Shape and Dynamics of Adhesive Cells: Mechanical Response of Open Systems

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Cell adhesion is an essential biological process. However, previous theoretical and experimental studies ignore a key variable, the changes of cellular volume and pressure, during the dynamic adhesion process. Here, we treat cells as open systems and propose a theoretical framework to investigate how the exchange of water and ions with the environment affects the shape and dynamics of cells adhered between two adhesive surfaces. We show that adherent cells can be either stable (convex or concave) or unstable (spontaneous rupture or collapse) depending on the adhesion energy density, the cell size, the separation of two adhesive surfaces, and the stiffness of the flexible surface. Strikingly, we find that the unstable states vanish when cellular volume and pressure are constant. We further show that the detachments of convex and concave cells are very different. The mechanical response of adherent cells is mainly determined by the competition between the loading rate and the regulation of the cellular volume and pressure. Finally, we show that as an open system the detachment of adherent cells is also significantly influenced by the loading history. Thus, our findings reveal a major difference between living cells and nonliving materials.

Adhesion of cells to an extracellular matrix or another cell plays a fundamental role in many physiological processes, such as cell migration, wound healing, cell recognition, and rigidity sensing [1–5]. The adhesion strength and the rupture force are the key parameters to characterize cell adhesion. Consequently, the quantitative measurement of these properties of adhesive cells is essential for understanding the fundamental mechanisms of the adhesion-related processes and phenomena.

With the development of experimental techniques, such as micropipette aspiration [6–8], atomic force microscopy [9,10], optical tweezing [11], and microplate manipulation [12–16], the properties of cell adhesion and cell deformability have been extensively explored experimentally. Conventionally, the extraction of these properties from experimental data is mostly based on contact mechanics models [17,18], the Young-Dupré equation [6,19], or the model proposed by Brochard-Wyart and de Gennes [20–22]. In these models, cell volume is either assumed to be constant or totally ignored. However, when cells suffer from large deformation, cell volume, cortical tension, and hydrostatic pressure usually change dramatically [23–29] due to the extensive exchange of water and ions with the environment. For example, cell volume can increase by 30% during the mitotic cell rounding from the adherent state [25], and decrease by 30% under shear stress [26,27]. Cell volume can also change more than 40% due to osmotic shocks [28,29]. However, in such a nonequilibrium open system, the shape and dynamics of adherent cells are affected by the cellular volume and pressure regulation is still elusive.

To answer this question, we focus on cells adhered symmetrically between two surfaces (Fig. 1) as frequently used in atomic force microscope, microplate manipulation, and micropipette aspiration experiments. One adhesive surface can be treated as a rigid body, and the other can be regarded as a cantilever with an equivalent spring stiffness [Fig. 1(c)]. First, the fixed end of the cantilever is moved downward $d_0$ to compress a spherical cell with an

\[ \delta = \frac{Fl}{3EI}, \]

where $F$ is the force applied by the cell and $EI$ is the bending stiffness of the cantilever. Thus, the cantilever can be treated as a spring with a stiffness of $k = 3EI/l^3$ and zero rest length. In (d) and (e), the cell shape is cylindrically symmetric and can be described by $r(s)$ and $z(s)$, where $s$ is the arc length. $\theta(s)$ is the tangential angle of the arc length, and $\theta_0$ is the contact angle. So the cell is convex when $\theta_0 < 90^\circ$ and concave when $\theta_0 > 90^\circ$. $r_a$ is the adhesion radius. $H$ is the cell height and $H_0$ is the separation of the adhesive surface and cantilever. $d(t)$ is the displacement of the fixed end of the cantilever. (f) The loading and unloading process.

FIG. 1. Schematic of cells adhered symmetrically between an adhesive surface and a cantilever. Panels (a) and (b) show convex and concave cells observed in experiments (adapted from Ref. [15] with permission). (c) The deflection of the cantilever is $\delta = Fl/3EI$, where $F$ is the force applied by the cell and $EI$ is the bending stiffness of the cantilever. Thus, the cantilever can be treated as a spring with a stiffness of $k = 3EI/l^3$ and zero rest length. In (d) and (e), the cell shape is cylindrically symmetric and can be described by $r(s)$ and $z(s)$, where $s$ is the arc length. $\theta(s)$ is the tangential angle of the arc length, and $\theta_0$ is the contact angle. So the cell is convex when $\theta_0 < 90^\circ$ and concave when $\theta_0 > 90^\circ$. $r_a$ is the adhesion radius. $H$ is the cell height and $H_0$ is the separation of the adhesive surface and cantilever. $d(t)$ is the displacement of the fixed end of the cantilever. (f) The loading and unloading process.
initial radius of $r_0$ [Fig. 1(f)]. Then, we stop and hold the cantilever for a duration of $t_w$. After the waiting time $t_w$, the cell becomes either convex [Fig. 1(a)] or concave [Fig. 1(b)] due to adhesion, although the cell is always convex initially. Finally, the cantilever is moved upward at a speed $k_d$ to induce detachment [Fig. 1(f)].

We treat cells as open systems, i.e., water and ions can pass through the cell membrane passively or actively. Therefore, the time evolution of the cellular volume $V$ and the total number of ions $n$ due to the transport of water and ions are [23]

$$
\frac{dV}{dt} = -L_pA_{\text{eff}}(\Delta P - \Delta \Pi),
$$

(1)

$$
\frac{dn}{dt} = A_{\text{eff}}(J_{\text{out}} + J_{\text{in}}),
$$

(2)

where $A_{\text{eff}}$ is the effective surface area, i.e., the difference between the total surface area and the adhesion area. $L_p$ is the membrane permeability rate to water. $\Delta P$ and $\Delta \Pi$ are the hydrostatic and osmotic pressure differences, respectively. $J_{\text{out}}$ reflects the ion efflux due to the opening of passive mechanosensitive channels. $J_{\text{in}}$ describes the influx of ions through ion pumps that actively pump ions into the cell. More details of the model are specified in the Supplemental Material [30].

The cell is surrounded by the cortical layer and cell membrane. Therefore, both the cortical tension $T_{\text{cortex}}$ and membrane tension $T_m$ contribute to the total surface tension $T_s$, i.e., $T_s = T_{\text{cortex}} + T_m$ [63,64]. The cortical layer is modeled as a fluidlike layer with a constant active stress $\sigma_a$ [65]. The stress in the cortical layer $\sigma_{\text{cortex}}$ is described by $\sigma_{\text{cortex}} = \eta \dot{e}_A + \sigma_a$ [66], where $\dot{e}_A$ is the strain rate of the cellular surface area and $\eta$ is the viscosity of the cortical layer. Thus, the cortical tension is $T_{\text{cortex}} = \sigma_{\text{cortex}} h_c$, where $h_c$ is the thickness of the cortical layer. The membrane tension is related to the membrane stress $\sigma_m$ by $T_m = \sigma_m h_m$, where $h_m$ is the membrane thickness. We can consider an equivalent surface stress $\sigma$ in these two layers as $T_s = \sigma h$, where $h = h_m + h_c$. Therefore, the surface stress can be determined by $\sigma(h_m + h_c) = \sigma_{\text{cortex}} h_c + \sigma_m h_m$. We can use a membrane reservoir model or a viscoelastic model to describe the membrane stress (see the Supplemental Material [30] for details), but we find the results of these two models are qualitatively the same (Figs. S3 and S5 of Ref. [30]). So we use the reservoir model for the simulations in the main text.

The force balance yields

$$
2\pi \sigma hr \sin \theta = \Delta P \pi r^2 + F,
$$

(3)

where $\theta$ is the tangential angle of the arc length, $r$ is the cell radius, and $F$ is the external force applied by the cantilever (Fig. 1). Notice that $F$ is positive when the cell is stretched.

The contact angle $\theta_0$ defined in Figs. 1(d) and 1(e) is given by the Young-Dupré equation as

$$
\gamma = \sigma h(1 - \cos \theta_0),
$$

(4)

where $\gamma$ is the adhesion energy density between the cell and substrate. When $\gamma = 0$, Eq. (4) is reduced to $\theta_0 = 0$, which is the situation discussed previously [23]. In general, $\gamma$ can vary with time due to the binding and unbinding of the ligand-receptor bonds. The time evolution of $\gamma$ is (see the Supplemental Material [30] for details)

$$
\frac{d\gamma}{dt} = \Gamma_0 k_0^0 \left[ 1 - \Gamma_0 \frac{\exp \left( aFV_{\text{e}} / k_B T \Gamma_1 r_{a0}^2 \right)}{\Gamma_1} \right],
$$

(5)

where $\Gamma_0$ is the equilibrium adhesion energy density when $F = 0$, and $k_0^0$ is the dissociation rate of ligand-receptor pairs when $F = 0$. $r_a$ is the adhesion radius, $a$ is the characteristic length of the bond deformation, $V_{\text{e}}$ is the rupture energy of a single bond [67], $k_B$ is Boltzmann’s constant, and $T$ is the absolute temperature. Notice that at the steady state ($d\gamma/dt = 0$), the equilibrium adhesion energy density $\Gamma_1$ for nonzero $F$ depends on the external force, i.e., $F = (k_B T T \pi r_{a0}^2 / aV_{\text{e}}) \ln(\Gamma_1 / \Gamma_0)$.

