2 a}{2\kappa} - \varepsilon_0\right)\right\} \tag{7}$$

where V_m is the volume of the membrane.

The characteristic time τ_r describing the approach of the reaction $\mathrm{L} + \mathrm{R} \rightleftarrows \mathrm{LR}$ to chemical equilibrium, under the condition of an excess of ligands, if the ligand-receptor pairs are not stressed, takes the form $\tau_r \approx (k_+ C_L)^{-1}$. The molar concentration can be calculated as $C_L = N_L/N_A V_m$, where $V_m = N a_{lip} d_L$ and a_{lip} is the area per lipid. In experiments (Prechtl et al. 2002) the ligand to lipid ratio of $N_L/N \approx 0.04$ has been used. Estimating $a_{lip} \approx 6 \times 10^{-19}$ m^2 and $d_L \approx 4 \times 10^{-9}$ m, one finds for this value of the N_L/N ratio the molar concentration $C_L \approx 0.03$ mol/L. Taking into account the proper orientation of ligands and receptors which yields the reaction rate $k_+ \approx 6 \times 10^5$ l/mol s (Boulbitch et al. 2001), one finds $\tau_p \sim 10^{-4}$ s.

The rim propagation process has, however, another characteristic time τ_p, during which the releasing energy $E_b a$ per pair exceeds $k_B T$. Representing $F = F' t$ (where the force rate F' is kept constant) one finds $\tau_p = 2\pi(2\kappa k_B T a^{-1})^{1/2}(F')^{-1}$. Estimating the force rate F' as ranging from 10^{-11} to 10^{-9} N/s as used in the experiments reported by Prechtl et al. (2002), one finds $\tau_p \sim 1$ to 0.01 s. This enables one to distinguish the regime of slow rim motion, $\tau_r << \tau_p$, from that of its rapid propagation.

Consider first the former regime. In this case the ligand-receptor pairs in front of the reaction zone (Fig. 1c, jj) have time to come to equilibrium; $K_d^{(0)}$ is obtained by taking the value equal to the dissociation constant in Eq. (7) with the equilibrium value of the torque $M = M_0$. One finds:

$$\frac{K_d}{K_d^{(0)}} = \exp\left(\frac{M^2 - M_0^2}{2\kappa k_B T} a\right) \tag{8}$$

Substitution of the torque (Eq. 2) and the ratio (Eq. 8) into the equation of the rim motion (Eq. 6) and integrating yields the radius of the adhesion rim:

$$r(t) = r_0 + v\left\{t + \frac{\tau_p \pi^{1/2}}{2} \exp\left\{-\frac{t^2}{\tau_p^2}\right\} \times \left[\mathrm{erfi}\left(\frac{t_0}{\tau_p}\right) - \mathrm{erfi}\left(\frac{t + t_0}{\tau_p}\right)\right]\right\} \tag{9}$$

where r_0 is the initial radius of the rim,

$$\mathrm{erfi}(z) = 2\pi^{-1/2} \int_0^z \exp(x^2)\, dx \tag{10}$$

and $t_0 = 2\pi M_0/F'$ is the time necessary for the external torque to become equal to M_0.

The motion described by Eq. (9) is highly non-uniform. The rim displacement is small during the initial time interval of few τ_p (Fig. 2a), and this is followed by a period of exponential acceleration (covering a fraction of the characteristic time τ_p, Fig. 2b). This explains the minor decrease in the size of the adhesion interface followed by an instantaneous (within 40 ms) break of the adhesion reported by Prechtl et al. (2002).

The force measurements can take place only during the regime of the slow motion. Assuming $(M^2 a/2\kappa - \epsilon_0)/k_B T << 1$ and $M_0 << F/2\pi$, and expanding the solution in series, one finds the time of the unbinding, t_*, obeying the condition $r(t_*) = 0$, to be:

$$t_* \approx 2\left(\frac{3\pi^2 \kappa k_B T r_0}{va}\right)^{1/3} (F')^{-2/3} \tag{11}$$

In the moment of time t_* the force takes its maximum value $F_* \approx F' t_*$, corresponding to the unbinding:

$$F_* = 2\left\{\frac{3\pi^2 \kappa k_B T r_0}{va}\right\}^{1/3} (F')^{1/3} \tag{12}$$

Thus, the dependence of the unbinding force upon the force rate obeys the power law $F_* \approx (F')^{\beta}$ with $\beta = 1/3$. Note that if the force applied to the vesicle is small so that $M_0 >> F/2\pi$, the same type of argument yields $\beta = 1/2$.