First, we consider the dynamic adhesion with constant $H_0$ (the end of the cantilever is fixed). Here, we assume $\Gamma_0$ is very small (weak adhesion) and the waiting time $t_w$ defined in Fig. 1(f) is long enough so that the cell has already reached the steady state. Then, we suddenly increase $\Gamma_0$ to find a new steady state. In this case, the contact angle $\theta_0$ and adhesion radius $r_a$ increase with time [Fig. 2(a), and Fig. S8 of Ref. [30]]. Meanwhile, the tip of the cantilever moves downward so that cell height $H$ decreases and $F$ increases until the cell reaches its new steady state.

For small $\Gamma_0$, we find the steady cell shape is convex ($\theta_0 < 90^\circ$), but the cantilever can apply a pulling ($F > 0$) or pushing ($F < 0$) force [Fig. 2(a), and Movies S1 and S2 of Ref. [30]]. For large $\Gamma_0$, the cell undergoes a transition from a convex shape to a concave shape as $\Gamma(t)$ increases with time [light green curve in Fig. 2(a), subplot (II), and Movie S3 of Ref. [30]], and $F$ changes from a pushing force to a pulling force. Therefore, there is a critical $\Gamma_0$, above which the steady adherent cell is concave ($\theta_0 > 90^\circ$). Besides $\Gamma_0$, we find the separation between the two adhesive surfaces $H_0$ can also affect the steady cell shape. The cell is more likely to be concave for larger $H_0$, as shown in the phase diagram (Fig. 3(a)).

Interestingly, we find that the steady cell shape depends not only on $\Gamma_0$ and $H_0$, but also on the initial cell size $r_0$, i.e., the radius of the spherical cells in suspension. If we decrease $r_0$ from 18 $\mu$m [Fig. 3(a)] to 10.5 $\mu$m [Fig. 3(b)], another region appears in the phase diagram [dark green region in Fig. 3(b), and Movie S4 in Ref. [30]], where the “spontaneous rupture” of cells occurs due to the
adhesion-induced tension increases. The membrane tension increases rapidly and its time derivative is diverging at the time of rupture [dark green curves in Figs. S9(e) and S10(e)]. In reality, when the tension is bigger than some critical value, the membrane and cortex will break. Here, because we did not consider the breakage of the membrane and cortex in the constitutive law, the membrane tension will keep increasing before cell rupture. This is similar to the rupture of red blood cells due to strong adhesion [68]. Mathematically, it indicates that for small cells there is a critical tension or cell height beyond which no catenoidal-like solution exists [69]. The critical condition for the tension-induced rupture is given by Eq. (S48) in the Supplemental Material [30]. In this case, cell height $H_0$ first decreases and then increases [dark green line in Fig. 2(b), subplot (III), and Movie S4 of Ref. [30]]. In contrast, $F$ first increases and then decreases.

If the cantilever stiffness $k$ decreases from 0.5 N/m [Fig. 3(b)] to 0.005 N/m [Fig. 3(c)], another region will emerge in the phase diagram [orange regions in Figs. 3(c) and 3(d), and Movie S5 of Ref. [30]]. In this case, the cell collapses to $H = 0$ when $\Gamma_0$ is large [inset in Fig. 3(d), orange region]. This is because under strong adhesion the cantilever is too soft to sustain the pulling force applied by the cell. Notably, the cell is easier to collapse for smaller $H_0$ [Figs. 3(c) and 3(d)]. Moreover, when $k$ and $H_0$ are small enough, the cell may never become concave as $\Gamma_0$ increases. Instead, the cell will collapse at the convex stage [the left side of point A in Fig. 3(c)]. In fact, recent experiments found that when a cell spreads between a flexible microplate and a rigid microplate, the cell height can decrease to almost zero [15]. This is similar to but slightly different from the cell collapse we found here since the adhesion energy density used in the experiment is usually not very large and the occurrence of the full collapse may also be prevented by the resistance of cell organelles.

Strikingly, when cell volume is conserved during the spreading, the two unstable states (spontaneous rupture and collapse) vanish in the phase diagram (Fig. S11 [30]), and it is very hard for the cells to form a concave shape when $k$ is small. Therefore, the regulation of cell volume and pressure directly induces the unique behaviors of spontaneous rupture and collapse we found here.

Now, we investigate the dynamic detachment of convex and concave cells. Here, we assume $t_w$ is long enough so that the cell can reach the steady state after $t_w$ (Fig. 1). Then, the fixed end of the cantilever is moved upward with a speed $k_d$ to detach the cell. Here, we neglect the dynamics of $\Gamma$ during detachment; i.e., $\Gamma$ is constant, since we want to
focus on how cell volume regulation influences cell detachment. For convex cells, $F$ first increases and then decreases slowly after reaching its maximum as the displacement $d$ increases [Fig. 4(a)]. At steady state, there are two types of convex cells ($F < 0$ or $F > 0$). So $F$ could be negative or positive initially. However, we find that the detachment processes of these two kinds of convex cells are qualitatively the same (Fig. S12 [30]). For concave cells, however, $F$ is always positive and $F$ decreases as $d$ increases [Fig. 4(g)], which is very similar to the rupture of liquid bridges [70–73].

We find that the response of cells greatly depends on the loading rate $k_d$. If $k_d$ is much larger than the speed of water and ion transport, the flux of water and ions is negligible and the cell volume is almost conserved [Figs. 4(b) and 4(h)]. In contrast, if $k_d$ is comparable to or even smaller than the speed of water and ion transport, the change of cell volume is significant and it will greatly influence the hydrostatic pressure difference, membrane tension, and contact angle (Fig. 4). Interestingly, cell volume increases (cell swelling) for convex cells [Fig. 4(b)], while it decreases (cell shrinkage) for concave cells [Fig. 4(h)] during detachment. Furthermore, under small $k_d$, the membrane reservoir can be activated for convex cells [Fig. 4(e)], since the cell volume (surface area) increases remarkably. Thus, there are some windings on the curves of $\Delta P$, $T_m$, and $\theta_0$. Depending on the cell volume change and $k_d$, the membrane tension $T_m$ could increase or decrease and it is not monotonic [Figs. 4(e) and 4(k)]. The change of $\theta_0$ [Figs. 4(f) and 4(l)] is inverse to the change of $T_m$ due to the constraint of the Young-Dupré equation [Eq. (4)]. Therefore, $\theta_0$ is not constant, which indicates the assumption of constant $\theta_0$ used previously [20] might be invalid if cells are treated as open systems.

For convex cells, the adhesion radius $r_a$ first decreases steadily as $d$ increases and then drops sharply when cell adhesion begins to rupture [Fig. 4(d)]. Conversely, for concave cells, $r_a$ does not always decrease, but increases rapidly before the rupture [Fig. 4(j)]. This may be because convex cells rupture at the contact surfaces, while concave cells rupture at the necking equatorial section. These rupture forms are very similar to the rupture of liquid bridges [74].

Strikingly, our results for the dynamic spreading and detachment can quantitatively explain many existing experimental data (Fig. S13 [30]). Furthermore, we find the dynamic detachment of adherent cells also depends on loading history. To demonstrate it, we assume that the cell has already reached a steady state, and then we apply the loading-unloading process in Fig. 1(f) with various waiting times $t_w$. We find that the force, cell volume, contact angle, and other variables are very different (Fig. 5). This is because $t_w$ is not long enough. Thus, the cell has not reached steady state before the cantilever is moved upward. In fact, the loading-unloading process in Fig. 1(f) is widely used in experiments [12–15], where the minimum $t_w$
needed to reach steady state can be affected by many factors, such as loading speed $k_r$, compression depth $d_0$, cell size, and cell type. Therefore, if $t_w$ is not long enough, the mechanical response of cells in different experiments may not be comparable to each other.

In conclusion, we treated cells as open systems and studied how cell volume and pressure regulation influence the shape and dynamics of adherent cells. Our work showed that the mechanical response of living cells significantly depends on the complex interplay of cell volume change, loading rate, and loading history. Therefore, water and ion exchange with the environment is an essential factor that discriminates living cells from nonliving materials. Our findings may also have important implications for other biological processes accompanied by significant cell volume changes, such as mitotic cell rounding, cell deformation due to external forces, and haptotaxis or durotaxis induced by heterogeneous adhesion energy density or substrate stiffness.