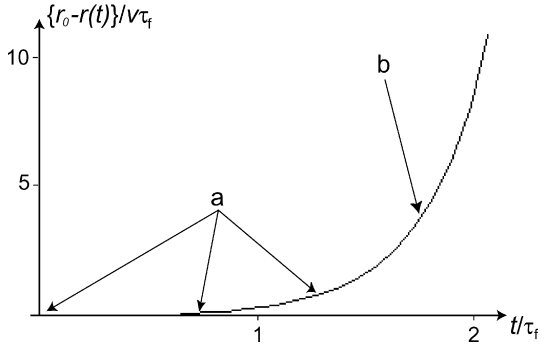

Fig. 2 Dependence of the position of the adhesion front r on time. (*a*) The initial regime of slow motion. (*b*) The regime of exponential acceleration. If the initial position of the rim, r_0, is chosen to be $r_0 = 10 v\tau_p$,one finds that 50% of the front displacement takes place in the time $t \approx 1.7\tau_p$, while the other 50% takes about 0.2τp

Discussion

The equation of motion (Eq. 6) with the expression for the dissociation constant (Eq. 7) enables one to describe the process of spontaneous adhesion of the loaded membrane as well as its enforced unbinding. We illustrated this using, as an example, the enforced unbinding of a vesicle from a substrate as reported by Prechtl et al. (2002). The dependence of F_* upon F' as measured in that work exhibited a dispersed set of data (which is natural, since the role of a rigid substrate was played by living endothelial cells). Its best fit with a power law (Eq. 1) yielded the exponent $\beta_{\mathrm{exp}} \approx 0.4 \pm 0.05$. Our theoretical arguments predict $\beta = 1/2$ when the small forces are applied and $\beta = 1/3$ in the opposite case. One can see that $1/3 < \beta_{\mathrm{exp}} < 1/2$, which may be an indication of a cross-over been the low- and the high-force regimes taking place in the experiments reported by Prechtl et al. (2002).

In the above arguments we did not take into account the contribution to the unbinding of the osmotic pressure of the laterally mobile repeller molecules, such as the glycocalix of the endothelial cell and the lipo-poly(ethylene oxide) reconstituted into the lipid bilayer of the vesicle (Prechtl et al. 2002). The experimental observation of its impact reported earlier (Boulbitch et al. 2001) shows that this contribution is important. Accounting for this contribution is out of the scope of the present letter. We note, however, that it results in dependence of $K_{\mathrm{d}}^{(0)}$ and v on the surface number density of the repellers, ρ_{REP}. Accounting for this contribution leaves, however, the form of Eqs. (6) and (8) unchanged. Since the glycocalix surface number density and its mobility are unknown, one cannot account for its contribution to the unbinding. Therefore, the present contribution predicts the value of the exponent β, rather than the pre-factor depending on $v = v(\rho_{\mathrm{REP}})$.

Acknowledgements The author is grateful to R. Merkel, E. Sackmann, and D. Pink for discussions and to R. Merkel and U. Seifert who sent their manuscripts before they were published. The work was supported by the Deutsche Forschungsgemeinschaft, grant SA246/28-3.

References

Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD (1994) Molecular biology of the cell. Garland, New York

Bell GI (1978) Models for the specific adhesion of cells to cells. Science 200:618–627

Bell GI, Dembo M, Bongrand P (1984) Cell adhesion. Competition between nonspecific repulsion and specific bonding. Biophys J 45:1051–1064

Bongrand P (1999) Ligand-receptor interaction. Rep Prog Phys 62:921–968

Boulbitch A, Guttenberg Z, Sackmann E (2001) Kinetics of membrane adhesion mediated by ligand-receptor interaction studied with a biomimetic system. Biophys J 81:2743–2751

Bruinsma R (1996) Adhesion and rolling of leukocytes: a physical model. In: Sherrington D (ed) Proceedings of the NATO advanced institute on the physics of biomaterials, Geilo, 1995. (NATO ASI series, vol 322) Kluwer, Dordrecht, p 61

Burton K, Taylor DL (1997) Traction forces of cytokinesis measured with optically modified elastic substrata. Nature 385:450–454

Chang KC, Tees DF, Hammer DA (2000) The state diagram for cell adhesion under flow: leukocyte rolling and firm adhesion. Proc Natl Acad Sci USA 97:11262–11267

Dammer U, Hegner M, Anselmetti D, Wagner P, Dreier M, Huber W, Guntherodt HJ (1996) Specific antigen/antibody interactions measured by force microscopy. Biophys J 70:2437–2441