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Supplemental Material for "Shape and Dynamic of Adhesive Cell: Mechanical Response of Open Systems"

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I. MODEL

A. Cell shape, effective surface area, and cellular volume

We assume that the cell shape is cylindrically symmetric and can be described by $(r(s), z(s))$, where $s$ is arc length (Fig. S1). Similar to previous works (Yoneda, 1964; Evans et al., 1980; Fischer-Friedrich et al., 2014), we deduce the two shape variables $r(s)$ and $z(s)$ mostly based on the force balance condition

$$2\pi \sigma hr \sin \theta = \Delta P \pi r^2 + F,$$  \hspace{1cm} (S1)

where $r$ is the cell radius, $\theta$ is the tangential angle of arc length, $\Delta P$ is the hydrostatic pressure differences, $F$ is the external force (see Fig. S1). We assume that $F$ is positive when cell is stretched, and $F$ is negative when cell is compressed. To simplify the problem, the membrane and cortex can be modeled as a single layer with an equivalent stress $\sigma$. And $h$ is the thickness of this layer, i.e., $h = h_m + h_c$, where $h_m$ is the thickness of membrane layer and $h_c$ is the thickness of cortical layer. From the force balance equation, we have

$$\sin \theta = Ar + B/r,$$  \hspace{1cm} (S2)

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where \( A = \Delta P/(2\sigma h) \) and \( B = F/(2\pi \sigma h) \).

Furthermore, the two shape variables \( r(s) \) and \( \theta(s) \) are related through the geometrical relation

\[
\frac{dr}{ds} = \cos \theta. \tag{S3}
\]

Substituting Eq. S2 into Eq. S3 yields

\[
\frac{dr}{ds} = \pm \sqrt{1 - (Ar + B/r)^2}, \tag{S4}
\]

where the positive and negative signs are taken for \( \theta < 90^\circ \) and \( \theta > 90^\circ \), respectively. Integrating Eq. S4, we can obtain

\[
\pm 2As = -\arccos \frac{2A^2r^2 - (1 - 2AB)}{\sqrt{1 - 4AB}} + C_0 \quad \text{when} \quad 1 - 4AB > 0, \tag{S5}
\]

where \( C_0 \) is an integration constant. \( C_0 \) is determined by enforcing \( r(0) = r_a \), where \( r_a \) is the adhesion radius. On the lower boundary \( \theta(0) = \theta_0 \), where \( \theta_0 \) is the contact angle. Therefore, on the boundary, we get sin \( \theta_0 = Ar_a + B/r_a \) based on Eq. S2. Notice that in this problem \( 1 - 4AB \geq 0 \) is always true since \( 1 - 4AB = (1 - 2Ar_a)^2 + 4Ar_an(1 - \sin \theta_0) \geq 0 \).

When the cell is cylindrical, \( 2Ar_a = 1 \) and \( \sin \theta_0 = 1 \). Therefore, in this case \( 1 - 4AB = 0 \) and the above solution in Eq. S5 does not exist. Thus, when cell is cylindrical we use another method to obtain the cell shape and we will discuss this in the section II.

From Eq. S5, we can obtain the cell radius \( r(s) \) as

\[
r^2 = \frac{1}{2A^2} [Q_1 + Q_2 \cos(2As + \alpha_0)], \tag{S6}
\]

where \( Q_1 = 1 - 2AB, Q_2 = \sqrt{1 - 4AB} \), and \( \alpha_0 = \arccos [(2A^2r_a^2 - Q_1)/Q_2] \). In contrary to Eq. S4, the positive and negative signs are taken for \( \theta > 90^\circ \) and \( \theta < 90^\circ \) in Eq. S6, respectively.

We can also obtain \( z(s) \) by integrating \( dz/ds = \sin \theta \) as

\[
z(s) = \frac{1}{A\sqrt{2(Q_1 + Q_2)}} \left[ (Q_1 + Q_2)E_2(As \pm \frac{\alpha_0}{2}, G) + 2ABE_1(As \pm \frac{\alpha_0}{2}, G) \right] + C_1, \tag{S7}
\]

where \( C_1 \) is a constant and \( G = 2Q_2/(Q_1 + Q_2) \). \( E_1(\theta, B) \) and \( E_2(\theta, B) \) are the incomplete elliptic integrals of the
first and second kind, respectively.

\[
E_1(\theta, m) = \int_0^\theta \frac{1}{\sqrt{1 - m \sin^2 x}} dx, \\
E_2(\theta, m) = \int_0^\theta \sqrt{1 - m \sin^2 x} dx.
\]

The boundary conditions for \( z(s) \) are

\[
z(0) = 0, \\
z(s_1) = H = 2r_0 + [d(t) - \delta],
\]

where \( s_1 \) is the total arclength, \( H \) is the cell height (Fig. S1), and \( r_0 \) is the initial cell radius, i.e., the radius of the spherical cells in suspension. \( d(t) \) is the displacement of the fixed end of the cantilever, and \( \delta \) is the deflection of the cantilever (Fig. S1). The arc length \( s_1 \) is established by the condition \( r(s_1) = r_a \). Therefore, from Eq. S6, we have \( s_1 = \alpha_0/A \) and \( s_1 = (\pi - \alpha_0)/A \) for convex cells and concave cells, respectively. From the boundary conditions, we can obtain the cell height \( H \).

For convex cells,

\[
H = \frac{\sqrt{2}}{A\sqrt{Q_1 + Q_2}} \left[ (Q_1 + Q_2)E_2(\frac{\alpha_0}{2}, G) + 2ABE_1(\frac{\alpha_0}{2}, G) \right].
\]

(S8)

For concave cells,

\[
H = \frac{\sqrt{2}}{A\sqrt{Q_1 + Q_2}} \left[ (Q_1 + Q_2) \left[ E_2\left(\frac{\pi}{2}, G\right) - E_2\left(\frac{\alpha_0}{2}, G\right)\right] + 2AB \left[ E_1\left(\frac{\pi}{2}, G\right) - E_1\left(\frac{\alpha_0}{2}, G\right)\right] \right].
\]

(S9)

The effective surface area \( A_{eff} \) (the difference between the total surface area and the contact area) and cellular volume \( V \) can be calculated according to \( A_{eff} = \int_0^{s_1} 2\pi r(s) ds \) and \( V = \int_0^{s_1} \pi r(s)^2 \sin \theta(s) ds \).

For convex cells,

\[
A_{eff} = \frac{2\sqrt{2}\pi}{A^2} \sqrt{Q_1 + Q_2}E_2(\frac{\alpha_0}{2}, G),
\]

(S10)

\[
V = \frac{\sqrt{2}\pi}{6A^3} \left\{ 2\sqrt{Q_1 + Q_2(3AB + 2Q_1)}E_2(\frac{\alpha_0}{2}, G) + (Q_2 - Q_1)\sqrt{Q_1 + Q_2E_1(\frac{\alpha_0}{2}, G)} \right. \\
\left. + Q_2 \sin \alpha_0 \sqrt{Q_1 + Q_2 \cos \alpha_0} \right\}.
\]

(S11)

For concave cells,

\[
A_{eff} = \frac{2\sqrt{2}\pi}{A^2} \sqrt{Q_1 + Q_2} \left[ E_2\left(\frac{\pi}{2}, G\right) - E_2\left(\frac{\alpha_0}{2}, G\right)\right],
\]

(S12)

\[
V = \frac{\sqrt{2}\pi}{6A^3} \left\{ 2\sqrt{Q_1 + Q_2(3AB + 2Q_1)} \left[ E_2\left(\frac{\pi}{2}, G\right) - E_2\left(\frac{\alpha_0}{2}, G\right)\right] \right. \\
\left. + (Q_2 - Q_1)\sqrt{Q_1 + Q_2} \left[ E_1\left(\frac{\pi}{2}, G\right) - E_1\left(\frac{\alpha_0}{2}, G\right)\right] - Q_2 \sin \alpha_0 \sqrt{Q_1 + Q_2 \cos \alpha_0} \right\}.
\]

(S13)

B. Cellular volume and pressure regulation

The time evolution of cellular volume \( V \) and ion number \( n \) due to the water and ions transport are given as

\[
\frac{dV}{dt} = -L_pA_{eff}(\Delta P - \Delta \Pi),
\]

(S14)

\[
\frac{dn}{dt} = A_{eff}(J_{out} + J_{in}).
\]

(S15)

where \( A_{eff} \) is the effective surface area without considering the adhesion area since there are no ion and water transport across the contact surfaces. \( L_p \) is the rate of membrane permeability to water. \( \Delta P = P_{in} - P_{out} \) and
\[ \Delta T = T_{in} - T_{out} \] are hydrostatic and osmotic pressure differences, respectively. The osmotic pressure inside the cell can be determined by the Van’t Hoff equation \[ \Pi = cRT, \] where \( c = n/V \) is the concentration of solutes, \( R \) is the gas constant, and \( T \) is the absolute temperature. For the time evolution of ion number, \( J_{out} \) is the ion efflux due to the opening of mechanosensitive channels, and \( J_{in} \) is the influx of ions through active ion pumps.

For a mechanosensitive channel, the opening probability \( P_{open} \) is a Boltzmann function of the surface tension \((\text{Sukharev et al., 1993})\). After approximating the Boltzmann function by a piecewise linear function \((\text{Jiang and Sun, 2013})\), we have

\[
J_{out} = \begin{cases} 0 & \text{if } \sigma < \sigma_c, \\ -\beta(\sigma - \sigma_c)\Delta T & \text{if } \sigma_c \leq \sigma \leq \sigma_s, \\ -\beta(\sigma_s - \sigma_c)\Delta T & \text{if } \sigma > \sigma_s. \end{cases}
\]  

(S16)

where \( \beta \) is the rate constant of efflux, \( \sigma_c \) and \( \sigma_s \) are the threshold stress (below which no mechanosensitive channel is open) and saturating stress (above which all mechanosensitive channels are open) of the mechanosensitive channels, respectively.

In addition to mechanosensitive channels, ion transporters actively pump ions against concentration gradients. In order to overcome the energy barrier from the ion concentration gradient, ion transporters utilize energy from ATP hydrolysis. We denote \( \Delta G_a \) as the free energy input during the pumping action. The free energy change during the pumping action is \( \Delta G = RT \log\left(\frac{c_{in}}{c_{out}}\right) - \Delta G_a \), where \( c_{in} \) and \( c_{out} \) are the ion concentration inside and outside the cell, respectively. The ion flux across transporters can be modeled as \( J_{in} = -\gamma \Delta G \), where \( \gamma \) is a constant. By assuming \( c_{in} - c_{out} \ll c_{in}, \Delta G \) can be linearized as \( \Delta G \approx RT\left(\frac{c_{in} - c_{out}}{c_{out}} - \Delta G_a = RT(\Pi_{in} - \Pi_{out})/\Pi_{out} - \Delta G_a \right) \). Therefore, the influx of ions can be described by \((\text{Jiang and Sun, 2013})\)

\[ J_{in} = \gamma(\Delta T_{cortex} - \Delta T) \]  

(S17)

where \( \gamma \) is a constant and \( \Delta T_{cortex} = \Pi_{out}\left[\exp(\Delta G_a / RT) - 1\right] \) is the critical osmotic pressure difference related to osmotic pressure outside the cells. The critical osmotic pressure difference is the osmotic pressure difference above which the energy input from ATP is insufficient for ion transporters to pump ions against the concentration gradient. The free energy from a mole ATP is \( \Delta G_a \approx 30kJ \), and the osmotic pressure of the growth medium is \( \Pi_{out} = 0.5MPa \), which yields a critical osmotic pressure difference \( \Delta T_{cortex} \approx 30GPa \).

C. Constitutive laws of the cortical layer and membrane layer

The surface tension of the cell, \( T_s \), is the combined result of cortical tension, \( T_{cortex} \), and membrane tension, \( T_m \), i.e., \( T_s = T_{cortex} + T_m \) \((\text{Dai and Sheetz, 1999; Diz-Múñoz et al., 2013})\). The cortical tension is related to the cortical stress as \( T_{cortex} = \sigma_{cortex}h_c \), where \( h_c \) is the thickness of cortical layer and \( \sigma_{cortex} \) is the cortical stress. The membrane tension is \( T_m = \sigma_mh_m \), where \( h_m \) is the thickness of membrane and \( \sigma_m \) is the membrane stress. We can define an equivalent surface stress \( \sigma \) in the combined layer by \( \sigma h = T_s \), where \( h = h_m + h_c \). Therefore, the surface stress can be determined by \( \sigma(h_m + h_c) = \sigma_{cortex}h_c + \sigma_mh_m \).

1. The constitutive law of cortical layer

The cortical layer can be modeled as a fluid-like layer with an active stress. Thus, the constitutive law of the cortical layer is given as

\[ \sigma_{cortex} = \eta \dot{\varepsilon}_A + \sigma_a, \]  

(S18)

where \( \eta \) is the viscosity of cortical layer, \( \dot{\varepsilon}_A \) is the strain rate of cellular surface area, and \( \sigma_a \) is the active stress of cortical layer due to the contraction of myosin motors.

2. The reservoir model of membrane

It is well known that the presence of membrane reservoirs can buffer the increase of membrane tension during the changing of cellular shape \((\text{Raucher and Sheetz, 1999; Figard and Sokac, 2014; Sinha et al., 2011})\). In the tether experiment carried out by Raucher et al with optical tweezers \((\text{Raucher and Sheetz, 1999})\), it has been found that the tether force shows three phases, i.e., an initial phase (the tether force increases with the tether length), an elongation
After the depletion of membrane reservoir, we assume the membrane stress, $\sigma$, is small, this constitutive law of the membrane reduces to an elastic constitutive law, i.e., $\sigma = \frac{E_m (A - A_0)}{A_0}$. The tether force is an indicator of the effective membrane tension. Thus, according to this experimental result, we can obtain the constitutive law of surface stress as (see Fig. S2)

$$
\sigma_m = \begin{cases} 
\frac{E_m (A - A_0)}{A_0} & \text{if } A < A_s, \\
\frac{E_m (A_s - A_0)}{A_0} & \text{if } A_s \leq A \leq A_c, \\
\frac{E_m (A_s - A_0)}{A_0} + E_n [e^{b(A - A_c)/A_0} - 1] & \text{if } A > A_c,
\end{cases}
$$

where $E_m$ is the elastic modulus of membrane in the initial phase, $A$ is the deformed surface area, $A_0$ is the reference surface area, $A_s$ is the critical surface area where the reservoir is activated, and $A_c$ is the critical surface area when the reservoir is depleted. Therefore, $A_c/A_s - 1$ is proportional to the size of membrane reservoir, and the reservoir size found in experiment is in the range of 1% $\sim$ 30% (Figard and Sokac, 2014; Sinha et al., 2011; Kosmalska et al., 2015). After the depletion of membrane reservoir, we assume the membrane stress, $\sigma_m$, is an exponential function of cellular surface area, i.e., $\sigma_m \propto E_n [e^{b(A - A_c)/A_0} - 1]$, where $b$ and $E_n$ are constant. When $A_c = A_s$, $E_m = bE_n$, and $(A - A_c)/A_0$ is small, this constitutive law of the membrane reduces to an elastic constitutive law, i.e., $\sigma_m = E_m (A - A_0)/A_0$. For simplicity, we assume $bE_n = E_m$ in our simulations. Substituting Eq. S18 and Eq. S19 into $h\sigma = h_m \sigma_m + h_c \sigma_{cortex}$, we can obtain the constitutive law of surface stress $\sigma$.

As shown in Fig. S3, for different $b$ and reservoir size $A_0/A_s$, the qualitative results of the phase diagram of the dynamic adhesion are the same. These results indicate that the adhesion behaviors, studied in this work, are not sensitive to the constitutive law of membrane.

3. The viscoelastic model of membrane

We can also use a viscoelastic model for the membrane. In this case, the general viscoelastic constitutive law of membrane layer is

$$
\sigma_m + a_1 \dot{\sigma}_m = b_0 \varepsilon_A + b_1 \dot{\varepsilon}_A,
$$

where $\dot{\sigma}_m$ is the stress rate of membrane layer, $\varepsilon_A$ is the area strain, $a_1$, $b_0$, and $b_1$ are constants. This viscoelastic constitutive law can be reduced to Kelvin-Voigt model when $a_1 = 0$, Maxwell model when $b_0 = 0$, three-element Kelvin model, and three-element Maxwell model.