Dembo M, Torney DC, Saxman K, Hammer D (1988) The reaction-limited kinetics of membrane-to-surface adhesion and detachment. Proc R Soc Lond Ser B Biol Sci 234:55–83

Dustin ML, Ferguson LM, Chan PY, Springer TA, Golan DE (1996) Visualization of CD2 interaction with LFA-3 and determination of the two-dimensional dissociation constant for adhesion receptors in a contact area. J Cell Biol 132:465–477

Evans EA (1985a) Detailed mechanics of membrane-membrane adhesion and separation. I. Continuum of molecular cross-bridges. Biophys J 48:175–183

Evans EA (1985b) Detailed mechanics of membrane-membrane adhesion and separation. II. Discrete kinetically trapped molecular cross-bridges. Biophys J 48:185–192

Evans E, Rawicz W (1990) Entropy-driven tension and bending elasticity in condensed-fluid membranes. Phys Rev Lett 64:2094–2097

Evans E, Ritchie K (1999) Strength of a weak bond connecting flexible polymer chains. Biophys J 76:2439–2447

Evans E, Leung A, Zhelev D (1993) Synchrony of cell spreading and contraction force as phagocytes engulf large pathogens. J Cell Biol 122:1295–1300

Guttenberg Z, Bausch AR, Hu B, Bruinsma R, Moroder L, Sackmann E (2000) Measuring ligand-receptor unbinding with magnetic beads: molecular leverage. Langmuir 16:8984–8993

Guttenberg Z, Lorz B, Sackmann E, Boulbitch A (2001) First order transition between adhesion states in a system mimicking cell-tissue interaction. Europhys Lett 54:826–832

Hammer DA (1991) Simulation of cell rolling and adhesion on surfaces in shear flow. Microvilli-coated hard spheres with adhesive springs. Cell Biophys 18:145–182

Hammer DA, Apte SM (1992) Simulation of cell rolling and adhesion on surfaces in shear flow: general results and analysis of selectin-mediated neutrophil adhesion. Biophys J 63:35–57

Hammer DA, Lauffenburger DA (1987) A dynamical model for receptor-mediated cell adhesion to surfaces. Biophys J 52:475–487

Landau LD, Lifshitz EM (1958) Statistical physics, vol 5. Pergamon, London

Landau LD, Lifshitz EM (1959) Theory of elasticity. Pergamon, London

Lehenkari PP, Horton MA (1999) Single integrin molecule adhesion forces in intact cells measured by atomic force microscopy. Biochem Biophys Res Commun 259:645–650

Lipowsky R (1991) The conformation of membranes. Nature 349:475–481

Merkel R, Nassoy P, Leung A, Ritchie K, Evans E (1999) Energy landscapes of receptor-ligand bonds explored with dynamic force spectroscopy. Nature 397:50–53

Oliver T, Dembo M, Jacobson K (1999) Separation of propulsive and adhesive traction stresses in locomoting keratocytes. J Cell Biol 145:589–604

Prechtl K, Bausch AR, Marchi-Artzner V, Kantlehner M, Kessler H, Merkel R (2002) Dynamic force spectroscopy to probe adhesion strength of living cells. Phys Rev Lett 89:028101

Sackmann E (1995) Physical basis of self-organization and function of membranes: physics of vesicles. In: Lipowsly R, Sackmann E (eds) Structure and dynamics of membranes. From cells to vesicles, vol 1. Elsvier, Amsterdam, pp 213–304

Seifert U (1991) Adhesion of vesicles in two dimensions. Phys Rev A 43:6803–6814
Seifert U (1995) Self-consistent theory of bound vesicles. Phys Rev Lett 74:5060–5063
Seifert U (1997) Configurations of fluid membranes and vesicles. Adv Phys 46:13–17
Seifert U (2000) Rupture of multiple parallel molecular bonds under dynamic loading. Phys Rev Lett 84:2750–2753
Seifert U (2002) Dynamic strength of adhesion molecules: role of rebinding and self-consistent rates. Europhys Lett 58:792–798
Seifert U, Lipowsky R (1990) Adhesion of vesicles. Phys Rev A 42:4768–4771
Tangemann K, Engel J (1995) Demonstration of non-linear detection in ELISA resulting in up to 1000-fold too high affinities of fibrinogen binding to integrin $\alpha_{IIb}\beta_3$. FEBS Lett 358:179–181
Veigel C, Bartoo ML, White DC, Sparrow JC, Molloy JE (1998) The stiffness of rabbit skeletal actomyosin cross-bridges determined with an optical tweezers transducer. Biophys J 75:1424–1438