Based on the constitutive laws of cortical layer and membrane, i.e., Eq. S18 and Eq. S20, we obtain

$$
h\sigma + a_1 h\dot{\sigma} = h_c (\eta \dot{\varepsilon}_A + \sigma_a) + a_1 h \eta \ddot{\varepsilon}_A + h_m (b_0 \varepsilon_A + b_1 \dot{\varepsilon}_A).
$$

When we use the three-element Maxwell model to describe the deformation of membrane (Fig. S4), the constitutive law of membrane Eq. S20 becomes

$$
\sigma_m + \eta_m/E_4 \dot{\sigma}_m = E_0 \varepsilon_A + (E_1 + E_0) \eta_m/E_4 \dot{\varepsilon}_A,
$$

FIG. S2 The constitutive law of cell membrane after considering the membrane reservoirs. Membrane stress increases linearly with cellular surface area in the initial phase. And the membrane stress is independent on cellular surface area in the reservoir phase. In the third phase, the membrane stress increases exponentially with surface area, i.e., $\sigma \propto E_n [e^{b(A - A_c)/A_0} - 1]$, where $b$ and $E_n$ are constant. $A_s$ is the critical surface area where the reservoir is depleted, and $A_c$ is the critical surface area when the reservoir is depleted.
FIG. S3 The phase diagrams of cell shapes for various stiffness of cantilever $k$ and cell size $r_0$, when we consider the effect of membrane reservoir for different $b$ and reservoir size $A_c / A_s$. (I) $b = 1$ and $A_c / A_s = 1.1$; (II) $b = 2$ and $A_c / A_s = 1.1$; (III) $b = 2$ and $A_c / A_s = 1.2$; (IV) $b = 3$ and $A_c / A_s = 1.1$. In each subfigure, (a) $r_0 = 18 \mu m$, $k = 0.5 N/m$; (b) $r_0 = 10.5 \mu m$, $k = 0.5 N/m$; (c) $r_0 = 10.5 \mu m$, $k = 0.005 N/m$; (d) $r_0 = 10.5 \mu m$, $k = 0.01 N/m$. We can find that for different constitutive laws, the qualitative results of dynamic adhesion are the same.

where $E_1$ and $E_0$ are the two spring constants of the three-element Maxwell model, and $\eta_m$ is the viscosity of membrane (Fig. S4).

Therefore the constitutive law of surface stress Eq. S21 becomes

$$h\sigma + \eta_m/E_1\dot{\varepsilon} + h_c(\eta^s\varepsilon_A + \sigma_0) + h_c\eta_m/E_1\dot{\varepsilon}_A + h_m[E_0\dot{\varepsilon}_A + (E_1 + E_0)\eta_m/E_1\dot{\varepsilon}_A].$$

(S23)

The elastic modulus of membrane ranges from $10^4$ Pa to $10^7$ Pa (Hochmuth and Mohandas, 1972; Hochmuth et al., 1973; Evans, 1989; Picas et al., 2012). Therefore, we take $E_0 = 100 \text{ kPa}$ and $E_1 = 40 \text{ kPa}$ in our simulation. It has been shown that the relaxation time of membrane is on the order of 0.1 second (Evans, 1989; Rand, 1964; Hochmuth and Waugh, 1987), which gives the ratio of the membrane viscosity, $\eta_m$, to the elastic modulus $E_1$. Thus, we take $\eta_m = 4000 \text{ Pa} \cdot \text{s}$. The viscosity of cortical layer measured in experiments is about $10^2 \sim 10^3 \text{ Pa} \cdot \text{s}$ (Evans and Yeung, 1989; Bausch et al., 1999; Koay et al., 2003; Bausch et al., 1998), so we take $\eta = 5000 \text{ Pa} \cdot \text{s}$.

We find that the qualitative results of the viscoelastic model are the same with the results of the reservoir model.
FIG. S4 The fluid-like cortical layer model with active contraction and the three-element Maxwell model of cell membrane. The cell surface stress $\sigma$ is the combined effect of membrane stress and cortical stress since these two layers are connected in parallel. $\eta$ is the viscosity of cortical layer and $\sigma_a$ is the active stress of cortex. $E_1$ and $E_0$ are the two spring constants of the three-element Maxwell model, and $\eta_m$ is the viscosity of membrane.

(compare Fig. S5(I) with Fig. S3). Therefore, we will take the reservoir model, Eq. S19, to describe the deformation of membrane in our main text.

4. The contribution of the viscosities of cortex and membrane

To investigate the roles of the viscosities of cortex and membrane in cell responses, we first study the dynamic adhesion of cell when we neglect the contribution of the viscous terms in Eq. S21 and Eq. S23. In this case, the constitutive law of surface stress reduces to an elastic constitutive law

$$h\sigma = h_m E_m (A/A_0 - 1) + \sigma_a h_c,$$

where $E_m$ is the Young’s modulus of membrane layer, $A$ and $A_0$ are the deformed and reference cellular surface areas, respectively. After taking an elastic constitutive law for the surface stress (Eq S24), the qualitative results of the

FIG. S5 The phase diagrams of cell shapes for various stiffness of cantilever $k$ and cell size $r_0$ when we take a viscoelastic (I, $\eta=5000$ Pa $\cdot$ s, $\eta_m=4000$ Pa $\cdot$ s) or an elastic (II, $\eta=0$ Pa $\cdot$ s, $\eta_m=0$ Pa $\cdot$ s) constitutive law of cortex and membrane. (a) $r_0 = 18\mu m$, $k = 0.5 N/m$; (b) $r_0 = 10.5\mu m$, $k = 0.5 N/m$; (c) $r_0 = 10.5\mu m$, $k = 0.005N/m$; (d) $r_0 = 10.5\mu m$, $k = 0.01N/m$. 

phase diagram of the dynamic adhesion behaviors of cell are the same with the results of the viscoelastic model (Fig. S5 I and II).

FIG. S6 The detachment of convex cells, when the viscosities of cortical layer and membrane layer are zero (solid curves) or nonzero (circles, \( \eta = 5000 \text{ Pa} \cdot \text{s} \) and \( \eta_m = 4000 \text{ Pa} \cdot \text{s} \)). (a) The adhesion radius, (b) contact angle, (c) external force, (d) cellular volume, (e) membrane tension, and (f) the hydrostatic pressure difference. The viscous properties of the cortical layer and membrane layer only slightly affect the response of cells when \( k_d > 10 \mu \text{m/s} \).

To what extent do the viscosities of cortex and membrane contribute to the responses of cell? As shown in Fig. S6, we compare the detachment results of the viscoelastic constitutive law (\( \eta = 5000 \text{ Pa} \cdot \text{s} \) and \( \eta_m = 4000 \text{ Pa} \cdot \text{s} \)) with the results of an elastic constitutive law (\( \eta = 0 \) and \( \eta_m = 0 \)). The loading speed \( k_d \) used in our simulation is \( 0.01 \sim 10 \mu \text{m/s} \) since the stretch speed used in experiment is \( 0.1 \mu \text{m/s} \sim 10 \mu \text{m/s} \) (Thoumine and Meister, 2000; Colbert et al., 2009, 2010; Chu et al., 2005). We find that the contributions of the viscosities of the fluid-like cortical layer and membrane to the detachment of cells are significant under high stretch speed.

D. The adhesion between cells and the two surfaces

The adhesion between cells and the two surfaces can be described by the Young–Dupré equation as

\[
\Gamma = \sigma h (1 - \cos \theta_0),
\]

where \( \Gamma \) is the adhesion energy density and \( \theta_0 \) is the contact angle.

The rate equation of the ligand-receptor bonds density \( \rho_{lr} \) is given by (Bell et al., 1978; Lin and Freund, 2007)

\[
\frac{d\rho_{lr}}{dt} = k_{on} \rho_l \rho_r - k_{off} \rho_{lr},
\]

where \( \rho_l \) is the ligand density and \( \rho_r \) is the receptor density. \( k_{on} \) and \( k_{off} \) are the association and dissociation rates, respectively. Here we assume that there are reservoirs for ligand and receptor so that the ligand density \( \rho_l \) and receptor density \( \rho_r \) are constants. We further assume that the association rate \( k_{on} \) is force independent, while the dissociation rate \( k_{off} \) increases exponentially with the external force \( f \) on the ligand-receptor bond according to Bell’s model (Bell et al., 1978; Lin and Freund, 2007)

\[
k_{off} = k_{off}^0 \exp(a f/k_B T),
\]

where \( k_{off}^0 \) is the dissociation rate of ligand-receptor pairs when \( f = 0 \), \( a \) is the characteristic length of the bond deformation, \( k_B \) is the Boltzmann’s constant, and \( T \) is the absolute temperature. We assume that the traction force \( F \) is equally shared by all the bonds in the adhesion area, i.e., \( f = F/(\pi r_a^2 \rho_{lr}) \), where \( r_a \) is the adhesion radius.
When the bonds are unloaded, on equilibrium we have \( k_{\text{on}} \rho_l \rho_r - k_{\text{off}}^{\text{eff}} \rho_r^0 = 0 \), where \( \rho_r^0 \) is the equilibrium ligand-receptor pair density when \( F = 0 \). So the rate equation reduces to
\[
\frac{d\rho_r}{dt} = k_{\text{off}}^{\text{eff}} \rho_r^0 - k_{\text{off}} \rho_r
\]  
(S28)

Substituting Eq. S27 to Eq. S28, the rate equation becomes
\[
\frac{d\rho_r}{dt} = k_{\text{off}}^{\text{eff}} \rho_r^0 \left[ 1 - \frac{\rho_r}{\rho_r^0} \exp\left( \frac{aF}{k_BT} \right) \right],
\]  
(S29)

If we assume the rupture energy of single bond is \( V_e \), then the adhesion energy density is \( \Gamma = V_e \rho_r \). Thus the time evolution of \( \Gamma \) is
\[
\frac{d\Gamma}{dt} = V_e \frac{d\rho_r}{dt} = k_{\text{off}}^{\text{eff}} \rho_r^0 \left[ 1 - \frac{\Gamma}{\Gamma_0} \exp\left( \frac{aFV_e}{k_BT\pi r_a^2} \right) \right],
\]  
(S30)

where \( \Gamma_0 = V_e \rho_r^0 \) is the equilibrium adhesion energy density when \( F = 0 \).

It should be noted that if we assume that only the ligand-receptor bonds adjacent to the periphery of adhesion region are being stretched, we only need to modify \( f = F/(\pi r_a^2 \rho_r) \) to \( f = F/(\pi r_a^2 \rho_r) \), where \( d \) is the width of the annular region. We find the results of these two cases are qualitatively the same.

Recent experiment demonstrated that the spread radius \( r_s \) is bigger than the cell body contact radius \( r_a \) due to the existence of lamellipodia (Fouchard et al., 2014). In our model, to simplify the problem we have neglected the lamella and assumed the spread area \( r_s \) is equal to the cell body contact radius \( r_a \). If we consider the difference between \( r_s \) and \( r_a \), we can simply modify \( f = F/(\pi r_a^2 \rho_r) \) to \( f = F/(\pi r_s^2 \rho_r) \). Therefore, we can determine the effective adhesion energy density from Eq. S30. It should be noted that if \( F \) is bigger than a critical value \( F_c = k_B T \pi r_a^2 \Gamma_0/(eaV_e) \), there is no steady solution in Eq. S30. However, we find that \( F \) is much smaller then \( F_c \) for the parameters used in our simulation.

### II. NUMERICAL METHOD

The analytical solution we obtained above has some limitations. It’s only suitable for simple cell shapes with monotonically changing \( \theta \). Furthermore, the analytical solution in Eq. S6 will break down for cylindrical cells since \( \theta = \pi/2 \) and Eq. S3 reduces to \( \frac{dr}{ds} = 0 \) in this case. Consequently, it’s very necessary to develop a method to solve for arbitrary cell shapes. Here, we obtain the cell shape by numerically solving a boundary value problem following our previous work (Jiang et al., 2007).

At any given time \( t \), the cell shape \( r(s) \) and \( z(s) \) can be described by the following ordinary differential equations (Chen et al., 2014)
\[
\frac{dr}{ds} = \cos \theta, \quad \frac{dz}{ds} = \sin \theta, \quad \frac{d\theta}{ds} = \frac{\Delta P}{\sigma h} - \frac{\sin \theta}{r} = \frac{B_1}{r} - \frac{\sin \theta}{r}, \quad \text{(S31, S32, S33)}
\]

where \( B_1 = \Delta P r_a/\sigma h \) is an unknown dimensionless variable. Eq. S31 and Eq. S32 are the geometric relations while Eq. S33 is deduced from Young–Laplace equation.

It is convenient to regard the effective surface area as a function of \( s \). We define \( A_s(s) \) as the effective surface area swiped by the arclength \( s \), similarly, we can define \( V_s(s) \). Thus, \( A_s(s) \) and \( V_s(s) \) obey the following differential equations
\[
\frac{dA_s}{ds} = 2\pi r, \quad \frac{dV_s}{ds} = \pi r^2 \sin \theta. \quad \text{(S34, S35)}
\]

The corresponding boundary conditions are \( A_s(0) = 0, A_s(s_l) = A_{eff}, V_s(0) = 0, \) and \( V_s(s_l) = V \), where \( A_{eff} \) and \( V \) are the effective surface area and the cellular volume of the whole cell, respectively. Other boundary conditions
include $r(0) = r_a$, $r(s_l) = r_a$, $\theta(0) = \theta_0$, $\theta(s_l) = \pi - \theta_0$, $z(0) = 0$, and $z(s_l) = 2r_0 + (d - \delta)$. Here $r_a$ is the adhesion radius, $\theta_0$ is the contact angle, and $2r_0 + (d - \delta)$ is the cell height as we discussed in the above sections.

The arclength $s_l$ is still unknown and must be solved for along with the cell shape. To determine $s_l$, we introduce a new variable $x$ with $s_l = s_l x$ and $x \in [0, 1]$ to reparametrize the problem (Jiang et al., 2007). Thus, the boundary conditions at $s = s_l$ transform to the boundary conditions at $x = 1$. And the differential equations are also modified to

$$
\frac{dr}{dx} = s_l \cos \theta, \\
\frac{dz}{dx} = s_l \sin \theta, \\
\frac{d\theta}{dx} = \frac{B_1}{r_0} - \frac{s_l \sin \theta}{r}, \\
\frac{dA}{dx} = 2\pi s_l r, \\
\frac{dV}{dx} = \pi r^2 s_l \sin \theta, \\
\frac{ds_l}{dx} = 0.
$$

(S36) (S37) (S38) (S39) (S40) (S41)

In our numerical approach, we treat these differential equations as a two-point boundary value problem, and we use the MATLAB function \texttt{bvp4c} to solve this boundary value problem.

### III. THE CRITICAL CONDITION OF TENSION-INDUCED RUPTURE

Since cell would spontaneously rupture under strong adhesion, it is necessary to obtain the critical condition for spontaneous rupture. The analytical relation between the equilibrium cell shape and mechanical parameters, such as surface tension $T_s$, hydrostatic pressure difference $\Delta P$, and the stiffness of cantilever $k$, at the time of rupture can be determined by the following analytic model.

The free energy of the system is

$$
G = \int \sigma h dS - \int \Delta P dV,
$$

(S42)

where $\sigma h$ is the surface tension, and $\Delta P$ is the hydrostatic pressure differences. By non-dimensionalizing the free energy with $\pi \sigma h r_0^2$, the free energy then becomes

$$
\tilde{G} = \frac{G}{\pi \sigma h r_0^2} = \int 2\tilde{r} \sqrt{1 + (d\tilde{r}/d\tilde{z})^2} d\tilde{z} - \int B_2 \tilde{r}^2 d\tilde{z},
$$

(S43)

where $\tilde{r} = r/r_0$, $\tilde{z} = z/r_0$, $B_2 = \Delta P r_0/(\sigma h)$ are dimensionless variables, and $r_0$ is the initial cell size (the radius of the spherical cell in suspension). We minimize the energy $\tilde{G}$ by taking the first variational derivative with respect to $\tilde{z}$ and obtain the following Euler-Lagrange equation

$$
\frac{2\tilde{r}}{\sqrt{1 + (d\tilde{r}/d\tilde{z})^2}} - B_2 \tilde{r}^2 = A_2,
$$

(S44)

where $A_2 = F/(\pi \sigma h r_0)$ is the conserved quantity of the system. When $\Delta P = 0$ (i.e. $B_2 = 0$), this Euler-Lagrange equation reduces to the shape equation of a catenoid (Powers et al., 2002). Integrating Eq. S44 yields the cell shape

$$
\tilde{z} = \begin{cases} 
F_1(\tilde{r}) - F_1(\tilde{r}_a) + \tilde{H} & \text{when } \theta < \pi/2, \\
F_1(\tilde{r}_a) - F_1(\tilde{r}) & \text{when } \theta \geq \pi/2,
\end{cases}
$$

(S45)

where $\tilde{r}_a$ and $\tilde{H}$ are the dimensionless adhesion radius and cell height, respectively. The detailed expression of $F_1(\tilde{r})$
is

\[
F_1(r) = \frac{\sqrt{1 + B_2^2 r^2} - P_1 \sqrt{1 + B_2^2 r^2}}{2 B_2 \sqrt{4 r^2 - (A_2 + B_2 r^2)^2}} \left[ P_1 E_2 [\phi(r), -P_2/P_1] + 2 \sqrt{1 - A_2 B_2 E_1 [\phi(r), -P_2/P_1]} \right],
\]

where \( P_1 = (1 - \sqrt{1 - A_2 B_2^2})^2 \), \( P_2 = (1 + \sqrt{1 - A_2 B_2^2})^2 \), and \( \phi(r) = \arcsin(B_2 r/(1 + \sqrt{1 - A_2 B_2})) \). \( E_1(\theta, m) \) and \( E_2(\theta, m) \) are the incomplete elliptic integrals of the first and second kind, respectively. For given surface tension \( \sigma_h \), hydrostatic pressure difference \( \Delta P \), cell height \( H \) and adhesion radius \( r_a \), the equilibrium cell shape is analytically determined by Eq. S45.

The separation between the adhesive surface and cantilever, \( H_0 \), is related to the cell height, \( H \), through \( H_0 = H + F/k \), where \( F \) is the external force applied by the cantilever and \( k \) is the stiffness of the cantilever. After non-dimensionalization, we have

\[
\tilde{H}_0 = \tilde{H} + A_2/\tilde{k} = 2 F_1(\tilde{r}_a) - 2 F_1(\tilde{r}_{min}) + A_2/\tilde{k}
\]

where \( \tilde{r}_{min} \) is the minimum cell radius where \( d\tilde{r}/d\tilde{z} = 0 \) at the equatorial plane (\( \theta = \pi/2 \)), and \( \tilde{k} = k/(\pi \sigma_h) \) is the dimensionless stiffness of the cantilever. Notice that, the adherent cell only ruptures at concave shape, so the cell radius at \( d\tilde{r}/d\tilde{z} = 0 \) is minimum. Since there is a maximum in the curve of \( \tilde{H} \) (marked by a red dot in Fig. S7(a)), there is a critical cell height \( \tilde{H}_c \) beyond which no solution exists. It indicates that for the cell height bigger than this critical height, there is no corresponding neck radius \( \tilde{r}_{min} \), i.e., no corresponding equilibrium cell shape exists.

The critical condition for the tension-induced rupture is

\[
\frac{d\tilde{H}}{dA_2} = \frac{2 \tilde{r}_a A_2 B_2 (2 - A_2 B_2 - B_2^2 \tilde{r}_a^2)}{A_2 (A_2 B_2 - 1) H_1(\tilde{r}_a) H_2(\tilde{r}_a) - \frac{2 A_2 B_2 \tilde{r}_{min} (2 - 2 B_2^2 \tilde{r}_{min}^2)}{A_2 (A_2 B_2 - 1) H_1(\tilde{r}_{min}) H_2(\tilde{r}_{min})} + \sqrt{P_1^2 - B_2^2 \tilde{r}_a^2}} H_2(\tilde{r}_a) \left[ P_1 E_2 [\phi(\tilde{r}_a), -P_2/P_1] - 2 \sqrt{1 - A_2 B_2 E_1 [\phi(\tilde{r}_a), -P_2/P_1]} \right] = 0,
\]

where \( H_1(r) = \sqrt{P_1^2 + B_2^2 r^2} \), and \( H_2(r) = \sqrt{P_2^2 - B_2^2 r^2} \). This critical condition indicates that the contact area, surface tension, hydrostatic pressure difference, cell height, and force should satisfy Eq. S48 at the critical point.

We also find that the critical cell height \( \tilde{H}_c \) increases with decreasing cantilever stiffness \( \tilde{k} \) (Fig. S7), which indicates that the spontaneous rupture region shifts right as the stiffness of the cantilever decreases (Fig. 3(b) and Fig. 3(d)). Since the spontaneous rupture region shifts right as the critical cell height, \( \tilde{H}_c \), increases.

Notice that the membrane tension increases rapidly when the cell begins to rupture and the corresponding curves are almost vertical, i.e., the time derivative of membrane tension is diverging (green curves in Fig. S9(e) and Fig. S10(c)). This means the time derivative of cellular surface area is also diverging, since the membrane tension is proportional to the cellular surface area (Eq. (S24)). Cells can dynamically enter “rupture” because the cell volume changes with time (see Fig. S8, S9 and S10). Even though the cell surface (cortical layer and membrane layer) can provide resistance to the stretch induced by adhesion, the membrane tension continues to increase with time as the cell spreads between the adhesive surface and cantilever. Once the membrane tension or the cell height increases to the critical value determined by Eq. (S48), the cell would not be able to bear such a high tension, and the cell would rupture and it results in a sharp decrease in stretch force (green curves in Fig. S9(a) and Fig. S10(a)). Mathematically, it indicates

\[
F_1(r) = \frac{\sqrt{1 + B_2^2 r^2} - P_1 \sqrt{1 + B_2^2 r^2}}{2 B_2 \sqrt{4 r^2 - (A_2 + B_2 r^2)^2}} \left[ P_1 E_2 [\phi(r), -P_2/P_1] + 2 \sqrt{1 - A_2 B_2 E_1 [\phi(r), -P_2/P_1]} \right],
\]
that there is a critical tension or cell height beyond which no catenoid-like solution exists (Powers et al., 2002). This is similar to the spontaneous rupture of red blood cells due to the high tension induced by strong adhesion (Hategan et al., 2003). Therefore, we denote this phenomenon as “spontaneous rupture”.

IV. SUPPLEMENTARY RESULTS

A. Dynamic adhesion of cells (supplementary figures to the Fig. 3 in the main text)

We only show several variables during the dynamic adhesion of cells in the Fig. 3 of the main text. Here we show how other variables evolve with time (see Fig. S8, Fig. S9, and Fig. S10).

FIG. S8 Dynamic adhesion of cells adhered to an adhesive surface and a cantilever, with $r_0 = 18 \mu m$ and $k = 0.5 N/m$. (a) The external force, (b) cellular volume, (c) cell height, (d) adhesion radius, (e) membrane tension, (f) the contact angle, (g) hydrostatic pressure differences, (h) ions number, (i) the flux of water, and (j) the flux of ions. The red, light blue and light green curves represent the dynamic process of reaching the three stable states: (1) cell is convex ($\theta_0 < 90^\circ$) and $F < 0$; (2) cell is convex and $F > 0$; (3) cell is concave ($\theta_0 > 90^\circ$) and $F > 0$. The dash lines in (a) and (f) indicate the lines of $F = 0$ and $\theta = 90^\circ$, respectively.

FIG. S9 Dynamic adhesion of cells adhered to an adhesive surface and a cantilever, with $r_0 = 10.5 \mu m$ and $k = 0.5 N/m$. (a) The external force, (b) cellular volume, (c) cell height, (d) adhesion radius, (e) membrane tension, (f) the contact angle, (g) hydrostatic pressure differences, (h) ions number, (i) the flux of water, and (j) the flux of ions. The red, light blue and light green curves represent the dynamic process of reaching the three stable states: (1) cell is convex ($\theta_0 < 90^\circ$) and $F < 0$; (2) cell is convex and $F > 0$; (3) cell is concave ($\theta_0 > 90^\circ$) and $F > 0$. The dark green curves represent the process of spontaneous rupture of cells. The dash lines in (a) and (f) indicate the lines of $F = 0$ and $\theta = 90^\circ$, respectively.
FIG. S10 Dynamic adhesion of cells adhered to an adhesive surface and a cantilever, with \( r_0 = 10.5 \mu m \) and \( k = 0.01 N/m \). (a) The external force, (b) cellular volume, (c) cell height, (d) adhesion radius, (e) membrane tension, (f) the contact angle, (g) hydrostatic pressure differences, (h) ions number, (i) the flux of water, and (j) the flux of ions. The red, light blue and light green curves represent the dynamic process of reaching the three stable states: (1) cell is convex (\( \theta_0 < 90^\circ \)) and \( F < 0 \); (2) cell is convex and \( F > 0 \); (3) cell is concave (\( \theta_0 > 90^\circ \)) and \( F > 0 \). The dark green and orange curves represent the processes of spontaneous rupture and collapse of cells. The dash lines in (a) and (f) indicate the lines of \( F = 0 \) and \( \theta = 90^\circ \), respectively.

B. The phase diagrams of cell shapes when cellular volume and pressure are constant.

To keep the cell volume constant, we assume the membrane permeability rates to water and ion are suddenly decreased to zero so that water and ion exchange between cell and environment is stopped. Therefore, we obtain \( dV/dt = 0 \) and \( dn/dt = 0 \) from Eq. (S14) and (S15). From these equations, we get \( V = V_0 \) and \( n = n_0 \), where \( V_0 \) and \( n_0 \) are the cell volume and ion number of the initial spherical cell, respectively. Furthermore, before the membrane permeability rates to water and ion are suddenly decreased to zero, we have \( dV/dt = -\alpha(\Delta P - \Delta \Pi) = 0 \) in equilibrium. Therefore, we obtain the hydrostatic pressure difference as \( \Delta P = \Delta \Pi = n_0 RT/V_0 - \Pi_{out} \), where \( R \) is the gas constant, \( T \) is the absolute temperature, and \( \Pi_{out} \) is the osmotic pressure outside the cell. After the membrane permeability rates are decreased to zero, we assume the expression of \( \Delta P \) remains unchanged. Since the cell volume \( V \) and ion number \( n \) are constant, the hydrostatic pressure difference \( \Delta P \) is also constant.

As shown in Fig. S11, when the cellular volume and pressure are constant during the dynamic spreading of cell, the cells would not spontaneously rupture or collapse. In this case, the cell is very hard to become concave when the stiffness of the cantilever is small (the green region in Fig. S11 (c) and (d) is small).

FIG. S11 The phase diagrams of cell shapes when the cellular volume and pressure are constant during the dynamic spreading of cells. (a) \( r_0 = 18 \mu m \) and \( k = 0.5 N/m \), (b) \( r_0 = 10.5 \mu m \) and \( k = 0.5 N/m \), (c) \( r_0 = 10.5 \mu m \) and \( k = 0.005 N/m \), (d) \( r_0 = 10.5 \mu m \) and \( k = 0.01 N/m \). The cells would not spontaneously rupture or collapse.
C. Dynamic detachment of convex cells with negative initial $F$

In the main text, we find that after the cells achieve their equilibrium adhesion state, the dynamic detachments of convex and concave cells are very different. But when the cell is convex, there are two stable states with positive $F$ or negative $F$. However, we find that the detachment processes of these two kinds of convex cells are qualitatively the same as shown in Fig. S12.

![Figure S12](image)

**FIG. S12** Dynamic detachments of convex cells whose initial $F$ is negative (dash curves) or positive (solid curves). (a) The external force, (b) cellular volume, (c) adhesion radius, (d) membrane tension, (e) contact angle, and (f) hydrostatic pressure differences versus the displacement of the fixed end of the cantilever $d(t)$ with various loading speed $k_d$.

V. THE RANGES OF PARAMETERS

In Table S1, we have discussed the range of the parameters we used in the simulation based on experimental data. In the phase diagram of cell shapes (Fig. 3 in the main text), we found that other variables, such as the stiffness of cantilever $k$, cell size $r_0$, the separation of the adhesive surface and cantilever $H_0$, and adhesion energy density $\Gamma_0$, are very important control parameters. Therefore, here we further discuss the realistic ranges of these parameters.

The adhesion energy density $\Gamma_0$ used in the phase diagram is in the range of $0 \sim 10^{-3} \text{J/m}^2$, which covers the range of the adhesion energy density used in experiments (around $10^{-4} \text{J/m}^2$) (Colbert et al., 2009, 2010; Chu et al., 2005). In our simulation, the cell diameter $2r_0$ is 21$\mu m$ and 36$\mu m$, and the separation of the adhesive surface and cantilever $H_0$ is smaller than $2r_0$. This is consistent with the fact that the cell diameter $2r_0$ is around tens of microns in the experiments (Fouchard et al., 2014; Fischer-Friedrich et al., 2016; Chaudhuri et al., 2009; Stewart et al., 2013; Webster et al., 2014; Thoumine and Ott, 1997; Desprat et al., 2005; Mitrossilis et al., 2009).

Based on the phase diagrams in Fig. 3 of the main text, it can be found that the unstable states are only shown when the cell is small. Therefore, to avoid the unstable states, one should use big cells for the measurements. In the case of small cells, the spontaneous rupture only appears when the separation of the adhesive surface and cantilever $H_0$ is big and the stiffness of the cantilever $k$ is small. In contrast, the collapse of cell occurs when the cantilever is very soft.

In Fig. 3(a) and (b), we use $k = 0.5N/m$, which is consistent with the order of the stiffness of atomic force microscope cantilever (around 0.1N/m) used in the experiments (Fischer-Friedrich et al., 2016; Chaudhuri et al., 2009; Stewart et al., 2013; Webster et al., 2014). In contrast, in Fig. 3(c) and (d), we use $k = 0.005N/m$ and $k = 0.01N/m$, which corresponds to the microplates manipulation experiments where the stiffness of the flexible microplate $k$ is on the order of 0.001–0.01 N/m (Fouchard et al., 2014; Thoumine and Ott, 1997; Desprat et al., 2005; Mitrossilis et al., 2009). Especially, when the flexible microplate is too soft, the cell height can decrease almost to zero when a cell spreads between a flexible microplate and a rigid microplate (Mitrossilis et al., 2010). The stiffness of flexible microplate in their experiment is 0.005N/m, which is the value we used in Fig. 3(c).
VI. THE QUANTITATIVE COMPARISONS WITH EXPERIMENTS

As shown in Fig. S13, we quantitatively compare the results of our model with three typical experiments, i.e., the spreading of cells adhered between two surfaces (Fig. S13(I) and (II)), cell compression (Fig. S13(III)), and cell detachment (Fig. S13(IV)).

For the comparisons with these experimental results, we only change the stiffness of cantilever \( k \), the initial compression of cell \( d_0 \), the adhesion energy density \( \Gamma_0 \), the unloaded dissociation rate of receptor-ligand pair \( k_{0ff} \), the cell size \( r_0 \) (regulated by the reference radius \( r_e \)), and the membrane elastic modulus \( E_m \) to fit these experimental results, since they are different in these experiments. In contrast, other parameters in Table S1 (Supplementary Material) are fixed.

In Fig. S13(I), we compare the dynamic adhesion results of our model with the experimental results when a cell spreads between two microplates (Fouchard et al., 2014). In these experiments, both the contact radius, \( R_e \), and the traction force exerted on cell increase with time during the spreading of cell (Fig. S13(I)). For the solid lines in Fig. S13(I), the fitting parameters are \( \Gamma_0 = 5.24 \times 10^{-3} J/m^2 \), \( k_{0ff} = 0.028/s \), and \( k = 12.5 nN/\mu m \). Other parameters are shown in Table S1. Notice that, the stiffness of the cantilever, \( k \), in our simulations are the same as the stiffness of the microplates in their experiment (Fouchard et al., 2014).

As shown in Fig. S13(II), during the dynamic spreading of the cell between the cantilever beam of AFM and a flat surface, the cell height first decreases and then increases, while the absolute value of the traction force exerted on the cell first increases and then decreases (Chaudhuri et al., 2009). These are similar to the results of the spontaneous rupture in our paper (red curves). In this case, the fitting parameters are \( \Gamma_0 = 2.2 \times 10^{-3} J/m^2 \), \( k = 0.0177 N/m \), \( r_e = 8.2 \mu m \), \( E_m = 90 kPa \), and \( d_0 = 2.3 \mu m \).

In Fig. S13(III), we compare the compression results of our model with the results of the compression experiment carried out with microplates. In this experiment, cell was compressed to 12\( \mu m \) in 10 s (Thoumine and Ott, 1997). It was found that the cell would shorten as it is compressed in the experiment. At the same time, the compression force first increases and then relax to an equilibrium value within 20 minutes. As confirmed by our simulation results (red lines in Fig. S13III), this relaxation may be induced by the efflux of water and ions. The fitting parameters for this experiment are \( r_e = 6.5 \mu m \), \( E_m = 314 kPa \), \( L_p = 4 \times 10^{-11} m/(Pa.s) \), \( \Gamma_0 = 1 \times 10^{-7} J/m^2 \), \( k_{0ff} = 0.01/s \), \( k = 2.9 \times 10^{-8} N/m \).

As shown in Fig. S13(IV), the detachment of cell carried out with micropipette under different membrane tension \( \gamma \) is the ratio of cell height to the cell width at the equatorial center. In (IV), \( R_e \) is the contact radius, \( R \) is the radius at the equatorial center, \( d \) is the displacement of micropipette, \( F \) is the traction force exerted on cell, and \( \gamma \) is the membrane tension of cell.

FIG. S13 The quantitative comparisons with experiments. The experimental data are adapted from (I) (Fouchard et al., 2014); (II) (Chaudhuri et al., 2009); (III) (Thoumine and Ott, 1997); (IV) (Pierrat et al., 2004). The shape index in (III) is defined as the ratio of cell height to the cell width at the equatorial center. In (IV), \( R_e \) is the contact radius, \( R \) is the radius at the equatorial center, \( d \) is the displacement of micropipette, \( F \) is the traction force exerted on cell, and \( \gamma \) is the membrane tension of cell.
TABLE S1 Parameters used in the simulations

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<tr>
<th>parameter</th>
<th>description</th>
<th>value (Ref)</th>
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<td>( h_c )</td>
<td>Thickness of cortical layer (nm)</td>
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<tr>
<td>( h_m )</td>
<td>Thickness of membrane layer (nm)</td>
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<td>( E_m )</td>
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<td>( b )</td>
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<tr>
<td>( \eta )</td>
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<td>( \sigma_a )</td>
<td>Active stress of actin cortex (Pa)</td>
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<td>Threshold stress of MS channels (Pa)</td>
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<td>Reference radius of cell (µm)</td>
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<td>( \gamma )</td>
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<td>( k_{off}^0 )</td>
<td>Unloaded dissociation rate ( (s^{-1}) )</td>
<td>0.01 (Thoumine and Meister, 2000)</td>
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</table>

References

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K. D. Webster, W. P. Ng, and D. A. Fletcher, Biophysical journal 107, 146 (2014).